Fiscal Year:	FY 2022	**Task Last Updated:**	FY 12/04/2021
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:**	10/01/2022
No. of Post Docs:	1	**No. of PhD Degrees:**	3
No. of PhD Candidates:	0	**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA ARC
Contact Monitor:	Zawaski, Janice	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 10/1/2022 per PI/CoI information (Ed., 2/4/22) NOTE: End date changed to 10/1/2021 per Space Radiation (Ed., 8/2/21) NOTE: End date changed to 9/30/2021 per L.Lewis/ARC HRP (Ed., 12/9/20) 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 - Left in 2019 - Eloise Pariset was on the project until January 2020
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:	The experimental work on the project has been significantly delayed by the ongoing Covid-19 pandemic. However, we were allowed to return to hands-on laboratory research in March 2021 and finished all particle irradiation experiments at Brookhaven National Laboratory (BNL) BNL21B run in June 2021. We have irradiated the peripheral blood mononuclear cells (PBMCs) from all remaining subjects, including the repeats of previous BNL experiments that we were unable to analyze previously due to Covid restrictions. We have analyzed their DNA repair kinetics using immunostaining with fluorescently-tagged 53BP1 antibody followed by semi-automated high throughput microscopy, image processing, and quantification. Currently, we are collaborating with the lab of Dr. Christopher Mason at Weill Cornell Medicine to match the phenotypic outcomes of DNA repair with genotypes based on low coverage whole genome sequencing. In summary, for this project we have collected DNA repair data from 750 subjects, whose PBMCs have been irradiated ex vivo with 3 types of particle radiation (350 MeV/n 28Si, 350 MeV/n 40Ar, 600 MeV/n 56Fe) as well as gamma rays, at 2 doses each (1.1 and 3 particle/100 micrometers2 fluence, which translates to 0.1 Gy and 0.3 Gy for 28Si, 0.18 Gy and 0.5 Gy for 40Ar, and 0.3 Gy and 0.82 Gy for 56Fe respectively; and 0.1 Gy and 1 Gy doses of gamma rays), and at 2 timepoints post irradiation: 4 and 24 hours; as well as at baseline that represents the time of collecting PBMCs. To our knowledge this is the largest such dataset of human ex vivo responses to simulated space radiation. We anticipate that our data, which we will publish open access on NASA GeneLab, will serve as a useful resource for multiple future investigations. Furthermore, we have collected data on oxidative stress and cell death from a subset of ~400 subjects, analyzed additional responses to 5-ion simplified simulated GCRs (0.25 Gy and 0.5 Gy doses, 4 h and 24 h post irradiation) and 250 MeV/n 4He (0.15 Gy and 0.5 Gy doses, 4 h and 24 h post irradiation) as part of piggyback experiments at NASA Space Radiation Laboratory (NSRL), and collected supernatant for quantifying secreted factors from all our samples for follow-up studies that will be available for potential collaborations. Additional supernatant samples from 24 most variable subjects in response to 56Fe irradiation have also been collected for exosome quantification as part of a Human Research Program (HRP) Augmentation Award to our former postdoctoral scholar Eloise Pariset (awarded January 2021). Finally, as part of a collaboration with the Mason lab, we have selected 96 subjects with maximal variability in DNA repair responses and collected their RNA for transcriptomic analysis after 56Fe and gamma irradiation (funded by the Mason lab) to validate whether genomic associations with radiosensitivity are reflected in changes in gene expression. This year we have one review article on DNA damage markers in press (Penninckx et al., Quantification of radiation-induced DNA repair foci to evaluate and predict biological responses to ionizing radiation, NAR Cancer--ed. note: see Bibliography section) and one primary research article under revision (Cekanaviciute et al., Mouse Genomic Associations with Ex Vivo Sensitivity to Simulated Space Radiation). Our research was presented at the Human Research Program Investigators' Workshop, the National Council on Radiation Protection (NCRP): Biomarkers & Countermeasures and Conclusions conference, the Radiation Research Society Annual Meeting, and the American Society for Gravitational and Space Research Annual Meeting (all Sylvain Costes, oral presentations) and will be presented at COSPAR 2022 (invited presentation, Sylvain Costes)). Our main future directions for this project are reflected in two key collaborations that we have started this year, with the goals to use the data from this project to generate new results: a) applying AI/ML (artificial intelligence/machine learning) methods to analyze our data (with NASA GeneLab and Frontier Development Lab); and b) using network analysis to compare the effects of spaceflight stressors and terrestrial diseases and repurpose Food & Drug Administration (FDA)-approved therapeutics as countermeasures for space radiation (with the SPOKE project and Baranzini Lab at the University of California, San Francisco, on which we have published a pilot study: Nelson et al., Life 2021).
Bibliography Type:	Description: (Last Updated: 05/01/2025)
Articles in Peer-reviewed Journals	Nelson CA, Acuna AU, Paul AM, Scott RT, Butte AJ, Cekanaviciute E, Baranzini SE, Costes SV. "Knowledge network embedding of transcriptomic data from spaceflown mice uncovers signs and symptoms associated with terrestrial diseases." Life (Basel). 2021 Jan 12;11(1):E42. https://doi.org/10.3390/life11010042 ; PMID: 33445483; PMCID: PMC7828077 , Jan-2021
Articles in Peer-reviewed Journals	Penninckx S, Pariset E, Cekanaviciute E, Costes SV. "Quantification of radiation-induced DNA double strand break repair foci to evaluate and predict biological responses to ionizing radiation." NAR Cancer. 2021 Dec;3(4):zcab046. https://doi.org/10.1093/narcan/zcab046 ; PMID: 35692378; PMCID: PMC8693576 , Dec-2021