Fiscal Year:	FY 2019	**Task Last Updated:**	FY 01/18/2019
PI Name:	Cunha, Micaela Ph.D.		
Project Title:	A Mechanistic Framework to Assess the Efficacy of Aspirin and Other Radio Protectors to Reduce Carcinogenesis by Space Radiations		
Division Name:	Human Research		
Program/Discipline:			
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Zip Code:	10032-3725	**Congressional District:**	13
Comments:			
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No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
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Contact Monitor:		**Contact Phone:**	
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Task Description:	POSTDOCTORAL FELLOWSHIP NASA is planning a 2-3-year inter-planetary mission to start around 2030, as well as subsequent Mars landing missions. Current data from human and animal studied suggests that exposure of astronauts to radiation in space, in particular to high linear energy transfer (LET) galactic cosmic rays (GCR) and neutrons, may result in increased cancer risks which are not yet adequately quantified. Thus, it is important to develop effective and safe biomedical countermeasures to minimize these risks. One possibility is to use drugs that have been shown to reduce the background spontaneous cancer risks, such as aspirin for gastrointestinal (GI) cancers. We have previously developed a mechanistic framework to evaluate the risk of radiation carcinogenesis and have successfully applied it, taking into consideration multiple variables such as low- and high-LET radiation, low and high dose rates, or age-at-exposure effects. The aim of this project is to extend this framework to assess the effects of biomedical countermeasures on GCR-induced cancer risks. We will start by analyzing data regarding aspirin and GI cancers, as there is convincing evidence that aspirin reduces the risk of colorectal cancer, but the ultimate goal of the proposed project is to provide a general methodology for the assessment of any anti-cancer agent under consideration for reducing the risks of GCR-induced carcinogenesis.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Astronauts in space are chronically exposed to low doses of a variety of densely ionizing radiations. On a long interplanetary mission such as on a journey to Mars, the risks to human health of exposure to the space radiation environment are currently the limiting factor, in particular for women and younger astronauts. However, the cellular mechanisms that are involved in the measurable biological response to this peculiar radiation environment are not well known yet, making it difficult to estimate the risks to human health, especially in terms of cancer and other late effects. Developing a mechanistic framework of radiation-induced carcinogenesis that integrates microdosimetric quantities to assess the potential radioprotective effect of chemical compounds will give an important contribution to expand the knowledge on the mechanisms that underlie the biological response to space radiation and will pave the way to more accurate predictions of cancer risks for astronauts.
Task Progress:	NASA is planning a 2-3-year inter-planetary mission to start around 2030, as well as subsequent Mars landing missions. Data from human and animal studies suggest that exposure of astronauts to radiation in space, in particular to high linear energy transfer (LET) galactic cosmic rays (GCR) and neutrons, may result in an increased cancer risk which is not yet adequately quantified. In fact, the potential radiation-induced fatal cancer risks are the key factors that limit mission length. It is therefore important to develop effective and safe biomedical countermeasures to minimize such risks. There is a variety of studies that demonstrate the potential of some drugs in protecting against radiation-induced cancer, acting as modulators of the different stages of the carcinogenesis process. The goal of this project was to develop a general theoretical and quantitative methodology to assess the effects of any potential biomedical countermeasures on GCR-induced cancer risks. This task would be accomplished by extending an already existing mechanistic framework developed for the evaluation of the risk of radiation-induced carcinogenesis and validated with data pertaining to low- and high-LET radiations at high and low dose rates, also considering age-at-exposure effects. A seemingly strong candidate to test this new methodology would be aspirin, which has been shown in observational studies to reduce the background spontaneous cancer risks, namely for gastrointestinal cancers. The hypothesis was that aspirin would also protect against space-radiation-induced carcinogenesis. Testing and validation of the newly developed methodology would be made by using a robust animal data set on 28Si-induced intestinal tumorigenesis produced by the Georgetown University NSCOR (NASA Specialized Center of Research), which included mice treated with several concentrations of aspirin irradiated with different doses of 28Si ions. Unfortunately, the results of these experiments did not show a radioprotective effect of aspirin against 28Si ions. Although other studies of aspirin effects against high LET radiation are still ongoing, the currently available data from Georgetown University could not be used to test the initial hypothesis. In order to try to find alternative data sets for this task, a comprehensive review of the literature on radioprotectors was carried out considering the specific requirements for this project: dose response curves regarding in vivo radiation-induced carcinogenesis or related in vitro endpoints (e.g., genomic instability, oncogenic transformation) for low doses of space-like radiation. Two data sets were found to be adequate: (1) vitamin A showed protection against rat skin fibroma after irradiation with 56Fe ions; (2) WR-1065, the active metabolite of amifostine, reduced genomic instability on RKO36 human carcinoma cells after exposure to photons and 56Fe ions. Each data set was comprised of 3-4 different dose points for each condition. A more simplified mechanistic framework was developed to describe these data from different biological endpoints across distinct systems, in function of both the radiation dose D and presence or not (R) of the radioprotector. The underlying assumption is that the data contain three overall key common components: (1) a background level of the measured biological response, b; (2) an increase in the response induced by the radiation, a, that may reach (3) a saturation or turnover point due to cell killing at higher doses. The radioprotection factor is represented by f. This model was fit to the two aforementioned data sets and yielded a reasonable agreement on both cases, providing a preliminary validation of the model. An additional scenario was also tested, where the radioprotector factor would also have an effect on cell killing, but it resulted in a less strong agreement with the experimental data. In view of the limited data available in the literature to develop a robust mechanistic framework for the evaluation of any biomedical countermeasure against GCR, it was decided to incorporate microdosimetric quantities in models of radiation-induced carcinogenesis, as it would provide additional insights into how radioprotectors affect biological responses. Microdosimetric quantities, such as lineal energy (y), provide information on the patterns of energy deposition at the micrometric scale. The mechanisms through which space radiation leads to carcinogenesis or other late effects are not well understood and experimental data are scarce. In particular, exposure to radiation in space is chronic and fluences of GCR are low. In this situation, the biological effects are likely driven by non-targeted effects, whereby intra- and inter-cellular signaling play a crucial role, potentially leading to harmful consequences in cells that were not directly hit by radiation. Lineal energy spectra can thus be used to estimate radiation quality factors (Q) for space-radiation-induced carcinogenesis in a more accurate manner than aggregate metrics like the linear energy transfer (LET). Developing mathematical models for the relationship between lineal energy and Q for both targeted and non-targeted effects can help improve the accuracy of risk predictions. In practice, this translates into integrating probability distributions of lineal energy, f(y) into a theoretical framework to estimate the quality factors of space radiations. Key to this is a model -- a function Q(y) for the dependence of quality factor of lineal energy. We can then calculate the average quality factor Q for a given lineal energy distribution f(y). Q(y) could for instance be an increasing function of

	y that saturates or decreases at very large y values. In order to test such assumptions and find the best values of the parameters in this function, we will use weighted least squares fits to published data on space-radiation-induced carcinogenesis in mice, including data sets on Harderian gland and intestinal carcinogenesis. Moreover, several alternative functions for Q(y) can be assessed by fitting the data and comparing information theoretic methods like the Akaike information criterion values. Using this approach with lineal energy spectra is a step forward in extending already validated models of carcinogenesis for space radiation doses, as well as in estimating the risk of developing cancer in space more accurately.
Bibliography Type:	Description: (Last Updated:)