

Fiscal Year:	FY 2024	Task Last Updated: FY 10/02/2023	
PI Name:	McGee-Lawrence, Meghan Ph.D.		
Project Title:	Osteocyte Plasma Membrane Disruptions in Skeletal Adaptation to Loading and Unloading		
Division Name:	Space Biology		
Program/Discipline:			
Program/Discipline-- Element/Subdiscipline:			
Joint Agency Name:		TechPort:	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	(1) Animal Biology: Vertebrate		
Space Biology Cross-Element Discipline:	(1) Musculoskeletal Biology		
Space Biology Special Category:	None		
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Comments:			
Project Type:	GROUND,New Investigation	Solicitation / Funding Source:	2018 Space Biology (ROSBio) NNH18ZTT001N-FG2. App D: Flight and Ground Space Biology Research
Start Date:	12/01/2020	End Date:	11/30/2023
No. of Post Docs:	1	No. of PhD Degrees:	1
No. of PhD Candidates:	4	No. of Master' Degrees:	0
No. of Master's Candidates:	0	No. of Bachelor's Degrees:	2
No. of Bachelor's Candidates:	2	Monitoring Center:	NASA ARC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Hamrick, Mark Ph.D. (Augusta University Research Institute, Inc.) Johnson, Maribeth M.S. (Augusta University Research Institute, Inc.)		
Grant/Contract No.:	80NSSC21K0274		
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Task Description:	<p>The skeleton's ability to adapt to mechanical loading is crucial for bone health, as exercise promotes hypertrophy but disuse (such as from spaceflight) leads to bone loss. We were the first to report that small, transient plasma membrane disruptions (PMD) develop with in vitro and in vivo mechanical loading in bone osteocytes. These disruptions initiate skeletal mechanotransduction, suggesting PMD are stimuli recognized by osteocytes to regulate bone adaptation to its loading environment. Importantly, we consistently observe that ~20% of long bone osteocytes develop PMD with routine cage activity in mice, suggesting that formation of osteocyte PMD may be essential to bone's sensation of and response to normal gravitational loads. Accordingly, our central hypothesis is that osteocyte PMD formation is impaired during skeletal disuse, leading to bone loss. Our goals are to test the effects of disuse on osteocyte PMD formation, to determine whether osteocytes become sensitized to PMD formation with impaired PMD repair or survival during reloading, and to determine whether modulating osteocyte PMD formation and/or repair affect these processes. Our strategy is to test these concepts in an in vivo murine model of hindlimb unloading, as well as with in vitro osteocyte models of unloading (rotating wall vessel bioreactor) and reloading (fluid shear stress). Our goals align with the NASA Space Biology program as they target Research Topic 3 (Animal Biology Studies in support of Human Space Exploration)/ Sub-Topic 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) by discovering the contribution of osteocyte PMD formation (and hypothesized impairment during disuse) to the skeleton's adaptation to its loading environment. This project will yield a new understanding of how complex organisms adapt to the space environment, using a ground-based analog for disuse from spaceflight; we anticipate that derived data will advance strategies for skeletal maintenance and prevention of bone fractures during disuse to promote and support human space exploration.</p>
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	<p>Disuse-induced bone loss, which occurs during prolonged exposure to microgravity during spaceflight and predisposes astronauts to risk of skeletal fractures, also occurs frequently on Earth in patients with spinal cord injuries, patients subjected to chronic/long-term bed rest, and in other cases of long-term decreased mobility. Furthermore, it is well understood that mechanical loading of the skeleton through physical exercise is beneficial for bone health across a wide spectrum of human patients, but there exists a substantial proportion of the population who cannot undertake regular vigorous exercise for a variety of reasons, including underlying health conditions, time constraints, or financial concerns. Therefore, understanding the fundamental mechanisms behind how bone senses and responds to changes in mechanical loading, and exploring ways to alter the skeletal response to a given level of mechanical loading (or withdrawal of loading), may lead to therapeutic interventions for improving bone health and reducing fracture risk.</p>
Task Progress:	<p>In the third year of this grant, we have made significant progress towards accomplishing the Specific Aims of the proposal. Major accomplishments include: identifying Poloxamer 188 (P188) as a repair-promoting pharmacological agent that improves plasma membrane disruption (PMD) mediated responses in vitro and in vivo, conclusively establishing that disuse sensitizes osteocytes to the formation of PMD upon reloading (consistent with our original hypotheses as presented in the grant application), and nearing the conclusion of in vivo studies on PMD repair-deficient Prkd1 conditional knockout animals. These experiments are described below.</p> <p>We have conclusively established methodology to successfully induce disuse in vitro, using the Synthecon slow turning lateral vessel (rotating wall vessel) bioreactor system. Building on Year 2 experiments, we now show that three days of culture in the bioreactor consistently up-regulates disuse-associated genes like sclerostin in these osteocyte populations. Moreover, we have confirmed across independent biological replicate experiments that exposure to disuse does sensitize osteocytes to the formation of PMD during re-loading. We are now working to define the mechanism by which disuse increases susceptibility to PMD.</p> <p>We have established a model of defective PMD repair in osteocytes by knockout of a protein called Prkd1, which is involved in membrane repair. This model demonstrated impaired adaptation to loading, consistent with a critical role for PMD-mediated mechanisms in bone mechanobiology. In the third year of the grant, we have conclusively established that enhancing membrane stability / repair can have therapeutic implications in terms of modifying the skeleton's response to changes in mechanical loading. Specifically, treating mice (in vivo) or immortalized or primary osteocytes (in vitro) with a Food and Drug Administration (FDA) approved drug agent that enhances membrane stability appears to fully rescue the defects caused by impaired PMD repair from Prkd1-deficiency. In particular, we have found that treatment of cells with Poloxamer 188 rescues PMD repair rates in Prkd1-inhibited or Prkd1-knockout osteocytes to control levels, and improves postwounding survival in these cells, even though it does not appear to further enhance repair behavior in wildtype (control) cells.</p> <p>We continue to support the professional development of students, having now supported a total of four PhD students, five medical students, four undergraduate students, and a high school student in completion of our funded experiments over the past two years. One PhD student has scheduled his PhD defense for January 2024. All of the students involved have received authorship on either journal manuscripts or conference abstracts stemming from their contributions. Therefore, this grant continues to support the career development of the next generation of scientists.</p> <p>PLEASE NOTE: we are requesting a 1 year No Cost Extension (NCE) to conclude in vivo disuse experiments, in vivo experiments with Prkd1 and Sptbn1 CKO mouse models, and in vivo experiments with Poloxamer 188 treatment as described in our Annual Progress Report.</p>
Bibliography Type:	Description: (Last Updated: 10/10/2023)
Abstracts for Journals and Proceedings	<p>Tuladhar A, Shaver J, McGee WA, Yu K, Horne JL, Bollag WB, Hamrick MW, McGee-Lawrence ME. "Poloxamer-188 treatment rescues osteocytes with an impaired ability to repair plasma membrane disruptions caused by mechanical loading." ASBMR (American Society for Bone and Mineral Research) 2023 Annual Meeting, Vancouver, BC, Canada, October 13-16, 2023.</p> <p>Abstracts. ASBMR (American Society for Bone and Mineral Research) 2023 Annual Meeting, Vancouver, BC, Canada, October 13-16, 2023; Plenary Poster #FRI-367/SAT-367. , Oct-2023</p>

Abstracts for Journals and Proceedings

Tuladhar A, McGee WA, Horne JL, Shaver J, Hamrick MW, McGe-Lawrence ME. "Exposure to disuse sensitizes osteocytes to the formation of plasma membrane disruptions (PMD) upon reloading. " ASBMR (American Society for Bone and Mineral Research) 2023 Annual Meeting, Vancouver, BC, Canada, October 13-16, 2023.
Abstracts. ASBMR (American Society for Bone and Mineral Research) 2023 Annual Meeting, Vancouver, BC, Canada, October 13-16, 2023; Poster #SUN-366. , Oct-2023