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Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
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Human Research Program Risks:	(1) **Cancer**:Risk of Radiation Carcinogenesis		
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Task Description:

Thirty percent of astronauts are women, but the risks of space radiation to women's reproductive health and risks of gynecological cancers remain poorly understood. Radiation treatment for cancer is known to cause temporary infertility and premature menopause. Premature menopause increases women's risks for cardiovascular disease, osteoporosis, and Alzheimer's disease. In addition, animal studies and studies of atomic bomb survivors have shown that radiation exposure increases the risk for ovarian cancer. Ovarian cancer has a high mortality rate and is the leading cause of gynecological cancer deaths in women. To best protect the health of women astronauts, it is important to understand whether space radiation has similar effects on the ovary as the types of radiation exposure that are common on Earth. Our prior pilot study showed that the ovary is highly sensitive to follicle destruction by charged particle radiation, typical of exposures in space. Exposure to charged iron and oxygen particles resulted in dose-dependent follicle depletion and premature ovarian failure. Exposure to charged iron particles induced epithelial ovarian tumors later in life; ovarian tissues from oxygen charged particle irradiated mice of two strains and charged iron irradiated mice of the second mouse strain were archived for future analysis for tumor endpoints. We propose to leverage these stored tissue and blood samples, together with ovaries from gamma-irradiated mice from the NASA tissue archive to 1) compare ovarian tumor prevalence and molecular characteristics after low dose charged particle irradiation (oxygen and iron ions) with gamma irradiation in adult female mice; 2) examine the persistence and types of ovarian oxidative damage after irradiation and evaluate serum concentrations of a clinically utilized biomarker of ovarian reserve, Anti-Müllerian Hormone (AMH), as a potential early biomarker of ovarian tumorigenesis. We will quantify the effects of charged particles on numbers of ovarian follicles and ovarian tumor number and size. We will use in situ methods to assess oxidative damage and to molecularly characterize the ovarian tumors. Our analyses will provide critical insights into whether preneoplastic changes in ovarian follicle numbers, serum AMH, as well as ovarian oxidative damage caused by exposure to charged particles demonstrate similar dose-response as ovarian tumor induction. The analyses will also examine the relative biological effectiveness of gamma versus charged particle irradiation for these endpoints. These studies will help to fill important gaps in our understanding of the effects of space radiation on ovarian function and ovarian carcinogenesis and will lead to better ways to prevent ovarian cancer and protect reproductive health in women astronauts.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

The research will increase understanding of the effects of low dose gamma- and charged particle radiation on the ovary. Both gamma and charged particle radiation are used for cancer therapy. Therefore, it is important to understand side-effects of radiation therapy that may impact cancer survivors' quality of life.

Introduction: Women made up 50% and 45%, respectively, of the 2013 and 2017 NASA astronaut classes. Astronauts are exposed to galactic cosmic rays (GCR) during travel in deep space. GCR consist of protons, helium ions, and charged particles heavier than helium, such as silicon, iron, and oxygen. Our published work (Mishra, Ortiz et al. 2016; Mishra, Ripperdan et al. 2017; see also previous NASA work https://) demonstrates profound sensitivity of the ovary to charged particle radiation, with destruction of the irreplaceable ovarian follicle pool and 4-fold as many ovarian tumors as in control non-irradiated mice. Comparison of our data with published studies of ovarian follicle depletion and ovarian tumorigenesis by exposure to gamma radiation suggest that charged particle radiation may be a more potent inducer of both premature ovarian follicle depletion and ovarian tumors, but this has not been directly tested.
We hypothesize that ovarian follicle depletion by iron and oxygen charged particle radiation is greater than ovarian follicle depletions by gamma-radiation at comparable doses and that silicon, iron, and oxygen charged particle radiation cause ovarian tumors at lower doses than gamma-radiation.

Aim 1: Utilize archived ovaries to compare ovarian tumor induction by irradiation with charged particles or gamma-rays. Our original aim was a comparison of ovarian tumors in 3-4 month old CB6F1 mice irradiated with 0.4, 0.8, 1.2, or 1.6 Gy gamma-rays or 0.04, 0.08, 0.16 and 0.32 Gy 260 MeV/u silicon and concurrent controls at 15-16 months after irradiation. We added analysis of ovarian tumors in mice of the same strain and age irradiated with 0, 0.10, or 0.20 Gy each of silicon, titanium, and iron ions in quick succession (mixed ion beam) and sacrificed 16 months after irradiation. We are conducting detailed histopathology of ovaries and molecular characterization of tumors using immunostaining for tumor markers.

Aim 2: Utilize archived ovaries harvested at various time points after irradiation with low doses of oxygen or iron charged particles to examine the persistence of ovarian oxidative lipid, protein, and DNA damage, archived serum to measure a biomarker of ovarian reserve, and evaluate these as potential early biomarkers of ovarian tumorigenesis. Irradiate mice with low doses of gamma-radiation and harvest ovaries at 1 week after irradiation in order to compare ovarian follicle depletion by charged iron or oxygen particles with gamma-radiation. Our published work (Mishra, Ortiz et al. 2016; Mishra, Ripperdan et al. 2017) demonstrates oxidative damage and dose-dependent apoptotic depletion of ovarian follicles after exposure to 0, 0.05, 0.3, and 0.5 Gy charged iron or oxygen particles. Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) were significantly elevated in 0.5 Gy-irradiated mice 8 wk after irradiation, consistent with loss of negative feedback due to follicle depletion, but serum LH and FSH are not optimal serum markers of ovarian reserve because they vary with estrous cycle stage and are secreted episodically, and we did not perform immunohistochemical analyses of ovaries at 8 wk after irradiation. We will examine oxidative lipid, protein, and DNA damage by immunostaining as potential biomarkers of ovarian tumor risk in archived ovaries from mice sacrificed 8 wk after irradiation with charged iron or oxygen particles. We will measure Anti-Müllerian Hormone (AMH), a serum marker of ovarian reserve that is used clinically, in archived serum from mice sacrificed 1 wk and 15 months after irradiation. 3-month old female C57BL/6J mice will be irradiated with 0, 0.05, 0.15, or 0.5 Gy gamma-rays and sacrificed one week post irradiation for ovarian follicle counts, which will be compared to our published data on charged iron or oxygen particle-irradiated mice.

Materials and Methods

Aim 1: Utilize archived ovaries to compare ovarian tumor induction by irradiation with charged particles or gamma-rays. Fixed ovary samples from female CB6F1 mice irradiated with 0, 0.4, 0.8, 1.2, and 1.6 Gy gamma-rays and 0, 0.04, 0.08, 0.12, and 0.32 Gy silicon charged particles or 0, 0.1, 0.2 Gy each silicon, titanium, and iron (hereafter referred to as mixed beam) and sacrificed 16 months after irradiation will be obtained from the NASA tissue bank. The ovaries will be processed for counting of ovarian follicles, ovarian tumor histopathology, and immunostaining for tumor markers.

Aim 2: Utilize archived ovaries harvested at various time points after irradiation with low doses of oxygen or iron

Task Progress:	charged particles to examine the persistence of ovarian oxidative lipid, protein, and DNA damage, archived serum to measure a biomarker of ovarian reserve, and evaluate these as potential early biomarkers of ovarian tumorigenesis. Irradiate mice with low doses of gamma-radiation and harvest ovaries at 1 week after irradiation in order to compare ovarian follicle depletion by charged iron or oxygen particles with gamma-radiation. 3-month old female C57BL/6J mice were irradiated with 0.05, 0.15, or 0.5 Gy gamma-rays or transported and restrained in an identical manner and not irradiated (0 Gy). All mice were sacrificed one-week post irradiation. One ovary per mouse was processed for counting ovarian follicles, and the other ovary was processed for immunostaining to measure proliferation, cell death, and oxidative damage. Blood serum was also collected from the gamma-irradiated mice, and together with archived serum from the Principal Investigator's published studies (Mishra et al. 2016) was analyzed for anti-Müllerian hormone (AMH), as a biomarker of ovarian reserve. Results Aim 1: Utilize archived ovaries to compare ovarian tumor induction by irradiation with mixed heavy ion beam of silicon, titanium, and iron ions, silicon charged particles only, or gamma-rays. Fixed ovaries were received from 55 mice sacrificed at 16 months after irradiation with 0.3 or 0.6 Gy mixed heavy ion beam and compared to control, unirradiated mice. The ovaries were embedded in paraffin, serially sectioned, and every 10th section was stained with hematoxylin and eosin. Thus far, slides with ovaries from 39 mice have been reviewed by a board-certified veterinary pathologist. There was a dose-dependent, highly statistically significant increase in ovarian tubular adenomas, with 91% of mice in the 0.6 Gy mixed beam group having unilateral or bilateral tumors, 8% having a unilateral tumor in the 0.3 Gy mixed beam group, and no ovarian tumors found in the control mice. Tubular adenomas are epithelial ovarian tumors, and positive immunostaining for epithelial markers using a pancytokeratin antibody confirmed that the tumors are epithelial. Aim 2: Utilize archived ovaries harvested at various time points after irradiation with low doses of oxygen or iron charged particles to examine the persistence of ovarian oxidative lipid, protein, and DNA damage, archived serum to measure a biomarker of ovarian reserve, and evaluate these as potential early biomarkers of ovarian tumorigenesis. Irradiate mice with low doses of gamma-radiation and harvest ovaries at 1 week after irradiation in order to compare ovarian follicle depletion by charged iron or oxygen particles with gamma-radiation. Ovarian follicle counts in the gamma-irradiated mice have been completed on 4-5 mice per group. Thus far, there are statistically significant effects of dose on primordial, primary, and secondary follicle numbers, with fewer primordial, primary, and secondary follicles in the 0.50 Gy compared to the 0 Gy group. Serum AMH concentrations at one week after irradiation did not vary significantly with dose of gamma- or 56Fe-radiation. There was a statistically significant effect of 16O irradiation dose (P=0.040), with dose-dependent decrease in serum AMH concentrations at 0.30 Gy compared to 0 Gy, but no difference in concentrations of AMH between the 0 compared to 0.05 and 0.50 Gy groups. The lack of dose-dependent decrease in serum AMH contrasts with the pronounced dose-dependent decrease in ovarian follicle numbers at one week after irradiation in the same mice exposed to 56Fe or 16O in our prior studies or the mice exposed to 0.5 Gy gamma-radiation described above. Conclusions We conclude that mixed heavy ion irradiation at 0.6 Gy total dose potently induces ovarian tumors, with 91% of the mice having ovarian tumors at 16 months after irradiation, while the 0.3 Gy total dose was much less effective at inducing ovarian tumors. We also conclude that serum AMH concentration at one week after irradiation does not correlate with primordial follicle numbers and therefore is not a useful biomarker of ovarian reserve at this time point after irradiation. References Mishra, B., L. Ortiz and U. Luderer (2016). "Charged Iron Particles, Typical of Space Radiation, Destroy Ovarian Follicles." Human Reproduction 31(8): 1816-1826. Mishra, B., R. Ripperdan, L. Ortiz and U. Luderer (2017). "Very Low Doses of Heavy Oxygen Ion Radiation Induce Premature Ovarian Failure." Reproduction 154(2): 123-133.
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