Fiscal Year:	FY 2018	**Task Last Updated:**	FY 02/09/2018
PI Name:	Costes, Sylvain Ph.D.		
Project Title:	Blood-based Multi-scale Model for Cancer Risk from GCR in Genetically Diverse Populations		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	No
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		
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Zip Code:	98104	**Congressional District:**	7
Comments:	NOTE: After retiring from NASA, the PI joined Blue Marble. Dr. Costes was previously at Lawrence Berkeley National Laboratory until December 2016.		
Project Type:	Ground	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-RADIATION. Appendix D: Ground-Based Studies in Space Radiobiology
Start Date:	02/04/2016	**End Date:**	09/30/2019
No. of Post Docs:	3	**No. of PhD Degrees:**	3
No. of PhD Candidates:	1	**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:**	
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Flight Program:			
Flight Assignment:	NOTE: Extended to 9/30/2019 per F. Hernandez/ARC (Ed., 2/18/19)		
Key Personnel Changes/Previous PI:	NOTE (January 2018): The lab moved from Lawrence Berkeley National Lab (LBNL) to NASA Ames Research Center in 2017, where it was established as the Radiation Biophysics Lab in Space Biosciences Division. Dr. Costes will continue collaborating with LBNL and some funding will be left at LBNL to cover more plate processing in collaboration with Dr. Weil, Colorado State University (CSU) and for support from Dr. Snijders for the writing of the animal data. April 2017 report: - Elodie Guiet was a full time technician with a Bachelor in microbiology and biotechnology, working on this project from March 2016 until February 2017 -- she did not stay on the project when the lab moved to NASA Ames ; - Louise Viger was a Postdoc working partly on this project from June 2016 to January 2017 -- she was only here for a quick postdoc, focused primarily on modeling ; - Charlotte Degorre was a Postdoc who helped executing BNL run 16C -- visiting scientist for 1 month ; - Sebastien Penninckx was a PhD student who has been helping on data analysis -- visiting scientist for 3 months ; - Shayoni Ray is a new recruit at NASA Ames, postdoctoral fellow working on doing genomic analysis between animal DNA repair phenotypic data and their individual genes -- new postdoc full time at NASA Ames, started on April 10 2017.		

COI Name (Institution):	
Grant/Contract No.:	Internal Project--ARC ; NNJ16HP24I
Performance Goal No.:	
Performance Goal Text:	
Task Description:	NOTE (January 2018): The lab moved from Lawrence Berkeley National Lab (LBNL) to NASA Ames Research Center in 2017, where it was established as the Radiation Biophysics Lab in Space Biosciences Division. Dr. Costes will continue collaborating with LBNL and some funding will be left at LBNL to cover more plate processing in collaboration with Dr. Weil, Colorado State University (CSU) and for support from Dr. Snijders for the writing of the animal data. Crews on future exploration missions to Mars and other destinations in our solar system will be exposed to acute low doses (<100 mSv) and chronic low doses (<0.1 mSv/min) of high-LET (linear energy transfer) ionizing radiation from solar particle events (SPE) and galactic cosmic radiation (GCR). Predicting cancer risk associated with these radiation types is a mission-critical challenge for NASA radiation health scientists and mission planners. Epidemiological methods lack sensitivity and power to provide detailed risk estimates for cancer, mainly because the number of exposed individuals to date is relatively small, limited to several hundred individuals exposed to trapped radiation in low Earth orbit and fewer than two dozen Apollo astronauts exposed to GCR for several days at a time. Moreover, population-based studies do not take individual radiation sensitivity into account, are sensitive to the presence of other confounding environmental insults, and require long follow-up times. In collaboration with the radiation Biodosimetry Laboratory and the modeling group at NASA Johnson Space Center and with the International Computer Science Institute (ICSI) at University of California (UC) Berkeley, our team will bring unique inter-disciplinary expertise to integrate the large array of cancer data generated over the past 25 years and archived by NASA under the various Human Research Program (HRP) funded projects. The main goal of this proposal is to identify factors influencing radiation-induced carcinogenesis and integrate them into a multi-scale model already started at the Berkeley Lab that encompasses DNA damage response and inter-cellular signaling to predict cancer risk for any types of HZE (high energy particles). Because experimental data are dispersed across many different cancer models, radiation qualities, and measurement types, this project will also generate a complete set of experimental data designed to fully inform and validate the model. In this project, the model will impose the types of measurements being made, with a strong emphasis on well-established blood biomarkers. In our approach we hypothesize that genetic factors strongly influence risk of cancer from space radiation and that biomarkers reflecting DNA damage and inflammatory processes in the blood are great tools to predict risk and monitor potential health effects post-flight. By using blood as a surrogate organ, the proposed work will allow extrapolation of cancer risk from mice to humans. A cohort of 6 different strains of mice (collaborative cross-mouse) with expected sensitivity to ionizing radiation will be monitored for biomarkers and cancer after exposure to 0.3 Gy of 1 GeV/amu Fe particle and compared to 1 Gy exposure of gamma ray control. Because we favor larger number of animals per radiation condition, we selected only one dose and the most carcinogenic particle to prove the principle of our approach while validating our model on a complete set of ex-vivo data and in-vivo longitudinal data. The collaborative cross-mouse model is an SFA resource that will make it possible for our team to examine the impact of genetic diversity in an animal model in a systematic and reproducible manner. In parallel, we propose to fully characterize the DNA damage response and cell death from ionizing radiation administered ex-vivo to 30 genetically different strains of mice and to 1000 human blood donors, matching the age and gender distribution of the astronaut population. Taken together, an array of ex-vivo phenotypic features will be associated to genetic traits across mice and humans as a function of age and gender. At the end of this proposal, our team will provide NASA with a model to estimate individualized risk for an astronaut before a flight as well as estimating the risk during the flight. Information generated in this proposal will also be useful to generate guidelines and suggest the best biomarkers to monitor the healthy recovery of astronauts post-flight.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	A current radiobiology challenge is the ability to predict cancer risk associated with exposure to acute (<100 mSv) and chronic (<0.1 mSv/min) low doses of high-LET ionizing radiation. Epidemiological methods lack the sensitivity and power to provide detailed risk estimates for cancer, mainly because the astronaut cohort exposed to galactic cosmic rays (GCR) is relatively small. Moreover, population-based studies do not take individual radiation sensitivity into account, are affected by the presence of other confounding environmental insults, and require long follow-up times. We have hypothesized that characterizing the dose and time dependence of 53BP1 radiation induced foci (RIF) after exposure to a systematic array of X-ray doses and time points is sufficient to describe someone's ability to respond to any other LET. The main concept is that the non-physiological response to high doses of low-LET in cells can be used to predict the response to low doses of high-LET, and that the response to low and high doses of radiation is modulated by different pools of genes. Such work provides a new approach combining novel biomarkers with sophisticated mathematical analysis to better characterize individual sensitivity to space radiation. Once validated across mice and eventually a large cohort of humans, this approach could be generalized to establish individualized health risk management for astronauts and for the population at large being exposed to ionizing radiation.
	In year 2, we have completed the first part of the study, which aims to identify the genomic risk factors of sensitivity to ionizing radiation in mice. The previously described experiments of exposing mouse skin fibroblasts to high-LET ionizing radiation and measuring the resulting DNA damage and repair allowed us to compare the mouse strains based on sensitivity to ionizing radiation-induced DNA damage. We then performed genome-wide association studies (GWAS) on these mouse strains in order to map the single nucleotide polymorphisms (SNPs) that are associated with ionizing radiation sensitivity. We identified seven significant associations on chromosomes 2, 3, 7, 10, 11, and 19 corresponding to 350 Mev/n Ar, three significant associations on chromosomes 10 and 13, corresponding to 600 MeV/n Fe, and two significant loci at chromosome 2 and 6, corresponding to 350 MeV/n Si. For both the high LET radiations, Ar and Fe, a common locus on chromosome 10 was identified, with peak SNP as UNC18214722 (p value = 7.22 x 10-7) along with fourteen genes affiliated with chromatin modification, DNA replication, transcription, and double stranded break repair. For 350 Mev/n

Task Progress:	Ar, additionally, two other peak SNPs were identified on chromosome 10 (JAX00021248, p = 4.24 x 10-6) and on chromosome 11 (UNC20271233, p = 4.03 x 10-6) with five DNA damage response genes. For low LET Si, out of 21 genes in the LD, one repair-associated gene at peak SNP JAX00629117 on chromosome 6 (p = 1.2 x 10-6) was identified. Pathway analysis using DAVID identified DNA repair response as the most enriched pathway. The second part of our study applies a similar approach to humans and aims to characterize the genomic risk factors associated with sensitivity to ionizing radiation in a large human cohort. We are in the process of collecting peripheral blood mononuclear cells (PBMCs) from a large cohort of at least 500 and up to 700 healthy human volunteers, combining samples from Institut Pasteur in France, Oklahoma Blood Institute, and NASA Ames. We have optimized all relevant protocols to isolate, freeze, thaw, and culture human PBMCs, and in order to measure DNA repair responses, we have developed an experimental setup for high-throughput immunocytochemistry for DNA repair markers 53-bp1 and gamma-H2AX on human PBMCs as well as automated image acquisition and analysis. We will also quantify primary human immune cell death and differentiation into pro- or anti-inflammatory phenotypes. We will participate in the BNL (Brookhaven National Laboratory) summer and fall 2018 runs where we will expose these human PBMCs to high-LET radiation. Specifically, in summer 2018 we will expose PBMCs from 100 subjects (50 of the most susceptible and 50 of the least susceptible to low-LET radiation) to 2 fluences (1.1 and 3 particles/100um^2) of 14Si, 18Ar, and 26Fe ions and isolate them at 4 h, 24 h, and 48 h after irradiation to measure the time course of DNA repair and cellular responses. In fall 2018, we will repeat this experiment with PBMCs from 300 subjects, focusing specifically on responses to Fe irradiation. In this way, we have expanded our original experimental plan to include more subjects, which will allow us to achieve more conclusive results on modeling responses to high-LET radiation-induced DNA damage and repair.
Bibliography Type:	Description: (Last Updated: 05/01/2025)
Articles in Peer-reviewed Journals	Cortese F, Klokov D, Osipov A, Stefaniak J, Moskalev A, Schastnaya J, Cantor C, Aliper A, Mamoshina P, Ushakov I, Sapetsky A, Vanheaelen Q, Alchinova I, Karganov M, Kovalchuk O, Wilkins RC, Shtemberg A, Moreels M, Baatout S, Izumchenko E, de Magalhães JP, Artemov AV, Costes SV, Beheshti A, Mao XW, Pecaut MJ, Kaminskiy D, Ozerov IV, Scheibye-Knudsen M, Zhavoronkov A. "Vive la radiorésistance!: converging research in radiobiology and biogerontology to enhance human radioresistance for deep space exploration and colonization." Oncotarget. 2018 Mar;9(18):14692-722. https://doi.org/10.18632/oncotarget.24461 ; PubMed PMID: 29581875; PubMed Central PMCID: PMC5865701 , Mar-2018
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