Fiscal Year:	FY 2011	**Task Last Updated:**	FY 08/01/2011
PI Name:	Cucinotta, Francis A Ph.D.		
Project Title:	Space Radiation Risk Assessment		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
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) **ARS**:Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (2) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (3) **Cancer**:Risk of Radiation Carcinogenesis (4) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes (5) **CNS**:Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (6) **Degen**:Risk of Cardiovascular Disease and Other Degenerative Tissue Effects From Radiation Exposure and Secondary Spaceflight Stressors		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	not available	**Fax:**	FY
PI Organization Type:	NASA CENTER	**Phone:**	(702) 895-4320
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City:	Las Vegas	**State:**	NV
Zip Code:	89154-3037	**Congressional District:**	1
Comments:	Formerly at NASA Johnson Space Center, until summer 2013 (Ed., Oct 2013)		
Project Type:	GROUND	**Solicitation / Funding Source:**	Directed Research
Start Date:	06/01/2006	**End Date:**	08/30/2013
No. of Post Docs:	4	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 8/30/2013 as PI retired then, per S. Monk/NASA Langley Research Center (Ed., 2/9/15)		
Key Personnel Changes/Previous PI:	December 2009 report: Dr. Deepa Sridharan joined the project as a Post-doc at LBNL (Lawrence Berkeley National Laboratory). Dr Zarana Patel left the project from USRA (Universities Space Research Association) in Houston.		
COI Name (Institution):	Pluth, Janice (Lawrence Berkeley National Laboratory) Cornforth, Michael (U TX Medical Branch) Ponomarev, Artem (Universities Space Research Association) Kim, Myung-Hee (Universities Space Research Association) Carra, Claudio (Universities Space Research Association Division of Life Sciences) Li, Yongfeng (Universities Space Research Association)		
Grant/Contract No.:	Directed Research		

Performance Goal No.:	
Performance Goal Text:	
Task Description:	The Risk Assessment Project at Johnson Space 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 fourfold: (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) assess the radiation risk to astronauts for ongoing missions in real time; and, (4) 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:	
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, CNS, 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. Our recent focus is the confounding role of tobacco on cancer and circulatory disease risk estimates. Understanding the effects of tobacco usage on radiation risk estimates benefits ground based use of diagnostic procedures that utilize radiation.
	Project A: Integration and Review: A review of current knowledge from space radiation physics was accepted for publication in Reviews of Modern Physics (Durante and Cucinotta, 2011). Several Graphical Users Interface's (GUI) of risk assessment models and computational tools were developed and published including: a) ARRBOD (Acute Radiation Risk and BRYTNRN Organ Dose); b) NSCR (NASA Space Cancer Risk) c) GERMCode (Galactic Cosmic Radiation, GCR, Event-based Risk Model); d) RITracks (Relativistic Ion Track Structure). The GERMcode was developed to accurately describe fragmentation in the NASA Space Radiation Laboratory (NSRL) beam-line and biological samples, and basic radiobiology experiments. Project B: Cancer Risk Projection Model and Uncertainties: New findings and knowledge from NSRL and other sources were used to revise the NASA's risk model for space radiation cancer risks: 1) Revised values for low LET risk coefficients for tissue specific cancer incidence. 2) An analysis of lung cancer and other smoking attributable cancer risks for never-smokers show significantly reduced lung cancer risks as well as overall cancer risks for astronauts as compared to the risk estimated for the average U.S. population. 3) Derivation of track structure based radiation quality functions that depend on charge number, Z, and kinetic energy, E, in place of a dependence on LET alone. The assignment of a smaller maximum in the quality function for leukemia than for solid cancers. 4) Revised uncertainty assessments for all model coefficients in the risk model (physics, low LET risk coefficients, dose and dose-rate effectiveness factor (DDREF), and quality factors), and an alternative uncertainty assessment that considers deviation from linear responses due to non-targeted effects (NTE). Results of calculations for the average U.S. population show more restrictive dose limits for astronauts above age 40 y as compared to National Council on Radiation Protection and Measurements (NCRP) Report 132, and a modest narrowing of uncertainties if NTEs are not included and much broader uncertainties with NTEs. Risks for never-smokers compared to the average U.S. population are estimated in a mixture model to be reduced by more than 20% and 30% for males and females, respectively. A larger reduction is possible if purely multiplicative risk transfer is assumed. Project C: Biochemical Kinetics Models of Molecular Pathways: A system biology model (Cucinotta et al., 2008) of the non-homologous end joining (NHEJ) pathway was developed and used to make quantitative descriptions of the gamma

Task Progress:	H2AX foci and double strand break (DSB) rejoining experiments. The model is extended to consider the radiation quality dependence of the relative fraction of simple and complex DSB, rejoining and associated repair defects, and the kinetics of various radiation induced foci (RIF). In further work, the addition of ataxia telangiectasia mutated (ATM) and the MRN complex to the model was achieved and the role of processing damaged ends by the Artemis proteins is being modeled (Li and Cucinotta, 2011). The interaction of several growth factors with NHEJ components was studied, including the interaction of the growth factors EGFR, IGF1, and TGFbeta-Smad with ATM and DNA-PK. New approaches to Green's functions for stochastic treatment of molecular diffusion processes were developed (Plante et al. 2011). Flow cytometry or immune-staining considers signals in individual cells and thus provides several unique capabilities to support computation modeling using stochastic approaches. In contrast, methods that average the values of many cells such as Western blots, gene arrays, etc. are limited in elucidating events at low dose where fluctuations are expected to be important. To improve our understanding of DNA repair complexes numerical approaches to simulate immunohistochemistry (Ponomarev et al., 2008, 2009) and flow cytometry experiments (Cucinotta , in preparation, Chappell et al., 2010) were developed. These models embed a basic understanding of track structure with statistical approaches of flow cytometry data sorted by cell cycle phase, and fluorescence intensity taking into account background levels. Following flow cytometry analysis, we were able to distinguish the kinetics of these phospho-proteins in relationship to the cell cycle and to each other in an individual cell. Results revealed a unique pattern of kinetics for high vs low LET radiation, with a failure to initiate full activation of the ATM pathway being evident following High LET exposure. In the process of these studies we have noted that different populations of cells making up normal human tissues can be sorted based on intrinsic qualities of the cells and differences in their radiation sensitivity have been noted. In addition, an increase in proliferation of a specific mammary cell population was observed with low doses of radiation. Project D: DNA Damage in Cancer Initiation and Genomic Instability: Foci size and clustering including strings of foci along high-Z high-energy (HZE) tracks, were modeled for the first time and provide a useful analysis tool of NSRL experiments on DNA damage foci. These models have been extended to predict chromosomal aberration formation including the distribution of small rings normally below detection levels with fluorescence in-situ hybridization (FISH) (<5 Mbp), and to describe complex aberrations. Stochastic track structure models were combined with a human genome model that considers random walk polymer models of each chromosomes pair built from 2 kbp monomers and constrained to nuclear territories in interphase (Ponomarev et al., 2007, 2009). Project E: Acute Radiation Risk Models: We extended the granulopoietic model for rodents for the prediction of solar particle effects in canines, non-human primates, and humans (Hu and Cucinotta, 2011). An important feature of this approach is that the dynamics of cell populations are described by non-linear differential equations. Validation of the model was achieved by comparison to comprehensive data sets for animals exposed to acute and chronic radiation and to the Chernobyl and other radiation accident victims.
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