9:00

4aBB4. Combined effect of ultrasound and liposomal doxorubicin on AT2 Dunning tumor growth in rats: Preliminary results. Lucie Somaglino (Inserm U556, 151 cours Albert Thomas, 69424 Lyon cedex 03, France and Univ. de Lyon, Lyon F-69003, France, lucie.somaglino@inserm.fr), Guillaume Bouchoux, Sabrina Chesnais, Anis Amdouni, Jean-Louis Mestas (Inserm U556, 69424 Lyon cedex 03, France), Sigrid Fossheim, Esben A. Nilssen (Epitarget AS, 0307 Oslo, Norway), Jean-Yves Chapelon, and Cyril Lafon (Inserm U556, 69424 Lyon cedex 03, France)

Previous in vitro studies conducted in our group have shown the feasibility of monitoring drug release from liposomes by an inertial acoustic cavitation index. We currently report in vivo experiments utilizing the cavitation index in combined treatment of AT2 Dunning tumor grafted rats with focused ultrasound and liposomal doxorubicin. Sixty-three rats were allocated into seven groups: control, low level ultrasound treatment, high level ultrasound treatment, free doxorubicin+high level ultrasound treatment, and liposomal doxorubicin, liposomal doxorubicin+low level ultrasound treatment, and liposomal doxorubicin+high level ultrasound treatment. Based on pharmacokinetic studies, it was decided to apply ultrasound to the tumor 48 h after drug injection. An experimental setup was built to perform repeatable and rapid sonications of tumors monitored by the cavitation index. Tumor growth was assessed for a period of 35 days after tumor inoculation. Results showed that liposomal doxorubicin significantly slowed down tumor growth. However, the synergy between ultrasound and liposomal doxorubicin could not be firmly demonstrated. The lack of synergy may be due to inefficient induction of drug delivery in vivo or too high liposome dosage hiding synergistic effects. [Work funded by the Norwegian Research Council (NANOMAT programme). Epitarget AS is acknowledged for the supply of liposomes.]

9:15

4aBB5. Ultrasound-enhanced drug delivery through sclera. Robin Shah and Vesna Zderic (Dept. of Elec. and Comp. Eng., The George Washington Univ., 801 22nd St. NW, Washington, DC 20052, zderic@gwu.edu)

Achieving an increase in drug delivery through the sclera is important in the treatment of the back of the eye diseases including macular degeneration, diabetic retinopathy, etc. Our objective is to utilize therapeutic ultrasound in enhancing drug delivery through the sclera. Porcine sclera was placed in a standard diffusion cell at a normal physiological temperature of 34 °C. Solution of sodium fluorescein, a hydrophilic drug-mimicking compound, was added to donor compartment, and receiver compartment was filled with saline. The sclera was exposed to ultrasound for 5 min (intensities 1.2–1.8 W/cm^2 and frequencies 0.5 to 5 MHz). After 60 min, solution samples were taken from the receiver compartment to determine the concentration of sodium fluorescein. The sclera permeability to the drug mimicking agent *in vitro* increased 3.5 times at 0.5 MHz (p-value of less than 0.05), 1.7 times at 1 MHz, 3.5 times at 3.5 MHz (p-value of less than 0.05), and 1.5 times at 5 MHz. The average temperature of the sclera during ultrasound exposure was 42 °C. No gross changes were observed in the sclera due to ultrasound application. Future work will focus on determination of optimal ultrasound parameters for the drug delivery through the sclera.

9:30

4aBB6. Direct observation of microbubble interactions with ex vivo microvessels. Hong Chen, Andrew A. Brayman, Michael R. Bailey, and Thomas J. Matula (Ctr. for Industrial and Medical Ultrasound, Appl. Phys. Lab., Univ. of Washington, Seattle, WA 98105, hongchen@apl.washington.edu)

The interaction between microbubbles with tissue is poorly understood. Experimental evidence, supported by numerical simulations, suggests that bubble dynamics is highly constrained within blood vessels. To investigate this further, a high-speed microimaging system was set up to study the effects of acoustically activated microbubbles on microvessels in ex vivo rat mesentery tissues. The microbubble-perfused tissues were placed under a microscope and insonified with MHz ultrasound. A variety of interactions was observed by a high-speed camera: arterioles, venules, and capillaries were all recorded to dilate and invaginate by activated microbubbles. For small diameter microvessels, dilation and invagination were nearly symmetric, and bubble-induced rupture of the vessel was observed at high pressure. For larger microvessels, the portion of the vessel nearest the bubble coupled the strongest to the bubble dynamics, and the extent of dilation was smaller than invagination. Tissue jetting toward the bubble was recorded in many cases. The interaction of multiple bubbles inside microvessels was also observed. Bubble oscillation, vessel wall velocity, and tissue jet velocity were quantitatively measured. Invagination of vessel walls, especially tissue jetting, may be the major mechanism for tissue injury by a bubble. [Work supported by NIH 5R01EB000350.]

9:45

4aBB7. Shell buckling enhances subharmonic behavior of phospholipid coated ultrasound contrast agent microbubbles. Jeroen Sijl, Timo Rozendal, Marlies Overvelde, Valeria Garbin, Benjamin Dollet, Nico de Jong, Detlef Lohse, and Michel Versluis (Phys. of Fluids Group, Univ. of Twente, Enschede, The Netherlands)

Subharmonic behavior of coated microbubbles can greatly enhance the contrast in ultrasound imaging. The threshold driving pressure above which subharmonic oscillations are initiated can be calculated from a linearized Rayleigh-Plesset-type equation. Earlier experimental studies on a suspension of phospholipid-coated microbubbles showed a lower threshold than predicted from traditional elastic shell models. Here we present an experimental study of the subharmonic behavior of individual BR-14 microbubbles (Bracco Research) with initial radii between 1.6 and 4.8 μm. The subharmonic behavior was studied as a function of the amplitude and the frequency of the driving pressure pulse. The radial response of the microbubbles was recorded with the Brandaris ultrahigh-speed camera, while the resulting acoustic response was measured with a calibrated transducer. It is shown that the threshold pressure is minimum near a driving frequency equal to half the resonance frequency of the bubble, as expected. We found a threshold pressure as low as 10 kPa for certain bubble sizes, which can be explained by the shell buckling model proposed by [Marmottant *et al.*, JASA (2005)]. We show that the origin of subharmonic behavior is a result of the discontinuous transition within the bubble shell from the elastic state to the tensionless buckling state.

10:00—10:30 Break

10:30

4aBB8. Shell buckling increases the nonlinear dynamics of ultrasound contrast agents at low acoustic pressures. Marlies Overvelde (Phys. of Fluids, Univ. of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands, m.l.j.overvelde@utwente.nl), Benjamin Dollet, Valeria Garbin (Univ. of Twente, Enschede, The Netherlands), Nico de Jong (Experimental Echocardiography, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands), Detlef Lohse, and Michel Versluis (Univ. of Twente, Enschede, The Netherlands)

The key feature of ultrasound contrast agents in distinguishing blood pool and tissue echoes is based on the nonlinear behavior of the bubbles. Here we investigate the nonlinear properties of the shell which lead to an increased nonlinear bubble response, especially at low acoustic pressures. The microbubbles were studied in free space away from the wall using the Brandaris camera coupled to an optical tweezers setup. The microbubble spectroscopy method [Van der Meer et al., JASA, **121**, 648 (2007)] was employed to characterize BR-14 microbubbles (Bracco, Geneva). For increasing applied pressures the bubble resonance curves become asymmetrical and the frequency of maximum response decreases, up to 50% at a pressure of 25 kPa. It was found that the skewing of the nonlinear resonance curve is the origin of the so-called thresholding behavior below resonance. Traditional bubble models account for a purely elastic shell predict linear behavior, whereas the shell buckling model by Marmottant et al. [JASA, **118**, 3499