Fiscal Year:	FY 2015	**Task Last Updated:**	FY 01/21/2015
PI Name:	Simon, Julianna Ph.D.		
Project Title:	Improving Kidney Stone Detection in Space Analogs		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Smart Medical Systems and Technology Team		
Joint Agency Name:		**TechPort:**	Yes
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Space Biology Special Category:	None		
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Comments:			
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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:			
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Flight Assignment:	NOTE: End date changed to 12/31/2016 per NSBRI (Ed., 10/19/15)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Bailey, Michael Ph.D. (MENTOR/ University of Washington)		
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POSTDOCTORAL FELLOWSHIP
1. Specific Aims/Objectives

The twinkling artifact (TA), a rapid color-shift that selectively highlights hard objects in color-Doppler ultrasound images, has the potential to improve kidney stone detection; however, its inconsistent appearance has limited its use. Recently, it was hypothesized that crevice bubbles on the surface of stones cause twinkling, and bubbles are going to be very sensitive to the changes in gravity and pressure that occur during space travel. Our objective is to develop an ultrasound imaging protocol to enhance kidney stone detection in space, addressing ExMC Gap 4.13.

AIM 1: Develop ultrasound imaging protocols to enhance kidney stone detection in space.

Task Description:	AIM 2: Manipulate existing elastic wave and bubble dynamic models to aid in refining kidney stone detection protocols. AIM 3: Determine how hypobaric and hyperbaric conditions alter the TA. AIM 4: Determine how urine pH and stone type affect the TA. AIM 5: Determine how exposure to gas concentrations unique to the space travel vehicles alters the TA. 2. Key Findings In ex vivo kidney stones of all major stone types, we found that increasing the acoustic energy delivered to the stone enhances the TA. Hypobaric conditions were found to enhance the TA and hyperbaric conditions were found to diminish the TA. High-magnification, high-speed imaging has found a crevice bubble on the stone surface that oscillated when exposed to ultrasound. The linear elastic stone model has been successfully coupled with a bubble dynamics model. A new hypothesis to describe the origin of the bubbles in twinkling - namely bacteria – was generated. Published 4 papers in scientific journals, including, "Focused ultrasound to displace renal calculi: threshold for tissue injury," "Preclinical safety and effectiveness studies of ultrasonic propulsion of kidney stones," "Ultrasound-guided tissue fractionation by high intensity focused ultrasound in an in vivo porcine liver model," and "Pulsed focused ultrasound treatment of muscle mitigates paralysis-induced bone loss in the adjacent bone: A study in a mouse model." Submitted 2 papers that are in review to J. Fluid Mech. and Ultrasound Med. Biol. Presented at 4 scientific conferences. Represented the National Space Biomedical Research Institute (NSBRI) at the 2014 congressional demonstration. Mentored a summer high-school student who finished with a demo at the Pacific Science Center. 3. Impact We have discovered methods to enhance the TA that can be programmed into NASA's flexible ultrasound system; some of these enhancements can also be implemented on commercial ultrasound machines. All of our experimental results support the original hypothesis that crevice bubbles on the kidney stone surface cause twinkling and, for the first time, we have observed a bubble on the stone surface. We have also hypothesized that bacteria cause these bubbles to form, which enhances our understanding of the etiology of the TA and stone disease. Furthermore, we have shown that stone composition and environment influence twinkling, which could be used to enhance stone detection or potentially be used to predict stone composition. 4. Proposed Research We will test the influence of breathing increased carbon dioxide levels on twinkling in a pig model. We will utilize modeling to determine what parameters most strongly influence twinkling. We plan to image more bubbles on the stone surface with higher magnification, high-speed imaging to look for correlations between the twinkling amplitude and number of bubbles. We will leverage the ex vivo hyperbaric experimental results in an IRB to test whether bubbles are present on in situ kidney stones by recruiting human subjects for tests in a hyperbaric chamber. We will grow calcium oxalate crystals in the lab to determine whether pure crystals twinkle. We plan to determine the bacteria load on fresh stones, comparing stones that twinkle with those that weakly twinkle.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The risk of renal stone formation (ExMC 4.13) is considered a shall for all missions beyond the International Space Station. On Earth, currently 1 in 11 Americans have been diagnosed with kidney stones and the prevalence is increasing worldwide. In the US, more than three million diagnoses and treatments are made annually at a cost calculated to be over two billion dollars. Specific in-flight conditions that contribute to an increased risk of renal stone formation include bone demineralization, dehydration, and stasis. US astronauts have reported 14 symptomatic stone events that have occurred pre- or post-flight; one notable in-flight stone instance has been described by the Russian space program, where a crewmate was found writhing in pain. While no US astronaut has experienced an in-flight kidney stone event, the importance of kidney stones in space is expected to rise as missions become longer and immediate transport to Earth becomes more problematic. Stone size is a significant predictor for the severity of a stone incident, as small stones may pass on their own causing relatively little pain. The Integrated Medical Model team defines two renal stone scenarios: the best case scenario (i.e., where stones pass safely and spontaneously) is predicted to occur 68% of cases where stones are small (< 5 mm diameter). However, as stones increase to 5-10 mm in diameter, stones are predicted to pass safely and spontaneously in less than 50% of cases. These data show the need for a diagnostic tool that allows for routine monitoring of people at risk for developing kidney stones, both on Earth and in space. Currently, kidney stones are detected with x-ray or CT, both of which expose the patients to ionizing radiation. Our technology will make ultrasound a more robust tool to detect small kidney stones, thereby reducing patient exposure to ionizing radiation and reducing the cost associated with kidney stones. This technology would allow emergency rooms to diagnose kidney stones immediately, rather than sending the patient to radiology for a CT. In addition, more than 50% of stone-formers have a repeat stone incident within 5 years. Our technology would allow for more routine monitoring so steps could be taken to avoid emergency surgery. In space, ultrasound is one of the few imaging technologies that can be flown, and our improved kidney stone detection protocols will make ultrasound a robust tool for early stone detection, which is critical for minimizing mission disruption and reducing the risk of an unpredictable and life-threatening renal stone incident.
	AIM 1: Develop ultrasound imaging protocols to enhance kidney stone detection in space. From experimental results thus far, we have found that increasing the energy delivered to the kidney stone enhances twinkling. This can be accomplished on commercially-available ultrasound machines by increasing the gain or amplitude of the ultrasound wave. On NASA's flexible ultrasound system, we can further enhance twinkling by increasing the number of cycles in the Doppler ensemble or increasing the amplitude of the Doppler pulse. AIM 2: Manipulate existing elastic wave and bubble dynamic models to aid in refining kidney stone detection protocols. The existing elastic wave and bubble dynamic model has been successfully coupled. We have also been able to observe one instance of a bubble oscillating on the stone surface with high-magnification, high-speed imaging when exposed to color Doppler ultrasound.

Task Progress:	AIM 3: Determine how hypobaric and hyperbaric conditions alter the twinkling artifact (TA). Task 3.1: To test the effect of increased and decreased ambient pressure on the TA in ex vivo human kidney stones. Increasing the ambient pressure has been found to diminish twinkling, with the exact pressure threshold to eliminate twinkling ranging from 3 atm (absolute) to greater than 8 atm, depending on the exact location and stability of twinkling on the individual stone, the gas content of the liquid and stone, and the amplitude and number of cycles in the Doppler pulse. On the other hand, hypobaric conditions have been found to enhance twinkling, which could be utilized in the first aim to enhance kidney stone detection in space. Task 3.2: To test the effect of increased ambient pressure on the TA in humans. We have reopened discussions with the Virginia Mason Hyperbaric Center and have successfully shown that twinkling can disappear in their chamber at physiologically safe pressure levels. We are pursuing an IRB to be able to complete this task. AIM 4: Determine how urine pH and stone type affect the TA. Preliminary results in solutions with acidic pH suggest that urine pH affects twinkling. Preliminary results monitoring twinkling in all major stone types indicate that twinkling occurs, though the strength and stability of twinkling is lower for some stone types, such as uric acid. AIM 5: Determine how exposure to gas concentrations unique to the space travel vehicles alters the TA. The concentration of gases in the solution surrounding the kidney stone influences the twinkling artifact. Preliminary results monitoring twinkling in solutions with increased carbon dioxide concentrations suggest that gas composition also affects the TA.
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