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PI Name:	Blattnig, Steve Ph.D.		
Project Title:	Space Radiation Risk Assessment Project		
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Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	No
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Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	steve.r.blattnig@nasa.gov	**Fax:**	FY
PI Organization Type:	NASA CENTER	**Phone:**	757-864-1421
Organization Name:	NASA Langley Research Center		
PI Address 1:	2 West Reid St., B1205, Rm. 206, Mail Stop 188E		
PI Address 2:			
PI Web Page:			
City:	Hampton	**State:**	VA
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Comments:			
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No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
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Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
Contact Email:	lisa.c.simonsen@nasa.gov		
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Key Personnel Changes/Previous PI:	January 2017: Carol Mullenax is new project manager.		
COI Name (Institution):	Kim, Myung-Hee Ph.D. (Wyle Laboratories, Inc.) Peterson, Leif Ph.D. (Houston Methodist Hospital Research Institute) Pluth , Janice Ph.D. (Lawrence Berkeley National Laboratory) Plante, Ianik M.D., Ph.D. (Wyle Laboratories, Inc.) Ponomarev, Artem L. Ph.D. (Wyle Laboratories, Inc.) Chappell, Lori (WYLE LABORATORIES, INC) Slaba, Tony Ph.D. (NASA Langley Research Center) Hu, Shaowen Ph.D. (WYLE LABORATORIES, INC)		
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Task Description:	The Risk Assessment Project at Langley Research Center is responsible for the integration of results from NASA space radiobiology research into computational models used for astronaut radiation risk assessments. The purpose of the Project is threefold: (1) evaluate the extent to which ongoing research leads to reduction in the uncertainty of risk assessments and provide, as a metric of program progress, the number of days in space during which the radiation exposure of astronauts remains below NASA limits within a 95% confidence interval ("safe days in space"); (2) perform mission planning studies to predict the number of safe days for any mission; (3) provide recommendations for research directions most likely to reduce risk or improve the accuracy of risk predictions. The four categories of risks from radiation in space are defined by the NASA Bioastronautics Roadmap (BR). They are:1) Carcinogenesis, 2) Acute and late effects to the Central Nervous System (CNS), 3) Degenerative Tissue Effects such as heart disease and cataracts, and 4) Acute Radiation risks. The number of safe days currently predicted for an astronaut's career is less than required by mission planning, due to the large uncertainties in risk prediction. In particular, a projection uncertainty below + or - 50% is the goal for the 1000-day Mars mission because the high level of risk will require high precision risk evaluations. The current approach used to project risk is based on epidemiology data and on phenomenological models used to derive risk prediction from them. This approach cannot lead to improvements in the accuracy of risk prediction beyond a factor of approximately 2. New approaches using molecular biology and genetics are the only viable ones for achieving the level of accuracy required by space exploration and a robust program to obtain the required data is supported by the Space Radiation Program. However, how to incorporate these data into risk prediction and assessment models is not well understood. This Project Plan describes the approaches that will be used to develop models of risk assessment based on mechanistic space radiobiology research funded by the Space Radiation Program, leading to incremental uncertainty reduction based on new experimental data, and to the development of application software to be used in the NASA operational radiation protection program. To accomplish these goals, we will establish new molecular based models of risk. The molecular pathways that are the hallmarks of genomic instability and cancer, and the perturbation of these pathways by radiation will be described using systems biology approaches and Monte-Carlo simulation. We will develop descriptive models of such pathways utilizing track structure models of biomolecular damage, and deterministic and stochastic kinetic models of dominant molecular pathways causative of BR radiation risks. These simulations will make maximum use of results from mechanistic space radiobiology, and will replace traditional hazard functions and their inherent uncertainties due to reliance on epidemiological or phenomenological approaches.
Rationale for HRP Directed Research:	This research is directed because it contains highly constrained research.
Research Impact/Earth Benefits:	Radiobiology research provides many important qualitative descriptions of biological effects of radiation on biomolecules, cells, and tissues. The Space Radiation Risk Assessment Project provides an important link that integrates qualitative experimental observations into detailed quantitative biophysical models of radiations risks. This research benefits all humans that will be exposed to ionizing radiation and supports the development of disease models in general. Models of cancer, heart disease, acute, and other risks developed by the Space Radiation Risk Assessment Project provide NASA with the ability to project risks and develop cost-effective mitigation approaches for future exploration missions.
	A combined modeling and experimental effort to characterize DNA damage responses induced from exposure to space radiation was performed. This data is being used as a surrogate indicator of radiation risk to systemically quantify dose-response, radiation quality, and dose-rate effects along with the associated uncertainties of these factors. Models are also being developed to help extrapolate results from available experimental data to a wider range of doses, particle types, and energies. Model outputs were used to calculate relative biological effectiveness (RBE) for DNA damage and chromosome damage. This effort will reduce the uncertainties in the RBE values for galactic cosmic radiation (GCR) spectrum. Experimental measurements: A database of existing experimental measurements continues, which can be used to validate and improve the computational models. It was expanded to include new experimental studies of low doses and low dose-rate effects, and how proton energy affects RBE. The dose response for induction of chromosome aberrations by high energy and charge (HZE) nuclei was investigated at exposures corresponding to less than one particle traversal per cell nucleus. Non-linear regression models were used to evaluate possible linear and non-linear dose-response models based on these data. The results suggest that chromosome exchanges in normal human fibroblasts have an important non-targeted effect (NTE) contribution at low particle fluence and this provides important evidence that contradicts the linear dose-response assumption used in radiation protection for HZE particles and other high LET (linear energy transfer) radiation at the dose range that is relevant for space flight exposures. An investigation was completed this year on chromosome exchanges induced in human cells by seven different energies of protons (5–2.5 GeV) with LET values ranging from 0.2 to 8 keV/µm. The linear dose–response term was similar for all energies of protons, suggesting that the decrease in LET with increasing proton energy was balanced by the increase in dose from the production of nuclear secondaries. RBE values for total chromosome exchanges was close to unity when measured against acute gamma rays, and the RBE approaches 2 when measured against low dose rate gamma rays. Additional studies of 50 g/cm2 aluminum shielded high-energy proton beams showed minor differences compared to the unshielded protons and lower RBE values found for shielded in comparison to unshielded 2 of 2.5 GeV protons. All energies of protons produced a much higher percentage of complex-type chromosome exchanges when compared to acute doses of gamma-rays, which could affect the risk from exposure to this type of radiation. In addition, work was done to identify biomarker panels that can quantitatively and robustly predict risk of cancer development from HZE exposures. Studies were completed using various types of cells to better understand how cell type influences response. Flow cytometery-based assays were used to detect biomarkers at earlier (<24 h), later (72 h), and weeks post high LET exposure to define the kinetics of the biomarkers response. Biomarkers such as DNA damage signaling, telomere length changes, centrosome aberrations, senescence, and stem cell populations were investigated to determine how they are modified with time post HZE exposure. More recently, to understand the underlying mechanism that drives changes associated with pre-malignant changes, investigations were conducted of how miRNA signatures associated with inflammation are altered post exposure using a flow-based method. Analysis of the data continues but

Task Progress:

initial findings indicate that specific miRNAs are elevated or decreased in a dose-dependent manner post HZE exposures. Further studies to allow additional multiplexing of biomarkers by flow or other rapid, high throughput means are in progress.

We built on findings from our previous study by defining additional relevant endpoints to improve our mechanistic understanding. We examined phosphorylation of fourteen key nodes in two different stress activated signaling pathways, namely, the receptor tyrosine kinase signaling pathway, and the TNF alpha signaling pathway. We identified four key nodes in these pathways whose phosphorylation levels increase with age after high dose exposure to high LET (linear energy transfer) radiation. These results provide clues to the involvement of proteins and their related mechanisms in the age specific generation of cancer biomarkers noted in previous studies. In addition, we have also identified unique phospho-signatures that may underscore strain specific differences in susceptibility.

Bioinformatics approaches investigated over the last year included an interactive networking approach for comparing host transcriptional response to low- and high- doses of ionizing radiation that could potentially eliminate the uncertainties associated with using individual gene or biological processes. In support of this effort a database of ionizing radiation-related gene expression profiles available from the public domain was compiled and included 78 datasets comprising 3,931 samples. A prototype web-database was generated for storing these data. In a second endeavor, to further understand the radiation and age dependent differences noted, we examined miRNA expression profiles in various age groups after high LET exposure. Overall, we have identified unique mechanistic signatures that underscore effects of age and individual susceptibility. These data together with our results on surrogate cancer risk markers will be crucial to reducing uncertainties pertaining to the effect of age and radiation quality in modeling cancer risk from heavy ion exposures.

Computational Modeling:

During the last year improvements were implemented in the computational risk assessment models: The RITRACKS (Relativistic Ion Tracks) code that provides stochastic track structure simulations of ions and electrons, was merged with atomistic DNA models to simulate DNA damage in much greater detail. To simulate the direct effects of ion tracks, the Binary-Encounter-Bethe (BEB) differential cross sections were calculated for each molecular orbital of the DNA and included in the electron and ion transport algorithms of RITRACKS. For indirect effects of exposure, Monte-Carlo simulation of radiolytic species diffusion and chemical reactions with the DNA bases was accomplished using an approach based on the Green's functions of the diffusion equation, which is often used to validate theories of chemical reactions. A new mixed irradiation field feature has also been implemented in RITRACKS. Updates have been published in several publications.

A new software tool, Biological Damage by Stochastic Tracks (BDSTRACKS), was developed to model the effects of space radiation on human cells and tissue. The software was developed by combining stochastic model of radiation tracks with cell nucleus, and DNA damage models. This new tool provides improved predictions of clustered and complex DNA damage in human cells and is expected to improve our understanding of DNA repair and signal transduction. BDSTRACKS was validated using experimental data and used to simulate dose responses for radiation induced DNA and chromosome damage, and this data was used to generate RBE values for these endpoints. A large database of simulated DNA double strand breaks, DNA fragments, and various chromosomal aberrations yields was generated for a large variety of possible space radiation scenarios. In addition this stochastic track model is able to simulate doses as low as 0.005 Gy and predicts a higher yield of small DNA fragments in this low dose range than has been reported in the experimental data or simulated using the amorphous track models. This may indicate that comparison to the experimental data is complicated due to a non-targeted effects. A non-targeted effect model is currently being integrated into the BDSTRACK tool for high-LET radiation exposure.

Work continued on the development and verification and validation of BDSTRACKS, which calculates chromosome aberrations using either the full Monte Carlo track structure simulation code RITRACKS or a simplified parametric track structure model. The code was modified to perform simulations for mixed fields in support of the galactic cosmic radiation (GCR) simulation effort. Also, photon transport was added to the Monte Carlo track structure model in order to better enable RBE (relative biological effectiveness) calculations. A significant effort was also made to streamline and test the code including comparisons of RITRACKS to TEPC (tissue equivalent proportional counter) data.

We used cellular computer automata to investigate the relative cancer contribution of immediate damage to cell at the moment of exposure against the effect of long-term systemic changes such as chronic inflammation following exposure. Our computer model was able to recapitulate spontaneous breast cancer incidence as well as the cancer incidence in the A-bomb survival cohort. The model was then tested to predict cancer incidence in the same artificial cohort exposed to space radiation that we refined our DNA damage cluster model, which can explain RBE greater than one for high LET without the need of introducing DNA damage complexity as a mechanism. Instead, we propose a formalism where the combination of nuclear repair domains with very high local doses along ion tracks is sufficient to explain and predict cell death for any LET. We are finalizing the production of both survival curves and mutation frequencies for the 252 LET and dose conditions, so we can generate appropriate RBEs.

Project II: Space Radiation Risk Assessment Tools

Cancer Risk Model Improvements: NASA Space Cancer Risk model was revised to include uncertainty assessments for all model coefficients (physics, low LET risk coefficients, dose and dose-rate effectiveness factor (DDREF), and quality factors), and an alternative uncertainty assessment was included that considers deviation from linear responses due to non-targeted effects. The sensitivity analysis helped identify the uncertainties in the cancer risk models that have the largest impact on the final Radiation Exposure Induced Death (REID) estimate.

New approaches to reduce uncertainties in the cancer model were evaluated: the data used to estimate RBE in the article published by Cucinotta in PloS One, "A New Approach to Reduce Uncertainties in Space Radiation Cancer Risk Predictions" (2015 Mar 19;10(3):e0120717) and the statistical methods used to combine the distributions in this approach were investigated. This is a first step to evaluating if the methods proposed in the article are appropriate to include in NASA's space cancer risk model. An updated version of the cancer model was delivered to Operations. An extensive software verification effort and a complete rewrite of the code to make it easily usable was performed. As part of this effort modifications were made to improve the numerical performance and correct bugs. In addition the code was: extended for multiple exposures, transport and radiation environmental models were updated, and the dose normalization scheme was improved to include active dosimetry.

	Overall, a healthier working population will have a lower all-cause morbidity (mortality) rate, ultimately shifting events to occur later in life. The healthy worker effect, also known as the healthy hired effect and healthy survivor effect, is a bias that causes morbidity or mortality to be lower among workers when compared with the general population, because unhealthy individuals are screened from or leave the workplace. In order to scope out the potential magnitude of the healthy worker effect, new estimates of survivor function for the astronauts were used to calculate an age-specific hazard function. The hazard function was employed during lifetime risk projections to generate baseline lifetime risks (BLR) and excess radiation-induced lifetime risks (ELR) of cancer mortality and incidence. Acute Radiation Exposure modeling: Acute radiation risk models were expanded to describe the dynamical alterations in the counts for four hematopoietic models and were incorporated into the software "HemoDose." Validation of the model by comparison to data sets from the 2011 Bulgaria radiation accident produced consistent results. Hematopoietic response to partial body radiation exposure, which may induce a different pattern of hematopoietic response compared to a homogeneous whole body exposure, is being investigated. A coarse-grained hematopoietic model was developed to simulate the dynamics of progenitor cells in bone marrow and granulocytes in peripheral blood in dogs that were exposed unilaterally and bilaterally. Further work will be conducted to extend the model to humans and investigate the efficiency of different schemes of partial body shielding to protect astronauts from hematopoietic injury in case of severe solar particle events. An approach was developed to directly use the particle data from multiple satellites to perform near real-time simulations of radiation exposure and the associated health risks for various exposure scenarios. Validation of this model was achieved by comparison with radiation exposure measurements from multiple instruments in space. A method of determining organ doses at different locations within a vehicle directly from dosimetry data from multiple locations was developed including initial testing with the Orion design. This will be a part of a tool being developed to monitor solar particle event exposures and potential acute radiation responses during missions. To this end, acute response modeling for the hematopoietic system was also improved to provide more clinically relevant information. In order to scope out the potential of such effects, initial calculations on the temporal profiles or organ dose rates for historical SPE (solar particle events) were performed.

Bibliography Type:	Description: (Last Updated: 06/30/2023)
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