Where to go from here?

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Godollo, Hungary

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www.oncotherm.com/sites/oncotherm/files/2021-02/Szasz_Wheretogo

Abstract

Introduction: Hyperthermic oncology has great achievements but also raises questions about the basic mechanisms and clinical applications of the method. Despite its long history, the debates about its possibilities are intensely vivid, the pros and cons strongly and rigidly polarize professionals and develop a barrier to wide application and approval by medical and governmental associations.

Method: It is a relevant requirement to clarify at least the most challenging questions about the basics from my long time experience in the field using my own results and considering the also widely available international literature together with professional expert's opinions.

Results: I list just a few sensitive challenges for questions that come up as standard in current oncology practice in relation to hyperthermia:

- What are the basic mechanisms behind successes and failures?
- Should local or systemic treatment be preferred?
- What is the optimal temperature?
- What is the dose that defines the treatments?
- What about monotherapy?
- Why is it mainly applied to locally advanced and non-metastatic cases?
- How is it related to emerging physical therapies?
- How is hyperthermia involved in the newer concepts of immunotherapy?
- Why is hyperthermia not widely accepted by the oncology community?

Discussion: The challenge is obvious. We have more and more proven details on the challenge that heat alone is not effective enough to solve the problems of cancer and its development, due to the various complex physiological feedback mechanisms in humans. Probably the heating provides hot environment to the tumor, which promotes molecular and physiological processes. This way hyperthermia in cooperation with applied complementary treatments influences the malignancy, eliminates the cancer cells and tries to restore healthy functions. The application of bioelectromagnetic effects could guide changing activities from general tumor destruction to complex regulated and controlled reactions to achieve curative goals.

Conclusion: My presentation would like to make decisive proposals on these hot topics and connected challenges and show what the necessary steps are to move forward.

ICHS 2020
Web-conference

Where to go from here?

Prof.Dr. Andras Szasz

Professor, Head of Department of Biotechnics,
St. Istvan University, Hungary

Skeptic development - What to blame?

- **(1964)** "All of these methods [hyperthermia] **impress the patient** very much; they **do not impress their cancer** at all." **[1]**.
- **(1979)** ... microwave hyperthermia device is a **"gun shooting in the dark room" [2]**.
- **(1993)** "The mistakes made by the hyperthermia community may serve as **lessons, not to be repeated** by investigators in other novel fields of cancer treatment" **[3]**.
- **(2001)** "The biological effects are impressive, but physically the heat delivery is problematic",... "The biology is with us, the **physics are against us**". **[4].**
- **(2004)** "The biology and the physics are with us, but the **physiology is against us**" **[5]**.
- **(2019)** "Physics is our friend, but **we have not noticed** it" **[6], [7], [8].**

[1] Bauer KH, (1964) Das krebsproblem, Springer, Berlin
[2] Susskind C., (1979) "The "story" of nonionizing radiation research," Bulletin of the New York Academy of Medicine, 55:1152–1163,
[3] Storm FK (1993) What happened to hyperthermia and what is its current status in cancer treatment? J Surg Oncol 53:141-143
[4] Nielsen OS, Horsman M, Overgaard J (2001) A future of hyperthermia in cancer treatment? (Editorial Comment), European Journal of Cancer, 37:1587-1589
[5] The Kadota Fund International Forum 2004-Clinical group.pdf
[6] Wust P, Ghadjar P, Nodobny J, beck M, Kaul D, Winter L, Zschaeck S, (2019) Physical analysis of temperature-dependent effects of amplitude-modulated electromagnetic hyperthermia, International Journal of Hyperthermia, 36:1245-1253,
[7] Wust P. (2019) Physical rationale about amplitude modulated radiofrequency hyperthermia, ESHO-2019 Warsaw, Poland, 22-24. 05. 2019
[8] Wust P. (2019) Advantages of amplitude modulation in the radiofrequency hyperthermia, IX. DGHT-Kongress, Berlin, 20-21. 09. 2019

The challenges: questions seeking answers

- ❑ The principial challenge
- ❑ The heating challenge
- ❑ The dosing challenge
- ❑ Technical challenge
- ❑ The immuno-oncology challenge
- ❑ Challenge of emerging therapies

Pitfall of oncology: lost of the complexity

Inductively
study the details and build up the systemic picture

Philosophy of Western medicine - Hippocrates (400 BC)

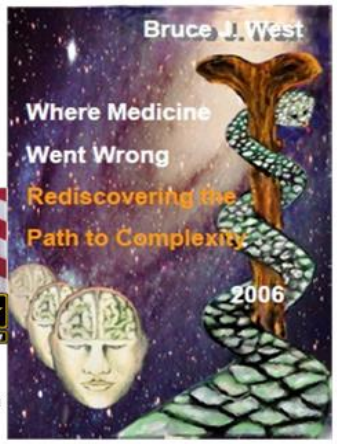
"Nil Nocere"
- Help the nature -

Oncology: hyperthermia

"organ (tissue) failure"
⟹ "reductional"

Reductionism dominates the present medical practice.

Bruce West
Chief scientist
Army Research Office (U.S.)



Deductively
study the system and deduct the details from it

Philosophy of Eastern medicine Lao Zi (500 BC)

"Be harmonic"
- Nature is harmonic -

Oncology: herbal medicine

"energetical failure?"
⟹ "holistic"

Both approaches are necessary!

Oncology ⟹

TASKS ⟹ Destroy the tumor effectively | Block the invasion & dissemination | Eliminate the metastases

Measure ⟹ Local control | Survival time and quality of life

Hyperthermia ⟹ destroy the cancer cells, (inductive way)
block their systemic effects, (deductive way)

Complex thinking is necessary in hyperthermia!

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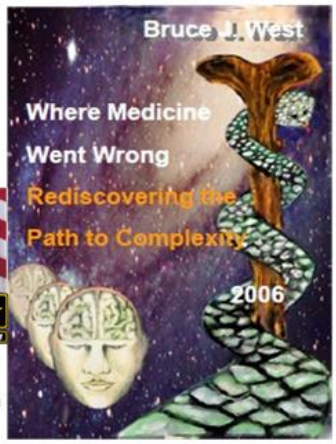

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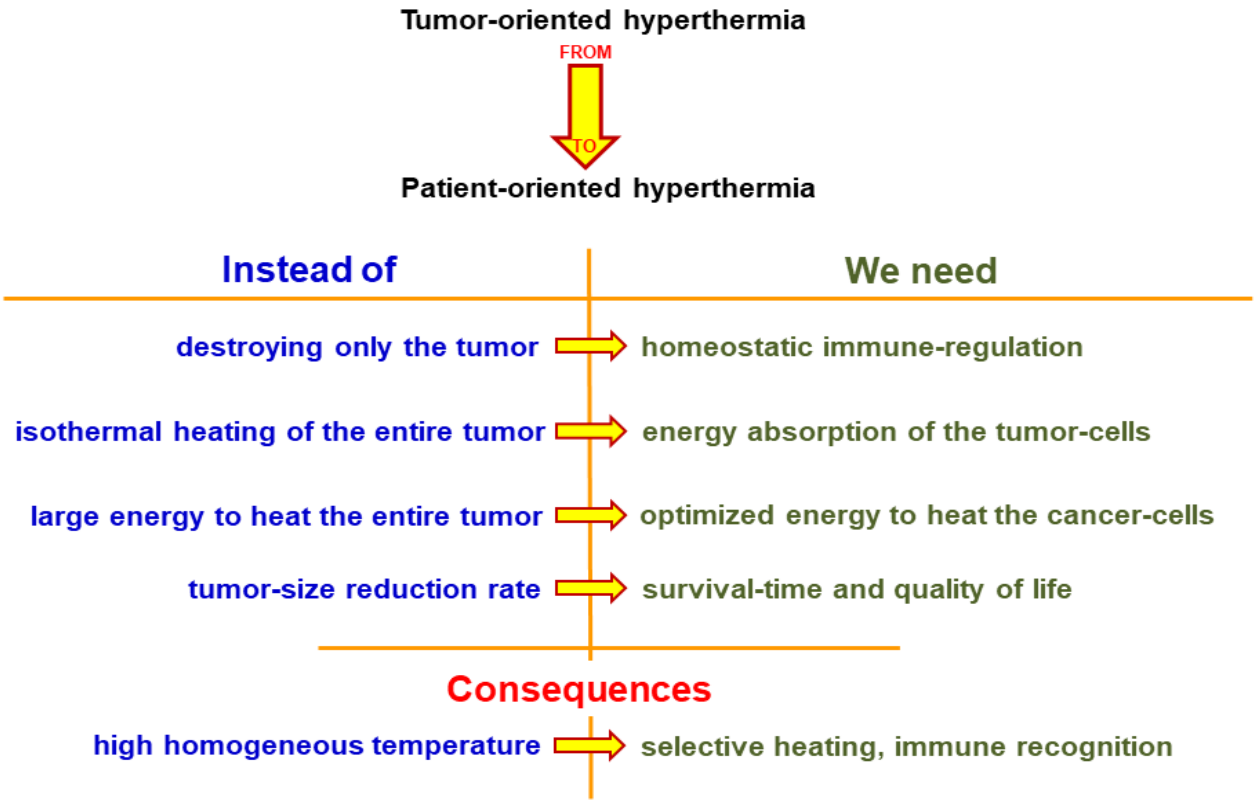
Change the treatment paradigm



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Dose-definition has to based on clinical results

Present dose unit $CEM43°CT_x$ (measured in minutes)

$$CEM43^0C = \sum_{\{i\}}^{steady\ -state} t_i R^{(43-T_i)}$$

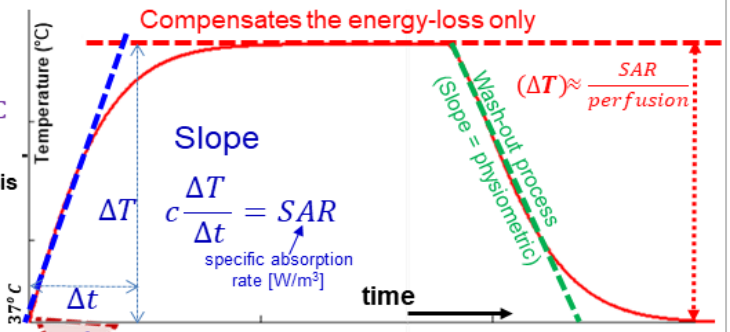
R=0.25, $T \leq 43°C$

R=0.5, $T > 43°C$

Arrhenius plot and its break fits to same damage necrosis for asynchronous Chinese hamster ovary cells, in vitro.

Challenge: Arrhenius plot may vary by cells, tissues, species and chosen endpoints

$(R_{mouse}^{43°C} = 0.25, 0.5; R_{human}^{43.5°C} = 0.13, 0.72)$



corresponding principle

Francena M, et al: Hyperthermia dose-effect relationship in 420 patients .... Eur. J. Cancer, 45:1969-1978 (2009)

Fits to the clinical data

Rough average

$$T_{RISE} = \frac{1}{\#sessions} \sum_{\#sessions} \int_0^{duration} \frac{(T_{50} - 37^oC)}{duration} dt$$

The correct clinical dose has to be a precise not only average measure

T_{50} = at least 50% of the target has such temperature

measured in J/kg [W*s/kg=J/kg=Gy]

$$SAR(t) = c\left(\frac{dT}{dt}\right)$$

$$Absorbed\ energy = \sum_{sessions} \int_0^{duration} \frac{1}{c}(SAR(t))dt$$

Technical requirement: high efficacy of energy absorption

When the energy-absorption is not concentrated on the cancer, it is necessary to measure the temperature, knowing the approximate energy absorption

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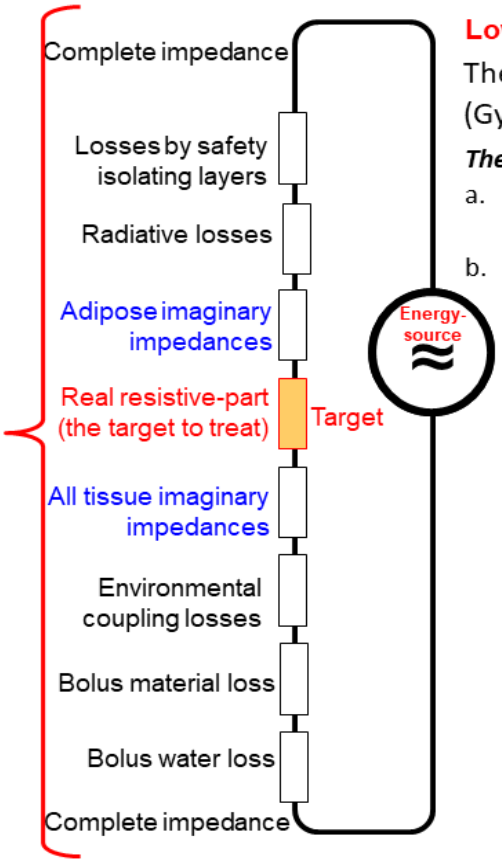
Technical demands and consequences



Low energy-loss allows to use the energy as dose.

The thermal dose characterizes the absorbed energy (Gy=J/kg), like in the practice of ionizing radiation

Thermometry is mandatory in the heating techniques where

a. the absorbed energy is not known (there are lot of energy losses), so the temperature guesses the absorbed energy in the target
b. it is for safety – avoid the risk to overheat the healthy tissues (like surface, deep hotspots, etc.)

Planning is a necessary tool estimating:

1. How much energy is absorbed?
2. Where is the energy focused?
3. How to avoid the unwanted hot-spots?

Planning has to be:

1. Adaptive for individual patients
2. Interactive during the implementation
3. Connected to the regulating software for in-situ adaptation of the treatment

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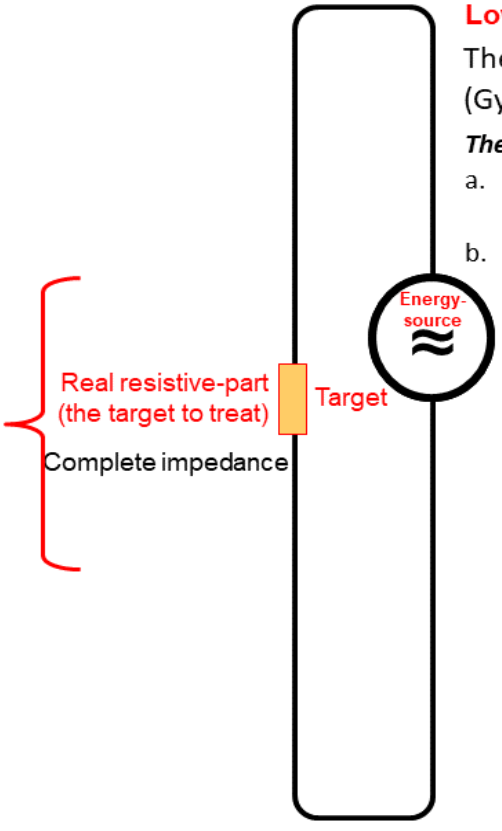

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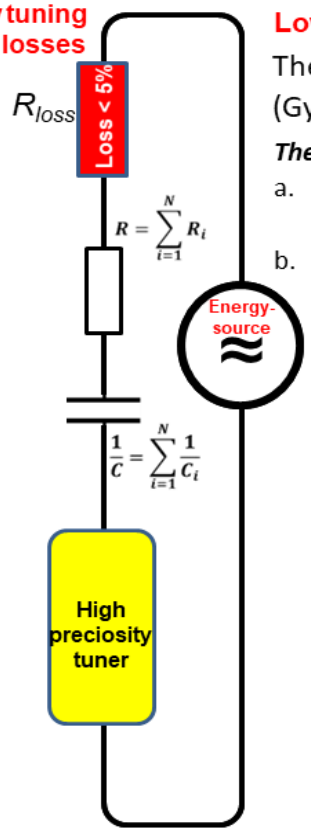
Technical demands and consequences

High preciosity tuning minimizing the losses



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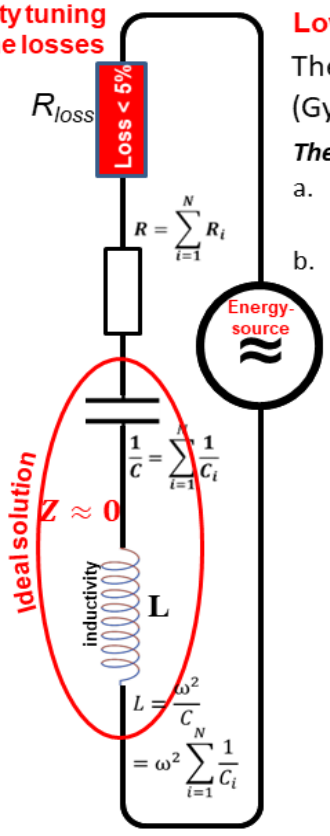

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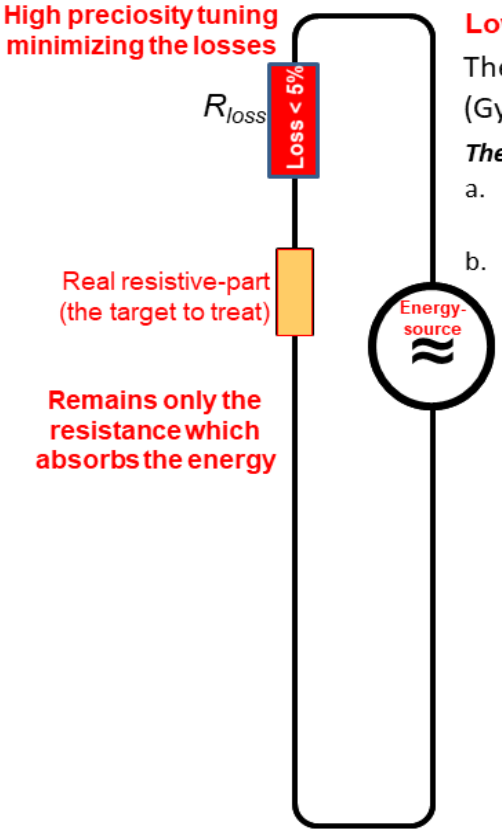

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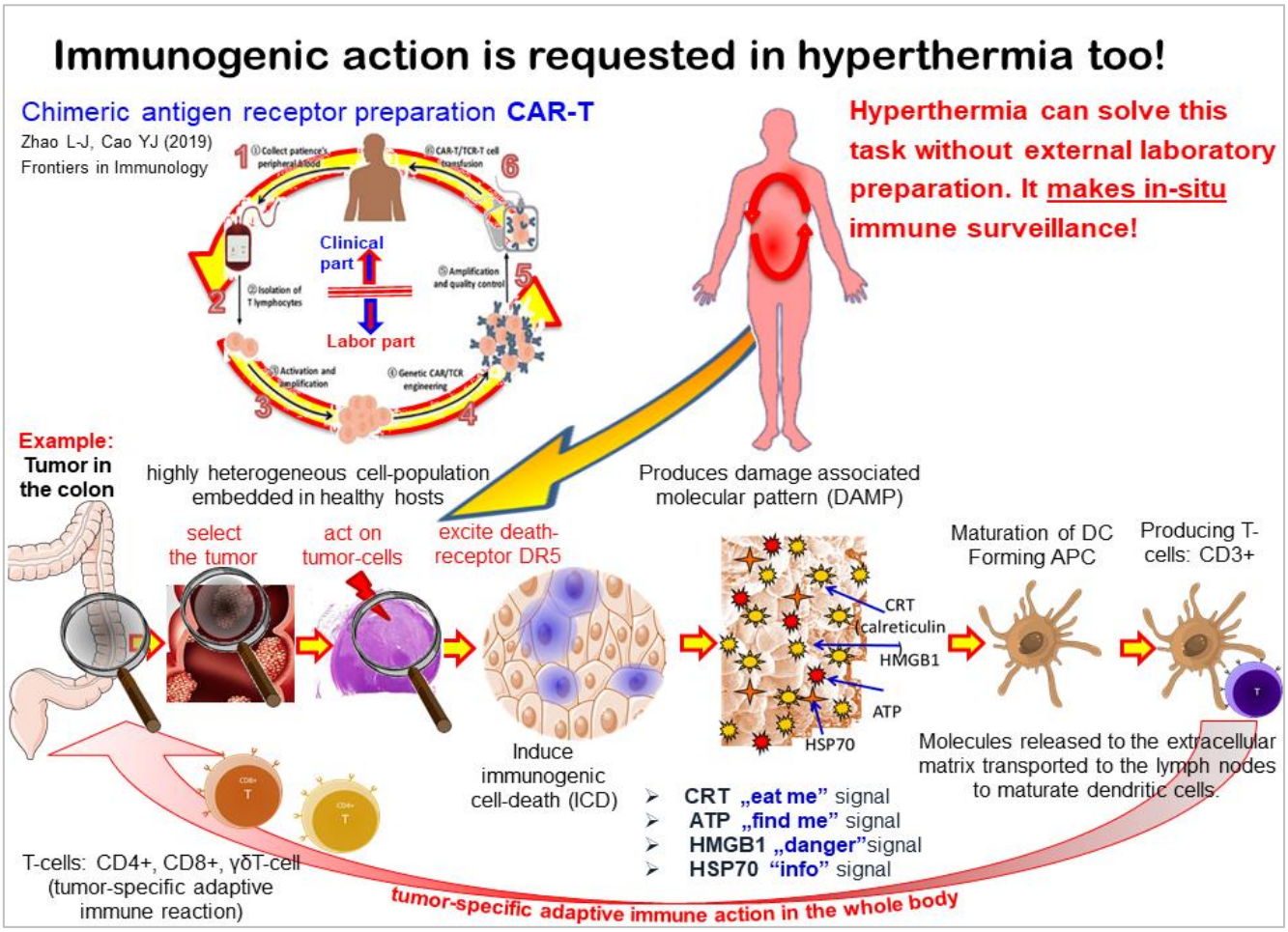

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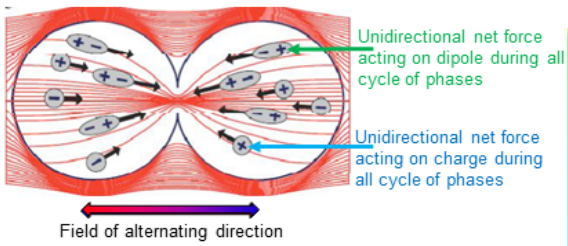
Cytokinesis block by tumor-treating-fields (TTF)

Principle of the tumor-treating-fields (TTF) (acts in cytokinesis)

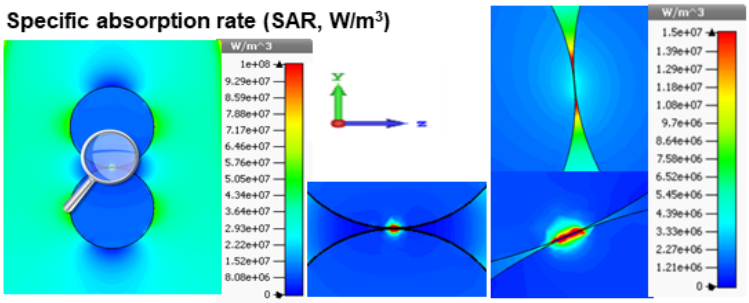


Kirson ED. et. al.: Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors, PNAS, June 12, 2007, Vol. 104. No. 24, 10152-10157

Selective hyperthermia also acts in cytokinesis, but in every directions

Effective in every directions

Specific absorption rate (SAR, W/m³)

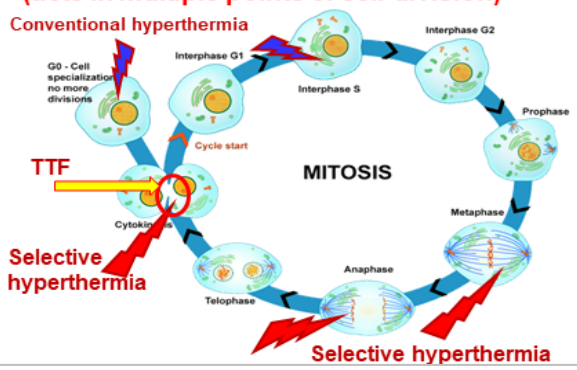


Papp E, et al. (2017) Energy absorption by the membrane rafts in the modulated electro-hyperthermia (mEHT), Open Journal of Biophysics, 7, 216-229

Multiple electrode-pairs for different directions, wear at least 18h/day

Carry it during the whole day even when asleep

Hyperthermia actions (acts in multiple points of cell-division)



Additionally: complex approach of hyperthermia

- ✓ applicable in most locations
- ✓ activates the immune-system
- ✓ makes abscopal effect
- ✓ sensitizes the radiotherapy
- ✓ has synergy with most chemotherapies
- ✓ less annoying for the patient

Answers are given according to my present knowledge

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Thank you for your kind attention

biotech@szie.hu

Challenge by dose - definition based on expriments

Hyperthermia dose definition

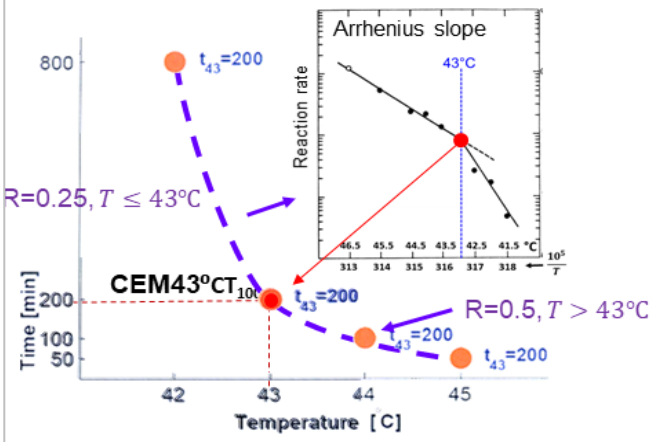
Cumulative Equivalent Minutes ← CEM | 43°C | T_x | [min]

Necrotic cell killing over 43°C

Percentage of the action on the target

Measured in minutes!

Asynchronous Chinese hamster ovary cells, in vitro,
Necrosis is measured in four points with the same damage



Sapareto SA, Dewey WC; (1984) Int.J.Rad. Oncol. Biol. Phys. 10:787-800)

$$CEM43^0C = \sum_{\{i\}}^{steady-state} t_i R^{(T_C - T_i)}$$

T_c=43°C

Complete dose unit forced to use:

$$CEM43°CT_x$$

(measured in minutes)

This dose considers immediate necrotic effect in vitro

Challenges: Arrhenius plot slopes may vary by

- Cells
- Tissues
- Endpoint
- Species

Arrhenius slope characteristics for mouse vs. human cells

		R value	
Species	Breakpoint	<Breakpoint	>Breakpoint
Mouse	43.0°C	0.25	0.5
Man	43.5°C	0.13	0.72

Yarmolenko PS. Thresholds of thermal damage and thermal dose models, https://www.icnirp.org/cms/upload/presentations/Thermo/ICNIRPWHOThermo_2015_Yarmolenko.pdf

Best fit R differs very much in other cells by temperatures over 43°C:
Cells with HSP: **R=0.311** (T=44°C)
Skin burns: **R=0.394** (T=44°C)
Microvascular disruption: **R=1.48** (T=44.5°C)
Muscle damage: **R=1.20** (T=50°C)
Skin burns: **R=1.20** (T=51°C)
PC3 cells: **R=1.08** (T=60°C)
HepG2 cells: **R=0.94** (T=70°C)

Pearce JA. (2013) Int.J.Hyperthermia 29:262-280