Fiscal Year:	FY 2009	**Task Last Updated:**	FY 06/05/2009
PI Name:	Midura, Ronald J Ph.D.		
Project Title:	Extent, Causes, and Countermeasures of Impaired Fracture Healing in Hypogravity		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Musculoskeletal Alterations Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Bone Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	midurar@ccf.org	**Fax:**	FY 216-444-9198
PI Organization Type:	NON-PROFIT	**Phone:**	216-445-3212
Organization Name:	The Cleveland Clinic Foundation		
PI Address 1:	Biomedical Engineering - ND20		
PI Address 2:	Lerner Research Institute		
PI Web Page:			
City:	Cleveland	**State:**	OH
Zip Code:	44195	**Congressional District:**	11
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2007 Crew Health NNJ07ZSA002N
Start Date:	06/01/2008	**End Date:**	05/31/2012
No. of Post Docs:	2	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Muschler, George (The Cleveland Clinic Foundation) Warden, Stuart (Indiana University-Purdue University at Indianapolis) Burr, David (Indiana University School of Medicine) Globus, Ruth (NASA ARC) Cavanagh, Peter (University of Washington) Hill, Esther (Lockheed Martin Mission Services)		
Grant/Contract No.:	NCC 9-58-MA01604		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Lunar missions will expose astronauts to continuous hypogravity and bouts of strenuous physical exertion. Accidental fractures during missions could present a commander with a potentially life threatening situation and a serious reduction in team effectiveness. Thus, the scope and extent of bone healing in a space environment needs to be investigated, as well as the development of countermeasures to augment bone healing responses. The healing of fibular fractures in rats during actual spaceflight or under simulated hypogravity conditions is deemed to be impaired. This application seeks to continue funding of NSBRI BL00405 which found that fibular osteotomy healing in hind limb unloaded (HLU) rats was delayed leading to a significant number of non-unions, and was associated with a substantially reduced number of marrow-derived osteoprogenitor cells providing a partial explanation for impaired healing. Also, bone anabolic drugs decreased the incidence of fibular non-unions and improved the number of osteoprogenitor cells. Altogether, this suggests that fracture healing in space is not Earth normal, and provides the rationale to further investigate whether impairment of fibular fracture healing would extend to more clinically relevant closed femoral fractures. Our global hypothesis is that long duration hypogravity impairs fracture healing. Our objectives are: (1) Determine the scope and extent of femoral fracture healing impairment, (2)Determine the underlying biological causes of the impairment, (3) Develop countermeasures to prevent fracture healing impairment, and (4) Determine whether current Earth-based clinical procedures will reverse severely delayed fracture healing situations resulting from hypogravity. HLU rats will undergo closed femoral fractures and healing will be assessed using (a) micro-CT bone imaging to evaluate hard callus structure, (b) hard callus strength via torsion testing, (c) callus tissue composition using histomorphometry, (d) colony forming unit assessments of marrow-derived osteoprogenitor cell numbers, and (e) measurements of osteoinductive, chondrogenic and angiogenic factor expression during early healing periods. In its first year, NSBRI MA01604 has determined visually using 3D micro-CT imaging that closed femoral fractures in HLU rats exhibit a delayed healing response when compared to weight bearing (WB) counterparts. In addition, this project has determined that HLU results in the regression of major blood vessels within the hind limb within the initial 2-weeks of HLU. Associated with this vessel regression was a noticeable drop in blood flow rates within the femoral artery. Altogether, these findings suggest healing of closed femoral fractures in HLU rats is impaired, though not to the same magnitude as fibular fractures.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Findings to date from NSBRI MA01604 suggest that closed femoral fracture healing is adversely affected by simulated hypogravity. Based on these initial findings, and those for fibular fractures determined from NSBRI BL00405, the impact of this research for NASA is that the rate of fracture healing and the integrity of the fracture callus are altered under unloaded conditions. The nature of these alterations seems to result in a delayed healing response (closed femoral fractures) and non-unions (open fibular fractures). The implication of these findings is that bone trauma repair in astronauts on long space missions might be compromised, and presents a potential threat to mission effectiveness and astronaut health. The research impact of our findings from MA01604 (and those from our prior award BL00405) for Earth based medical practice would suggest that an extended period of unloading of normally weight bearing bones should manifest an impaired bone healing response. This information may have relevance towards a better understanding of the underlying causes of impaired bone healing in patients experiencing paralysis, chronic immobility or extended bed rest. Previous data obtained from our prior award period suggested that treatments with bone anabolic therapies seem to partially counteract the impairment of bone healing under a non-weight bearing situation. Our current award will explore this potential countermeasure in the third year and may also offer potential treatments for augmenting bone healing in Earth-bound, non-weight bearing patients.
Task Progress:	1) Designed and fabricated rat cages that duplicate HLU rat mobility as set in the original NASA designed cages by Dr. Emily Morey-Holton for HLU studies. 2) Re-designed and fabricated two 3-point bending devices adapted from the original design published by Bonnarens and Einhorn. One of these devices will stay at the Cleveland Clinic throughout the duration of the 4-year project, while the second one has been shipped to NASA-Ames Research Center for the completion of their subcontract work. The re-design of these devices has resulted in a more consistent generation of closed femoral fractures having a simple transverse pattern within the mid-diaphysis. 3) Design of a threaded titanium rod that (1) ensures that there is no rod slippage or backing out of rods from the femur post surgery and (2) allows for clear micro-CT images (no beam hardening as occurs with stainless steel rods) that are used to determine the hard callus parameters. Thus, we have adapted the Bonnarens & Einhorn closed fracture procedure to be compatible with micro-CT imaging. 4) Software modification for hard callus parameter analyses is currently underway. Existing programs are being modified to account for the titanium rod in the analyses thereby extracting 3-D bone volumes from both in vivo and ex vivo micro-CT imaging. 5) RT-PCR protocol development for the harvest of fracture callus. Primers for gene expression analysis of factors associated with osteogenesis, chondrogenesis, angiogenesis, and inflammation have been identified and specificity checked. Optimal PCR conditions for each primer pair are currently being determined for use in real-time quantitative PCR (Q-PCR). 6) Site visits have been made to both Indiana University (May-June 2008) and NASA-Ames Research Center (April-May 2009). In this first year with Indiana University, standardization of specimen transfer for histomorphometric analyses has been developed. Training of the NASA-Ames personnel and transfer of the standard protocols that will be utilized by all sites has been completed and studies are expected to start mid-summer of this year. Technical support will continue to be provided by personnel at the Cleveland Clinic as needed throughout the second year of this grant.
Bibliography Type:	Description: (Last Updated: 03/01/2017)