Fiscal Year:	FY 2020	**Task Last Updated:**	FY 11/13/2019
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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PI Organization Type:	NASA CENTER	**Phone:**	650-604-5343
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City:	Moffett Field	**State:**	CA
Zip Code:	94035-0001	**Congressional District:**	18
Comments:	NOTE: 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:**	05/31/2021
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 ARC
Contact Monitor:	Lewis, Laura	**Contact Phone:**	
Contact Email:	laura.lewis@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: Extended to 5/31/2021 per L. Lewis/ARC HRP (Ed., 9/24/20) NOTE: Extended to 5/31/2020 per PI (Ed., 11/15/19) 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 used in this work was a resource from the low dose program at DOE (Department of Energy) developed by the Lawrence Berkeley National Laboratory that has made 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.

Task Progress:	During year 4, the Radiation Biophysics Lab at NASA Ames has completed the majority of experiments in the human research part of the proposal. We have also received a costed extension to expand the sample numbers to over 750 subjects instead of the original 500 for a more rigorous analysis of genomic associations with responses to ionizing radiation, and to finish the project by May 31, 2020. The human blood sample collection is complete: we have collected samples from 762 healthy subjects, 18-75 years old, 50/50 male/female, of Northern European origin. We have irradiated all primary immune cell samples from all subjects (compared to 192 irradiated at the time of the previous report) at Brookhaven National Laboratory (BNL) in the spring 19A run and fall 19C run. We have also isolated DNA from all subjects and prepared libraries for sequencing that is scheduled in December 2019. This year we have published one primary research manuscript on the comparison of radiation sensitivity between mouse lines6 and have submitted a review on radiation countermeasures in the central nervous system (Pariset, Malkani, Cekanaviciute and Costes, International Journal of Radiation Biology). During year 3, the Radiation Biophysics Lab at NASA Ames has finished the mouse research component and significantly moved forward with the human research component of this proposal. Human blood sample collection to investigate genomic associations with radiation sensitivity began in February 2018, and by December 2018 we have collected, isolated, and stored peripheral blood mononuclear cells (PBMCs) from 602 healthy subjects, 18-75 years old, 50/50 male/female, of Northern European origin. We have irradiated primary immune cells from the first 192 subjects at Brookhaven National Laboratory (BNL) in the summer 18B run using 350 MeV/n 28Si, 350 MeV/n 38Ar, and 600 MeV/n 56Fe ions and gamma rays, immunostained them with DNA damage marker anti-53BP1, performed high-throughput imaging and quantification of DNA damage foci, and are in the process of analyzing the results. In addition, we have designed a flow cytometry-based analysis of oxidative stress and cell death and used it to quantify the cellular responses to particle and gamma radiation from the first 192 BNL samples. We have also started collecting the supernatants from irradiated cells for potential future analysis of secreted biomarkers of human radiation sensitivity.
Bibliography Type:	Description: (Last Updated: 06/01/2023)
Articles in Other Journals or Periodicals	Pariset E, Malkani S, Cekanaviciute E, Costes SV. "Ionizing radiation-induced risks to the central nervous system and countermeasures in cellular and rodent models." International Journal of Radiation Biology (in press as of November 2019). , Nov-2019
Articles in Peer-reviewed Journals	Cekanaviciute E, Rosi S, Costes SV. "Central nervous system responses to simulated galactic cosmic rays." Int J Mol Sci. 2018 Nov 20;19(11):E3669. https://doi.org/10.3390/ijms19113669 ; PubMed PMID: 30463349; PubMed Central PMCID: PMC6275046 , Nov-2018
Articles in Peer-reviewed Journals	Ochola DO, Sharif R, Bedford JS, Keefe TJ, Kato TA, Fallgren CM, Demant P, Costes SV, Weil MM. "Persistence of gamma-H2AX foci in bronchial cells correlates with susceptibility to radiation associated lung cancer in mice." Radiat Res. 2019 Jan;191(1):67-75. Epub 2018 Nov 6. https://doi.org/10.1667/RR14979.1 ; PubMed PMID: 30398394 , Jan-2019
Articles in Peer-reviewed Journals	Penninckx S, Cekanaviciute E, Degorre C, Guiet E, Viger L, Lucas S, Costes SV. "Dose, LET and strain dependence of radiation-induced 53BP1+ foci in 15 mouse strains ex vivo introducing novel DNA damage metrics." Radiat Res. 2019 Jul;192(1):1-12. Epub 2019 May 13. https://doi.org/10.1667/RR15338.1 ; PubMed PMID: 31081741 , Jul-2019