Fiscal Year:	FY 2017	**Task Last Updated:**	FY 04/19/2017
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:**	02/03/2019
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:			
Key Personnel Changes/Previous PI:	NOTE: 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 (CSU) and for support from CoI 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):	Pluth, Janice Ph.D. (Lawrence Berkeley National Laboratory) Snijders, Antoine Ph.D. (Lawrence Berkeley National Laboratory)		

Grant/Contract No.:	NNJ16HP24I
Performance Goal No.:	
Performance Goal Text:	
Task Description:	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.
Task Progress:	Skin fibroblast cells were extracted and cultivated from 72 individual mice. This cohort was made on average of 3 males and 3 females from 15 different strains of mice with various genetic backgrounds, including the collaborative cross (CC) genetic model (10 strains) and five known reference mice. Cells were exposed to two fluences of three HZE particles at Brookhaven National Laboratory (Si 350MeV/n, Ar 350MeV/n and Fe 600 MeV/n) and to 0.1, 1, and 4 Gy from 160 kV X-ray at Lawrence Berkeley National Laboratory. Individual radiation sensitivity was investigated by DNA repair kinetics high throughput measurement evaluating RIF numbers at various time following the different doses and fluences for each radiation type. The high-LET particle dose response shows a linear dependence that is unchanged and very close to the number of track per cell for both 4 and 8 hours post-irradiation, even though each track are known to induce multiple DNA double strand breaks (DSB). By comparing the slope of the high-LET dose dependence to the expected number of tracks per cell for each dose, we propose a new approach where the number of remaining unrepaired tracks are evaluated against the time post-irradiation. The results obtained using this approach show that the percentage of unrepaired track over a 48 hours follow-up is strain dependent and is slower as the LET increases. We also observe a strong correlation between the high dose repair kinetic following exposure to 160 kV X-ray and the repair kinetic of tracks, with an increasing correlation with higher LET. At the in-vivo level for the 10 CC strains, we observe that drops in the number of T-cells and B-cells found in the blood of mice 24 hours after exposure to 0.1 Gy of 320 kV X-ray correlate well with slower DNA repair kinetic in skin cells. Overall, our results suggest that repair kinetic found in skin is a surrogate marker for in vivo radiation sensitivity in other tissue, such as blood cells and such response is modulated by genetic. On the other hand, different genes seem to be

	involved for low dose of low-LET sensitivity versus high dose low-LET or high-LET sensitivity. This work also validates our hypothesis showing that DNA repair kinetic following high doses of X-ray is an accurate predictor for radiation sensitivity to high-LET when evaluated on cell culture. Single-nucleotide polymorphism arrays are currently being used to identify potential pools of genes responsible for radiation sensitivity to low-LET and/or high-LET. To the best of our knowledge, this work is one of the most extensive studies done on such a large animal genetic diversity regarding both low dose radiation and high-LET. NOTE: 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 (CSU) and for support from CoI Dr. Snijders for the writing of the animal data.
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