Guest Editorial
Introduction to the Special Issue on Histotripsy: Approaches, Mechanisms, Hardware, and Applications

HISTOTRIPSY is a therapeutic ultrasound technology to liquefy tissue into acellular debris using sequences of high-power focused ultrasound pulses. Research on histotripsy has been rapidly growing in the past decade; newer applications are being proposed and evaluated for clinical use. In contrast to conventional high-intensity focused ultrasound (HIFU) thermal therapy, the major mechanism of histotripsy is mechanical, which enables localized tissue disintegration at the target sites without thermal damage to overlying and surrounding tissues. Two major approaches, cavitational histotripsy and boiling histotripsy, with two different mechanisms, have been extensively explored lately. Histotripsy therapy is being evaluated for treating cancer, thrombosis, hematomas, abscess, neurological diseases, for inducing an enhanced immune response and performing noninvasive biopsy in preclinical studies with small and large animal models. The first clinical trials using histotripsy for benign prostatic hyperplasia, liver cancer, and calcified aortic stenosis have been undertaken.

On March 27, 2020, Prof. Charles Cain, an IEEE fellow and a former Associate Editor of IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS AND FREQUENCY CONTROL (TUFFC) who coined the term histotripsy in 2003, passed away. With increasing interest from both the basic science and clinical communities and in honor of the pioneering work of Dr. Cain, IEEE TUFFC organized this first Special Issue on histotripsy, titled "Histotripsy: Approaches, Mechanisms, Hardware, and Applications" to provide a timely platform for dissemination of new findings in this area. The Special Issue includes 15 articles, covering the latest research on developing new methods, exploring the physical mechanisms, designing specified hardware, and clinical applications of histotripsy.

Histotripsy uses approaches that are different from conventional therapeutic ultrasound and relies on generating cavitation bubbles via very short (microsecond to millisecond length), high-pressure ultrasound pulses that are typically distorted in shape due to nonlinear propagation effects. Unlike ultrasound thermal therapy, histotripsy mechanically breaks down target tissue into liquid-appearing acellular homogenate. Therefore, designing histotripsy exposure protocols and monitoring histotripsy treatment require different approaches. This Special Issue includes three articles on histotripsy approaches addressing nonlinear propagation effects ("HIFU Beam: A Simulator for Predicting Axially Symmetric Nonlinear Acoustic Fields Generated by Focused Transducers in a Layered Medium" by Yuldashev *et al.*), histotripsy lesion monitoring ("Contrast-Enhanced Ultrasound: A Useful Tool to Study and Monitor Hepatic Tumors Treated With Histotripsy" by Serres-Créixams *et al.*), and motion compensation ("Partial Respiratory Motion Compensation for Abdominal Extracorporeal Boiling Histotripsy Treatments With a Robotic Arm" by Thomas *et al.*).

The primary mechanisms underlying histotripsy are based on the initiation (nucleation) and dynamic behavior of cavitation and vapor bubbles. This Special Issue includes two articles on the mechanisms of histotripsy focusing on bubble nucleation ("Modeling the Physics of Bubble Nucleation in Histotripsy" by de Andrade *et al.*) and cavitation behaviors ("Inertial Cavitation Behaviors Induced by Nonlinear Focused Ultrasound Pulses" by Bawiec *et al.*)

Because histotripsy relies on microsecond to millisecond length pulses with very high pressure (peak negative pressure >10 MPa) and low duty cycle ($<5\%$), in most cases it requires special hardware different from ultrasound thermal therapy that uses continuous wave or long pulses with intermediate pressure but high duty cycle ($>20\%$). It is challenging to produce very high-pressure ultrasound pulses with a small aperture transducer for endoscopic histotripsy, and as a result, endoscopic histotripsy is only now becoming possible. This Special Issue includes two articles on the latest progress in endoscopic histotripsy transducers ("Endocavity Histotripsy for Efficient Tissue Ablation—Transducer Design and Characterization," by Stocker *et al.*, and "A Dual-Frequency Lens-Focused Endoscopic Histotripsy Transducer" by Mallay *et al.*). "Transcranial MR-Guided Histotripsy System" by Lu *et al.* is related to developing hardware for monitoring histotripsy treatment. "Dual-Use Transducer for Ultrasound Imaging and Pulsed Focused Ultrasound Therapy," by Karzova *et al.*, reports on a new design of a diagnostic-type transducer for enhancing drug delivery without contrast agents and with real-time ultrasound imaging.

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Histotripsy has been investigated in a wide range of preclinical applications, and several clinical trials have been conducted and are ongoing. This Special Issue includes preclinical applications under investigation, such as treatments of blood clots ("Clot Degradation Under the Action of Histotripsy Bubble Activity and a Lytic Drug" by Hendley *et al.*) and liver tumor ("Histotripsy for the Treatment of Cholangiocarcinoma Liver Tumors: *In Vivo* Feasibility and *Ex Vivo* Dosimetry Study" by Hendricks-Wenger *et al.*), disintegration of biofilms ("Focused Ultrasound Biofilm Ablation: Investigation of Histotripsy for the Treatment of Catheter-Associated Urinary Tract Infections (CAUTIs)" by Childers *et al.*) and tendon tissue ("Focused Ultrasound Mechanical Disruption of *Ex Vivo* Rat Tendon" by Smallcomb *et al.*). In addition, the latest research has shown that histotripsy can induce local and systemic immune responses. Histotripsy-induced immunostimulation in a preclinical tumor model is discussed in "Histotripsy Ablation Alters the Tumor Microenvironment and Promotes Immune System Activation in a Subcutaneous Model of Pancreatic Cancer" by Hendricks-Wenger *et al*. Finally, a clinical case report on the abscopal effect in histotripsy treatment of liver cancer, likely induced by histotripsy immunostimulation, is reported in "Liver Histotripsy Mediated Abscopal Effect—Case Report" by Vidal-Jové *et al*.

The Editors would like to thank the IEEE TUFFC Editor-in-Chief, Prof. Peter Lewin, who gave an idea, encouraged, and supported our efforts to make this Special Issue possible. Prof. Zhen Xu and Prof. Vera A. Khokhlova initiated the process and teamed with the Associate Editor-in-Chief, Dr. Keith A. Wear, and Associate Editors, Prof. Jean-François Aubry and Prof. Timothy A. Bigelow. It has been a pleasure to work together through the peer-review process. Special thanks to the transaction officers Natalie Cicero, Eileen McGuinness, and John Wright for their help and organization of the process. And most thanks to the authors who contributed to this Special Issue and to all the anonymous reviewers who contributed their time and effort in evaluating the submissions and providing professional comments to improve them. We hope very much that this Special Issue will help attract new scientists and engineers to the emerging field of histotripsy and help move it toward clinical use.

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Dr. Xu received the UFFC Outstanding Paper Award in 2006, the Frederic Lizzi Early Career Award from ISTU in 2015, a fellow of the American Institute of Medicine and Bioengineering in 2019, and the Lockhart Memorial Prize for Cancer Research in 2020. She is an Associate Editor of the IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL (TUFFC) and *BME Frontiers*, the Deputy Vice President of the Ultrasonics Standing Committee (USSC) of UFFC, and a Board Member of the International Society of Therapeutic Ultrasound (ISTU).

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Dr. Aubry has been elected as the President of the International Society for Therapeutic Ultrasound (2015–2018).

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After completing his education, he was a Visiting Assistant Professor with the Electrical and Computer Engineering Department, University of Illinois at Urbana–Champaign, for a year. Then, he was an Assistant Professor in electrical engineering with the University of North Dakota for three years prior to coming to Iowa State University in August 2008, where he was promoted to an Associate Professor in electrical/computer engineering in 2014. His research interests focus on improving the diagnostic and therapeutic effectiveness of medical ultrasound, quantifying the physical properties of tissue for diagnostic purposes using backscattered ultrasound signals, applying ultrasound-induced cavitation to destroy unwanted cells, and exploring new ultrasound-induced biological effects for both ultrasound safety and ultrasound therapy applications.

Dr. Bigelow currently serves as an Associate Editor-in-Chief as well as an Associate Editor for the IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control journal.