

**European Society for Hyperthermic Oncology  
Hyperthermia Newsletter  
First Edition June 2014**



Dear friends and colleagues,

Hyperthermia in all aspects of technology, basic research and clinical activities is more recently growing in Europe!

The new findings support its strong potential for the treatment of cancer if combined with standard modalities.

The ESHO Newsletter provides most relevant developments in order to spread the knowledge among the different disciplines.

Hopefully this first edition will meet its expectations and may even stimulate your interest in the fascinating field of Hyperthermia.

With best regards

A handwritten signature in blue ink, appearing to read "R. Issels". The signature is written on a light yellow background.

Rolf Issels MD PhD  
Chair of ESHO Clinical Committee

The first ESHO Newsletter informs you about most recent events

## USA

The 31<sup>st</sup> Annual Meeting of the Society of Thermal Medicine (STM) has taken place in Minneapolis, MN, from May 6 to May 10, 2014. As Congress President served

**Robert J. Griffin, PhD,**

University of Arkansas for Medical Sciences

Dept of Radiation Oncology

Little Rock, AR

The following **keynote speakers** included:



**Michael Garwood, PhD**

Professor Center for Magnetic Resonance Research

University of Minnesota

Minneapolis, MN

### **“Advanced Magnetic Resonance Imaging Approaches to Thermal Therapy and Nanomedicine Biodistribution”**

In spite of preliminary clinical trials in Europe and promising preclinical studies, the successful use of magnetic nanoparticle (mNP) hyperthermia cancer treatment will depend on many factors, including: 1) A safe and adaptable nanoparticle platform; 2) A non-toxic, targetable, nanoparticle-activating alternating magnetic field (AMF); 3) Non-invasive *in vivo* nanoparticle imaging; 4) Relevant and translatable pre-clinical studies; 5) Thermal dosimetry and *in vivo* validated computational models allowing for nanoparticle-AMF treatment planning; 6) Understanding interactions of mNP hyperthermia with conventional adjuvant therapies; 7) Well planned, early-phase clinical studies in humans.

One of the most critical aspects of performing successful and sophisticated mNP-AMF based hyperthermia treatment is the generation of an accurate radiologic-based mNP and anatomic imaging system which can not only assess tumor and normal tissue anatomy and geometry but can detect and quantify the mNPs (Fe) levels and biodistribution in a spatially accurate, sensitive and robust manner. CT imaging is capable of detecting and quantifying mNPs at levels above 10 mg/gram tissue (tumor); unfortunately this level is unlikely to be clinically achievable in most situations. Conventional gradient-echo MRI methods are also capable of detecting mNPs/Fe, although only when mNP/Fe levels are below the grossly quantifiable therapeutic hyperthermia threshold (~ 0.1 mg Fe/gm tissue/tumor when using dextran coated 60-100 nm ferromagnetic NPs). Recently, we solved this problem by using a new MRI technology called SWIFT (SWEEP Imaging with Fourier Transformation). With SWIFT, mNPs in aqueous environments can be visualized clearly with positive contrast (ie, images display hyperintensity in regions where mNPs are located). Furthermore, the concentrations of the mNP/Fe visualized in SWIFT images can be quantified by measuring the longitudinal relaxation time  $T_1$  of the water protons. Experiments on dispersed mNPs in gels show  $1/T_1$  to be linearly proportional to Fe concentration up to at least 3 mg Fe/mL (Zhang et al, *Magn Reson Med*, in press). Such high concentration exceeds that measured in previous MRI studies by roughly an order of magnitude. Of particular note, the measured  $1/T_1$  values of both dispersed and aggregated mNPs in gels were found to be predictive of AMF heating (SAR) (Etheridge et al, submitted). *In vitro* and *in vivo* (mouse tumor model) SWIFT studies and the future of SWIFT imaging in clinical mNP cancer treatment trials, will be discussed.



**Katherine Ferrara, PhD**  
Professor Biomedical Engineering  
University of California-Davis  
Davis, CA

### **“Ultrasound-guided drug and gene delivery”**

Our objective in this presentation is to explore the mechanisms and technologies that are exploited to enhance drug and gene delivery with ultrasound. Physical mechanisms including cavitation, radiation force and hyperthermia can alter the local concentration of the drug or gene, enhance transport across the vascular surface and cell membrane and result in changes in the number or phenotype of immune cells. In addition, we will describe technologies for guiding and assessing delivery, including direct imaging of the therapeutic cargo with positron emission tomography or optical imaging, imaging of temperature elevation, imaging of the mechanical properties of tissue and imaging of tissue perfusion. Finally, we will summarize the delivery vehicle technologies that are showing promise for improving therapeutic efficacy.

Nanostructures, including microRNA, 4x4x14 nm albumin, 15-nm micelles, 100-nm liposomes and micron-diameter microbubbles, have been labeled for nuclear imaging of the shell and in parallel the core of the particle has been imaged with ultrasound, hyperspectral optical methods or magnetic resonance imaging. In pre-clinical models, we find that molecular targeting of particles as large as liposomes can result in rapid (~1 minute) endothelial targeting of cardiac vasculature of ~40% ID/g. The accumulation of targeted microbubbles on tumor endothelium is similarly rapid, although the accumulated particle fraction is substantially smaller. While the accumulation of nanoparticles within cancerous tumors is substantially slower, stable particles typically accumulate to ~5-10% ID/g within 24 hours. Such accumulation can be locally increased 2-3 fold with the application of therapeutic ultrasound.

A significant outstanding challenge is the design of therapeutic nanoparticles that remain stable in circulation but are efficacious at the disease site. One approach that we have followed is to form a precipitate complex between copper and doxorubicin within nanoparticles. The advantage of this approach is that the particles are loaded at neutral pH and the copper-doxorubicin complex remains intact until a low pH environment is encountered in a lysosome or tumor or release is facilitated by ultrasound. We find that such a strategy can achieve complete regression of local cancers.



**Gosse Adema, PhD**  
Professor Department of Tumor Immunology  
Radboud University Nijmegen  
Nijmegen, The Netherlands

### **“Local Tumor Ablation plus Immune Stimulation: Towards in situ Cancer Vaccines”**

**Background:** Local tumor destruction by heating or freezing is used clinically to eliminate tumors difficult to excise by conventional techniques for anatomical reasons. Interest in technologies for minimally invasive and local therapies is increasing rapidly as it may represent a promising alternative strategy for certain types of surgery. Successful local tumor control is often not curative as a consequence of tumor micro-metastases being already present prior to treatment. This indicates the need for additive treatments inducing systemic responses. We are exploring the combination of tumor ablation plus immune stimulation to make use of tumor debris to induce systemic anti-tumor immunity.

**Methods:** Different tumor ablation technologies were tested alone or in combination with different immunotherapy treatments for their ability to create an effective in situ cancer vaccine. Extensive immune monitoring combined with immune cell biological studies were performed to unravel the fundamental mechanisms determining success or failure of tumor ablation immunotherapy in the treatment of cancer.

**Results and conclusion:** We have developed unique murine models for cryo-, radiofrequency and HIFU mediated tumor ablation and reported that tumor ablation by itself can efficiently deliver antigens for the *in vivo* induction of anti-tumor immunity. Yet, tumor ablation alone resulted in only weak immune responses and partial protection against a subsequent tumor-challenge. These results imply that approaches directed at immune stimulation in combination with tumor ablation may be beneficial. Indeed, combining ablation plus immune activation by either immune checkpoint blockade antibodies or Toll Like Receptor (TLR)-Ligands results in strong protection against a subsequent tumor re-challenge and the eradication of untreated metastases in mice. Efficacy was dependent on both tumor ablation and immune stimulation and correlated with the presence of anti-tumor immune cells.

These data thus show that tumor debris left behind after in vivo tumor destruction can provide the immune system with an effective antigen source for the induction of anti-tumor immunity. Based on these results clinical trials in humans and dogs with cancer have been initiated. Data on the development of optimal tumor ablation plus immune stimulation strategies and the role of the professional antigen presenting Dendritic Cells in this process will be presented and discussed.

## Two Award & Lectures were given:

The 2<sup>nd</sup> William Dewey Award was given to



**Mark W. Dewhirst, PhD**  
Department of Radiation Oncology  
Duke University  
Durham, SC

### **The William Dewey Award: “Lessons learned and passed forward”**

I was fortunate to have Dr. Dewey on my graduate committee. In many ways, he served as my mentor as much as my primary mentor, Edward Gillette. However, both shaped my career in significant ways. Over the years, I have mentored well over 70 graduate students, postdoctoral fellows medical students, residents and faculty. In 2011, I was named the first Associate Dean for Faculty Mentoring by the Duke University School of Medicine.

Mentoring has been my passion throughout my career and I have been fortunate to be mentor to many students who were involved in studies involving hyperthermia. In this lecture, I will review some of their work, but the emphasis will be on the principles that I have attempted to pass forward to this next generation. I am honored to receive this award and hope to make this lecture something that will be remembered in the future, particularly by the young trainees who will be attending the meeting.

The 25<sup>th</sup> J. Eugene Robinson Award was given to



**Rolf Issels, MD PhD**

Medical Center Grosshadern  
University of Munich – Sarcoma Center  
and  
HelmholtzZentrum münchen – German Research Center for Environmental Health

**J. Eugene Robinson Award Lecture: “Regional hyperthermia combined with chemotherapy - from the bench to bedside”**

The hallmarks of hyperthermia and its pleiotropic effects are in favour of its combined use with chemotherapy. Preclinical research reveals that for heat killing and synergistic effects the thermal dose is most critical. Thermal enhancement of drug cytotoxicity is accompanied by cellular death and necrosis without increasing its oncogenic potential. The induction of genetically defined stress responses can deliver danger signals to activate the host's immune system. The positive results of randomised trials have definitely established hyperthermia in combination with chemotherapy as a novel clinical modality for the treatment of cancer. Hyperthermia targets the action of chemotherapy within the heated tumour region without affecting systemic toxicity. In specific clinical settings regional hyperthermia (RHT) or hyperthermic perfusion has proved its value and deserve a greater focus and investigation in other malignancies. In Europe, more specialised centres should be created and maintained as network of excellence for hyperthermia in the field of oncology.



Rolf Issels presenting the J. Eugene Robinson Award Lecture. The introduction was made by Gerard van Rhooen, President elect of ESHO.

In addition an update of the Japanese Thermal Medicine trial was given:

**“Efficacy of Gemcitabine combined with Hyperthermia therapy in the treatment of unresectable pancreatic cancer : Phase II study”**



Satoshi Kokura MD PhD  
Kyoto Gakuen University  
Kameoka, Japan

**Background:** Pancreatic cancer is an aggressive malignant tumor. Gemcitabine is the standard first line therapy for pancreatic cancer. Several gemcitabine based chemotherapy combinations were studied for the treatment of pancreatic cancer, but these combination therapies showed no major success over single agent gemcitabine in the treatment of pancreatic cancer. Hyperthermia has been shown to increase the cytotoxic effects of some anticancer agents by facilitating drug penetration into tissue, and Gemcitabine has recently been shown to be a potent hyperthermic sensitizer in preclinical studies. We conducted a phase II study to determine the availability of combination therapy with gemcitabine and hyperthermia in the treatment of unresectable pancreatic cancer.

**Methods:** Patients who participated in the study had advanced pancreatic cancer and their performance status score were 0-2. The primary end point was one-year survival rate. And the secondary end points were safety and response rate. We set the expectation one year survival rate to 30% Gemcitabine(1000mg/m<sup>2</sup>) was given weekly for 3 weeks(day 1,8,15) in four-week cycles, and hyperthermia(40min/once) weekly. This schedule was repeated until disease progression.

**Result:** From November 2008 to November 2009,18 patients were enrolled in this study. Median patient age was 64 years old(range 47-78),male/female:10/8 All patient died until September 2011,and the one year survival rate is 33.3%, exceeded the expected rate. Disease control rates (CR+PR+SD) were 61.1% (PR/SD/PD=2/9/7). Median survival times were 6 months. Adverse events (Grade3/4) were neutropenia(16.7%),anemia(16.7%), anorexia(5.6%) ,gastrointestinal bleeding(5.6%).

**Conclusion】** Combination therapy with gemcitabine and hyperthermia is both a safe and effective treatment in patients with advanced unresectable pancreatic cancer. To clarify the effects of sequential combination of hyperthermia and Gemcitabine as compared with Gemcitabine monotherapy, further studies should be performed, particularly prospective randomized trials.

12 STM New Investigator Travel Awards sponsored by the NCI/NIH and Radiation Research Society were given to:



**Balidemaj, E** – Academic Medical Center, University of Amsterdam, Netherlands

*Imaging electric tissue properties using MRI for improved SAR assessment during Hyperthermia Treatment*



**Oei, Arlene Leonie** - Academic Medical Center, University of Amsterdam, Laboratory for Experimental Oncology and Radiobiology (LEXOR), Center for Experimental Molecular Medicine, The Netherlands

*PARP1-Inhibition sensitizes combined hyperthermia-radiation and combined hyperthermia-cDDP treatment of cervical carcinoma cells*



**Li, Li** - Duke University, USA & Erasmus Medical Center, Rotterdam, The Netherlands

*The effect of heat cycling on intratumoral liposome accumulation and triggered drug release.*



**McWilliams, Brogan**, Kansas State University, USA

*A directional interstitial antenna for microwave tissue ablation: theoretical and experimental investigation*



**Ku, Amy** - Roswell Park Cancer Institute, USA

*Myeloid-Derived Suppressor Cells Subvert the Immunostimulatory Activity of Systemic Thermal Therapy by Blocking T cell Trafficking in the Tumor Microenvironment*



**Kumar, Gaurav** - Beth Israel Deaconess Medical Center, USA

*Celecoxib suppresses local inflammatory and systemic pro-oncogenic effects of hepatic radiofrequency (RF) ablation in small animals*



**Adams, Matthew** University of California San Francisco, USA

*Theoretical Design and Evaluation of Endoluminal Ultrasound Applicators for Thermal Therapy of Pancreatic Cancer under Image Guidance*



**Attaluri, Anilchandra** - Department of Radiation Oncology & Molecular Radiation Sciences, Johns Hopkins University School of Medicine, USA

*Magnetic nanoparticle hyperthermia as a radiosensitizer for locally advanced pancreas cancer: An in-vitro and in-vivo study*



**Chiang, Jason** - University of Wisconsin-Madison, USA

*Water Vapor Transport during Microwave Ablations: Numerical Simulation and Experimental Validation*



**Wong, Andrew** - University of California, Davis, USA

*Overcoming accelerated blood clearance of Cu-Doxorubicin nanoparticles with MR guided focused ultrasound thermal ablation*



**Soetaert, Frederik** - Ghent University, Belgium

*Optimal switch-off times of pulsed currents in bipolar radiofrequency ablation*



**Dillon, Christopher** - University of Utah, USA

*A novel method for quantifying perfusion-induced energy losses in magnetic resonance-guided focused ultrasound*

The Congress Program included in addition 10 symposia, 5 workshops and 9 refresher courses.

Industrial sponsors of the STM Meeting in Minneapolis included:

Celtic, Philips, BSD, Alpinion, Oncotherm, Verasonics, Fujifilm, Quantum Design, Monteris and Informa Healthcare

## **EUROPE**

The next **29<sup>th</sup> Annual Meeting of the European Society for Hyperthermic Oncology (ESHO)** will take place in

Torino, Italy

On June 11 to 14 under the slogan "Firing Up Cancer Treatment"

Congress President: Pietro Gabriele MD

Director of Radiotherapy Department

Fondazione del Piemonte per l'Oncologia (FPO)

Scientific Institute for Research and Treatment of Cancer (IRCCS)

Candiolo/Turin, Italy

The program addresses hot topics of developments in Nanotechnology, Diagnostic Imaging and Drug Delivery, Tumor Biology, HIFU and Thermal Ablation, HIPEC and Isolated Limb Perfusion (ILP) and the status of clinical studies.

(for further information see [www.esho2014.org](http://www.esho2014.org))