Fiscal Year:	FY 2006	**Task Last Updated:**	FY 05/09/2006
PI Name:	Wiese, Claudia Ph.D.		
Project Title:	A role for homologous recombination in complex DSB repair after HZE particles		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
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:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:	For information purposes only--PI moved in June 2014; however, funding did not go with her. As of 6/1/14, Colorado State University, Department of Environmental and Radiological Health Sciences, 485 MRB - 1618 Campus Delivery, Fort Collins, CO 80523-1618, Office: (970) 491 7618, Email: Claudia.Wiese@colostate.edu		
Project Type:	GROUND	**Solicitation / Funding Source:**	2004 Radiation Biology NNH04ZUU005N
Start Date:	10/01/2005	**End Date:**	09/30/2009
No. of Post Docs:	0	**No. of PhD Degrees:**	
No. of PhD Candidates:	0	**No. of Master' Degrees:**	
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: project extended for full length of proposal, per J. Dardano (2/06)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):			
Grant/Contract No.:	NNJ05HI36I		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Overall Rationale: The overall goal of this proposal is to investigate whether homologous recombinational DNA repair (HRR) contributes to the repair of double-strand breaks (DSBs) generated by the radiation types found in the space radiation environment. This proposal is a continuation of our previous work demonstrating that recombination is induced in human cells exposed to Fe ions. Here, we aim to directly assess the role of HRR in the repair of DNA damage after high linear energy transfer (LET) radiation in mammalian cells, an investigation that has never been carried out before. High LET charged particles deposit large amounts of energy along the ion trajectories, leading to the induction of highly localized DNA damage. These spatially correlated DSBs rejoin with slower kinetics and to less completeness than DSBs induced by low LET radiation. In mammalian cells, X-ray induced DSBs are primarily repaired by non-homologous end joining (NHEJ) in G1, but HRR plays a critical role in S- and G2-phases of the cell cycle. Several reports indirectly suggest that HRR, generally a precise form of DNA repair, plays an important role in the repair of correlated DSBs. Importantly, radiation-induced human tumors arise through a multi-step process of genetic change, and defects in HRR leading to the stimulation of error-prone DNA repair pathways may accelerate this process. For this reason, it is important to investigate directly whether alterations in the ability to perform HRR can sensitize humans to HZE particles. Approach: We will determine in syngeneic human cells whether defects in HRR affect the extent of cell killing and the mechanism of mutagenesis by densely ionizing Fe ions. RNA interference technology will be used to impair HRR (targeting XRCC3, Rad51D or Rad51) in the human lymphoid cell line WTK1. For comparison purposes, NHEJ will also be targeted, and X-rays will be used to test high vs. low LET radiation effects. The Fe particle-induced mutation frequencies will be determined at the autosomal TK1 locus and at the X-linked HPRT locus for parental WTK1 cells and for one representative derivative of WTK1 cells with a ‘loss-of-function’ phenotype for HRR and for NHEJ. Sets of TK1 mutants will be collected and the Fe ion-induced, X-ray-induced and spontaneous mutation spectra will be compared to discriminate between recombinational and deletional events. Furthermore, we will investigate in hamster and in human mutant cells whether impaired HRR enhances the cytotoxic effects of Fe ions. Wild-type CHO cells and CHO mutant cell lines impaired in HRR (Rad51D, XRCC3) or in NHEJ (DNA-PKcs) will be compared. Both asynchronous and synchronous cell cultures will be used and the relative contributions of both DNA repair pathways to cell survival will be assessed. DSB repair in CHO mutant cell lines and wild-type cells will be measured using a recently described assay that quantifies DSB rejoining by gH2AX foci formation. The effect of the loss of XRCC3 on the cellular sensitivity to Fe particles in an hTERT-immortalized human fibroblast strain will also be determined.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	
Task Progress:	Please note that this is a new grant for the FY 2006 year. The investigator will provide a task progress at the time of the one year anniversary of the grant. If you need more information, please contact the Task Book Help Desk at taskbook@nasaprs.com.
Bibliography Type:	Description: (Last Updated: 04/11/2018)