The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL: ESR8 (UCOM)

PROJECT DETAILS	
Project Title:	Development of therapeutic ultrasound applications based on acoustic cavitation (ESR8)
Short Project Title:	**Therapeutic ultrasound cavitation**
SUPERVISORY TEAM	
Primary Supervisor:	Gail ter Haar
Associate Supervisor:	Ian Rivens
Backup Supervisor:	Emma Harris
Lead contact person for the project:	Gail ter Haar
DIVISIONAL AFFILIATION	
Primary Division:	Division of Radiotherapy and Imaging
Primary Team:	Therapeutic Ultrasound
PROJECT PROPOSAL	

BACKGROUND TO THE PROJECT

The ICR is a member of an exciting new EU funded innovative training network (ITN) which aims to exploit EU wide experience of industrial and biomedical ultrasound cavitation and sonochemistry. This ambitious overall programme will take a systematic approach towards understanding ultrasound cavitation better using a combination of experiments and simulations. The ITN includes academic and non-academic partners from the EU, Switzerland and Singapore, and beneficiaries and partners from medical/biomedical fields.

From the experimental point of view, the research programme focuses on the onset of cavitation in tissue and tissue mimicking materials, ultrasound assisted drug delivery techniques, bubble cleaning, fundamental bubble dynamics and shock tube tests.

At a theoretical/numerical level, the focus is placed on developing, improving and validating new state-of-the-art tools for ultrasound cavitation modelling in tissue and tissue mimics, heterogeneous bubble nucleation at walls, shock wave/bubble interaction (including deformable surfaces/cell membranes) and chemical reactions inside collapsing bubbles.

The proposed work will provide a unique training opportunity for the student who will gain knowledge, skills and expertise through state-of-the-art experimental and simulation methods, alongside gaining experience at the premises of internationally renowned universities, biomedical research institutes and industry, and core studies at their host institution.

The therapeutic ultrasound team at the ICR has a world-leading reputation as a result of its extensive experience in developing and implementing ultrasound based therapeutic approaches to cancer treatment. Most recently, we have been looking at a therapeutic approach that exploits ultrasound cavitation using pulsed exposures, often referred to as histotripsy.

Applications are invited for a 4 year PhD studentship (aka Early Stage Researcher or ESR position). The first 3 years are EU funded and the 4th year is funded by the ICR. The preferred state date for the projects is June 2019.

Applicants must be able to demonstrate that they have spent fewer than 12 months working in the UK in the last 3 years, and should have a minimum of a BSc, but preferably an MSc, in a relevant physical science or engineering subject, and be able to demonstrate strong experimental and mathematical modelling capabilities.

For more information please contact Professor Gail ter Haar: gail.terhaar@icr.ac.uk.

If you wish to apply, please do so via: https://euraxess.ec.europa.eu/jobs/326464 (ICR projects are listed as ESR7 and ESR8).

PROJECT AIMS

- **Development of methods of analysing acoustic cavitation signals**
- **Determine the cavitation threshold for a range of fresh mammalian tissues under different physiological and ultrasound exposure conditions**
- **Determine the nuclei content of tissue mimicking materials developed by ESR7**
- **Determine the cavitation threshold for tissue mimicking materials developed by ESR7 for different exposure conditions**
- **Develop mathematical models to describe bubble activity under different exposure conditions.**
- **Validate mathematical models produced in appropriate phantoms**

RESEARCH PROPOSAL

Ultrasound at sufficiently high peak negative pressures can cause the ex-solution of dissolved gases and thus the formation of microbubbles. The pressure thresholds for such bubble nucleation vary significantly between different tissues and different materials. Furthermore, the microbubbles can undergo different types of oscillation once formed. At lower pressures, bubbles may oscillate in a "stable" manner whilst at higher pressures the bubbles may undergo "inertial" cavitation resulting in bubble collapse (implosion). Bubbles undergoing different activity will emit acoustic signals that differ in nature and potentially allow the type of activity to be externally monitored. Therapeutic ultrasound normally exploits the use of a focused beam to achieve the desired destructive effect within the focus while sparing surrounding and overlying tissues. As a result, a significant tissue volume is exposed at any one time, and it is likely that multiple bubbles will be produced and that different cohorts of these will be undergoing different behaviours during any exposure.

ESR10's first objective will be to review the existing literature and to determine ways of measuring acoustic cavitation thresholds, and identify methods for cavitation detection data analysis (McLaughlan et al., 2010). For sustainable acoustic cavitation, it will be necessary to monitor bubble activity in real-time in order to implement feedback mechanisms that allow exposure modulation in order to achieve this.

ESR10 will undertake extensive cavitation threshold characterisation in a range of clinically relevant tissues such as skin, fat, muscle, and major organs (e.g. liver, kidney, brain, etc). Measurements will be made at a range of temperatures relevant to therapeutic applications of ultrasound, and for a clinically relevant range of exposure conditions ranging from those for drug delivery up to those for bubble induced tissue damage (histotripsy). Cavitation characterisation will also be undertaken in a range of clinically relevant tissue mimicking materials

identified by another ICR PhD student (ESR7).

Knowledge of the properties of tissue mimics will be shared with the UCOM consortium so that ESRs in other establishments can investigate their fluid dynamics, cavitation and chemical properties both numerically and experimentally. Ultimately this will allow tissue mimics to be used in studies for shock wave device design, allowing further studies of dependence on pulse type, mechanisms of damage and the importance of heating effects, as well as studies aimed at controlling the stochastic nature of cavitation.

Mathematical models will be developed in collaboration with other UCOM consortium members to model bubble formation and activity within tissue and tissue mimics in order to investigate the best ultrasound exposure conditions to achieve therapeutic outcomes e.g. (Singhal et al., 2002, Kreider et al., 2011). The modelling will be validated using a bespoke phantom in which to simulate ultrasound enhanced drug delivery developed by ESR7.

Outcomes:

1. Development of cavitation data analysis methods
2. Development of cavitation monitoring with up to real-time performance
3. Comprehensive list of acoustic cavitation thresholds in tissues/tissue mimics
4. Development of mathematical models of ultrasound cavitation in tissue/tissue mimics
5. Model validation in a tissue mimicking phantom

LITERATURE REFERENCES

HILL, BAMBER, TER HAAR (Ed) Physical Principles Of Medical Ultrasonics, Ed (Second Edn) Pub. John Wiley & Sons, 2004

JENSEN, C. R., RITCHIE, R. W., GYONGY, M., COLLIN, J. R., LESLIE, T. & COUSSIOS, C. C. 2012. Spatiotemporal monitoring of high-intensity focused ultrasound therapy with passive acoustic mapping. *Radiology,* 262**,** 252-61.

LAUTERBORN, W., KURZ, T., GEISLER, R., SCHANZ, D. & LINDAU, O. 2007. Acoustic cavitation, bubble dynamics and sonoluminescence. *Ultrason Sonochem,* 14**,** 484-91.

MCLAUGHLAN, J., RIVENS, I., LEIGHTON, T. & TER HAAR, G. 2010. A study of bubble activity generated in ex vivo tissue by high intensity focused ultrasound. *Ultrasound Med Biol,* 36**,** 1327-44.

SINGHAL, A. K., ATHAVALE, M. M., LI, H. & JIANG, Y. 2002. Mathematical Basis and Validation of the Full Cavitation Model. *Journal of Fluids Engineering,* 124**,** 617.

XU, Z., FOWLKES, J. B. & CAIN, C. A. 2006. A new strategy to enhance cavitational tissue erosion using a high-intensity, Initiating sequence. *IEEE Trans Ultrason Ferroelectr Freq Control,* 53**,** 1412-24.

KREIDER, W., CRUM, L. A., BAILEY, M. R. & SAPOZHNIKOV, O. A. 2011. A reduced-order, single-bubble cavitation model with applications to therapeutic ultrasound. *J Acoust Soc Am,* 130**,** 3511-30.

CANDIDATE PROFILE

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)

Pre-requisite qualifications of applicants: e.g. BSc or equivalent in specific subject area(s)	BSc is essential, MSc desirable
Intended learning outcomes: Please provide a bullet point list (maximum of seven) of the knowledge and skills you expect the student to have attained on completion of the project.	Characterisation methodology Data analysis techniques Scientific rigor Mathematical modelling

	Experimental design Scientific writing and publication
ADVERTISING DETAILS	
Project suitable for a student with a background in:	☐ Biological Sciences ☒ Physics or Engineering ☐ Chemistry ☐ Maths, Statistics or Epidemiology ☐ Computer Science ☐ Other (provide details)
Keywords: Please provide 4-6 words/short phrases that potential students may type into search engines (e.g. Google) to search for PhDs similar to yours – e.g. 'cancer predisposition genes', 'physics PhD London' etc.	**1. acoustic cavitation**
	2. Ultrasound enhanced drug delivery
	3. Tissue characterisation
	4. Mathematical modelling and validation
	5.
	6.
FUNDING (only complete this section if this project already has full/partial funding)	
☒ This project is fully funded	*Full-funding details (this must include stipend, fees and consumables) including the source of funding:* ***UCOM EU funded ITN full funds first 3 years, ICR underwrote the costs of the 4th year at the time of application***