| | | | |
|---|---|---|---|
| **Fiscal Year:** | FY 2022 | **Task Last Updated:** | FY 12/09/2021 |
| **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 | | |
| **PI Email:** | Russell.Turner@oregonstate.edu | **Fax:** | FY 541 737 6914 |
| **PI Organization Type:** | UNIVERSITY | **Phone:** | 541 737 9545 |
| **Organization Name:** | Oregon State University | | |
| **PI Address 1:** | Nutrition & Exercise Sciences/Skeletal Biology Laboratory | | |
| **PI Address 2:** | Milam Hall, Mail Stop 107B | | |
| **PI Web Page:** | | | |
| **City:** | Corvallis | **State:** | OR |
| **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:** | 01/30/2023 |
| **No. of Post Docs:** | | **No. of PhD Degrees:** | |
| **No. of PhD Candidates:** | 1 | **No. of Master' Degrees:** | |
| **No. of Master's Candidates:** | | **No. of Bachelor's Degrees:** | 1 |
| **No. of Bachelor's Candidates:** | 3 | **Monitoring Center:** | NASA ARC |
| **Contact Monitor:** | Griko, Yuri | **Contact Phone:** | 650-604-0519 |
| **Contact Email:** | Yuri.V.Griko@nasa.gov | | |
| **Flight Program:** | | | |
| **Flight Assignment:** | NOTE: End date changed to 1/30/2023 per F. Hernandez/ARC (Ed., 4/25/22)<br>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 )<br>Iwaniec, Urszula Ph.D. ( Oregon State University )<br>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.<br>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.<br><br>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:<br><br>Specific Aim 1: Determine the contribution of increased adaptive thermogenesis to bone loss during HLU in mice housed at room temperature.<br><br>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).<br><br>Specific Aim 2: Determine the lowest sub-thermoneutral housing temperature able to prevent adaptive thermogenesis-associated bone loss.<br><br>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.<br><br>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:** | Description of Scientific Goals<br>Mice are currently the preferred animal model for evaluating adaptive responses to spaceflight. They have several important advantages over other animal models for microgravity studies, including small size and ease of genetic manipulation. Although mice and humans share many common characteristics, thermoregulation differs markedly between the two species. We hypothesized that activation of adaptive thermogenesis in mice housed at room temperature introduces unrecognized and uncontrolled confounding variables into spaceflight/simulated spaceflight studies. This hypothesis was based on evidence that adaptation to room temperature housing in mice (1) results in increases in sympathetic tone, thermogenesis, glucocorticoid production, energy expenditure, blood pressure, and heart rate, and that (2) the collateral effects of these adaptive responses include rapid bone loss, immune suppression, and altered tissue and tumor response to ionizing radiation. Strategies used by weight-bearing mice to minimize heat loss during room temperature housing (e.g., huddling and postural adjustments) are hypothesized to be less effective during spaceflight and simulated spaceflight. This would result in increased dependence on adaptive thermogenesis, likely exaggerating the negative physiological effects of microgravity.<br><br>The studies reported here were designed to explore the individual and combined effects of mild cold stress induced by room temperature housing and hindlimb unloading (HLU) on premature bone loss in C57BL6 (B6) mice, a strain commonly used in spaceflight/simulated spaceflight studies.<br><br>To accomplish our goal, we proposed two Specific Aims: |

| | |
|---|---|
| | Specific Aim 1: Determine the contribution of increased adaptive thermogenesis to bone loss during HLU in mice housed at room temperature. Specific Aim 2: Determine the lowest sub-thermoneutral housing temperature able to prevent adaptive thermogenesis-associated bone loss.<br><br>Progress on Specific Aim 1: Determine the contribution of increased adaptive thermogenesis to bone loss during 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 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.<br><br>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.<br><br>To date, we have published 6 peer-reviewed manuscripts describing our results. See Cumulative Bibliography hyperlink. |
| **Bibliography Type:** | Description: (Last Updated: 03/06/2024) |
| **Articles in Peer-reviewed Journals** | Gamboa A, Branscum AJ, Olson DA, Sattgast LH, Iwaniec UT, Turner RT. "Effects of spaceflight on cancellous and cortical bone in proximal femur in growing rats." Bone Rep. 2021 Jun;14:100755. https://doi.org/10.1016/j.bonr.2021.100755 ; PMID: 33665238; PMCID: PMC7907224 , Jun-2021 |
| **Articles in Peer-reviewed Journals** | Wong CP, Iwaniec UT, Turner RT. "Evidence for increased thermogenesis in female C57BL/6J mice housed aboard the International Space Station." npj Microgravity. 2021 Jun 18;7(1):23. https://doi.org/10.1038/s41526-021-00150-y ; PMID: 34145277 ; PMCID: PMC8213760 , Jun-2021 |
| **Articles in Peer-reviewed Journals** | Martin SA, Riordan RT, Wang R, Yu Z, Aguirre-Burk AM, Wong CP, Olson DA, Branscum AJ, Turner RT, Iwaniec UT, Perez VI. "Rapamycin impairs bone accrual in young adult mice independent of Nrf2." Exp Gerontol. 2021 Oct 15;154:111516. Epub 2021 Aug 10. https://doi.org/10.1016/j.exger.2021.111516 ; PMID: 34389472 , Oct-2021 |