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Renewing Oncological Hyperthermia—Oncothermia

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ABSTRACT

Hyperthermia was the very first oncotherapy in human medicine, but its applicability in modern oncology was dubious. The discovery of electromagnetism gave new hope a century ago, however, until up to now, it has been suffering from lack of wide acceptance. Oncological hyperthermia suffers from multiple unsolved medical and technical problems. The accurate selection of malignant tissue and its proper heating in depth are real challenges together with the control and repeatability of the treatments. However, the center of the problems is not technical: the living system tries to keep its homeostatic equilibrium and creates active feedback mechanisms to eliminate or at least correct the constrain heating in depth. The proper reaction on the "gage of battle" has to involve the physiology, handle it complexly together with bio-electromagnetism and update connected technology. The solution has to be the integration of the natural bio-effects into the technological constrains, acting in synergy with the physiological feedback mechanisms, and without forcing effects out of the homeostatic control. The solution lies in strict selection and adequate action in nanoscopic range, without exciting the robust transport-mechanisms to operate against the energy delivery to the tumor. Together with the local optimization, the systemic effects have to be considered, because malignancy is not a local disease. This concept needs interactions with the immune-system being effective on the disseminated cell in far distance too. Our objective is to present a complex technical solution to this complex problem.

Keywords: Hyperthermia; Oncothermia; Oncology; Nano-Heating; Focusing; Selection; Apoptosis; Immune-Support

1. Introduction

Hyperthermia is an ancient treatment. Hyperthermia means overheating of the living objects completely (systemic) or partly (regionally or locally). "Overheating" is understood as "a higher temperature than normal".

The fire and the radiation of the Sun had sacral significance in the ancient human cultures. In consequence, heat delivery was naturally on top of the curative possibilities. The ancient heat delivery, however, was ineffective and uncontrolled. Deep heating was almost impossible. The method had its renaissance, when the modern electromagnetic heating techniques were applied to control the heating process more precisely even in depth of the body.

All the possibilities were activated to deliver the energy in depth. The electric conductive heating started in the late 19th century and was called "galvanocautery" [1]. The first capacitive coupled device on conductive basis was the "Universal Thermoflux". It was launched onto the market by such a giant of the electric industry in that time as Siemens. A new capacitive-technology was introduced in 1976 [2] and has been widely applied since [3-5]. The other technical line of hyperthermia is based on radiative heat-absorption, and it forms an antenna array [6,7]. The applied heat delivery by magnetic induction [8] was widely replaced by heating with magnetic materials, dominantly magnetic nanoparticles and suspension in the tumor [9]. Together with the local heating efforts, whole-body hyperthermia was also applied [10,11].

Hyperthermia is a relatively simple and long-living method with highly fluctuating, hectic successes. To blame the "physics" (means technical insufficiency) for inadequate treatments is generally in the field of oncological hyperthermia. Most oncologists, who are familiar with the method, share the opinion expressed in the editorial comment of the European Journal of Cancer in 2001: "The biology is with us, the physics are against us" [11]. Recognizing the complexity of the problem which includes multiple physiological modifiers, the opinion is shifted a little: "The biology and the physics are with us, but the physiology is against us" [12].

2. Challenges

To focus the RF-energy into the depth of the body is not

an easy task, but not impossible. However, the focus of the energy does not mean the focus of the temperature. The temperature naturally spreads by the convective and conductive heat-flow (**Figure 1**) derived from the temperature gradient and controlled by the physiologic constrains. The local heating is always far from the equilibrium, due to the fact that the rest of the body is not heated and a remarkable gradient of temperature exists.

To follow the temperature distribution is a safety issue, the local burn of the healthy tissue should be blocked while the temperature for necrosis in the tumor should be allowed. The temperature control clearly shows the temperature spreading as well as the formation of the unwanted and uncontrolled hot-spots [13-16].

The locally or systemically increased blood-flow tries to compensate the growing temperature and cools down the target volume. The blood-flow drastically modifies the active part of the SAR value in depth, irrespective of how accurately it was focused. In consequence of the intensive heat-exchange governed by the blood-flow, the SAR mapping and the temperature mapping of the targeted volume are significantly different [17]. Only the heating-time limits the heated volume. The isotherms of the heating can be defined only when we consider the time too; the heating depends on the dynamism of the heat delivery, [18], because the heat-diffusion and the physiological reaction time is relatively long. This highly non-equilibrium condition in local-regional heating could not be stabilized; the stationer process is strongly influenced by the temperature regulation of the body.

Together with the heating-cooling "rivalry", a bitter competition starts between the cell-killing potential of the heat and the cancer-supporting potential of the blood-supply. Namely, the increased blood-flow delivers glucose to supply the growth of the tumor *in-situ*, furthermore, it promotes the dissemination of the malignant cells through the intensified transport, and risks the metastatic development in distant locations.

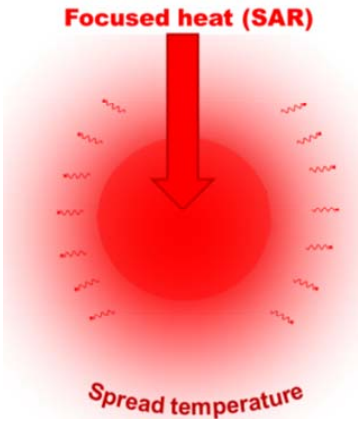

Figure 1. Focus of the energy is a technical trick. However, the spread of the temperature is a natural process, its termination is impossible. (SAR = specific absorption rate, measures the absorbed power in W/kg).

The heating in depth is limited by the healthy surface which conducts the energy in depth. The blistering (safety) limit depends on the density of energy (W/cm^2) and the duration time of its application, [19]. This limit usually does not allow enough energy for deep-heating. To avoid the overheating of the surface an intensively cooled transmitter (bolus) is applied in most of the electromagnetic heating techniques. However, the negative feedback control acts again depleting the blood-flow from the overcooled surface region trying to keep the homeostasis, changing the heat- and electric-conductivity as well as the dielectric properties of the skin layers [20]. When the constrained forwarded power is applied, the voltage drop on the isolating (cooled) layer will be high, forcing to pump through the requested constrain power. The relatively high voltage lowers the current so less RF-current reaches the targeted deep-volumes, lowering the efficacy of the heating. The uncontrolled "wasted" energy by cooling lowers the useful energy intended to be absorbed, and hence we lose the dosing facility by the forwarded energy.

Additional problems arise in medical considerations. The malignant tumor looks local but it is systemic; the main danger is the formation of metastases. The survival prognosis drastically worsens when the tumor is disseminated and metastasized. The local treatment is whole-some when it does not only kill the cells in the actual target of heating, but blocks the dissemination of the cells and presents antigens for the immune-system to fight the micro- and macro-metastases of the same malignancy in the far distance too.

3. Solution—Oncothermia

There is a new method emerging: oncothermia [21]. It is a precise impedance matched system based on capacitive coupling. The idea is the intensive local heating, but not equal in macroscopic range as the conventional heating. It is a nanoscopic heating, it avoids the psychological feedback macro reactions. The energy is mostly liberated on the membrane of the malignant cells, using local heating with high efficacy [22,23].

The well balanced energy range, the specially constructed asymmetric electrode geometry and the time-fractal amplitude modulation of 13.56 MHz carrier realize the nanoheating technology. The nanoscopic selection has no extra nano-particles or other materials, the selected energy-absorption is realized by definite bio-electromagnetic differences of malignant cells from their healthy counterpart.

Oncothermia technology heats non-equally; concentrates the absorbed energy on the membranes and the extracellular electrolytes of malignant cells [24]. The mi-

croscopically inhomogeneous heating is far from the thermal equilibrium [25]. Oncotherm applies cellular approach selective heating up the malignant cells individually and liberating the incident energy in nanoscopic range at the cell-membrane. The heating energy is not liberated in a sudden single step but regulated in multiple small energy-absorption processes. This makes the control of the energy-liberation possible, and avoids the overheating of the healthy parts.

Malignant and healthy cells are definitely different. The main differences are:

1) The energy-consumption of malignant cells is certainly higher. Their permanent proliferation requests much more ATP than in healthy state [26]. The huge demand cannot be fulfilled by the complicated Krebs cycle in the mitochondria. It starts a simple fermentative glycolysis despite its low efficacy [27]. This is the Warburg effect [28].

2) The collective behavior is completely different. The healthy cells are well connected by special signals [29] commonly regulating and controlling the system. The realization of the signaling has well defined connections between the healthy cells (adherent connections, junctions, pattern forming self-organization) regulating their life-processes on the collective basis. The malignant cells are autonomic [30]. Information exchange with their neighbors is mostly terminated or rearranged, connections are destroyed, topologic arrangement differs [31, 32]. They are characterized more by their autonomy than by collective control.

3) Mechanical properties of malignant cells are completely different. These cells are "softer", they change their form easier than their healthy counterparts [33].

4) The membrane structure of malignant cells also differ [34] and their membrane potential is certainly lower than that of the healthy cells, [35].

5) Additional to the above listed micro-effects, a special macro-behavior also distinguishes the tumor tissue from their healthy reference. This macro character is the pathologic tissue investigation used mostly for the first diagnosis and identification of the tumor. The macroscopic pattern of cancer is well distinguishable and can be characterized by pattern recognition based on fractal structure evaluation, [36].

We summarized the above differences and their primary consequences in **Figure 2**.

Applying radiofrequency current through the tissue, the above differences create characteristic changes, producing automatic selection between the cells, preferring to attack the malignant ones (**Figure 3**). The higher ionic concentration in the vicinity of the malignant cells creates high current density in the immediate neighborhood, and drives the intensive heat-flow to the cytosol through the membrane. The absorbed energy by the healthy cells is smaller, and anyway, the good network connections (gap-junctions, tight-junctions, adherent bonds) help to distribute the extra energy. The autonomic malignant cell is not able to pass the anyway larger extra heat to the neighborhood. The complete process is far from equilibrium, neither thermal nor electric equilibrium could be defined; the created gradients increase the entropy production. However, due to the fix boundary conditions, the minimal entropy production could be valid [37]. The membrane, softening of malignant cells, allows them to

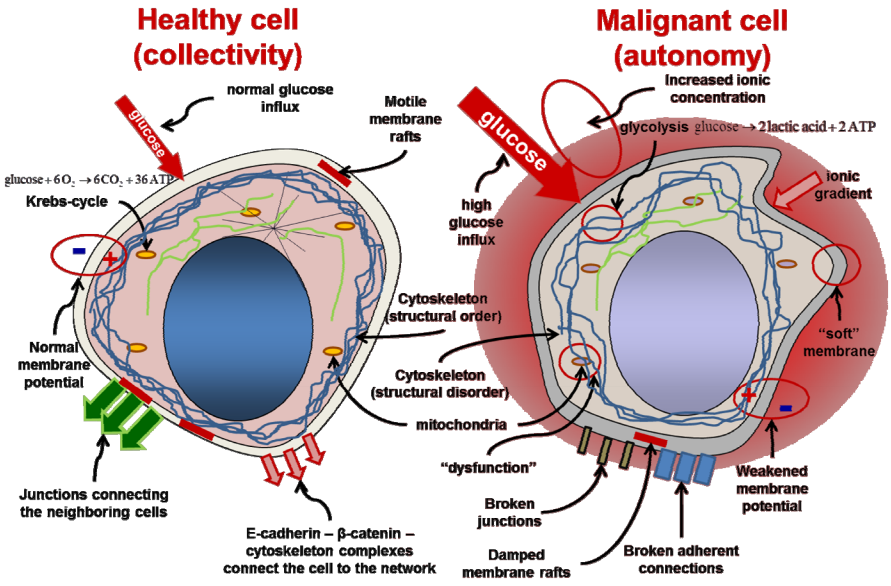

Figure 2. Main biophysical differences between the healthy and malignant cells, which are used for selection between them. The collective network of healthy cells and the autonomy of malignant cells are additional macroscopic factor, widely used in pathological evaluation.

change their shape to invade among epithelial cells to the blood-stream. The larger membrane curvature supports all the non-equilibrium conditions.

The consequences appear in dramatic changes for the malignant cells, including the apoptosis and the immuno-active processes in long time scale, (**Figure 4**).

The gained current density could produce extra high temperature in nanoscopic local volumes (like the short circuit produces extra heat in one point). A certain temperature gradient occurs, reaching as high as 1 mK/nm (106˚C/m), which induces multiple changes [38]. This effect is promoted by the selected β/δ frequency-dispersion and by the rectification effect of the membrane.

This nanoscopic heating is very similar to the routine microwave sterilization of the foodstuff, [39,40]. There the bacteria are selected by the electromagnetic way, and heated nanoscopically inside the mass of the matter. The selectivity of the bacteria is made by the conductivity

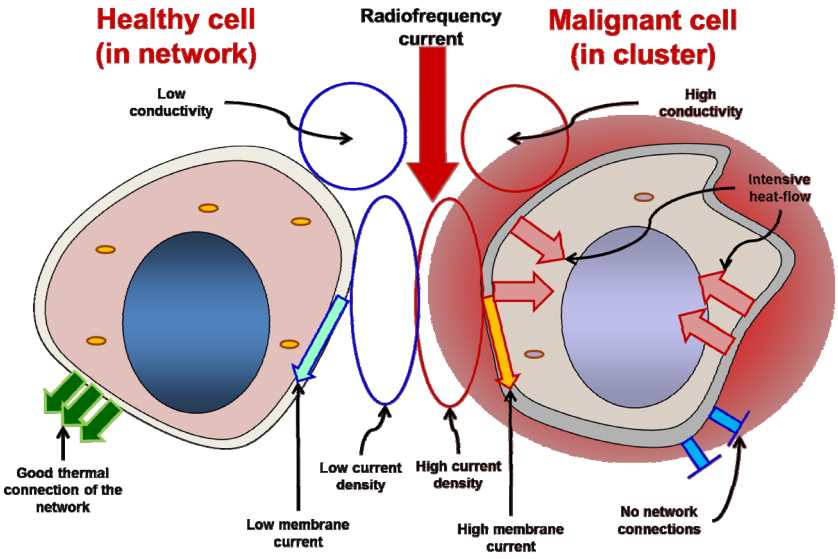

Figure 3. Electromagnetic consequences of the cellular differences. The selection is automatic, depends solely on the RF-current.

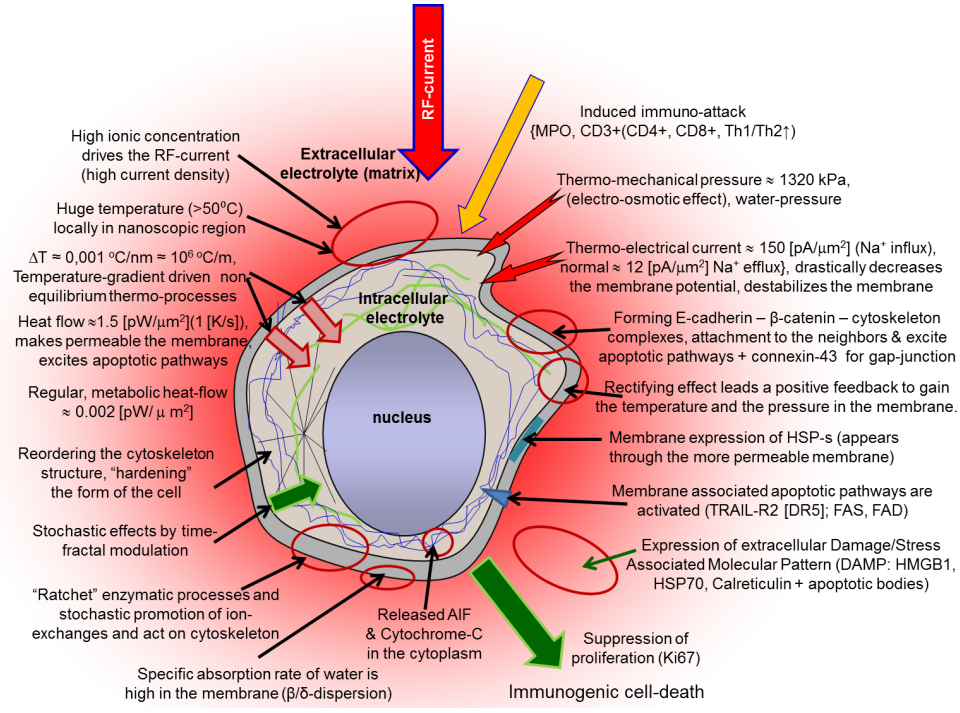

Figure 4. The complex changes at the malignant cells forced by actions of the amplitude modulated radiofrequency current.

differences, [41]; like oncothermia does it too [42]. Nanothermia seeks to act by promoting the natural physiologic feedback loops (**Figure 5**) to eliminate the extraneous structures, correcting the cooperative harmony of the system and eliminating the autonomic, parasitic cancer which misuses the resources of the system [43,44].

The right selection of the cells could concentrate energy on the membrane of the malignant cell. The dynamism of the temperature equalization through the cell-membrane allows small relaxation time ($\tau \approx 10$ - 7 s) to equalize the gradient on the 5 nm thick lipid layer, [44]. This rapid process will be constantly active till the gradient through the membrane exists. It is determined by the time during which the complete cell cytoplasm becomes in thermal equilibrium (equal temperature) with the extracellular milieu.

The induced heat-flow (≈ 1.5 [pW/μm^2]), is opposite than the metabolic one, and is higher more than three-orders of magnitudes. The heat-flow is accompanied by multiple extensive acting by basic laws of non-equilibrium thermodynamics (Onsager's relations, [45]). The water-influx increases the internal pressure by >30%, the thermo-electric current will be opposite and ten times larger than normal. The modulation enhances the stochastic processes. The enzymatic "ratchet" [46] promotes the ionic exchange and excites the cytoskeleton, which "hardens" the shape of the cell, suppressing its motility, and definitely suppresses the proliferation ability (Ki67, [47]). The anyway high concentration of chaperons will be able to move from the cytosol through the membrane, expressing the internal stress and inducing immune attacks. Indeed, a certain invasion sphere was observed around the tumor after a week [48] of the treatment, showing intensive immune effects (high mileoperoxidase (MPO) level, increased CD3 and CD4, CD8 expression, increased Th1/Th2 ratio). Cell death occurs mainly by apoptotic way [49], starting from the cell-membrane, by the membrane expression of the death-toll receptors (TRAIL-R2 [DR5]; FAS, FAD) [50]. Finishing the apoptotic process developed extracellular Damage/Stress Associated Molecular Pattern (DAMP) and additional to the apoptotic bodies HMGB1, HSP70, Calreticulin appears. The immunogenic cell death makes both the innate and adaptive immune systems active, and so the effect becomes non-local.

This un-local effect well fits to the malignancy, having possibility to block the tumor-growth not only in primary but in metastatic localizations as well, (**Figure 6**). In this way oncothermia acts as complexly as necessary, and does not remain in the frame of the local treatments only.

In summary the complete oncothermia effect is summarized in technical point of view, (**Figure 7**). The cellular selectivity is the natural, no such constrain which induces blood-flow feedback. Its cellular selectivity is automatic and is based on the higher conductivity of extracellular matrix (consequence of the Warburg effect), the higher permittivity of the membrane vicinity (consequence of Szent-Gyorgyi effect), and certain variations of the pattern (pathology observed fractal pattern). Its natural behavior is simple: the non-necrotic (apoptotic) cell-death suppresses the extra proliferation and does not disturb the homeostatic control. Through these the non-ocality of the treatment is developed. Disseminations are blocked by the blocking invasion of the cells. This has two factors: the reestablished adherent bonds and other cellular connections "glue" the cells to their place, and

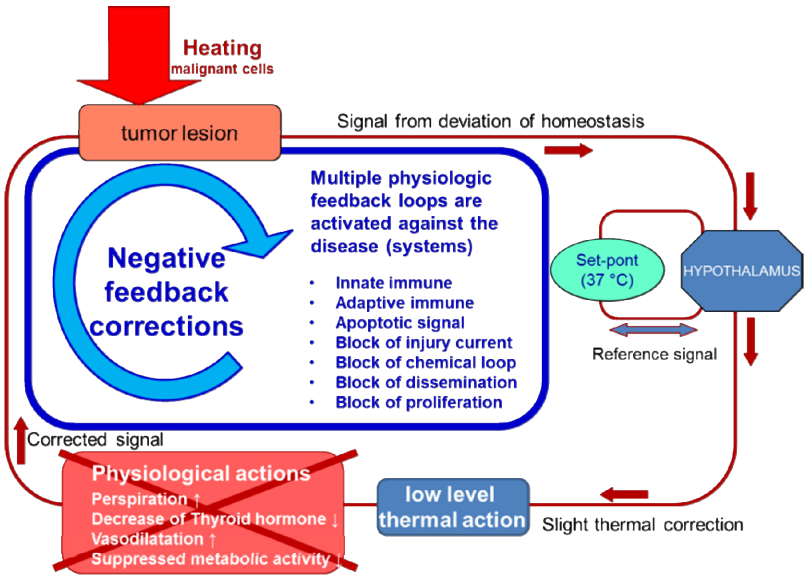

Figure 5. Oncothermia acts differently from the constrained classical hyperthermia. It does not change the global physiological heat-control, but it helps the physio-feedback loops for natural corrections.

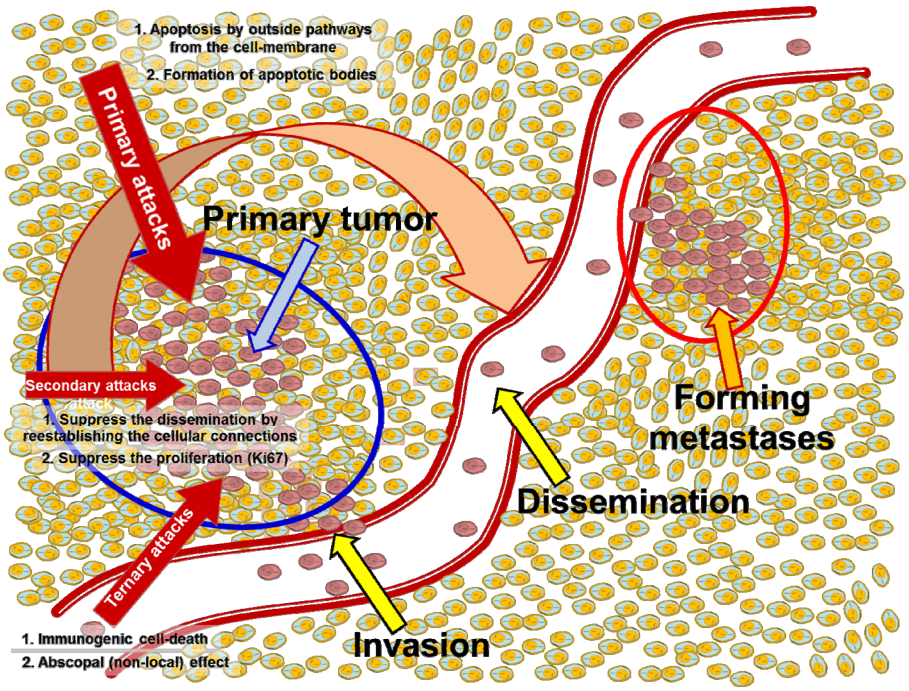

Figure 6. Complex action of oncothermia. It is important that the nanoscopic treatment induces immune-effects which extends systemic the impact.

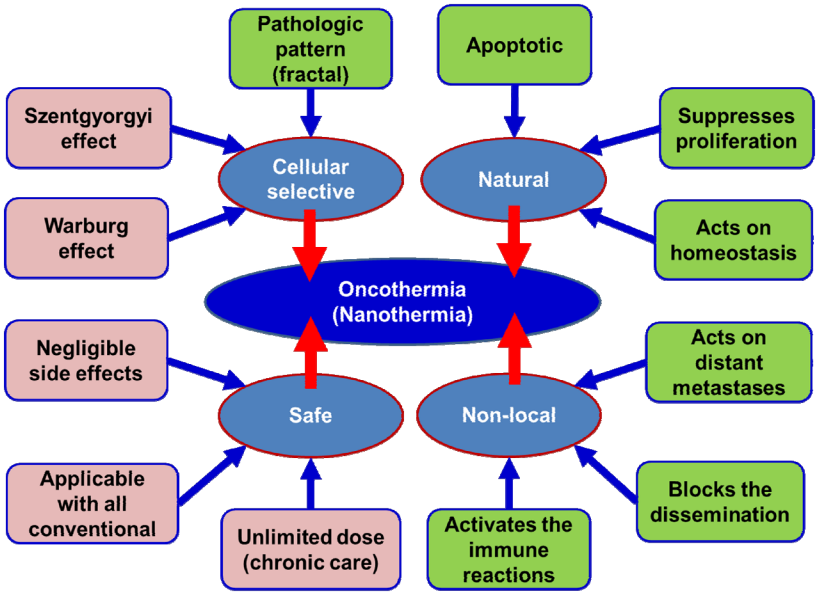

Figure 7. Technical summary of oncothermia. The pink boxes are dose dependent. (Dose does not exceed the blistering limit; (<0.5 W/cm^2). The green boxes are modulation dependent.

the rebuilt cytoskeleton blocks the soft-amoeba-like motility. The immune system is activated by immunogenic cell-death, which is a promising direction for the tumor-vaccination in the future. As all the technical solutions in medicine, oncothermia is also safe, it has few side-effects, there is no limit of their complementary application with any other conventional treatments and has no dose limit in repeated treatment sessions. The modulation and dose (intensity) dependent parts are of course not sharply disjunct, the effects are complexly interacting. However, the modulation has serious technical challenges from the side of bioelectromagnetics and fractal physiology.

4. Conclusion

Nanoheating technology offers a renewing of conven-

tional hyperthermia. It is a synergy of the bioelectromagnetism and the fractal physiology. The oncothermia approach opens the possibilities of a stable, controlled treatment without controversial challenges. It is a vivid way to solve the old problems in hyperthermic oncology: it is a controlled, reproducible and reliable treatment.

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