

Oncothermia development in Hungary

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Outline

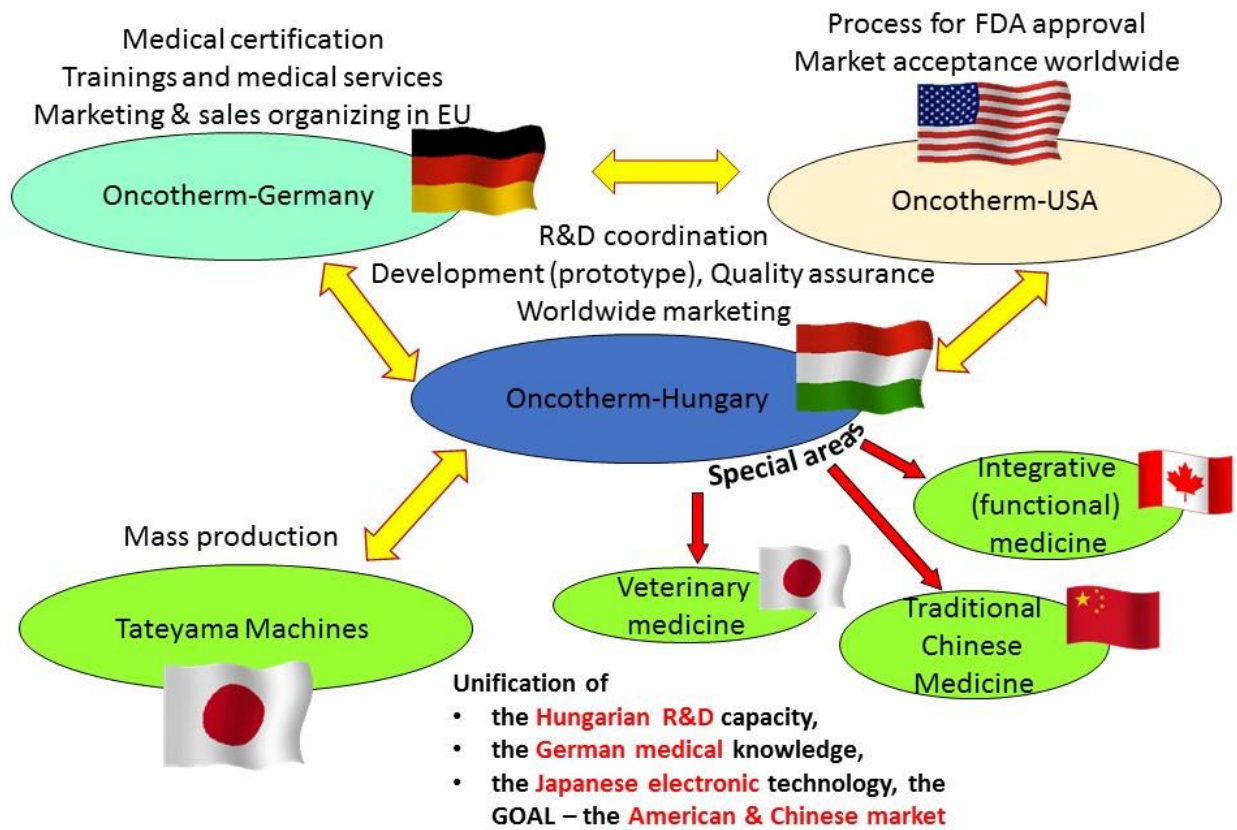
Historical notes

Concept

Realization

Presence

Oncotherm company organization



Philosophy of Oncotherm research



History

Short history of the Company:

- The Oncotherm was established by Prof. Dr. András Szász in 1988.
- Clinical studies started in Germany in 1990 (GS-certificate in 1994).
- We got the CE certification four years later from the first clinical trials in 1998.
- The Oncotherm GmbH was established with a German investor in 2002.
- The Oncotherm Kft. bought the share of the German investor in 2011, and a new partner, Tateyama joined the company.

Certifications and approvals:

- The device has CE certification (tradable in all the EU countries).
- The Company has ISO 9001 and ISO 13485 certifications (general and medical device production).
- Further certifications all over the world:



Outline

Historical notes

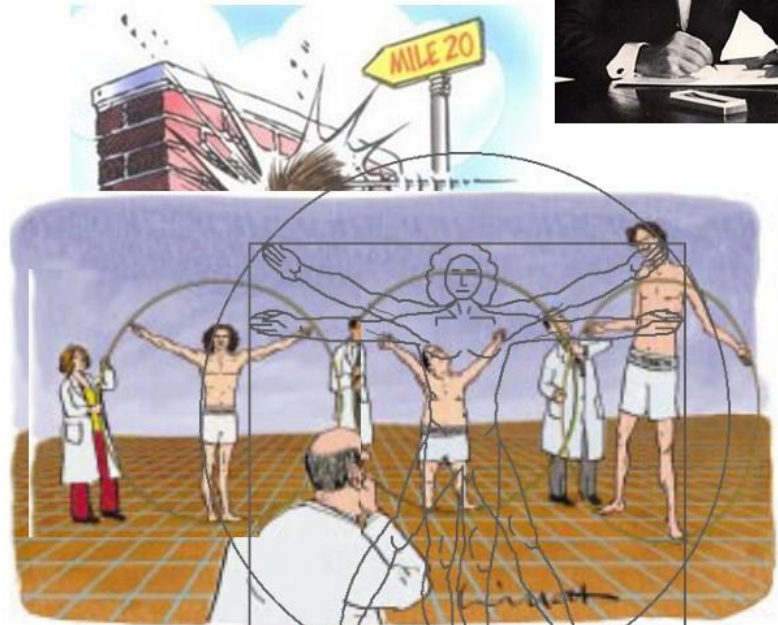
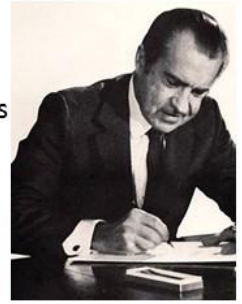
Concept

Realization

Presence

The war

The **war on cancer** began with the National Cancer Act of 1971, a United States federal law. (Signed by the president of the USA, Richard Nixon)



Oncothermia is a committed warrior in the battle

RI n. 1, 2015, 15. Research into complementary and alternative medicine: problems and potential, *Bmj* 322:161-164

Oncothermia philosophy

Oncothermia combines the ancient hyperthermia treatment with an electrical field and is applied with the standard treatments of school medicine (chemo- and radiotherapy).

3E EFFICACY of the energy-absorption
 EFFICACY of the selective focusing
 EFFICACY of the survival elongation

+

3S SAFETY for patients by high standards
 SAFETY for doctors by low radiation
 SAFETY for the enterprise by high science

No special attention is taken on the popular "endpoints" of studies

(usually measured by pharmaceutical trials)

- the immediate clinical response (shrinking of tumor)
- the disease-free survival
- the relapse-free survival
-

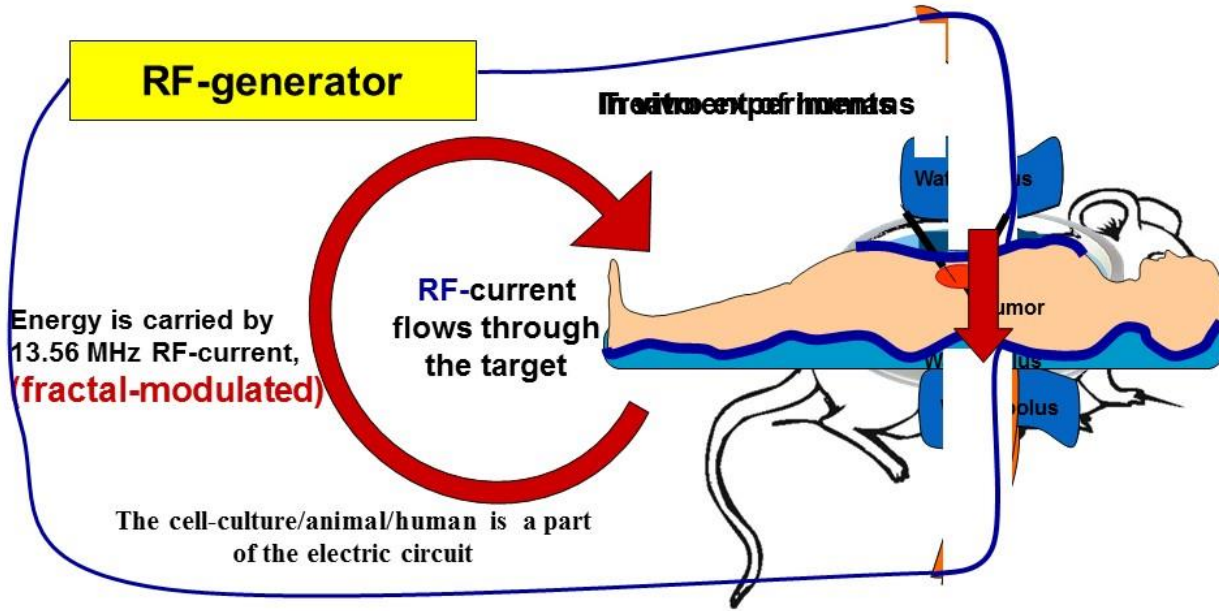
Two connected parameters are in the center of our attention:

**the survival time
 &
 the quality of life**

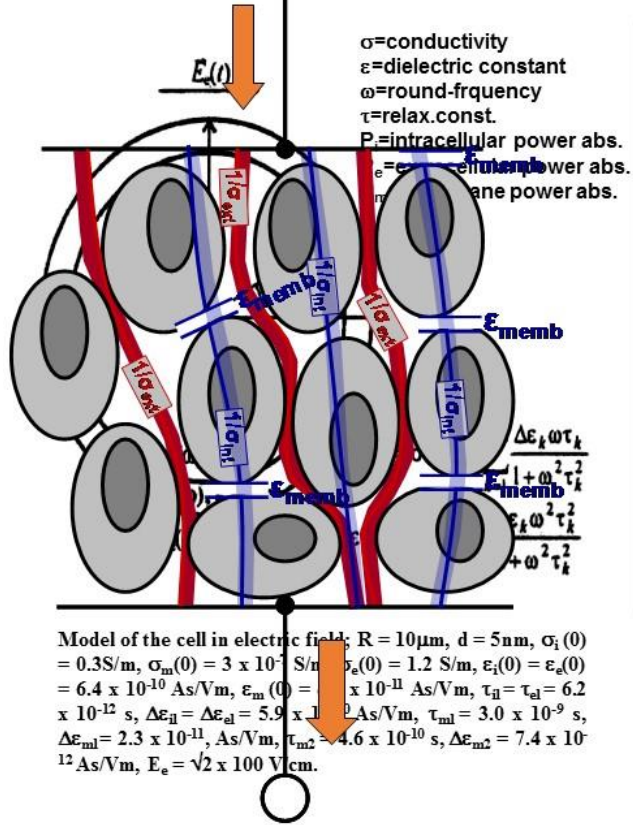
Principles of modulated electro-hyperthermia (oncothermia)

Modulated electro-hyperthermia is a new kind of hyperthermia in oncology

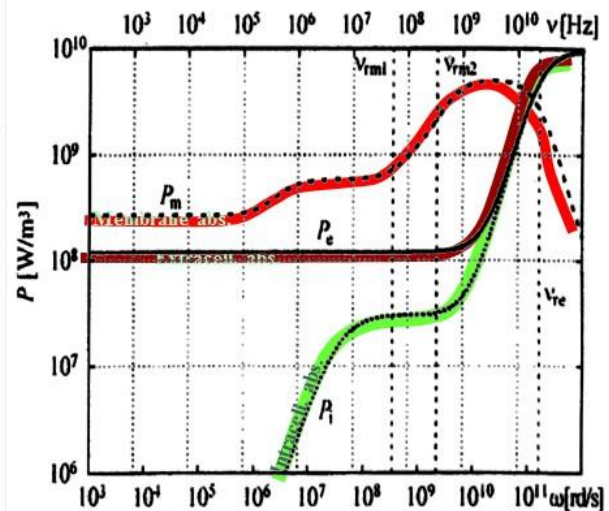
The target (in clinical the patient) is an active part of the electric circuit, which allows its precise tuning and controlling.



Select the membrane rafts of malignant cells



Model of the cell in electric field; $R = 10 \mu\text{m}$, $d = 5 \text{nm}$, $\sigma_i(0) = 0.3 \text{S/m}$, $\sigma_m(0) = 3 \times 10^{-1} \text{S/m}$, $\sigma_e(0) = 1.2 \text{S/m}$, $\epsilon_i(0) = \epsilon_e(0) = 6.4 \times 10^{-10} \text{As/Vm}$, $\epsilon_m(0) = 1 \times 10^{-11} \text{As/Vm}$, $\tau_{i1} = \tau_{e1} = 6.2 \times 10^{-12} \text{s}$, $\Delta\epsilon_{i1} = \Delta\epsilon_{e1} = 5.9 \times 10^{-12} \text{As/Vm}$, $\tau_{m1} = 3.0 \times 10^{-9} \text{s}$, $\Delta\epsilon_{m1} = 2.3 \times 10^{-11} \text{As/Vm}$, $\tau_{m2} = 4.6 \times 10^{-10} \text{s}$, $\Delta\epsilon_{m2} = 7.4 \times 10^{-12} \text{As/Vm}$, $E_e = \sqrt{2} \times 100 \text{V/cm}$.

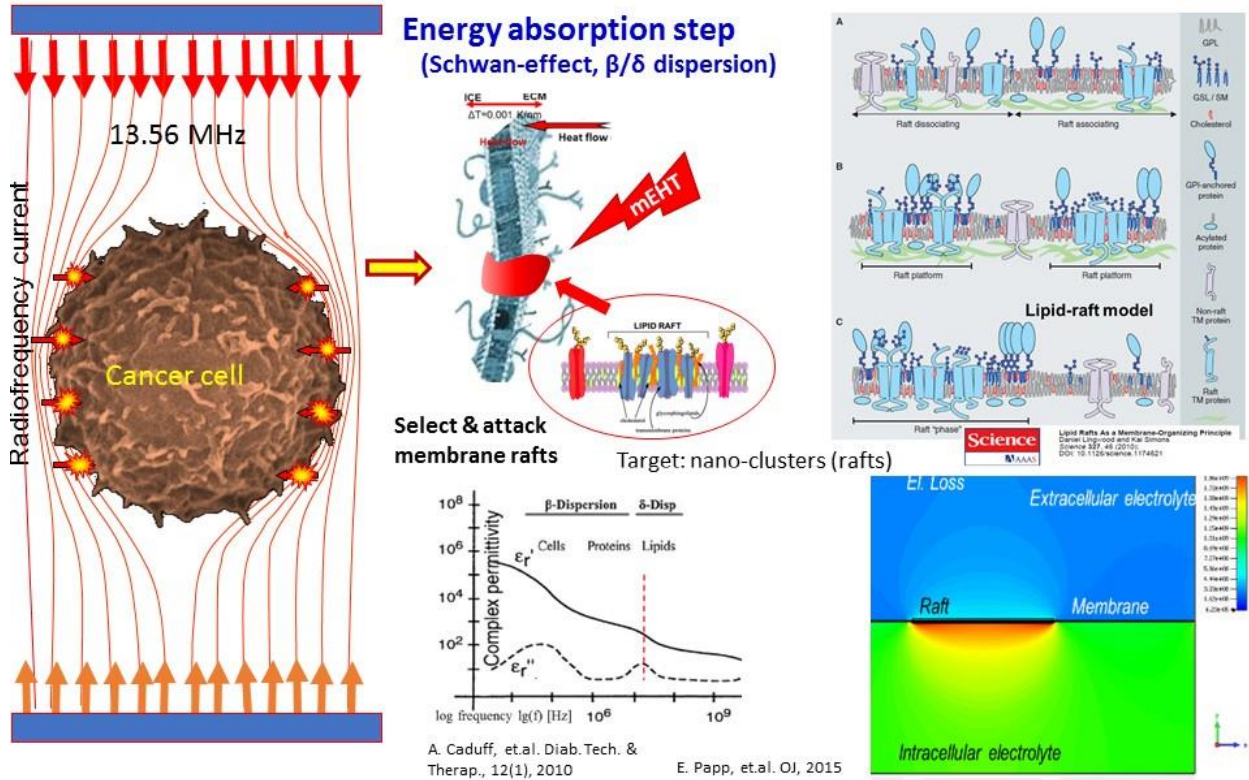


The power dissipation per unit volume in the cytoplasm (P_i), in the membrane (P_m), and in the extracellular medium (P_e) as functions of frequency. The three bold dotted verticals correspond to the relaxation frequencies; from left to right: $V_{rm1} = 1/(2\pi\tau_{m1})$, $V_{rm2} = 1/(2\pi\tau_{m2})$, $V_{re} = 1/(2\pi\tau_e)$.

Kotnik et.al: BEMS Twenty-Second Annual Meeting, Germany, June 11-16, 2000.

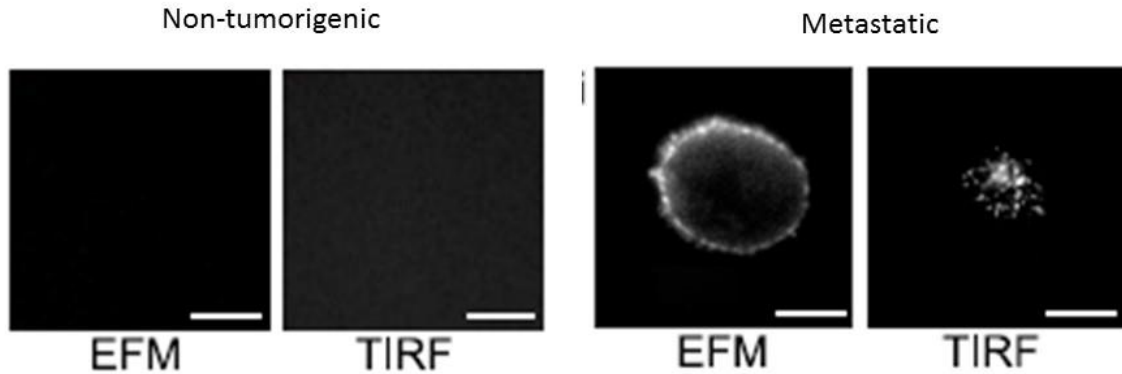
Target, heat the malignant cells by oncothermia

Oncological hyperthermia is a method to destroy malignant cells by heat-inducing absorbed energy



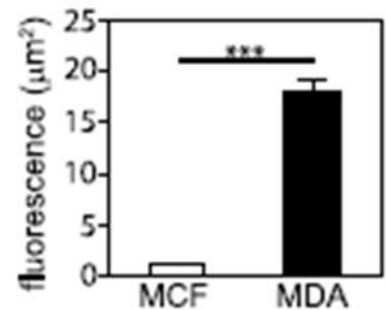
Lipid-raft distribution

Staunton JR et al, The Physical Sciences - Oncology Centers Network; (2008) A physical sciences network characterization of non-tumorigenic and metastatic cells; Scientific Reports, 3:1449



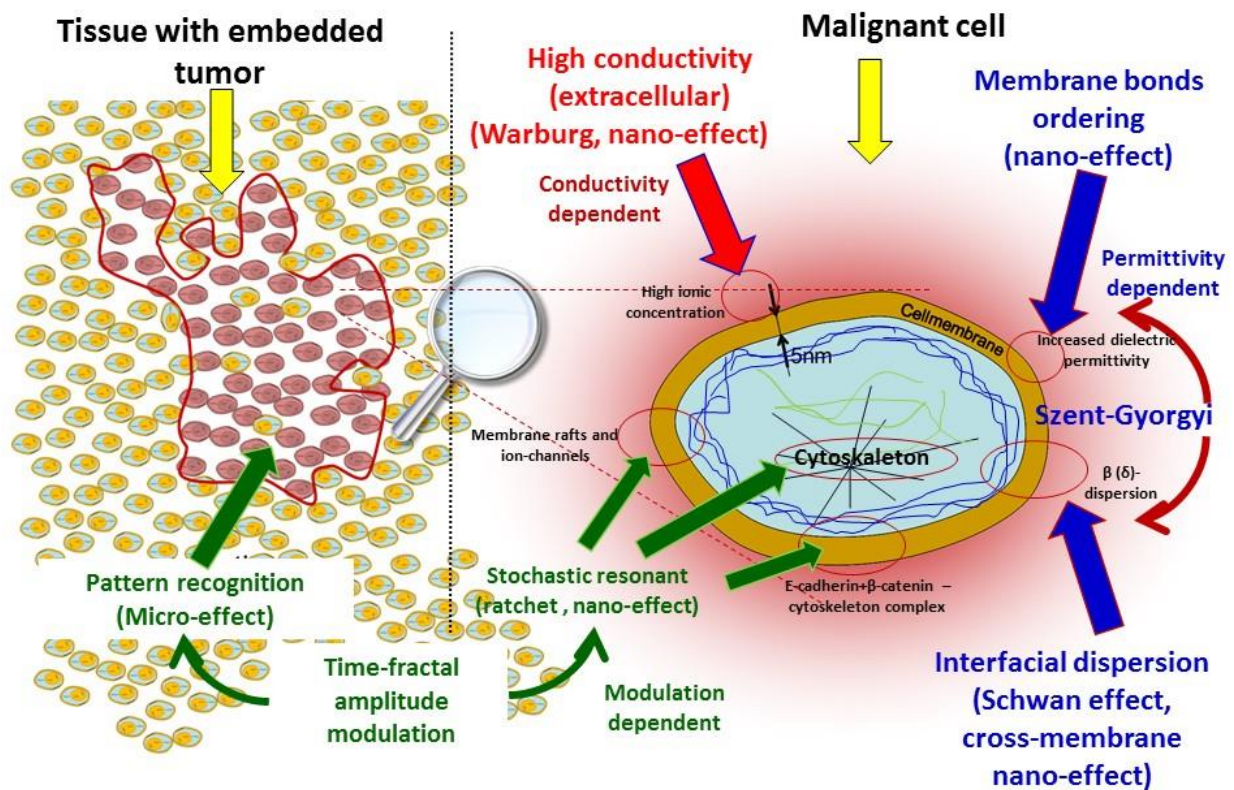
Epifluorescence microscopy (EFM) Total internal reflection fluorescence (TIRF).

All scale bars are 5 μm.



All p-values are indicated according to the Michelin guide scale (p # 0.001: [***]; 0.001, p # 0.01: [**]; 0.01, p # 0.05: [*]; 0.05, p: ns).

The various bioelectromagnetic effects in oncothermia

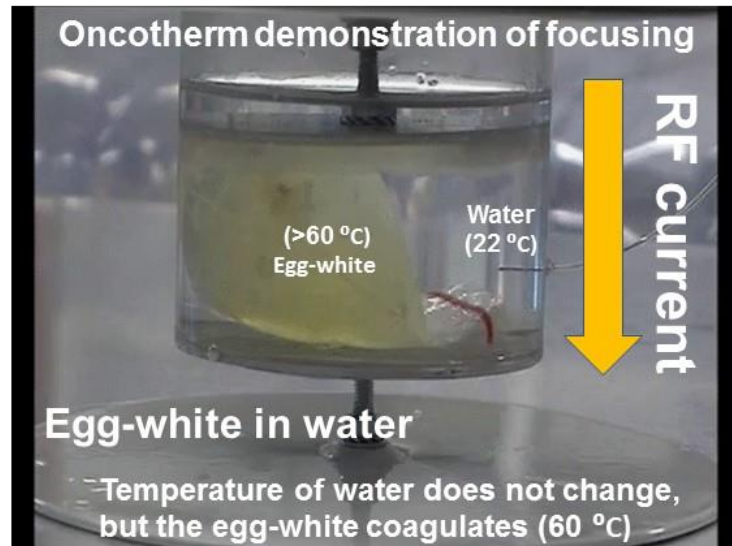


Outline

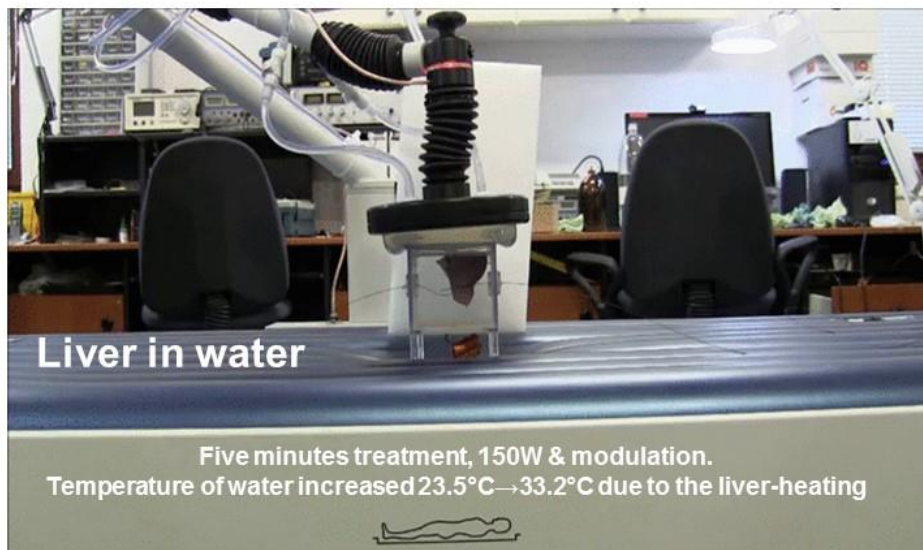
- Historical notes
- Concept
- Realization
- Presence

Egg-white coagulation

Auto-focusing by oncothermia

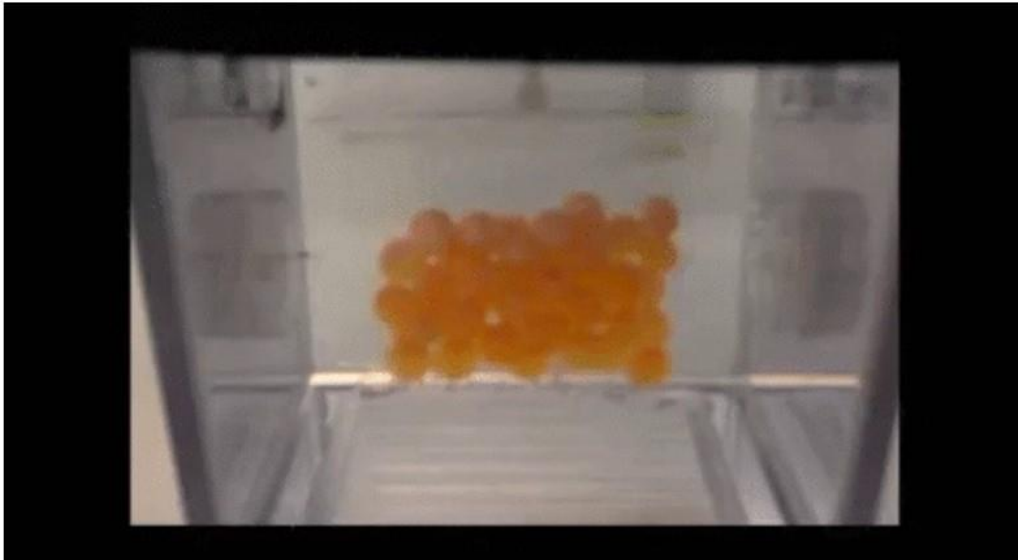


Heating and focusing

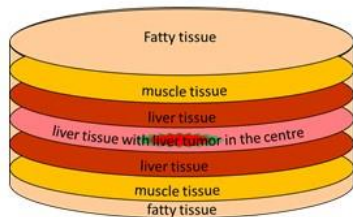


Caviar treatment

- In this experiment 13.56 MHz of RF waves are sent through a container of distilled water and red caviars in a plastic bag.
- Distilled water is electrically neutral. The caviar in this experiment acts like a capacitor would in an electric circuit.
- At the end of the experiment, the temperature of the water was measured at 29° Celsius while the caviar was cooked.



Heterogeneous liver phantom



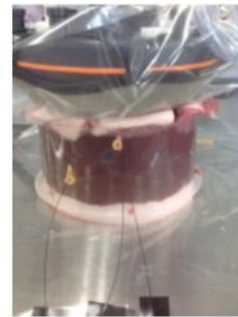
The structure of the phantom



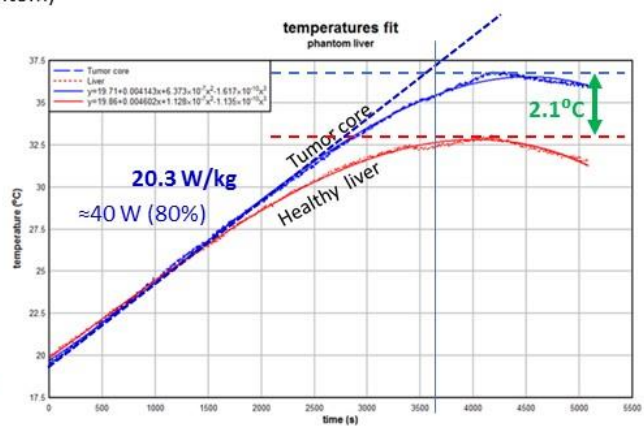
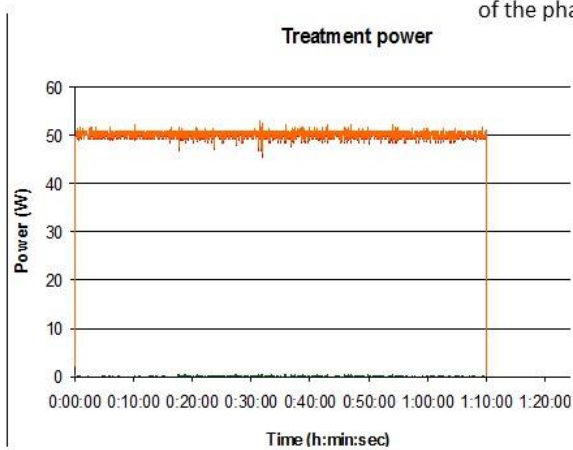
Fat (down) and muscle layer (same on the top of the phantom)






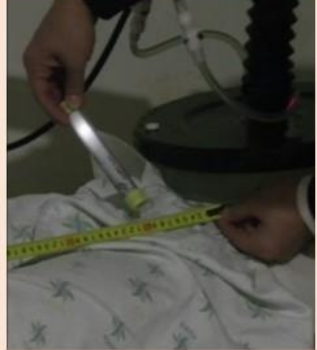
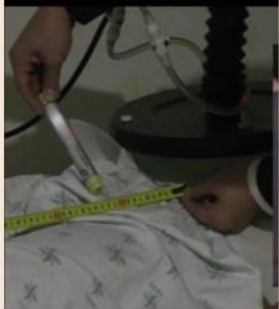

Pig liver layer with cancer in the middle



Complete phantom with the electrode on its top



Technical verification

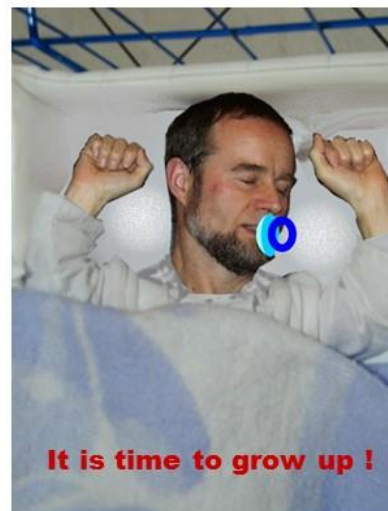
<p>Other capacitive coupling: long distance radiation, even without patient</p>  	<p>Oncothermia, RF-current coupling: short distance radiation</p>     <p>No field far from the patient and it exists only when the current flows through the body</p>
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Is the long history positive? Are we proud of it?

Contrary to that hyperthermia was the very first treatment in oncology it is not widely accepted. It is in childhood yet!



The babyhood is natural at the beginning



It is time to grow up !

However to be baby too long is unacceptable

We need new devices: ONCOTHERMIA

EHY-2000 Series

Loco-regional electro-hyperthermia device

- EHY-2000plus is a widely accepted system for loco-regional deep Hyperthermia applications
- This model has been used for treatment worldwide for more than 20 years
- Popular, versatile device, applicable for all kind of solid tumors
- It has been improved by considering the experiences of our doctors and experts, and the requirements of patients and the people treating them
- The EHY-2000plus is easy to use and reliable device



EHY-3000 Series

Multilocal Hyperthermia device

- EHY-3010 is designed for the simultaneous multi-local treatment of advanced, metastatic disseminated, malignant and solid tumors
- The pioneering breakthrough in the field of multi-local tumor therapy
- This system uses textile electrodes, which are even more flexible to adjust to the treatment area



EHY-1000 Series

Professional device for treating prostate diseases

- Our professional device for treating prostate diseases
- Both malignant and benign tumors (BPH) can be treated
- A catheter with built-in electronics and counter electrode
- Compact and easy to use.
- The method has been successfully used by our customers for many years
- The results of the treatment are excellent and nevertheless



EHY-2030

Loco-regional and multilocal Hyperthermia System

- Plug-in PMS-100
- Smart Electrode System
- New automatic controlled step motor tuning system
- Electronically controlled electrode arm
- User friendly touch screen display with full system control
- New shape and design to ease patient anxiety
- Changeable stretchy textile electrode for the smart electrode system and bed
- Newly developed RF generator with increased power





LabEHY

Inspection of the oncothermia method in laboratory environment



LabEHY In-vitro system



In-vitro applicators

VetEHY System

New development of Oncotherm and Tateyama for veterinary treatments (Prototype)



Outline

- Historical notes
 - Concept
 - Realization
 - Presence
-

- Australia
- Austria
- Belgium
- Brazil
- Canada
- Czech Republic
- China
- Denmark
- Egypt
- Germany
- Greece
- Hungary
- Israel
- Italy
- Japan
- Jordan
- Korea
- Lebanon
- Netherlands
- Pakistan
- Poland
- Romania
- Russia
- San Marino (IT)
- South Africa
- Pakistan
- Spain
- Switzerland
- Taiwan
- Thailand
- Turkey
- Ukraine
- United Kingdom
- USA
- Vietnam

Oncotherm worldwide



**450+ devices,
In 30+ countries,
In 5 continents**

**25+ university
activity in 12 countries**

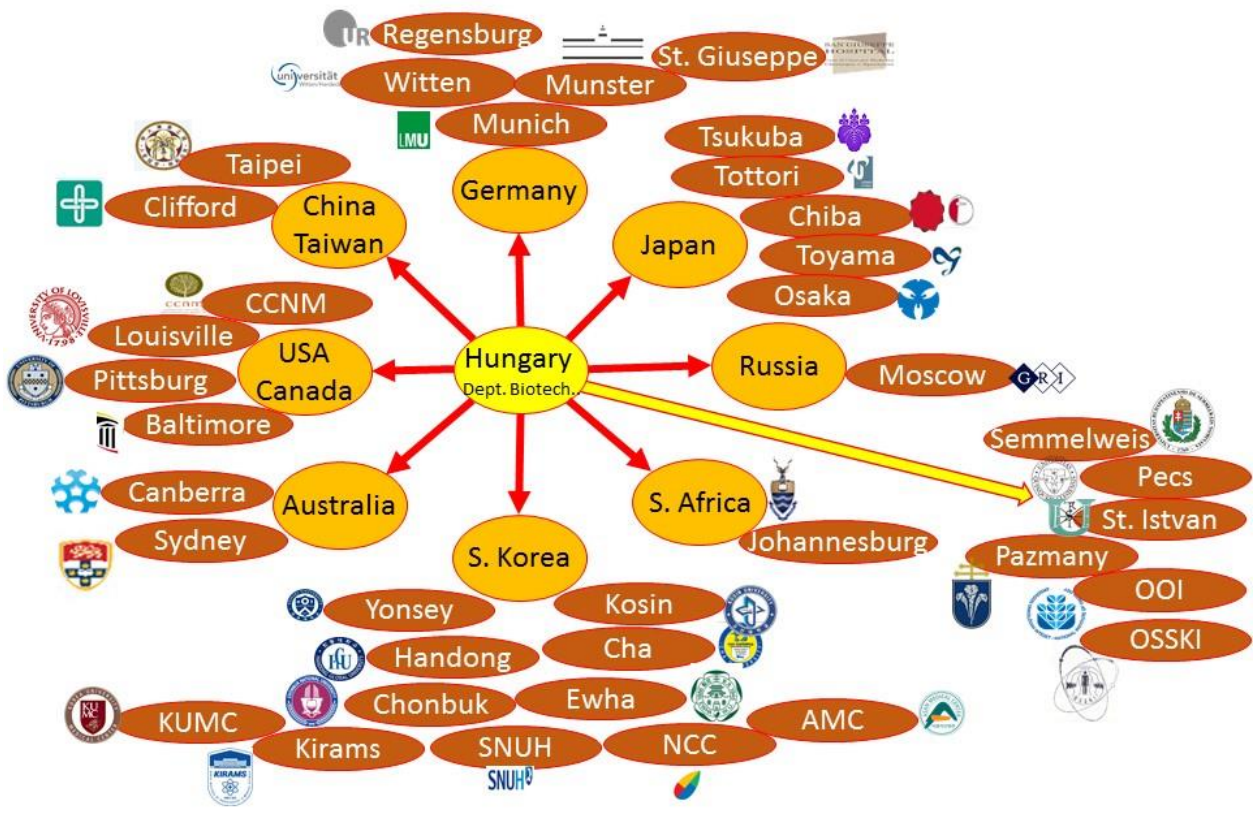
● University



- Accession :
- Algeria
 - Argentina
 - Chile
 - Colombia
 - Dubai
 - Ecuador
 - France
 - Guatemala
 - India
 - Mexico
 - Peru
 - Portugal
 - Saud-Arabia
 - Serbia
 - Sweden

200.000+ treatments/year

Scientific cooperation worldwide (historic view)



Human clinical studies, trials (name/ institute)					
Leaogranisla okkara hyperthermia (EHT) haikany si pjanak raadk mizil, olinvraia klinisai vaipjan dlochadhad calorimdia ordon, isogoridha, madiglad naj mactanias hotoglad, maachasasiva pallisai xasimias komatogripad		Preoperatively randomized phase III clinical study of reloaded, refractive ovarian malignancies by oncothermia therapy		Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer	
Leaogranisla okkara hyperthermia (EHT) haikany si pjanak raadk mizil, olinvraia klinisai vaipjan dlochadhad primer hypocoelidicis caachama konykandi, aachasasiva pallisai xasimias komatogripad		Ovarian cancer memo		A pilot study of prop. CRT combined with radiofrequency hyperthermia for the treatment of locally advanced rectal cancer and response prediction by FDG-PET	
Radio-komaterapia hotoglad dlochadhad mihayak karcaimias ma lakidha dlochadhadogripad vaay azidid		POPOPO trial for ovarian cancer		Breast, Liver, pancreas: An effectiveness evaluation of neo-adjuvant chemotherapy and hyperthermia treatment of LABC and Hyperthermia mono therapy in advanced stage RCC-A prospective randomized controlled trial	
Transcranial electro-hyperthermia combined with all latest chemotherapy in patients with relapsed high-grade glioma: phase I clinical results		Effect of oncothermia on improvement of QOL in unresectable pancreatic cancer patients		Retrospective clinical study for advanced brain-glioma by adjuvant electro-hyperthermia treatment	
A randomized trial investigating the benefits of the addition of oncothermia to chemo-radiation for cervical cancer in HIV positive and negative women in South Africa		Pancreatic cancer Ph II		Randomized Phase II-Studie einer kombinierten Tiefenhyperthermisch-Chemotherapeutik mit Tomosamid (Tomodal) zur Bestimmung der Wirksamkeit und Verträglichkeit bei verobachteten Patienten mit inoperablen Astrozytom und Glioblastomen	
Oncothermia for Ovarian Cancer		Temp in cervix ca.		Randomized Phase II-Studie einer kombinierten Tiefenhyperthermisch-Chemotherapeutik mit 5-Fluorouracil/Nitrosimidazol und Mitomycin zur Bestimmung der Wirksamkeit und Verträglichkeit bei verobachteten Patienten mit inoperablen kolorektalen Lebertumoren ohne andere Organmetastasen	
Ovarian cancer combi- / 3 cancer		Safety in cervical cancer with CRT+Oncothermia		Whole body hyperthermia combined with carboplatin/paclitaxel in patients with ovarian carcinoma -Phase II-study	
POPOPO trial for ovarian cancer		A phase I/II study of EHY-2000 oncothermia therapy for advanced epithelial cancer		Prospectively randomized phase II trial of lipon-metoprolol Docetaxel and Cisplatin +/- leucovorin hyperthermia in patients with metastatic breast cancer (MammaTherm)	
Results of Oncothermia Combined with Operation, Chemotherapy and Radiation Therapy for Primary, Recurrent and Metastatic Sarcoma		Oncothermia in combination with advanced drug care as a novel immuno-oncology strategy for treatment of aggressive cancers (metastatic breast cancer, melanoma, lung and pancreatic cancer)		A phase II clinical study on relapsed malignancies treated with electro-hyperthermia	
Cases that respond to oncothermia monotherapy		The effect of electro-hyperthermia in group CRT followed by delayed operation for locally advanced rectal cancer		Deep Electro-Hyperthermia with radiofrequency combined with docetaxel-erectin in patients with liver metastases from colorectal cancer (CRQ): A phase II clinical study	
The outcome of chemotherapy and oncothermia for far advanced adenocarcinoma of the lung		Localized hyperthermia in the care of patients with advanced cancer, Open label, phase I/II clinical study		Positive response of a primary breast carcinoma of the breast following salvage hyperthermia and paclitaxel	
The Outcome of the Chemotherapy and Oncothermia for Far Advanced Adenocarcinoma of the Lung: Case Reports of Four Patients		Advanced pancreas study by oncothermia, checkpoint inhibitors		Effect of Modulated Electro-hyperthermia on the Pharmacokinetics of Oral Transcranial Fentanyl Citrate in Healthy Volunteers	
Prospectively Randomized Phase III Clinical Study of Reloaded, Refractive Ovarian Malignancies by Oncothermia Therapy		Local modulated electro-hyperthermia in combination with traditional Chinese medicine vs intraperitoneal chemotherapy for the treatment of peritoneal carcinoma mouse with malignant ascites		A randomized, single-dose, cross-over, open-label clinical trial to investigate the effect of the oncothermia device on the pharmacokinetic properties of Acyclovir capsules in healthy volunteers	
Ph I/II for 3rd line of Ovarian Malignancies with Oncothermia Therapy		Traditional Chinese Medicine and Oncothermia		Current Status of Oncothermia Therapy for Lung Cancer	

Research (name/ institute)					
Molecular biology in co-culture		Oncothermia unit is used to treat several tumor cell lines that are established in vitro, as well as in small laboratory animals by heating them up to 42-43°C for an hour		Appearance of colocality in two-dimensional cellular structures	
DNA fragmentation and caspase-independent programmed cell death by modulated electrohyperthermia		Synergy between Oncothermia and Traditional Chinese Medicine		Hyperthermic radiology: Why is combined?	
Personalized dosing of hyperthermia		Hyperthermia versus oncothermia: Cellular effects in complementary cancer therapy		Nonequilibrium thermodynamic and quantum model of a damaged oscillator	
Immune effects by selective heating of membrane ratio of cancer-cells		Oncothermia: a new paradigm and promising method in cancer therapies		Challenges and Solutions in Oncological Hyperthermia	
Upregulation of heat shock proteins and the promotion of drug-associated molecular pattern signals in a colorectal cancer model by modulated electrohyperthermia		On the Dynamic Equilibrium in Hemostasis		Heating, efficacy and dose of local hyperthermia	
Nanoheating without artificial nanoparticles Part II: Experimental support of the modulated electro-hyperthermia method, using U937 cell suspension model		Strong synergy of heat and modulated electromagnetic field in tumor cell killing		Generalization of the Thermal Dose of Hyperthermia in Oncology	
Electro-hyperthermia inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis		Oncothermia Project Proposal		On the Aberrant-Wafer's law	
2 Pancreatic(SNUBR, AMC)		Oncothermia treatment of cancer: from the laboratory to clinic		On the thermal noise limits of cellular membrane	
Electric field distribution effects (in silico)		Pink-noise behaviour of biotissues		Resolving Oncological Hyperthermia—Oncothermia	
Colorectal metastasis models		Oncothermia – Nano-Heating Paradigm		Hyperthermia in der Onkologie mit einem historischen Durchblick	
In vivo ovarian experiments		Deep concept of oncological hyperthermia: Heat-coupling considering the cell destruction		Electro-hyperthermia: a new paradigm in cancer therapy	
Oncothermia and Medicine combination		Hyperthermia, a Modality in the Wings		Hyperthermia as an adjuvant to chemotherapy	
Oncothermia comparison to simple heating		Hierarchisierung septischer toxischer Sepsisfolgen		Local Hyperthermia in Oncology – To Choose or not to Choose?	
Application of oncothermia using LabEHY-100 inhibit cell growth of ovarian and cervical cancer cells		Metabolic spectra and specific absorption rate a mouse adults and children using mobile phones at 900/1800/2100 MHz		Heating of membrane ratio of cancer-cells	
Comparative study of various hyperthermia methods		New Theoretical Treatment of the Resonance Biological Phenomena: Bioclectromagnetism		Nanoheating without Artificial Nanoparticles	
Antitumor effect analysis by low power type hyperthermia machine Lab-EHY		An Energy Analysis of Extracellular Hyperthermia		Antial-vector interaction with bio-systems	

Oncothermia Research Information

We continue our scientific activity in hyperthermia field



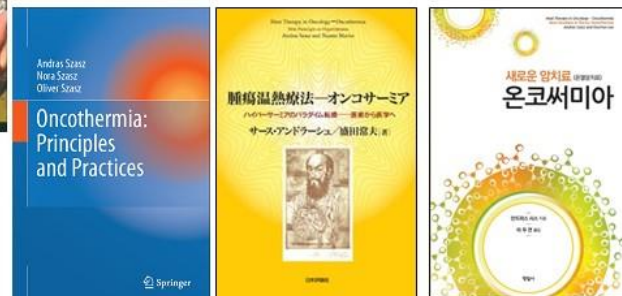
Monthly informative letter, distributed by Email

Quarterly medical journal for professionals distributed in printed form (ISSN number)

Own books helping oncothermia users

... and many academic publications (>>100)

Book chapters



...and oncothermia monographs

Oncotherm Group

For your Life



Thank you for your attention!