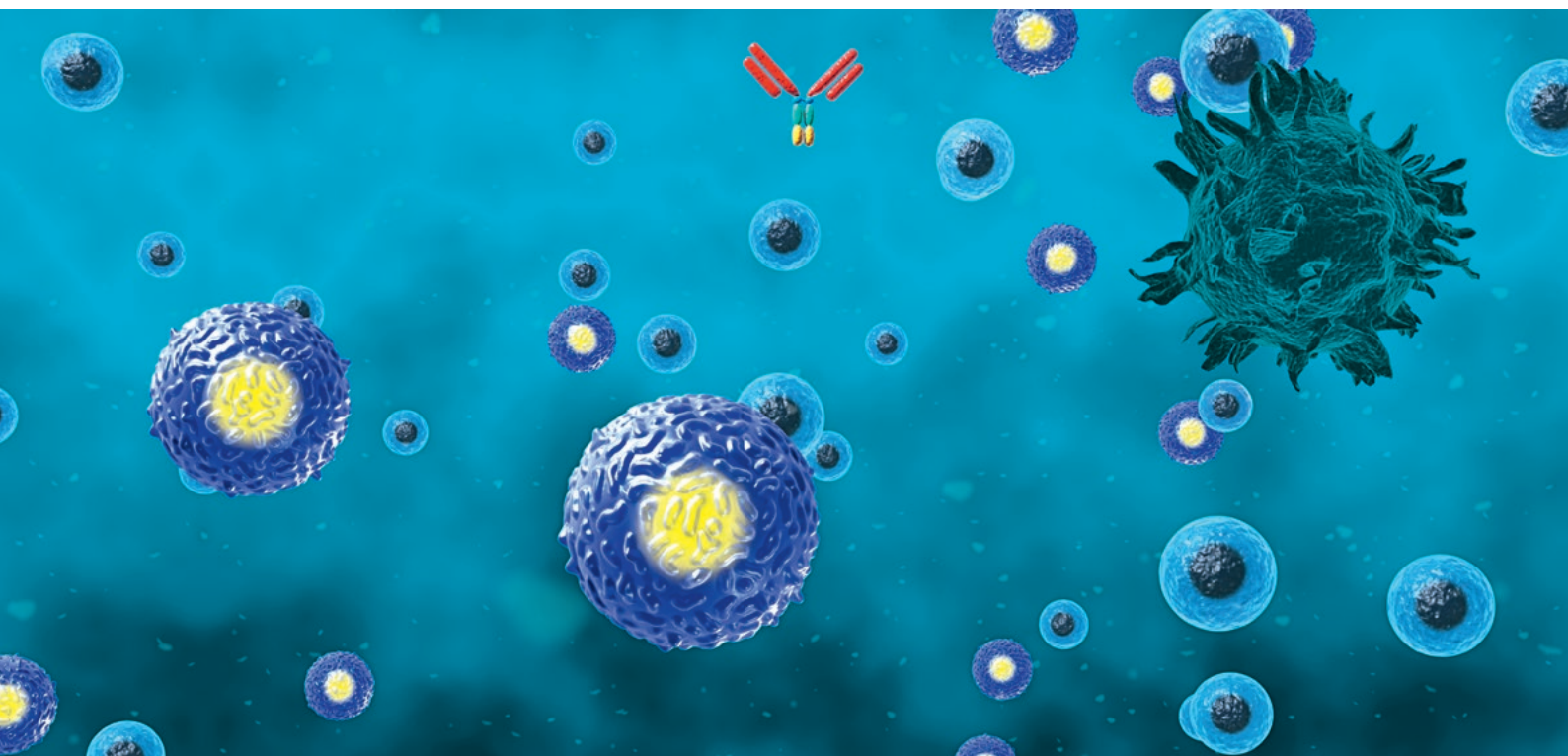


HYPERTHERMIA AS THE FOURTH COLUMN IN ONCOLOGY

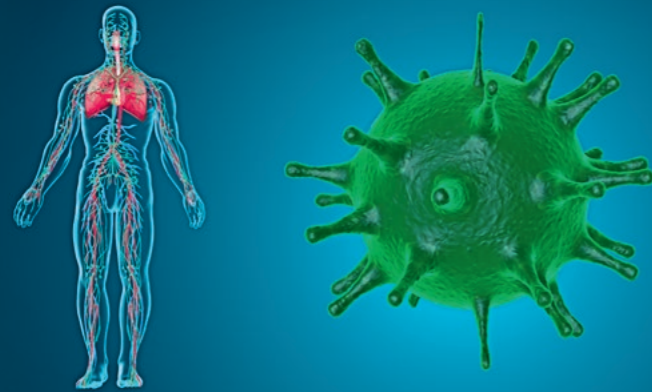
Scientific principles of heat therapy



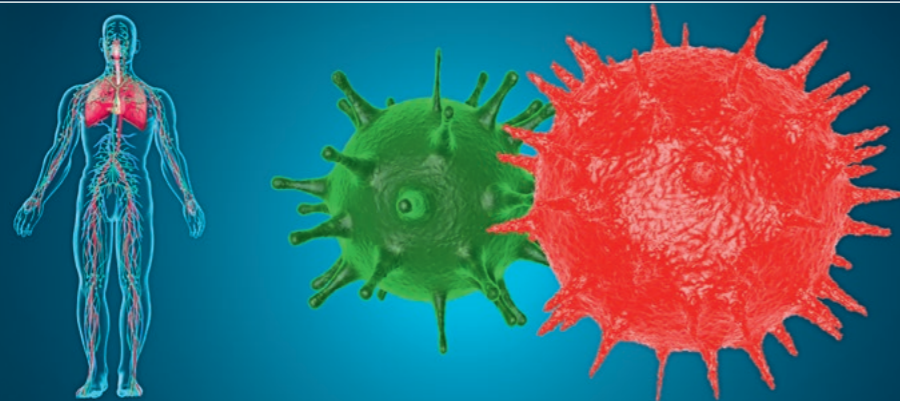
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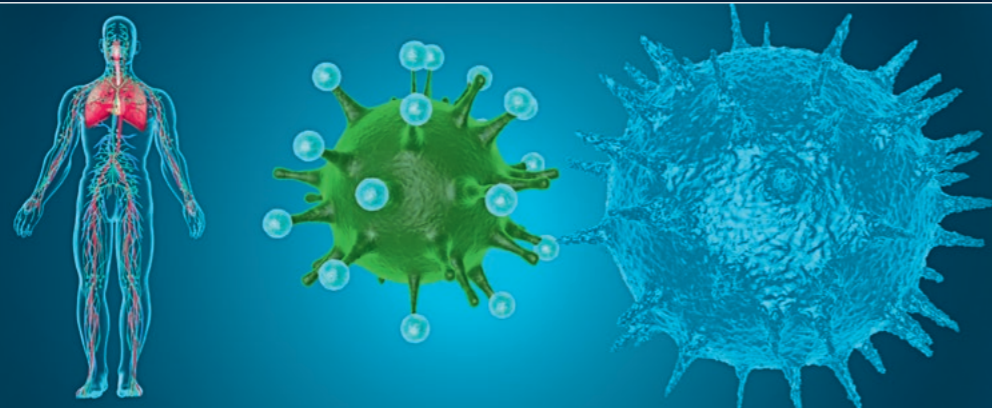
HYPERTHERMIA - MORE RECOGNIZED THAN EVER



IMMUNE CELLS PROTECT THE BODY



TUMOR CELLS ESCAPE IMMUNE SURVEILLANCE



STIMULATION OF IMMUNE CELLS AGAINST TUMOR CELLS CAN RESULT IN SYSTEMIC TUMOR CURE

HYPERTHERMIA AS THE FOURTH COLUMN IN ONCOLOGY

„The Heat is on in Oncology” – research into and the clinical application of heat therapy has been and continues to be strongly promoted under this slogan. While some years ago hyperthermia was considered a therapeutic approach with no proven efficacy, nowadays numerous renowned university hospitals are using this technically sophisticated procedure in the fight against cancer. It is a procedure that – and this is important to note – is only effective and lowers side effects in combination with radio- or chemotherapy in fighting tumors and improving the quality of life.

Radio frequency-induced hyperthermia can significantly increase the survival rate of cancer patients.

On our website www.sennwald.de you will find hyperthermia clinical studies over the past three decades on the effectiveness of adding superficial and regional hyperthermia to radiation therapy and/or chemotherapy.

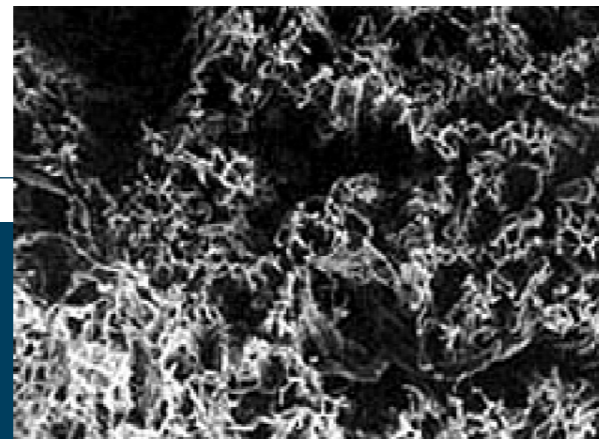
WEAKNESSES IN MALIGNANT TUMORS

Malignant tumors result from the growth of mutated cells, which require more energy to survive than normal cells. The existing blood vessels that provide nourishment and oxygen for the cells provide insufficient energy for the uncontrolled multiplication of these cells. For this reason, malignant tumors stimulate the growth of additional blood vessels. However, these new blood vessels exhibit chaotic structures, when compared to blood vessels in normal tissue. They are of an unusual size and have kinks and dead ends. Often, large areas of tumors are hypoxic because of the irregular structure of these blood vessels. And because hypoxic cells cannot sufficiently eliminate contaminants via the blood, they exhibit a lower pH value.

Additionally, significant changes in perfusion can often be observed with these tumors because the unstable blood vessels periodically collapse and deprive the cells of oxygen. It is extremely difficult to kill oxygen-deficient cells with ionizing radiation (which forms oxygen radicals that attack DNA) or chemotherapy (which requires blood flow to transport the cytostatic agents). Because hypoxic cells tend to metastasize, their destruction is a high priority in cancer treatment.



Mutated blood vessels from cancerous tissue



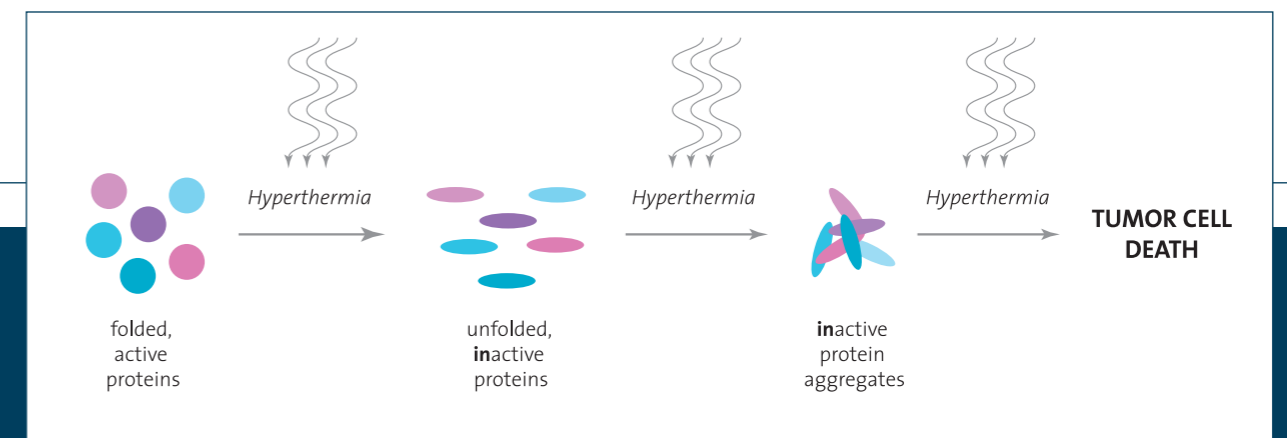
Normal blood vessels in healthy tissue

THE EFFECT OF HYPERTHERMIA AT THE BIOCHEMICAL LEVEL

Hyperthermia destroys cancer cells by raising the temperature in the cell to between 41.5°C and 43°C. It takes advantage of the weaknesses in malignant tumors described above. Since the body reduces temperature through perfusion, tumors with low or irregular perfusion remain at a higher temperature level during hyperthermia, while the surrounding normal tissue, with regular perfusion, remains at a lower temperature.

This is the result of their inability to eliminate anaerobic metabolites. Hyperthermia attacks the overacidified cells, breaches the stability of the cellular proteins, leads to their aggregation, finally resulting in cell death.

Science attributes the death of cancer cells at hyperthermic temperature to damage of the plasma membrane, the cell skeleton, and the cell nucleus. Cancer cells are particularly susceptible to hyperthermia treatment due to their high acidity.



Biochemical mode of action of hyperthermia

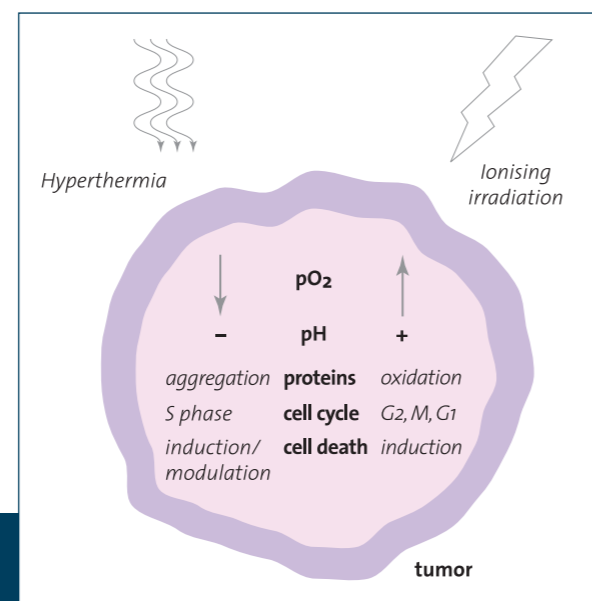
HYPERTHERMIA & RADIATION THERAPY

HYPERTHERMIA INCREASES THE EFFICACY OF RADIATION THERAPY BY UP TO A FACTOR OF FIVE

Hyperthermia and radiation therapy complement one another. The thermal stimulus associated with hyperthermia treatment causes improved blood circulation and therefore improved oxygen supply to the tumor. This is important for increasing the efficacy of radiation therapy. Ionizing radiation destroys cancerous tissue primarily through the generation of oxygen radicals that attack the DNA of the cancer cells. Tumor cells containing insufficient oxygen are three times more resistant to ionizing radiation than normal cells. Thus, there is a direct relationship between hypoxia in human tumors and radiation therapy failure. Conversely, the higher the oxygen content in the cancerous tissue, the more effective the radiation therapy.

In addition to the creation of oxygen radicals that attack cancer cell DNA, hyperthermia also causes the accumulation of proteins in the cell nucleus. This prevents the self-repair of cancer cell DNA that is damaged by the ionizing radiation. In addition, ionizing radiation can damage cells during different phases of the cell cycle. Tumor cells are resistant to ionizing radiation during the synthesis phase, but they are susceptible to the destructive effects of hyperthermia during this phase. Poorly perfused tumor tissue that is resistant to ionizing radiation is susceptible to hyperthermia.

In contrast, tumor tissue with good blood circulation does not react to the heat, but is susceptible to ionizing radiation. This complementary interaction is a compelling reason for combining hyperthermia and radiation therapy (thermoradiotherapy). In-vivo studies have shown that the use of hyperthermia can increase the effects of radiation therapy by a factor of between 1.2 and 5. This means that hyperthermia is one of the most effective potentiators of radiation therapy.



Synergistic mode of action of radiotherapy and hyperthermia

HYPERTHERMIA & CHEMOTHERAPY

HYPERTHERMIA INCREASES THE EFFICACY OF CYTOSTATICA

Hyperthermia can also significantly increase the effectiveness of chemotherapy. As with radiation therapy, the primary reason is increased perfusion in the tumor tissue. The improved blood flow simplifies the uptake of cytostatica through the cell membranes. In addition, the increased temperature functions as an activator for the drug therapy because the chemical reactions are accelerated by the heat.

When treating large tumors in particular, hyperthermia represents an ideal supplement to chemotherapy. Often, the center and other regions of cancer foci of large tumors have poor blood circulation, retarding cell growth. As a result, they are not reached by cytostatica that primarily attack quickly dividing cells. Hyperthermia significantly increases the perfusion of the tumor cells and therefore the uptake of the drug.

Hyperthermia has been used with liposomes to target release of the cytostatica directly in the tumor. The cytostatica are into the liposomes, tiny spheres of fat. Using an intravenous drip, these liposomes are injected into the patient's blood. When they reach a part of the body that has been warmed to 42°C the liposomes melt, releasing their contents. This enables large quantities of chemotherapy drugs to be delivered directly to the tumor, significantly reducing side effects.

PROMISING RESEARCH RESULTS

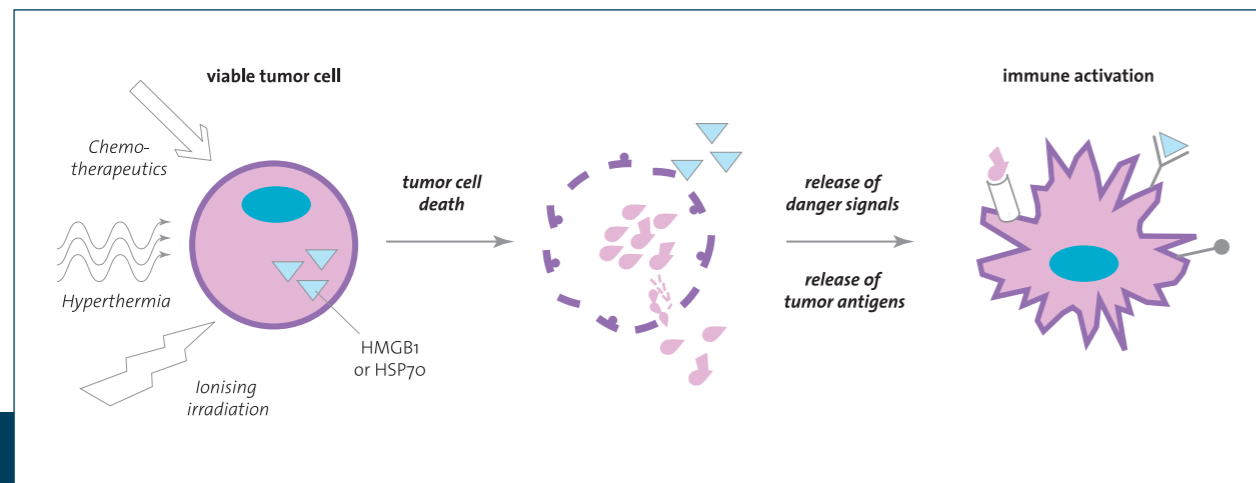
HYPERTHERMIA AND BIOLOGICAL/IMMUNOLOGICAL THERAPIES

For **immunotherapy** and the development of anti-tumor vaccines, hyperthermia plays a critical role. Heat puts cancer cells under stress. This results in the formation of heat shock proteins (e.g., HSP70) and cellular danger signals that in turn activate the immune system. This knowledge is the basis for the many research projects focused on how to develop immunotherapies using these heat shock proteins, and how to combine various vaccination methods with hyperthermia.

Over the past few years it has been discovered that hyperthermia also influences (the behavior of) immune checkpoint molecules, which are decisive in controlling how the immune system acts toward tumor cells.

This means hyperthermia will also be of great interest in combination therapies consisting of radio- and chemotherapy with immune checkpoint inhibitors.

With respect to **antiangiogenesis**, research results indicate that hyperthermia contributes here as well because it blocks the formation of new blood vessels. As a result, it is suitable as an accompanying therapy to angiogenesis inhibitor drug therapy for surviving tumor cells in low perfusion regions.



Immune activation induced by hyperthermia

IMPROVED PATIENT WELL-BEING

HYPERTHERMIA SIMPLIFIES SURGERY

Because it kills many cells, hyperthermia treatment often dramatically shrinks tumors, making surgical removal of the tumor easier or, in some cases, possible. Hyperthermia offers enormous pre-surgical therapeutic value, especially when resection of the tumor would be dangerous or impossible due to its proximity to sensitive structures.

Additional advantages of hyperthermia include fewer disfiguring surgeries in visible areas of the body; e.g., tumors in the head and neck area, if tumors are shrunk prior to surgery.

HYPERTHERMIA AND QUALITY OF LIFE

Many studies show that the quality of life of cancer patients is substantially improved when radiation or chemotherapy is combined with hyperthermia treatment. The combined treatment results in a significant, long-lasting reduction in side effects.

Hyperthermia stimulates the immune system and helps the body recover from the toxic side effects of standard therapies. And even in palliative cases, patients benefit from hyperthermia, as it alleviates bleeding, pain, and infection.

OVERVIEW

THERAPEUTIC GAINS FROM HYPERTHERMIA

- ▶ Improvement in survival rates
- ▶ Improvement in local tumor control and the duration of local tumor control
- ▶ Increased remission rates
- ▶ Reduced morbidity
- ▶ Direct destruction of the tumor cells
- ▶ Improved palliation and durability of palliation
- ▶ Improved quality of life
- ▶ Increased effectiveness of other forms of treatment, without increased toxicity
- ▶ Improvement in tumor oxygenation, which increases the effectiveness of radiation therapy
- ▶ Destruction of both heat sensitive and radiation-resistant cells
- ▶ Improvement in the response rate to cytostatica
- ▶ Specific activation of the immune system
- ▶ Expansion of the treatable range of tumors in terms of size and status
- ▶ Increased uptake of cytostatica in cells
- ▶ Synergistic interaction with cytostatica
- ▶ Destruction of chemotherapy-resistant cells
- ▶ Efficient immunomodulator
- ▶ Improvement of innovative multimodal radio-chemo-immunotherapies
- ▶ Reduction in tumor size to enable resection and/or make resection safer
- ▶ Reduced disfiguration due to surgical tumor resection
- ▶ Improvement in functional results after surgery
- ▶ Improved results when combined with radiation therapy and chemotherapy (thermoradiochemotherapy)
- ▶ Increased effectiveness in patients who have received previous radiation therapy

DR. SENNEWALD MEDIZINTECHNIK GMBH

Dr. Sennewald Medizintechnik was founded with the aim of discovering innovative and beneficial cancer therapies and we have since amassed over 30 years of experience in regional and superficial hyperthermia. Our aim is to help improve the range of products on offer, to support the growth of this proven technology and so increase the survival rate among cancer patients. To help us achieve this goal, we have entered into a long-term partnership with the pioneers and world leaders, Pyrexar Medical, to further develop the manufacture of hyperthermia systems. These high-quality medical devices are designed for maximum efficacy combined with minimum risk for greater patient comfort and are installed in oncology departments, research organizations and leading universities throughout Europe. Our unrivaled links to the scientific community have led to the acceptance of hyperthermia, the development of dedicated software, reimbursement of hyperthermia and its use in the treatment of children. Strategic partnerships with medical centers have resulted in phase III clinical studies demonstrating that Pyrexar systems offer a significant increase in cancer response rates, and are the only ones to have received FDA approval.

The success of Dr. Sennewald Medizintechnik GmbH is a result of continuity. We are able to draw on our many years of experience for our in-depth knowledge of customers' clinical requirements and of the precise technical specifications for all the hyperthermia systems we offer. In addition, our teams of engineers, technicians and software developers remain as close to customers as possible, offering support in the planning, installation and set-up of the systems, as well as after-sales service.

One example of this is Ludwig-Maximilians University (LMU) of Munich, Germany, which has installed a new image-guided hyperthermia system at Großhadern University Hospital. A pioneer in cancer treatment with hyperthermia, the hospital has carried out over 15,000 patient treatments using this method, many of whom had soft tissue sarcoma tumors. The facility has been leading a phase III clinical study which illuminated the long-term survival benefits of adding hyperthermia to chemotherapy and LMU is also at the center of the HEAT (Hyperthermia European Adjuvant Trial) study, a randomized, dual-arm trial for pancreatic cancer using chemotherapy plus hyperthermia.



- ▶ SALES
Frank Mittnacht
Phone: +49 89 542143-0
frank.mittnacht@sennewald.de
- ▶ PRODUCT MANAGEMENT
Dr. Maria Meindl
Phone: +49 89 542143-10
maria.meindl@sennewald.de
- ▶ MARKETING DIRECTOR
Monica Sennewald
Phone: +49 89 542143-0
monica.sennewald@sennewald.de
- ▶ OUR ADDRESS
Dr. Sennewald Medizintechnik GmbH
Schatzbogen 86
81829 Munich
Germany

www.sennewald.de

