Fiscal Year:	FY 2024	**Task Last Updated:**	FY 12/14/2023
PI Name:	Yeung, Catherine Ph.D.		
Project Title:	Extended Culture of Kidney MPS and Organoids to Model Acute and Chronic Exposure to Drugs and Environmental Toxins		
Division Name:	Space Biology		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:	NIH, BARDA, FDA	**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	(1) Cell & Molecular Biology		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	(1) Cell Culture		
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Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2021 Space Biology NNH21ZDA015N. Extended Longevity of 3D Tissues and Microphysiological Systems for Modeling of Acute and Chronic Exposures to Stressors
Start Date:	11/15/2022	**End Date:**	11/14/2026
No. of Post Docs:		**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA HQ
Contact Monitor:	Koniges, Ursula	**Contact Phone:**	202-256-8786
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Flight Program:			
Flight Assignment:	Per the Research Announcement for this solicitation: this effort is a collaboration between NASA; the National Institutes of Health (NIH); the Biomedical Advanced Research and Development Authority (BARDA); and the Food and Drug Administration (FDA).		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Bammler, Theodor Ph.D. (University of Washington) Freedman, Benjamin Ph.D. (University of Washington) Himmelfarb, Jonathan Ph.D. (University of Washington) Kelly, Edward Ph.D. (University of Washington) Thummel, Kenneth Ph.D. (University of Washington) Zelnick, Leila Ph.D. (University of Washington)		
Grant/Contract No.:	80ARC023CA001		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Kidney disease is a public health problem affecting 850 million people worldwide, 37 million people in the US adult population, and is the 9th leading cause of death. Loss of kidney function is often associated with chronic hypertension, diabetes, or exposure to pathogens, drugs, or environmental chemicals, and in many cases, takes many months or years to manifest clinically. Finding efficacious therapeutics and preventing disease progression require fundamentally new strategies, assays, and models of the kidney to improve patient outcomes. Until recently, the lack of human in vitro models that recapitulate critical aspects of kidney physiology, mimic the unique complexities of specific nephron segments, model disease heterogeneity, or assess reparative mechanisms in response to injury has hindered progress. Our team has approached the scientific challenges of studying kidney disease pathophysiology, novel therapeutic agents, and drug/ environmental toxicity by establishing two innovative human models: the proximal tubule kidney chip microphysiological system (PTEC MPS) and the iPSC (induced pluripotent stem cell)-derived kidney organoid. We have developed validation assays for short-duration (2-10 day) exposures in both ground-based laboratories and aboard the International Space Station. The goal of this project is to demonstrate models with extended (6 month) longevity to better understand the role of chronic stressor exposure on kidney disease initiation and progression. Based on previous studies, we hypothesize that human kidney systems will remain viable and functionally stable for at least 6 months and will respond physiologically to extended exposure to stressors. Phase I – Description and Tasks. Establish extended longevity and functionality (6 months) of kidney microphysiological systems and organoids. The contractor shall: • Determine longevity of the proximal tubule kidney chip (PTEC) MPS at 2.5, 5, and 6 months by employing cell viability (live/dead staining), metabolic function (conversion of 25(OH)VitaminD3 to 1a25(OH)2 VitaminD3), toxic response (resulting in KIM-1 [kidney injury molecule-1] expression), stable expression of immunomodulators (e.g., IL[interleukin]-6, IL-23A, TNF [tumor necrosis factor], IL-32), and global RNA transcript profile. • Determine longevity and stable function of kidney organoids at 2.5, 5, and 6 months by conducting observation of distinct tubules with specific multiple nephron and stromal lineages in segmented structures (immunocytochemical staining), and stable global single cell RNA transcript profile. Phase II – Description and Tasks. Test structural and functional outcomes after sustained exposure to drugs, environmental toxins, and pathogens and post-exposure cellular recovery. The contractor shall: • Determine functional outcomes of PTEC MPS after exposure to agents known to cause nephrotoxicity after 5 months exposure (PMB [polymyxin B] or other nephrotoxin) followed by 1 month recovery by evaluating structural derangement (de-polarization of transporter proteins), production of injury biomarkers (KIM-1, HO-1 [heme oxygenase-1], cystatin), and altered regulation of immunomodulators (e.g., IL-6, IL-23A, TNF, IL-32). • Evaluate kidney organoid responses to pathogenic stimuli and known nephrotoxins using fluorescent reporters for real-time detection of infection and injury in response to acute (3 days) and extended (5 months) exposure followed by 1 month of recovery.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Developing a kidney microphysiological system and kidney organoids with extended longevity will allow us to model the effects of stressors like drugs, environmental toxins, pathogens, and microgravity on kidney cell structure and function, and to determine if, and how, kidney cells can recover from stress. A better understanding of kidney injury and recovery from chronic stressor exposure can accelerate the development of better and safer medications and treatments to prevent and cure kidney diseases.
Task Progress:	We have demonstrated MPS viability and maintenance of tubular conformation for 6 months as shown by brightfield and fluorescence (green-fluorescent calcein-AM and red-fluorescent ethidium homodimer-1) microscopy. Of six lumens seeded, three survived to six months and two continue to show >90% viability at almost 10 months. We have demonstrated stable function of PTEC MPS tubules by observing stable secretion of KIM-1 (Kidney Injury Molecule-1) and IL-6 over 5-6 months of culture. RNA for RNAseq analysis has been extracted from all tubules from 0-6 months and are pending analysis and informatics. We have also been able to maintain viable kidney organoids for at least six months. Kidney organoid structure and organization was consistent throughout the experiment. To analyze function, we demonstrated proximal tubule function in the kidney organoids via dextran absorption over the course of the experiment, supporting the idea that these cells were functional after 180 days. We have collected and analyzed RNA from organoids on day 25 and day 180 for single cell RNA sequencing. Dr. Edward Kelly, a Co-Investigator on this grant, also contributed to a National Academies of Sciences Decadal Survey publication entitled, "Thriving in space: Ensuring the future of biological and physical sciences research: A decadal survey for 2023-2032." [Ed. Note: See Bibliography.]
Bibliography Type:	Description: (Last Updated: 12/14/2023)
Abstracts for Journals and Proceedings	Jones-Isaac KA, Lidberg KA, Yang J, Bain J, Ruiz M, Koenig G, Koenig P, Countryman S, Himmelfarb J, Yeung CK, Kelly EJ. "Development of a kidney microphysiological system hardware platform for microgravity studies." ISSRDC 2023 (International Space Station Research and Development Conference), Seattle, WA, July 31-Aug 3, 2023. Poster. Abstracts. ISSRDC 2023 (International Space Station Research and Development Conference), Seattle, WA, July 31-Aug 3, 2023. , Jul-2023
Abstracts for Journals and Proceedings	Lidberg KA, Jones-Isaac KA, Bain JD, Yang J, Calamia J, Thummel KE, Yeung CK, Countryman S, Koenig P, Himmelfarb J, Kelly EJ. "Impact of microgravity on a three-dimensional microphysiologic culture of the human kidney proximal tubule epithelium: Cell response to serum and vitamin D." American Society for Gravitational and Space Research Annual Meeting, Washington DC, November 14-18, 2023. Poster. Abstracts. American Society for Gravitational and Space Research Annual Meeting, Washington DC, November 14-18, 2023. , Nov-2023
Articles in Other Journals or Periodicals	National Academies of Sciences, Engineering, and Medicine. "Thriving in space: Ensuring the future of biological and physical sciences research: A decadal survey for 2023-2032." Washington, DC: The National Academies Press, 2023. Prepublication. https://doi.org/10.17226/26750 , Sep-2023