

## Supplementary Tables

**Suppl. Table 1. Studies reporting the impact of MB-FUS delivery of anticancer agents in murine brain tumor models.**

Therapeutic agent	Size	Tumor model <sup>a</sup>	Fold increase in DD (W.R.T. drug only)	Increase [%] in median survival (W.R.T. drug only)	Ref
<b>Chemotherapy</b>					
Doxorubicin	580 Da	GL261 and SMA-560 glioma (B6-albino mouse)	4-fold	68.2%	[1]
Doxorubicin	580 Da	9L Gliosarcoma (Rat)	2-fold	-	[2]
BCNU	214 Da	C6 glioma model (Rat)	3-fold	65.6%	[3]
Temozolomide (TMZ)	194 Da	9L Gliosarcoma (Rat)	1.7-fold	12.2%	[4]
Temozolomide (TMZ)	194 Da	9L Gliosarcoma (Rat)	-	-	[5]
Temozolomide (TMZ)	194 Da	U87 glioma model (Mouse)	2-fold	12.5%	[6]
Carboplatin	380 Da	F98 glioma (Rat)	2.9-fold	48%	[7]
Irinotecan	580 Da	F98 glioma (Rat)	3.2-fold	0% (No improvement)	[8]
Doxorubicin	580 Da	SU-DIPG-17 orthotopic xenografts (mouse)	4-fold	0% (No improvement)	[9]
Etoposide	590 Da	MGPP3 glioma (mouse)	3.5-fold	31.6%	[10]

Carboplatin	588 Da	U87 and 6240 PDX (mouse)	No quantification for carboplatin in tumor.	-	[11]
Doxorubicin	580 Da	Human HER2 <sup>+</sup> BT474 (mouse)	7-fold	-	[12]
Etoposide	590 Da	Diffuse intrinsic pontine glioma (mouse)	5-fold	-	[13]
<b>Antibody</b>					
Herceptin (trastuzumab)	148 kDa	Human HER2-positive BT474 (Rat)	-	-	[14]
HER2-targeting antibodies (trastuzumab and pertuzumab)	148 kDa	Human HER2-positive MDA-MB-361 (Rat)	-	-2.7%	[15]
Interleukin-12 (IL-12)	75 kDa	C6 glioma (Rat)	1.5-fold	15.4%	[16]
Bevacizumab	150 kDa	U87 glioma (Mouse)	6-fold	58.7%	[17]
EphA2-4B3 (IgG2a)	130 kDa	High grade glioma (PDX)	2-fold	-	[18]
Anti-CD47	150 kDa	GL261 Glioma (mouse)	2.2-fold	40%	[19]
ado-trastuzumab emtansine (T-DM1)	148 kDa	Human HER2 <sup>+</sup> BT474 (mouse)	2-fold	-	[12]
Anti-PD-1	32kDa	GL261 glioma model (mouse)		48.7%	[20]
<b>Nanoparticles</b>					
Liposomal doxorubicin (Doxil)	90 nm	9L Gliosarcoma (Rats)	-	0% (No improvement)	[21]
AP-1 targeted - Liposomal doxorubicin	116± 30 nm	Human GBM 8401 (NOD-scid)	2.5-fold	-	[22]

(AP-1-Lipo-DOX)		Mice)			
Liposomal doxorubicin (Lipo-DOX); AP-1 targeted - Liposomal doxorubicin (AP1-Lipo-DOX)	100-120 nm	Human GBM 8401 (NOD-scid Mice)	4.4-fold (untargeted liposomal doxorubicin) 3.7-fold (AP-1 liposomal doxorubicin)	-	[23]
Liposomal doxorubicin (Lipo-DOX)	90 nm	9L Gliosarcoma (Rat)		72%	[24]
Cisplatin in Brain-Penetrating Nanoparticles	60 nm	9L Gliosarcoma and F98 glioma (Rats)	28-fold	0% (No improvement)	[25]
Paclitaxel liposomes (PTX-LIPO)	~90 nm	U87 MG glioblastoma (Mice)	2-fold	14.8%	[26]
Liposomal doxorubicin (Lipo-DOX)	90 nm	9L Gliosarcoma (Rat)	2-fold	-	[27]
Cilengitide (CGT) (Peptide)	100 nm 588.67 g/mol	C6 glioma model (Rat)	-	17.4% (CGT-modified-NP) 166.4% (CGT-NP)	[28]
$\alpha$ EGFR-SERS440 Gold Nanoparticles (GNPs)	50-120 nm (PEG-coated)	9L gliosarcoma model (Rat)	no <i>in vivo</i> statistics were provided	-	[29]
IL-4 receptor targeted Liposomal doxorubicin (IL-4-Lipo-DOX)	100-120 nm	Human GBM 8401 model (NOD-scid Mice)	2-fold	15.4%	[30]
Liposomal doxorubicin (Lipo-DOX)	90 nm	9L Gliosarcoma (Rat)	7-fold	-	[31]
Liposomal doxorubicin (Doxil)	90 nm	F98 glioma (Rats)	10-fold		[32]

Albumin-bound paclitaxel	130 nm	MES83 and GBM12 Glioma PDX (mice)	-	12.9% (MES83) 7.9% (GBM12, not statistically significant)	[33]
Folate-conjugated Polymersomal (Doxorubicin) (FPD)		C6 glioma model (Rat)	5.1-fold	51.7%	[34]
Hollow mesoporous organosilica NPs (Doxorubicin)	50 nm	U87 glioblastoma model (Mice)	-	48.6%	[35]
cisplatin-gold-NP conjugates	7 nm	U251 GBM xenograft (NOD-scid Mice)	-	-	[36]
brain-penetrating nanoparticle (BPN) gene vectors	50-100 nm	U87 glioma B16F1 melanoma (mice)	2.3-fold	-	[37]
LPH (siRNA)	40-50 nm	GL261 Glioma, SMO medulloblastoma (mice)	10-fold	-	[38]
<b>Magnetic Nanoparticles</b>					
BCNU - MNP	~10–20 nm	C6 glioma (Rat)	-	no survival values were provided	[39]
Epirubicin - MNP	~12 nm	C6 glioma (Rat)	2.6-fold	-	[40]
Doxorubicin – SPIO	~36 nm (SPIO); ~3 μm; (MBs)	C6 glioma (Rat)	2-fold	-	[41]
<b>Microbubble-drug conjugates</b>					
BCNU	214 Da (BCNU); ~1 μm (MBs)	C6 glioma (Rat)	8-fold	12%	[42]

VEGFR2-BCNU (Antiangiogenic-targeting)	214 Da (BCNU); ~1.8 µm (MBs)	C6 glioma (Rat)	-	61.5%	[43]
Doxorubicin – SPIO	~36 nm (SPIO); ~1 µm (MBs)	C6 glioma (Rat)	1.6-fold	-	[44]
shBirc5-lipo-NGR (NGR peptide and shRNA dual targeting)	2.9 µm MB-drug complex	C6 glioma (Rat)	-	40.7%	[45]
PEBCA-based NP (nanoparticles)	274nm (NP); 1.6 µm (MBs)	H1_DL2 Melanoma brain metastases (NOD-scid Mice)	No quantification for NP in tumor.	-	[46]
LPHNs-cRGD (nanoparticles loaded with CRISPR/Cas9 plasmids)	179 nm (NP) 2.9 µm (MB-drug complex)	T98G Glioma (NOD-SCID mice)	-	65.4%	
<b>Virus</b>					
Herpes virus gene (HSV1-tk) with Ganciclovir prodrug (GCV)	5.5 MDa (152 kbp)	F98 glioma (Rats)	3-fold	-	[47]
Herpes virus gene (HSV1-tk) with Ganciclovir prodrug (GCV)	5.5 MDa (152 kbp)	C6 glioma (Rat)	2.3-fold	Survival for drug only not reported	[48]

**Suppl. Table 2. Summary of studies reporting the impact of MB-FUS on BBB in healthy animals that included information about the acoustic emissions and tissue damage; summarized in Fig. 4.**

Animal	Pressure	Frequency	Harmonic	U-harmonic	Broadband	BBB Opening	Damage	Ref.
Rat	371 kPa	0.230MHz	Yes	Yes	Yes	Yes	Yes	[49]
Macaque	100 kPa	0.22MHz	NO	NO	NO	NO	NO	[50]
	150 kPa	0.22MHz	YES	NO	NO	YES	NO	
	300 kPa	0.22MHz	YES	YES	NO	YES	YES	
Macaque	175 kPa	0.257MHz	NO	NO	NO	NO	NO	[51]
	275 kPa	0.257MHz	YES	YES	SOME	YES	NO	
	275 kPa	0.257MHz	YES	YES	YES	YES	YES	
Mouse	300 kPa	1.5MHz	YES	NO	NO	YES	NO	[52]
	450 kPa	1.5MHz	YES	YES	SOME	YES	YES	
	600 kPa	1.5MHz	YES	YES	YES	YES	YES	
Macaque	300 kPa	0.5MHz	YES	YES	FEW	YES	NO	[53]
	450 kPa	0.5MHz	YES	YES	SOME	YES	NO	
	600 kPa	0.5 MHz	YES	YES	YES	YES	YES	
	275 kPa	0.5 MHz	YES	NO	NO	YES	NO	
	400 kPa	0.5 MHz	YES	YES	NO	YES	NO	
	450 kPa	0.5 MHz	YES	YES	YES	YES	NO	
Mouse	150 kPa	1.53 MHz	SOME	NO	NO	NO	NO	[54]
	300 kPa	1.53 MHz	YES	YES	NO	YES	NO	
	450 kPa	1.53 MHz	YES	YES	SOME	YES	NO	
	600 kPa	1.53 MHz	YES	YES	YES	YES	YES	
Mouse	150 kPa	1.5 MHz	YES	NO	NO	NO	NO	[55]
	300 kPa	1.5 MHz	YES	NO	NO	NO	NO	
	450 kPa	1.5 MHz	YES	YES	YES	YES	NO	
	600 kPa	1.5 MHz	YES	YES	YES	YES	YES	
	150 kPa	1.5 MHz	YES	NO	NO	NO	NO	
	300 kPa	1.5 MHz	YES	NO	NO	YES	NO	
	450 kPa	1.5 MHz	YES	YES	YES	YES	YES	
	600 kPa	1.5 MHz	YES	YES	YES	YES	YES	
	150 kPa	1.5 MHz	YES	NO	NO	NO	NO	
	300 kPa	1.5 MHz	YES	NO	NO	YES	NO	
	450 kPa	1.5 MHz	YES	YES	YES	YES	YES	
600 kPa	1.5 MHz	YES	YES	YES	YES	YES		
Macaque	275 kPa	0.5 MHz	YES	YES	NO	YES	NO	[56]
	350 kPa	0.5 MHz	YES	YES	NO	YES	NO	
	450 kPa	0.5 MHz	YES	YES	NO	YES	NO	
	600 kPa	0.5 MHz	YES	YES	NO	YES	NO	
Mouse	0.41 MI		YES	NO	NO	YES	NO	[57]
	0.56 MI		YES	NO	NO	YES	NO	
	1.12 MI		YES	YES	YES	YES	YES	
	0.43 MI		YES	NO	NO	YES	NO	
	0.83 MI		yes	yes	yes	yes	yes	

Rabbit	140 kPa	0.26 MHz	YES	NO	NO	NO	NO	[58]
	290 kPa	0.26 MHz	YES	YES	NO	YES	NO	
	400 kPa	0.26 MHz	YES	YES	SOME	YES	YES	
	570 kPa	0.26 MHz	YES	YES	YES	YES	YES	
Mouse	150 kPa	1.5 MHz	NO	NO	NO	NO	NO	[59]*
	300 kPa	1.5 MHz	YES	NO	NO	YES	NO	
	450 kPa	1.5 MHz	YES	YES	NO	YES	NO	
Mouse	450 kPa	1.5 MHz	YES	SOME	NO	YES	NO	[60]**
	1500 kPa	1.5 MHz	YES	YES	YES	YES	YES	
Mouse	450 kPa	1.5 MHz	YES	NO	NO	NO	NO	[61]
	750 kPa	1.5 MHz	YES	YES	YES	YES	YES	
Mouse	225 kPa	1.5 MHz	YES	NO	NO	NO	NO	[62]***
	300 kPa	1.5 MHz	YES	NO	NO	YES	NO	
	450 kPa	1.5 MHz	YES	YES	SOME	YES	NO	
	600 kPa	1.5 MHz	YES	YES	YES	YES	YES	
Mouse	200 kPa	0.5 MHz	YES	YES	NO	YES	NO	[63]
	300 kPa	0.5 MHz	YES	YES	YES	SOME	NO	
	600 kPa	0.5 MHz	YES	YES	YES	YES	YES	

\* Only data from OFB were used.

\*\* Only data from Definity were used.

\*\*\* Only data from C24, 1000 cycles were used.

Note : The metanalysis contains publications in which focal pressure, excitation frequency, level of harmonics, ultraharmonics, broadband, BBB-opening evidence, and T2/histology were reported. Mechanical indices were calculated by dividing reported/estimated in-skull pressure (in megapascals) by square root of frequency in megahertz).

**Suppl. Table 3. Summary of studies reporting the impact of MB-FUS alone on survival in murine brain tumor models.**

Tumor model	Frequency [MHz]	Pressure ( $P_{-}$ ) [MPa]	M.I.	Microbubble Type	Key findings
SMA-560 glioma (B6-albino mouse)	0.6	0.4	0.52	BG6895 infusion	No difference in median survival time. [64]
C6 glioma (Rat)	0.4	0.62	0.98	Sonovue 0.0025 mg/kg	Median survival time decreased by 10.5% after FUS (not statistically significant). [65, p.]
U87 glioma (Mouse)	0.5	0.3 - 0.7	0.42 - 0.99	Sonovue 4 $\mu$ g	Modest improvement in survival (IST median 8.6%). Not statistically significant. [66]
MGPP3 glioma (mouse)	1.5	0.7	0.57	Lipid shell 1 mL/kg	No difference in median survival time. [67]
C6 glioma (Rat)	0.5	0.36 - 0.7	0.51 - 0.99	Sonovue 0.1 mL/kg	Modest improvement in survival (IST median 9.5%). Not statistically significant. [68]
U87 glioma (Mouse)	0.4	0.4	0.63	Sonovue 10 $\mu$ L	Modest improvement in survival (IST median 9.68%). Not

					statistically significant (P=0.5407). [69]
GL261 Glioma (mouse)	1.1	0.4	0.38	Albumin shell 1E5 MBs/g	No statistically significant difference in median survival time. [70]
9L Gliosarcoma (Rat)	1.7	0.6	0.46	Definity 0.01 mL/kg	No difference in median survival time. [71]
9L Gliosarcoma (Rat)	0.69	0.55 - 0.81	0.66 - 0.98	Definity 0.01 ml/kg	Multiple treatments with ultrasound shows no difference in median survival time compares to non-FUS group.[72]
U87 glioma (Mouse)	1.1	0.6	0.57	Lipid shell 0.2 ml/kg	No difference in median survival time. [73]
U87 glioma (Mouse)	1	0.3	0.3	-	No difference in median survival time. [74]
C6 glioma (Rat)	1	-	-	Lipid shell bubble	Modest improvement in survival (IST median 14%). Not statistically significant. [75]
Average	-	0.48 - 0.58	0.55 - 0.68	-	No statistically significant improvement in survival
Median	-	0.4 - 0.6	0.52 - 0.57	-	

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