2022 全國兒童神經精神科學 勵翔獎–首獎

Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors

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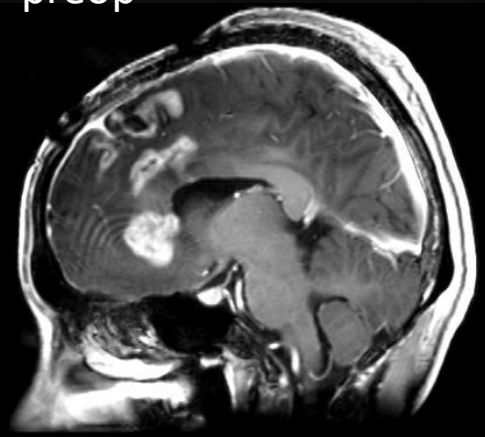
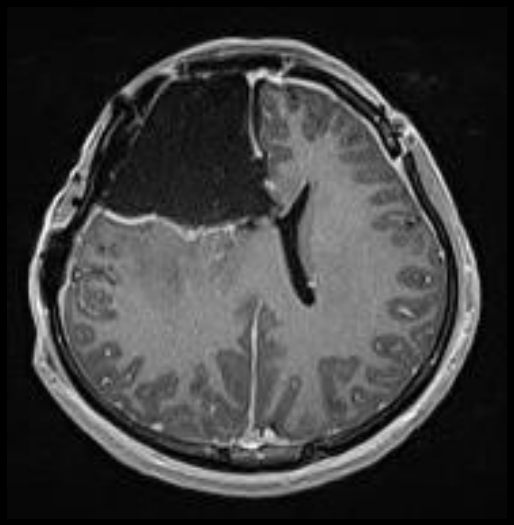
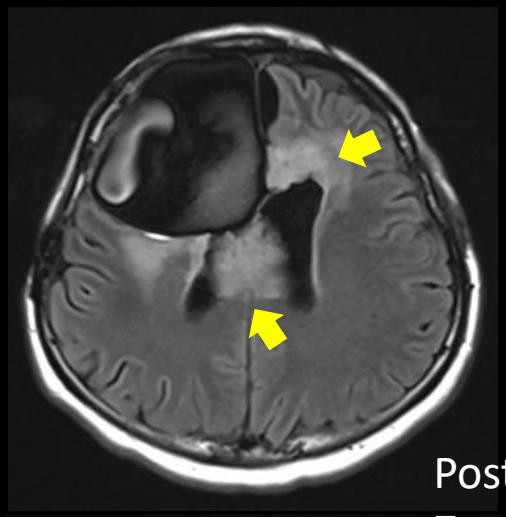
Recurrence is an inevitable fate in GBM patients

preop

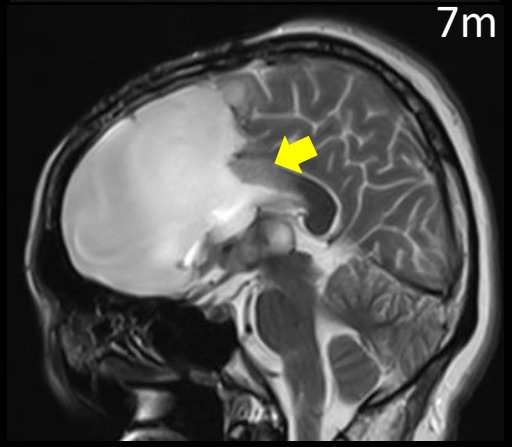




Maximal safe resection
+ adjuvant CCRT + TMZ

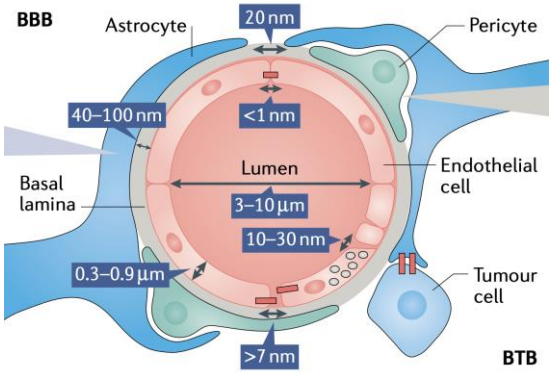


Postop
7m



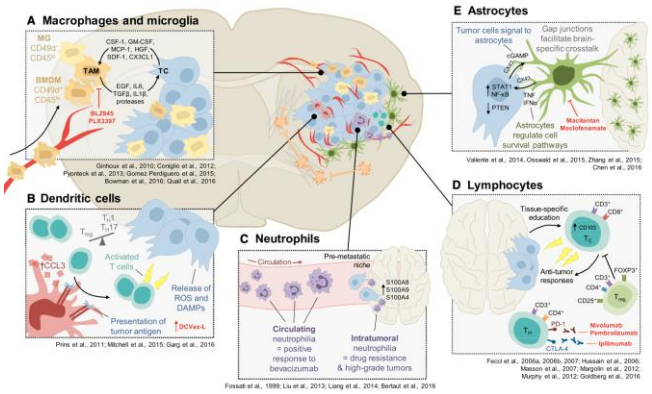
The dilemma of treating glioma

- **The paucity of agents that effectively cross the BBB**
- The relative lack of ”easy” targets such as *BRAFV600E* mutations
- Redundant signaling pathways
- Tumor heterogeneity



Arvanitis et al. 2020, Nature Reviews Cancer

- **Immunosuppressive “cold” tumor microenvironment**
  - A paucity of neoantigens (low mutation burden)
  - A paucity of tumor infiltrating lymphocytes (TIL)
  - Active inhibition: TGF-β, IL-10, PGE2
  - Recruit suppressive myeloid cells and Treg, exhaustion of TILs
  - Systemic immunosuppression: depleting and sequestering T lymphocytes in the bone marrow

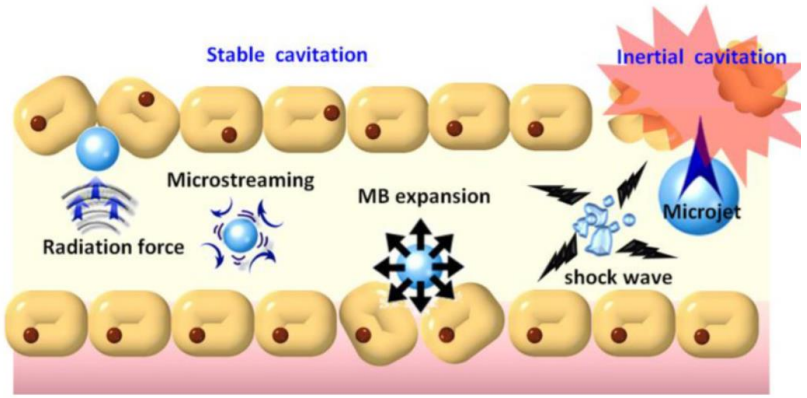


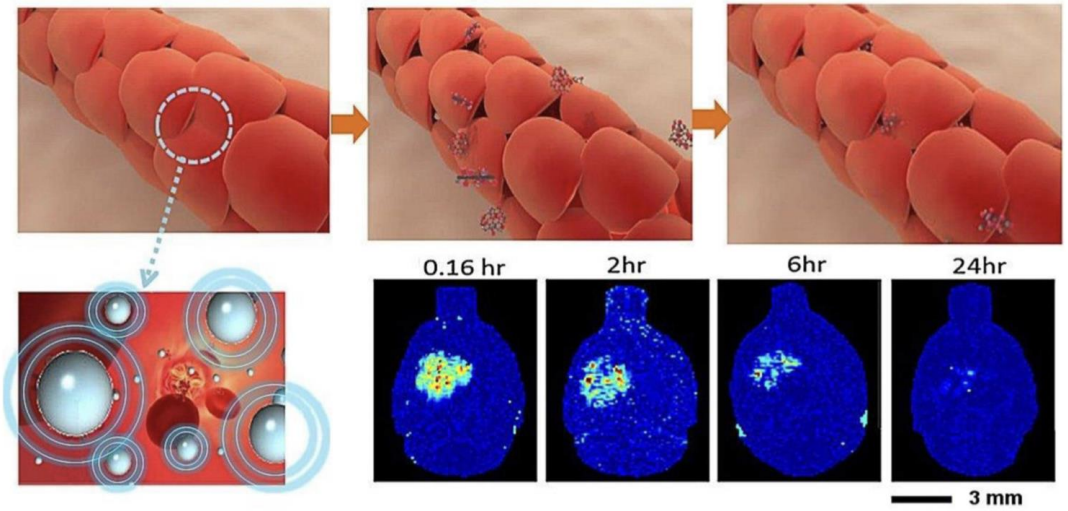
Quail et al. 2017 Cancer Cell

Wen et al. Neuro-Oncology 22(8), 1073-1113, 2020

Preclinical

FUS-BBBO is focal, transient and reversible

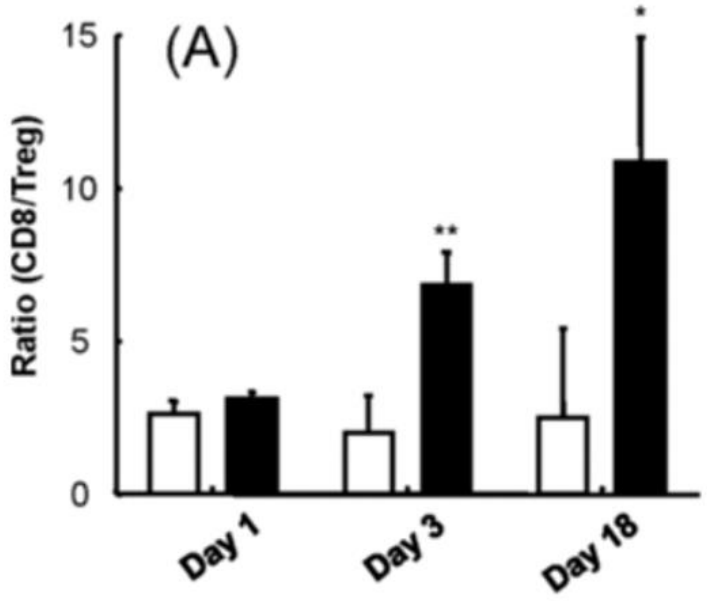


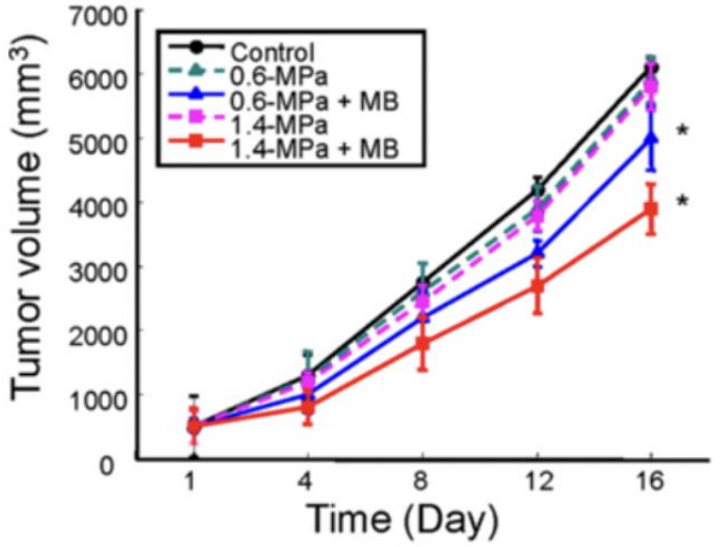


Liu et al. 2014, Theranostics; Chen et al. 2019, Frontiers in Pharmacology

Preclinical

Low-pressure pulsed MBFUS may promotes **anticancer immunological response**





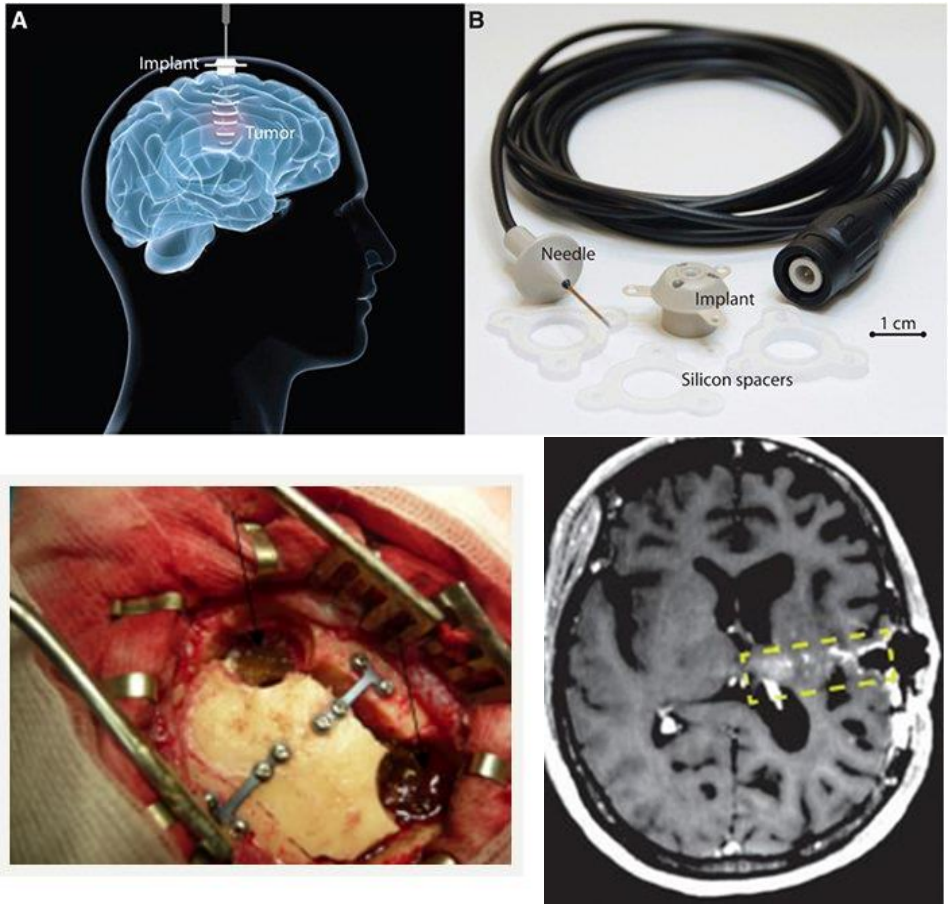
Liu et al. J Transl Med. 2012, 10: 221

Implanted ultrasonic device

(Carthera®, Sonocloud)

1

- Phase 1/2a clinical trial
- 2014~2016, **15 rGBM patients**, 41 sonications
- Up to 1.1 MI (1MHz probe provide 1.1 MPa); Microbubbles: 0.1 mg/kg
- US followed by systemic carboplatin
- **Radiologically BBBO > 0.8 MPa**



Carpentier et al. 2016. Science Translational Medicine

2

MR-guided FUS
(Insightec®, Exablate)

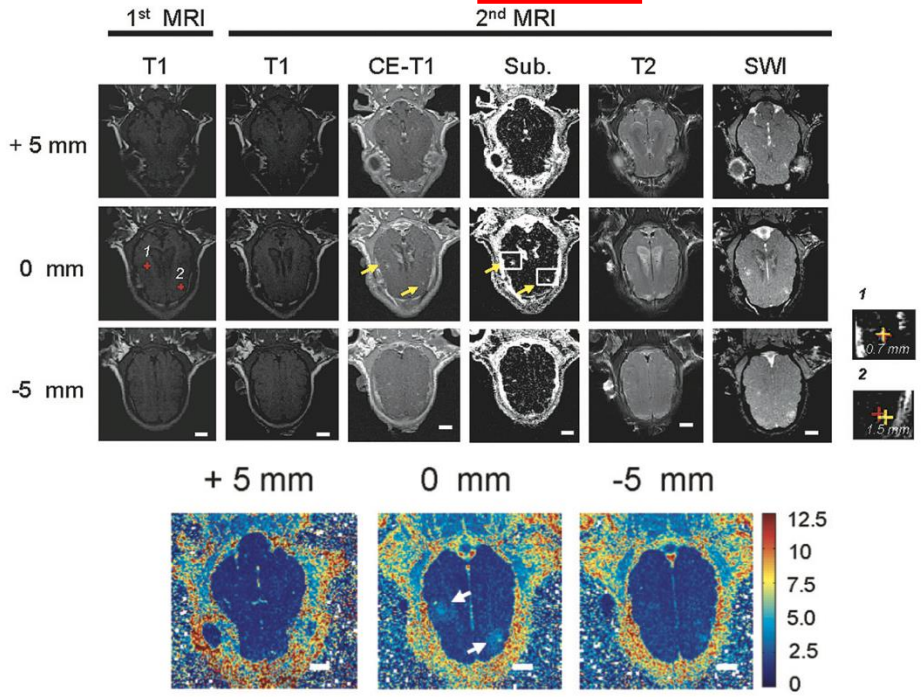
- Phase 1 clinical trial
- 2015~2017, **5 rGBM patients**, 18 sonications
- 4-15 W, with real-time acoustic feedback control; Microbubbles: 4 µl/kg
- FUS followed by systemic temozolomide or IV doxorubicin
- **Radiologically BBBO in all subjects**

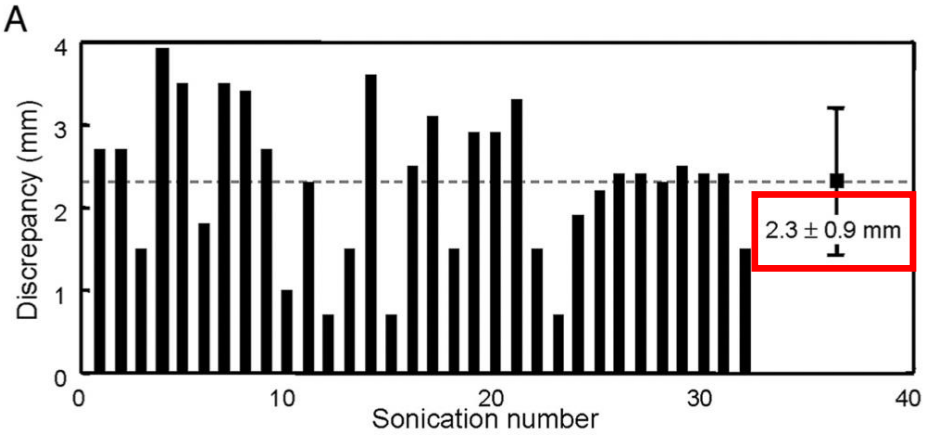
Mainprize et al. 2019. Scientific Reports

Proof-of-Concept

Neuronavigation-Guided Focused Ultrasound-Induced Blood-Brain Barrier Opening: A Preliminary Study in Swine

K.-C. Wei, H.-C. Tsai, Y.-J. Lu, H.-W. Yang, M.-Y. Hua, M.-F. Wu, P.-Y. Chen, C.-Y. Huang, T.-C. Yen, and H.-L. Liu



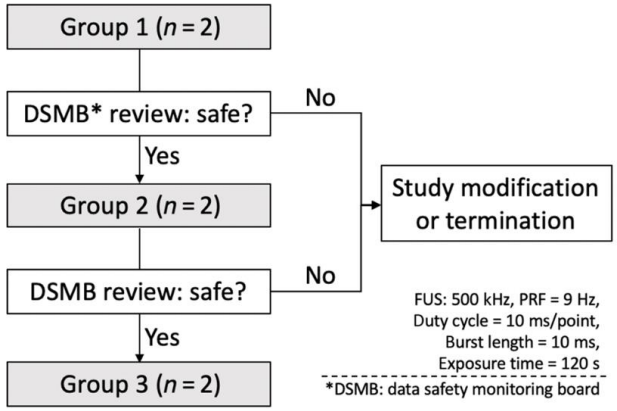


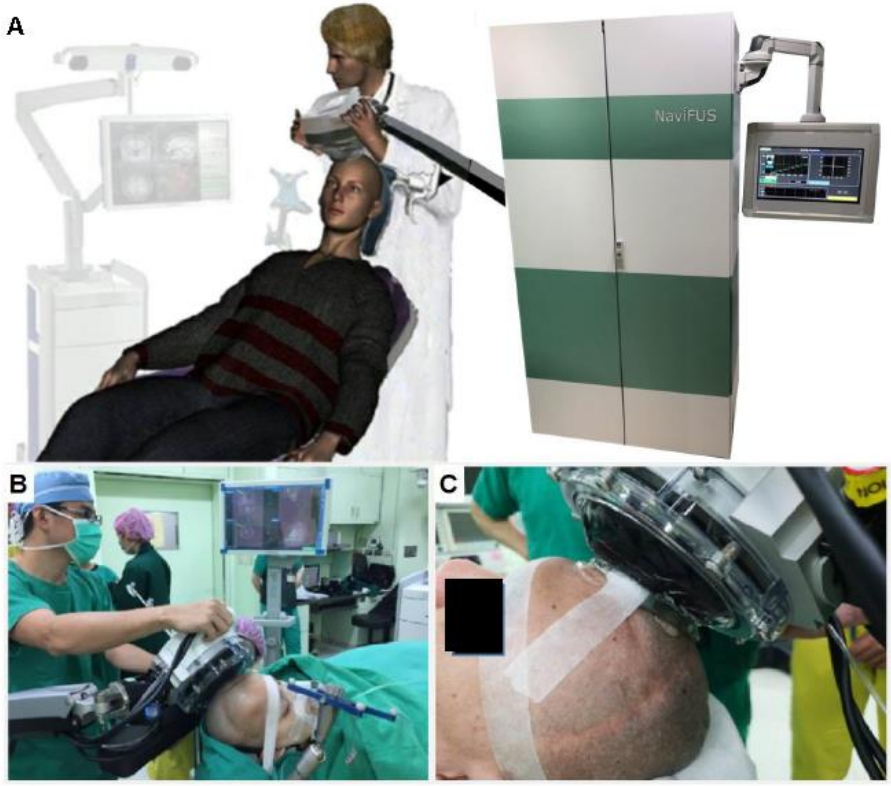
Wei et al. Am J Neuroradiol 34:115-120 Jan 2013

3

Navigation-guided FUS (NaviFUS®, NaviFUS)

- Phase I clinical trial
- 2018~2019, **6 rGBM**, 6 sonications at 1 week before their scheduled surgical resection
- Dose escalation: 0.48, 0.58, 0.68 MI





Chen et al. Sci. Adv. 2021; 7: eabd0772

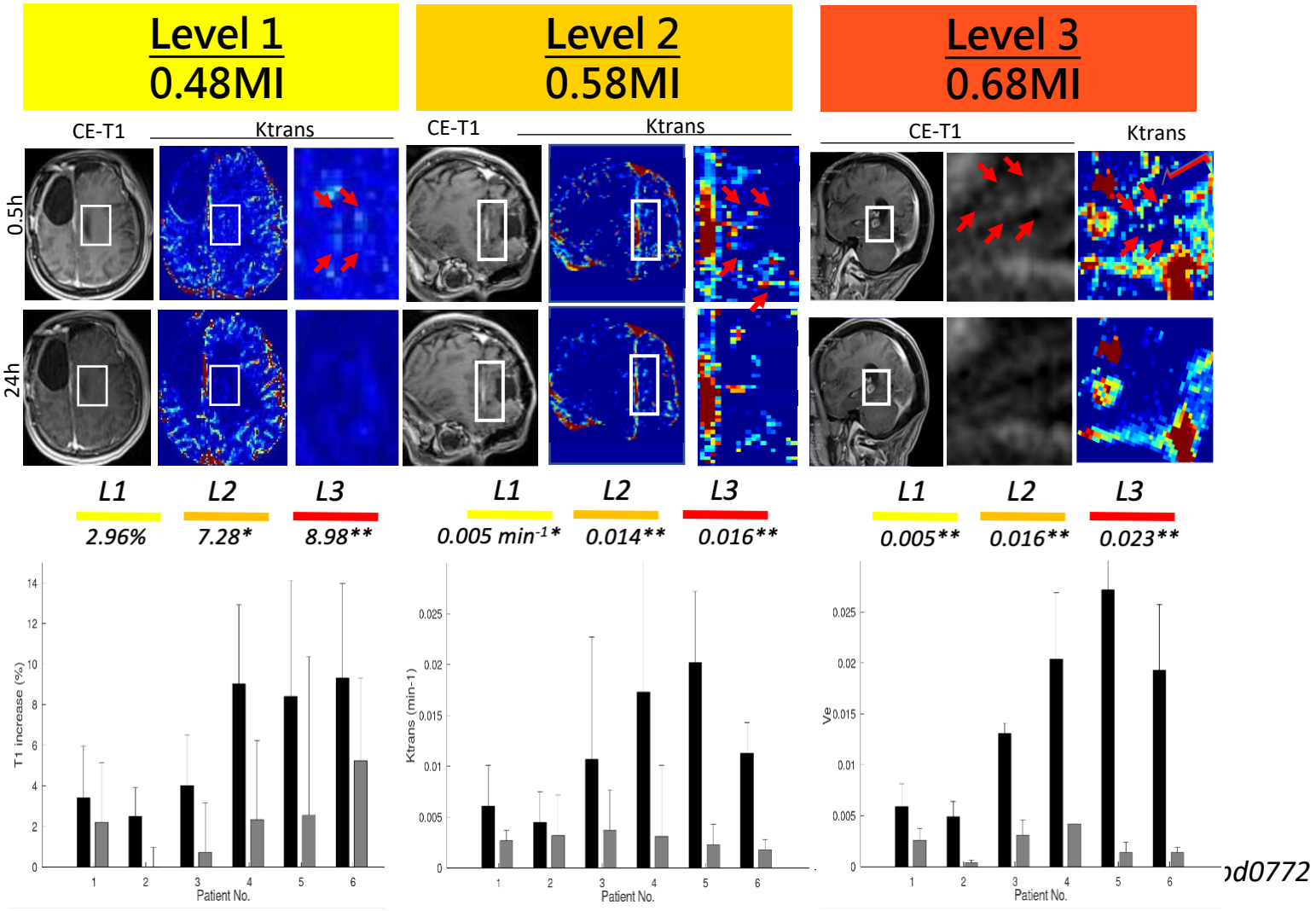
Target at peritumoral regions (3.85cm from inner skull)

Table 1. Summary of patients with rGBM receiving FUS treatment: demographic data and treatment plans ($n = 6$). BW, body weight; BMI, body mass index; Preop, preoperative; M, male; F, female; KPS, Karnofsky performance status.

Patient number	1	2	3	4	5	6	Means ± SD
Level	1	1	2	2	3	3	
Age	80	39	32	36	67	43	49.5 ± 19.4
Sex	M	F	M	M	F	F	
BW (kg)	63	55	82.5	92.1	69	54.5	69.4 ± 15.2
BMI (kg/m^2)	22.6	21.6	25.5	29.8	27	23.6	25.0 ± 3.1
Preop KPS	70	100	100	100	70	100	
Definition of progressive disease*	New enhancing lesion	Increase in FLAIR	New enhancing lesion	Increase in FLAIR	New enhancing lesion	New enhancing lesion	
Site of sonication	Peritumoral	Peritumoral	Peritumoral	Peritumoral	Peritumoral	Peritumoral	
Location	Temporoinsular	Frontal periventricle	Frontal subcortical	Frontal periventricle	Frontal subcortical	Occipital periventricle	
Depth from inner skull (cm)	4.1	3.9	3.1	4.6	2.7	4.7	3.85 ± 0.80
SAE (times)	2†	0	0	0	0	0	

*Progression of tumor was defined according to response assessment in neuro-oncology for gliomas (RANO) criteria, including new enhancing lesion or notable increase T2/FLAIR nonenhancing region. †All SAEs occurred in this study were judged as definitely not related to the FUS treatment and SonoVue in causality.

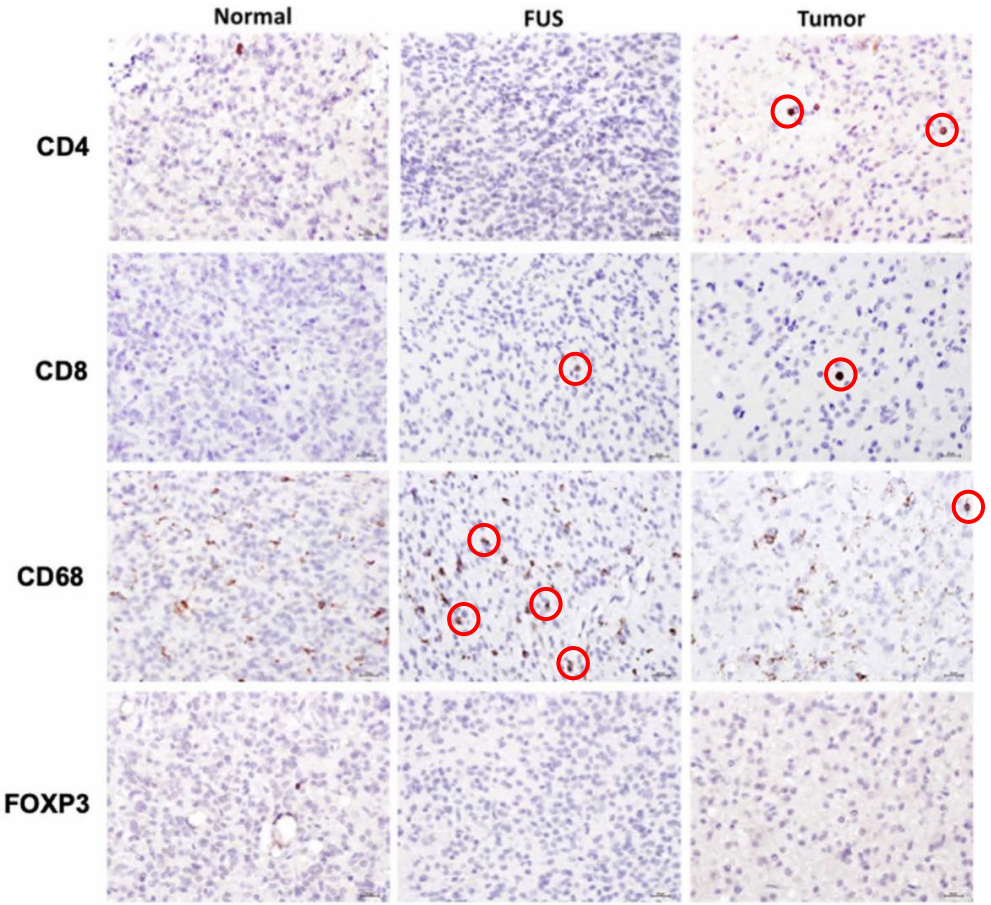
Chen et al. Sci. Adv. 2021; 7: eabd0772


Level 1
0.48MI
Level 2
0.58MI
Level 3
0.68MI
CE-T1
Ktrans
CE-T1
Ktrans
CE-T1
Ktrans
0.5h
24h
L1
L2
L3
2.96%
7.28*
8.98**
L1
L2
L3
0.005 min-1*
0.014**
0.016**
L1
L2
L3
0.005**
0.016**
0.023**
T1 increase (%)
Patient No.
Ktrans (min-1)
Patient No.
Ve
Patient No.

d0772

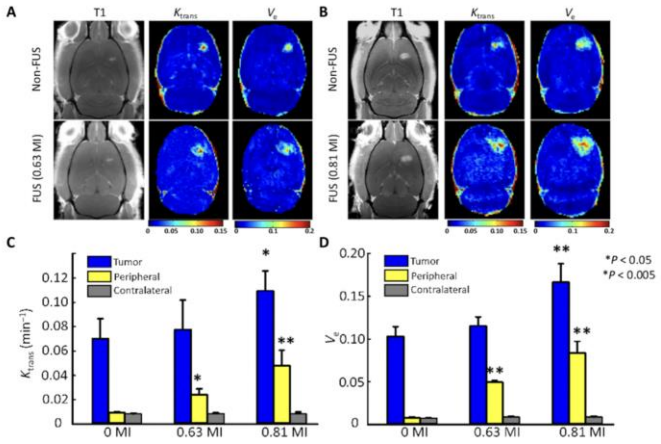
Immune cell infiltration in human tissues 7 days after FUS treatment

No immunological response by examined the resected FUS-targeted tissues.



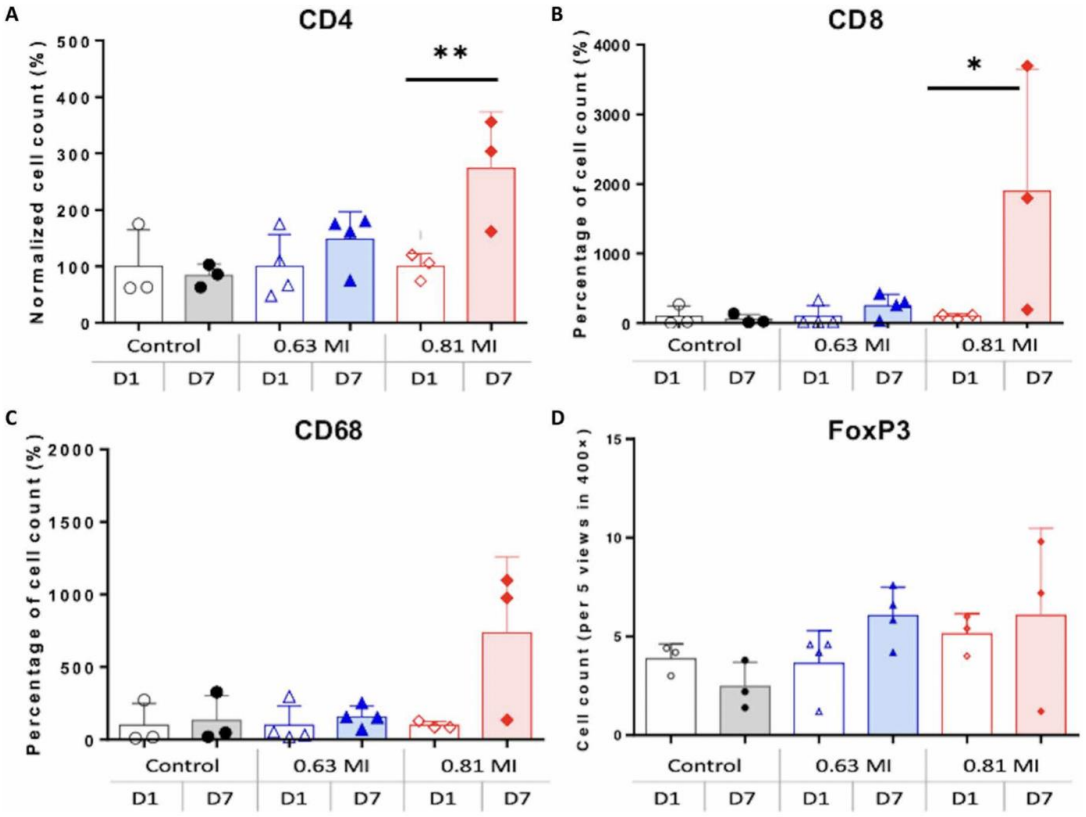
Chen et al. Sci. Adv. 2021; 7: eabd0772

A parallel design of immunostimulatory effect in animal model



An increment of CD4⁺ and CD8⁺ T cells was found 7 days after FUS with **0.81 MI but not 0.63 MI** (comparative to human 0.68 MI) in animal model

Chen et al. Sci. Adv. 2021; 7: eabd0772



Conclusions

- Neuronavigation-guided focused ultrasound has been safely and precisely applied to patients with recurrent GBM.
- A dose-dependent BBB-opening effect has been observed which reverted to baseline within 24 hours.
- No immunological response was observed clinically under the applied FUS level in humans
- A higher level FUS energy in animals resulted in immunostimulation, as confirmed preclinically by the recruitment of lymphocytes into the tumor microenvironment in a rat glioma model.

SCIENCE ADVANCES | RESEARCH ARTICLE

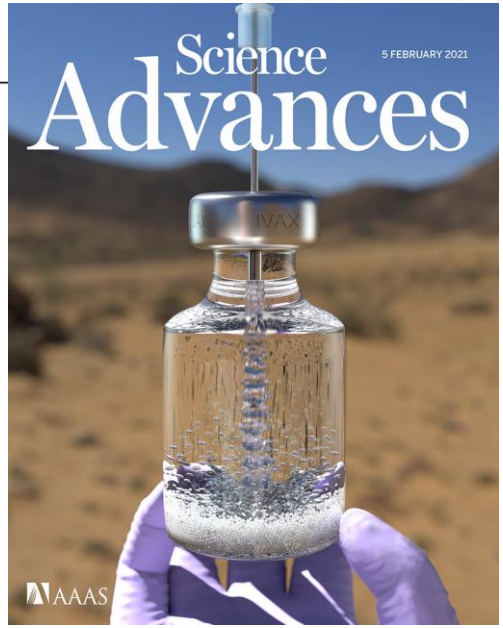
APPLIED SCIENCES AND ENGINEERING

Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors

Ko-Ting Chen[1,2], Wen-Yen Chai[3], Ya-Jui Lin[1,4], Chia-Jung Lin[5], Pin-Yuan Chen[6,7], Hong-Chieh Tsai[1], Chiung-Yin Huang[8], John S. Kuo[9], Hao-Li Liu[5]*, Kuo-Chen Wei[1,7,8]*

2021 Impact factor: 14.980

Chen *et al.*, *Sci. Adv.* 2021; **7** : eabd0772 5 February 2021



致謝

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