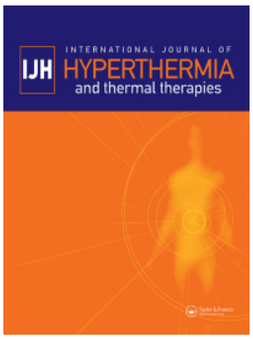

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Cellular and vascular effects of hyperthermia

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FOREWORD

Cellular and vascular effects of hyperthermia

This special issue of the *International Journal of Hyperthermia* contains the proceedings of the Third European Society for Hyperthermic Oncology (ESHO) educational day symposium on hyperthermia entitled 'Cellular and Vascular Effects of Hyperthermia'. The symposium was held on 13 June 2007 in the historic Bethlehem Chapel located in the Old Town of Prague in the Czech Republic. It was held in conjunction with the 24th Annual Meeting of ESHO (14–16 June 2007), in the same facility. On behalf of the ESHO Biological Committee, Valeria Milani and Michael Horsman were asked to organize an educational meeting on those hyperthermia-related topics in the field of biology relevant for understanding the results of clinical trials and of particular interest for the development of targeted therapies in combination with hyperthermia. The goal was to give new perspectives in the field of clinical and technical hyperthermia and create an environment to stimulate collaborations between basic researchers and clinicians. This educational activity was designed for academic scientists including biochemists, biophysicists, cell biologists, and medical and radiation oncologists interested in the application of hyperthermia. The symposium was divided into two sessions: the first concerned the cellular response to heat, while the second was on the vascular mediated responses to heat. As a result, this special issue contains nine articles and is designed to provide a founded knowledge on the cellular and vascular response to heat.

The first article in this issue is an overview on the cellular responses to hyperthermia by Roti Roti, in which he focuses on those factors that contribute to direct cell killing by heat and those that play a role in the heat enhancement of ionizing radiation and chemotherapeutic agents. While high temperature thermal ablation treatments can induce direct DNA damage, lower hyperthermic treatments primarily affect cellular macromolecular functions. Thus he presents evidence demonstrating that both cell killing and the enhancement of conventional treatments by hyperthermia are mediated through protein-related changes that influence DNA replication, chromosomal aberrations, and DNA repair. Heat mediated effects on DNA repair is also the basis of the next article by Iliakis et al., which deals with the issue of thermal radiosensitization. They present the historical concept that the enhancement of radiation damage was originally believed to be the result of an inhibition of radiation-induced DNA double strand breaks (DSB). However, more recent studies in mutants with defective DSB repair, but still showing heat radiosensitization, led to the proposal that other mechanisms were responsible. In this review the authors revisit the issue and propose a model that still supports the role of an inhibition of DSB repair in heat radiosensitization. Another critical topic of relevance to the cellular affects of heat is stress proteins that confer resistance to physical stresses, especially heat shock (heat shock proteins, HSPs). The article by Calderwood and Ciocca gives a comprehensive review of HSPs in terms of the molecular aspects of the regulation of the stress response in cells and the diverse functions of HSPs. However, aside from discussing their role in influencing tumour growth and resistance to therapy the authors also discuss in detail the potential of targeting HSPs as a form of therapy using either pharmacological or immunological approaches. The relationship between hyperthermia and immunological affects was also the basis of the next article by Dayanc et al. These authors presented a summary of the literature regarding the role of temperature and natural killer (NK) cell anti-tumour activity. They show that while moderate thermal stress can both enhance and inhibit the cytotoxic action of NK cells against tumour cells, fever-range thermal stress only improves NK mediated tumour cell killing. After proposing several mechanisms for this enhancement they conclude that NK cells may play a significant role in enhancing the long-term efficacy of clinical hyperthermia.

In the second half of this special issue the articles deal with various aspects related to the tumour vasculature. The first article by Horsman begins with a brief review of angiogenesis, the process by

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which tumours develop their own functional vasculature from the surrounding normal tissue vessels. This was followed by a discussion of how the tumour neovasculature can be targeted for therapy. Since such a therapeutic approach will change tumour blood flow and the tumour microenvironment, it is ideal for combining with both hyperthermia and thermoradiation. The pre-clinical studies that have investigated these combinations in tumours and normal tissues were reviewed and the therapeutic benefit demonstrated, thus establishing the rationale for future clinical trials. Tumour vasculature, or rather the endothelial cells lining blood vessels, was also the basis of the next article by Evans et al. More specifically, this paper dealt with the ability of immune-protecting lymphocytes to traffic across vasculature, which is well characterized in lymphoid organs, but not so well known in tumour tissues. The paper summarizes the evidence that lymphocyte extravasation across specialized high endothelial venules of lymphatic organs is promoted by inflammatory cues associated with fever-range thermal stress. It further discusses how thermal-based strategies can be used to improve lymphocyte delivery to the tumour microenvironment during T cell based immunotherapy. The tumour vascular supply also plays an important role in influencing drug delivery to tumours and the physiological effects of hyperthermia are known to modify this delivery. Hyperthermia can also be used to increase local delivery of drugs to tumours if the drugs are incorporated into heat sensitive liposomes. This latter point is the basis of the article by Tashjian and colleagues. They start with a brief review of liposomes as drug carriers. This is followed by an overview of how liposomal drug delivery during hyperthermia can be non-invasively monitored using nuclear medicine and magnetic resonance imaging (MRI) techniques, and discusses the advantages of having such information available both during and after combined heat and drug treatment. Non-invasive imaging, especially with dynamic contrast enhanced (DCE)-MRI, is the topic of the article by Lüdermanns et al. Hyperthermia can change tumour blood perfusion and tumour vessel permeability and both these parameters can be detected by DCE-MRI. This paper reviews the pros and cons of using DCE-MRI to monitor these changes and discusses how this DCE-MRI method can be utilized to observe the effects of hyperthermia. Combining anti-vascular therapies or targeted treatments with hyperthermia is clearly a clinical option that should be pursued. This aspect is the focus of the final review by Dahl and co-workers. Here the authors highlight the development of anti-vascular approaches with specific reference to randomized clinical trials. Being aware of how these agents have developed is critical to our understanding of how such therapeutic approaches should be applied in clinical hyperthermia. This more clinically based paper gives a nice conclusion to the vascular mediated responses to hyperthermia.

We would like to express our thanks to the ESHO Biological Committee for their scientific support, and the ESHO organisation and Dr Sennewald Medizintchnik GmbH for financial support. Thanks must also go to Dr Vrba and his colleagues at the Czech Technical University, whose local organizational efforts allowed the meeting to run so smoothly. Without the excellent presentations by the invited speakers and the active participation of all who attended the meeting this symposium would not have been such a success and these efforts are appreciated. Finally, thanks are also due to the *International Journal of Hyperthermia* and its publishers for allowing the proceedings to be published.

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