Oncothermia – Nano-Heating Paradigm
Oliver Szasz* and Andras Szasz
Biotechnics Department, St. Istvan University, Hungary

Abstract
To face the challenges in hyperthermic oncology we have made research on nano-heating the malignant and healthy cells and this review paper shows our results which were presented at the largest OMICS Group Conference in the United States in 2013. We introduced nano-heating technology which means selecting and heating the membrane of the malignant cells purely by the electromagnetic effects without any extra nano-particle applications. The technology (called modulated electrothermia or oncothermia) is impedance controlled capacitive coupling; no plane-wave radiation is dominating as in other capacitive (radiative) solutions. The nano-selection is based on the metabolic, on the adherent and on the organizing deviations of the malignant cells from their healthy hosts. The cell-killing mechanism is connected to the intensive, but very local, nano-range heating. These effects are proven in silico, in vitro and in vivo experiments, as well as in pre-clinical and veterinarian applications. Based on the controllable and safe methodology the treatment is applied in human clinical practice. My objective is to summarize the results which are connected with oncothermia method.

Keywords: Nano-heating; Oncothermia; Apoptosis; Abscopal effect; Immune activation; Electromagnetic heating

Introduction
Hyperthermia in oncology is a typical scientific see-saw. Despite its privilege as the very first oncological therapy in human medicine, it is not accepted in the clinical practice as a daily routine. Its development was an almost unbroken success-story at the start when the effects were also directly connected to various religious beliefs, venerating the Sun and the radiated heat/fire as overall force in nature. The popular medicine of heat has been introduced to the households, and even today it is one of the most frequently applied home-cure for various diseases. However, the medical profession needs more efficacy and explanations too. Soon, it was realized in the middle ages that there are some shortcomings of hyperthermia in oncology, which were believed to be the consequence of the technological limits, such as the lack of deep-heating technology and proper safety control. More and more doubts were formulated and the method was rejected among the professionals until the discovery of electromagnetic heat-delivery. These kind of technical solutions were promising; they were used to deliver deep and accurately focused energy to fulfill the requirements of the classical thoughts about the healing values of high temperatures. A funny situation occurred: on the basis of the ancient knowledge, a relatively new and powerful technology, the “modern in time” electromagnetic heating started to be applied believing the accurate heat delivery can heal patients. There are numerous results showing the significant effects of this classical hyperthermia approach in oncology. Then, the basic explanation was the larger heat-sensibility of the cancer than that of the healthy tissue. The technology has been developing fast to fulfill the demands:

- Good heating techniques has been developed
- Powerful energy-delivery has been realized
- Various solutions to focus the energy in depth has been solved
- Numerous high-ranked research institutes have been included in the intensive research
- Some excellent clinical trials have been performed

What else was necessary to make the overall acceptance common in oncology? The reproducibility of the results, the dosing for control and the deep understanding of the effects were missing. Unfortunately, the general strategic goal of the treatment also lost its original direction. The classical hyperthermia substituted the goal of cure with the tool, requesting higher and higher local temperatures instead of optimizing the effects. The strategic disorientation is even deeper to see how classical hyperthermia concentrates on the local tumor instead of the patient who has the tumor. Furthermore, this loss of medical orientation caused a real mistake too: regarding the tumor as local disease, but the cancer is only apparently that local tumor; it is malignant, which definitively has systemic effect; only the benign tumor would be local. The discrepancy of the non-locality of the tumor and the local treatment is a central problem in case of hyperthermia, because the patients are treated with this method in higher lines only. The "gold standards" have some advantages; those are applied first of course. Despite the tremendous number of books published on hyperthermia in oncology, [1-20] the complete history of oncological hyperthermia was fluctuating between the "beliefs" and "disbeliefs" (Figure 1), the success and failures [21].

The problems have obvious reasons (Figure 2) [22]:

- The focus of energy does not mean the focus of the temperature. The temperature (and the heat to what the absorbed energy is converted) naturally spreads all over the neighborhood until the thermal equilibrium.
- The temperature and the heat energy are not simply correlated, because the equally heated volume has no equal cooling by heat-conduction and heat-convection. Here, the heat convection (the various change of the blood-flow which cools down the volume) has the largest modification factor.

*Corresponding author: Oliver Szasz, Associate Professor, Biotechnics Department, St. Istvan University, Oncotherm Kft. Ibolya u. 2. 2071 Páty, Hungary, Tel: +36 (23) 555 510; Fax: +36 (23) 555 515; E-mail: biotech@gek.szie.hu

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serve as lessons, not to be repeated by investigators in other novel fields.

physiological feedback by the increase of the blood-flow.

our goal without heating up the whole tumor gaining the unwanted membrane, which we have to target and modify. If we are able to target only where it is necessary to destroy the malignant cell. This is the complete target? We have to heat the malignant cells, and add energy which have to be our only targets. Why are we forced to heat up the compartments, and only a part of it contains tumorous cells –, up is only a tool, to lead us to the real goal: destroy and eliminate the

ago [26]:

hyperthermia [25]. An important message was formulated a long time

The definition of dosing has to be fixed for a future development of

"Reference point is needed" as formulated clearly in the literature [24].

clinical trials of conventional hyperthermia are questioned [23].

Method-Nano-Heating Technology

The definite aim is not to heat-up the targeted volume. This heating up is only a tool, to lead us to the real goal: destroy and eliminate the malignant cells. The tumor is a complex structure, having various compartments, and only a part of it contains tumorous cells -., which have to be our only targets. Why are we forced to heat up the complete target? We have to heat the malignant cells, and add energy only where it is necessary to destroy the malignant cell. This is the membrane, which we have to target and modify. If we are able to target the cellular membrane of the malignant cells only, then we can reach our goal without heating up the whole tumor gaining the unwanted physiological feedback by the increase of the blood-flow.

For the new paradigm we have to bear in mind these three definite points:

(1) Accurate selection of malignant cells
(2) Avoid gaining the blood-flow
(3) Use effective cell-killing.

These are interconnected when we choose the very local pointing of the energy liberation. In this case the concentrated energy heats up and excites the malignant cells, but does not heat up the complete tissue to avoid the negative feedback of the homeostatic control. This construction will automatically avoid the sudden increase of the blood-flow in the heated target. This method is the modulated electro-hyperthermia (oncothermia) [27].

The accurate selection of malignant cells is a key step in the proper oncothermia. There are robust electromagnetic differences between the malignant and healthy cells in vivo. The biological processes and structures of the healthy cells are distinguishably different from the malignant ones. These differences make it possible to accurately select the cancer-cells by their electromagnetic behaviors and actively destroy them without damages to their healthy neighborhood [28].

The thermal effect itself is important, but has to be limited to the very local “points” which are most sensitive to any lethal attack on the malignant cells. The first is the well-chosen radiofrequency current [29], which constructs thermal gradient between extra- and intra-cellular electrolytes, Figure 3. The applied 13.56 MHz carrier frequency with proper time-fractal modulated current [30] is essential to have proper effect. (its technical description can be found elsewhere [31].) This gradient could be the driving force of the of the membrane excitation for signal propagation. These effects are thermal, but not temperature dependent [32,33], they depend on the temperature differences through the membrane, and act like the usual first order phase transition with latent energy exchange at constant (transition) temperature.

The proper attack has to be localized on the cell-membrane of the malignant cells, which uses the specialty of the metabolic rate of the malignant cells (Warburg effect [34]). For this pointing oncothermia uses the differences in the dielectric constant of the extracellular electrolyte and membrane-bound water of the malignant and healthy cells (Szent-Gyorgyi effect [35]; combined with δ (δ) dispersion, Schwan effect [36]). A special spatio-temporal fluctuation characterizes the homeostatic equilibrium [37]. A new approach of the living state has been developed: the fractal physiology [38]. In the living system, instead of the deterministic actions, stochastic processes occur, so the predictions always have random, unpredictable elements. Considering these the applied modulation in oncothermia [39] helps to localize the malignancy in a complex target [40] (Figure 4).

The effects of the above mentioned selective actions completely complete each other as shown in Figure 5 [41].

Results

The synergy of electric field with the thermal effects has more efficacy than the conventional hyperthermia has [42]. The temperature
gradient changes the membrane processes and promotes signal pathways for natural apoptosis [43], instead of the thermal necrosis. Temperatures above 41-42°C produce substantial cellular damage [44].

The apoptotic cell-death and any systemic immune-action following it would be more natural than the necrosis which is the standard goal of the classical hyperthermia dosing the complete problem by the necrotic standard (CEM43°C). The apparent contradiction of conventional hyperthermia is solved by oncothermia, having high temperature on the cellular membrane but in average on a larger volume the complete temperature remains under the limit helping the immuno-effective processes, which need the average temperature to remain under 40°C limit [45].

In oncothermia applications the apoptosis becomes robust after 24 h [46]. The complete time course studies clearly show the details of the apoptotic process [47]; which is measured histochemically with various methods. Measurements in time-course very clearly show the development of the natural apoptotic processes in xenograft model (in vivo, HT29, Figure 6) [48,49]. It is important that after the apoptosis, a special invasion ring was formed around the treated tumor and the neutrophil and monocytes activity were measured in the region indicating immune activation of oncothermia process. The expression of CD3, CD4 and CD8 gave enough information expecting certain abscopal (bystander) effect by local oncothermia [50]. Massive apoptotic signal-transduction starts from the membrane by the electric excitation [51], which is well proven, in mRNA level too [52]. The important results are the possible immune effects of oncothermia, which could lead to a systemic action too [46].

The time delay indicates the long-duration processes, which were identified as programmed cell-death (apoptosis), by various investigations: macro- and micro-morphology, enhanced activity of p53 tumor-suppressor, cleaved caspase 3 involvement, Tunel reaction, DNA fragmentation (laddering), etc. were carefully measured [53]. Massive presence of apoptotic bodies can also be observed together with the typical TUNEL reaction.

Despite the fact that oncothermia is a local treatment, it acts systemically, Figure 7. Oncothermia suppresses the proliferation rate in the remaining living part of the treated tumor too. A measurement was provided by Ki67 proliferation marker, [54]). The surviving, living malignant cells in the treated tumor definitely and significantly suppressed the Ki67 marker compared to its untreated counterpart in all the investigated time-scales. Together with the certain suppression of the proliferation, the adherent connections are reestablished [55] blocking the disseminative processes. New connections make the
missing signal-transmissions possible too. An important observation was the reestablishment of the E-cadherin bonds between the cells [46], well forming a complex with the β-catenin for signal transduction. This cell-cell connection is not only an effective signal transmitter, but it can also block the invasion of the primer tumor, and also acts on far distant metastases through the immune-recognizing of the actual malignancy.

The research results are well applied in the treatment practices being followed from the laboratory to the clinical bed, showing proofs of the above principles [55]. The veterinarian, pre-clinical level [49] together with wide range of clinical studies and practical clinical applications show the feasibility of oncothermia [26,46,56-60] as a complementary treatment to multiply other conventional oncotherapies. Its application as a monotherapy, when other treatments fail, is also promising [61].

Conclusion

Oncothermia shows its definite advantages in local cell-killing and in blocking the metastatic processes too. It is a feasible method to become the reliable and controllable basis of the modern hyperthermia demands in oncology.

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Declaration of Interest

Author is presently CEO of Oncotherm company.

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