Project Acronym: SOUNDPET

(INTEGRATED/0918/0008)

MRI-guided Focused ultraSOUND system for cancer in PETs (dogs and cats)

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Title: Presentation at a scientific conference

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Antria Filippou (CUT)

Date: 30/06/2023

SOUNDPET
Animal therapies with focused ultrasound

Ευρωπαϊκή Ένωση
Ευρωπαϊκά Διαρθρωτικά και Επενδυτικά Ταμεία

Κυπριακή Δημοκρατία

Διαρθρωτικά Ταμεία της Ευρωπαϊκής Ένωσης στην Κύπρο

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Executive summary

This deliverable presents the Conference papers that were presented during the 3rd reporting period of the SOUNDPET project. The papers covered multiple topics related to Focused Ultrasound (FUS), including the development of robotic systems for FUS applications in small animal models and pets, the development of tumor-bearing gel phantoms for Magnetic Resonance Imaging (MRI)-guided FUS applications, as well as the FUS ablation of naturally occuring mammary tumors in pets. Causion was given to avoid disclosure of the SOUNDPET system's features and components prior to the relevant patent application.

Table 1 lists the title and type (oral/poster) of each paper, along with the name and dates of the conference at which it was presented. The oral and poster presentations given can be found in the Appendix (in the order they appear in Table 1).

It is noted that some of the research work carried out under the SOUNDPET project was a synergy with other projects running at the same time.

Table 1: List of conference papers presented during the 3rd reporting period of the SOUDNPET project.

#	Title	Conference	Date	Type	Online/ In-person
1	Two simple 3D printed robotic systems for opening the blood brain barrier of small animals	*8th International symposium on Focused ultrasound*, Bethesda, USA	23-25 October 2022	Oral	Online
2	Challenges regarding MR compatibility of an MRGFUS robotic system	*13th Interventional MRI Symposium*, Leipzig, Germany	14-15 October 2022	Poster	In person
3	Focused Ultrasound Ablation Of Canine Mammary Cancer	*UltraCon Annual Meeting 2023*, Orlando, Florida, USA	25-29 March 2023	Poster	In person
4	Focused Ultrasound Phantom With Inclusion Of Tumour	*UltraCon Annual Meeting 2023*, Orlando, Florida	25-29 March 2023	Poster	In person
5	MRI guided focused ultrasound system for veterinary oncology	*12th Veterinary Forum on companion animal medicine*, Thessaloniki, Greece	01-02 April 2023	Poster	In person
6	T1 and T2 values of an Agar-based phantom with inclusion of tumour	*12th Veterinary Forum on companion animal medicine*, Thessaloniki, Greece	01-02 April 2023	Poster	In person
7	Treatment of cancer with focused Ultrasound in cats and dogs	*The 22nd Annual International Symposium on Therapeutic Ultrasound (ISTU)*, Lyon, France	17-20 April 2023	Poster	In person
8	Ultrasound and MRI guided focused ultrasound system for veterinary applications	*The 29th annual international conference of the Australian sonographers association*, Brisbane, Australia	26-28 May 2023	Oral	In person
9	MR thermometry for a multipurpose phantom for focused ultrasound	*6th International Caparica Conference on Ultrasonic-based applications from analysis to synthesis*, Caparica, Portugal	26–29 June 2023	Poster	In person
10	Opening of the Blood-brain barrier using focused ultrasound with simultaneous delivery of anti-Aβ antibodies in a 5XFAD amyloid beta mouse model	*6th International Caparica Conference on Ultrasonic-based applications from analysis to synthesis*, Caparica, Portugal	26–29 June 2023	Poster	In person

Submitted abstracts

1. 8th International symposium on Focused ultrasound, Bethesda, USA

Two simple 3D printed robotic systems for opening the blood brain barrier of small animals.

Anastasia Antoniou, Marinos Giannakou, Christakis Damianou

Electrical Engineering department, Cyprus University of Technology.

Abstract

Background: Two different 3D printed robotic systems have been developed for accessing small animals (rats and mice). The first one is a two axes robotic system for navigating a single element HIFU transducer. The second robotic includes a motorized vertical axis to deliver HIFU into the brain of the animal. The devices were engineered to facilitate opening of blood brain barrier (BBB).

Methods: Microbubbles in synergy with pulsed ultrasound were administered to wild type mice for the disruption of the BBB. Both robotic systems are MR compatible. Both robotic devices are driven by piezoelectric motors. A single element transducer operating at a frequency of 1 MHz was used to penetrate the intact scull.

Results: Both systems were evaluated in mice for BBB opening using microbubbles and a pulse ultrasound protocol. After performing experiments in 10 mice, the protocol was calibrated properly to open the BBB as it was evidence by Evans blue staining.

Conclusions: BBB opening was achieved with both robotic systems. The first device presented some difficulties in accommodating the anesthesia needle. This issue was addressed and solved with the proper design of the second version. The first robotic system can be used also for medium size animals such as rabbits.

2. 13th Interventional MRI Symposium, Leipzig, Germany

Challenges regarding MR compatibility of an MRgFUS robotic system

Nicolas Evripidou, Marinos Giannakou, Christakis Damianou
Department of Electrical Engineering, Computer Engineering, and Informatics,
Cyprus University of Technology, Limassol, Cyprus.

ABSTRACT

Background: This study presents a comprehensive assessment of the MRI compatibility issues of Magnetic Resonance guided Focused Ultrasound (MRgFUS). The effect of coil type, target size and coil placement are a few of the conditions examined. In the effort to minimize image distortion and interference with the magnet, various set-up parameters were examined.

Methods: The experiments were performed in a 1.5 T and 3 T MRI scanners. The main quantity measured for MRI compatibility was the signal to noise ratio (SNR). Measurements were carried out in a tissue mimicking phantom and freshly excised tissue under various activation states of the robotic system and ultrasonic transducer.

Results: Significant image distortion occurred when the transducer was activated due to coil and target vibrations and was getting worse as the output power was increased. It was proven that the use of a multi-channel fixed coil and a stable target was critical in increasing SNR. The motors and associated electronics should be placed outside the coil detection area so that image quality is not jeopardized. It is also crucial to have the encoders' counting pulses turned off during image acquisition since this was also shown to increase SNR remarkably. The SNR in a 3 T was much highr than the 1.5 T, and therefore it is easier to place focused ultrasound systems in higher field MRIs

Conclusions: The study contributes towards addressing major challenges regarding operation of an MRgFUS system in the MRI environment and raises awareness for potential sources of noise and distortion to researchers in the field. Although many years ago placing electronic systems in the MRI was challenging, it is now a common routine.

Focused Ultrasound Ablation Of Canine Mammary Cancer

Anastasia Antoniou, Nikolas Evripidou, Christakis Damianou*

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* *Corresponding author. email: christakis.damianou@cut.ac.cy*

ABSTRACT

Objectives

Veterinary medicine is continuously expanding its applications beyond traditional approaches. In this regard, the Focused Ultrasound (FUS) technology has many potential applications, including tumor destruction, drug delivery, pain relief, and noninvasive spaying. The current study examined the feasibility of FUS in the treatment of naturally occurring canine superficial mammary cancer using an existing preclinical MRI-compatible FUS robotic system.

Methods

The robotic system utilized comprises a positioning mechanism for navigating a single element spherically focused transducer of 2.6 MHz in four PC-controlled axes. For each cage dog (n=5), the system was installed in the respective veterinary clinic. The dog was comfortably positioned on the device so that the tumour is located in the acoustic opening directly above the FUS transducer. Degassed water was used for ultrasonic coupling. The treatment protocol was adjusted based on the tumour size and location. The motion and ultrasonic parameters were controlled through dedicated FUS software. Post-sonication the tumours were removed and sent for histological examination.

Results

All procedures were implemented successfully, with no recorded adverse events compromising pet welfare. Hematoxylin and eosin (H&E) staining demonstrated well-defined regions of coagulative necrosis in the treated tumours with no off-target damage, except from minor red blood cell extravasation observed in some cases at the borderline of thermal lesions.

Conclusions

In this study, FUS ablation of canine mammary cancer under proper monitoring was proven safe and feasible. The FUS robotic system and related software offered an efficient procedural workflow. Veterinary clinical trials offer the opportunity for FUS to benefit family pets by providing them an alternative non-invasive cancer treatment.

4. UltraCon Annual Meeting 2023, Orlando, Florida, USA

Focused Ultrasound Phantom With Inclusion Of Tumour

Christakis Damianou*, Anastasia Antoniou, Nikolas Evripidou

Department of Electrical Engineering, Computer Engineering, and Informatics, Cyprus University of Technology, Limassol, Cyprus.

* *Corresponding author. email: christakis.damianou@cut.ac.cy*

ABSTRACT

Objectives
An agar-based mimicking material which includes a tumour was developed. The phantom can be used to evaluate the temperature produced by a focused ultrasound transducer.

Methods
The tumour model was made out of water, agar (6 % w/v) and 4 % w/v silica. In the tissue surrounding the tumour no silica was used.

Results
The slight difference in silica content between tumour and surrounding tissue resulted in excellent contrast between tumour and tissue in Magnetic Resonance Imaging (MRI). Based on coronal images showing the transducer and tumour/tissue it was possible to precisely move the focused ultrasound beam within the phantom using an MR compatible positioning device. MR temperature was detected within the tumour and outside the tumour. T1 and T2 values were measured in a 3 T MRI.

Conclusions
Due to the inclusion of silica in the tumour the absorption was increased within the tumour, and therefore, higher temperatures were measured in the tumour. Temperature across a plane parallel to the beam showed some deflection of the beam in areas of tumour curvature. This is an excellent tumour model that can be used to evaluate the physics of focused ultrasound.

5. 12th Veterinary Forum on companion animal medicine, Thessaloniki, Greece

MRI guided focused ultrasound system for veterinary oncology

Damianou C.,[1] Spanoudes K.,[2]

[1]PhD, Professor, University of Technology, Limassol, Cyprus

[2]DVM, PhD student, VET EX MACHINA LTD, Nicosia, Cyprus

Introduction: In this paper Focused Ultrasound (FUS) technology was used for veterinary oncology applications. This modality is an additional tool beyond traditional approaches. In this study we investigated the ability of FUS to precisely ablate hypothetical targets mimicking canine and feline tumours

Materials and methods: Agar based targets were ablated with a Magnetic Resonance guided FUS (MRgFUS) robotic system featuring a single element spherically focused transducer of 2.7 MHz. The robotic system includes 3 linear cartesian axes**.**

Results: The MRgFUS system was capable of producing well-defined overlapping lesions in the mimicking tumours. The tumour mimicking phantom was imaged using MRI**.**

Conclusions: This technology has potential as a therapeutic solution for veterinary cancer. Although the device is MRI compatible, it can be used also outside the MRI setting using ultrasonic imaging. The next step is to apply this technology in animals and in humans.

Reference: Spanoudes K., Evripidou N., Giannakou M., Drakos T, Menikou G., Damianou C. (2021) A high intensity focused ultrasound system for veterinary oncology applications. J. Med. Ultrasound 29, 195-202.

T1 and T2 values of an Agar-based phantom with inclusion of tumour

Damianou C.,[1] Spanoudes K.,[2]

[1]PhD, Professor, University of Technology, Limassol, Cyprus

[2]DVM, PhD student, VET EX MACHINA LTD, Nicosia, Cyprus

Introduction: An agar-based mimicking material which includes a tumour was developed. The phantom can be used to evaluate the temperature produced by a focused ultrasound transducer.

Materials and methods: The tumour model was made out of water, agar (6 % w/v) and 4 % w/v silica. In the tissue surrounding the tumour no silica was used.

Results: The slight difference in silica content between tumour and surrounding tissue resulted in excellent contrast between tumour and tissue in Magnetic Resonance Imaging (MRI). Based on coronal images showing the transducer and tumour/tissue it was possible to precisely move the focused ultrasound beam within the phantom using an MR compatible positioning device. MR temperature was detected within the tumour and outside the tumour. T1 and T2 values were measured in a 3 T MRI.

Conclusions: Due to the inclusion of silica in the tumour the absorption was increased within the tumour, and therefore, higher temperatures were measured in the tumour. Temperature across a plane parallel to the beam showed some deflection of the beam in areas of tumour curvature. This is an excellent tumour model that can be used to evaluate the physics of focused ultrasound.

Reference: Antoniou, A., Damianou, C. (2022) Simple, inexpensive, and ergonomic phantom for quality assurance control of MRI guided Focused Ultrasound systems. J Ultrasound (https://doi.org/10.1007/s40477-022-00740-w)

7. The 22nd Annual International Symposium on Therapeutic Ultrasound (ISTU), Lyon, France

Treatment of cancer with focused Ultrasound in cats and dogs

Anastasia Antoniou, Nikolas Evripidou, Kyriakos Spanoudes, Christakis Damianou

Department of Electrical Engineering, Computer Engineering, and Informatics,

Cyprus University of Technology, Limassol, Cyprus.

ABSTRACT

The current study is a feasibility study using MRI guided focused ultrasound (FUS) for the treatment of canine and feline cancer therapy.

FUS was delivered by a 2-MHz single-element spherically MRI compatible focused ultrasonic transducer which was integrated with an existing robotic positioning device. The functionality of the FUS system and sonication protocol in efficiently and safely ablating live tissue was initially validated in a rabbit thigh model in laboratory environment. The positioning device had 4 computer-controlled axes.

Eleven (11) referrals for dogs and cats with superficial mammary cancer were collected through a national recruitment champagne, from which 9 were considered to fulfill the set safety criteria. The eligible veterinary patients underwent FUS ablation followed by immediate surgical resection of the entire malignancy.

Histopathology examination demonstrated well-defined regions of coagulative necrosis in all treated tumors with no damage in the surrounding tissue. Further study with a larger patient population for other type of tumours is needed to confirm the findings and demonstrate the feasibility of thermal FUS to safely ablate deep seated tumors.

Keywords: high intensity focused ultrasound; mammary cancer; robotic device; thermal ablation; dogs; cats

8. The 29th annual international conference of the Australian sonographers association, Brisbane, Australia

Ultrasound and MRI guided focused ultrasound system for veterinary applications

Nikolas Evripidou, Anastasia Antoniou, Christakis Damianou

Department of Electrical engineering, Computer engineering and Informatics, Cyprus University of Technology

Objective: In this paper Focused Ultrasound (FUS) technology was used for oncology applications for veterinary applications. This modality is an additional tool beyond traditional approaches. In this study we investigated the ability of FUS to precisely ablate hypothetical targets mimicking canine and feline tumours

Material and methods:

Agar based targets were ablated with a Magnetic Resonance guided FUS (MRgFUS) robotic system featuring a single element spherically focused transducer of 2.7 MHz. The robotic system includes 3 linear cartesian axes.

Results

The MRgFUS system was capable of producing well-defined large lesions produced by navigating the transducer in a grid formation with 3 mm step in the mimicking tumours. The tumour mimicking phantom was imaged using ultrasound imaging and MRI.

Conclusions

This technology has potential as a therapeutic solution for veterinary cancer. Although the device is MRI compatible, it can be used also outside the MRI setting using ultrasonic imaging. The next step is to apply this technology in animals and in humans.

9. 6th International Caparica Conference on Ultrasonic-based applications from analysis to synthesis, Caparica, Portugal

MR thermometry for a multipurpose phantom for focused ultrasound

Christakis Damianou*, Nikolas Evripidou, Andreas Georgiou

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* christakis.damianou@cut.ac.cy

Abstract

Agar based phantoms were proven a valuable tool for preclinical MRI-guided Focused Ultrasound (MRgFUS) applications [1]. In this article we present our experience in acquiring thermal maps in a multipurpose phantom for a FUS system operated under MRI monitoring. An Agar based phantom was used as the background tissue. The phantom contained a cyst mimic, a bone mimic, a stone mimic and a tumour mimic. A single element transducer was used operating at 2.7 MHz. The robotic system included 3 cartesian axes (X,Y,Z) and one angular axis. A Siemens Magnetom 3 T MRI scanner was used. Temperature maps were acquired in the agar-based phantoms. The FLASH pulse sequence was optimized to provide noise-free temperature maps. It was found that the bone and stone mimic blocked ultrasound. The cyst mimic allowed ultrasound to pass through and the tumour mimic absorbed sufficient ultrasound. This inexpensive phantom was proven successful in studying the penetration of focused ultrasound through these mimics.

References

[1] McGarry, C.K. *et al.* Tissue mimicking materials for imaging and therapy phantoms: A review. *Physics in Medicine and Biology,* **2020,** 65. https://doi.org/10.1088/1361-6560/abbd17.

Acknowledgements

The study was co-funded by the European Structural & Investment Funds (ESIF) and the Republic of Cyprus through the Research and Innovation Foundation (RIF) under the projects SOUNDPET (INTEGRATED/0918/0008) and FUSVET (SEED/1221/0080).

Opening of the Blood-brain barrier using focused ultrasound with simultaneous delivery of anti-Aβ antibodies in a 5XFAD amyloid beta mouse model

Anastasia Antoniou[1]*, Nikolas Evripidou[1], Marios Stavrou[2], Ioanna Kousiappa[2], Elena Georgiou[3], Kleopas A. Kleopa[3], Christakis Damianou[1]

[1] Elentrical Engineering Department, Cyprus University of Technology, Cyprus. [2] Department of Neurobiology, The Cyprus Institute of Neurology and Genetics, Cyprus. [3] Department of Neuroscience, The Cyprus Institute of Neurology and Genetics, Cyprus

* anastasiaantoniou12@gmail.com

Abstract

Amyloid-β (Aβ) peptides constitute the major component of amyloid plaques in the Alzheimer's disease (AD) brain and a main target in AD therapeutics [1]. In this study we investigated the delivery of anti-Aβ antibody in a mouse model of AD in synergy with microbubbles-enhanced Focused Ultrasound (FUS) in order to open the Blood-brain barrier (BBB) using an MR-compatible positioning device. The initial experimental work involved Wild type mice and was devoted to selecting the sonication protocol for efficient and safe BBB opening. Mechanical-based FUS was applied using a single-element FUS transducer of 1.05 MHz (80 mm radius of curvature and 50 mm diameter). The success and extent of BBB opening was assessed by Evans Blue extravasation. Brain damage was assessed by hematoxylin and eosin staining. 5XFAD AD mice were divided into 3 subgroups; FUS+MBs alone, antibody alone, and FUS+antibody combined. The changes in antibody deposition among groups were determined by immunohistochemistry analysis. It was confirmed that the antibody could not normally enter the brain parenchyma. With a single treatment with MBs-enhanced pulsed FUS using the optimized protocol (1 MHz, 0.5 MPa in situ pressure, 10 ms bursts, 1% duty factor, 100 s duration) the BBB was consistently disrupted allowing for non-invasive antibody delivery to amyloid plaques within the sonicated brain regions in 10 mice. These preliminary findings should be enhanced by longer-term studies examining the antibody effects on plaque clearance and cognitive benefit for developing disease-modifying anti-Aβ therapeutics for clinical use.

References

[1] Fu, H.J. *et al.* Amyloid-β Immunotherapy for Alzheimer's Disease. *CNS Neurol Disord Drug Targets,* **2010,** 9, 197–206. https://doi.org/10.2174/187152710791012017.

Acknowledgements

The study was co-funded by the European Structural & Investment Funds (ESIF) and the Republic of Cyprus through the Research and Innovation Foundation (RIF) under the project SOUNDPET (INTEGRATED/0918/0008).

Appendix: Oral and Poster presentations given

Two simple 3D printed robotic systems for opening the blood brain barrier of small animals.

*Anastasia Antoniou, Marinos Giannakou, Christakis Damianou**

Presenter: Anastasia Antoniou, PhD candidate

Department of Electrical engineering,

Cyprus University of Technology

**Corresponding author*

ROBOTIC DEVICE
VERSION I

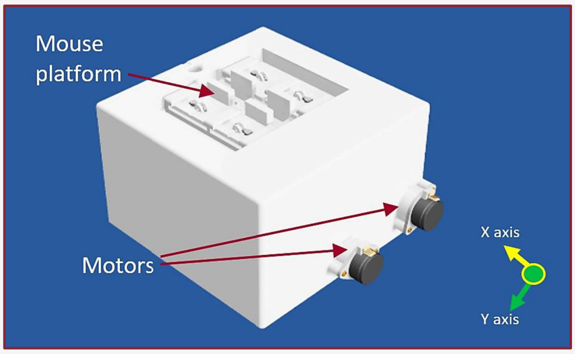
Intended Use:

FUS mediated opening of the Blood Brain Barrier (BBB) in mice and rats.

Main features:

- 3D printed (F270, Stratasys, USA)
- **2 degrees of freedom (DOF): X, Y axes**
- Actuated by piezoelectric motors (USR30-S3, Japan).
- Controlled by optical encoders (US Digital Corporation, USA).
- Single element spherically focused transducer of 1 MHz
- Bottom to top ultrasound approach
- MRI compatible

CAD drawing of robotic device VI



ROBOTIC DEVICE
*VERSION **II***

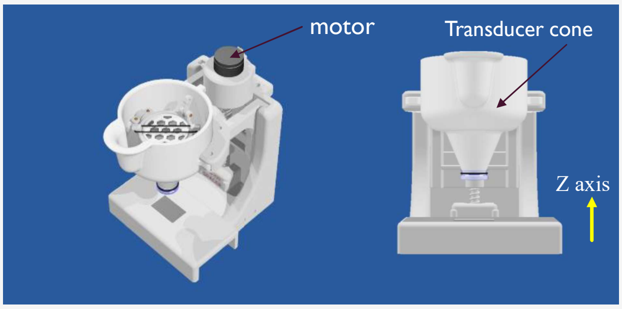
Intended Use:

FUS mediated opening of the Blood Brain Barrier (BBB) in mice and rats.

Main features:

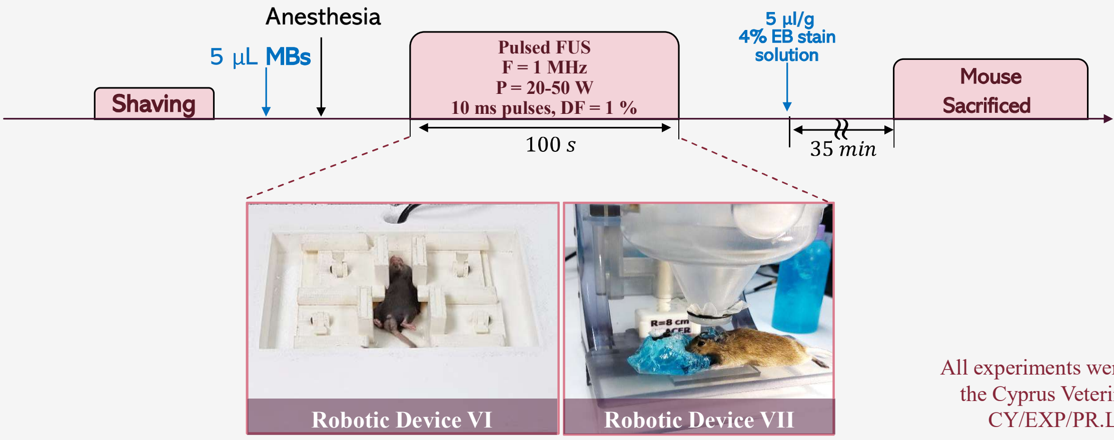
- 3D printed (F270, Stratasys, USA)
- **1 vertical DOF: Z axis**
- Actuated by piezoelectric motor (USR30-S3, Japan).
- Controlled by optical encoder (US Digital Corporation, USA).
- Single element spherically focused transducer of 1 MHz
- Top to bottom ultrasound approach
- MRI compatible

CAD drawing of robotic device VII



FEASIBILITY STUDY IN MICE
EXPERIMENTAL PROCEDURE

- Wild type (WT) mice (n=10)



All experiments were approved by the Cyprus Veterinary Service CY/EXP/PR.L05/2021.

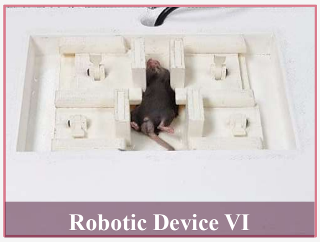
FEASIBILITY STUDY IN MICE
EXPERIMENTAL PROCEDURE

- Wild type (WT) mice (n=10)

	n=1	n=1	n=8
EB	×	✓	✓
FUS & MBs	×	×	✓

Assessment of BBB opening

- Evans Blue (EB) dye (Sigma, St. Louis, MO, USA) method.
- Immunostaining with Fibrinogen and Fibronectin antibodies (DAKO, Glostrup, Denmark).


Robotic Device VI

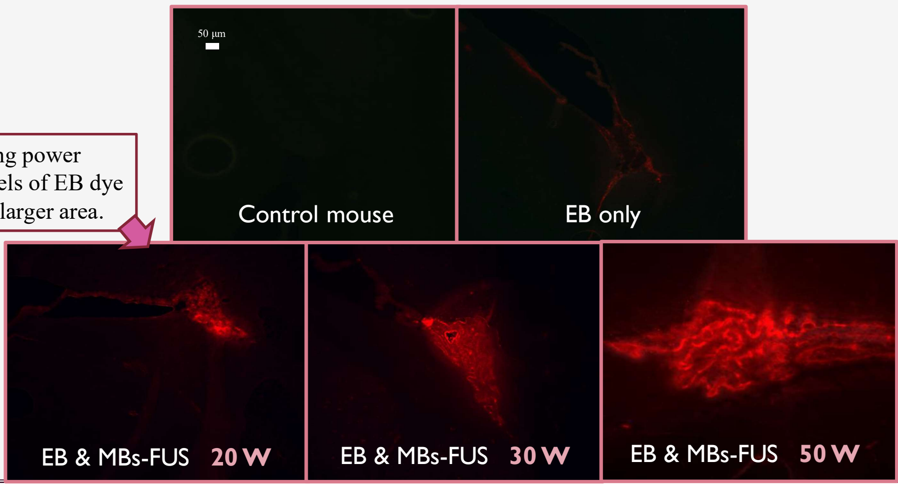

Robotic Device VII

All experiments were approved by the Cyprus Veterinary Service CY/EXP/PR.L05/2021.

FEASIBILITY STUDY IN MICE
INDICATIVE RESULTS

EB staining: Fluorescence images of unstained brain sections at the level of the lateral ventricles.

Increasing power
⇒ higher levels of EB dye
covering a larger area.



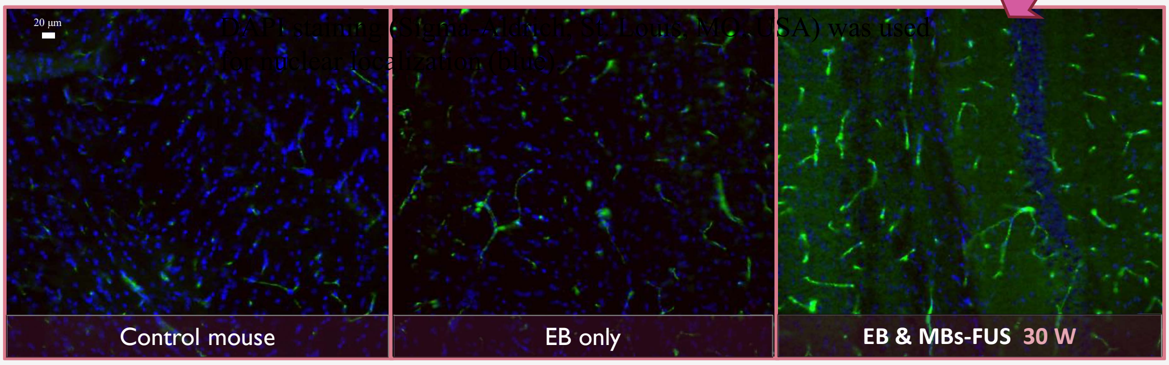
FEASIBILITY STUDY IN MICE

INDICATIVE RESULTS

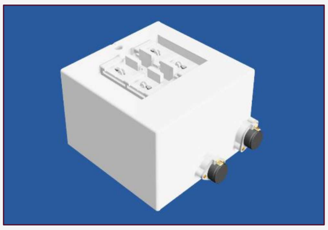
Immunofluorescence staining: Fluorescence images of immunostained brain sections at the level of the corpus callosum.

Fibronectin: light green
Cell nuclei: blue

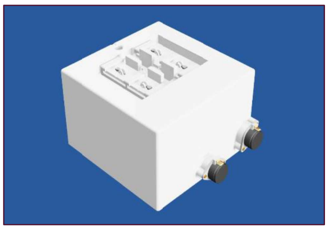
High levels of serum protein in brain tissue

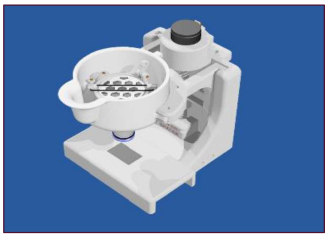


DISCUSSION



- BBB opening was achieved with both robotic systems.
- *version I:*
  - Suitable for medium size animals (e.g., rabbits).
  - Difficulties in accommodating the anesthesia needle.
- *version II:*
  - Direct access for administration of anesthesia.
  - No possibility for water leakage.
  - Prone - more stable mouse positioning.
  - Visual confirmation of proper acoustic coupling.





Conclusions:

- The proposed devices constitute **cost-effective & ergonomic solutions for FUS mediated BBB disruption in small animal models**, such as mice and rats.
- Experimental setup can be prepared within a few minutes taking up minimal space.
- Follow up studies will focus on delivering chemotherapeutic drugs through the opened BBB.

FUNDED BY:

PARTNERS:

PROJECT: **SOUNDPET** (INTEGRATED/0918/0008)

ACKNOWLEDGEMENTS

CHALLENGES REGARDING MR COMPATIBILITY OF AN MRgFUS ROBOTIC SYSTEM

Anastasia Antoniou[a], Leonidas Georgiou[b], Nikolas Evripidou[a], Natalie Panayiotou[b], Cleanthis Ioannides[b], Christakis Damianou[a]*

[a]Department of Electrical Engineering, Computer Engineering, and Informatics, Cyprus University of Technology, Limassol, Cyprus
[b]German Oncology Center, Department of Interventional Radiology, Limassol, Cyprus

INTRODUCTION

Numerous challenges are faced when employing Magnetic Resonance guided Focused Ultrasound (MRgFUS) hardware in the Magnetic Resonance Imaging (MRI) setting. The current study aimed to provide insights on this topic through a series of experiments performed in the framework of evaluating the MRI compatibility of an MRgFUS robotic device.

METHODS

All experiments were performed in a 1.5 T MRI scanner. The main metric for MRI compatibility assessment was the signal to noise ratio (SNR). Measurements were carried out in a tissue mimicking phantom and freshly excised tissue under various activation states of the system. In the effort to minimize image distortion and interference with the magnet, various set-up parameters were examined.

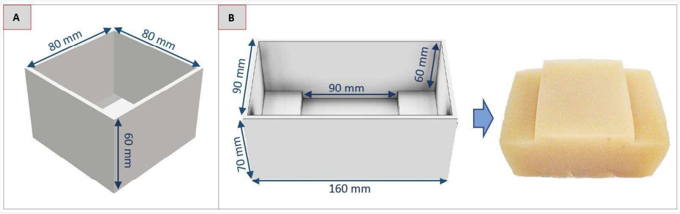


Figure 1: 3D printed molds used for manufacturing the (A) small size square phantom and (B) the larger phantom of complex shape.

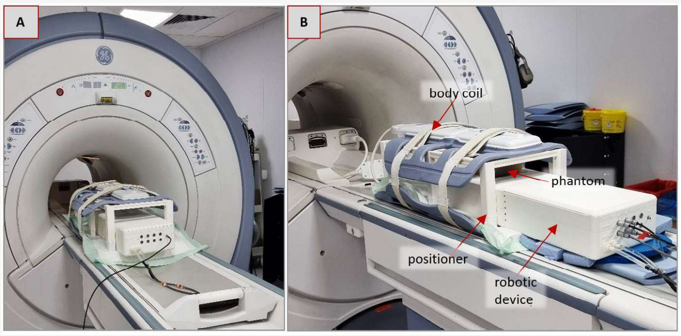


Figure 2: The robotic device sited on the table of the 1.5 T MRI scanner with the multi-channel body coil securely mounted on the positioner with the electronic parts (A) within the coil detection area and (B) outside the coil detection area.

RESULTS

Significant image distortion occurred when the transducer was activated mainly owing to coil and target vibrations and was getting worse as the output power was increased. Multi-channel coils increased the SNR by up to 50 % compared to single-channel coils. Placement of the electronics outside the coil detection area and deactivation of the encoder's counting pulses were also proven to improve the SNR remarkably.

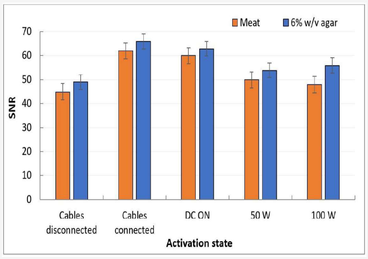


Figure 3: Bar charts of the SNR acquired in excised meat and 6% w/v agar phantom using the SPGR sequence under different activation states of the ultrasonic transducer.

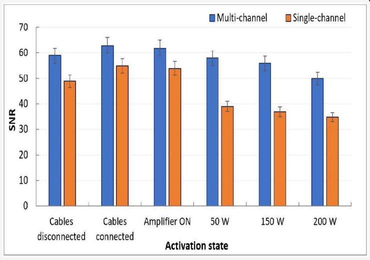


Figure 4: Bar charts of the SNR acquired with the multi-channel and single-channel coils using the SPGR sequence under different activation states of the ultrasonic transducer.

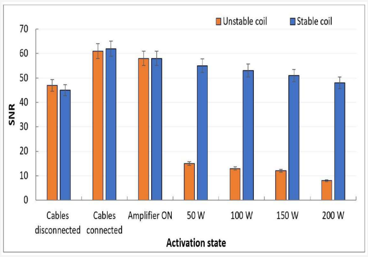


Figure 5: Bar charts of the SNR acquired using the SPGR sequence with the multi-channel body coil being placed without any supporting structure above the phantom (unstable) and securely mounted on a dedicated plastic supporting structure (stable) for different activation states of the ultrasonic transducer.

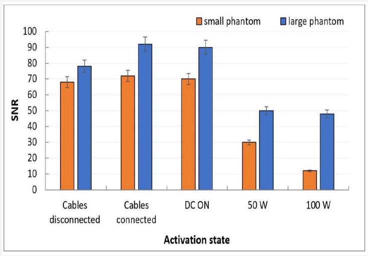


Figure 6: Bar charts of the SNR acquired in the small and large phantom using the SPGR sequence under different activation states of the ultrasonic transducer.

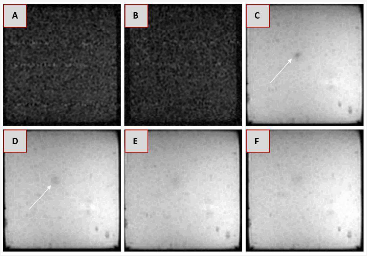


Figure 7: SPGR axial images acquired with the unsupported coil in a 6% agar phantom during and after sonication at 200 W for 12 s at acquisition times of (A) 4 s, (B) 8 s, (C) 12 s, (D) 16 s, (E) 20 s, and (F) 24 s.

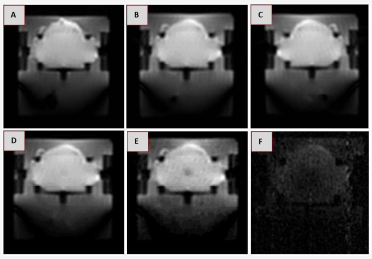


Figure 8: Example of SPGR axial images acquired in excised meat with the (A) Cables disconnected, (B) Cables connected, (C) DC ON, and power ON at (D) 10 W, (E) 50 W, and (F) 100 W.

CONCLUSIONS

The study contributes towards addressing major challenges regarding operation of an MRgFUS system in the MRI environment and raises awareness for potential sources of noise and distortion to researchers in the field.

ACKNOWLEDGE

The study was funded by the Research and Innovation Foundation of Cyprus under the project SOUNDPET (INTEGRATED/0918/0008).

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Διαρθρωτικά Ταμεία της Ευρωπαϊκής Ένωσης στην Κύπρο

Focused Ultrasound Ablation Of Canine Mammary Cancer

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* *Corresponding author*

INTRODUCTION

The current study examined the feasibility of Focused Ultrasound (FUS) in the treatment of naturally occurring canine superficial mammary cancer using an existing preclinical MRI-compatible FUS robotic system.

METHODS

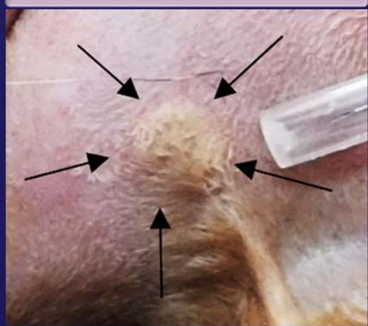
The robotic system utilized comprises a positioning mechanism for navigating a single element spherically focused transducer of 2.6 MHz in four PC-controlled axes. For each case dog (n=5), the system was installed in the respective veterinary clinic.

The treatment protocol included partial tumor ablation and was adjusted based on the tumor size and location. The motion and ultrasonic parameters were controlled through dedicated FUS software. Post-sonication the tumors were removed and sent for histological examination.

RESULTS

All procedures were implemented successfully, with no recorded adverse events. Hematoxylin and eosin (H&E) staining showed well-defined necrotic regions in all treated tumors. Red blood cell extravasation was observed at the lesion borderline in one case (1/5).

Example photo of thermal lesion

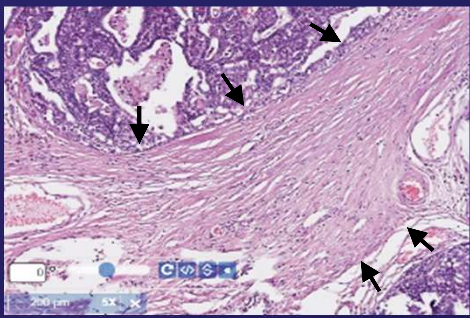


Black arrows indicate thermal lesion inflicted on mammary tumor using 45-W acoustic power; focal intensity of 1590 W/cm^2 and sonication duration of 20 s.

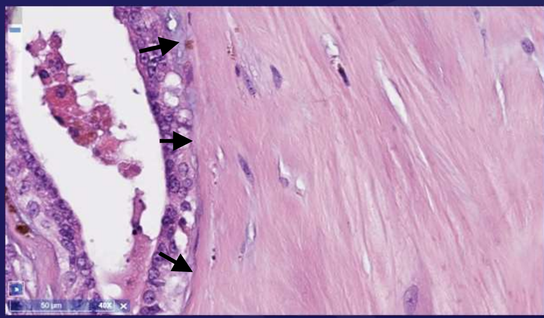
RESULTS

Indicative histological slides

Black arrows delineate the area of thermal necrosis.



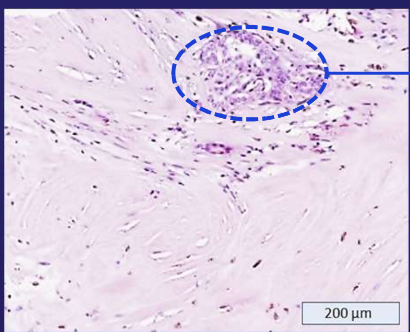
5X Magnification. Necrotic area crated by sonication at 60 W; focal intensity of 2116 W/cm² for 10 s at 2.5-cm focal depth.



40X Magnification. Necrotic area created by sonication at 60 W; focal intensity of 2116 W/cm² for 10 s at 2.5-cm focal depth.

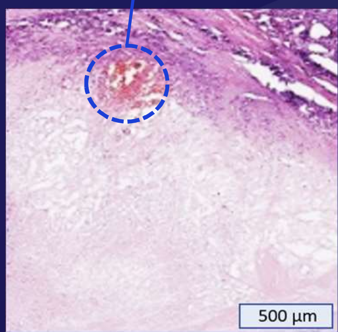
RESULTS

Indicative histological slides



Intact cancer structure within the necrotic area.

Minor hemorrhage observed at lesion borderline.



CONCLUSIONS

FUS ablation of canine mammary cancer under proper monitoring was proven safe and feasible. The FUS robotic system and related software offered an efficient procedural workflow.

Further research is required to examine the phenomenon of residual cancer structures and the feasibility of safely ablating the entire tumor volume, as well as deep-seated tumors. Veterinary clinical trials may offer the opportunity for FUS to benefit family pets by providing them an alternative non-invasive cancer treatment.

ACKNOWLEDGEMENTS

The study was funded by the Research and Innovation Foundation of Cyprus under the projects:
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Cyprus University of Technology

Focused Ultrasound Phantom With Inclusion Of Tumour

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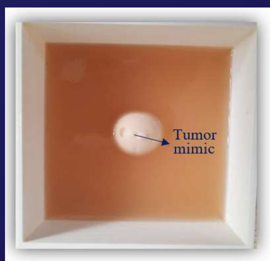
* *Corresponding author*

INTRODUCTION

An agar-based tissue mimicking material which includes a tumour was developed. The phantom can be used to evaluate the temperature produced by a focused ultrasound (FUS) transducer.



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METHODS

The tumour model was made of water, agar (6 % w/v) and (4 % w/v) silica. In the material surrounding the tumour no silica was used.

The phantom was assessed in a 3T Magnetic Resonance Imaging (MRI) scanner in terms of T1 and T2 relaxation properties and overall MRI appearance. FUS sonications were performed in the phantom using an MR compatible positioning device to examine its response to thermal heating using MR thermometry.

Experimental setup for phantom sonication.

RESULTS

The slight difference in silica content between tumour and surrounding tissue resulted in excellent contrast between tumour and tissue in MRI.

T2-W TSE image of the phantom

Imaging Parameters: TR = 2500 ms, TE = 52 ms, FA =180°, ETL =12, FOV = 260 x 260 x 10 mm^3, matrix size = 128 x 128, and NEX = 2.

Estimated relaxation times

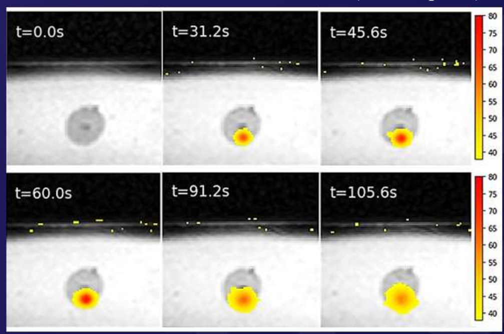
Material	T1 (ms)	T2 (ms)
Tumor mimic (6 % agar, 4 % silica)	2099	36
Background material (6 w/v agar)	2136	40

RESULTS

Based on coronal images showing the transducer and tumour/tissue it was possible to precisely move the FUS beam within the phantom. MR temperature was detected within the tumour and outside the tumour.

Coronal view

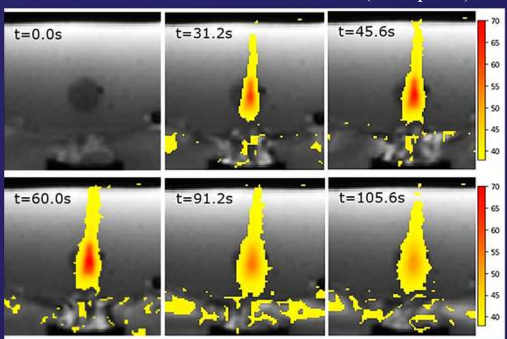
Indicative thermal maps acquired during and after sonication within the tumour mimic (coronal plane):



Coronal thermal maps extracted from FLASH images. Imaging parameters: TR=25 ms, TE=10 ms, FOV = 280×280x3 mm^3, NEX = 1, FA = 30^o, ETL = 1, matrix = 96 x 96. Sonication parameters: acoustic power = 60 W, duration = 60 s, and focal depth = 35 mm at 2.4 MHz.

RESULTS

Indicative thermal maps acquired during and after sonication within the tumour mimic (axial plane):

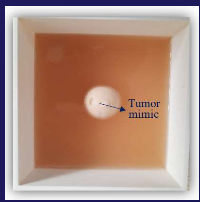


Axial thermal maps extracted from FLASH images. Imaging parameters: TR=25 ms, TE=10 ms, FOV = 280×280x3 mm^3, NEX = 1, FA = 30^o, ETL = 1, matrix = 96 x 96. Sonication parameters: acoustic power = 60 W, duration = 60 s, and focal depth = 35 mm at 2.4 MHz.

A peak temperature of 75 ºC was estimated by MR thermometry within the tumour, whereas outside of the tumour a smaller peak temperature of 65 ºC was recorded (baseline of 37 ºC).

CONCLUSIONS

Due to the inclusion of silica in the tumour, the absorption was increased within the tumour, and therefore, higher temperatures were measured in the tumour. Temperature across a plane parallel to the beam showed some deflection of the beam in areas of tumour curvature. This is an excellent tumour model that can be used to evaluate the physics of focused ultrasound.



ACKNOWLEDGEMENTS

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Cyprus University of Technology

MRI guided focused ultrasound system for veterinary oncology

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[2]DVM, PhD student, VET EX MACHINA LTD, Nicosia, Cyprus

INTRODUCTION

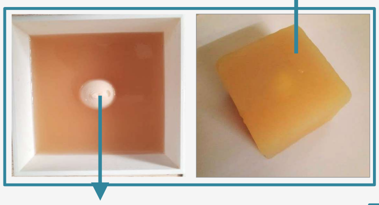
In this study, we investigated the ability of Focused Ultrasound (FUS) to precisely ablate targets mimicking canine and feline tumours using a Magnetic Resonance guided FUS (MRgFUS) robotic system. This modality could be an alternative therapeutic tool beyond traditional approaches.

METHODS

Agar based targets were ablated with a MRgFUS **robotic system** featuring a single element spherically **focused transducer** of 2.7 MHz. The robotic system includes 3 linear cartesian axes.

Robotic device

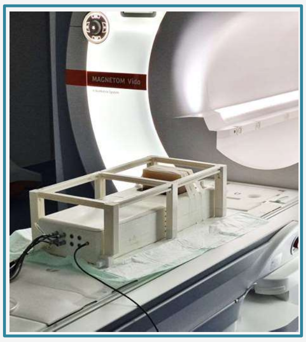
FUS transducer



The tumour simulator was made of water, agar and silica, whereas in the material surrounding the tumour no silica was used.

The tumour mimicking phantom was imaged in a 3T MRI scanner (Magnetom Vida, Siemens Healthineers).

MR thermometry maps were produced to assess the thermal evolution during FUS sonications.



Experimental setup for phantom sonication in the 3T MRI scanner.

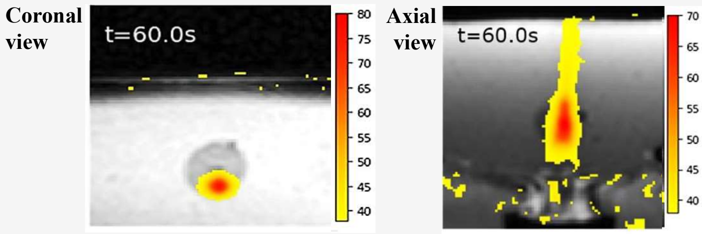
RESULTS

The tumour simulator was visualized by MRI with excellent contrast from the surrounding material.

T2-W TSE image of phantom (TR = 2500 ms, TE = 52 ms, FA = 180^o, ETL = 12, FOV = 260 x 260 x 10 mm^3, matrix size = 128 x 128, and NEX = 2).

Based on coronal images of the transducer and tumour, it was possible to precisely move the FUS beam within the phantom. The MRgFUS system was capable of producing ablative temperatures within the tumour mimics.

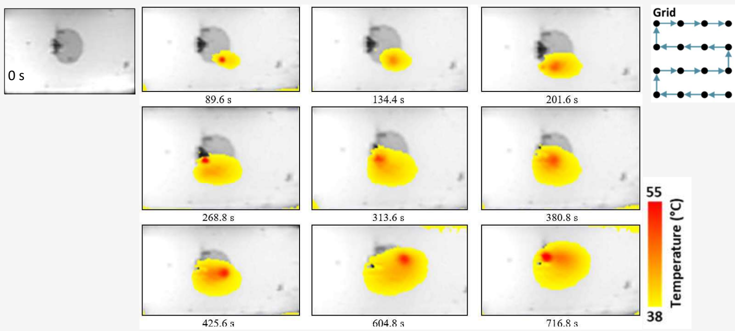
Indicative example of single sonication:



Thermal maps acquired at the end of sonication (60 W acoustic power, 60-s duration, 35-mm focal depth) **in the tumour mimic** extracted from FLASH images (TR=25 ms, TE=10 ms, FOV = 280×280x3 mm^3, NEX = 1, FA = 30^o, ETL = 1, matrix = 96 x 96).

A peak temperature of 75ºC was recorded within the tumour (baseline of 37ºC) using acoustic power of 60 W for 60 s.

Indicative example of grid sonication:



Indicative thermal maps acquired during sonication (45 W acoustic power, 30-s duration, 40-mm focal depth) in 4x4 grid (10-mm step, 30-s delay) **in the tumour mimic** extracted from FLASH images (TR=25 ms, TE=10 ms, FOV = 280×280x10 mm^3, NEX = 1, FA = 30^o, ETL = 1, matrix = 128x128).

CONCLUSIONS

This technology has potential as a therapeutic solution for veterinary cancer. Although the device is MRI compatible, it can be used also outside the MRI setting using ultrasonic imaging. The next step is to apply this technology in animals and in humans.

The study was funded by the **Research and Innovation Foundation of Cyprus** under the projects:

FUSVET (SEED/1221/0080)

SOUNDPET (INTEGRATED/0918/0008)

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T1 and T2 values of an Agar-based phantom with inclusion of tumour

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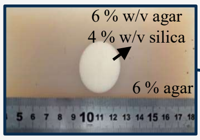
[2]DVM, PhD student, VET EX MACHINA LTD, Nicosia, Cyprus

ΕΛΕΚΖΣ HCAVS

INTRODUCTION

An agar-based mimicking material which includes a tumour was developed. The phantom can be used to evaluate the temperature produced by a focused ultrasound (FUS) transducer.

METHODS



phantom

FUS robotic device

The tumour model is composed of water, agar and silica. In the tissue surrounding the tumour no silica was included.

The T1 and T2 relaxation times of the phantom were measured in a 3T Magnetic Resonance Imaging (MRI) scanner (Magnetom Vida, Siemens Healthineers). Sonications were carried out with an MRI compatible FUS robotic system featuring a single element spherically focused transducer. The temperature was detected within the tumour and outside of the tumour by MR thermometry.

CONCLUSIONS

Due to the inclusion of silica in the tumour the absorption was increased within the tumour, and therefore, higher temperatures were measured in the tumour. Temperature across a plane parallel to the beam showed some deflection of the beam in areas of tumour curvature. This is an excellent tumour model that can be used to evaluate the physics of the FUS technology.

ACKNOWLEDGEMENTS

The study was funded by the **Research and Innovation Foundation of Cyprus** under the projects:
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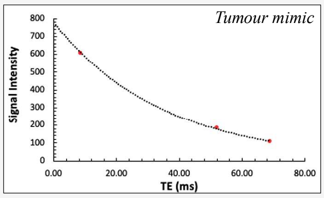
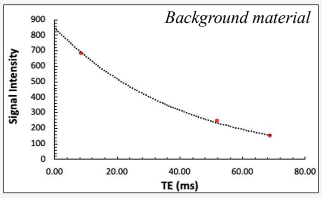
RESULTS

The slight difference in silica content between tumour and surrounding tissue resulted in excellent tumour visualization in MRI. The tumour mimic showed lower relaxation times owing to the addition of silica.

Indicative results of T1 and T2 mapping:





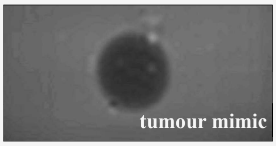
Signal intensities measured from T2-W Turbo Spin Echo (TSE) images using varied Echo time (TE) values for T2 mapping.

Material	T1 (ms)	T2 (ms)
Tumour mimic	2099.2	35.7
Background material	2135.8	40.0

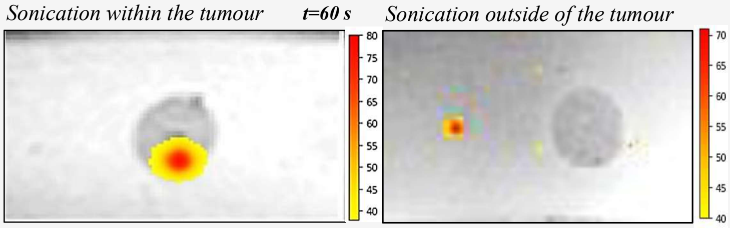
***T2 mapping**: T2-W TSE sequence with varying TE values of 8 to 69 ms*
(TR = 250 ms, FA = 180°, FOV = 260 × 260 x 10 mm^3, matrix size =128 × 128, NEX = 2, ETL = 12).
***T1 mapping**: Gradient Echo (GRE) sequence with varying FA values of 3 to 15°*
(TR = 15 ms, TE = 1.93 ms, FOV = 250 x 250 x 5 mm^3, matrix size = 256 x 256, NEX = 1, ETL = 1).

Based on coronal images showing the transducer and tumour it was possible to precisely move the FUS beam within the phantom using the MR compatible positioning device.

A maximum temperature of 65 ºC was recorded outside of the tumour using acoustic power of 60 W for 60 s. A higher temperature of 75ºC was reached within the tumour (baseline of 37ºC).



***T2-W TSE images** (TR = 2500 ms, TE = 52 ms, FA =180°, ETL =12, FOV = 260 x 260 x 10 mm^3, matrix size = 128 x 128, and NEX = 2).*



***Thermal coronal maps** acquired at the end of sonication (60 W acoustic power, 60-s duration, 35-mm focal depth) extracted from FLASH images (TR=25 ms, TE=10 ms, FOV = 280×280x3 mm^3, NEX = 1, FA = 30°, ETL = 1, matrix = 96 x 96).*

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Treatment of cancer with focused Ultrasound in cats and dogs

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Electrical Engineering Department, Cyprus University of Technology, Cyprus

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ISTU EUFUS 2023

OBJECTIVES

The current study is a feasibility study using MRI guided focused ultrasound (FUS) for canine and feline cancer therapy using an existing preclinical MRI-compatible FUS robotic system.

METHODS

FUS was delivered by a 2-MHz MRI compatible single-element spherically focused ultrasonic transducer which was integrated with an existing robotic positioning device with 4 computer-controlled axes. The functionality of the FUS system and sonication protocol in efficiently and safely ablating live tissue was initially validated in a rabbit thigh model in laboratory environment.

Pet trials

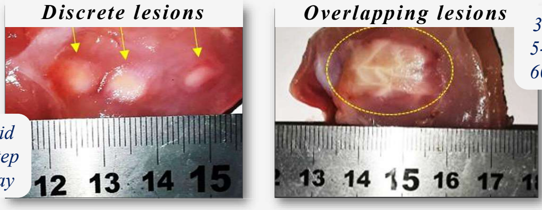
For the pet trials, the treatment protocol included partial tumor ablation and was adjusted based on the tumor size. The motion and ultrasonic parameters were controlled through a dedicated FUS software. Post-sonication the tumors were removed and sent for histological examination.

RESULTS

The system was capable of accurately delivering FUS to ablate live rabbit tissue. Both discrete and overlapping lesions of variable dimensions were inflicted in rabbit thigh by adjusting the ultrasonic parameters and spatial step between adjacent sonications.

Typical results of rabbit thigh ablation

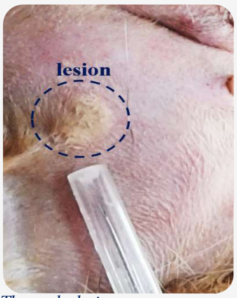
Discrete lesions | *Overlapping lesions*



1 × 3 grid
10-mm step
60-s delay

3 x 3 grid
5-mm step
60-s delay

Top photos of rabbit thigh after muscle exposure. Sonications at 60 W (focal intensity of 2116 W/cm²) for 10 s at 1-cm focal depth.

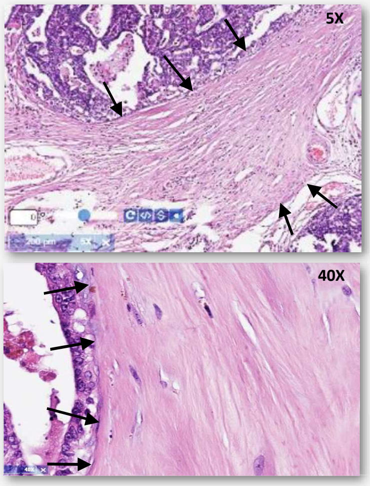


Thermal lesion on mammary tumor using 45 W (focal intensity of 1590 W/cm²) for 20 s.

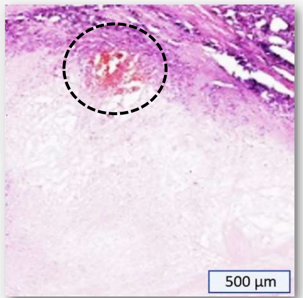
Nine (9) dogs and cats with superficial mammary cancer were recruited through a national champagne, according to set safety criteria. The veterinary patients underwent FUS ablation followed by immediate surgical resection of the tumor. All procedures were implemented successfully, with no recorded adverse events.

Hematoxylin and eosin (H&E) staining showed well-defined necrotic regions in all treated tumors. Red blood cell extravasation was observed at the lesion borderline in one case.

Indicative histological slides



Black arrows delineate the area of necrosis. Sonications at 60 W (focal intensity of 2116 W/cm²) for 10 s at 2.5-cm focal depth.



Minor hemorrhage at lesion borderline (dotted circle).

CONCLUSIONS

FUS ablation of mammary cancer under proper monitoring was proven safe and feasible. The FUS robotic system and related software offered an efficient procedural workflow. Further study with a larger patient population is needed to confirm the findings and demonstrate the feasibility of thermal FUS to safely ablate the entire tumor volume, as well as deep seated tumors.

ACKNOWLEDGEMENTS

The study was funded by the

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ULTRASOUND AND MRI GUIDED FOCUSED ULTRASOUND SYSTEM FOR VETERINARY APPLICATIONS

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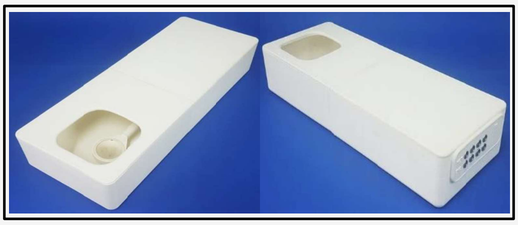
Department of Electrical engineering, Computer engineering and Informatics

Cyprus University of Technology

**Corresponding author*

ROBOTIC SYSTEM

Magnetic Resonance-Guided Focused Ultrasound (MRgFUS) robotic system for preclinical applications.



Main features:

- 3D printed (F270, Stratasys, USA).
- 4 computer-controlled motion axes.
- Dimensions: 57 cm (L) x 21 cm (W) x 11.5 cm (H)
- MRI compatible materials.

ROBOTIC SYSTEM

Motion principle:

- ❑ Actuated by <u>piezoelectric motors</u> (USR30-S3N, Shinsei, Japan).
- ❑ Controlled by <u>optical encoders</u> (US Digital Corporation, USA).

MRgFUS software:

- ❑ Remote control of robotic motion and ultrasonic parameters.
- ❑ Treatment planning/ monitoring capabilities.

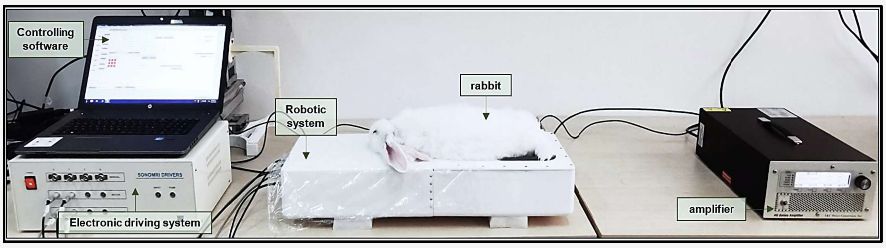
FUS transducer:

- ❑ Single element spherically-focused ultrasonic transducer
- ❑ **2-MHz** central frequency.
- ❑ MRI compatible.

SYSTEM EVALUATION IN A RABBIT THIGH MODEL

Experimental protocol:

- ❑ FUS ablation of rabbit thigh under continuous anesthesia.
- ❑ Grid sonications with varying ultrasonic and grid parameters.



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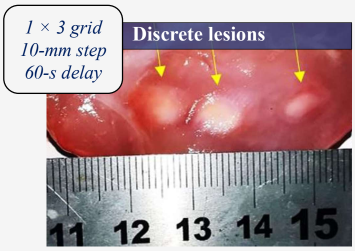
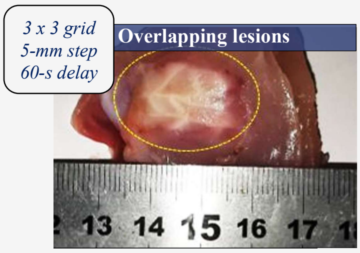
SYSTEM EVALUATION IN A RABBIT THIGH MODEL

- ❑ The system was capable of accurately delivering FUS to ablate live rabbit tissue.
- ❑ Discrete & overlapping lesions of variable dimensions were inflicted in tissue.
- ❑ Rabbit experiments provided proof of safety ⇒ Recruitment of pets (dogs/cats).

Typical results of rabbit thigh ablation:





Top photos of rabbit thigh after muscle exposure. Sonications at 60 W; focal intensity of 2116 W/cm2 for 10 s at 1-cm focal depth.

study license: CY/EXP/PR.L01/2020

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FEASIBILITY STUDY IN CANINE /FELINE CANCER PATIENTS

Nine (9) dogs and cats with superficial mammary cancer were recruited through a national champagne.

Treatment protocol:

- ❑ Partial tumor ablation using high intensity FUS.
- ❑ Single OR Grid sonications depending on tumor size.
- ❑ Tumor excision following FUS.
- ❑ Histological examination.

Animal placement on the device at veterinary premises.

study license: CY/EXP/PR.L01/2020/R1/2021

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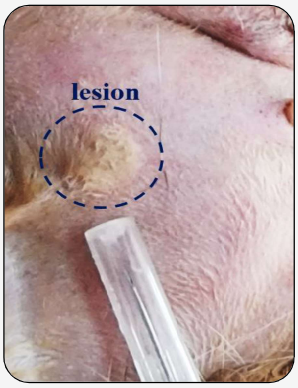
FEASIBILITY STUDY IN CANINE /FELINE CANCER PATIENTS

Outcomes:

- ❑ All procedures were implemented successfully.
- ❑ NO recorded adverse events.
- ❑ Well-defined lesions were observed on tissue.



Lesion inflicted on mammary tumor using 45 W (focal intensity of 1590 W/cm^2) and sonication duration of 20 s.

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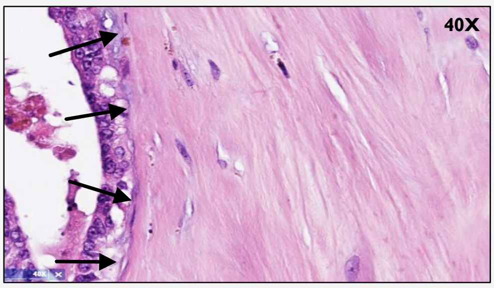
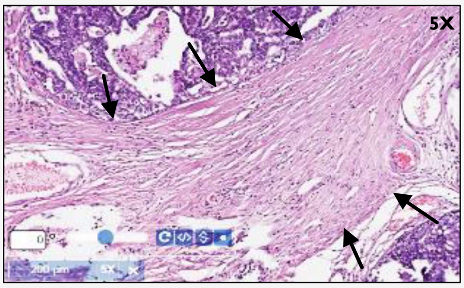
Histological examination:

- ❑ Hematoxylin and eosin (H&E) staining showed well-defined necrotic regions in all treated tumors.





Indicative histological slides: Black arrows delineate the area of thermal necrosis.
Sonications at 60 W (focal intensity of 2116 W/cm^2) for 10 s at 2.5-cm focal depth.

study license: CY/EXP/PR.L01/2020/R1/2021

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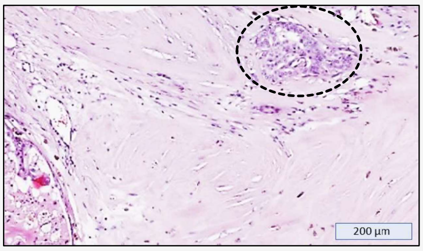
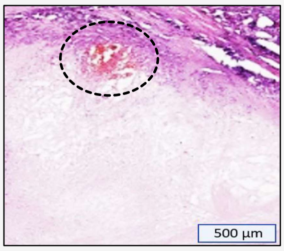
FEASIBILITY STUDY IN CANINE /FELINE CANCER PATIENTS

Histological examination:

- ❑ Red blood cell extravasation was observed at the lesion borderline in one case.
- ❑ Intact cancer structures were observed occasionally within lesions.



Intact cancer structure within the necrotic area (dotted circle).



Minor hemorrhage at lesion borderline (dotted circle).

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CONCLUSIONS & FUTURE PROSPECTS

- ❑ **FUS ablation of mammary cancer** under proper monitoring was proven **safe** and **feasible**.
- ❑ The **FUS robotic system** offered an **efficient procedural workflow**.
- ❑ **Further study** is needed to:
  - ❑ Examine the phenomenon of **intact cancer structures**.
  - ❑ Assess the feasibility of **safely ablating** the **entire tumor volume** & **deep-seated tumors**.

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FUNDED BY:

RESEARCH & INNOVATION FOUNDATION

2016-2020 RESTART SEARCH

ΠΡΟΓΡΑΜΜΑΤΑ ΕΡΕΥΝΑΣ, ΤΕΧΝΟΛΟΓΙΚΗΣ ΑΝΑΠΤΥΞΗΣ ΚΑΙ ΚΑΙΝΟΤΟΜΙΑΣ

Κυπριακή Δημοκρατία

Ευρωπαϊκή Ένωση
Ευρωπαϊκό Ταμείο
Περιφερειακής Ανάπτυξης

Διαρθρωτικά Ταμεία
της Ευρωπαϊκής Ένωσης στην Κύπρο

PROJECTS: SOUNDPET (INTEGRATED/0918/0008)
FUSVET (SEED/1221/0080).

PARTNERS:

Cyprus University of Technology

German Oncology Center

MEDSONIC

ACKNOWLEDGEMENTS

Thank you for your attention!

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MR thermometry for a multipurpose phantom for focused ultrasound

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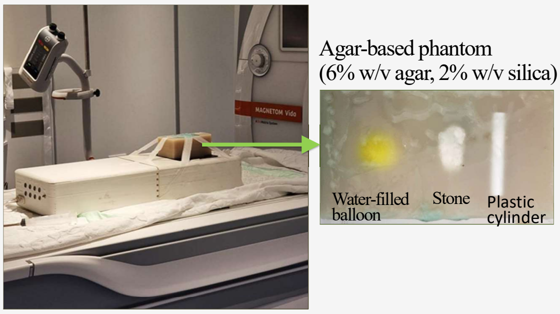
OBJECTIVES

In this article we present our experience in acquiring thermal maps in a multipurpose phantom for a Focused Ultrasound (FUS) system operated under MRI monitoring.

METHODS

An agar based phantom was used as the background tissue. The phantom contained a cyst mimic, a bone mimic, and a stone mimic.

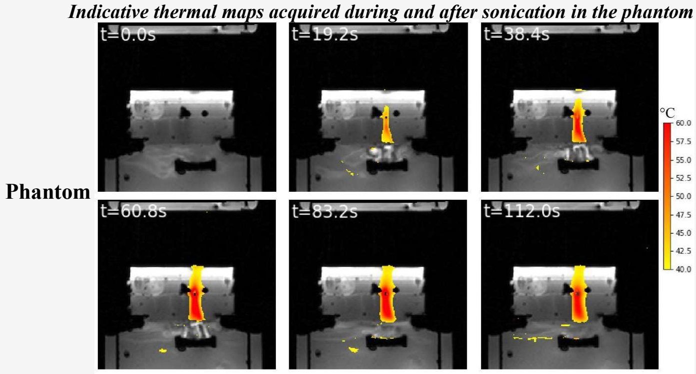


A single element transducer was used operating at 2.7 MHz. The robotic system included 3 cartesian axes (X,Y,Z) and one angular axis. Phantom sonications were carried out in a Siemens Magnetom 3 T MRI scanner using acoustic power of 60 W for 60 s. MR thermomerty was performed using a FLASH pulse sequence, which was optimized to provide noise-free temperature maps.

RESULTS

- Sonication at 60 W for 60 s resulted in a focal temperature increase of 33.7°C, raising the phantom temperature to ablative levels.

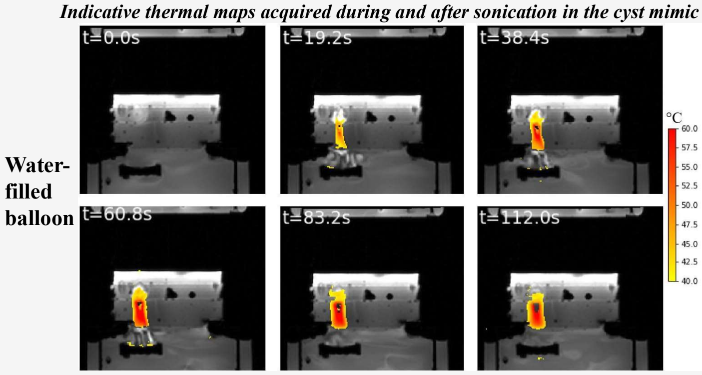
Indicative thermal maps acquired during and after sonication in the phantom



Axial thermal maps derived from FLASH sequence (TR = 25 ms, TE= 10 ms, slice thickness = 6 mm, flip angle =30°, NEX = 1, Pixel bandwidth = 240 Hz/pixel, Matrix size = 128x128) during and after sonication at focal depth of 45 mm.

- The cyst mimic allowed ultrasound to pass, demonstrating a smooth increase in temperature, which was about 2-fold smaller (ΔT=16°C) than that observed in the phantom.

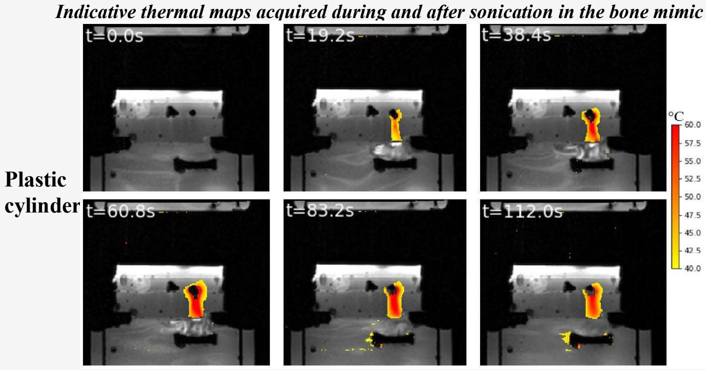
Indicative thermal maps acquired during and after sonication in the cyst mimic



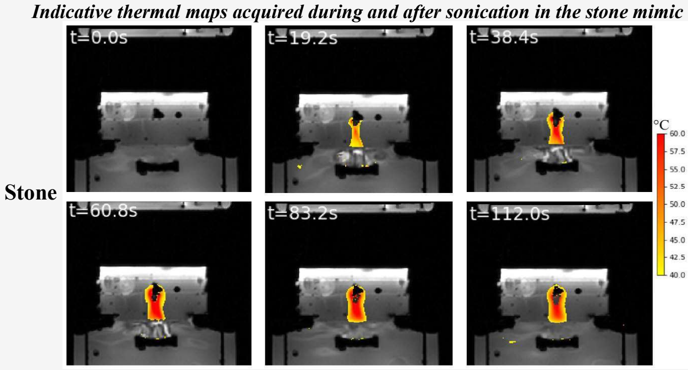
Axial thermal maps derived from FLASH sequence (TR = 25 ms, TE= 10 ms, slice thickness = 6 mm, flip angle =30°, NEX = 1, Pixel bandwidth = 240 Hz/pixel, Matrix size = 128x128) during and after sonication at focal depth of 45 mm.

- It was found that the bone and stone mimic blocked ultrasound.

Indicative thermal maps acquired during and after sonication in the bone mimic



Indicative thermal maps acquired during and after sonication in the stone mimic



Axial thermal maps derived from FLASH sequence (TR = 25 ms, TE= 10 ms, slice thickness = 6 mm, flip angle =30°, NEX = 1, Pixel bandwidth = 240 Hz/pixel, Matrix size = 128x128) during and after sonication at focal depth of 45 mm.

CONCLUSION

This inexpensive phantom was proven successful in studying the penetration of focused ultrasound through these mimics. It could serve as a useful model for evaluating the physics of focused ultrasound.

ACKNOWLEDGEMENTS

The study was co-funded by the European Structural & Investment Funds (ESIF) and the Republic of Cyprus through the Research and Innovation Foundation (RIF) under the projects SOUNDPET (INTEGRATED/0918/0008) and FUSVET (SEED/1221/0080).

Ευρωπαϊκή Ένωση
Ευρωπαϊκά Διαρθρωτικά και Επενδυτικά Ταμεία
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Opening of the Blood-brain barrier using focused ultrasound with simultaneous delivery of anti-Aβ antibodies in a 5XFAD amyloid beta mouse model

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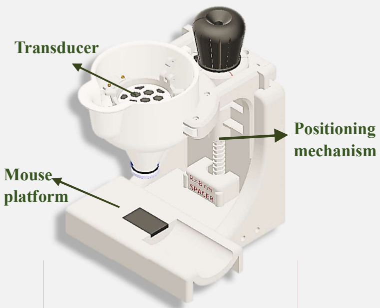
[3] Department of Neuroscience, The Cyprus Institute of Neurology and Genetics, Cyprus

OBJECTIVES

In this study we investigated the delivery of an anti-Aβ antibody in a mouse model of the Alzheimer's disease (AD) using microbubbles (MBs)-enhanced Focused Ultrasound (FUS) to open the Blood-brain barrier (BBB).

METHODS

Mechanical-based FUS was applied using a single-element FUS transducer of 1.05 MHz (80 mm radius of curvature and 50 mm diameter) as integrated with a manual positioning device.

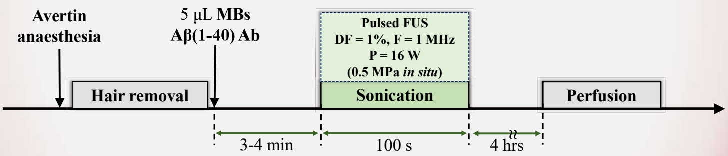


The initial experimental work involved Wild type mice and was devoted to selecting the sonication protocol for efficient and safe BBB opening. The success and extent of BBB opening was assessed by Evans Blue (EB) extravasation. Brain damage was assessed by hematoxylin and eosin (H&E) staining.

In the main experiment, 5XFAD AD mice were divided into 3 subgroups; **FUS+MBs alone (control)**, **antibody alone**, and **FUS+antibody** combined. The changes in antibody deposition among groups were determined by immunohistochemistry analysis.

RESULTS

Experiments in WT mice allowed for optimizing the protocol for safely and efficiently opening the BBB. 5XFAD mice (n=10) received pulsed FUS with the optimized protocol following antibody (Ab) injection.



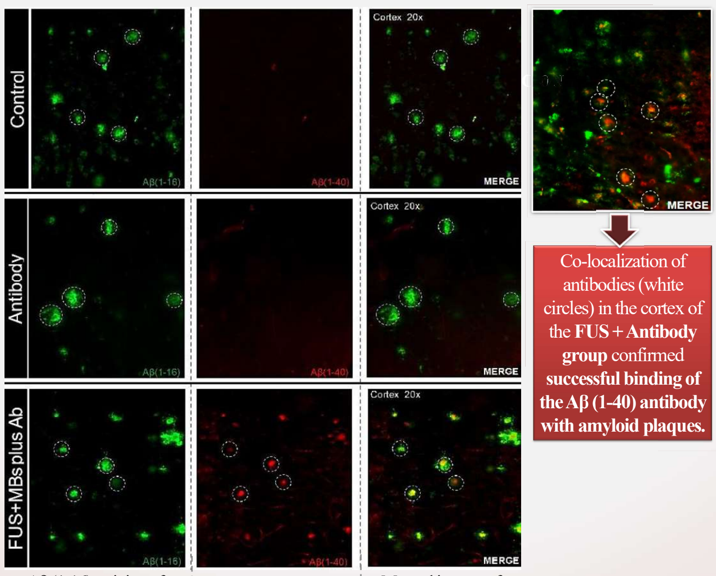
Protocol for antibody delivery in 5XFAD mice.

The selected FUS protocol showed consistent BBB opening as evidenced by EB leakage in fluorescence microscopy, and no evidence of brain damage in H&E staining.

Fluorescence images (5X) of unstained brain sections at the level of the cortex. Red color = EB dye.

It was confirmed that the antibody could not normally enter the brain parenchyma. With a single treatment with the proposed FUS protocol the BBB was consistently disrupted allowing for non-invasive antibody delivery to amyloid plaques within the sonicated brain regions in all 10 mice.

Indicative results of immunohistochemistry analysis of the treated cortex:



Aβ (1-16) staining of amyloid plaques (green) in the cortex. | Aβ (1-40) antibody staining in red color. | Merged images of antibody and plaques staining.

CONCLUSIONS

These preliminary findings are very promising but should be enhanced by longer-term studies examining the antibody effects on plaque clearance and cognitive benefit with the potential of developing disease-modifying anti-Aβ therapeutics for clinical use.

ACKNOWLEDGEMENTS

The study was co-funded by the European Structural & Investment Funds (ESIF) and the Republic of Cyprus through the Research and Innovation Foundation (RIF) under the project SOUNDPET (INTEGRATED/0918/0008).

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