

## Hyperthermia – Heat Shock for Tumors

Prof. Rolf Issels, head of the Clinical Cooperation Group “Hyperthermia” at the GSF, started his work for the benefit of regional deep hyperthermia (RHT) for cancer therapy back in the mid-eighties. Since 1993 RHT has been applied as a therapy in a model project by the statutory health insurances. In 1999 the KKG was founded with research ranging from clinical research to deep hyperthermia and biological research in the field of immunology and cell biology.

**E**levated body temperature causes stress to cells including tumor cells: if they are heated to 40 to 44 °C by electromagnetic waves, collective cell death sets in at a temperature of 42 °C. Temperatures of more than 40° make tumor cells more vulnerable to natural defense processes and radia-

tion or chemotherapy. “Due to the dissipation of heat from sites with good blood circulation we cannot heat the tumor uniformly,” explains Professor Rolf Issels, head of the Clinical Cooperation Group Hyperthermia. “The areas with good circulation, however, are reached particularly well by cytostatics.”

## Symbiosis of Biological Research and Clinic

Quite in the spirit of the translational approach to research of the GSF it is not only the purely clinical studies, but also associated biological research aspects which have higher priority in the Clinical Cooperation Group "Hyperthermia." Various groups focus mainly on two areas: the influence of heat shock proteins on the immune system, and liposome research.

### Heat Shock Proteins – Activators of the Immune System

In biological terms treatment with hypothermia means that heat shock proteins (HSPs), also called stress proteins, are induced in the tumor. They are of interest to cancer research, because they interfere with the body's own immune system in different ways. Among other things they mark tumor cells and make them visible to the killer cells of the immune system. Therefore, cells producing HSP can be destroyed more effectively by killer cells and the immune system can fight the tumor more effectively. In their studies Issels and his colleagues found out that the induction of protein HSP 70 intensifies the immune response against the tumor in two ways. On the one hand HSP 70 acts as a danger signal for natural killer cells and for dendritic cells, which increases their proliferation and cytotoxic activity. In addition to this cytokine function an antigen-specific T-cell response could be achieved with HSP 70 from human melanoma cells: if HSP complexes are isolated from the melanoma cells and put on dendritic cells, they will mature to become antigen-presenting cells (APCs) which process antigens and present them on

their cell surface, so that they can be recognized by the T-cells. The studies on the dendritic cells were conducted in close cooperation with Dr. Elfriede Nössner from the GSF Institute of Molecular Immunology.

### Liposomes as Ferries

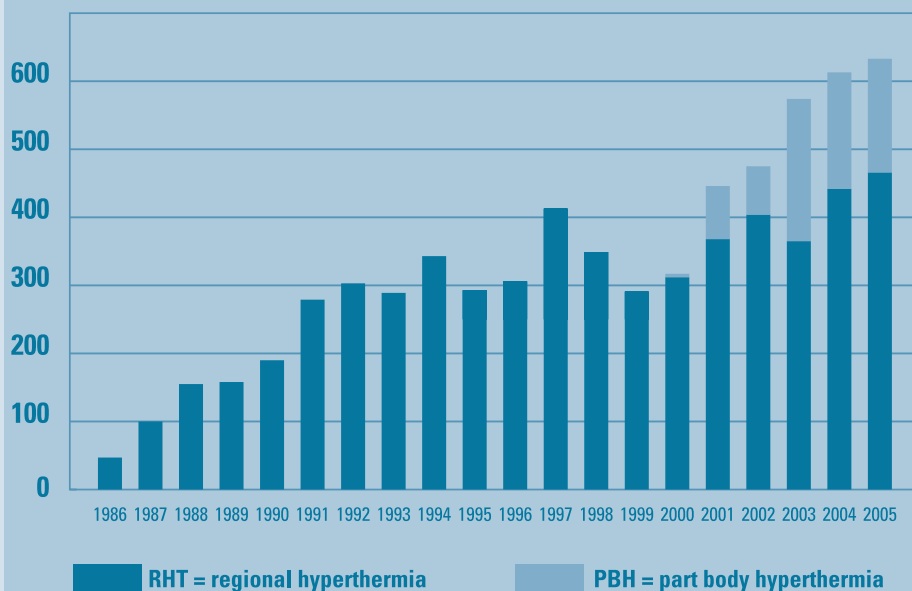
The second important supporting pillar of biological research in the KKG "Hyperthermia" are liposomes. These artificial globules of phospholipids into which active substances can be introduced, are "highly interesting", Issels says with great enthusiasm. In cooperation with the MPI for Biophysical Chemistry in Göttingen his colleague Dr. Lars Lindner could produce thermo-susceptible liposomes, which open at certain temperatures (41 to 42°C) and release their contents. This opens up undreamt-of possibilities for the therapy with hyperthermia: highly toxic cytostatics could be transported to the tumor with the liposomes and released there specifically by heating. This is being investigated for the KKG's own liposomes using the model of the amelanotic melanoma on the Syrian hamster. On the same model another possibility for the use of liposomes is also being investigated of late: temperature-sensitive liposomes filled with a contrast medium are supposed to make temperature control during hyperthermia treatment easier. If the contrast medium is released at defined temperatures and becomes visible in the NMR, invasive temperature control using probes might become superfluous. This would mean considerable relief for the patient, because "it would allow proper non-invasive temperature measurement, not only the monitoring of hot spots," Issels says taking a look into the future. Lindner's working group was recently awarded a prize at the Munich Business Plan Competition.

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### Clinic and Laboratory Benefit from Each Other

"With the clinical studies and the simultaneous connection with fundamental research, the KKG is an ideal instrument of translational research," Issels concludes. "I think that the establishment of this particular KKG was most decisive for the progress of a new treatment technique with all facets of research."

Treatment with regional and part body hyperthermia  
1986 to 2005





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Issels first started his work for the benefit of regional deep hyperthermia (RHT) for cancer therapy in 1986 as one of the pioneers in this field. From the start Issels used soft tissue and bone tumors as model tumors, which start in the connective and supporting tissues and are called sarcomas. In the clinical area Issels and his colleagues were particularly interested in when a particular soft tissue sarcoma can be treated better by the combination of hyperthermia with other therapies. A phase III study was started with high-risk soft tissue sarcoma patients, which should show whether the combination of hyperthermia and chemotherapy improves the chances for recovery compared to chemotherapy only for these deep-seated, large tumors. A previous phase II study showed encouraging results: it was shown that patients responding to hyperthermia treatment have a significantly greater chance to live without any tumors after a period of five years.

## New Form of Part Body Treatment

Issels has meanwhile transferred the knowledge gained for sarcomas to colon and rectal cancer as well as very recently to the locoregionally advanced stage of pancreatic cancer. It is being investigated whether the combination of chemotherapy and/or radiochemotherapy with hyperthermia improves the success of the therapy. For these tumors in the abdomen or pelvis the clinical cooperation group (KKG) has a novel hybrid system consisting of a hyperthermia device and an NMR tomograph. Using this system the complete area from the pelvis to below the lungs can be heated in one go. This NMR tomograph also prevents healthy tissue from being damaged due to excessive temperatures in so-called "hot spots". "In Germany our KKGs at Klinikum Großhadern and Charité in Berlin are the only centers doing part body hyperthermia in model projects," Issels reports proudly. In 1991 Issels was awarded the German Cancer Award for his work on clinical hyperthermia. Under the guidance of the GSF a "Virtual Institute of Excellence" has been established between the two centers through the Initiative and Networking Fund of the Helmholtz-Gemeinschaft for an initial period of three years.



In the SIGMA EYE MR applicator, a hybrid system consisting of a hyperthermia device and an NMR tomograph, tumor patients receive part body treatment. Apart from Charité in Berlin the GSF is the only institution offering this extended method.