Fiscal Year:	FY 2017	**Task Last Updated:**	FY 03/10/2017
PI Name:	Mishra, Birendra D.V.M., Ph.D.		
Project Title:	Effects of Charged Particles on the Uterus		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Radiation Effects Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	bmishra@uci.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	
Organization Name:	University of California, Irvine		
PI Address 1:	5171 California Avenue, Suite 150		
PI Address 2:	Department of Medicine		
PI Web Page:			
City:	Irvine	**State:**	CA
Zip Code:	92617-3055	**Congressional District:**	45
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2015 NSBRI-RFA-15-01 First Award Fellowships
Start Date:	11/01/2015	**End Date:**	10/31/2016
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Luderer, Ulrike (MENTOR/ University of California, Irvine)		
Grant/Contract No.:	NCC 9-58-PF04302		
Performance Goal No.:			
Performance Goal Text:			
	POSTDOCTORAL FELLOWSHIP In NASA space missions about 15% of astronauts are women, and women made up half of the 2013 NASA Astronaut Class. Normal uterine structure and function is required for a healthy pregnancy and optimal development and subsequent health of the offspring. Uterine function in adults is largely regulated by ovarian steroid hormones secreted from the growing pool of follicles. Recently we have shown that exposure to charged particles induces premature ovarian failure and ovarian cancer in mice. Radiotherapy for the treatment of cancer and/or atomic bomb survivors in Japan have been shown to alter the uterine functions and uterine tumor. However, risks of uterine exposure to galactic cosmic rays and solar particle events during space missions remain completely unknown. Based on epidemiological data and situation in the space, we have hypothesized that charged particles alter uterine function. To understand the acute exposure of charged particles on the uterine functions, uterine samples were collected from three-month-old female		

Task Description:	mice (C57BL/6J) exposed to low dose (0, 5, 30, and 50 cGy; n=8/treatment) iron at 6 h, 1 wk and 8 wks after irradiation. Two groups were irradiated at the highest dose for each of the two charged particles, one fed AIN-93M chow and the other fed the same chow supplemented with 150 mg/kg chow of the antioxidant alpha lipoic acid began one week before irradiation and continued until sacrifice. To understand the chronic effects of charged particles on the uterine functions, uterine samples were collected from three-month-old female mice (C57BL/6J) exposed to low dose (0 and 50 cGy; n=15/treatment) iron at 15 months after irradiation. Average uterine weight remained unchanged among the treatment at 6 h, 1 wk, and 8 wks after radiation. At 15 months after radiation, average uterine weight was significantly decreased in 50 cGy treated mice (108.8±31.6 mg) compared to control (198±50.8 mg). To understand the acute effects of charged particles radiation on the uterus, uterine histomorphology were analyzed using H&E stained slides. At 6 h and 1 wks, uterine morphology was normal among the treatment but it was quite abnormal at 8 wks after radiation. Most importantly, luminal epithelial layer had decreased the number of epithelial cells, and many of them had the abnormal shape. Furthermore, the number uterine glands were significantly decreased, and the number of cystic glands was decreased in 50 cGy irradiated mice compared to control. To delineate the primary mechanism involved in the damage of uterine lumen, the DNA double-strand breaks in the luminal epithelial were analyzed using gH2AX immunostaining. Histone 2Ax protein gets phosphorylated in response to DNA double-strand breaks. Percentage of gH2AX was significantly higher in 50 cGy treated mice compared to control. The mice supplemented with alpha lipoic acid along with 50 cGy had similar uterine morphology and gH2AX immunostaining as seen for 50 cGy iron alone. In conclusion, our study suggests that charged iron particles radiation damages the luminal and glandular epithelial which are essential for the embryo implantation and placental development for the successful gestation.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Women are not only exposed to charged particles during space missions but also during cancer radiotherapy. Recently charged particle radiotherapy with proton and carbon ions are being used to treat cancer. However, there were no prior studies of the effects of charged particle therapy on reproductive tissues. Our study is therefore also relevant to understanding potential side effects of charged particle therapy on the uterus.
Task Progress:	Aim 1: Acute exposure to low dose HZE particles induces uterine oxidative stress and alters pregnancy outcomes. Three-month-old female mice (C57BL/6J from Jackson Labs) were exposed to low dose (0 and 50 cGy; n=8/treatment) iron (LET = 179 KeV/µm) at an energy of 600 MeV/u. Two groups were irradiated at the highest dose for each of the two charged particles, one fed AIN-93M chow and the other fed the same chow supplemented with 150 mg/kg chow of the antioxidant alpha lipoic acid. Uteri were collected at 6 h, 1 wk, and 8 wks after irradiation. At 6 h and 1 wk time point, mice were sacrificed without knowing the stage of the estrous cycle. At 8 wks time-point, mice were sacrificed at the metestrus stage of the cycle to avoid cycle-stage related variations in reproductive hormones. To understand the effects of charged particles radiation on the uterus, average uterine weight at 6 h, 1wk, and 8wks after IR were analyzed. Average uterine weight remained unchanged among the treatment at 6 h, 1 wk, and 8 wks after radiation suggesting that charged particle exposure does not effect on uterine mass. To understand the acute effects of charged particles radiation on the uterus, uterine histomorphology was analyzed using H&E stained slides. At 6 h and 1 wks, uterine morphology was normal among the treatment, but it was quite abnormal at 8 wks after radiation. Most importantly, the luminal epithelial layer had decreased the number of epithelial cells, and many of them had an abnormal shape. Furthermore, the number of uterine glands were significantly decreased, and the number of cystic glands was decreased in 50 cGy irradiated mice compared to control. To delineate the primary mechanism involved in the damage of uterine lumen, the DNA double-strand breaks in the luminal epithelial were analyzed using gH2AX immunostaining. Histone 2Ax protein gets phosphorylated in response to DNA double-strand breaks. Percentage of gH2AX was significantly higher in 50 cGy treated mice compared to control. The mice supplemented with alpha lipoic acid along with 50 cGy had similar uterine morphology and gH2AX immunostaining as seen for 50 cGy iron alone. Aim 2: Exposure to charged particles causes uterine cancer. Three-month-old female mice of two strains, one thought to be sensitive to radiation-induced tumors (B6C3F1) and one thought to be less sensitive to radiation-induced tumors (C57BL/6J) were exposed to low dose (0 and 50 cGy; n=15/treatment) iron (LET = 179 keV/µm) and aged to 18 months. Uteri were collected at 15 months after irradiation. These tissues were fixed with 4% PFA or 10% Formalin for histomorphology and immunohistochemistry analysis. At 15 months after radiation, average uterine weight was significantly decreased in 50 cGy treated mice (108.8±31.6 mg) compare to control (198±50.8 mg) in both strains of mice.
Bibliography Type:	Description: (Last Updated: 06/22/2020)
Abstracts for Journals and Proceedings	Mishra B, Ortiz L, Luderer U. "Space radiation causes premature ovarian failure and epithelial ovarian tumors in mice." 2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016. 2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016. , Feb-2016
Abstracts for Journals and Proceedings	Mishra B., Ripperdan R, Ortiz L, Luderer U. "Charged iron particles, components of space radiation, cause premature ovarian failure and epithelial ovarian tumors in mice." Systems Biology of Reproduction SSR 49th Annual Meeting, San Diego, CA, July 16-20, 2016. Systems Biology of Reproduction SSR 49th Annual Meeting, San Diego, CA, July 16-20, 2016. , Jul-2016
Articles in Peer-reviewed Journals	Mishra B, Ortiz L, Luderer U. "Charged iron particles, components of space radiation, destroy ovarian follicles." Human Reproduction. 2016 Aug;31(8):1816-26. http://dx.doi.org/10.1093/humrep/dew126 ; PubMed PMID: 27251203; PubMed Central PMCID: PMC4974665 , Aug-2016
Articles in Peer-reviewed Journals	Mishra B, Ripperdan R, Ortiz L, Luderer U. "Very low doses of heavy oxygen ion radiation induce premature ovarian failure." Reproduction. 2017 Aug;154(2):123-33. https://doi.org/10.1530/REP-17-0101 ; PMID: 28528322; PMCID: PMC5598766 , Aug-2017

Articles in Peer-reviewed Journals	Mishra B, Lawson GW, Ripperdan R, Ortiz L, Luderer U. "Charged-iron-particles found in galactic cosmic rays are potent inducers of epithelial ovarian tumors." Radiat Res. 2018 Aug;190(2):142-50. https://doi.org/10.1667/RR15028.1 ; PMID: 29781764; PMCID: PMC6112765. , Aug-2018
Awards	Mishra B. "Systems Biology of Reproduction SSR 49th Annual Meeting, Larry Ewing Memorial Trainee Travel Fund Award, July 2016." Jul-2016
Awards	Mishra B. "School of Medicine, University of California Irvine Travel award, July 2016." Jul-2016
Awards	Mishra B. "University of California Irvine Postdoctoral Scholar Symposium Poster competition: Second place, September 2016." Sep-2016