Fiscal Year:	FY 2008	**Task Last Updated:**	FY 02/17/2009
PI Name:	Nickerson, Cheryl A Ph.D.		
Project Title:	Evaluation of Host-Pathogen Interactions During Exposure to Microgravity Analogues		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SHFH**:Space Human Factors & Habitability (archival in 2017)		
Human Research Program Risks:	(1) **Immune**:Risk of Adverse Health Event Due to Altered Immune Response (2) **Microhost**:Risk of Adverse Health Effects Due to Host-Microorganism Interactions		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	Cheryl.Nickerson@asu.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	480-727-7520
Organization Name:	Arizona State University		
PI Address 1:	Center for Infectious Diseases and Vaccinology/The Biodesign Institute		
PI Address 2:	1001 S McAllister Avenue		
PI Web Page:	https://		
City:	Tempe	**State:**	AZ
Zip Code:	85287-5401	**Congressional District:**	9
Comments:	NOTE PI moved from Tulane University to Arizona State University in 2006.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2003 Biomedical Research & Countermeasures 03-OBPR-04
Start Date:	09/01/2006	**End Date:**	08/31/2009
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Sonnenfeld, Gerald (Binghamton University, State University of New York)		
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Performance Goal No.:			
Performance Goal Text:			
	Changes that occur to both the host immune system and pathogenesis of microbes during spaceflight could represent a formidable challenge to the successful transition from short-to-long-duration spaceflight. This is a critical issue to address for several reasons, since a) in-flight infections could potentially pose serious risks to the health, safety, and performance of the flight crew, b) studies have indicated that spaceflight negatively impacts the immune system in both humans and animals, and c) culture of the ubiquitous human bacterial pathogen, Salmonella typhimurium, under conditions simulating aspects of spaceflight has been shown to increase the disease causing property of this organism. Microbiological risks associated with spaceflight are expected to increase with the length of mission duration. However, the effect(s) of microgravity on the risk of infectious disease events during spaceflight is not well characterized. In particular, no information is available regarding the ability of microgravity to alter the dynamics of the host-pathogen		

Task Description:	interaction which leads to infection. Moreover, the biological importance of the immunological changes induced by spaceflight with regard to resistance to infection remains to be established. A significant application of this research is that by investigating host susceptibility to infection when both the host and pathogen are exposed to microgravity analogues – we can identify mechanistic effects of spaceflight on host resistance to infection. Specifically, we will examine the effect of hindlimb unloading (HU) on the innate immunity, production of stress hormones, and susceptibility of mice to infection with Salmonella typhimurium cultured under conditions of modeled microgravity (MMG). Hindlimb unloading of rodents is one of the most commonly used ground-based models to simulate aspects of spaceflight on the immune system. In the HU model, rodents are suspended in a harness by the tail with no load bearing on the hindlimbs and with a head-down tilt (i.e. antiorthostatic). These conditions induce muscle and bone loss, a fluid shift to the head, and altered immune responses, which are similar to changes induced by spaceflight. In addition, we will use both male and female mice in many of the proposed studies to determine the effects of sex-differences on the course of infection and the immune response. The use of male and female mice in our studies may provide important insight into sex-specific differences in immunological responses to infection among astronauts. This project uses a unique ground-based model of infection wherein both the host and pathogen are exposed to microgravity analogues to investigate the mechanistic effect of spaceflight on host resistance to infection. By investigating the effect of HU on innate immunity, production of stress hormones, and susceptibility of both male and female mice to infection with S. typhimurium cultured under MMG, this study will be the first of its kind to investigate the mechanistic effects of microgravity analogues on both the host and pathogen in a sex-specific fashion. Published findings by both the PI and Co-PI demonstrate that a) hindlimb unloading in rodents can suppress host innate immune responses, change production of stress hormones, and alter resistance to infection and, b) MMG culture of S. typhimurium results in increased virulence, stress resistance, and global alterations in gene expression and physiology. Thus, we anticipate that results generated during the course of these studies will be instrumental to understanding the effect of spaceflight on host resistance to infection, and the risk of in-flight infectious disease. Moreover, these studies will provide a solid foundation for the development of vaccines and other novel countermeasures, which are not achievable by any other ground-based means, for the treatment and prevention of infectious diseases occurring during spaceflight and on Earth. ADDENDUM - 2005: The hypothesis of the revised scope of work for this grant will remain the same under the new NASA funding. In order to retain maximum science recovery that falls within the new NASA funding requirements, we will delete Aim 1 and replace the use of the hindlimb unloaded mouse model with biologically relevant 3-D cell culture models under Aim 2. We hypothesize that the conditions experienced by both the host and pathogen during co-culture in spaceflight analogues will alter their interactions and thus the risk for infectious disease. A significant application of the proposed research is that by investigating host susceptibility to infection when both the host and pathogen are exposed to microgravity/spaceflight analogues, it will be possible to identify mechanistic effects of spaceflight on host resistance to infection. The proposed work will examine the effect of modeled microgravity (MMG) on the interactions between host (3-D models of human cell cultures) and relevant pathogens (bacterial and viral) when both are simultaneously exposed to this environmental condition. Endpoints to be assayed include adherence, invasion, and intracellular survival profiles, tissue pathology, innate immune responses, and select genomic/proteomic responses of the infected host. The results generated during the course of the proposed studies will provide important insight into the effect of spaceflight on host resistance to infection, and the risk of in-flight infectious disease to ensure crew health and safety. These studies may provide a foundation for the future development of vaccines and other novel countermeasures for the treatment and prevention of infectious diseases during spaceflight and on Earth.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This research will enrich life on Earth through the use of space technology and the application of biomedical knowledge. Specifically, this study will provide a solid foundation for the development of vaccines and other novel countermeasures, which are not achievable by any other ground-based means, for the treatment and prevention of infectious diseases occurring both on Earth and during spaceflight.
Task Progress:	Appropriately simulating the 3-D environment in which organs and tissues normally function is necessary for development of cultures that realistically resemble in vivo tissues and organs. At the same time, it is essential to accommodate experimental flexibility and high throughput analysis. For these reasons, the availability of reliable, reproducible 3-D tissue assemblies that effectively model the structure and function of human tissues holds tremendous promise for infectious disease research. Our lab has used innovative bioengineering technology developed by NASA to establish biologically meaningful 3-D models of human tissues that recapitulate many aspects of the differentiated structure and function of the parental tissue in vivo. We have applied these models to study infectious disease caused by a variety of microbial pathogens (bacterial and viral). A variety of different 3-D models have been established by our lab that have been/are being used in infection studies - including small intestine, colon, lung, placenta, bladder, periodontal ligament, vaginal and neuronal models. Published work from our lab has shown that our 3-D models respond to infection with bacterial and viral pathogens in ways that reflect the infection process in vivo. Our establishment and characterization of biologically meaningful 3-D cultures of human cells and tissues and their practical application in modeling infectious disease provide specific examples of how the study of bacterial and viral pathogenesis can benefit from an appropriate, biologically meaningful 3-D tissue model. In addition, we continue to enhance the physiological relevance of our 3-D cell culture models by developing multicellular 3-D co-culture models. Thus, in our hierarchical tissue modeling approaches, we strive to recapitulate both the 3-D architecture and multicellular complexity that is inherent in functional tissues in vivo. These physiologically relevant model systems are reproducible, experimentally flexible, cost effective, and offer high throughput platforms that hold promise for the translational advancement of human health. Our work with the 3-D model systems established and funded by this grant and their subsequent application to infectious disease studies has: 1) Facilitated meaningful dissection of molecular mechanisms of infectious disease caused by bacterial and viral pathogens, including the identity of novel host biosignatures in response to infection (including Salmonella sp, Norwalk virus, and Pseudomonas aeruginosa). 2) Allowed the study of infectious disease agents that lack suitable cell culture and animal models - Norwalk virus 3) Shown exciting potential for the development of novel diagnostics, vaccines, and therapeutic strategies for prevention & treatment

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