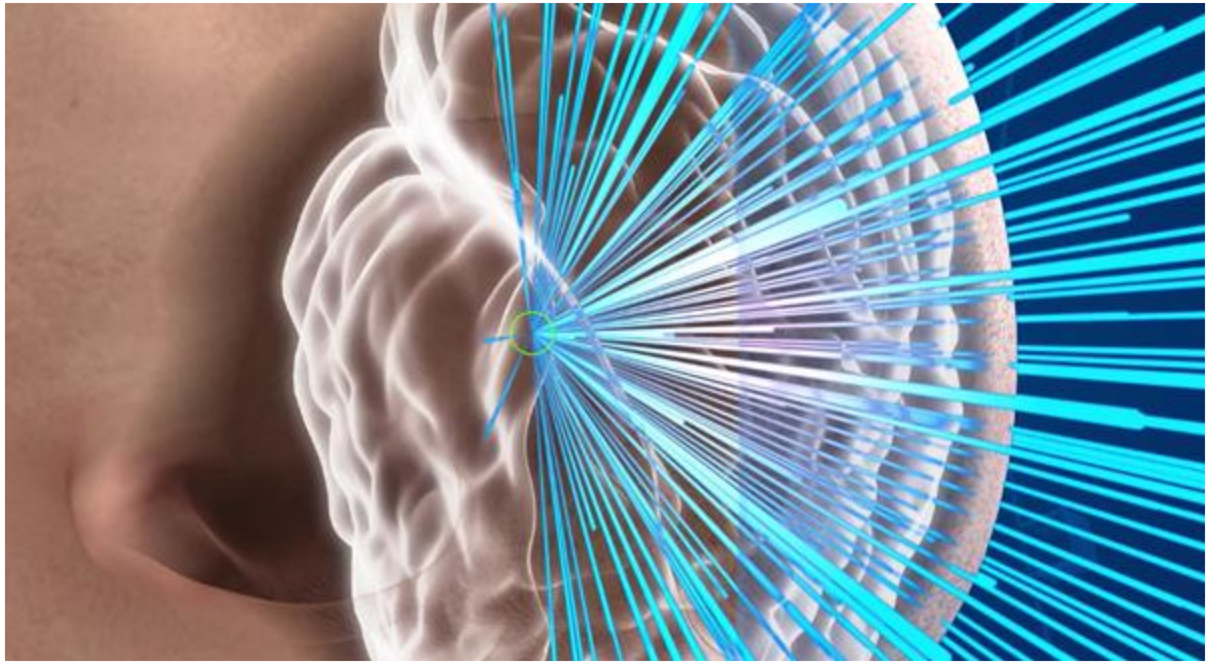
Low intensity focused ultrasound based therapeutic technologies for neurodegenerative and neurooncological diseases

Allegra Conti

Sezione di Fisica Medica, Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma ‘Tor Vergata’

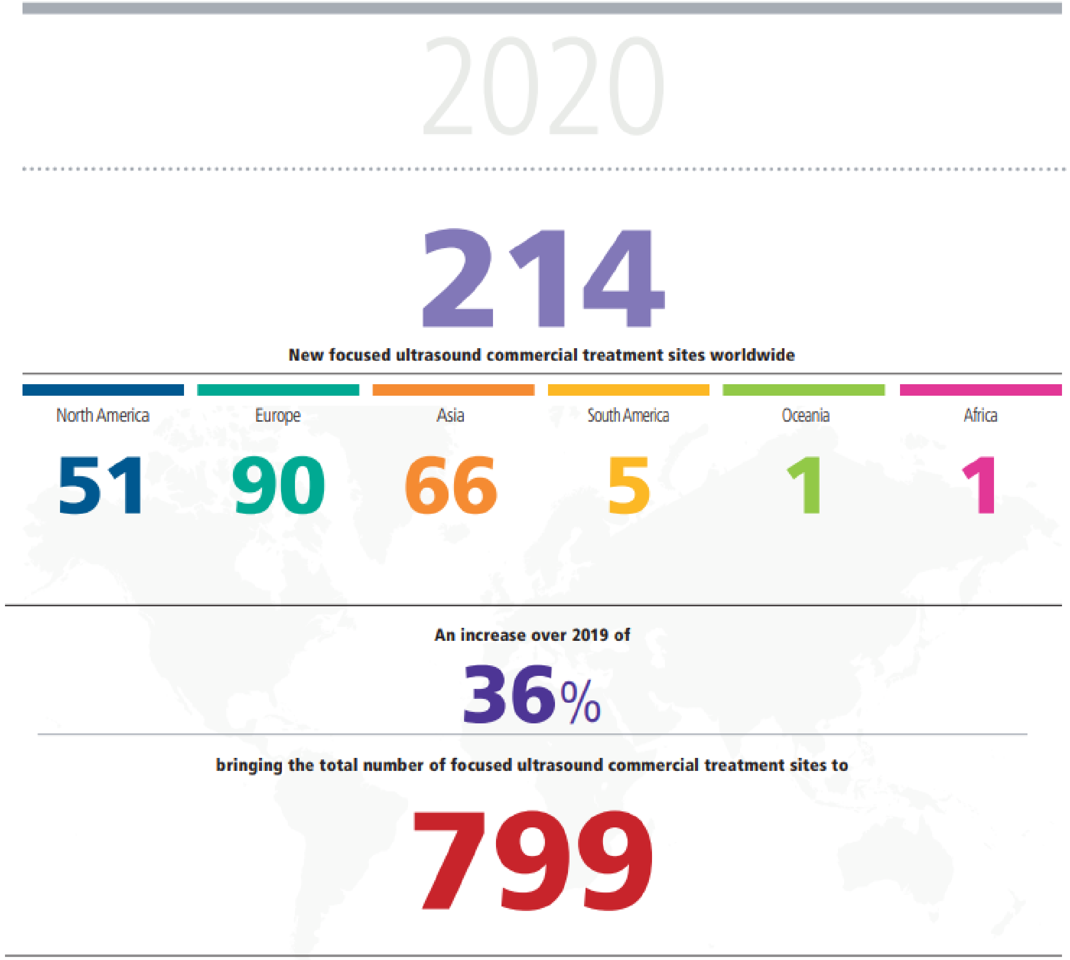


TOR VERGATA
UNIVERSITÀ DEGLI STUDI DI ROMA

Therapeutic Low intensity focused ultrasound

What is Focused Ultrasound?

Like a magnifying glass focuses light, focused ultrasound **concentrates ultrasound energy** on a target in the **body without harming nearby tissue.**



HIFU vs LIFU

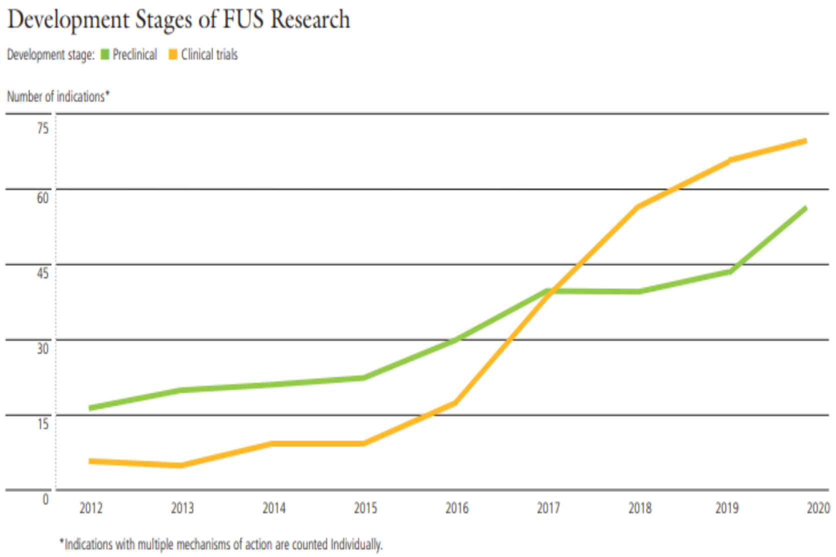
High Intensity focused ultrasound (HIFU)

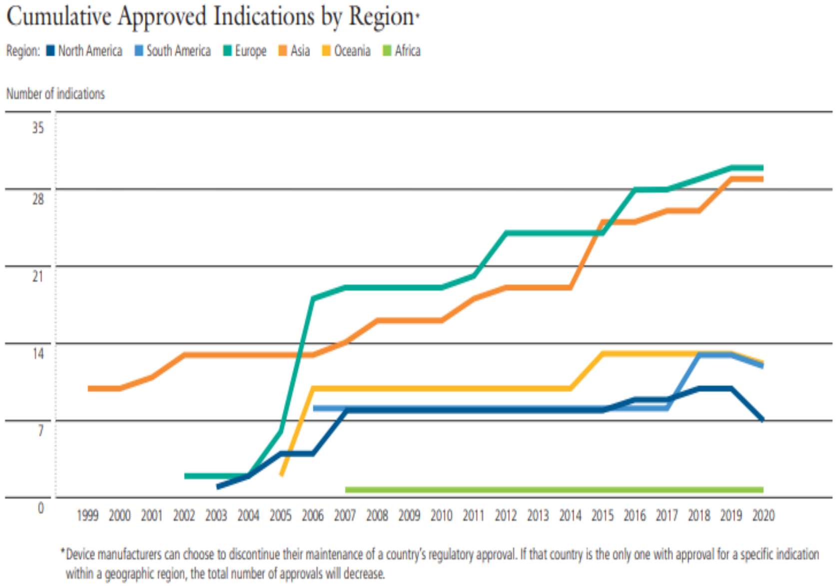
- Irreversible cell death
- Surgical Ablation (e.g. Essential tremor)

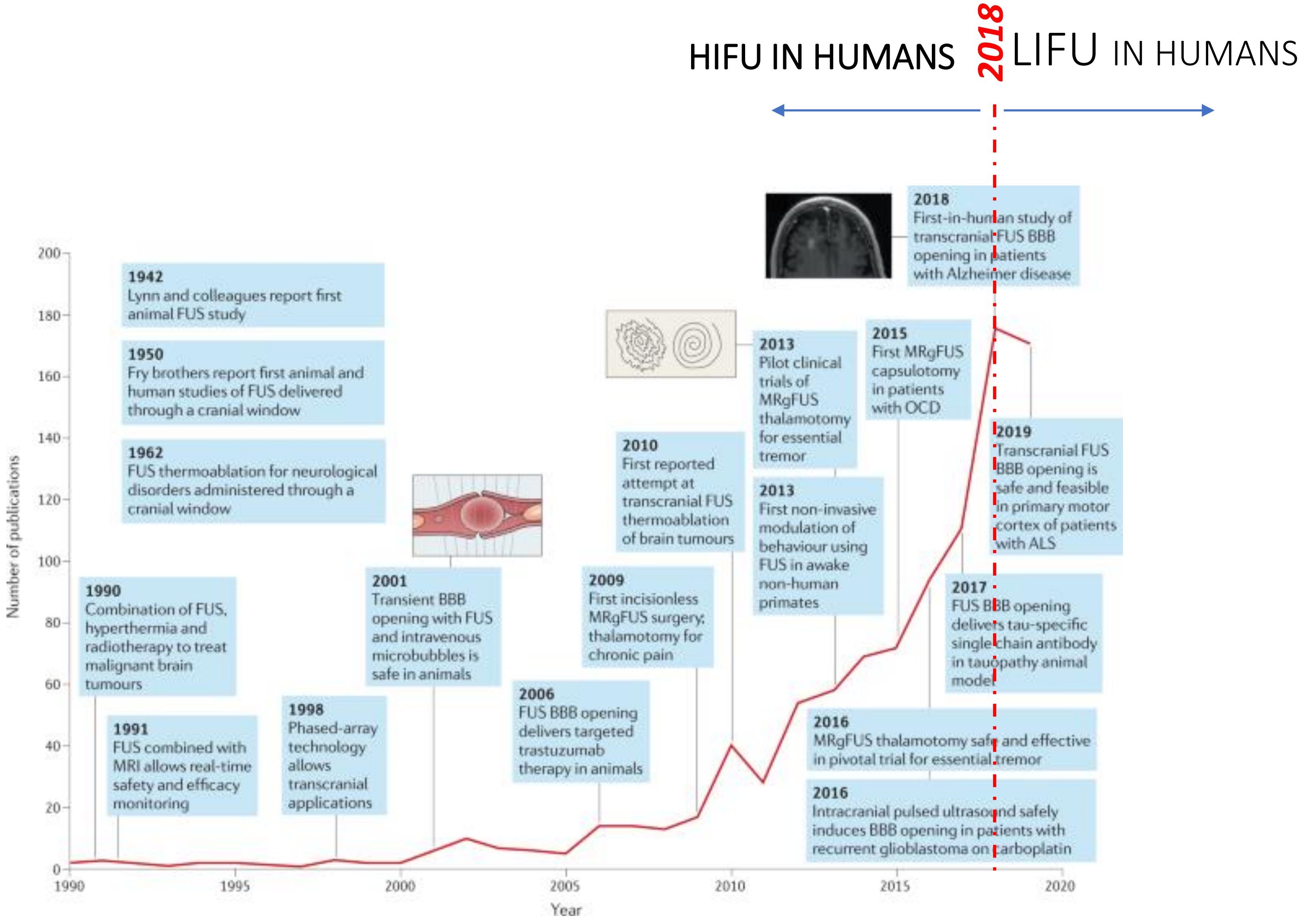
Low-intensity focused ultrasound (LIFU)

- Reversible biological effects
- Safe and repeatable
- More focused than e.g. magnetic/electric fields
- Manifold applications in e.g. tissue permeabilization, neuromodulation, WPT
- Poised to enter more and more field in biomedical research

Therapeutic Low intensity focused ultrasound





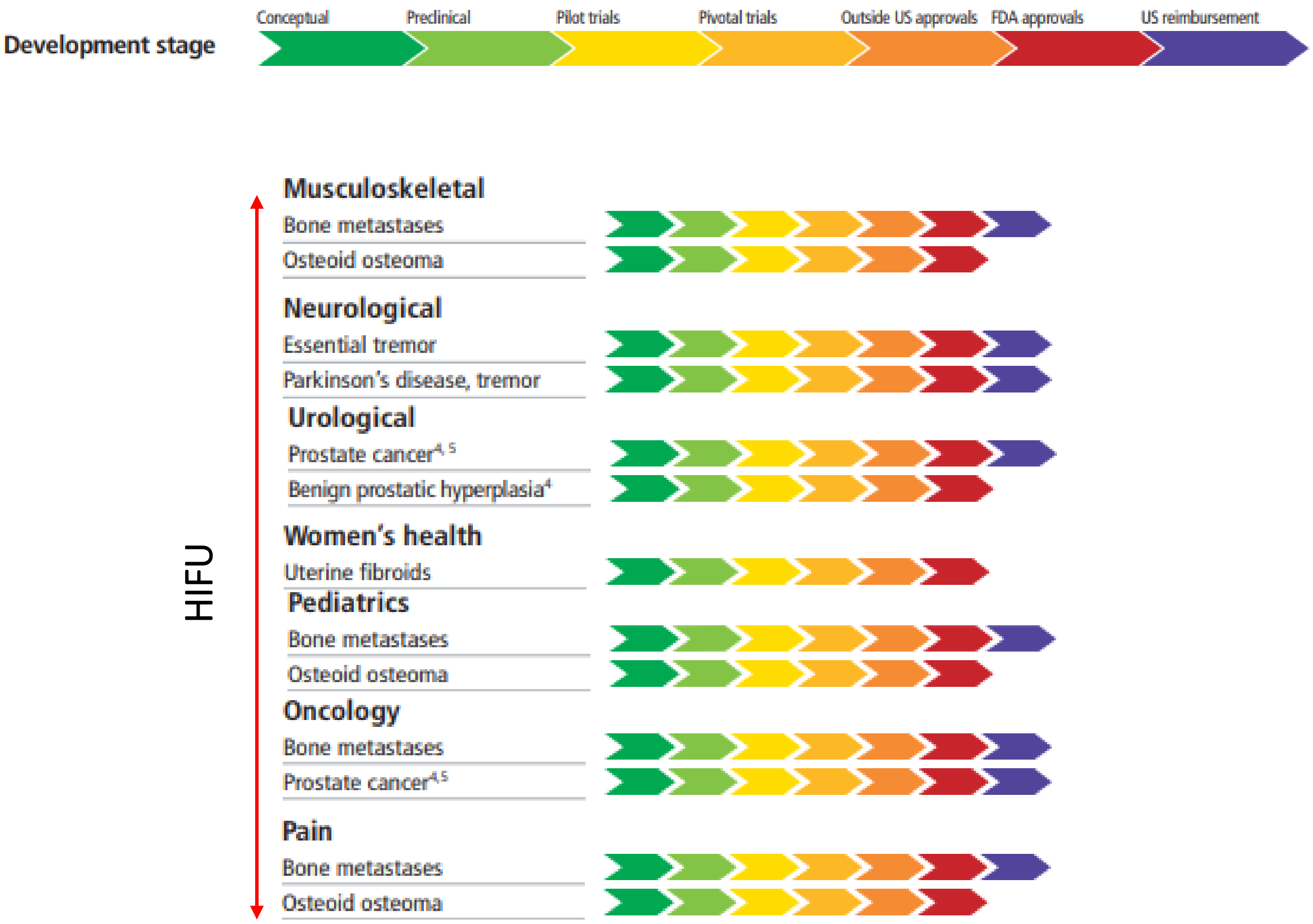


Therapeutic Low intensity focused ultrasound

What Can it Treat?

Worldwide, focused ultrasound is approved to treat more than 20 diseases and is being researched to treat many more.

Note: ALL HIFU



Therapeutic Low intensity focused ultrasound

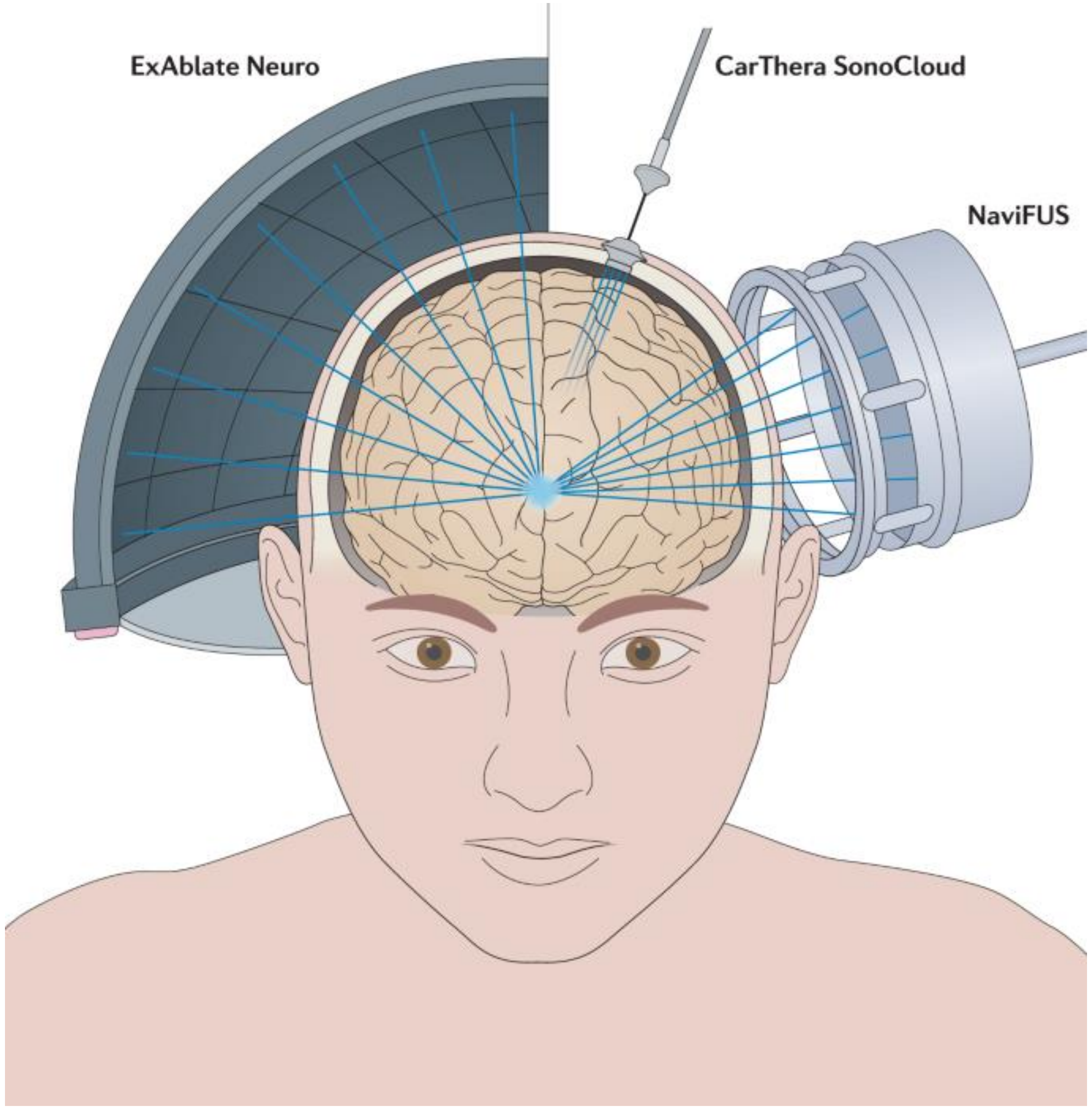
Therapeutic applications range from **deep brain neuromodulation** to reversible **blood-brain barrier opening** for a local enhancement of therapeutics uptake into the brain tissue.

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
Nonthermal | Neuromodulation				
Alzheimer's disease	1	–	1	**2**
Cancer pain	1	–	–	**1**
Depression	4	4	–	**8**
Epilepsy	9	3	–	**12**

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
Nonthermal - BBB opening | Drug delivery, vehicle				
Glioblastoma	1	–	–	**1**
Nonthermal - BBB opening | Gene delivery				
Huntington's disease	1	–	–	**1**
Parkinson's disease, tremor	1	–	–	**1**
Parkinson's disease, underlying cause	4	–	–	**4**
Rett syndrome	1	–	–	**1**
Nonthermal - BBB opening | Stem cell delivery				
Alzheimer's disease	1	–	–	**1**

Ultrasound application | Biological effects	Stages: Preclinical	Clinical	Commercial	Total[1]
Nonthermal - BBB opening | BBB opening				
Alzheimer's disease	7	6	–	**10**
Amyotrophic lateral sclerosis	1	–	–	**1**
Brain tumors, general	2	–	–	**2**
Breast tumors, malignant	1	–	–	**1**
Dementia	1	–	–	**1**
Epilepsy	1	–	–	**1**
Glioblastoma	–	7	–	**7**
Opioid and other addictions	1	–	–	**1**
Parkinson's disease, underlying cause	–	1	–	**1**
Nonthermal - BBB opening | Drug delivery				
Alzheimer's disease	7	5	–	**11**
Amyotrophic lateral sclerosis	1	–	–	**1**
Astrocytoma	2	–	–	**2**
Brain metastases, breast cancer	2	1	–	**2**
Brain tumors, general	1	1	–	**2**
Dementia	–	1	–	**1**
Epilepsy	2	–	–	**2**
Glioblastoma	14	5	–	**16**
Neuromyelitis optica	1	–	–	**1**
Parkinson's disease, underlying cause	6	1	–	**6**
Pontine glioma	1	–	–	**1**
Spinal cord injury	2	–	–	**2**
Stroke, intracerebral hemorrhage	1	–	–	**1**
Stroke, thromboembolic	2	–	–	**2**
Traumatic brain injury	1	–	–	**1**
Nonthermal - BBB opening | Drug delivery, immunotherapeutic				
Alzheimer's disease	2	–	–	**2**
Astrocytoma	1	–	–	**1**
Glioblastoma	1	–	–	**1**

Low intensity focused ultrasound systems



Meng et al., Nature reviews (2020)

- ExAblate Neuro INSIGHTEC

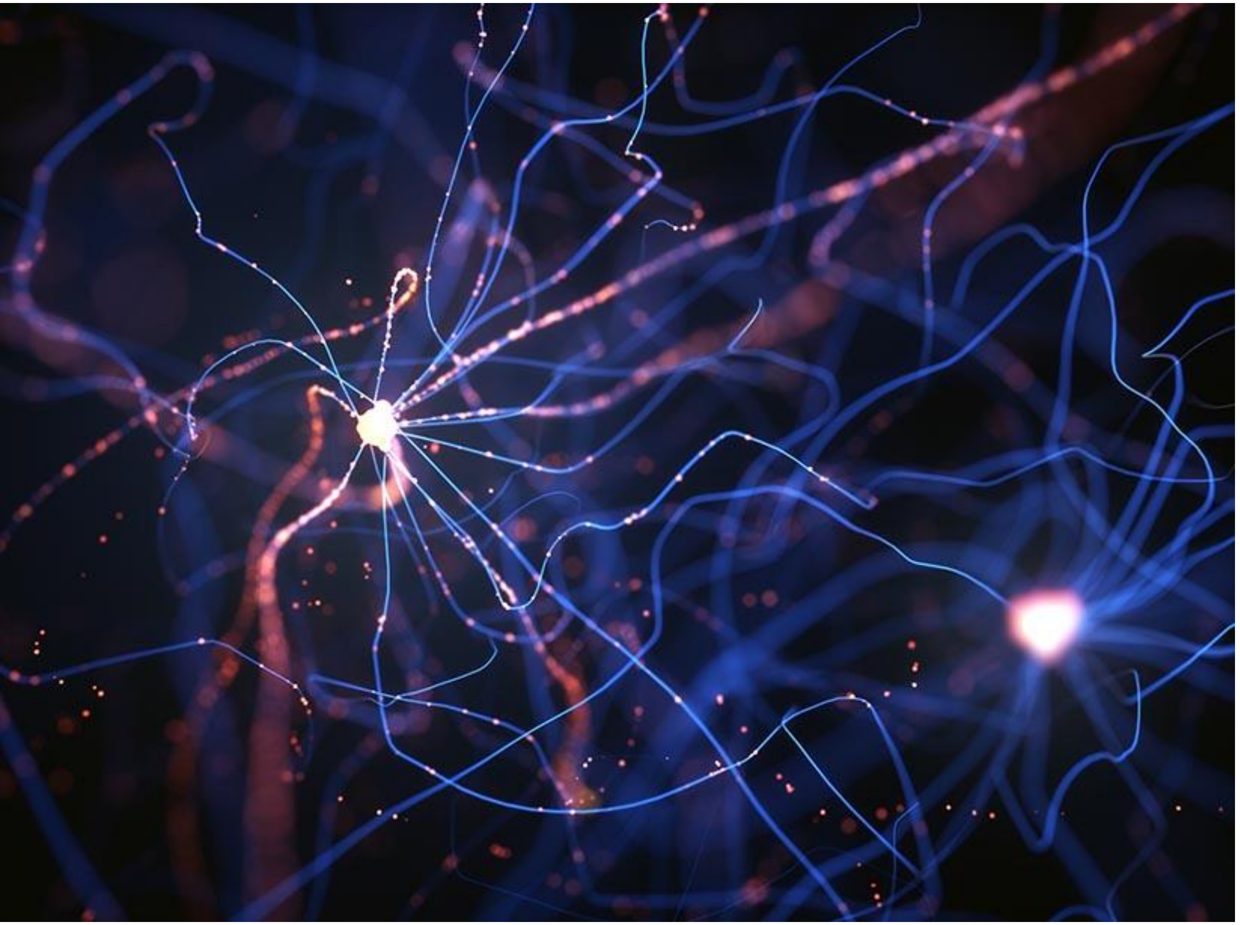
✓ Very precise (MR guidance and multi array)
X Expensive
X It's use for LIFUS applications limited by the company

- SonoCloud CARTHERA Advanced Brain Therapy Through Innovation

✓ Already in use in clinical trials aiming at treating brain tumors
X Suitable only for BBB opening and drug delivery
X Invasive

- NaviFUS NaviFUS

✓ Already in use in clinical trials
✓ Suitable both for BBB opening and NeuroStimulation
✓ Less expensive than ExAblate
X Single Element transducer (larger focus than with phase arrays)
X Not MR guided



Acoustic Neuromodulation

Acoustic Neuromodulation: Mechanisms

There are numerous hypotheses that aim to explain the modulation mechanisms induced by FUS.

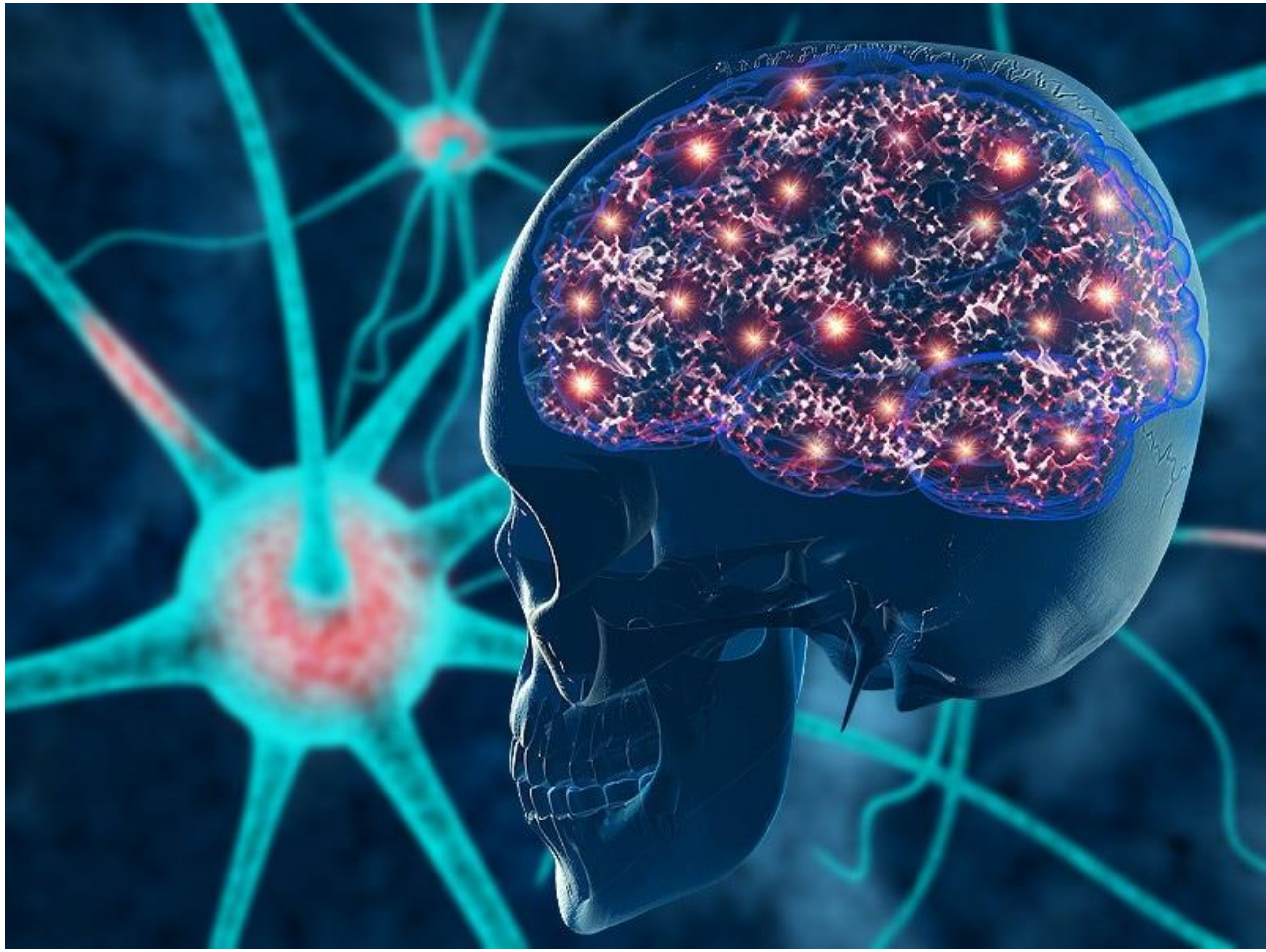
These assumptions are based on

- Mechanical Effects:

The interference of ultrasound with the depolarization of the membrane through its mechanical deformation.

Activation of mechanosensitive ion channels in neurons and other types of brain cells such as astrocytes

- Thermal effects



Acoustic Neuromodulation: Mechanisms

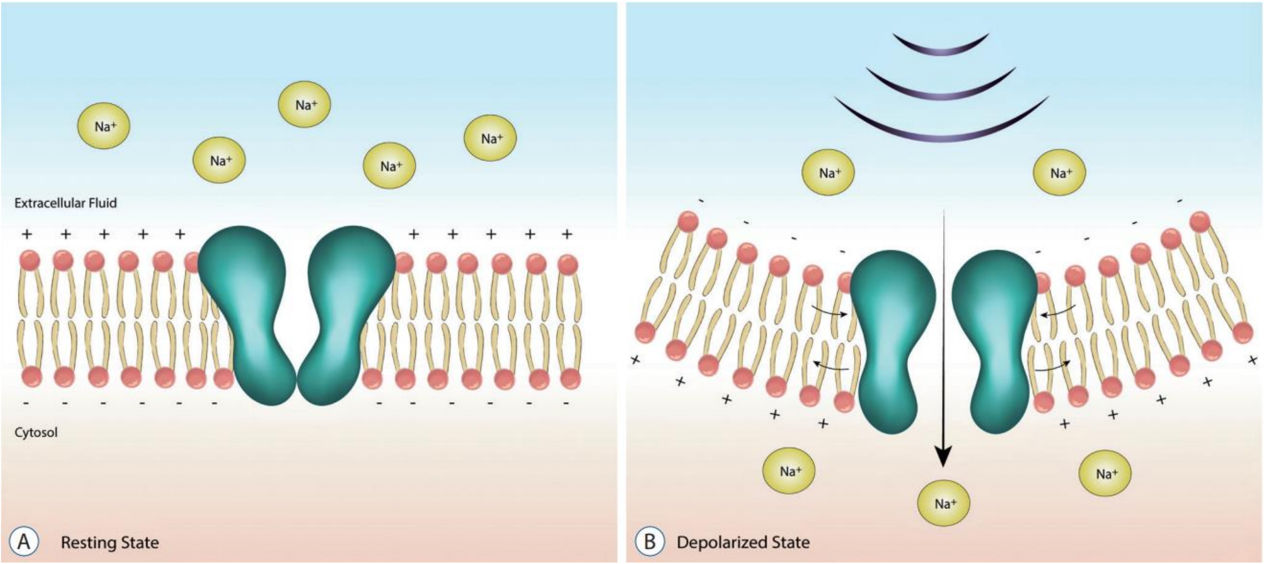
Mechanical Effect

The mechanical energy of ultrasound generates periodic expansions and contractions of the membrane.

The effect is mediated by various mechanisms.

1st mechanism: activation of mechanosensitive proteins

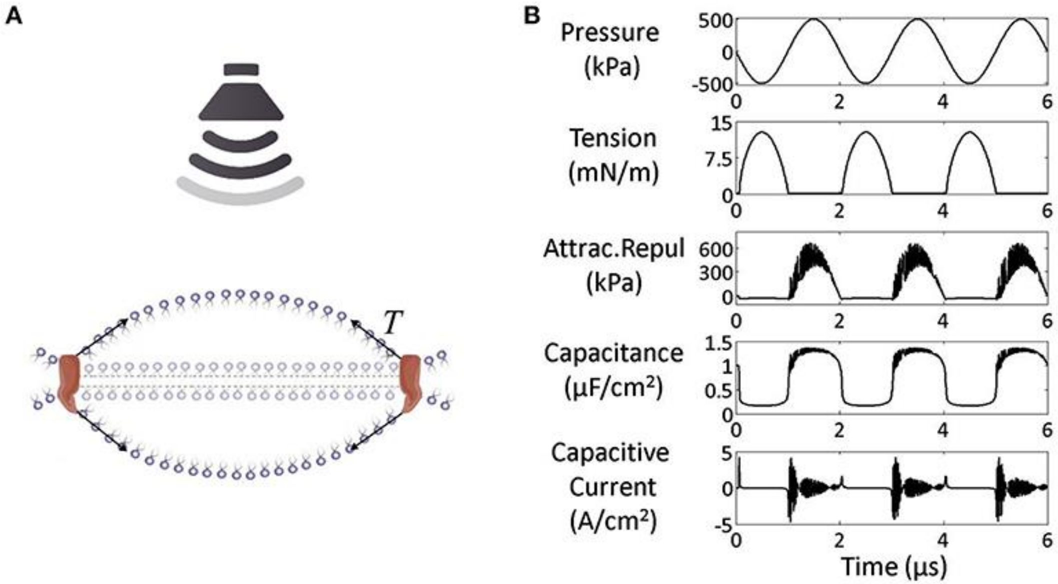
The pressure of the acoustic radiation mechanically lengthens the lipid bilayer of neurons by opening voltage-gated ion channels with mechanosensitive properties, including sodium, calcium and potassium channels (Na +, Ca2 + and K +), which in turn cause depolarization and neuronal excitation .



Lee et al., Journal of Korean Neurosurgical Society (2018)

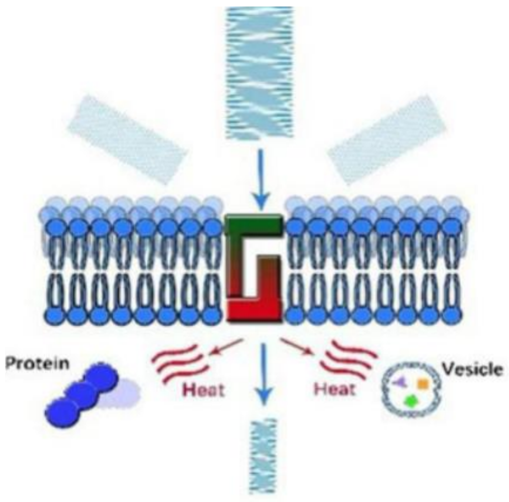
2nd mechanism: Cavitation

The mechanical energy of ultrasound generates periodic expansions and contractions of the membrane (CAVITATION) which modify its capacity. This phenomenon creates capacitive currents, which can potentially activate voltage-gated sodium and potassium channels



Di Biase al., Frontiers in Neurology (2019)

Acoustic Neuromodulation: Mechanisms



Thermal Effect

Only in certain acoustic regimes (high intensity, DC, RPF).

The acoustic energy is absorbed and dispersed in the passage of the FUS in the tissues. The energy released by the ultrasonic beam to the tissues is converted into heat, which generates a **local temperature rise and modification the capacity of the membrane.**

The thermal effect can alter neuronal functions **

- **Reversibly modify synaptic transmission (therapeutic action)**
- Irreversibly denaturing proteins (harmful action)
- Thermoablating the tissue (non-functional action to neurotransmission)

** To avoid potentially harmful overheating effects, the American Institute of Ultrasound in Medicine (AIUM) has set the following acoustic intensity limits not to be exceeded in experiments on mammals (including humans)

intensity <100 mW / cm^2 / temporal exposure <500 s for unfocused ultrasound
intensity <1 W / cm_2 / temporal exposure <50 s for FUS.

Acoustic Neuromodulation: Possible applications

FUS treatments:

- Alzheimer's Disease
- Depression
- Epilepsy

Alzheimers Dement (N Y). 2021; 7(1): e12121.
Published online 2021 Feb 25. doi: 10.1002/trc2.12121
PMCID: PMC7906128
PMID: 33681449

Transcranial ultrasound pulse stimulation reduces cortical atrophy in Alzheimer's patients: A follow-up study

Tudor Popescu,[1,2] Cyril Pernet,[3] and Roland Beisteiner[2]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Received: 4 July 2020 | Revised: 5 September 2020 | Accepted: 24 September 2020
DOI: 10.1111/cns.13463

CNS Neuroscience & Therapeutics WILEY

ORIGINAL ARTICLE

Low-intensity pulsed ultrasound ameliorates depression-like behaviors in a rat model of chronic unpredictable stress

Jinniu Zhang[1] | Hui Zhou[2] | Jian Yang[1,3] | Jun Jia[4] | Lili Niu[2] | Zuoli Sun[1] | Dandan Shi[1] | Long Meng[2] | Weibao Qiu[2] | Xiaomin Wang[4] | Hairong Zheng[2] | Gang Wang[1,3]

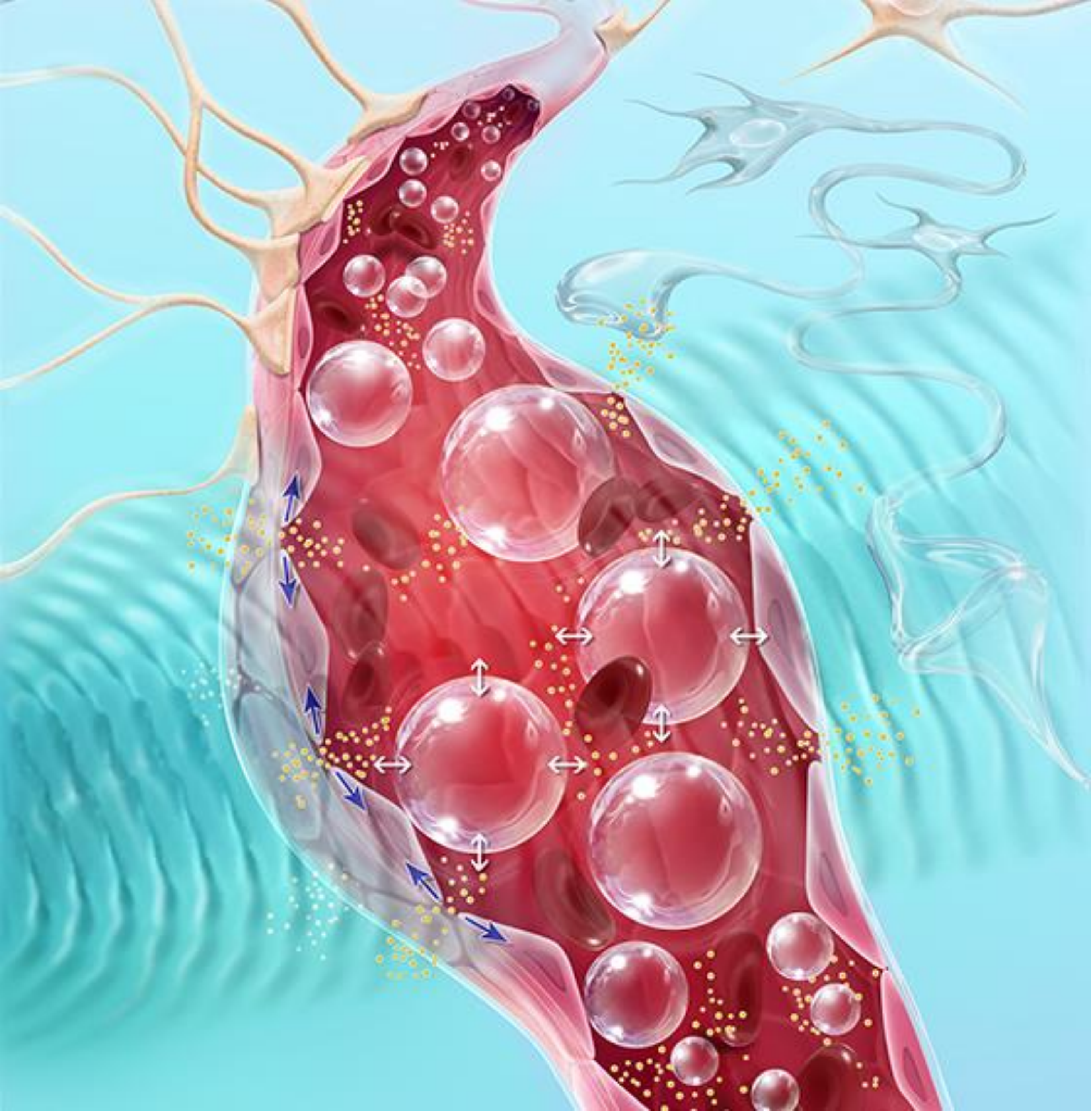
Received: 3 June 2021 | Revised: 7 October 2021 | Accepted: 7 October 2021
DOI: 10.1111/epi.17105

Epilepsia

RESEARCH ARTICLE

Pilot study of focused ultrasound for drug-resistant epilepsy

Cheng-Chia Lee[1,2,3] | Chien-Chen Chou[2,3,4] | Fu-Jung Hsiao[3] | Yi-Hsiu Chen[1] | Chun-Fu Lin[1,2] | Ching-Jen Chen[5] | Syu-Jyun Peng[6] | Hao-Li Liu[7] | Hsiang-Yu Yu[2,3,4]



FUS-induced
Blood- Brain Barrier Opening

The blood-brain barrier is the limiting factor to cure brain diseases but it can be transiently disrupted using ultrasound

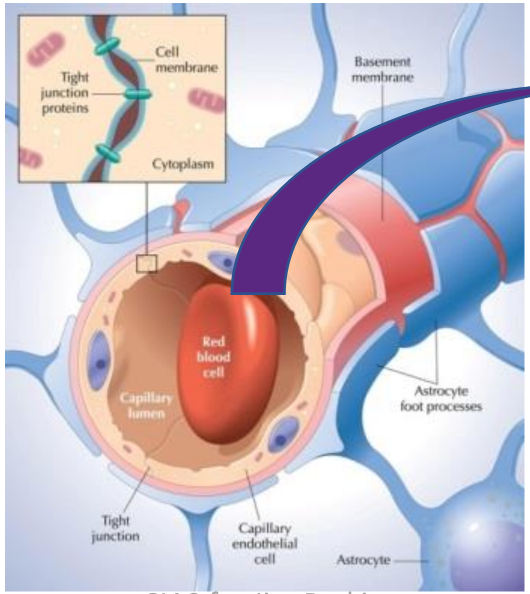
Blood Brain Barrier:

Allows:

- ✓ the passage of water, some gases, and lipid-soluble molecules by passive diffusion
- ✓ the selective transport of molecules such as glucose and amino acids that are crucial to neural function

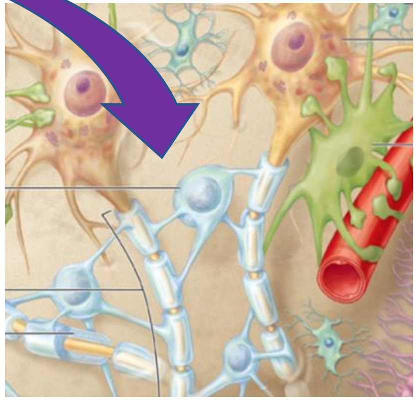
Impedes:

- X the passive diffusion of 95 % of small molecules and 100% of biotherapies, especially ionic, hydrophilic or large (> 400 Da) molecules



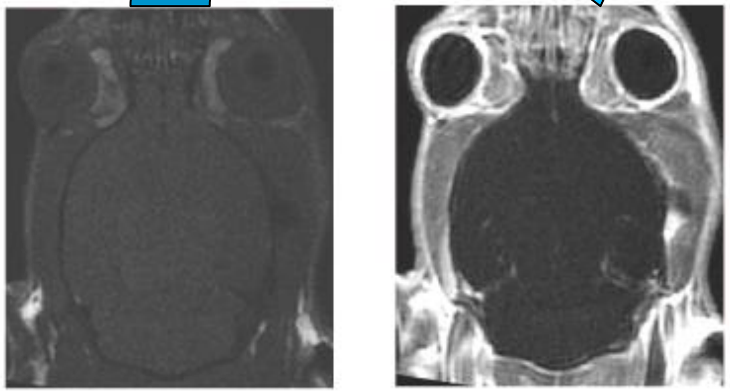
CIAS for Jim Perkins

- ✓ Water
- ✓ Oxygen
- ✓ Glucose



Brain Extracellular Space

Injection of MRI T_1 contrast agent (Dotarem, 500 Da)



..but it can be transiently opened by using ultrasound!

Ultrasound aided drugs delivery within the brain

microbubbles intravenous injection

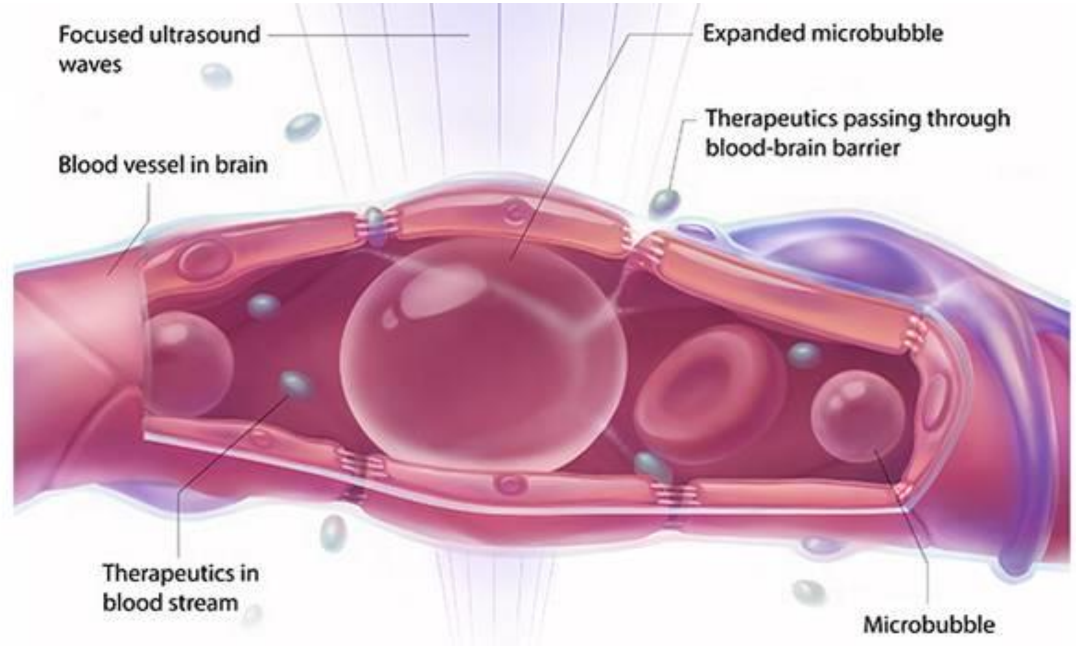
+

low intensity pulsed focused ultrasound

=

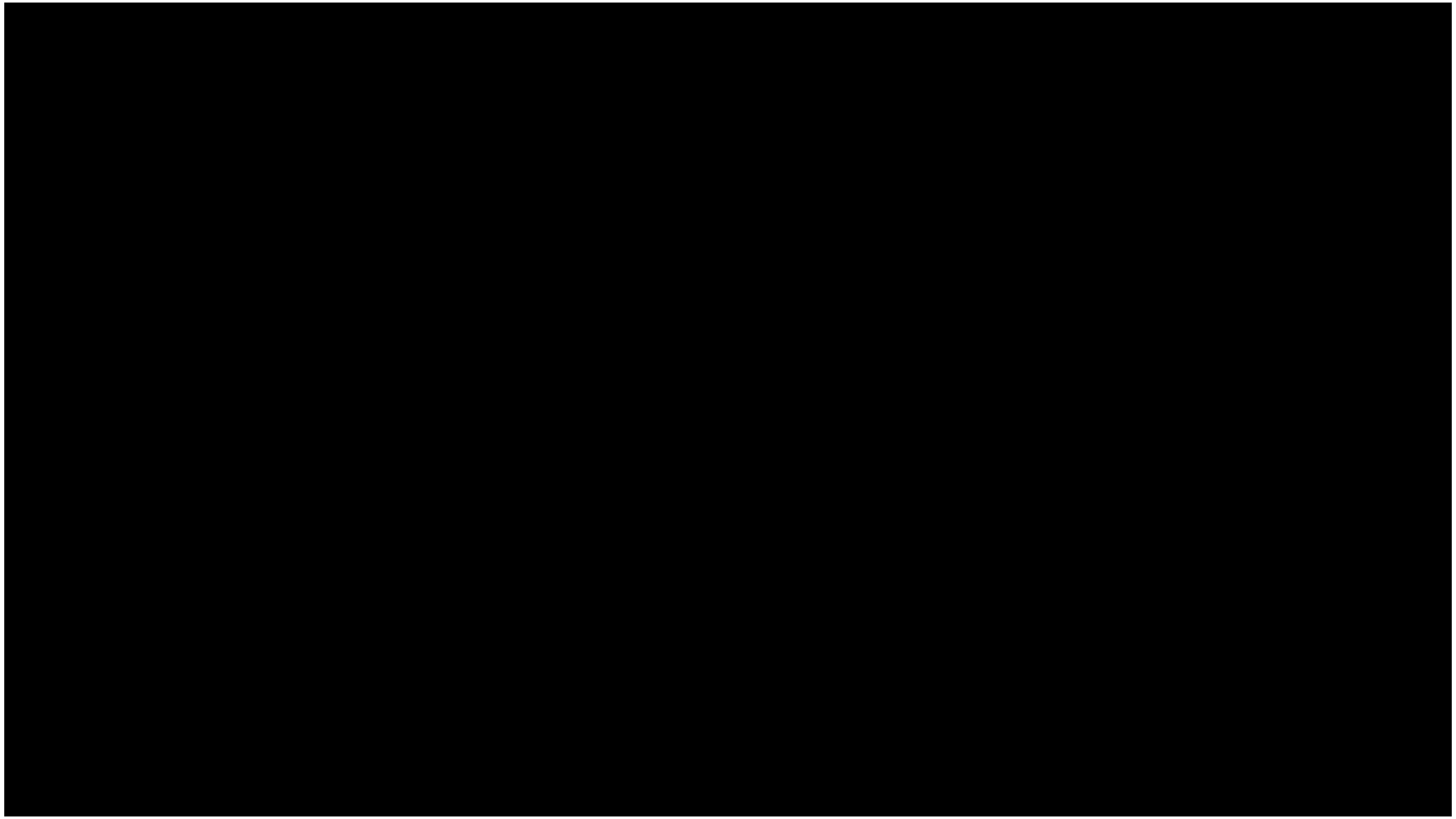
Reversible BBB opening

(Hynynen et al., Radiology, 2001)



Prof. I. Aubert, University of Toronto

Ultrasound aided drugs delivery within the brain



Ultrasound aided drugs delivery within the brain

Technique mainly used to:

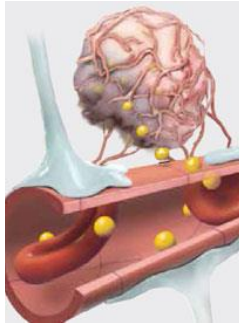
- **Target Delivery of theranostics particles/ therapeutics molecules to specific regions of the brain** (e.g. anti-amyloid antibodies delivered to reduce widespread plaque pathology antibodies, plasmids and viral vectors)

- **Treatment of brain tumours where the access of the drug would be limited to the tumour and it's periphery** (principally chemioterapeutics)

- reducing of the administrated particles dose
- preventing from accessing the remaining healthy brain tissue

Ultrasound aided drugs delivery to brain tumors

Brain tumors therapy is limited by



- Blood-Tumor Barrier, more permeable than BBB
- Blood-Brain Barrier, still intact in the infiltrative areas.

Previous studies have already used Ultrasound to deliver particles to brain tumors…

Table 2. Summary of using MB-FUS BBB opening for preclinical brain tumor therapy.

Author, Year	MBs type	Animal model	Substance delivered	Study conclusion	Ref.
Treat et el, 2007, 2012	Optison	Rat 9L glioma model	Liposomal-DOX [70-100 nm]	MB-FUS + Liposomal-Dox delivery controlled tumor progression and improved animal survival	[78,79]
Liu et al., 2010	Sonovue	Rat C6 glioma model	Evans Blue [960 Da], BCNU [214 Da *]	Unfocused low-frequency (28-kHz) US with 6-10 min exposure Obtain wide areas of BBB opening and low incidence of hemorrhagic complications	[111]
Liu et al., 2010	Sonovue	Rat C6 glioma model	BCNU [214 Da], Evans Blue [960 Da *], Magnevist [928 Da]	Delivery of chemotherapeutic agent BCNU MB-FUS + BCNU provide better tumor progression control and animal median survival improved by 72%	[81]
Liu et al., 2010	Sonovue	Rat C6 glioma model	Epirubicin [544 Da], MNP [6-12 nm], Evans Blue [960 Da *], Magnevist [928 Da]	Delivery of chemotherapeutic agent Epirubicin conjugated on magnetic nanoparticle Epirubicin-loaded MNPs + FUS + MT increase in MNP delivery and slowed tumor growth	[106]
Chen et al., 2010	Sonovue	Rat C6 glioma model	BCNU [214 Da], BCNU on Fe_3O_4SPAnH nanoparticles [10-20 nm], Magnevist [928 Da]	Delivery of chemotherapeutic agent BCNU conjugated with magnetic Fe3O4SPAnH particles following FUS and magnet applied for 24 h to target Improved BNCU delivery	[112]
Yang et al., 2012	Sonovue	Rat F98 glioma model	Evans Blue [960 Da *], Omniscan [573 Da], 99mTc-DTPA [492 Da]	Applied SPECT/CT to monitor MB-FUS-BBB opening	[59]
Yang et al., 2011	Sonovue	Rat F98 glioma model	Evans Blue [960 Da *], Omniscan [573 Da]	Increase in EB extravasations in sonicated brain with significant EB concentration increase Damage occurred after repeated sonication	[50]
Yang et al., 2012	Sonovue	Mice GBM-8401 model	Liposomal-DOX [70-100 nm]	Radio-labeled liposomal-DOX to perform PK analysis in nuclear imaging Animals receiving the drugs followed by MB-FUS-BBB opening	[113]
Yang et al., 2012	Sonovue	Mice GBM-8401 model	Liposomal-DOX [70-100 nm]	MB-FUS-BBB opening enhanced accumulation of the drug in tumor cells Significantly inhibited tumor growth compared with chemotherapy alone	[114]
Ting et al., 2012	BCNU-loaded MBs (Self-made)	Rat C6 glioma model	BCNU [214 Da], Evans Blue [960 Da *]	Development of BCNU drug-loaded MBs for drug delivery BCNU-MBs prolonged half-life of BCNU by over 5-fold Tumor progression was successfully suppressed by BCNU-MBs + FUS	[103]

Theranostics 2014, Vol. 4, Issue 4 432
IVYSPRING INTERNATIONAL PUBLISHER
Theranostics
2014; 4(4):432-444. doi: 10.7150/thno.8074

Review

Combining Microbubbles and Ultrasound for Drug Delivery to Brain Tumors: Current Progress and Overview

Hao-Li Liu[1], Ching-Hsiang Fan[2], Chien-Yu Ting[2], and Chih-Kuang Yeh[2,✉]

…ontrolled Release
…28 April 2013, Pages 167–174
ELSEVIER

Ultrasound-aided microbubbles facilitate the delivery of drugs to the inner ear via the round window membrane

Cheng-Ping Shih[a, b], Hsin-Chien Chen[b], Hang-Kang Chen[b], Min-Chang Chiang[b], Huey-Kang Sytwu[c], Yi-…
…ung Wang[a, b, c, e]

ELSEVIER
Journal of Controlled Release
Volume 138, Issue 3, 15 September 2009, Pages 268–276

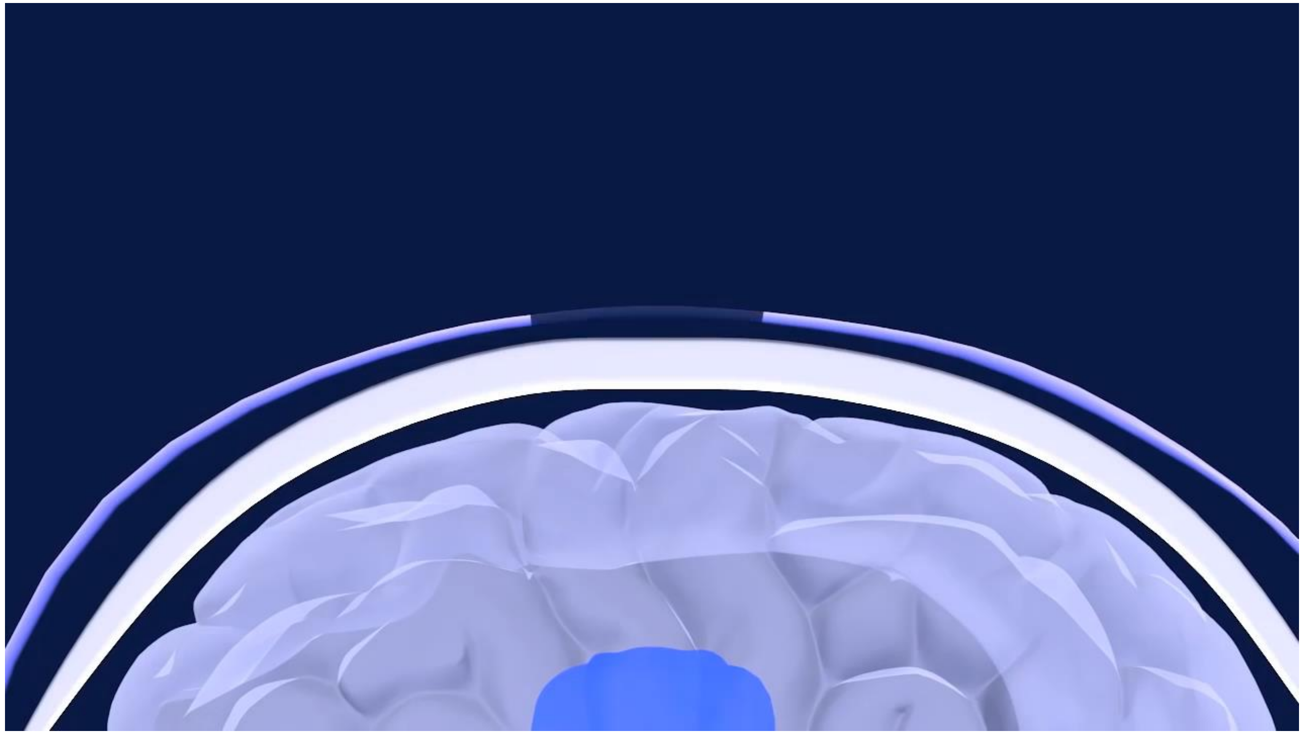
Controlled and targeted tumor chemotherapy by ultrasound-activated nanoemulsions/microbubbles

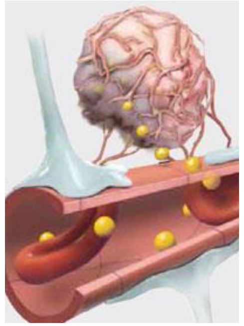
Natalya Y. Rapoport[a], Anne M. Kennedy[b], Jill E. Shea[c], Courtney L. Scaife[c], Kweon-Ho Nam[a]
Show more

Ultrasound aided drugs delivery to brain tumors

Brain tumors therapy is limited by

- Blood-Tumor Barrier, more permeable than BBB
- Blood-Brain Barrier, still intact in the infiltrative areas.





CARTHERA
Advanced Brain Therapy Through Innovation

- <u>Invasive</u>
- <u>The position of the transducer is fixed: **only one region of the brain can be treatead**</u>

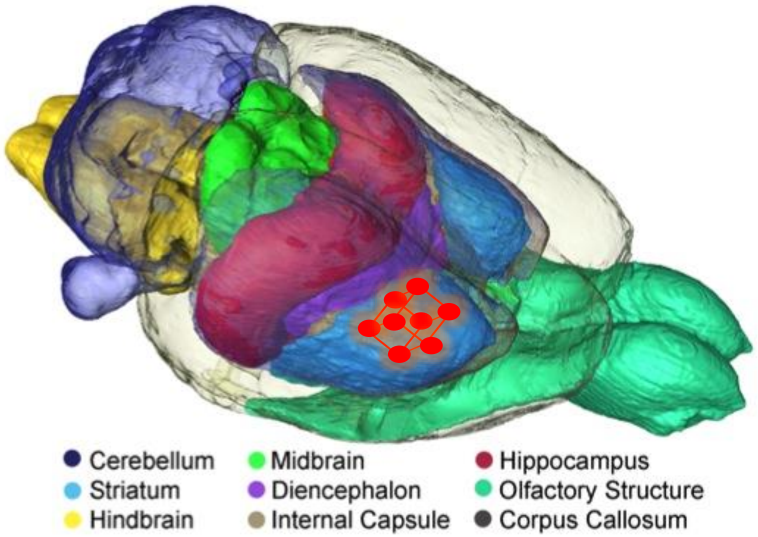
Ultrasound aided drugs delivery to brain tumors

The goal of this study:

- **Enhancing radiosensitizing nanoparticles concentration within tumors, by using delivery induced by focused ultrasound**

- **Study their uptake and clearance to choose the best time for radiotherapy**

8 points sonication
covering the peripheric areas of the tumors



Materials and Methods:

Animals:

8 Ficher rats (WT)

Age: 6 months old

Sex: Female

Weight: 250 g (before tumor implantation)-180 g (at the sacrifice)

Tumor cells: 9Lp + 12.5 µL (20 millions/mL)

Implantation of two tumors (one used as control)

Treatment: 2-3 weeks after the tumor implantation

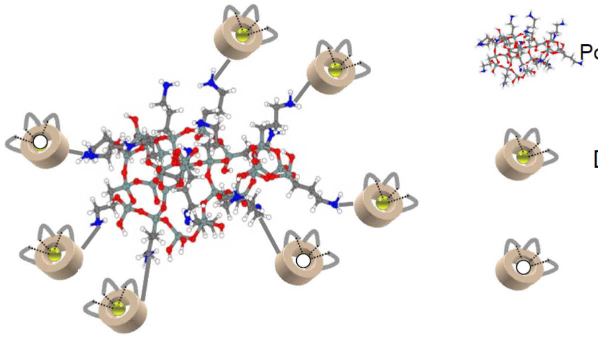
Ultrasound: 8 points sonication, 1.2 MPa, 1.5 MHz, 3% DC (3 ms time per shot/ 115 ms pause)

Materials and Methods:

Compound used:

AGuIX : 50 µmol of powder diluted in 200 µL pf PPI water + 160 µL of Dextran (25 mg/mL, size 70 kDa).

AGuIX ® TherAguix



Kotb *et al*, Theranostics 2016

Main Characteristics of AGuIX Nanoparticles	
Chemical composition	$Gd_{10}Si_{40}C_{200}N_{50}O_{150}H_x$
Molar mass	8.5 ± 1 kDa
Size	3 ± 0.1 nm
Zeta potential	9.03 ± 5.5 mV

AGuiX is a theranostic agent since :

- **The efficacy of radiotherapy can be boosted by using high-atomic-number materials such as gadolinium to increase the target's absorption of ionizing radiation.**

- **Gadolinium acts as an MRI contrast agent.**

Ultrasound aided drugs delivery to brain tumors

Materials and Methods:

Compound used: AGuIX

NIH U.S. National Library of Medicine
ClinicalTrials.gov

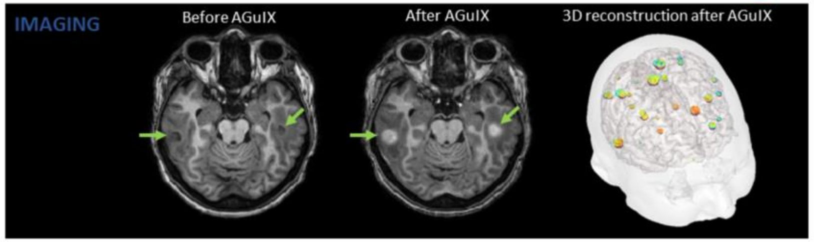
HEALTH AND MEDICINE

Targeting brain metastases with ultrasmall theranostic nanoparticles, a first-in-human trial from an MRI perspective

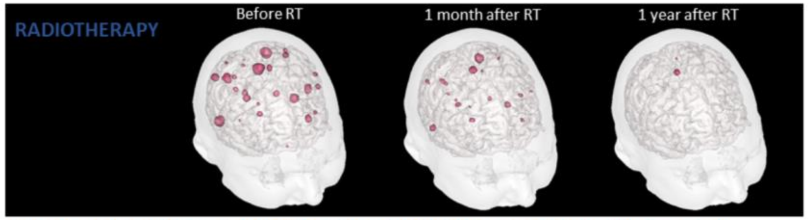
Camille Verry[1], Sandrine Dufort[2], Benjamin Lemasson[3], Sylvie Grand[1], Johan Pietras[4], Irène Tropres[4], Yannick Crémillieux[5]*, François Lux[6], Sébastien Mériaux[7], Benoit Larrat[7], Jacques Balosso[1], Géraldine Le Duc[2], Emmanuel L. Barbier[3], Olivier Tillement[6]

NANORAD Phase1b trial

Radiosensitization of brain metastases using AGuIX with Radiotherapy
Selected example



Targeting and contrast enhancement after AGuIX intravenous injection @100 mg/kg on a brain metastases patient
The targeting was proven on 15 patients over 15



Reduction of the total tumor size of 45 % 1 month and of 97 % 1 year after initiation of the treatment
Clinical benefit was shown for 13 patients over 14

Row	Saved	Status	Conditions	Locations
1	☐	Completed	• Brain Metastases	• University Hospital Grenoble Grenoble, France
2	☐	Recruiting	• Brain Metastases, Adult • Radiotherapy	• Institut Régional du Cancer Montpellier, Occitanie, France • Institut Claudius Regaud Institut Universitaire du Cancer Toulouse Oncopole Radiothérapie Toulouse, Occitanie, France • Centre Leon Berard Lyon Lyon, Rhones Alpes, France • (and 12 more...)
3	☐	Recruiting	• Glioblastoma	• CHU de Brest Brest, France • Centre Jean Perrin Clermont-Ferrand, France • CHU de Grenoble Grenoble, France • (and 3 more...)
4	☐	Terminated	• Brain Metastases	• Centre Léon Bérard Lyon, France • Centre Antoine Lacassagne Nice, France
5	☐	Recruiting	• Brain Cancer • Brain Metastases • Melanoma • (and 13 more...)	• Brigham and Women's Hospital Boston, Massachusetts, United States • Dana Farber Cancer Institute Boston, Massachusetts, United States
6	☐	Recruiting	• Non-small Cell Lung Cancer • Advanced Pancreatic Adenocarcinoma • Unresectable Pancreatic Cancer • Ductal Adenocarcinoma of the Pancreas	• Brigham and Women's Hospital Boston, Massachusetts, United States • Dana Farber Cancer Institute Boston, Massachusetts, United States
7	☐	Recruiting	• Gynecologic Cancer	• Centre Hospitalier Lyon Sud Pierre-Bénite, Rhône, France • Gustave Roussy Villejuif, Val De Marne, France
8	☐	Not yet recruiting	• Recurrent Cancer • Previous Radiation	

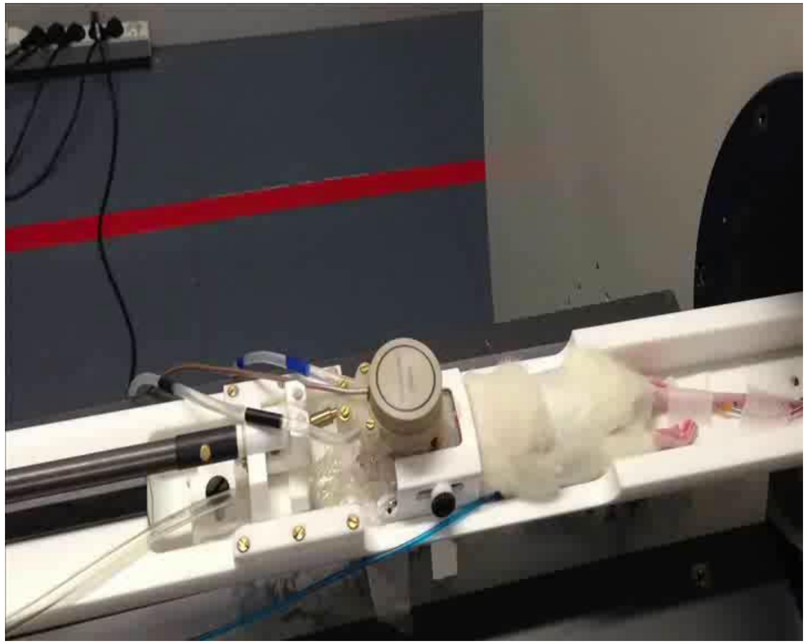
Validation of the model through *in vivo* experiments

Experimental set up to open BBB under MRI

Motors to target and choose the location and extent of the BBB disruption

7T MRI scanner

Larrat et al., 2010
Magnin et al., 2015



1.5 MHz transducer
1.2 MPa
3% duty cycle for 120s

Thermoguide software

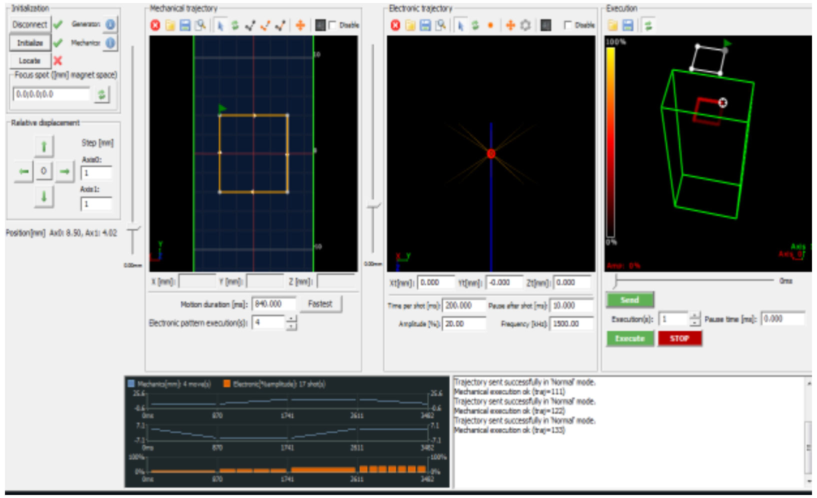
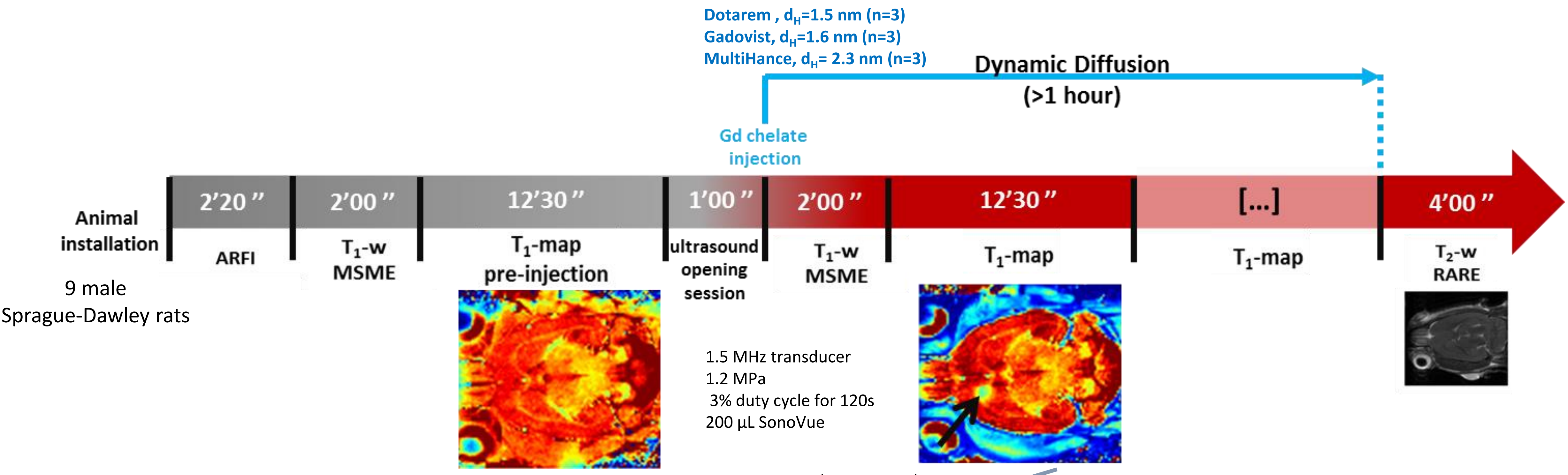


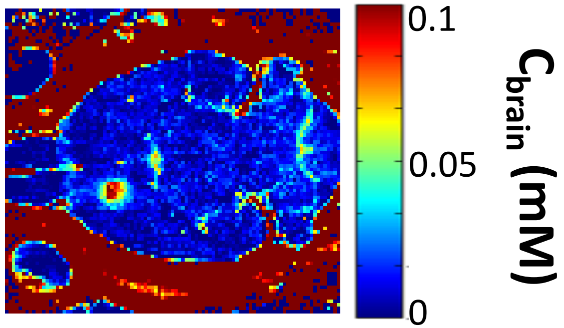
Image Guided Therapy

Experimental protocol to open BBB under MRI



$$[Gd] = \frac{1}{r_1} \cdot \left(\frac{1}{T_1} - \frac{1}{T_{1,0}} \right)$$

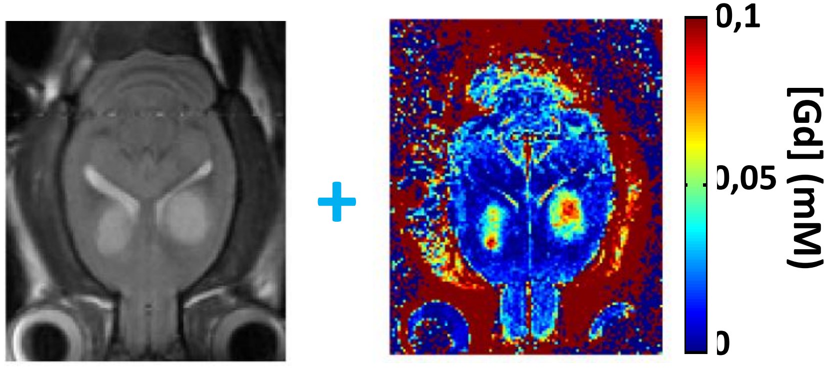
Concentration map



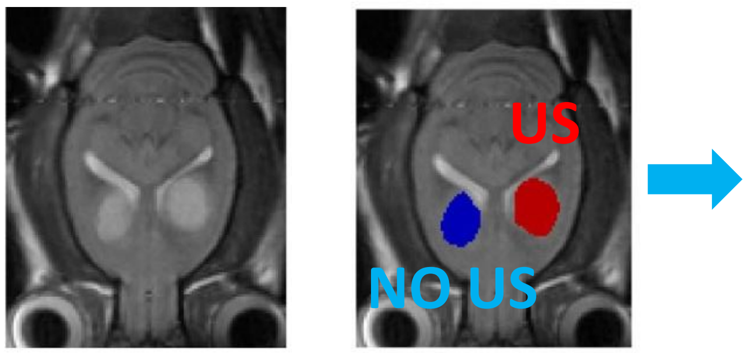
Tumor delivery of radiosensitizing nanoparticles

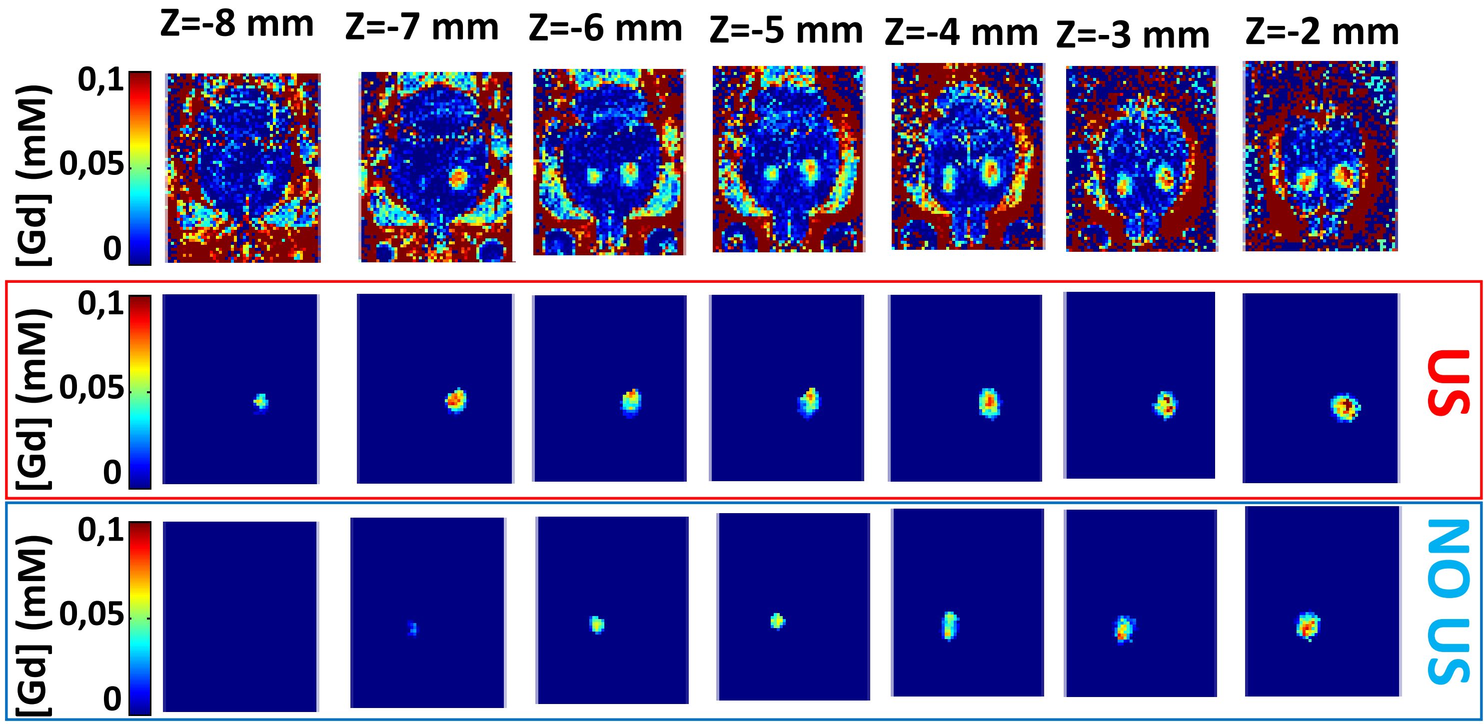
Post-processing:

1) Co-registration of the T_{2w}-images with the concentration maps



2) Manual definition of a 3D ROI inside each tumor





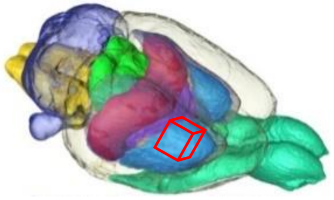
3) Study of the AGuiX concentration in the ROIs, both in the sonicated and in the control tumor, over time

Tumor delivery of radiosensitizing nanoparticles

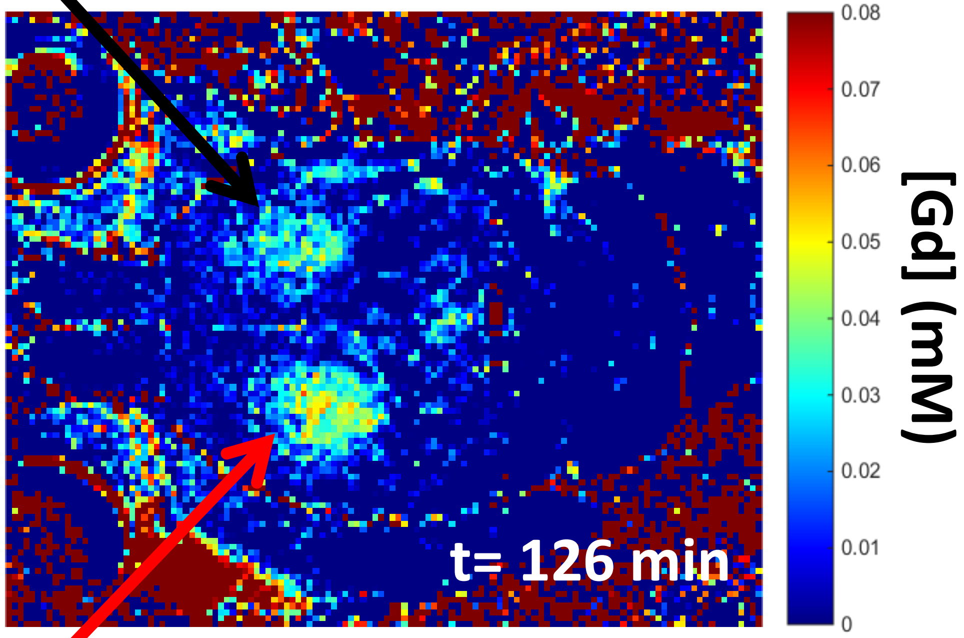
What happens along time?

Visually..

8 points sonication



NO US



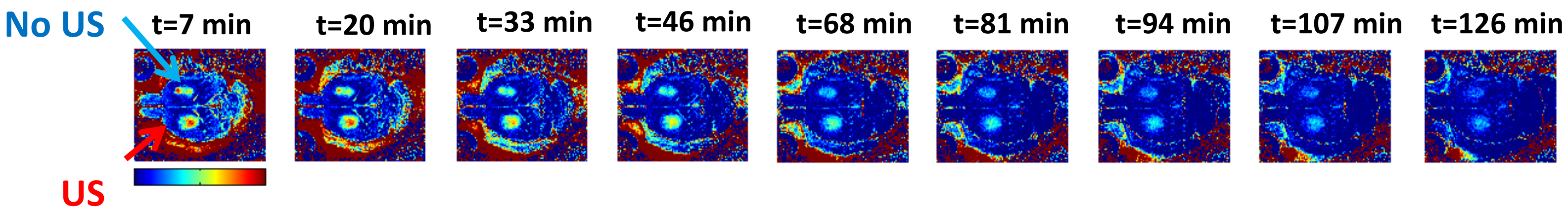
US

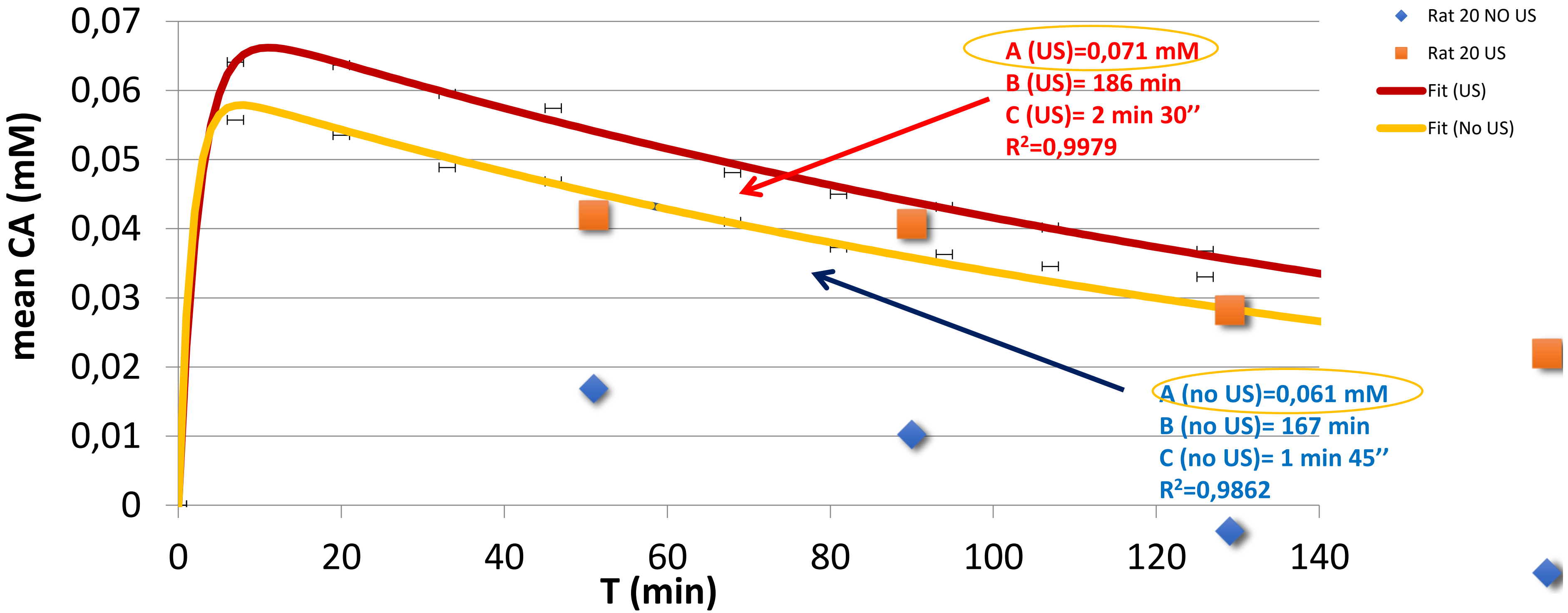
Tumor delivery of radiosensitizing nanoparticles

Results

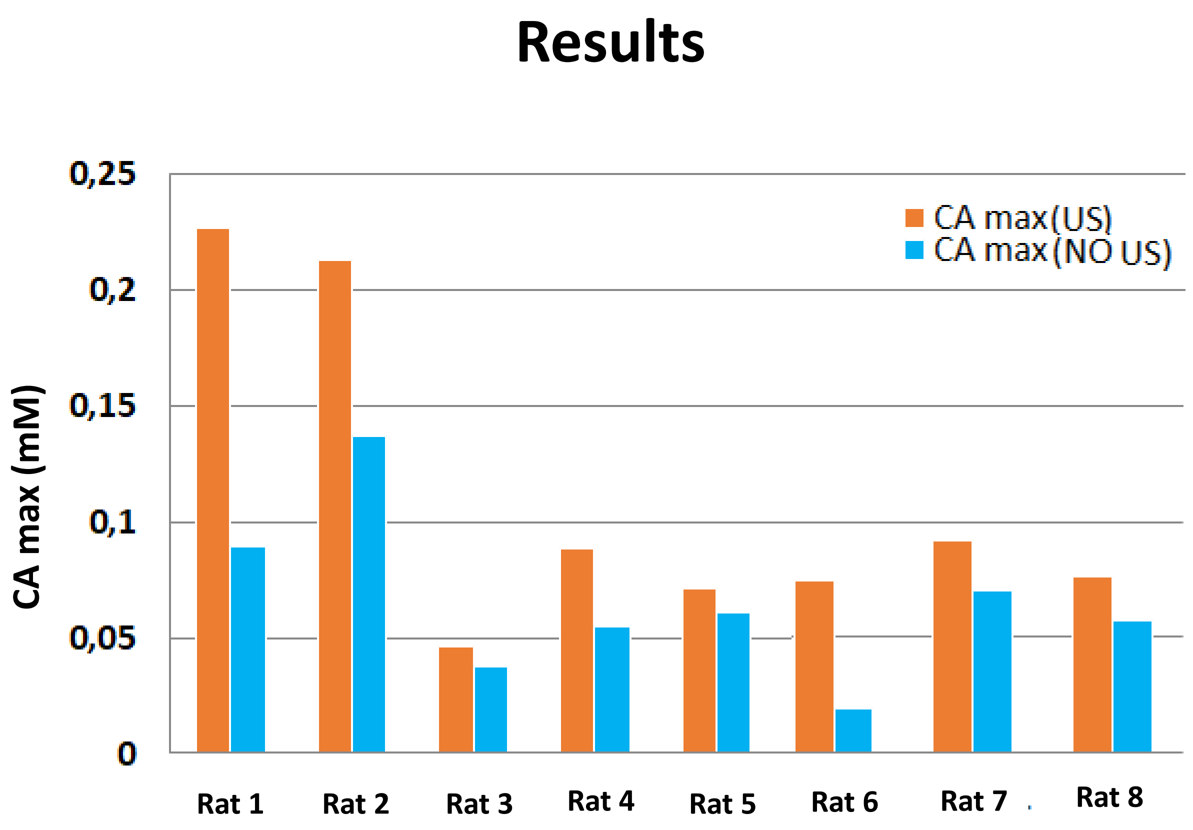
Mean concentrations' Fit (Wash-in, wash out model): $CA(t) = A \cdot \left(1 - e^{-\frac{t}{C}}\right) \cdot e^{-\frac{t}{B}}$

(*Tofts et al*, JMRI. 1999 Sep;10(3):223-32)





Nanoparticles concentration delivered with both methods

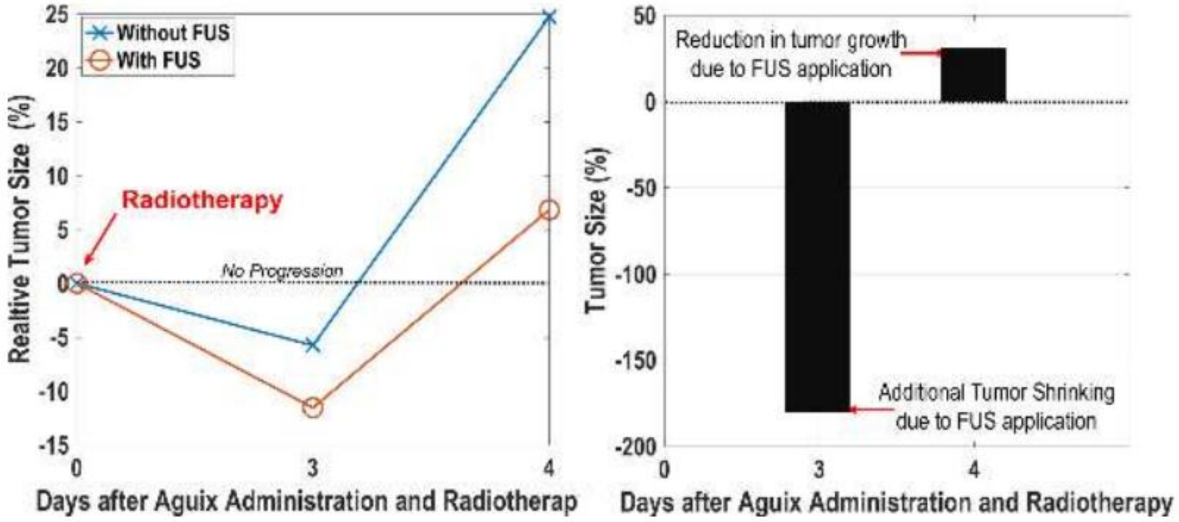


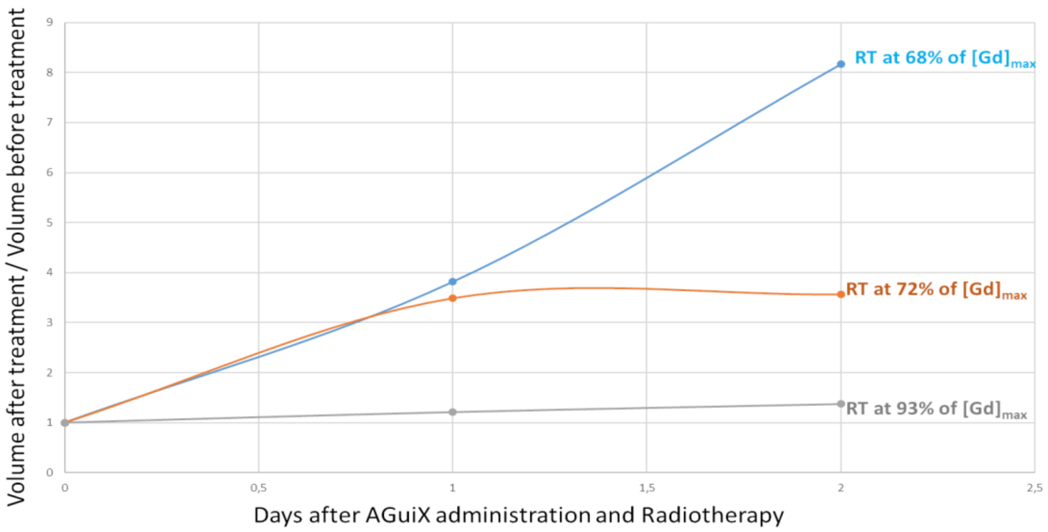
Sonicated tumor shows higher nanoparticles maximum concentrations for both acoustic strategies

Radiotherapy effects

Comparison of the effects of a single dose of AguiX-enhanced RT (25 Gy) in animals carrying GBM with or without FUS.

- Combining AguiX + RT actually induces tumor shrinking. Crucially, the extent of this shrinking is enhanced by approximately 170% by FUS application.
- Also, after tumor growth resumes at a later timepoint, when using FUS + AguiX it is still only at 27% of the tumor growth observed when using AguiX alone
- Evolution of tumor volumes after radiotherapy administration. Blue, orange and grey curves represent tumors treated when 68%, 72% and 93 % of the maximum amount of AGuiX deliverable are present within their volume.





MFAG 2020 ID24636

SG-2019-12369035

FUSRadio enhancing radiotherapy in Glioblastoma through focused ultrasound

FONDAZIONE AIRC PER LA RICERCA SUL CANCRO

Ministero della Salute

FONDAZIONE PTV POLICLINICO TOR VERGATA

TOR VERGATA UNIVERSITÀ DEGLI STUDI DI ROMA

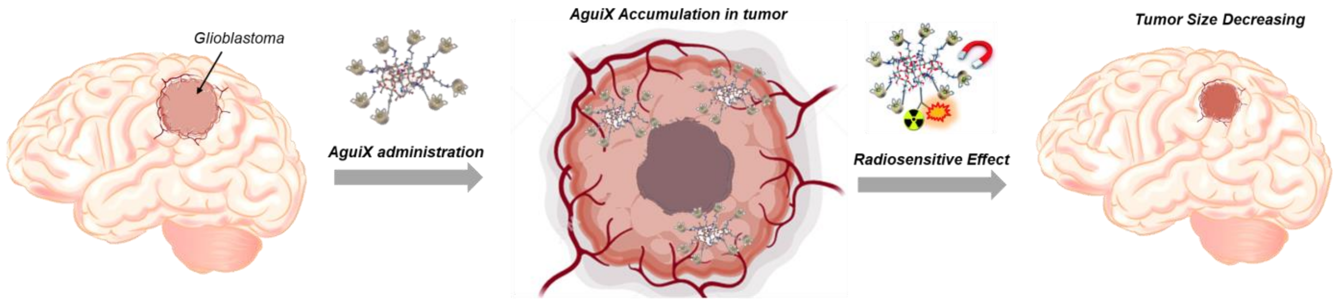
TheraFus Lab

FUSRADIO: enhancing radiotherapy in persistent Glioblastoma through focused ultrasound

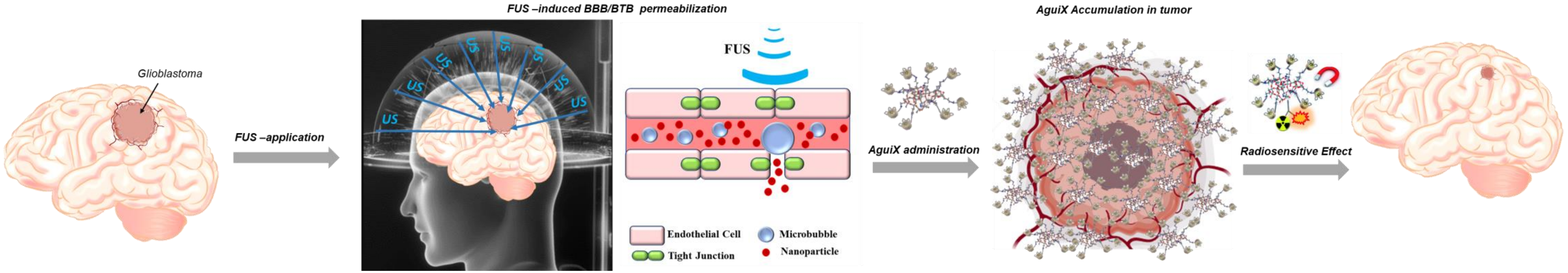
NanoGBM-Precision

- ✓ AIFA approved
- ✓ Approved by the local ET
- ✓ Insurance insurance taken out

(A) Glioblastoma treatment with Radiotherapy + AguiX administration



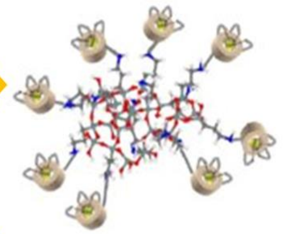
(B) Glioblastoma treatment with Radiotherapy + FUS-induced BBB/BTB permeabilization + AguiX administration



FUSRADIO: enhancing radiotherapy in persistent Glioblastoma through focused ultrasound

30 GBM
Two stage Simon
Phase II Trial

AguiX administration

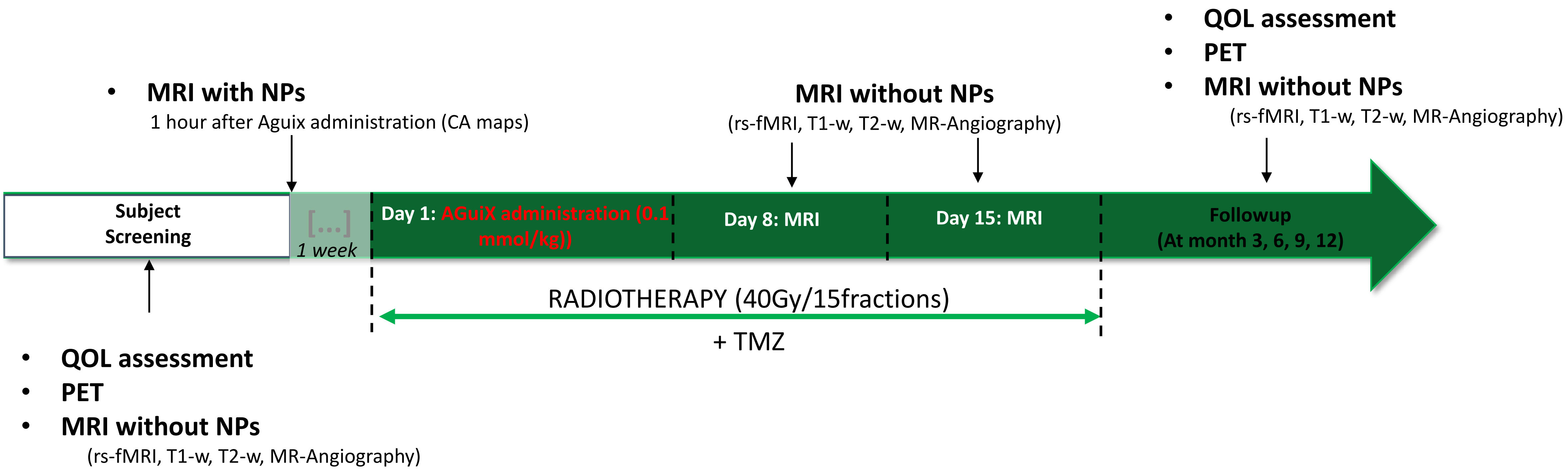


Radiotherapy

EXCLUSION CRITERIA
Contra-indication, sensitivity or allergy to gadolinium
Patients unable to undergo or tolerate MRI
Previous brain irradiation
< 18 yo

INCLUSION CRITERIA
Previous partial resection, biopsy or radiological diagnosis
Not fit for Standard Radiotherapy (60 Gy/30 fractions of 6 weeks)

FUSRADIO: enhancing radiotherapy in persistent Glioblastoma through focused ultrasound



Expected to start the recruitment in January 2023

Objectives:

- **Assessment of AGuIX Activity as a RT therapy enhancer for treating pGBM.**

Evaluation of the effects of the AGuIX+RT protocol in pGBM on:
Tumour volume Volume;
Tumour vasculature and metabolism;
Progression-free survival (PFS)
Overall Survival (OS);
Quality of life (Qol);
Cognitive abilities;
The evaluation of side effects arising during RT+TMZ.

Grazie per l'attenzione

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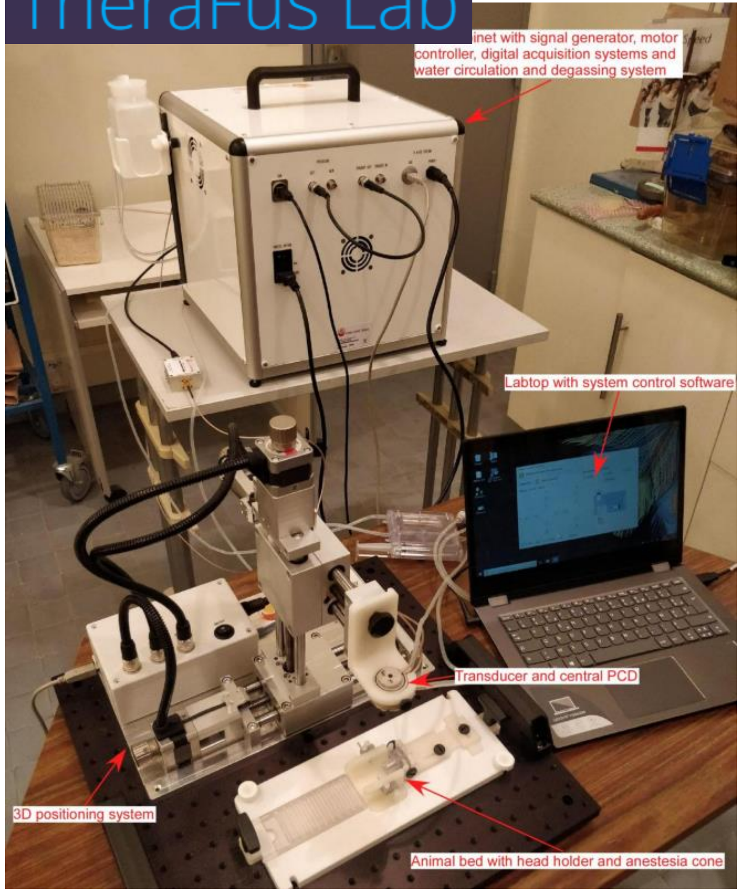
Sezione di Fisica Medica, Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma 'Tor Vergata'

TheraFus Lab



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