

Increased efficacy in treatment of glioma by a new modulated electro-hyperthermia (mEHT) protocol

István Portoro¹, Lea Danics¹, Daniel Veres², Tamas Kaucsar¹, Ildiko Horvath², Jeremiah Thomas¹, Csaba Schvarcz¹, Krisztian Szigeti², Domokos Mathe², Peter Hamar¹, Zoltan Benyo¹

¹ Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

² Department of Biophysics and Radiation Biophysics, Semmelweis University, Budapest, Hungary

Presented at 36th ICHS, Budapest, 2018

Cite this article as:

Portoro I. (2018); Increased efficacy in treatment of glioma by a new modulated electro-hyperthermia (mEHT) protocol; *Oncothermia Journal* 24:344-356

www.oncothermia-journal.com/journal/2018/Increased_efficacy_in_treatment.pdf

Increased efficacy in treatment of glioma by a new modulated electro-hyperthermia (mEHT) protocol

István Portoro¹, Lea Danics¹, Daniel Veres², Tamas Kaucsar¹, Ildiko Horvath², Jeremiah Thomas¹, Csaba Schvarcz¹, Krisztian Szigeti², Domokos Mathe², Peter Hamar¹, Zoltan Benyo¹

¹ Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

² Department of Biophysics and Radiation Biophysics, Semmelweis University, Budapest, Hungary

Introduction

Modulated electro-hyperthermia (mEHT) is an effective and widespread supplemental therapy in cancer treatment using the radiofrequency (RF) of 13.56 MHz and a fractalphysiology-based modulation frequency based on selective heating of the tumors. From the Pennes equation... We used an animal model to demonstrate the hypothesis in vivo.

Methods

RG2 [D74] (ATCC®, CRL 2433™) glioma cell line was inoculated into the parietal lobe of syngeneic Fischer 344 rats. This model mimics the human malignant astrocytoma by having incompetent BBB. A gadolinium-based MRI contrast agent (MAGNEVIST®, 0.5 mmol/mL, 0.2 mL/kg bdw) was used to detect lesions associated with altered blood-brain barrier and the volume of the tumor was quantificated at the 8th and 15th days after inoculations (AMIDE® software). The animals was divided randomly in 4 groups: sham (3), treated with classical mEHT protocol (3), treated with new mEHT protocol (3), treated with classical mEHT protocol and with the temozolamide (30 mg/kg bdw for 5 days), an oral chemotherapy drug used as a second-line treatment for astrocytoma and a first-line treatment for glioblastoma multiforme (1). We applied the mEHT treatment at 6th, 9th, 11th and 13th days after inoculations.

Results

As a result of a technological improvement we used a new cooling system wich was able to prevent the overheating of the skin below the RF electrode and above the skull with high electrical impedance. Consequently based on a stepwise protocol we could apply extremly high energies (even 10 W) to reach as soon as possible the requested temperature into the brain. The brain temperature was evaluated indirectly by the measurement of the temperature in the middle ear and by using a correlation curve set up in an earlier experiment. The tumor growing rate between the 8th and 15th days after inoculations was in the case of sham animals: 23.73 ± 12.15 , treated with classical mEHT protocol: 19.08 ± 0.49 , treated with new mEHT protocol: 6.83 ± 2.02 , treated with classical mEHT protocol and with the temozolamide: 7.99.

Conclusion

Text The application of the new cooling system allowed us to set up in the case of glioma a new mEHT protocol which is based on that principle to reach a very high specific absorption rate in the treated tissue. This new protocol was more efficient as the classical one and

surprisingly looks like more efficient/similarly efficient than the classical one combined with chemotherapy.

This study was supported by the Hungarian National Research, Development and Innovation Office (NVKP_16-1-2016-0042)

Increased efficacy in treatment of glioma by a new modulated electro-hyperthermia (mEHT) protocol

**István Portör¹, Lea Danics¹, Dániel Veres², Tamás Kaucsár¹, Ildikó Horváth²,
Jeremiah Thomas¹, Csaba Schvarcz¹, Krisztián Szigeti²,
Domokos Máthé², Péter Hamar¹, Zoltán Benyó¹**

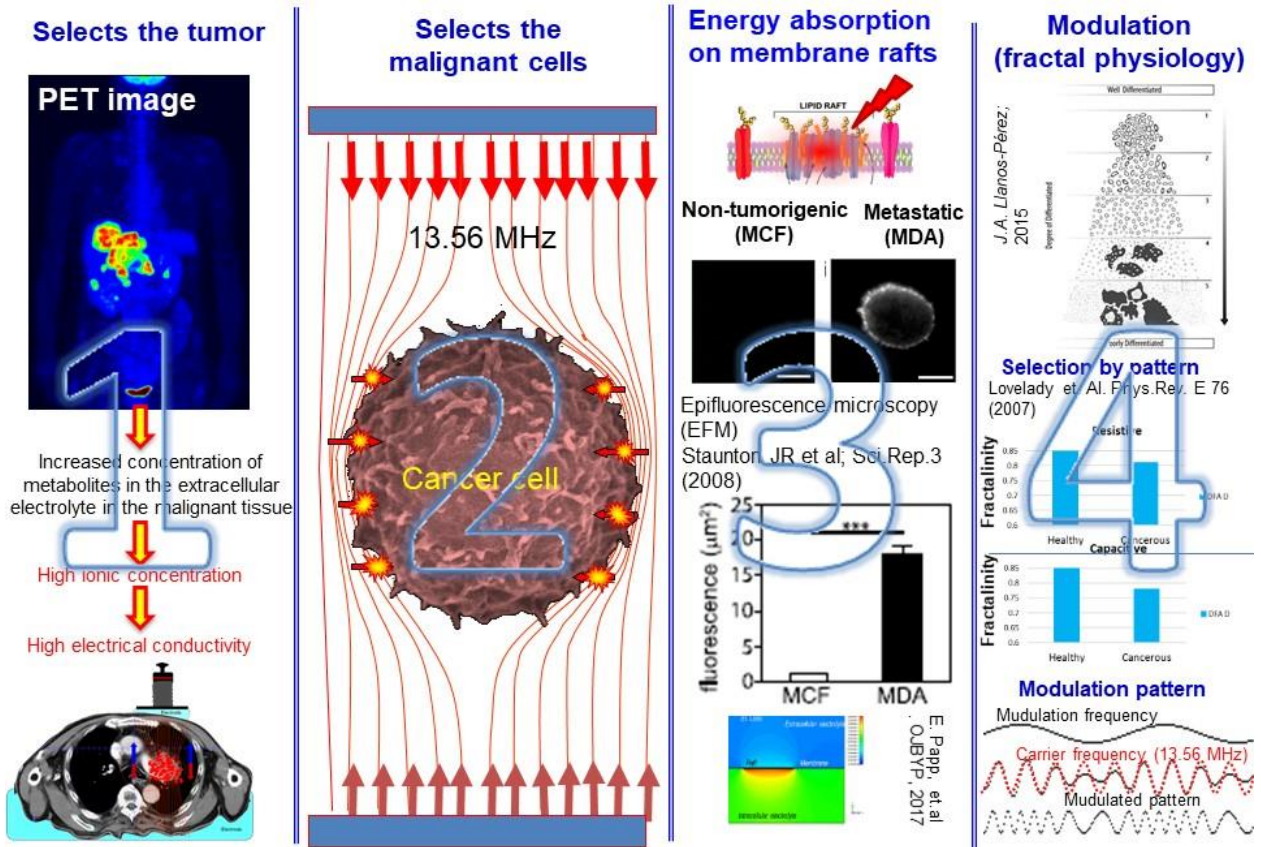
¹ Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

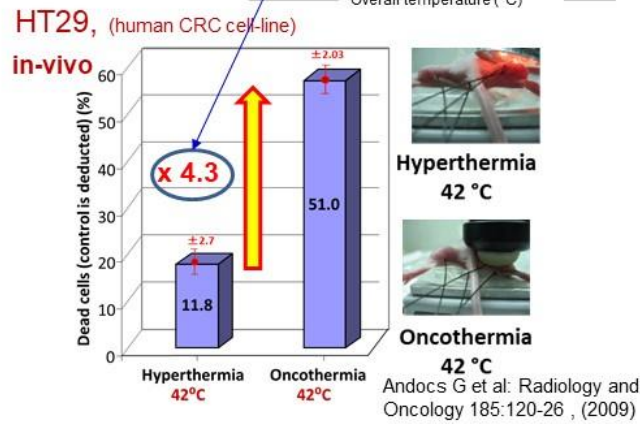
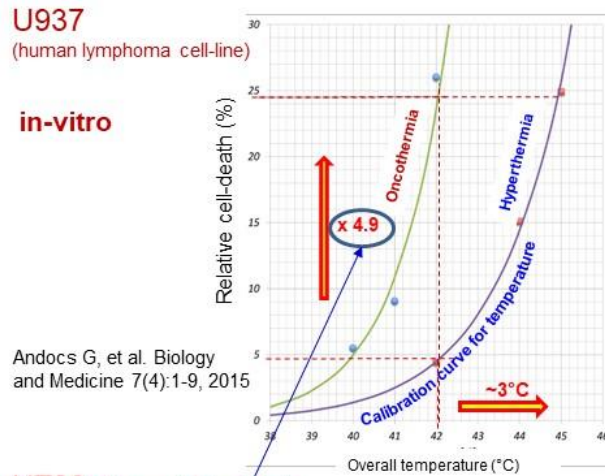
² Department of Biophysics and Radiation Biophysics, Semmelweis University, Budapest, Hungary

This study was supported by the Hungarian National Research,
Development and Innovation Office (NVKP_16-1-2016-0042)



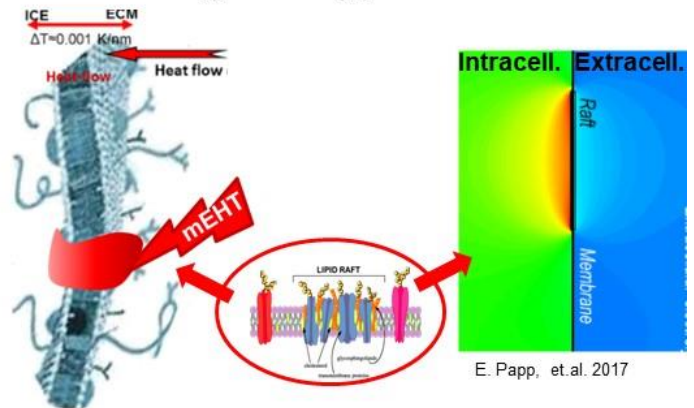
Selection of the malignant cells by biophysical differences



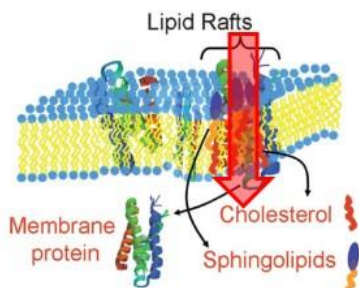


Challenge of the dose of oncological hyperthermia

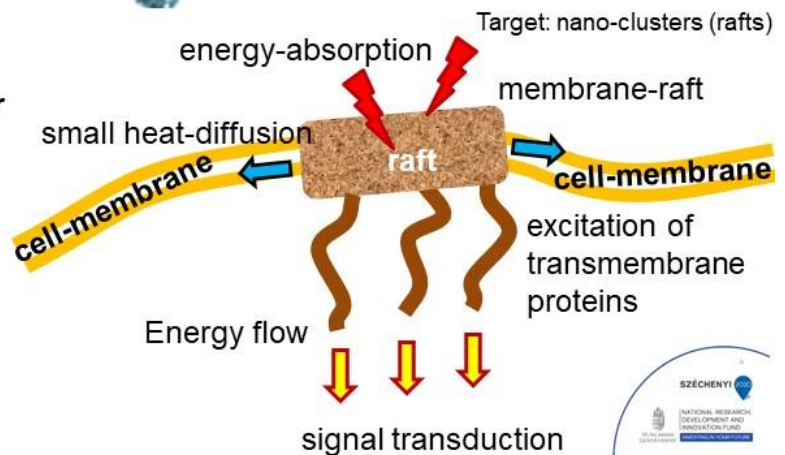
mEHT heats the cell-membrane rafts



quasi adiabatic energy transfer



Kulkarni CV. (2017) Nanoscale 4(19):5779-91



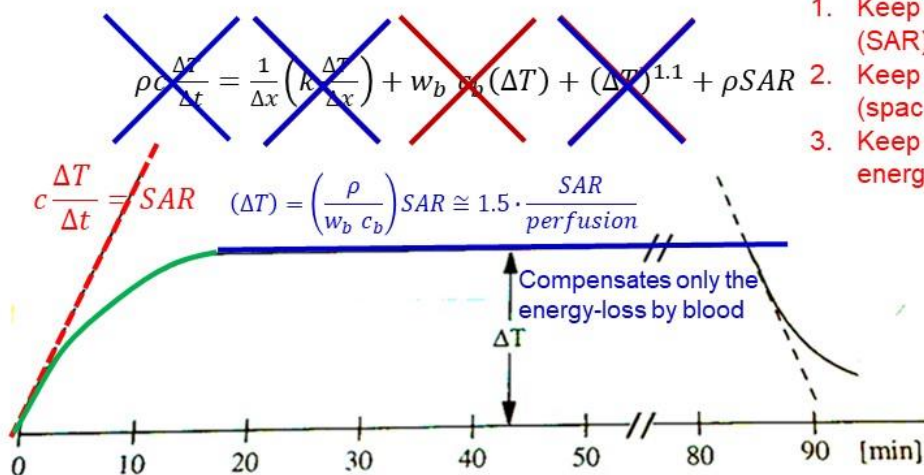
Power equation (Pennes equation)

$$\rho c \frac{\partial T}{\partial t} = \nabla(k \nabla T) + w_b c_b (T_a - T) + q_m + \rho SAR$$

Change by time Change by space Change by blood Change by metabolism **Hyperthermia Pumped-in power**

where ρ , c , and k are the density (kg/m^3), the specific heat (J/(kgK)), and the tissue thermal conductivity (W/(m.K)), respectively; w_b is the mass flow rate of blood per unit volume of tissue ($\text{kg/(sm}^3\text{)}$); c_b is the blood specific heat; q_m is the metabolic heat generation per unit volume (W/m^3); T_a represents the temperature of arterial blood (K); T is the actual temperature risen above the ambient level; $\partial T/\partial t$ is the rate of temperature rise. (**SAR (Specific Absorption Rate) – (W/kg)**)

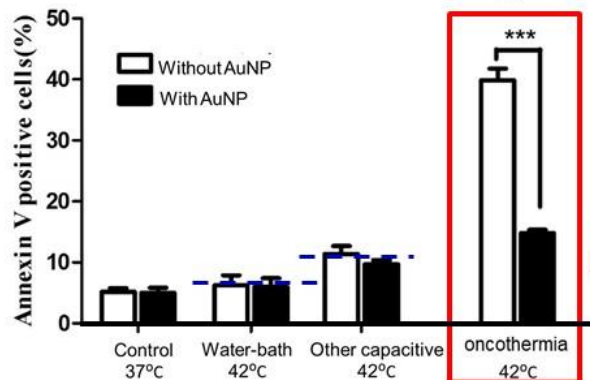
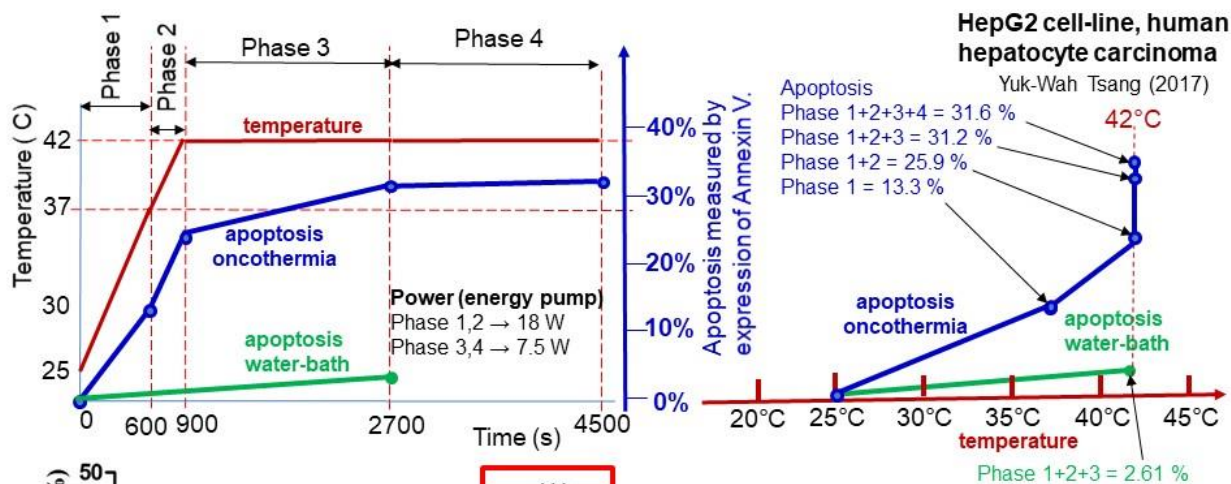
Simplified (no derivatives)



Our tasks:

1. Keep the time-dependent part (SAR) large
2. Keep the environmental (space-dependent) part small
3. Keep the compensating energy small

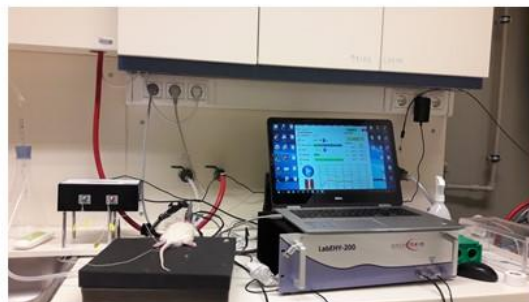
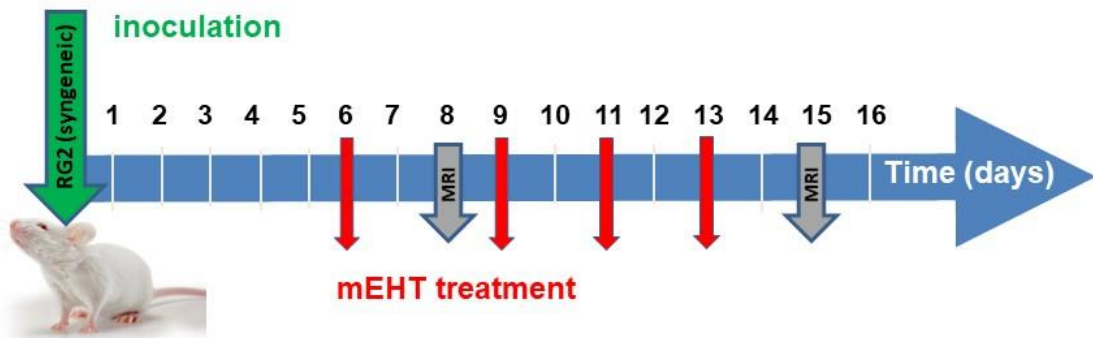
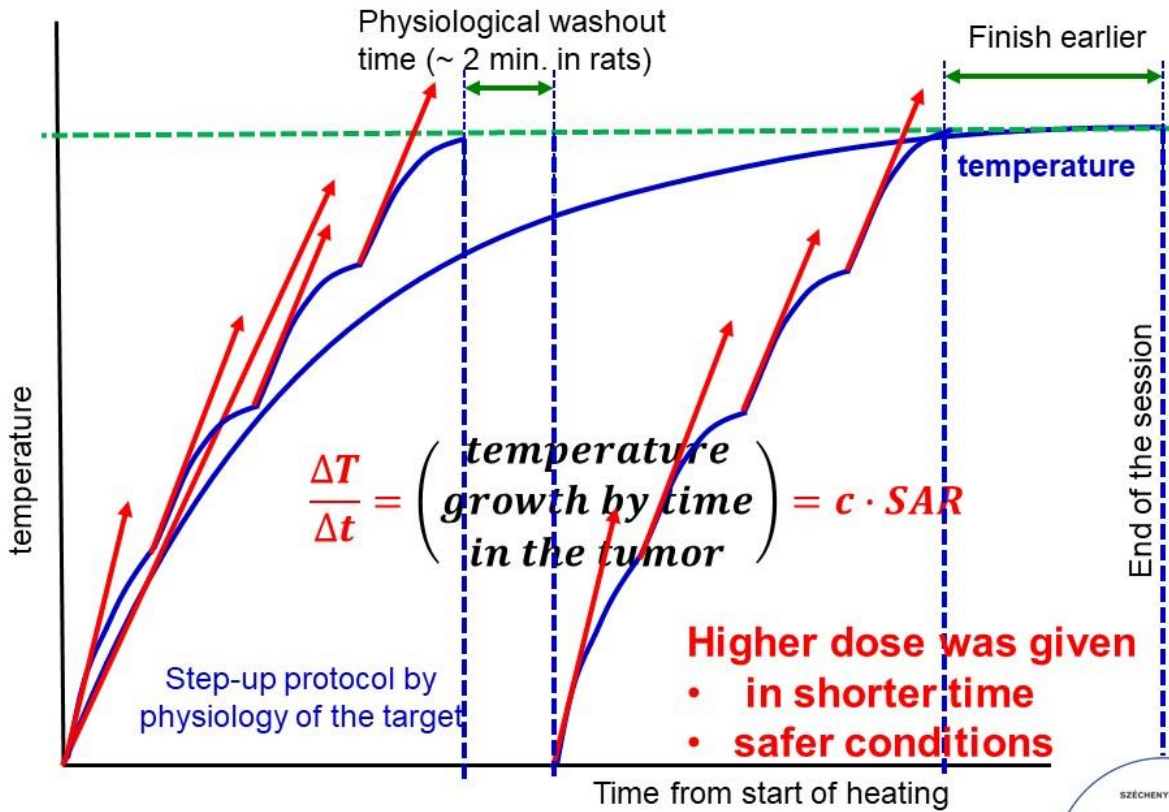
Challenge of the dose of oncological hyperthermia



AuNP heats conventionally, produces the same apoptotic rate than without when heated to the same temperature **but**

AuNP heated with oncothermia the effect of apoptosis decreases, because less energy is given to the malignant cells directly when AuNP is also heated

Challenge of the dose of oncological hyperthermia



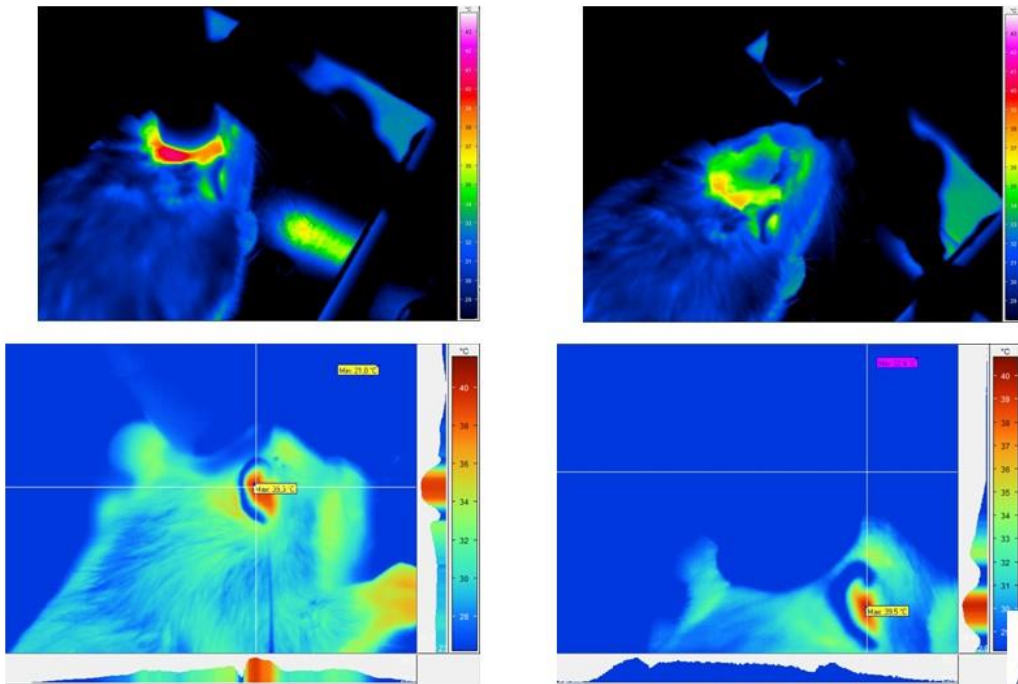
Development on an evaporation-based cooling system

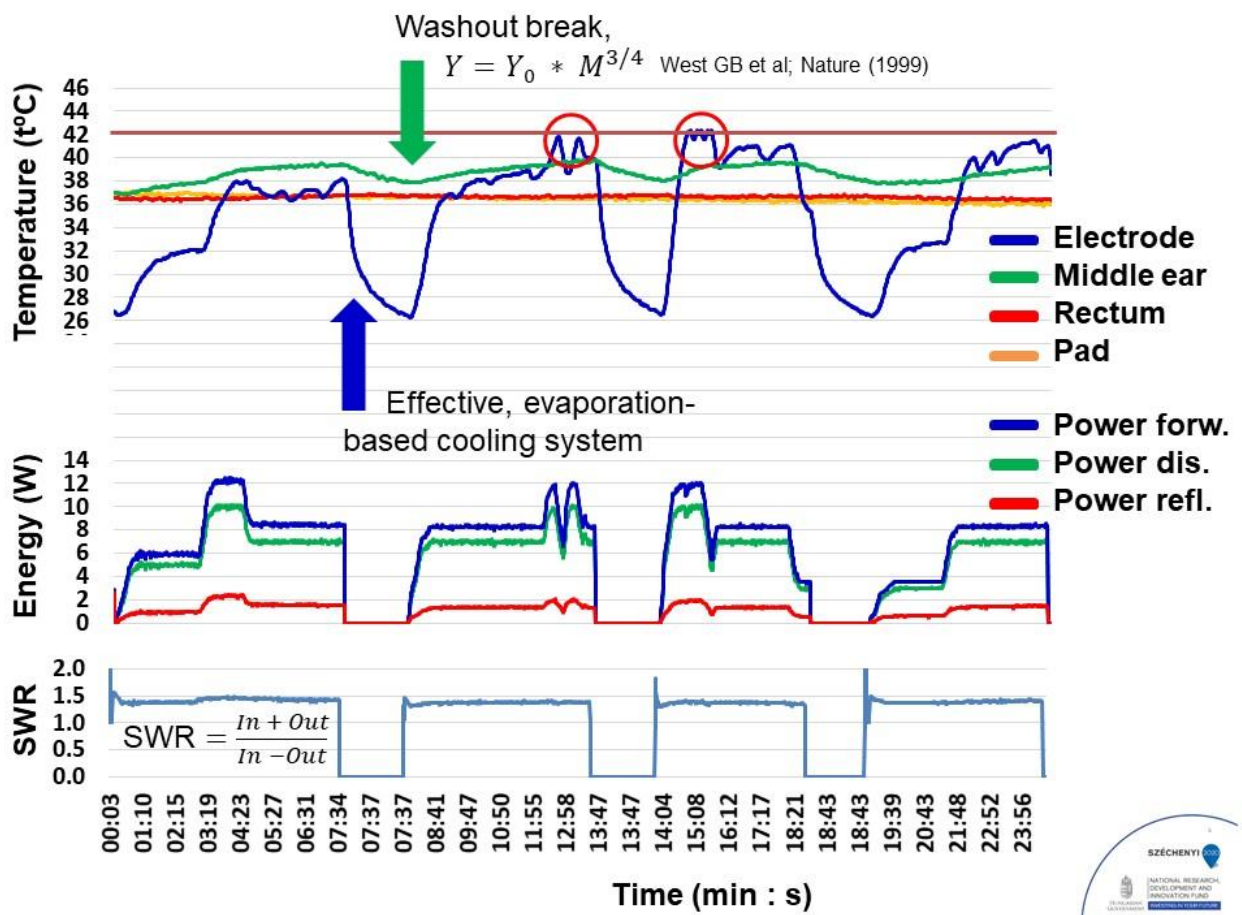


Calibration curve:
The temperature in the brain area
under the electrode is 1,78 C higher
than in the middle ear

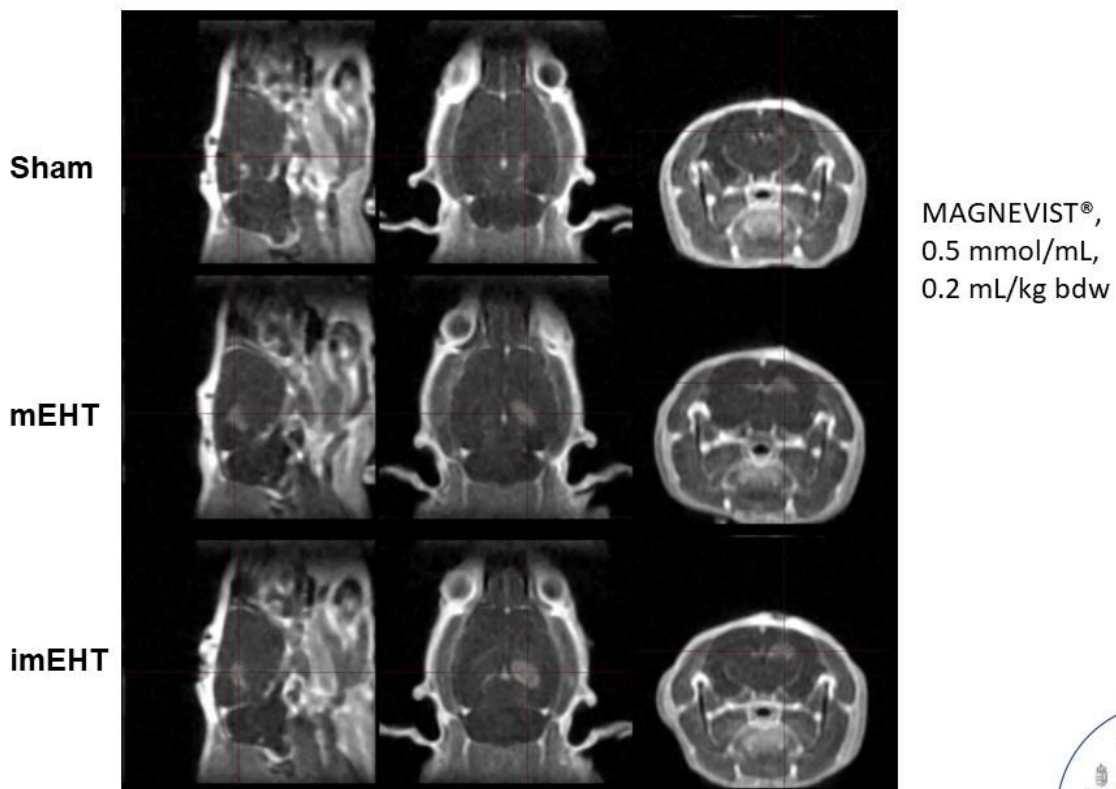


The application of the new cooling system allowed us to achieve a very high quasi adiabatic specific absorption rate in the treated tissue.

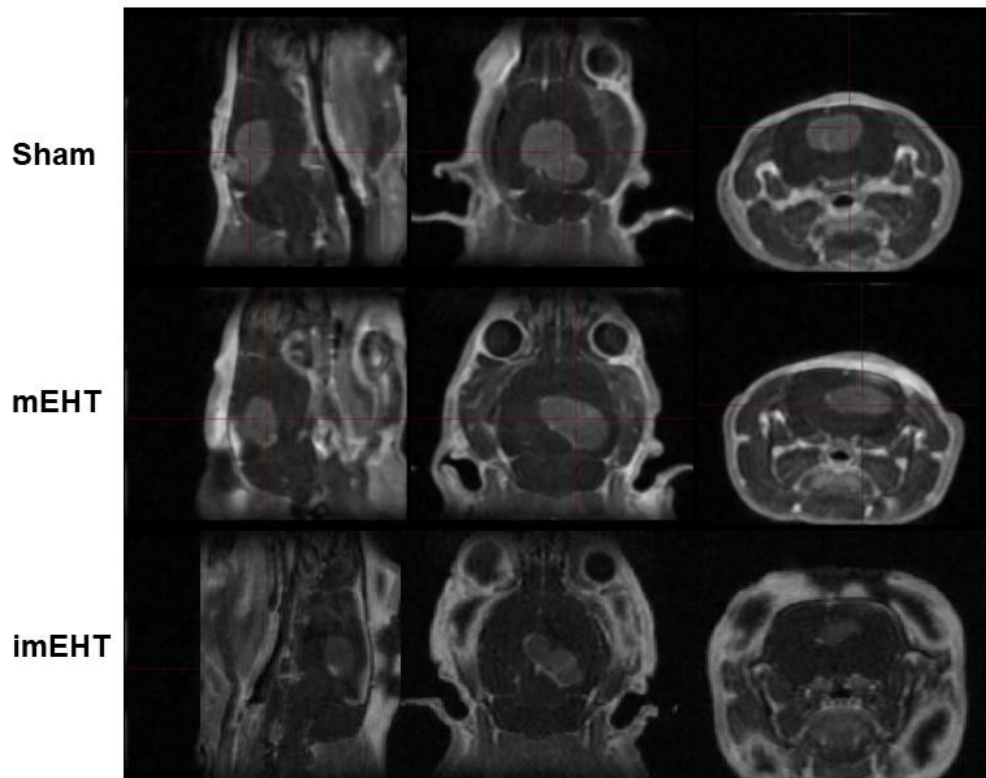




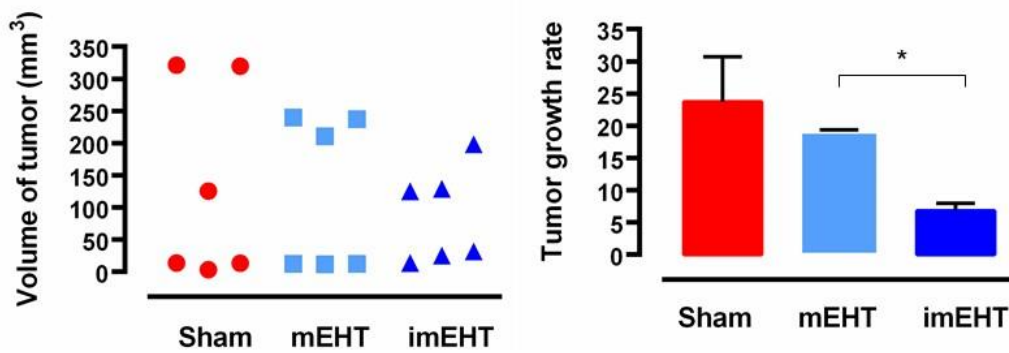
**Mediso nanoScan 1T small animal MRI system
 and a 3D image acquisition sequence**



Tumor size after the treatment (15th day)



Quantification of the MRI results



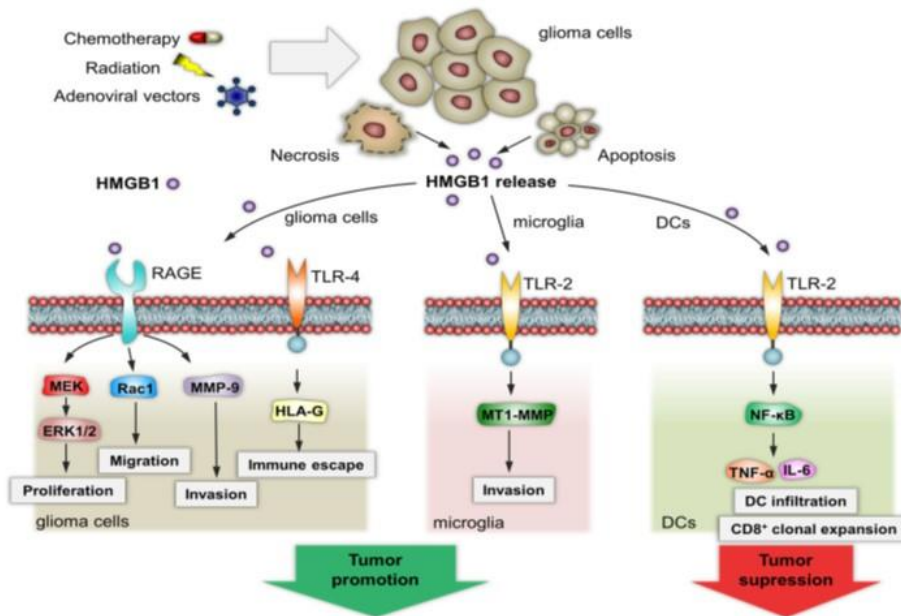
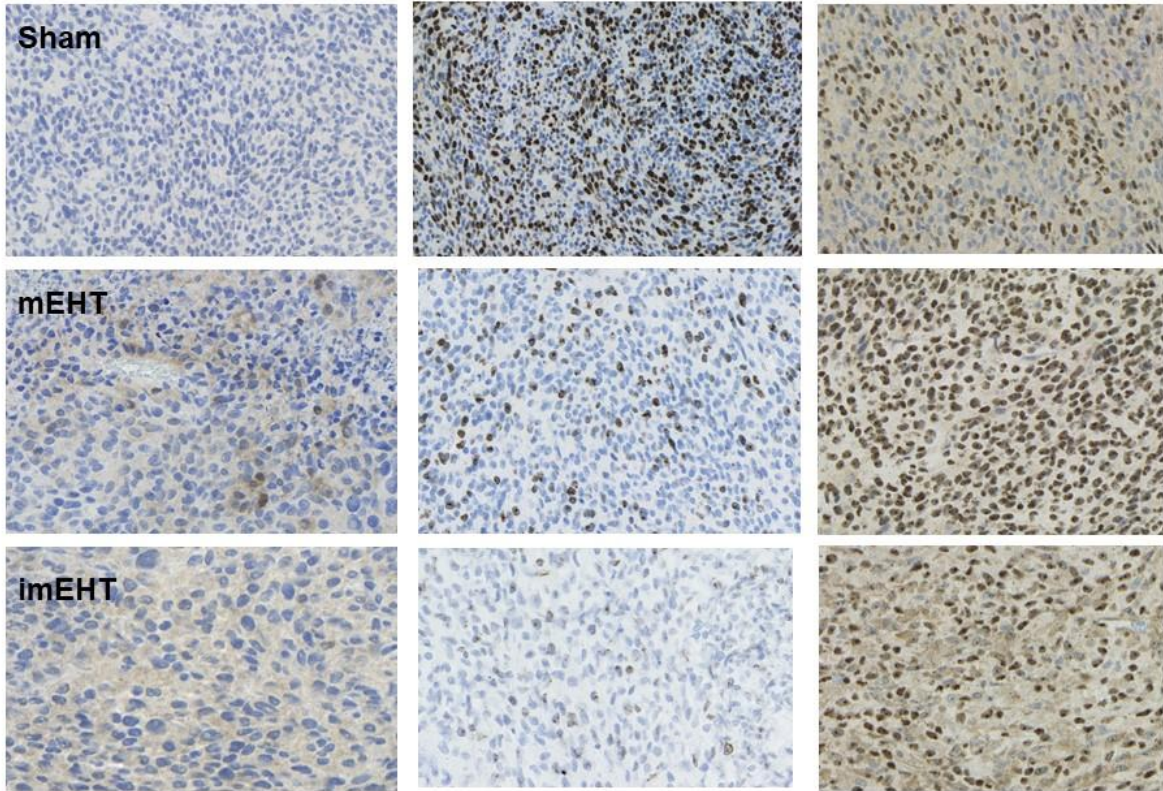
	Sham		mEHT		imEHT	
(volume, mm ³)	8 th day MRI	15 th day MRI	8 th day MRI	15 th day MRI	8 th day MRI	15 th day MRI
	13,76342773	321,4416504	12,35961914	239,6240234	13,79394531	125,213623
	3,479003906	125,5187988	11,35253906	210,3271484	24,99389648	128,7231445
	13,58032227	319,6105957	12,23754883	236,9689941	31,58569336	198,2116699
Mean	10,2742513	255,5237	11,98324	228,9734	23,45785	150,7161
SD	5,885568985	112,5913	0,549599	16,20259	8,994785	41,16974



HSP70

Ki67

HMGB1



Angelopoulou et al; J Mol Med (2016)



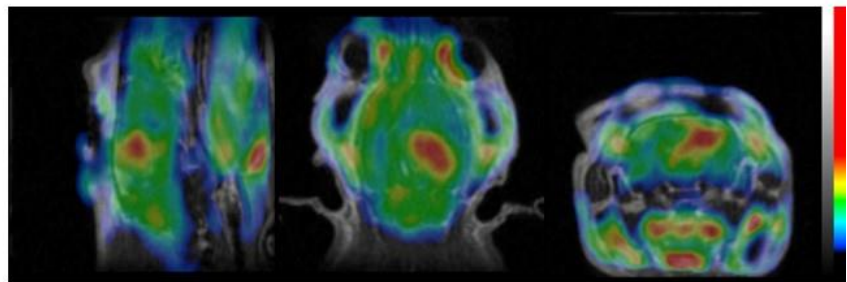
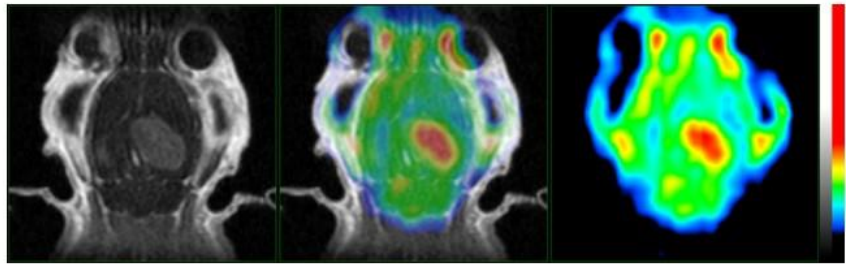
microPET

12.8 MBq 18F-FDG i.v.
through the tail vein

Continuous measurement
for 50 minutes with
microPET P4 (Concorde
microsystems)

The image reconstructed
after 10 minutes of
measurement 40 minutes
after FDG administration
(spatial resolution
1.8x1.8x1.8 mm)

Manually MRI
Corregistration with
VivoQuant



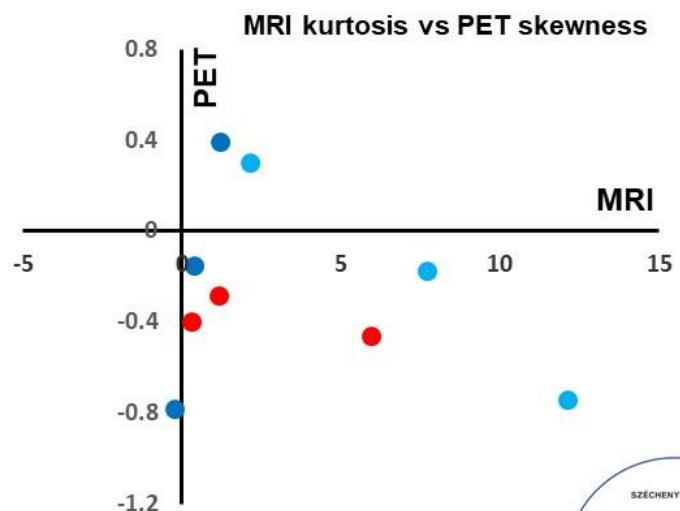
microPET

12.8 MBq 18F-FDG i.v.
through the tail vein

Continuous measurement
for 50 minutes with
microPET P4 (Concorde
microsystems)

The image reconstructed
after 10 minutes of
measurement 40 minutes
after FDG administration
(spatial resolution
1.8x1.8x1.8 mm)

Manually MRI
Corregistration with
VivoQuant



Thank you for your attention!

