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Acoustic bubbles in therapy: recent advances with  
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Guest editors:

Michiel POSTEMA<sup>1,2,3,\*</sup>, Ayache BOUAKAZ<sup>1</sup>

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# Acoustic bubbles in therapy: recent advances with medical microbubbles, clouds, and harmonic antibubbles

Guest editors:

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## Editorial

Although the use of microbubbles has become common in ultrasound diagnostics, microbubbles are not that often seen in therapeutic applications. To share recent advances in the development and application of microbubbles in therapy, LE STUDIUM Loire Valley Institute for Advanced Studies and Inserm Research unit U1253: Imaging and Brain of the University of Tours organised an international conference on this topic. The event was held on 23 and 24 October, 2017, in the Hôtel de Ville of Tours, France, and hosted by Michiel Postema and Ayache Bouakaz from the University of Tours.

Plenary sessions covered a wide range of topics, including bubble physics, bubble acoustic phenomena, bubble engineering and design, *in-vitro* evaluation, preclinical validations, and clinical studies. The conference was attended by 70 scientists, medical professionals, and industrial representatives (*cf.* Figure 1).

The opening session on sonochemotherapy was chaired by Annemieke van Wamel from the Norwegian University of Science and Technology and Michiel Postema from the University of the Witwatersrand, Johannesburg, in residence at the University of Tours. The keynote lecture by Pintong Huang from the Second Affiliated Hospital of Zhejiang University School of Medicine was on

the antitumour efficacy of ultrasonic cavitation combined with drug-loaded microbubbles when targeting tumour angiogenesis in a fluorescent human colon cancer mouse model [1]. Jean-Michel Escoffre from the University of Tours presented a study on the delivery of cetuximab to colorectal cancer using microbubble-assisted ultrasound [2]. Diane Bressand-Falewee from the University of Tours presented an *in-vitro* and *in-vivo* evaluation of the delivery of Nab-Paclitaxel in pancreatic tumours with sonoporation. Spiros Kotopoulos from Haukeland University Hospital lectured on low-intensity sonoporation from lab to patient bedside and elaborated on what we know and where to go from here [3].

Following a live hydrophone demonstration by Andrew Hurrell and Jessica Dendura, both from Precision Acoustics Ltd [4], the session on bubble imaging was chaired by Paul Prentice from the University of Glasgow and Steven Wrenn from Drexel University. Invited speaker Steven Freear from the University of Leeds spoke about ultrafast plane-wave imaging for nonlinear detection of therapeutic microbubbles [5]. Katrien Vanderperren from Ghent University gave a presentation on contrast-enhanced ultrasound of kidneys in hyperthyroid cats [6]. Erik Verboven from Ghent University presented a study on ultrasound-based dosimetry for radiotherapy, including the *in-vitro* and *in-vivo* proof-of-principle.

The session on acoustic cluster therapy was chaired by Katrien Vanderperren from Ghent University and Olivier Couture from the Langevin Institute. The speakers had been kindly invited by Phoenix Solutions. Per Sontum from Phoenix Solutions gave the introductory talk, titled “Acoustic cluster therapy — a novel approach for ultrasound-mediated targeted drug delivery: technology basics and proof of concept” [7]. Invited speaker Annemieke van Wamel from the Norwegian University of Science and Technology showed that acoustic cluster therapy boosts the delivery of drugs in brains and tumours [8]. Invited speaker Paul Prentice from the University of Glasgow spoke of shocking bubbles: cavitation in focussed ultrasound [9]. Keynote speaker Nobuki Kudo from Hokkaido University demonstrated a high-speed observation system for elucidating mechanisms of sonoporation [10].

The session on new insights in therapeutic bubbles was chaired by Benoît Larrat from the Alternative Energies and Atomic Energy Commission and Albert Poortinga from Eindhoven University of Technology. Key-note speaker Eitan Kimmel from Technion — Israel Institute of Technology spoke about acoustics in medicine in view of the intramembrane cavitation model [11]. Vincent Hingot from the Langevin Institute lectured on subwavelength far-field

ultrasound-targeted drug delivery [12]. Bjoern Gerold from Theraclion discussed the efficiency and safety issues when controlling cavitation in focussed ultrasound surgery [13].

Frédéric Patat from the University of Tours gave an invited public lecture on the many facets of ultrasound, including detecting, seeing, and treating [14]. This lecture was attended by 100 interested people from Tours.

The session on bubbles, antibubbles, and droplets was chaired by Christine Contino-Pépin from the University of Avignon and Charles Sennoga from the University of Tours. Invited speaker Albert Poortinga from Eindhoven University of Technology lectured on a new kind of acoustic bubble, called the antibubble [15, 16]. Steven Wrenn from Drexel University presented a voltage-activated ultrasound contrast agent for myocardial perfusion imaging [17]. Stéphane Desgranges from the University of Avignon demonstrated stable formulations of perfluorocarbon droplets for tumour detection and treatment [18]. Sigrid Berg from SINTEF and the Norwegian University of Science and Technology spoke about nanoparticle-stabilised microbubbles and ultrasound for enhanced drug delivery [19].

The session on the blood–brain barrier was chaired by Jean-Michel Escoffre from the University of Tours and Spiros Kotopoulis from Haukeland University Hospital. Invited speaker Alexandre Carpentier from Sorbonne University lectured on low-intensity pulsed ultrasound to disrupt the blood–brain barrier followed by intravenous carboplatin chemotherapy in patients with recurrent brain tumours [20]. Invited speaker Benoît Larrat from the Alternative Energies and Atomic Energy Commission followed with MRI-guided ultrasound-mediated blood–brain barrier opening in non-human primates using passive cavitation detection feedback control [21]. Barbara Cerroni from the University of Rome Tor Vergata spoke about targeting brain tumour vasculature with RGD-decorated microbubbles [22].

Although the posters were on display throughout the conference, a dedicated poster session has held as well. Nigel Bush from the Institute of Cancer Research showed with a poster that acoustic cluster therapy enhances the therapeutic efficacy of Doxil<sup>TM</sup> for treatment of triple negative breast cancer in mice [7]. Anastasiia Panfilova from Eindhoven University of Technology had a poster presentation on the relation between contrast-ultrasound kinetic features and microvascular density by acoustic angiography [23]. Katrien Vanderperren from Ghent University presented a poster on renal ageing in cats assessed by contrast-enhanced ultrasound [24] and a poster on the evaluation of renal perfusion using contrast-enhanced ultrasound in cats with chronic

kidney disease [25]. Letizia Oddo from the University of Rome Tor Vergata showed in a poster the next generation of ultrasound platforms for theranostics [22]. Florian Gailliègue from Institut Gustave Roussy showed a poster with numerical and experimental characterisation of a biochip for sonoporation studies [26]. Emma Kanbar from the University of Tours presented a poster on enhanced subharmonics by acoustic deflation [27]. Simona Turco from Eindhoven University of Technology demonstrated a poster on the pharmacokinetic modelling of targeted microbubbles and the applications thereof in angiogenesis imaging and therapy monitoring [28]. Stéphane Desgranges from the University of Avignon presented a poster on optimised perfluorocarbon nanodroplets for theranostics applications [18]. Nicolas Taulier from the University of Avignon gave a poster presentation on the encapsulation of drugs in perfluorocarbon droplets and drug delivery triggered by HIFU [29]. Nasma Mazzawi from Technion — Israel Institute of Technology showed in a poster the effect of low-intensity ultrasound and MET signalling on cancer cell motility for improved diagnosis and treatment [30]. Jean-Louis Mestas from the University of Lyon 1 presented a poster on doxorubicin delivery in CEM and MDA cell lines without contrast agent [31].

Parallel to the poster session, a representative from La Cellule Mutualisée « Europe-Recherche » gave a presentation on funding opportunities in the EU Horizon 2020 framework programme.

The session on bubble dynamics was chaired by Nobuki Kudo from Hokkaido University and Eitan Kimmel from Technion — Israel Institute of Technology. Invited speaker Alexander Doinikov from Université Grenoble-Alpes lectured on the dynamics of bubbles in a confined space [32, 33]. Kristoffer Johansen from the University of Glasgow presented a comparison of single-bubble and cloud models for non-stable cavitation and the emissions generated [9]. Mounir Tarek from the University of Lorraine spoke about the generation and outcome of reactive oxygen species produced by ultrasound-stimulated microbubbles, unraveling a potential mechanism for sonoporation using molecular simulations. Claude Inserra from the University of Lyon 1 showed the threshold, dynamics, and nonlinearity of nonspherical oscillations of gas microbubbles [34, 35].

In conclusion, the conference brought together scientists, medical professionals, and industrial representatives, who shared their most recent findings. We trust that, in the near future, many collaborative projects will be initiated owing to the inspirational multidisciplinary environment and the high scientific level of the presentations at this first conference on acoustic bubbles

in therapy.



Figure 1: Participants of the first conference on acoustic bubbles in therapy: recent advances with medical microbubbles, clouds, and harmonic antibubbles, Tours, 2017.

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