Fiscal Year:	FY 2023	**Task Last Updated:**	FY 12/20/2022
PI Name:	Turner, Russell T Ph.D.		
Project Title:	Housing Temperature: An Important Variable for Simulated Spaceflight Studies Using Mice		
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:	(1) Translational (Countermeasure) Potential		
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Zip Code:	97331-8558	**Congressional District:**	4
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2016-17 Space Biology (ROSBio) NNH16ZTT001N-FG. App G: Flight and Ground Space Biology Research
Start Date:	01/31/2019	**End Date:**	01/30/2024
No. of Post Docs:		**No. of PhD Degrees:**	1
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NASA ARC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 1/30/2024 per NSSC information (Ed., 8/6/23) NOTE: End date changed to 1/30/2023 per F. Hernandez/ARC (Ed., 4/25/22) NOTE: End date changed to 1/30/2022 per F. Hernandez/ARC (Ed., 1/18/21)		
Key Personnel Changes/Previous PI:	November 2019 report: No changes in key personnel.		
COI Name (Institution):	Branscum, Adam Ph.D. (Oregon State University) Iwaniec, Urszula Ph.D. (Oregon State University) Wong, Carmen Ph.D. (Oregon State University)		
Grant/Contract No.:	80NSSC19K0430		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Spaceflight, by altering the differentiation program of hematopoietic and mesenchymal stem cells residing within bone marrow, results in bone loss, increased bone marrow adiposity, anemia, and impaired immune function. These closely associated disturbances may compromise the success of long-term missions. Thus, there exists an urgent need to identify the underlying mechanisms and implement effective countermeasures. Mice are currently the preferred animal model for evaluating adaptive responses to microgravity experienced during spaceflight and simulated spaceflight (e.g., hindlimb unloading). Mice have important advantages over other animal models for spaceflight studies, including small size and ease of genetic manipulation. Although mice and humans share many common characteristics, fundamental species differences in thermoregulation may contraindicate the mouse, as currently applied, as a model for human spaceflight. Humans are homeotherms and when exposed to a cold environment defend their core body temperature, whereas mice are obligatory daily heterotherms and experience cyclic changes in core temperature when subjected to cold stress (i.e., temperature below thermoneutral). Mice are typically housed at or near room temperature (~22°C), which is well below the thermoneutral zone for the species (~32°C). Therefore, mice must expend energy to maintain core body temperature. Cold stress induced by sub-thermoneutral housing increases sympathetic outflow to peripheral tissues, including brown adipose tissue, and has profound effects on metabolism. We have recently shown that cold stress induced by room temperature housing results in rapid cancellous bone loss in mice. Based on this finding, we hypothesize that activation of adaptive thermogenesis in mice housed at room temperature introduces unrecognized and uncontrolled confounding variables into mouse studies. Strategies used by weight-bearing mice to minimize heat loss during room temperature housing (e.g., huddling or postural adjustments) are less effective during spaceflight and simulated spaceflight. This results in increased dependence on adaptive thermogenesis, likely exaggerating the negative physiological effects of skeletal unloading on bone and immune cells. Additionally, the thermogenic mechanisms mediating cold stress-induced changes in metabolism in mice are unlikely to be directly translatable to astronauts and could therefore confound interpretation of experimental results as applicable to humans. This proposal will explore the individual and combined effects of mild cold stress induced by room temperature housing and hindlimb unloading (HLU) on the skeleton in C57BL6 (B6) mice, a strain commonly used in spaceflight and HLU studies. To accomplish our goal, we propose 2 Specific Aims: Specific Aim 1: Determine the contribution of increased adaptive thermogenesis to bone loss during HLU in mice housed at room temperature. We will accomplish this aim by comparing HLU-induced bone loss in mice housed at room temperature (22°C) with mice housed at thermoneutral (32°C). Specific Aim 2: Determine the lowest sub-thermoneutral housing temperature able to prevent adaptive thermogenesis-associated bone loss. We will accomplish this aim by performing temperature response studies (20-32°C) to evaluate induction of adaptive thermogenesis. Once we identify the lowest sub-thermoneutral housing temperature that does not induce adaptive thermogenesis, we will perform a long-term study to verify that minimal premature bone loss occurs and that magnitude of HLU-induced bone loss does not differ from mice housed at thermoneutral. Successful completion of the proposed research will provide guidance to investigators for insuring housing conditions minimize the confounding effects of species-specific differences in thermoregulation on experimental outcomes with the ultimate goal of optimizing the mouse to model human responses to spaceflight.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	One of our goals is to establish mouse models that more accurately replicate human physiology. Mice, because of their small size, short lifespan, and ease of genetic manipulation, are a mainstay for cutting edge research in fundamental skeletal biology, and are increasingly being used as preclinical models for skeletal disuse and metabolic bone disease. There is, however, a critical need to identify and address major limitations of mice as models for human physiology. For example, in contrast to humans, mice experience bone- and bone compartment-specific cancellous bone loss while growing. This premature age-related bone loss is a concern because the most common metabolic bone diseases preferentially target the aged or during conditions such as long duration spaceflight believed to accelerate aging. An important difference between mouse and human physiology that may contribute to premature age-related bone loss is the tight coupling of bone metabolism to thermoregulation in mice. If our hypothesis is correct, mild temperature stress induced by room temperature housing is responsible for premature cancellous bone loss in mice and factors that influence thermoregulation in mice may further compromise studies designed to model human responses by independently altering bone metabolism.
Task Progress:	Progress on Specific Aim 1: Determine the contribution of increased adaptive thermogenesis to bone loss during hindlimb unloading (HLU) in mice housed at room temperature. We proposed to accomplish this aim, in part, by comparing HLU-induced bone loss in male and female mice housed at room temperature (22°C) with mice housed at thermoneutral (32°). We have completed the animal studies for female mice and are well into data collection and analysis. The findings to date demonstrate remarkable differences in response to HLU between growing female mice housed at 22°C and those housed at 32°C. Progress on Specific Aim 2: Determine the lowest sub-thermoneutral housing temperature able to prevent adaptive thermogenesis-associated bone loss. We proposed to accomplish this aim by performing temperature response studies (20°C to 32°C) to measure adaptive thermogenesis as a function of housing temperature (Subaim 1). Once we identified the lowest sub-thermoneutral housing temperature that does not induce adaptive thermogenesis and premature bone loss, we proposed to perform a long-duration study to verify that the magnitude of HLU-induced bone loss in mice housed at this temperature does not differ from mice housed at thermoneutral (Subaim 2). Summary of Results to Date

	Specific Aim 1: We have evidence that adaptation to cold stress is responsible for ~50% of bone loss in the femur of growing HLU mice. When we consider the cancellous compartment, the impact of housing temperature is even more striking; HLU prevented bone accrual at 32°C and resulted in bone loss at 22°C. In contrast, HLU prevented bone accrual in mice housed at 32°C but did not induce cancellous bone loss. Even more striking was our finding that HLU induced bone loss in humerus, a bone subjected to near normal weight bearing in the HLU model. Taken together, these findings provide evidence that adaptation to cold stress induced by room temperature housing is an important modifier of the skeletal response to HLU in mice. In addition, analyses of splenocytes suggests that increased cytokine secretion may contribute to excess bone loss induced by HLU in room temperature-housed mice. Specific Aim 2: Room temperature housing-induced premature cancellous bone loss in growing mice is not sex specific; although male mice have higher peak bone mass, the magnitude of bone loss in room temperature housed mice did not differ between male and female mice. Housing mice at 26°C reduced but did not prevent premature cancellous bone loss in either male or female growing mice. However, the observed differences between mice housed at 22°C and 26°C indicate that even small differences in housing temperature influence bone mass in growing mice.
Bibliography Type:	Description: (Last Updated: 06/16/2025)
Articles in Peer-reviewed Journals	Turner RT, Nesser KL, Philbrick KL, Wong CP, Olson DA, Branscum AJ, Iwaniec UT. "Leptin and environmental temperature as determinants of bone marrow adiposity in female mice." Front Endocrinol. 2022 Oct 6;13:959743. https://doi.org/10.3389/fendo.2022.959743 ; PMID: 36277726; PMCID: PMC9582271 , Oct-2022
Papers from Meeting Proceedings	Sattgast LH, Wong CP, Olson DO, Branscum AJ, Iwaniec UT, Turner RT. "Effects of below thermoneutral housing on bone metabolism in female C57BL/6J mice. " EB 2022, Federation of American Societies for Experimental Biology (FACEB), Philadelphia, PA, April 2-5, 2022. Abstracts. EB 2022, Federation of American Societies for Experimental Biology (FACEB), Philadelphia, PA, April 2-5, 2022. , Apr-2022