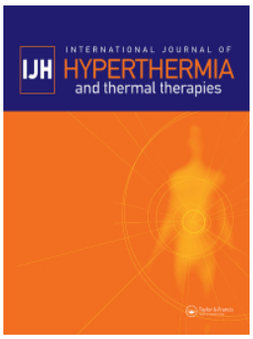

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EDITORIAL

Progress in development of biomedical applications of heat shock proteins and thermal stress

I am pleased to have the opportunity to serve as the Editor for this special issue of the *International Journal of Hyperthermia* summarising current progress in biomedical applications of heat shock proteins and thermal stress. I know that readers of the journal will benefit greatly from the insights offered by this international group of longstanding leaders in this field, each of whom has made extensive original research contributions to the subspecialities they are summarising in this collection of reviews and original research articles. Indeed, some of the earliest scientific meetings of researchers interested in the therapeutic potential of hyperthermia (meetings which would eventually lead to today's Society for Thermal Medicine (STM), as well as this journal) included individuals who were interested in heat shock proteins (HSPs) and their functions. A member of this early group, John Subjeck, is fittingly recognised in this special issue as the 2012 J. Eugene Robinson Awardee (presented at the 2012 STM meeting in Portland, Oregon) for his lifetime of achievements in the study of the large heat shock/stress proteins and for defining new approaches for their use in the development of novel cancer vaccines, a technology that has recently reached the clinic (see the Robinson tribute by Stuart Calderwood in this issue [1]).

Beginning in the early 1980s, the increasing recognition of the importance of HSPs and stress responses in cancer and several other diseases (including inflammatory diseases, rheumatoid arthritis and other forms of autoimmunity, myopathies, and pathologies associated with aging) not only helped to strengthen the STM, but led eventually to the formation of the Cell Stress Society International (CSSI). In addition, attesting to the rapid growth of interest in this field, a separate meeting has occurred every two years, i.e., the International Symposium on Heat Shock Proteins in Biology and Medicine, where members of both STM and CSSI meet to present new findings. This special issue is composed of reviews and new research contributed by many of the presenters at the most recent of these meetings (Co-organised by Stuart Calderwood, Alex Asea and Larry Hightower) held in Alexandria, Virginia, 7–12 November 2012.

A major theme in this special issue relates to the chaperone function of HSPs and the ability to exploit this function for therapy. Although the large stress/HSPs (Hsp110 and Grp170 were identified over 30 years ago (see review by Xiang-Yang Wang and John Subjeck in this issue [2]) these abundant and highly conserved molecules have received much less attention compared to other HSPs. Wang and Subjeck [2] review aspects of the structure and function of these large stress proteins and their roles as molecular chaperones in the biology of cell stress and current applications for their use in immune regulation and cancer immunotherapy. They also discuss the recently revealed immunosuppressive activity of scavenger receptor A that binds to Hsp110 and Grp170 as well as the feasibility of targeting this receptor to promote T cell activation and anti-tumour immunity induced by large HSP vaccines and other immunotherapies. Focusing as well on the chaperone abilities of HSPs, Jianlin Gong, Stuart Calderwood and colleagues have been exploring the use of Hsp70 (which is isolated from tumour cell/dendritic cell fusions) as an anti-cancer vaccine. Here, Stuart Calderwood et al. [3] present a variety of observations using this vaccine which is highly effective in triggering specific anti-tumour T cell immunity. Moreover, the authors highlight the exciting possibility of using different tumour cell subpopulations, such as drug-resistant cancer cells, or cancer stem cells for cell fusions from which the Hsp70 is isolated, thus potentially targeting specific tumour cell subsets that express cell-specific tumour antigens.

Research from Michael Graner's lab highlights the use of concentrated fractions of tumour cell lysates, consisting of numerous chaperone/heat shock protein complexes, including Hsp70, Hsp90, Grp94 and calreticulin, as cancer vaccines. While this group has previously documented that their 'tumour-derived chaperone-rich cell lysate' (CRCL) preparation helps to trigger antigen presenting cell activation, here (Michael Graner et al. [4]) describe the use of mass spectrometry techniques to help define the 'peptidome' of potential antigens extracted from a murine tumour. Interestingly, many of the peptides identified possess amino acid sequences that would allow their putative binding – not only to Hsp70-type chaperones, but also to MHC class I and II molecules, suggesting a direct mechanism by which immune cells can be activated by these complexes [4]. In a second paper from this group (Laura Epple, et al. [5]), a case report is presented that suggests that this CRCL vaccine (used with topical imiquimod) can be a safe and effective treatment for canine bronchoalveolar adenocarcinoma. Here, a significantly prolonged survival following a diagnosis of grade III/stage III bronchoalveolar adenocarcinoma in a canine patient was observed.

There has been growing interest in the role of extracellular HSPs, and the laboratory of Boris Margulis has been

interested in the potential differences between intracellular and extracellular Hsp70 chaperones in cancer immunotherapy as well as their roles in the protection of tumour cells from cancer therapeutics. Irina Guzhova et al. [6], have contributed a review of these differences and also highlight a recurrent theme in this special issue, which is the dual activity of Hsp70 released from stressed cancer cells in both serving as a danger signal as well as helping to recruit cells responsible for generation of innate and adaptive immune responses against tumour cells.

Andre-Patrick Arrigo and Benjamin Gilbert [7] have contributed a review on recent discoveries in the field of small human HSPs (particularly HspB1, HspB5 and HspB8), and their work clearly points to the important roles played by these ATP independent chaperones in the regulation of a large spectrum of cellular processes and in several different pathological diseases. This review contains a very useful summary of literature that is organised according to functional activity, a plan that will greatly help readers to understand the current status of information surrounding these small HSPs and their interactions, which reflect numerous functional activities in the cell. The authors stress that much more information concerning the interactions between client protein targets and small HSPs, as well as their multiple combinatorial oligomeric complexes, is needed so that the most rational use of these HSPs can be developed for therapeutic purposes.

A second major theme in this issue relates to stress responses in general and their relationship to physiological, immunological and pathological processes. Ishwar Singh and Jeffrey Hasday [8] present a comprehensive review on the intriguing overlaps between the febrile response and the heat shock response and the fact that they each activate some of the same transcriptional programmes, including stress-activated transcription factor, heat shock factor-1 (HSF1), to modify host defences in the context of infection, inflammation and injury. This review also focuses on how body temperature elevation (fever) that often accompanies infections and inflammation acts as a biological response modifier and modifies innate immune responses. For example, typical pro-inflammatory agonists such as Toll-like receptor agonists modify the heat shock induced transcriptional programme; this relationship reveals the existence of complex reciprocal relationships between inflammatory pathways and the heat shock response pathway.

Toshihiko Torigoe and colleagues are investigating the role of stress response genes in cancer stem-like cells (or tumour initiating cells). Cancer stem-like cells (CSCs) are defined as the small population of cancer cells that have stem cell-like phenotypes and a high capacity for tumour initiation. Since CSCs are now thought to be highly resistant to standard chemo- and radiation therapy, it is highly likely that they are responsible for significant disease recurrence. The review by Toshihiko Torigoe et al. [9] considers recent findings on stress response genes that are preferentially expressed in CSCs and describes their potential role in promoting tumour growth. These authors also reflect on the serious concern that under conditions in which stress resistance genes are up-regulated (such as during chemotherapy, radiation or thermal therapies), stem cell characteristics and tumour initiating capacity might be augmented, thus aggravating the malignant phenotype.

Stress, HSPs and chaperone activity have also been linked to aging and lifespan in several organisms, and in a very interesting review Ayesha Murshid et al. [10] review the data showing that decreases in HSPs in aging is associated with disruption of cellular homeostasis which causes diseases such as cancer, cell senescence and neurodegeneration. Aging also causes attenuation of many signalling pathways as well as the expression of transcription factors such as HSF1. This review deals in depth with the role of HSF1 pathways, as well as several others in regulation of longevity and aging. The authors also discuss the exciting potential for increasing HSPs during aging which could potentially maintain protein homeostasis and longevity by refolding the damaged proteins which accumulate during aging and are toxic to cells.

Manipulation of specific components of the immune system by either direct effects of heat (or HSPs) on immune cells (or on cytokine mediators) or by indirect effects on tissues which interact with immune cells, such as vascular endothelium, has been addressed by several contributors. For example, rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by excessive immune activity resulting in damaging inflammation in the joints. Willem van Eden has been interested in targeting regulatory T cells (Tregs) to dampen immune activity as an exciting strategy to achieve tolerance. The antigen specificity of Tregs is crucial for their effectiveness and could allow for very specific targeting of these cells; however, it is difficult to determine which antigen is suitable for RA because the auto-antigens are largely unknown. As outlined here by Martijn van Herwijnen et al. [11], HSPs are up-regulated during inflammation, and since their bound peptides are immunogenic they can be recognised by a variety of immune cells, including Tregs. Therefore, future research is needed to identify suitable epitopes that can be recognised by suppressive T cells, as well as expansion protocols for HSP-specific Tregs that can be used for adoptive transfer therapy.

Hsp70 itself has also been demonstrated to have anti-inflammatory and protective effects in diverse mouse models of inflammation. Cristina Bonorino's lab has been investigating mechanisms used by Hsp70 to regulate the production of pro-inflammatory cytokines and other aspects of the immune system. Their recent work has focused on a group of transcription factors that are important for pro-inflammatory cytokine production – the CCAAT/enhancer-binding proteins (C/EBPs). Thiago Borges et al. [12] report that both C/EBPβ and C/EBPγ transcription factors are inhibited by Hsp70 treatment, and this inhibition is dependent upon the TLR2-ERK-STAT3-IL-10 pathways in dendritic cells. Collectively, these data contribute to a better molecular understanding of how Hsp70 reduces inflammation, thus opening many opportunities for new clinical interventions.

In a novel approach for manipulation of specific arms of the anti-tumour immune response, Sharon Evans and her team have been focusing on their discovery of the ability of mild (fever-range) thermal stress to modulate the surface molecules on vascular endothelium that control T cell trafficking. They are exploiting this observation to solve the problem of poor access of cytotoxic T cells to the tumour microenvironment

and to identify strategies for improved adoptive T cell therapy. In this issue, Mary Ann Mikucki et al. [13] summarise exciting mechanistic evidence showing that systemic thermal therapy can be used as a preconditioning regimen which can 'hijack' the normally pro-tumorigenic, pro-inflammatory activity of IL-6 for improving anti-tumour immunity in the tumour microenvironment by mobilising T cell trafficking.

Selective effects of thermal therapy on tumour vasculature are also being exploited in the laboratory of Robert Griffin and his colleagues. In their report [14] the use of prior treatment with mild hyperthermia to enhance selective uptake of drugs from the tumour vasculature into the tumour microenvironment is described. Exploiting this function, they show significant enhancement of laser thermal ablation in solid tumours when tumours are previously treated with hyperthermia, which enhances the uptake of the drug indocyanine green dye, which can convert near infrared laser light into heat, thereby enhancing thermal injury of tumour blood vessels.

Natural killer (NK) cells have also been recognised as an important immune cell target for thermal therapy. Previous work from Elizabeth Repasky's lab has demonstrated that mild (fever-range) thermal stress increases NK cell-mediated tumour cell cytotoxicity, and that this effect is associated with reorganisation of specific plasma membrane domains containing NKG2D, a major NK cell activating receptor. In this issue, Emre Dayanc et al. [15], present their finding on the role of the transcription factor HSF1 in thermal regulation of *MICA* gene, which controls tumour cell surface expression of a major target of NK cell activity. They report that there is significant up-regulation of *MICA* gene expression (as well as surface protein expression of MICA) in tumour cell targets by mild thermal stress and determined that this up-regulation is dependent upon HSF1, providing yet another linkage between mild thermal stress, HSF1-dependent stress responses, and immune function.

The plasma membrane and membrane fluidity have long been suspected as being important targets of hyperthermia, and this effect could help to explain the pleotropic impact of thermal stress in the organism. However, specific physiological responses of cells to hyperthermia, particularly mild hyperthermia that are mediated through changes in plasma membrane properties have not been well understood. Laszlo Vigh has long been interested in how membrane structure and organisation controls the expression and cellular distribution of stress proteins and conversely, how the membrane association of HSPs can alter cellular function. In their report, Balint Csoboz et al. [16] review the fascinating data surrounding their hypothesis that elevated extent of membrane fluidity and reorganisation of lipid rafts that must be key determinants in the broad cellular effects of hyperthermia, including altered metabolism, cell signalling, and the onset of thermotolerance. They describe evidence that helps to define the properties that allow the plasma membrane to become the key determinant of cellular heat stress signalling, and present some new data supporting the idea that the amount of HSPs produced is not the sole factor in the development of thermotolerance.

In summary, this special issue contains a variety of comprehensive reviews and new data from expert leaders, and probably most importantly, contains insightful summaries of current problems and future goals, which are likely to drive research in this field for years to come. Therefore, experienced and new investigators alike will benefit by exploring the challenges set forth in these articles as they consider new research directions in their own laboratories, and are invited to attend meetings of the STM and CSSI to present their contributions to this rapidly expanding and exciting field of research.

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Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the writing and content of this article.

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