Fiscal Year:	FY 2011	**Task Last Updated:**	FY 09/08/2011
PI Name:	Crum, Lawrence A. Ph.D.		
Project Title:	Smart Therapeutic Ultrasound Device for Mission-Critical Medical Care		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Smart Medical Systems and Technology Team		
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **ExMC**:Exploration Medical Capabilities		
Human Research Program Risks:	(1) **Medical Conditions**:Risk of Adverse Health Outcomes and Decrements in Performance Due to Medical Conditions that occur in Mission, as well as Long Term Health Outcomes Due to Mission Exposures		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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City:	Seattle	**State:**	WA
Zip Code:	98105-6606	**Congressional District:**	7
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2007 Crew Health NNJ07ZSA002N
Start Date:	08/01/2008	**End Date:**	09/30/2012
No. of Post Docs:	4	**No. of PhD Degrees:**	0
No. of PhD Candidates:	3	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date should be 9/30/2012 (previously 7/31/2012) per NSBRI (Ed., 5/22/2012)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Bailey, Michael (University of Washington) Carter, Stephen (University of Washington) Sapozhnikov, Oleg (University of Washington)		
Grant/Contract No.:	NCC 9-58-SMST01601		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

The major goal of this effort is to utilize existing ultrasound platforms and the concept of image-guided therapy to control traumatic bleeding, ablate benign and malignant tumors, and to diagnose and reposition kidney stones. Our methods and devices are countermeasures to specific risks described in the Human Research Program Integrated Research Plan, viz.,
(1) Lack of advanced therapeutic capability,

(2) lack of capability to treat renal stones, and

(3) lack of non-invasive diagnostic imaging capabilities.

The original specific aims are:

Specific Aim 1: Support ongoing leveraged efforts in Acoustic Hemostasis (AH) and HIFU Tumor Ablation (TA) by addressing fundamental scientific issues as well as to ensure NSBRI relevance.

Specific Aim 2: Develop methods and technologies that would enable detection of renal stones with ultrasound.

Specific Aim 3: Develop technology and perform in vitro studies of stone comminution.

Specific Aim 4: Utilizing technology and protocols developed in SAs 2 and 3, perform in vivo studies in a porcine model.

The main findings and associated research productivity for year 3 are:

- We have continued to advance ultrasound technology to detect and reposition kidney stones. The imaging technology provides an alternative to imaging techniques that expose the patient to ionizing radiation on earth and provides a user-friendly technique to detect even small stones in space. The repositioning technology provides an adjunctive treatment to surgery by which to facilitate the passage of residual fragments that my regrow to new stones, and provides a way to prophylactically remove small stones before they require surgery. This year, we have accomplished the following:

- Obtained approval from the University of Washington Institutional Review Board (IRB) for clinical testing of the stone detection technology.

- Obtained NIH Funding for regulatory consultants (Drug and Device Development Co. and Institute of Translational Health Sciences) to help us prepare an application to the U.S. Food and Drug Administration (FDA) for an Investigational Device Exemption (IDE) for an investigator-driven, pilot clinical trial of detecting and repositioning stones.

- Collected and documented about half the required safety data for the IDE application.

- Developed three iterations of a business plan culminating in one funded by NASA and NSBRI to be completed by Virtual Incubation Company, LLC. Our approach has been to not start a company yet, but instead to leverage university resources (research team, Center for Commercialization, Entrepreneur-in-Residence, and non-diluting state, federal and foundation funding to remove risk and attain the critical inflection point of "first in man." The business plans center on commercial partnerships or a start-up as well as NASA implementation at that inflection point.

- Filed a U.S. patent application that encompassed all the technologies.

- Developed a prototype from commercial-off-the-shelf (COTS) hardware, which will arguably accelerate production and regulatory approval of an eventual commercial product.

- The hardware for our prototype has advantages for space flight, namely radiation hardening, and with the ExMC Imaging Integration Team and the manufacturer, we are developing a system suitable for deployment and testing on ISS. We use the HDI-5000 probes currently available on ISS. The ultrasound system is a single box that was adapted to work with the IBM Lenovo laptops currently used on ISS. The system is open-architecture, software based, COTS technology, meaning that other NASA or NSBRI countermeasures could easily be implemented on it and upgrades do not require up-mass. Proposals for flight-testing, for integration of NSBRI countermeasures on the platform, for implementation of new technology, and for radiation testing were submitted with NSBRI, NSBRI researchers, ExMC, and NASA Glenn.

- Successfully completed a collaboration with Siemens of a DARPA-funded Phase II project to develop an automated system to detect and control bleeding on the battlefield and in remote environments. Phase III funding is pending. NSBRI funding was used to automate the detection and treatment for ease-of-use in a portable system. That work was published in year 2. The results were presented at international meetings.

- Developed a method and device to characterize the acoustic output of high intensity focused ultrasound (HIFU) devices. The University of Washington (UW) Center for Commercialization (C4C) has filed a provisional patent. The technique was added to the IEC 60601-2-62 standards document. The technology was demonstrated on a Philips clinical HIFU system.

- Developed a method to accelerate and control tissue ablation with transcutaneous ultrasound. In particular, tissue was mechanically emulsified by millisecond bursts of HIFU at output levels that produce shock waves. C4C has filed a U.S. patent application. The Philips machine was modified to produce these outputs. Our method has several potential advantages over technique used in competitor's $11 million start-up.

- Negotiations are underway among UW, Philips, and a drug company for clinical trials for pancreatic cancer. Our measurements were used to define the "dose" to be applied to patients.

- Completed initial investigation of HIFU-induced, tumor-specific auto-immune response in collaboration with Fred Hutchinson Cancer Research Institute.

- Demonstrated with statistical significance in a small cohort that application of shocked ultrasound waves accelerated wound healing in a rat model over sham exposures.

- Obtained funding from US Army to investigate the application of shocked ultrasound to slow bone loss in a murine paralysis model. Our new approach was found to significantly slow, and in some cases halt, bone loss.

Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	We have been encouraged by our interactions with the urology, ultrasound, and business communities that our technology to detect and reposition stones could significantly alter the way kidney stones are treated in clinical medicine. We have won awards in the six poster or business plan competitions we have entered. Most stones are small enough to pass naturally and thus patients are encouraged, through hydration, to try to pass the stone without intervention. This natural process might take 6-8 weeks and result in considerable discomfort to the patient over this interval. With our innovative technology, a stone could potentially be cleared in the first office visit. Many stones do not clear with hydration, and thus more aggressive approaches are required. More invasive procedures are often necessary if the stone is in the lower pole because even if fragmented, the pieces are unlikely to pass from this location. Our technological approach would keep the least invasive option open for these patients. In most existing procedures, there is a significant chance stone pieces will remain behind as seeds for future stones and further surgery. Our technology could help these pieces pass. In addition, stones are often recurrent; recurring-stone patients are often monitored, so that new stones can be detected early - this monitoring could be done with our precise stone imaging approach. Our technology could also move these stones to the kidney exit before they are symptomatic. This technology reduces risk of surgery, complications of surgery for the patient, and the cost of surgery to the insurance companies; furthermore, the technology does not preclude any surgical options. Lastly, the algorithms to detect kidney stones alone stand to spare many patients the ionizing radiation of a CT scan, or to provide options to pregnant women or children with stones who are unlikely to receive CT. NSBRI quickly recognized the value of this technology and helped us initiate our commercialization effort that now has the full support of the UW, the Washington Research Foundation, and a commercial hardware provider, as well as the interest of several venture capitalists and ultrasound companies. The applications of our technology to the control of bleeding and for tumor ablation are at least as profound. Specifically, this year we have worked with the latest clinical HIFU machine - one developed by Philips Medical. This machine is intended for many clinical applications. We have used some of our effort to characterize the output of the machine and assess its potential bio-effects. Our work provides the clinicians, who intend to use this machine, the ability to select a treatment dose. At UW alone, it helps train the clinicians and establish the specificity of what size targets are treated. With our contribution, the clinicians are then likely to pursue their own clinical studies, and regulatory approval for various tumor treatments. Before our involvement, the machine sat dormant for a year. We are also exploring the effects of HIFU on the immune system and have proposed clinical trials to combine HIFU with chemical therapeutic agents. We believe that our efforts to carefully describe outputs and bio-effects will help the US catch up with the rest of the world where over 400,000 patients have been treated by HIFU. In addition, our intimate knowledge of these details enables us to consider ways in which a similar, much reduced-in-size system could be developed for NASA to reduce some critical risks to astronauts during long duration space travel.
Task Progress:	Task 1A. Perform studies of bleeding detection in a flow-phantom model: Successfully detected and treated sites in a phantom developed with DARPA and FDA in a blind test with an automated system. Task 1B. Perform studies to determine pressure and temperature in ex vivo tissue exposed to HIFU: Published paper "Shock-induced heating and millisecond boiling in gels and tissue due to high intensity focused ultrasound", Michael Canney, et al., Ultrasound Med. & Biol., 36, 250-267 (2010), which led to invitation to join IEC working group on HIFU standards and to measure acoustic output of Philips clinical HIFU machine. Also, discovered and submitted patent application for method to emulsify tissue with ultrasound. Task 2A. Develop new stone detection techniques based on radiation force and reverberation responsible for twinkling artifact: As part of our graduate student's dissertation, efforts continue toward understanding the origins of the twinkling artifact and to further refine the algorithms we have developed, implemented, tested, and patented. Task 2B. Test stone sizing technology in tissue: Published paper, M.D. Sorensen, et al., "Proof of Principle of a Prototype Ultrasound Technology to Size Stone Fragments During Ureteroscopy," J. Endourology, 2009, 1161-1164; filed U.S. and international utility patent applications, and are negotiating licensing. We have initiated human clinical studies to test ultrasound stone sizing versus CT. Task 3A. Utilize the YUANDE HIFU tumor ablation device as a test platform: Performed a number of studies. Task 3B. Engineer and optimize an image-guided, two-frequency HIFU system for renal stone comminution: We are working with ExMC to fly one platform that detects, repositions, and comminutes stones. All are implemented in a prototype for which we are pursuing an investigational device exemption (IDE) with the FDA. We have developed a concept of expelling small stones from a kidney before they require comminution or surgery. A system to detect and reposition stones based on an OEM diagnostic ultrasound platform has been built and demonstrated to be safe and effective in studies in a porcine model. Commercialization efforts have begun. An update report on progress won best poster at the American Urology Association meeting. Task 4A. Perform in vivo tests of the imaging protocols developed in Task 2: Paper in preparation comparing twinkling to standard B-mode for stone detection in patients. New algorithm for stone detection implemented on clinical machine and tests of the algorithm initiated on human subjects. Task 4B. Perform studies to determine the potential for HIFU-induced stone comminution as well as any associated tissue injury: In vivo studies of our stone clearance system have been shown to be safe and effective. A safety study in pigs is complete and a study of safety under realistic clinical conditions in pigs has just begun. These data will be presented to the FDA to pursue a clinical trial.
Bibliography Type:	Description: (Last Updated: 03/22/2019)
Articles in Peer-reviewed Journals	Khokhlova TD, Canney MS, Khokhlova VA, Sapozhnikov OA, Crum LA, Bailey MR. "Millisecond bursts of focused ultrasound shock waves to produce boiling and tissue emulsification." Journal of the Acoustical Society of America. In press, as of September 2011. , Sep-2011

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Articles in Peer-reviewed Journals	Kreider W, Sapozhnikov OA, Crum LA, Bailey MR. "Observations of the collapses and rebounds of millimeter-sized lithotripsy bubbles." Journal of the Acoustical Society of America. In press, as of September 2011. , Sep-2011
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Articles in Peer-reviewed Journals	Shah A, Harper JD, Cunitz BW, Wang YN, Paun M, Simon JC, Lu W, Kaczkowski PJ, Bailey MR. "Focused ultrasound to expel calculi from the kidney." Journal of Urology. In press, as of September 2011. , Sep-2011
Articles in Peer-reviewed Journals	Shah A, Owen NR, Lu W, Cunitz BW, Kaczkowski PJ, Harper JD, Bailey MR, Crum LA. "Novel ultrasound method to reposition kidney stones." Urol Res. 2010 Dec;38(6):491-5. Epub 2010 Oct 22. PMID:20967437 ; http://dx.doi.org/10.1007/s00240-010-0319-9 , Dec-2010
Awards	Simon J. "Recipient, Baker Award Fellowship, UW College of Engineering, May 2011." May-2011
Awards	Bailey M. "Appointment Adjunct Assist. Prof. of Urology, May 2011." May-2011
Awards	Bailey M. "Appointment Assist. Prof. of Mechanical Engineering (WOT), September 2010." Sep-2010
Awards	Hsi R. "Best Poster American Urological Assoc. Annual meeting, May 2011." May-2011
Awards	Khokhlova V. "Elected to Board, International Society for Therapeutic Ultrasound, April 2011." Apr-2011
Awards	Lu W. "Winner, Business Plan Poster Competition UW SEBA, February 2011." Feb-2011
Significant Media Coverage	Assimos D. "Urolithiasis/Endourology. The PI's article, 'Novel ultrasound method to reposition kidney stones,' from Urol Res (http://dx.doi.org/10.1007/s00240-010-0319-9) was chosen to be highlighted in the Journal of Urology, which is rare for a basic science article. The Editor provided favorable comment." Urolithiasis/Endourology Urological Survey Journal of Urology. 2011 Jun;185(6):2186-9. , Jun-2011