

<b>Fiscal Year:</b>	FY 2022	<b>Task Last Updated:</b> FY 01/04/2022	
<b>PI Name:</b>	Rosa-Caldwell, Megan Ph.D.		
<b>Project Title:</b>	Influence of Sex Hormones on Nervous System and Musculoskeletal Health in Micro- and Martian Fractional Gravity in Rat Analogues		
<b>Division Name:</b>	Space Biology		
<b>Program/Discipline:</b>			
<b>Program/Discipline--Element/Subdiscipline:</b>			
<b>Joint Agency Name:</b>		<b>TechPort:</b>	No
<b>Human Research Program Elements:</b>	None		
<b>Human Research Program Risks:</b>	None		
<b>Space Biology Element:</b>	(1) Animal Biology: Vertebrate		
<b>Space Biology Cross-Element Discipline:</b>	(1) Musculoskeletal Biology (2) Neurobiology		
<b>Space Biology Special Category:</b>	None		
<b>PI Email:</b>	<a href="mailto:merosaca@bidmc.harvard.edu">merosaca@bidmc.harvard.edu</a>	<b>Fax:</b>	FY
<b>PI Organization Type:</b>	UNIVERSITY	<b>Phone:</b>	913-744-9019
<b>Organization Name:</b>	Beth Israel Deaconess Medical Center, Inc./Harvard Medical School		
<b>PI Address 1:</b>	330 Brookline Ave, TCC-810		
<b>PI Address 2:</b>			
<b>PI Web Page:</b>			
<b>City:</b>	Boston	<b>State:</b>	MA
<b>Zip Code:</b>	02215-5400	<b>Congressional District:</b>	7
<b>Comments:</b>			
<b>Project Type:</b>	GROUND	<b>Solicitation / Funding Source:</b>	2018 Space Biology (ROSBio) NNH18ZTT001N-FG2. App D: Flight and Ground Space Biology Research
<b>Start Date:</b>	01/04/2021	<b>End Date:</b>	01/03/2023
<b>No. of Post Docs:</b>	1	<b>No. of PhD Degrees:</b>	
<b>No. of PhD Candidates:</b>		<b>No. of Master' Degrees:</b>	
<b>No. of Master's Candidates:</b>		<b>No. of Bachelor's Degrees:</b>	
<b>No. of Bachelor's Candidates:</b>		<b>Monitoring Center:</b>	NASA ARC
<b>Contact Monitor:</b>	Loftus, David	<b>Contact Phone:</b>	650-604-1011
<b>Contact Email:</b>	<a href="mailto:david.j.loftus@nasa.gov">david.j.loftus@nasa.gov</a>		
<b>Flight Program:</b>			
<b>Flight Assignment:</b>			
<b>Key Personnel Changes/Previous PI:</b>	No significant personnel changes.		
<b>COI Name (Institution):</b>	Bouxsein, Mary Ph.D. ( Beth Israel Deaconess Medical Center, Inc./Harvard Medical School ) Rutkove, Seward M.D. ( Mentor: Beth Israel Deaconess Medical Center, Inc./Harvard Medical School )		
<b>Grant/Contract No.:</b>	80NSSC21K0311		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

<p><b>Task Description:</b></p>	<p><b>POSTDOCTORAL FELLOWSHIP</b></p> <p>In this postdoctoral fellowship, we propose to evaluate the impact of sex hormones on neuronal and musculoskeletal health in micro and Martian gravity environments by assessing naïve and castrated/ovariectomized male and female rats. We hypothesize micro- and fractional gravity will result in differential aberrations to sex hormone status in female and male rats; these sex hormone aberrations will moderate neurological and musculoskeletal declines in micro- and fractional gravity environments. We will study these rats over a 4-week period and investigations will include a series of neurophysiological and functional measures, blood analyses, and a detailed series of post-mortem histological studies. With completion of this work, we will have a far deeper understanding of the relationship between hormonal status and neuronal and musculoskeletal function. This proposed work will be specifically responsive to the following subtopics in Appendix D:</p> <ul style="list-style-type: none"> <li>• (AB1-A): Behavior and underlying neural function, including circadian effects, controlling ability of animals to sense and respond to their environment.</li> <li>• (AB1-B): Studies to characterize interactions between multiple physiological systems.</li> <li>• (AH1-E): Effects of fractional gravity provided by spaceflight centrifugation or ground microgravity/partial gravity analogs to gain insights into mechanisms of how animals sense, respond, and adapt to gravity shifts that are less than 1G.</li> </ul>
<p><b>Rationale for HRP Directed Research:</b></p>	<p>This project investigates how sex hormones influence musculoskeletal health in both males and females during conditions that produce muscle loss. This work has impact on life on Earth because it is important to understand how different atrophic conditions (for example, bed rest) may differ between males and females. Additionally, understanding if, or how, sex hormones interact with muscle and bone health during atrophic conditions will develop our overall understanding of muscle biology, as well as facilitate the development of possible interventions to blunt muscle loss for patients on Earth.</p>
<p><b>Research Impact/Earth Benefits:</b></p>	<p>The goal of this proposal is to investigate the influence of sex hormones and biological sex on musculoskeletal changes in micro- and Martian gravity environments. Within this overall goal, we have three sub-goals:</p> <p>A.) Establish the impact of sex hormones on neurological and musculoskeletal systems in these gravitational analogues;</p> <p>B.) Identify potential sex differences in response to Martian fractional gravity;</p> <p>C.) Determine the influence of micro- and partial- gravity environments on circulating hormonal status in males and females.</p> <p>After ~ 1 year of working on this project, we are happy to report substantial progress towards successfully completing this project.</p> <p>In this proposal, we have male and female Fischer rats divided into different gravitational and hormonal conditions. Specifically, animals are divided into either ovariectomized/castrated or sham operated. Animals are then further sub-divided into three different gravitational loads 1g (control), 0.4g (simulating Martian gravity), or 0g (simulating micro-gravity). This design results in a total of 12 groups, including:</p> <p>Male-Sham-1g, Male-Sham-0.4g, Male-Sham-0g, Male-Castrated-1g, Male- Castrated-0.4g, Male-Castrated-0g, Female-Sham-1g, Female-Sham-0.4g, Female-Sham-0g, Female-Ovariectomized-1g, Female-Ovariectomized-0.4g, and Female-Ovariectomized-0g.</p> <p>Animals would have respective surgeries and then have a 2-week recovery period. After the recovery period, animals have baseline testing of various musculoskeletal and neurological parameters. Animals are then assigned to their appropriate gravitational loads (1g, 0.4g, or 0g) and remain in those interventions for 28 days. After 28 days, animals again undergo testing for musculoskeletal and neurological parameters. Animals are then euthanized and tissues collected for additional analysis.</p> <p>Additionally, in the female animals, after surgeries we also monitor estrous cycle in female rats through daily vaginal lavages. Vaginal cells are collected using sterile water and a pipette. Then cells are placed on a microscope slide and allowed to dry. Slides are then stained in crystal violet staining solution and visualized with a microscope. Phase of estrous cycle is determined based on the relative amount of different cell types.</p> <p>Upon receiving notification of selection in September, we immediately started planning so the study could start as soon as funds became available. We originally planned to complete the surgeries in our own laboratory; however, we learned that Charles River Laboratories (Charles River) could complete the surgeries before shipping animals. We opted for this option because completing the surgeries in our home laboratory would require borrowing surgical spaces shared with other researchers, and this option would allow us to complete more animals in a shorter time period. In a minor change from the original proposal, animals had surgeries completed at 11 weeks of age and arrived at Beth Israel Deaconess Medical Center at 12 weeks of age (as opposed to surgeries at 12 weeks of age). After the appropriate acclimation period (48 hours), we then began estrous cycle monitoring of female rats. This 2-week measurement period allowed for determination of baseline estrous cycle for each animal, as well as confirmation of the ovariectomy surgery. Males still had this 2-week waiting period, but were just gently handled without any additional monitoring/measurements.</p> <p>Since starting data collection in January of 2021, we have thus far completed 86 through the entire protocol and will have 92 animals completed by the end of 2021. Given this current trajectory, we anticipate all animal studies will be completed no later than July 2022.</p> <p>Thus far, our preliminary data appears to suggest that micro- and partial gravity may influence cognitive function as measured by Novel Object Recognition, though at this point it is too early to deduce if there are any sex or hormone related differences in these outcomes. Additionally, our preliminary data seems to imply females may have exacerbated losses in electrically stimulated muscle strength compared to males; however, as we still have ~1/2 of female rats left to complete, this finding is very preliminary. We look forward to further disseminating our final conclusions when all animals have completed the protocol and we can holistically examine all the data.</p> <p>With the preliminary data generated from this grant, we have submitted 3 abstracts for virtual and in-person scientific meetings. Additionally, a symposium proposal on space physiology was accepted for the Northeastern Chapter of the American College of Sports Medicine regional meeting in October 2021, which includes data from this project. We</p>
<p><b>Task Progress:</b></p>	

	<p>anticipate once all animal studies are collected, scientific manuscripts will be submitted in 2022.</p> <p>Additionally, during the primary animal studies associated with this grant, we also added analysis of estrous cycle in our laboratory's other currently funded NASA project (80NSSC19K9518). Through the monitoring of estrous cycle in those hindlimb unloaded and partially recovered female rats, we found estrous cycle strongly correlated with muscle size and strength in hindlimb unloaded female rats. Moreover, the degree of estrous cycle alterations corresponded to the degree of muscle recovery after cessation of hindlimb unloading. These findings have since been published in the scientific journal <i>Experimental Physiology</i>. Since being published in September, this article already has an Altmetric score of 7, placing it in the top 25% of all research outputs scored by Altmetric.</p> <p>Overall, we have made significant progress in the completion of this project and believe, given the current trajectory, will successfully complete this project within our designated timeframe.</p>
<b>Bibliography Type:</b>	Description: (Last Updated: 03/05/2024)
<b>Abstracts for Journals and Proceedings</b>	<p>Rosa-Caldwell M, Mortreux M, Sung D-M, Schreurs A-S, Boussein M, Rutkove S. "Low testosterone status differentially affects musculoskeletal outcomes after exposure to micro- or partial gravity." 37th Annual Meeting of the American Society for Gravitational and Space Research, Baltimore, MD, November 3-6, 2021.</p> <p>Abstracts. 37th Annual Meeting of the American Society for Gravitational and Space Research, Baltimore, MD, November 3-6, 2021. , Nov-2021</p>
<b>Abstracts for Journals and Proceedings</b>	<p>Rosa-Caldwell ME, Mortreux M. "Spaceflight and musculoskeletal health: Progressing beyond low Earth orbit to the Moon, Mars, and beyond. " Annual Fall Conference of the New England Chapter of the American College of Sports Medicine, Providence, RI, October 21-22, 2021.</p> <p>Abstracts. Annual Fall Conference of the New England Chapter of the American College of Sports Medicine, Providence, RI, October 21-22, 2021. , Oct-2021</p>
<b>Articles in Peer-reviewed Journals</b>	<p>Rosa-Caldwell ME, Mortreux M, Kaiser UB, Sung DM, Boussein ML, Dunlap KR, Greene NP, Rutkove SB. "The oestrous cycle and skeletal muscle atrophy: Investigations in rodent models of muscle loss." <i>Exp Physiol</i>. 2021 Sep 26. <a href="https://doi.org/10.1113/EP089962">https://doi.org/10.1113/EP089962</a> ; PMID: 34569104; PMCID: PMC8639792 , Sep-2021</p>
<b>Papers from Meeting Proceedings</b>	<p>Rosa-Caldwell ME, Mortreux M, Sung D-M, Schreurs A-S, Boussein ML, Kaiser UB, Rutkove SB. "Musculoskeletal alterations in male and female rats exposed to in micro- and partial gravity environments." Biennial Meeting of the American Physiological Society, 7th Conference on New Trends in Sex and Gender Medicine, Virtual, October 19-22, 2021.</p> <p>Abstracts. Virtual Poster presented at Biennial Meeting of the American Physiological Society, 7th Conference on New Trends in Sex and Gender Medicine, Virtual, October 19-22, 2021. , Oct-2021</p>