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Future Directions for Therapeutic Ultrasound

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To the Editor-in-Chief:

Therapeutic applications of ultrasound, including microbubble-enhanced sonoporation, are stimulating widespread research activity aimed at both the characterization and control of ultrasonically mediated bioeffects. Advances in this field were recently reported and discussed at the *Scottish Sonoporation Symposium* held in August 2006 at the University of Dundee. This meeting, of close to 50 experts from the United Kingdom and abroad, stimulated an assessment of future directions for therapeutic ultrasound, which prompted us to write this letter.

Modern medical ultrasonics may be viewed as having evolved through three generations of applications. The first generation emphasizes diagnostic imaging, employing ultrasound fields not intended to have tissue effects. The second generation has deliberately exploited more aggressive ultrasound regimes for direct interventional approaches, including lithotripsy (of ductal calculi), phacoemulsification (of cataracts), and high intensity focused ultrasound (HIFU) for tumour ablation, thrombolysis, and haemostasis.

A third and emerging area involves an indirect therapeutic application of ultrasound to sensitize tissue actively, or otherwise enhance the efficacy for parallel administration of biotherapeutics. Here, particular progress has been achieved with ultrasound assisted transdermal delivery. However, this has been facilitated, in part, because the target tissue (i.e., stratum corneum) is non-viable. Perhaps the most challenging avenue for therapeutic ultrasound is to facilitate molecular delivery whilst retaining tissue viability, the criteria necessary for drug- and gene-based therapies. Excitingly, initial *in vitro* demonstrations of enhanced transfection, and also increased sensitivity to chemotherapeutic agents, have now also been realized with compelling *in-vivo* validations.

Evidently, this latter category of ultrasound-mediated therapy holds promise for a diversity of potential uses. However, reducing the multiplicity of these abstract possibilities to the more refined base of concrete realizations that are best suited to ultrasonic enhancement requires strategic action. Targeting research with the greatest impact requires an understanding of the strengths and weaknesses of ultrasonic bioeffects, which remain poorly understood at a mechanistic level. This situation hinders insight and indeed foresight into the future of this field.

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A first subject that requires additional analysis is the nature of ultrasound that is most desirable for a given application. Useful bioeffects may be generated using ultrasound regimes that straddle the spectrum of available thermal and mechanical indices. Are the primary effects of ultrasound itself responsible for bioeffects, or are secondary effects involving shock waves, fluid shearing, and sonochemistry involved? If so, what is the relative importance of each in dictating overall bioeffect? Which forms of ultrasonic effects are responsible for increased sensitivity to gene transfection, to cancer therapy, to intracellular drug delivery? Can ultrasonic effects that are effective *in vitro* be reproduced *in vivo*, where perfusion of cavitation nucleation sites (e.g., contrast agent) and stimulation of bubble activity in the dense environment of a solid tissue may be difficult? Can isolated cell and single-bubble experiments *in vitro* predict behaviour of multicellular tissue exposure to bubble clouds found *in vivo*? Finally, which physical properties should micro-bubbles exhibit in order to target specific therapies, and how should ultrasound transducers be designed to control and optimize cavitation and other activity within the body?

A second subject area requiring attention involves the formal identification of those bioeffects that are most desirable, and indeed those which must be avoided, for a given application? Downstream effects of, for example, increased gene expression are clearly desirable for gene therapy, but what intermediate effects, and side effects, contribute to that end product? Is gene expression enhanced by increased intracellular delivery of DNA across the plasma membrane and possibly the nuclear membrane? If so, what are the short-term and long-term side effects of cell membrane disruption? Is gene expression enhanced by more efficient DNA processing by the cell mediated by activation of to-be-determined biochemical processes, and what are the side effects of this activation? In other contexts, ultrasound has been shown to stimulate heat shock protein release, activate apoptosis, and increase intracellular calcium levels. What other cellular and physiological pathways are influenced by ultrasound and are they stimulated by direct pressure oscillations, heating, or cavitation activity?

Finally, which strategic and infrastructural resources, and collaborative alliances are required, at local, national and international levels, to address the objectives outlined above? It will be critical to foster this research environment, because answers to these questions will both highlight and constrain the most suitable applications for impact on healthcare.

Drug delivery, gene therapy and other therapeutic applications of ultrasound offer exciting possibilities motivated by compelling *in vitro* and *in vivo* results. However, progress in the field is clearly limited by a lack of mechanistic understanding. Addressing mechanistic issues, including the list of questions posed here, will help elucidate the most appropriate future directions for therapeutic ultrasound and, thereby, motivate focused work on the concrete subset of applications most suited to ultrasonic enhancement.