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MEETING REVIEW

The VIII International Congress on Stress Proteins in Biology and Medicine: *täynnä henkeä*

Cristina Bonorino[1] · Lea Sistonen[2] · John Eriksson[2,3] · Valérie Mezger[4,5] · Gabriella Santoro[6,7] · Lawrence E. Hightower[8]

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Abstract

About 150 international scientists gathered in Turku, Finland, in August of 2017 for the eighth in a series of international congresses about the roles of stress proteins in biology and medicine. The scientific theme and title of the 2017 Congress was "Stress Management Mechanisms and Pathways." The meeting covered a broad range of topics, reflecting the wide scope of the Cell Stress Society International (CSSI) and highlighting the numerous recent breakthroughs in stress response biology and medicine. The keynote lecturers included Marja Jäättelä, Richard Morimoto, Anne Bertolotti, and Peter Walter. The Executive Council of the CSSI elected new Fellows and Senior Fellows. The Spirit of Budapest Award was presented to Peter Csermely, Wolfgang Schumann, and Subhash Lakhotia in recognition of pioneering service contributions to the CSSI. The CSSI Medallion for Career Achievement was awarded to Larry Hightower and CSSI president Gabriella Santoro proclaimed Tuesday, August 15, 2017, Robert M. Tanguay Day at the congress in recognition of Robert's many years of scientific accomplishment and work on behalf of the CSSI. Additional special events were the awarding of the Ferruccio Ritossa Early Career Award to Serena Carra and the Alfred Tissières Young Investigator Award to Ayesha Murshid. As is the tradition at CSSI congresses, there were social events that included an exciting piano performance by a trio of young Finnish pianists, at the Sibelius Museum.

Keywords Stress Management Mechanisms and Pathways · The 2017 Congress · Cell Stress Society International

In Finnish, the word "*henki*" means the spirit, the life force associated with the soul. On the week of August 13, *henki* was high in a conference room overlooking the Aura River in Turku, Finland. The VIII International Congress on Stress Proteins in Biology and Medicine entitled "Stress Management Mechanisms and Pathways" was taking place, gathering a group of scientists from all over the world, exchanging the latest breakthroughs in the field. Approximately 150 colleagues attended the Congress including faculty and student commuters from nearby universities (Supplementary Fig. 1). The organizing committee consisted of Lea Sistonen (Åbo Akademi University), John Eriksson (Åbo Akademi University and University of Turku), Lawrence Hightower (University of Connecticut), Valérie Mezger (CNRS, Université Paris Diderot), and Helen Neumann (Cell Stress Society International (CSSI)) (Supplementary Fig. 2).

Principal organizer Professor Lea Sistonen opened the scientific program and noted that the program reflected the broad scope of the CSSI and the many recent scientific breakthroughs in our field. Each morning session started with a keynote address by pioneering scientists including Marja Jäättelä, Richard Morimoto, Anne Bertolotti, and Peter Walter. The sessions included invited speakers and those selected from submitted abstracts. Special events included the

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✉ Lawrence E. Hightower
Lawrence.Hightower@uconn.edu

[1] Pontificia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil

[2] Äbo Akademi University, Turku, Finland

[3] University of Turku, Turku, Finland

[4] CNRS, UMR7216 Épigénétique et Destin Cellulaire, Paris, France

[5] Université Paris Diderot, Sorbonne Paris Cité, 75205 Paris Cedex 13, France

[6] University of Rome Tor Vergata, Rome, Italy

[7] Institute of Translational Pharmacology, CNR, Rome, Italy

[8] University of Connecticut, Storrs, USA

awarding of the CSSI Medallion for Career Achievement to Larry Hightower, election of new CSSI Fellows and Senior Fellows, and the proclamation of Robert M. Tanguay Day, Tuesday August 15, 2017, to which session 5 was dedicated in recognition of Robert's many years of scientific accomplishment and work on behalf of the CSSI, including his successful effort to bring cell stress response and chaperone research to China. Additional special events were the awarding of the Ferruccio Ritossa Early Career Award to Serena Carra (University of Modena and Reggio Emilia) and the Alfred Tissières Young Investigator Award to Ayesha Murshid (Harvard Medical School and Beth Israel Deaconess Medical Center).

The remaining special event requires some explanation as earlier awards were made to Lawrence Hightower, Robert Tanguay, Antonio De Maio, and Helen Neumann during biennial meetings of CSSI Executive Council, and so they are not broadly known. The 2017 recipients of the Spirit of Budapest CSSI Pioneer Award were Peter Csermely, the founding secretary-treasurer of the CSSI and the principal organizer of two international congresses in Budapest, along with Wolfgang Schumann and Subhash Lakhotia, pioneers of the CSSI International Workshop Series.

This award continues a tradition started by Peter Csermely, who in 1999 brought to the CSSI international workshop in Wuhan, China, a miniature gold leaf print of a famous square in Budapest showing Stephen I, the first king of Hungary, and also the Fisherman's Bastion. Peter wanted to surprise and thank Larry for his work as founding president. The gesture has been adopted by the CSSI to recognize pioneering service contributions to our Society.

CSSI President Gabriella Santoro welcomed the attendees and chaired the award session along with Antonio De Maio. The meeting started with Gabriella bestowing the 2017 CSSI Medallion for Career Achievement upon one of the founding members of the society and its most enthusiastic promoter, Larry Hightower, acknowledging 40 years of stress as well as wishing him 40 more (Supplementary Fig. 3). Only at a CSSI meeting, could this be the highest of compliments. Previous awardees of the CSSI Medallion for Career Achievement include: Takashi Yura, 2000; Susan Lindquist 2003; Aaron Ciechanover, 2005; R. John Ellis, 2007; Costa P. Georgopoulos, 2009; Ferruccio Ritossa, 2010; and Kazutoshi Mori, 2015. Like them, Larry is a true pioneer, being responsible for the development of a whole new chapter in the history of the cell stress response: an extracellular role for stress proteins. In 1989, he described that rat embryo cells would specifically release heat shock proteins, in a non-conventional secretion pathway, possibly in response to perturbations to their homeostasis. His discovery changed the way we think of stress proteins and opened the way to figuring out a whole new way by which cells can communicate with each other. In recent years, Larry in collaboration with George Perdrizet and Charles Giardina has concentrated on the application of hyperbaric oxygen treatment to mouse models and diabetic patients in order to alleviate stress and kidney damage through the induction of cytoprotective responses.

The CSSI Executive Council elected eight new Senior Fellows: Peter Csermely, Linda Hendershot, Harm Kampinga, Subhash Lakhotia, Gabriele Multhoff, Leonard Neckers, Lea Sistonen, and Wolfgang Schumann (Supplementary Fig 4). Twelve new Fellows were elected by Council: Ivor Benjamin, Serena Carra, Carmen Garrido, Irina Guzhova, Iara Linhares, Meran Lloyd-Owen, Michael Lynes, Boris Margulis, Valérie Mezger, Richard Morimoto, Elizabeth Repasky, and Michael Sherman. The awards were presented by President Gabriella Santoro and Secretary-treasurer Larry Hightower (Supplementary Fig. 5).

Marja Jäätelä, from the Danish Cancer Society Research Center, engaged the audience during the first keynote address, with the recollections of an amazing journey of her own. Marja recalled that a fortuitous malfunction of her incubator, some 30 years ago, allowed her to observe that an increase in temperature would protect cancer cells from death caused by TNF-alpha. It was destiny that Lea Sistonen was working in a lab next door, and she suggested that heat stress-induced proteins could be the ones preventing tumor cells from dying. This led to the findings that Hsp70 depletion could activate a tumor-specific death program independent of caspases and Bcl-2, associated with lysosome enzymes. Marja's group found out that Hsp70 would stabilize lysosomal membranes, due to its ability to interact with lipids. Giving CADs, cationic amphiphilic drugs, could destabilize lysosomes and kill cells; giving cells Hsp70 could reverse or stop this process. This led Marja to pursue the repurposing of CADs, traditionally thought of as anti-histamines, for use in cancer therapy.

The next session focused on stress management in human disease. Dennis Thiele, from Duke University, showed how preventing HSF1 from degradation in Huntington's disease is crucial to avoid protein aggregation, and can be used to manage the neuronal dysfunction and muscle degeneration characteristic of this syndrome. He also presented a new model of binding of HSF1 and HSF2 to DNA. He emphasized the dichotomy of HSF1's critical role in neuroprotection on one hand and its roles in promoting cancer and neurodegenerative diseases on the other. Carmen Garrido, from the University of Bourgogne, highlighted the exclusive presence of Hsp70 in tumor exosomes, and how they can be used as a diagnostic marker for disease. She also proposed the inhibition of exosomes containing Hsp70 as a possible strategy in cancer therapeutics aimed at boosting patients' immune responses against cancer. Her group has started a human patient study to determine whether Hsp70-exosomes are useful for early diagnosis of metastasis. Early results have been very encouraging. An Hsp70 peptide aptamer has been obtained that

specifically binds to the extracellular domain of membrane-bound Hsp70 and is useful in capturing these exosomes. In addition, an miRNA signature has been found that reveals the cellular origin of these exosomes and consequently of the metastasis as well. Elizabeth Repasky, from Roswell Park Cancer Center, brought compelling evidence that beta-adrenergic signaling can suppress CD8 T cell function against tumors, demonstrating how a beta-blocker like propranolol can reverse this, and even sensitize for immune checkpoint treatment of resistant tumors. Toshihiko Torigoe, from the Sapporo Medical University, Japan, and Irina Ghuzova, from the Russian Academy of Science, also contributed to the discussion, showing mechanisms of HSF1 involvement in cancer stem cell propagation and Hsp70 protection from neurodegeneration, respectively.

Roles for stress proteins in longevity were discussed next, and the data highlighted mechanisms that link heat shock proteins and protein control. A pathway involving IGF, DAF-2, HSF1, and caveolin for longevity in *Caenorhabditis elegans* was mapped by Ehud Cohen, from Hebrew University in Israel. Also in *C. elegans*, GPCRs appear to be regulators of ER stress, as presented by Max Guerrero, from the Max Planck Institute in Germany. In *C. elegans*, heat shock can turn the entire embryo into muscle; Anat Ben-Zvi, from Ben-Gurion University of the Negev in Israel, showed mechanisms of protein quality control in different tissues, searching for explanations on why protein aggregation diseases are tissue specific. And connections between Hsps and proteasomal protein degradation in naked mole rats, an important model for longevity studies, were presented by Rochelle Buffenstein, from Calico Labs, USA.

A new session in honor of one of the field's most influential pioneers, Susan Lindquist, was held after the posters and titled "Susan Lee Lindquist Science Without Boundaries: Women's Health and HSP90." This session was sponsored by a fund opened by the CSSI to commemorate Susan's life and career (Supplementary Fig. 6). Both of the topics in the inaugural session were important to Susan both personally and professionally. We plan to have more sessions at future meetings that pair topics not usually discussed together in memory of Susan's approach to science without boundaries. Steven Witkin (Weill Cornell Medical College, NY) and Iara Linhares (Sao Paolo University) shared data about Hsps of vaginal microbiota from Brazilian subjects. Iara discussed evidence that the Hsp60 of *Chlamydia trachomatis* is the most sensitive indicator of blocked fallopian tubes. She also showed evidence that the detection of IgM anti-Hsp70 in fetal sera of mothers infected with cytomegalovirus is a very sensitive indicator of fetal infection and its consequences. Steve reminded the audience that women are the only mammals in which lactobacilli, especially *Lactobacillus crispatus*, are the dominant vaginal bacteria. There is a symbiosis between *L. crispatus* and vaginal epithelial cells, which possess toll-like receptors that respond defensively to pathogenic bacterial components. These cells produce glycogen to support the lactobacilli and allow them to maintain low vaginal pH by producing lactic acid as another defense. Intracellular Hsp70 levels were lowest when *L. crispatus* dominated the vaginal fluid as were extracellular Hsp70 levels in vaginal fluid. Marius Locke, from the University of Toronto, showed that estrogen deprivation affects the cell stress response in rat skeletal muscle. Mario Galignana from the University of Buenos Aires, Argentina, talked about how Hsp90 can interact with, and increase activity of TERT in breast tumors leading to oncogenic effects. Anais Aulas, from Harvard Medical School, reported cytoprotective effects of stress granules in cancer after chemotherapy, and Dimitra Bourboulia, from SUNY Upstate Medical University, NY, showed how Hsp90 can inhibit metalloproteinase activity. And this was just the first day!

The second day started with another engaging keynote lecture by Richard Morimoto, when he reminisced on his trajectory in demonstrating HSF1 as a key player in longevity. His findings on how the proteostasis network was really a major system and how disruption of protein folding could impact all development were published in articles in *Nature and Science*. *C. elegans* encodes 200 chaperones, but there was a core set of chaperones that was important for every biological process. It was not just about stress. His work with Lea Sistonen showed that SIRT1 deacetylase regulated HSF1, also a Science paper, and that proteostasis works well when you are sleeping and not eating. Senescence studies showed that HSF1 declined with age, and so did Hsp70. What was the relationship between biological and chronological senescence? Collapse of proteostasis of *C. elegans* indicates an important event of aging. Development requires HSF-1 and E2F to regulate a subnetwork of specific chaperones for anabolic metabolism; the HSF-1 network is the core system required for development. This is the same set of genes activated constitutively in cancer, allowing it to grow. Of these 20 chaperones, which ones are essential in each of these processes and which ones can be manipulated to revert disease? Can we map the activity of these core proteins in integrating signals from outside and inside of the cell and between tissues, organs, and systems in the body? Can you reset the system? Morimoto thinks we can.

Following the theme, a session on global regulatory networks of stress genes was next. Brian Freeman from the University of Illinois, USA, Akira Nakai, from Yamaguchi University in Japan, Ritwick Sawarkar, from the Max Planck Institute in Germany, and Anniina Vihervaara from Åbo Akademi University in Finland and Cornell University in the USA reported genome-wide studies on how stress-inducible chaperones coordinate transcription of key genes in different experimental systems. A major theme was that proteotoxic stress and genotoxic stress networks mutually affect each other. Anniina Vihervaara described findings made

with her colleagues that both common and distinctive features of chromatin architecture are responsible for orienting transcription at divergent regulatory elements. These features also effect genome-wide transcriptional priming of promoters and enhancers. Ritwick Sawarkar discussed a new regulatory layer in which Hsp90 uncouples phenotypic outcomes from individual genotypes.

The session was followed by a tribute to another pioneering CSSI member, Robert M. Tanguay. Tuesday, August 15, 2017, was proclaimed Robert M. Tanguay Day at the Congress by President Gabriella Santoro, who presented a proclamation to Robert (Supplementary Fig. 7). Robert has likely done more that any scientist in our field to personally spread interest and participation in the heat shock field. He has truly been the great ambassador of our field. During the presentations, William Currie described Robert's professional life as a Canadian scientist at the Université Laval in Québec and although Tangchun Wu, Robert's colleague and guide to China was unable to attend, he shared his experiences of "China: Enjoying with Robert" via commentary by William Currie and Larry Hightower. Carmen Garrido completed the session with a lovely tribute titled "Robert, Québec, France and the small heat shock proteins: "une histoire d'amour" featuring descriptions of Robert's trips to France and especially Paris where he spent sabbatical time in the laboratories of colleagues with his wife Nicole. Robert then presented some of his recent results about the small mitochondrial heat shock protein, DmHSP22, and their implications for mitochondrial homeostasis (Supplementary Fig. 8).

Later that night, after posters, two parallel sessions, one on oxidative/reductive stress, chaired by Michael Lynes from the University of Connecticut, and another on global regulatory networks of stress genes, chaired by Matthias Mayer from the University of Heidelberg, fueled discussions before dinner. Claudina Rodrigues-Pousada, ITQB, Portugal, opened the latter session by presenting biochemical evidence that the yeast regulatory protein Yap8 uses specific cysteine residues to sense the presence of arsenate in the cytosol. She also reported for the first time on the essential role of the Mediator complex in the transcriptional activation of ACR2 by Yap8. Jorma Palvimo, University of Eastern Finland, followed with the results of a genome-wide study of the role of SUMOylation on chromatin structure and transcriptional regulation. It was proposed that cell stress-triggered SUMOylation regulates pausing by RNA polymerase II whereas deSUMOylation alters the function of chromatin anchors responsible for the maintenance of chromatin loops and for the spatial organization of chromatin. Wolfgang Schumann from the University of Bayreuth discussed the heat shock stimulons of *Escherichia coli*, *Bacillus subtilis*, and *Streptomyces*, explaining why bacterial species organize their heat shock genes in different ways. He compared the two types of induction pathways employed by bacteria to induce their heat shock genes, sensing of denatured proteins by molecular chaperones, resulting in altered stability of transcriptional regulators, and secondary structure control of pre-existing and nascent mRNA by RNA thermometers to regulate translation. Matthias Mayer completed the session with a talk on the molecular mechanism of activation of HSF1. His group has shown previously that HSF1 directly senses temperature changes. They have now identified single amino acid replacement variants that are constitutively monomeric, dimeric, or trimeric. Analyses of their functions supported their hypothesis about temperature sensing by wild-type HSF1.

Michael Lynes opened the session on oxidative and reductive stress responses with a discussion about metallothionein (MT) as a pro-inflammatory agent with an anti-oxidant biochemistry. MT is now recognized as one of the most rapidly and highly induced proteins when cells are mounting defensive responses to oxidative stress. It is a regulator of both innate and adaptive immune activities. It shares the property with Hsp70 of being present both inside and outside of cells where it mediates chemotactic responses. This extracellular presence also includes activities as an antagonist of other chemokines. Thus, manipulation of MT levels may provide an approach to managing immune changes associated with cellular stress.

Anna-Liisa Levonen from the University of Eastern Finland concentrated her talk on the molecular mechanisms used to activate the redox-sensitive transcription factor Nrf2. In addition to inducing anti-oxidant and phase II genes to protect cells from oxidative stress, Nrf2 regulates pro-survival genes and pathways including proteasomal degradation and nutrient metabolism. Thus, it is poised to affect a range of diseases that involve inflammation and oxidative damage. Ivor Benjamin from the Medical College of Wisconsin followed with more about Nrf2. In humans, nuclear factor (erythroid-derived 2)-like 2 is encoded by the *NFE2L2* gene, so the human transcription factor is often called NFE2L2 instead of Nrf2. He summarized pioneering work by his group and others about the effects of the pleiotropic functions of NFE2L2 as a stress sensor and modulator of host defenses, especially during chronic cardiac proteotoxicity. Ivor pointed out that metabolic imbalances caused by reductive stress can be life-threatening and have been overlooked due in part to the emphasis on oxidative stress. A balance between oxidative and reductive processes is required to maintain cellular energy homeostasis. Like oxidative stress, reductive stress also activates the NFE2L2 pathway via increases in reactive oxygen species in cells. He emphasized the critical role of the complementary functions of transcriptional regulatory pathways that he identified as "key stress sensors" to augment constitutively expressed molecular chaperones and the inducible stress responses that occur in different cellular compartments including the nuclear/cytoplasmic compartment, the endoplasmic

reticulum, and the mitochondrion. These responses are aimed at restoring the cellular proteostasis network and also the complementary cellular energy homeostasis network. Larry Hightower gave this latter network a new, descriptive name during his presentation, calling it the caloristasis network and pointing to the overlapping nature of these two dominant sets of pathways. Essentially, all of the enzymatic reactions that use chemical energy, such as ATP and GTP, to maintain the very energy-demanding proteostasis network also belong to the caloristasis network.

Albena T. Dinkova-Kostova, University of Dundee, UK, continued this session with an update on small molecular activators of cellular stress responses, emphasizing the importance of the dose for on-target selectivity. She provided an excellent summary of the phase 2 response and the heat shock response as two essential parts of the mammalian stress response controlled by Nrf2 and HSF1, respectively. Her group has found unexpected flexibility in the sensing mechanism during the response of KEAP1, the main negative regulator of Nrf2, to inducers representing a range of potencies and selectivity. The least potent inducers were found to be the least selective as well, activating both Nrf2 and HSF1. These observations will affect the interpretation of the results of ongoing clinical trials employing several isothiocyanates and cyanoenones.

Anna Paszek from the Maria Sklodowska-Curie Institute Oncology Center in Poland closed the session with a summary of recent work on crosstalk mechanisms using time-lapse fluorescent microscopy of single cells. Her group investigated the effects of heat shock on NF-κB responses. Elevated temperature attenuated cytokine-induced NF-κB responses, resulting in unexpected responses of single cells. Anna emphasized that crosstalk behavior involving NF-κB is important for understanding chemoresistance and radioresistance to cancer treatments.

The last day was focused on protein aggregation and quality control and started with the keynote talk by Anne Bertolotti, from the MRC Laboratory of Molecular Biology, UK, reminding us how cells and organisms are normally resilient to disease-causing proteins and survive the threat of misfolded proteins up to a point. Unfortunately, these cellular defenses against misfolded proteins weaken with age, and this process is only accelerated by neurodegenerative diseases. Anne highlighted the importance of the ongoing research in our field in order to help patients survive the threat of misfolded proteins and to avoid protein quality control catastrophes. She also made a strong point that protein phosphatases are drug targets and selective inhibition of their subunits may have therapeutic potential for late-onset protein misfolding diseases. Her laboratory has identified a small molecule they named Sephin1, as it is a selective inhibitor of a holophosphatase. In mice, Sephin1 prevents two different neurodegenerative diseases and has no deleterious side effects. Their work demonstrates that phosphatases can be inhibited by targeting their regulatory subunits.

Next, Harm Kampinga presented the Ferruccio Ritossa Early Career Award to Serena Carra from the University of Modena, Italy (Supplementary Fig. 9). In amyotrophic lateral sclerosis (ALS) mouse models, in the presence of mutant proteins, HSPB8 is upregulated both in spinal cord and muscle. HSPB8 interacts with the HSP70 co-chaperone BAG3 and enhances the degradation of misfolded proteins. Serena showed that HSPB8 acts by facilitating autophagy and preventing misfolded protein accumulation. The talk was followed by a short session dedicated to the ER protein quality control mechanisms. Linda Hendershot from St. Jude Children's Research Hospital asked why the ER protein BiP has two nucleotide exchange factors (NEFs) and found that it was neither due to different tissue specificities nor distinct roles in folding, but rather that they performed unexpected functions. One of them, Sil1, facilitates the release of BiP from unfolded protein substrates, enabling the subsequent folding and transport of the protein. Mutated Sil1 leads to Marinesco-Sjögren syndrome, in which mutant proteins are particularly unstable and either form large aggregates in the ER or are rapidly degraded via the proteasome, leading to the multisystem disorder disease phenotype. Kazuhiro Nagata, from Kyoto Sangyo University, Japan, identified ERdj5 as a master regulator of ER calcium homeostasis, highlighting the relevance of cross talk among redox, Ca^{2+} and protein homeostasis in the ER. A surprising finding was that the reductive power needed by ERdj5 comes from nascent polypeptides entering the ER using the PDI/ERO1 system. This mechanism reveals a new link between the caloristasis and proteostasis networks.

The following sessions focused on the roles of molecular chaperones in proteostasis. Harm Kampinga, from the University of Groningen in the Netherlands, proposed the concept of Hsp70 as a machine driven by members of the DNAJ protein family. In his view, a DNAJ would recognize a motif that indicated aggregation, like polyQ. Hsp70 alone cannot prevent its aggregation, but with DNAJB6, at a 1:100 ratio, it can work even outside cells. Len Neckers, from the National Cancer Institute in Washington, DC, knowing that Hsp90 inhibitors block ATP binding/hydrolysis, inhibit chaperone function, and deplete oncogenic client proteins, asked why they are not effective in humans for anti-cancer therapy. In the presence of Hsp90 inhibitors, Hsp90 is dissociated from HSF1 that would be free to trimerize, but he finds no evidence of that, in contrast with Hsp70, which is found associated with HSF1. Instead, it is the HSP90 conformational state that identifies unique HSF1 interaction domains, and drug design needs to be improved. Kevin Morano, from the University of Texas Health Science Center at Houston, asked why Hsp70 would have so many NEFs (Hsp110, HspBP1, and BAG1). He presented evidence for a hierarchical functional

specificity of these NEFs in yeast. Heath Ecroyd, from the University of Wollongong in Australia, presented a new tool to study protein aggregation and the molecular chaperone action of heat shock proteins in cells based on flow cytometry, while Mehdi Mollapour, from SUNY Upstate Medical University, showed how the phosphatase PP5 regulates cell signaling and Hsp90 function depending on post-translational modifications.

Len Neckers chaired the Alfred Tissieres Young Investigator Award presented to Ayesha Murshid, from Harvard Medical School (Supplementary Fig. 10). Ayesha is investigating the role of extracellular Hsp90 (eHsp90) in removing beta-amyloid aggregates characteristic of Alzheimer's disease. She is focused on identifying the receptors for eHsps and their roles in the cross-presentation of antigens. She wants to understand the functions of eHsp90 in removing the beta-amyloid aggregates from cells. Ayesha presented evidence about an extracellular role for eHsp90 in removing beta-amyloid aggregates through autophagy, by a mechanism mediated by Nrf-2.

Session 10 titled "New Drugs and Therapeutic Interventions in Stress and Aging-related Disease" was chaired by Diana Toivola from Åbo Akademi University. M. Bishr Omary, from the University of Michigan, reported that over 70 human diseases are related to keratins and other intermediate filaments, one of them being K18 deficiency in liver. Hsps of the 70 kDa family associate with K8/K18 fibers via binding to K8, and parthenolide, a flower substance identified using a small molecule screening library, can mitigate this disease. Jane Trepel, from the National Cancer Institute, reported on the current clinical trials using Hsp inhibitors for cancer. Early uses of Hsp90 inhibitors like geldanamycin were shown to induce Hsp70, and this was initially used as a marker of response, but instead it turned out to be a marker of resistance. She also remarked that we now know that Hsp90 inhibitors sensitize for radiotherapy, but we need a better understanding of how Hsp90 works in order to optimize their use. Valérie Mezger, from the University of Paris Diderot, closed the session, pondering how the HSF pathway has both beneficial and detrimental effects in fetal brain development. She has found alcohol-induced specific heterotrimers of HSF1 and HSF2, and that HSF2 has a role in the deposition of epigenetic markers in fetal alcohol syndrome.

The last two sessions were held in parallel. Session 11 titled "Molecular Chaperones and Proteostasis (Part 2)" was chaired by William Currie from Dalhousie University in Nova Scotia, and session 12 titled "Molecular Chaperones in Development, Growth and Disease" was chaired by Antonio De Maio from the University of California San Diego. Gabriella Santoro from the University of Rome Tor Vergata opened session 11 with an update on work from her group about the molecular mechanisms that govern the nucleolar stress response. They have identified a new, non-classical Hsp, human NKRF (NF-κB repressing factor), as a nucleolar Hsp. It is essential for nucleolar homeostasis and cell survival during proteotoxic stress. NKRF transcription is controlled by HSF1. It is a thermosensor that translocates from the nucleolus to the nucleoplasm during heat stress. NKRF interacts with the 5′-to-3′ exoribonuclease XRN2 to control pre-rRNA cleavages and rRNA maturation and discarded rRNA degradation. Next, Michael Sherman from Boston University Medical School discussed his recent studies of the Hsp70-Bag3 complex in sensing proteotoxicity in mammalian cells. He found that this complex is an important signaling node that not only senses the accumulation of aberrant proteins, but also can trigger several pathways that control cell physiology including the process of aggresome formation in cells. The session ended with three short talks, the first one by Aileen Boshoff from Rhodes University in South Africa describing several Hsp70 escort proteins that regulate the mitochondrial Hsp70s. She focused on the Hep1 escort proteins that inhibit self-aggregation of mtHsp70. This is particularly important to understand in parasites for which mtHsp70 is essential for viability in the infected host cells and for which Hep1 could be used to target mtHsp70 inactivation. Henna Tyynismaa, from the University of Helsinki, discussed the roles of mitochondrial GRPEL proteins in cellular proteostasis. Using CRISPR technology in human cells and also knockout mice, she provided evidence that the mammalian GRPEL proteins may have overlapping and yet partly independent stress-related functions needed to fine-tune adaptation to changing environmental conditions. Alexey Moskovtsev from the Institute of General Pathology and Pathophysiology in Russia closed this session by presenting evidence that ER stress can trigger small RNome remodeling. This includes downregulation of miRNA biogenesis and upregulation of tiRNA, another class of small RNA which Alexey suggested to be a significant regulator of the ER stress response independent of transcriptional control.

Cristina Bonorino, from PUCR, Brazil, opened the last session of the Congress with evidence of immunosuppressive roles for DnaK of *Mycobacterium tuberculosis* in graft rejection, asthma, and sepsis models. These represent extracellular roles for Hsps that are released from cells to participate in intercellular communication as signaling molecules. Extracellular *M. tuberculosis* DnaK interacts with dendritic cells and macrophages resulting in the inhibition of T cell activation and thus causing immunosuppression. She pointed out that the mammalian Hsp70 does not have the same effects, due to differences in interaction with a receptor complex composed by Siglec-E and Lox-1. In a provocative talk entitled "Sex, Stress and Self or anti-Self," David Lawrence discussed differences in the responses of males and females to a variety of environmental stresses likely due to differences in male and female immune and neuroendocrine networks. He used differential responses to lead exposure as an example. It has been suggested that lead induces higher levels of oxidative stress in

females and a greater up-regulation of genes that respond to oxidative stress than in males in which elevated levels of proteolysis may occur. Higher estrogen levels may in part explain the female response. These differences in female and male responses to stress may ultimately affect longevity. Antonio De Maio next provided some exciting new information about the effects of extracellular Hsp70 (eHsp70) on A-beta-amyloid peptides in Alzheimer's disease. His group found that incubation of eHsp70 with A-beta-amyloid peptides dramatically altered the assembly process by blocking oligomer formation. In addition, the combination of eHsp70 and A-beta-amyloid peptides reduced the cytotoxicity of the peptides for cultured neuronal (N2A) cells. These data suggest a novel approach to reducing the detrimental effects of A-beta peptides in Alzheimer's disease. Kamal Moudgil from the University of Maryland School of Medicine closed the final session by sharing new data about the cytokine immune response against defined mycobacterial stress proteins during adjuvant arthritis in Lewis rats. These results from his group provide a new perspective on the role of newer cytokines such as IL-17, IL-27, IL-33, and IL-36 and T cell subsets such as Th17 and Treg in the pathogenesis of and therapeutic approaches to autoimmune arthritis.

The last keynote lecture was given by Peter Walter who summarized the unique regulatory mechanisms of the distinct arms of the ER stress pathways, collectively termed the Integrated Stress Responses. His presentation highlighted the importance of discovery science for understanding the structural and functional relationships between the key protein quality control mechanisms and development of inhibitors and activators of specific components of these pathways against detrimental human diseases, such as cancer, diabetes, and neurological disorders.

The meeting had a golden (and delightfully surprising) finale, when, before the banquet, all participants were treated to a lovely piano performance by a trio of young Finnish pianists at the Sibelius Museum. The playful and creative atmosphere was in agreement with all of the scientific sessions, full of *henki*, full of spirit, *täynnä henkeä*. We all look forward to the next meeting, in 2019, in San Diego, CA.

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