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Conference Report

Stop Aging Disease! ICAD 2014

Ilia Stambler

Department of Science, Technology and Society, Bar Ilan University, Ramat Gan, Israel

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ABSTRACT: On November 1-2, 2014, there took place in Beijing, China, the first International Conference on Aging and Disease (ICAD 2014) of the International Society on Aging and Disease (ISOAD). The conference participants presented a wide and exciting front of work dedicated to amelioration of aging-related conditions, ranging from regenerative medicine through developing geroprotective substances, elucidating a wide range of mechanisms of aging and aging-related diseases, from energy metabolism through genetics and immunomodulation to systems biology. The conference further emphasized the need to intensify and support research on aging and aging-related diseases to provide solutions for the urgent health challenges of the aging society.

Key words: aging, longevity, aging-related diseases, biogerontology, regenerative medicine, geroprotectors, health research policy, International Society on Aging and Disease (ISOAD)

The urgency of research of aging and aging-related diseases

On November 1-2, 2014, there took place in Beijing, China, the first International Conference on Aging and Disease (ICAD 2014) of the International Society on Aging and Disease (ISOAD). The primary stated goal of the International Society on Aging and Disease is "to improve the quality of lives through stimulating research into the association between aging and aged-related disease" [1]. The society's concise motto is simply: "Stop Aging Disease!" The conference made yet another step in advancing this goal by "fostering communication among researchers and practitioners working in a wide variety of scientific areas with a common interest in fighting aging and aged-related disease" [2].

The importance of those goals cannot be overestimated, and this importance was further emphasized in the conference resolution and in the position paper issued by the ISOAD following the conference [3,4]. As the resolution and the position paper state, the degenerative aging processes and related diseases are the gravest challenge to global public health. They cause the largest proportion of disability and mortality worldwide, and should be addressed with the urgency and effort corresponding to the severity of the problem. The weight of the problem of aging-related degeneration and the urgent need for solutions was acknowledged by the conference participants. Yet, beyond the description of the problem, the conference presented a wide array of strategies to tackle it. It emphasized the paramount strategy of connecting the study of aging and aging-related diseases, no longer just exclusively addressing individual diseases and symptoms, but relating them to their unifying determinative factors – the degenerative processes of ageing. And then a wide front of research directions and potential areas of intervention was presented. (The entire book of abstracts is available [5].)

***Correspondence should be addressed to:** Ilia Stambler, Department of Science, Technology and Society, Bar Ilan University, Ramat Gan 52900, Israel. Email: ilia.stambler@gmail.com

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Regenerative medicine

Probably one of the most promising ways to address the problem of age-related degeneration is by the use of regenerative therapy, repairing the failing structure and function of an aging organism, in particular using therapies based on stem cells and their products. (Of course immense technical difficulties and safety concerns yet need to be addressed.) In this area, the conference showcased formidable advances.

The tone was set by one of the chief conference organizers, Chair of the International Society on Aging and Disease and an Editor in Chief of the society's journal – *Aging and Disease* [6] – Dr. Kunlin Jin of the Department of Pharmacology and Neuroscience at the University of North Texas Health Science Center at Fort Worth, USA. His main area of study is adult neurogenesis and endogenous neuroprotective proteins, capable of restoring the brain function in response to ischemic injury, particularly in relation to aging. It has been rather conclusively shown that a promising therapeutic strategy for the treatment of neurodegenerative age-related brain diseases can be cell replacement using stem cells. Among the foremost lines of evidence, Dr. Jin first discovered that brain injuries, including those caused by stroke and age-related neurodegenerative diseases such as Alzheimer's disease, can stimulate stem cells to generate new neurons in rodents as well as in humans (contrary to the previously held dogma that nerve cells do not regenerate). Even more encouragingly, he showed that these neural stem cells can be manipulated by growth factors, such as FGF-2, EGF, VEGF and SCF, even after intranasal administration. Those findings strengthen the grounds for using cell-based regenerative medicine to ameliorate aging-related degeneration.

During the conference, Dr. Jin, together with his collaborators, in particular from Wenzhou Medical University, China, showcased several additional lines of advancement in regenerative medicine. Thus, together with Dr. Peng Wang and others of the Department of Neurosurgery, Wenzhou Medical University, they reported findings on a *reversal* of focal cerebral ischemia-induced neurological deficits in aged rats by administration of young blood plasma. And together with Dr. Hongxia Zhang and others of the Zhejiang Provincial Key Laboratory of Aging and Neurological Disorder Research, Wenzhou Medical University, they further tested the potential therapeutic mechanism of transplantation of human neural stem cells (hNSCs) as a regenerative cell replacement therapy for neurodegenerative diseases. The therapeutic mechanism likely involves hNSC-induced modulation of immune cells or "cross talk" between the stem cells and immune cells. Thus, the addition of hNSCs increased the proportion of regulatory T cells (Tregs), reduced pro-inflammatory cytokines and increased anti-inflammatory cytokines, whereas in turn peripheral blood mononuclear cells (PBMCs) helped to significantly promote the proliferation and differentiation of hNSCs. In another study, together with Dr. Jiangnan Hu, Dr. Qichuan Zhuge and others, they found that the cell death inhibiting calpain inhibitor MDL28170 could improve the functional recovery after traumatic brain injury via increasing the number of surviving transplanted neural stem cells. Yet another study, together with Dr. Lijie Huang, Dr. Qichuan Zhuge and others, related to nanomedicine. The group investigated nanoparticle-based thrombolysis as a treatment for stroke, investigating the efficacy of targeted thrombolysis using recombinant tissue plasminogen activator (rtPA). The clot-breaking rtPA was covalently bound to magnetic nanoparticle (MNP) and retained to the target site by an external magnet. They found that polyacrylic-acid-coated magnetic targeted nanoparticles, combined with the plasminogen activator, could reduce infarction area in brain stroke. This approach may achieve feasible and effective treatment against embolic cerebral ischemia, in fact against a variety of blood flow obstructions so prevalent in aging.

Further breakthrough directions of regenerative stem cell research were reported at the conference. Thus, Dr. Chun-Li Zhang of the Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center at Dallas, USA, revealed a brand new strategy to regenerate the damaged and age-degenerated central nervous system. The technique creates functional neurons through reprogramming the reactive glial cells (the main component of brain scar tissue produced by degenerative damage as well as by acute brain injury). In this way, a patient's own cells can be used for regenerative medicine without the need for cell transplantation. Briefly, reactive astrocytes, a major cell type forming the glial scar, were converted to functional neurons by inducing lentivirus-mediated gene expression under the human GFAP promoter. The results showed that the transcription factor SOX2 alone could induce the appearance of neuroblasts (neuronal precursors) within the adult or even aged mouse brain striatum. The induced neuroblasts become functionally mature and integrated when additional signaling molecules, such as brain-derived neurotrophic factor (BDNF), BDNF/Noggin, or valproic acid (VPA), were applied.

Further development of direct cell reprogramming technology for the cell-based treatment of neurodegenerative diseases (specifically Alzheimer's disease) has been reported by Dr. Jialin Zheng of the Laboratory of Neuroimmunology and Regenerative Therapy of the University of Nebraska Medical Center,

Omaha, USA. His group achieved a direct conversion of somatic cells from one cell type to another by ectopic expression of specifically defined transcription factors. Nine candidate transcription factors – Pou3f2 (Brn2), Nr2e1 (TLX), Sox2, Gli2, Myc, Klf4, Bmi1, Hes1, and Hes5 – demonstrated the ability to directly convert fibroblasts into Neural Progenitor Cells (NPCs). Some of their combinations could directly convert adult dermal fibroblasts into induced NPC-like cells, (iNPC) which exhibited the same properties as primary NPCs, including proliferation, self-renewal and differentiation.

The presentation of Dr. Zhiguo Chen of the Cell Therapy Center, Xuanwu Hospital, Capital Medical University, Beijing, China, further strengthened the hope for using cell reprogramming technologies to produce regenerative cell therapy for Parkinson's disease. As he demonstrated, recent advances in cell reprogramming technologies, using plasmid induction vectors encoding for particular transcription factors within the cell, may provide an alternative for the previously unsuccessful Parkinson's disease cell therapy that employed fetal ventral mesencephalon (fVM) tissues. The new techniques using induced pluripotent stem cells (iPSCs) and induced neural stem cells (iNSCs) show promise for generating clinical grade dopaminergic (DA) neural cells that are safe, homogeneous, scalable and standardizable, thus renewing the hope to soon bring back clinical trials using cell therapy for Parkinson's disease.

Further, to facilitate stem cell therapy for neurodegenerative diseases, Dr. Joanne Conover of the Center for Regenerative Biology, University of Connecticut, in Storrs, USA, reported on maintaining adult neurogenic stem cell niches or environments of the brain favorable for stem cell populations, neurogenesis and regenerative repair. She pointed to the lateral walls of the lateral ventricles of the adult rodent brain as a stem cell niche capable of an array of regenerative and reparative functions that persist throughout adulthood, as a proof of feasibility. Yet, utilization of such niches for human regenerative medicine will yet require much work to overcome current technical limitations, including dissimilarities between animal and human models.

Stem cell therapy can be potentially useful for an array of aging-related diseases, including vascular diseases. Thus, Dr. Guo-Yuan Yang of Med-X Research Institute and School of Biomedical Engineering, at Shanghai Jiao Tong University, Shanghai, China, explored the therapeutic mechanism of endothelial progenitor cell (EPC) transplantation for ischemic stroke. They found evidence that the brain remodeling and repair by transplanted EPCs is promoted by high expression of the damage-associated molecular-pattern (DAMP) mediator called astrocytic-high mobility group box1 (HMGB1), maintaining DNA stability. In ischemic stroke, at the initial acute stage, HMGB1 involved an inflammatory response, yet at a later stage promoted blood vessels formation (angiogenesis). The study concluded that patient-specific peripheral blood-derived endothelial progenitor cells are an ideal source of stem cells for the ischemic stroke treatment, and that the therapeutic mechanism of exogenous (transplanted) EPCs is associated with paracrine secretion function of the EPCs.

As a summary, Dr. Zhong Chao Han of the Beijing Institute of Hematology, Chinese Academy of Medical Sciences, further emphasized the possibility of using stem cells as currently one of the most promising strategies for the struggle with debilitating aging processes and associated diseases. He emphasized the fundamental nature of aging as a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. Several hallmarks represent common denominators of aging and aging-related diseases in different organisms, including cellular senescence and stem cell exhaustion. Therefore, stem-cell based replacement therapies represent a pivotal anti-aging strategy as well as a crucial strategy against the spread of non-communicable diseases. Yet, this strategy should be combined with other strategies, including pharmacological means and Information and Communication Technologies, in a holistic and population-wide framework.

Geroprotective substances. Modulation of energy metabolism

Further lines of attack concerned pharmacological geroprotective substances. Very promising results were reported by Dr. James W. Simpkins, from the Center for Basic and Translational Stroke Research, West Virginia University, Morgantown, USA, for the use of low-dose non-feminizing estrogen as a geroprotective and neuroprotective substance. The positive effects were shown in experimental models for stroke, traumatic brain injury and Alzheimer's disease. The study provided evidence for several potential protective mechanisms, suggesting estrogen as a potential multi-targeted therapy in a single molecule. The phenolic A ring of estrogen appeared to be an essential element for the neuroprotection. Some of the proposed protective mechanisms included inhibition of lipid peroxidation, neutralizing reactive oxygen species and activating a number of anti-apoptotic signaling pathways. An additional potent neuroprotective mechanism may be via the preservation of brain energy metabolism by preventing the mitochondrial toxicity effects of Amyloid Beta (Aβ) aggregates. A drug discovery program has been underway to develop estrogen into a safe and effective

therapy for a number of acute neuronal compromising conditions, as well as several neurodegenerative diseases, and potentially even as a general neuroprotective, geroprotective and lifespan-extending therapy.

Yet hormone modulation for anti-aging is multifaceted, and can be a double-edged sword. This was made clear by the presentation of Dr. Holly M. Brown-Borg of the University of North Dakota School of Medicine and Health Sciences, at Grand Forks, USA. She reported findings from genetically engineered mice with hereditary dwarfism (Ames' dwarf mice) and growth hormone (GH) deficiency who exhibit delayed aging. Such mice live more than a year longer than normal siblings (50-70% increase in lifespan) due to differences in antioxidant defense capacity, lower DNA damage and altered energy metabolism. Dr. Brown-Borg's group studied the effects of Growth Hormone on the metabolism of methionine (a sulfur-containing proteinogenic amino acid) and aging. They observed that long-living GH signaling deficient (Ames, GHRKO) mice were not able to discriminate differences in dietary methionine in terms of lifespan. In contrast, GH-elevated short-living transgenic mice and the wild type mice from each line lived longer when fed methionine-restricted but not methionine-supplemented diets. Among other findings, evaluation of the DNA methylation data set suggested that the Ames mice maintain their epigenome better (from young to old) than wild type mice, supporting the hypothesis that epigenetic stability contributes to longevity. Dr. Brown-Borg emphasized that Growth Hormone is often promoted and sold as an 'anti-aging' factor. Yet, in fact, it suppresses antioxidative enzymes, lowers defense mechanisms, alters DNA methylation and is associated with a shorter lifespan.

Several other potential geroprotective substances were suggested to act through protection of energy metabolism. Among others, this was suggested by Dr. Shaohua Yang of the Department of Pharmacology and Neuroscience, University of North Texas Health Science Center at Fort Worth, Texas, USA. While decreased energy metabolism is the hallmark of neurodegenerative diseases, cancers are characterized by a switch of respiration metabolism from the highly efficient oxidative phosphorylation to the low efficient aerobic glycolysis pathway, the latter conducive to biosynthesis and cell proliferation (the Warburg effect). Dr. Yang's group offered a strategy to combat both age-related phenomena. They found that the heterocyclic aromatic compound Methylene Blue (MD), a century old drug, modified the mode of metabolism. They found that the drug can affect the respiratory chain, by receiving an electron from NADH in the presence of Complex I and donating it to Cytochrome C. Thus, it can provide an alternative pathway for electron transfer, enhancing oxidative phosphorylation. Apparently thanks to this mechanism, Methylene Blue was shown to increase oxygen consumption, decrease glycolysis, and increase glucose uptake in vitro. In vivo, it enhanced glucose uptake and regional cerebral blood flow in rats upon acute treatment, and provided protective effects for neurons and astrocytes against various insults in rodent models of Parkinson's disease and ischemic stroke. In glioblastoma cancers, Methylene Blue reversed the Warburg effect by enhancing mitochondrial oxidative phosphorylation and inhibiting lactate production, and was capable of arresting the glioma cell cycle. This research provided a proof of concept that enhancement of mitochondrial oxidative phosphorylation can offer protective action against neurodegenerative diseases and inhibit glioblastoma proliferation, and may potentially serve as a general geroprotective treatment improving respiration and metabolism.

Yet another intervention into mitochondria metabolism was studied by Dr. Hong-Seob So of the Center for Metabolic Function Regulation at Wonkwang University School of Medicine, in South Korea. Their method of preventing age-related hearing loss (which may perhaps be generalized to other forms of age-related degeneration) involved the pharmacological modulation of NAD+/NADH ratio that plays a determinative role in the respiratory chain. Recent findings suggest that a disturbance (often decrease) of intracellular NAD+ levels is clinically related to the progression of age-associated disorders. Therefore, maintenance of optimal intracellular NAD+ levels (NAD+ also serving as a substrate for some longevity-associated maintenance enzymes, such as the histone-deacetylating Sirtuins) may be a critical factor for preventing cellular senescence, and thus for the understanding, prevention and treatment of Acute Age-Related Hearing Loss (ARHL), as well as other age-related diseases. The study provided evidence that a decline in the Sirtuins (SIRT1 and SIRT3) levels aggravated the hearing loss by increasing acetylation (activation) of the inflammation-related factor NF-kB and of the tumor suppressor protein p53. This suggested that the age-related hearing loss may occur through the induction of inflammatory responses and oxidative stress as well as the mitochondrial dysfunctions, leading to apoptotic cell death in cochlear tissues. Dr. So's group presented pharmacological strategies for restoring NAD+ levels and thus affecting NAD+-dependent cellular pathways. The therapies target specific components of the respiratory chain, for example using the naphthoquinone drug β-lapachone, which targets the proton-translocating NADH-quinone oxidoreductase (NQO1).

A number of other presentations considered the improvement of energy metabolism, protective and anti-aging effects, conferred by enhanced Sirtuin expression.

A well acknowledged stimulant of Sirtuin (SIRT) expression is Resveratrol, a natural polyphenolic compound, among other sources found in red wine. Its effects were the subject of the presentation by Dr. Ashok K. Shetty of the Institute for Regenerative Medicine, Texas A&M Health Science Center College of Medicine, at Temple, USA. The presentation proposed that Resveratrol, due to its ability for up-regulating SIRT1 (an acknowledged longevity gene important for cognitive function and synaptic plasticity) and suppressing inflammation, appears to be ideal for easing neurodegenerative age-related changes, among others counteracting age-related memory impairment. The healing effects were specifically evaluated in the hippocampus area of the brain, which is chiefly responsible for the memory function. These effects were tested in rats. Dr. Shetty's group found that rats receiving Resveratrol exhibited increased neurogenesis and enhanced expression of genes vital for learning and memory function, such as SIRT1, FOXO3 (a substrate of SIRT1 believed to promote cell longevity and healthy aging), CREB1 (a regulator of neuronal survival, learning and consolidation of memory) and PRKACA (cAMP-dependent protein kinase catalytic subunit alpha, important for many cellular functions including memory). Resveratrol treatment also enhanced the expression of genes encoding neurotrophic factors (NF) important for neurogenesis and memory (FGF-2, NGF, VEGF and CNTF), a synaptic protein (Synaptotagmin V) and a neuropeptide (Neuropeptide Y). Moreover, Resveratrol treatment reduced the expression of MAPK1 (an Alzheimer disease associated gene that induces hyper-phosphorylation of tau protein) and increased the expression of IL10 (an anti-inflammatory cytokine), as well as decreased the concentration of pro-inflammatory cytokines (IL-1b and TNF-a) in the hippocampus of Resveratrol-treated animals. These common beneficial anti-aging effects provided novel evidence that Resveratrol treatment in late middle age can be efficacious for neuroprotection and prevention of memory dysfunction in old age.

Further benefits of Resveratrol were indicated by Dr. Raghavan Raju of the Departments of Laboratory Science, Surgery, and Biochemistry and Molecular Biology of Georgia Regents University, in Augusta, Georgia, USA. Dr. Raju again emphasized the crucial ability of aging to increase predisposition to critical illness and its role as an independent and strong risk factor for mortality in critically ill patients. Declining energy supply function of the mitochondria plays a fundamental part in both aging and critical illnesses. Using their custom-made mitochondrial gene chip (RoMitochip), Dr. Raju's group identified alterations of a number of genes related to cellular energetics, following trauma-hemorrhage (T-H) in 6 and 22 month old rats. In aged rats, there was a decline in the number and amplitude of expression of mitochondria-related genes, compared to the younger rats, following T-H. In particular, the study registered a decline in Sirtuin 1 expression upon trauma-hemorrhage, which identified SIRT1 as a potential molecular target in this condition. Activation of SIRT1 was accomplished by Resveratrol administration (which increases SIRT1 affinity for both NAD^+ and the acetylated substrate), leading to a significant improvement of clinical status, such as improvements in left ventricular function. In rats subjected to T-H, Resveratrol treatment restored the expression of SIRT1, Pgc-1 and c-Myc proteins, as compared to vehicle treated group subjected to T-H. The authors concluded that modulation of mitochondrial function by SIRT1 activation may have beneficial effects in reducing cardiovascular functional decline following hemorrhagic injury, especially vital for the resuscitation of a traumatized aging organism.

Dr. Rui-Hong Wang of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), of the National Institutes of Health (NIH), at Bethesda, Maryland, USA, too believes that disruption of cellular energy metabolism is a common path for age-related diseases and that Sirtuin enzymes (in particular SIRT1) are the key mediators of the metabolism, positioned at the crossroad of cancer, metabolism and aging. Using SIRT1 as a model molecule, Dr. Wang's group has generated SIRT1 knockout and transgenic mouse models in multiple organs, and discovered that SIRT1 is a tumor suppressor and regulates glucose production and beta cell development. Its suppression led to hyperglycemia, fatty liver, type 2 diabetes, carcinomas and lymphomas, disruption of the circadian clock, and premature aging phenotype. This provided further evidence that utilization of SIRT1 stimulating agonists (such as Resveratrol and its analogs) might generate considerable clinical benefits for the aged. The importance of optimal energy metabolism, and the role of Sirtuins, was yet again stressed by Dr. Nannan Zhang's group of the MOE Key Laboratory of Protein Sciences, School of Medicine, Tsinghua University, Beijing, China, who demonstrated that calorie restriction can delay renal senescence through a SIRT6 mediated signaling pathway.

Another potential healthspan-extending medication was studied by Dr. Yuehua Wei of No.3 People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China. His presentation clarified the mechanism for the life-prolonging effects of Calorie Restriction (CR) and CR-mimetic immunosuppressant drug Rapamycin. Dr. Wei's group found that Maf1, a protein involved in transfer-RNA synthesis, is required for the life-extending effects of Calorie Restriction and of the inhibition of Molecular Target of Rapamycin (mTOR – a serine/

threonine protein kinase) complex 1 (mTORC1). Here too mitochondria energy metabolism was found to play a crucial part. mTORC1 inhibition by Rapamycin induces mitochondrial hyper-fusion, up-regulation of mitochondrial antioxidant enzymes and enhanced respiration, all of which were found to be dependent on Maf1. Dr. Wei's analysis suggested that transfer-RNAs may play a key role in mediating Maf1's life-prolonging effects. It was suggested that, in response to Calorie Restriction, Maf1 acts as a key activator of mitochondrial stress response to promote longevity.

Rapamycin was also the focus of Dr. Veronica Galvan of the Barshop Institute for Longevity and Aging Studies, at the University of Texas Health Science Center at San Antonio, USA. Her group showed that chronic treatment with the target-of-rapamycin (TOR) inhibitor rapamycin, a drug that was generally found to extend lifespan and delay aging in mice, was also effective against particular aging-related diseases, such as Alzheimer's disease. The drug was found capable of halting and even reversing Alzheimer's disease (AD)-like memory deficits and reducing Amyloid Beta (Aβ) accumulation – a hallmark of Alzheimer's disease, in brains of hAPP(J20) mice modeling the condition. Potential therapeutic mechanisms likely included improvements of protein homeostasis (proteostasis) via enhanced elimination of Amyloid Beta by autophagy and chaperone protein regulation response. Moreover, the attenuating TOR activity restored cerebral blood flow (CBF) and vascular density (VD) via activating Reactive Nitrogen Species (RNS/NO) signaling by Nitric Oxide Synthase (eNOS) activation in brain vascular endothelium. Rapamycin also reduced Cerebral Amyloid Angiopathy (CAA) and micro-hemorrhages, and reestablished blood-brain barrier integrity in brains of hAPP(J20) mice. Furthermore, reducing TOR activity was able to restore cognitive function, CBF and VD, in mice modeling atherosclerosis, as well as in aged rats, in which reduced TOR activity was associated with complete recovery of cortical network activation and functional hyperemia evoked by somatosensory stimulation. Thus, the mechanisms by which TOR attenuation restores cerebral blood flow (vasodilation) may be common to different models of age-associated neurological diseases and to brain aging generally.

Another suggested way to affect energy metabolism to provide therapeutic benefits may be by measured use of alcohol (ethanol). This was proposed for stroke by Dr. Yuchuan Ding of the Department of Neurological Surgery, Wayne State University School of Medicine, in Detroit, Michigan, USA. Rather than enhancing the respiratory and metabolic function, the use of ethanol actually decreases brain energy metabolism, protecting the impaired brain from energy "overdrive". The neuroprotective mechanisms of ethanol may involve: reducing hyperglycolysis, lactic acidosis and thus reducing Reactive Oxygen Species (ROS) generation (possibly through down-regulating the expression of glucose transporter GLUT1/3 and Phosphofructokinase enzymes), reducing Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase (NOX) activity and protein expression, which ameliorates ROS generation, diminishing hyperactivity of mitochondrial enzyme (cytochrome c oxidase). Thus it can be considered as a form of "Hibernation Therapy" (there may be other forms of Hibernation Therapy, such as hypothermia induction) for the protection of age-impaired tissues.

More strategies were related to manipulating the reductive-oxidative metabolism of the aging organism. Those were explored by Dr. Sasanka Chakrabarti of the Department of Biochemistry, Institute of Post-graduate Medical Education and Research, in Kolkata, India. He again emphasized the crucial connection and commonality between aging and aging-related disease, while using the aging brain as a model for Alzheimer's disease (AD). He pointed out that the current Alzheimer's disease research is largely dominated by a restrictively "genetic" approach, commonly employing AD transgenic models to explore single or multiple mutations of human familial AD-related genes. Rather, the disease should be considered as a complex of *gene-environment* interactions. In line with this vision, it appears a promising strategy to manipulate the aging brain internal milieu to improve its metabolism, including amyloid beta (Aβ) aggregation, mitochondrial function and redox status. Dr. Chakrabarti's group found that iron was accumulated in aged rat brain compared to that in the brain of young animals, presumably as a result of over-expression of transferrin receptor and ferritin, concomitant with an accumulation of Amyloid Precursor Protein (APP) and Aβ42. Yet the application of the iron-binding chelator, deferasirox, regularly with the diet, was able to reverse most of the age-dependent changes in iron and amyloid beta metabolism in the brain. Additional positive results were produced by an anti-oxidant cocktail, including N-acetyl cysteine, α-tocopherol and α–lipoic, reducing amyloid formation and its toxic effects on the mitochondria (such as impaired mitochondria integrity, membrane depolarization, reduced phosphate utilization and ATP synthesis, and Cytochrome C release). These findings furnished further proofs of the principle that by pharmacological interventions into the metabolism of aging, it may be possible to arrest aging-related diseases.

A series of other potential anti-aging and life-extending substances have been studied by Dr. Kyung-Jin Min of the Department of Biological Sciences, Inha University, South Korea. The substances formerly studied included curcumin, D-chiro-inositol and mistletoe

extracts. In the current presentation, Dr. Min focused on the anti-aging and lifespan-extending effects of Ginseng Berries extracts (compared to the commonly used Ginseng Root extracts) in Drosophila flies and C. Elegans worms. The study found that both root and fruit extracts extended the lifespan of the flies and the worms at least 10%. The ginseng berry extract proved more effective for life-extension in the flies than the root extract. The active component of lifespan extension by ginseng berry appeared to be the polyphenol syringaresinol, possibly acting via up-regulation of Sirtuin expression (improving energy metabolism). The presentation concluded: "The Fountain of Youth – Have We Found It? Yes! Eat less, drink wine and eat ginseng!" But still let us keep on searching!

Finding and eliminating sources of damage

Of course it is not just important to find and apply life-extending means, but also to avoid life-shortening ones. One among many substances that can exacerbate aging and should be guarded against is endogenous formaldehyde. This was the theme of Dr. Rongqiao He of the State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, in Beijing. The accumulation of endogenous formaldehyde with aging was associated with age-related cognitive impairment, presumably through inducing metabolic response and abnormal modifications of cellular proteins such as hyperphosphorylation of Tau protein in particular of nucleus Tau. This was shown in senescence-accelerated mice. Interestingly, epidemiological investigation of the human population showed that the intrinsic formaldehyde level of aging people (over 65 years old) is closely related with their education levels, namely the illiterate persons have high concentrations of intrinsic formaldehyde, but those with high education (more than 12 years) have relatively low concentrations. This may suggest improving education and brain activity as a means to combat age-related formaldehyde accumulation and related cognitive decline, alongside possible chemical means of formaldehyde elimination.

As the famous Paracelsian dictum states, "All things are poison and there is nothing without poison; only the dose makes that a thing is not a poison" or in short "the dose makes the poison" [7]. A presentation from Dr. Kyung Jin Min's group (together with Dr. Woong Seo and others) exemplified this principle. They showed that a common artificial seasoning, the L-glutamic acid (monosodium glutamate, MSG) decreases lifespan in *Drosophila melanogaster* flies in a dose and life-stage dependent manner.

Further Dr. Yulin Deng, of the School of Life Science, Beijing Institute of Technology, China, suggested that endogenous neurotoxins, Salsolinol- and N-methyl-salsolinol, are likely important factors in α-synuclein protein aggregation (a hallmark of neurodegeneration, prominent in Parkinson's disease), and thus possibly cause a vicious circle eventually leading to cell death and neurodegeneration. Though seemingly not directly proposing therapeutic strategies, the presentation nonetheless pinpointed several important sources of degenerative damage and thus opened a way for potential future interventions.

The question of toxicity is really a question of excess over optimal balanced values. This was the subject of the presentation published by Dr. Elena Lugovaya's group, of the Scientific Research Center "Arktika" of the Russian Academy of Sciences, at Magadan, Russia. They discussed the role of microelement balance in aging. Is aging a consequence of age-related deterioration of mineral metabolism (impaired absorption of essential elements, slow elimination and accumulation of toxic elements), or is the imbalance of a microelements' status of an aging person one of the side effects of programmed diseases of aging? In any case, the level and interaction of certain microelements in the human organism can be a clear indicator of personal health or predisposition to pathology in old age. The debilitating effects could be ameliorated either by removing excess elements by stimulating elimination processes – though these are generally difficult to manipulate; or replenishing deficient elements through supplementation – though establishing therapeutic thresholds for microelements homeostasis and avoiding overdoses is key.

The importance of metal homeostasis in aging and aging-related diseases (such as Alzheimer's) was further emphasized in the presentation of Dr. Xiangshi Tan of the Institute of Biomedical Sciences and Department of Chemistry, Fudan University, Shanghai, China. Dr. Tan's group investigates aberrant metal homeostasis as a potential inducer of Alzheimer's disease, with special reference to transitional metal homeostasis of copper, zinc and iron, regulated by related proteins: amyloid beta, amyloid precursor protein, and metallothionein-III. Their findings highlighted metabolic changes, involving metal-protein interaction, of the anterior and posterior cingulate brain cortices with age, which could be compensatory to an increased energy demand coupled with lower cerebral blood supply.

As the reports generally indicated, nutritional imbalances and toxicities (including microelements) can be associated with degenerative aging and aging-related diseases, including neurodegeneration and arteriosclerosis. Yet, restoring the balance through appropriate diet or chemical means of elimination or supplementation could be curative.

Continued search for geroprotective substances. The proteomics and genomics approaches

It may be noticed that the majority of therapeutic approaches presented at the conference involved various means of manipulating the energy metabolism of the aging organism. Yet, there were several exceptions that predominantly used genomics and proteomics approaches to identify potential targets for intervention. The omics approaches are of course related to the modification of energy metabolism (through identifying the expression of particular genes and proteins involved in the energy metabolism), yet there is a difference of emphasis.

Thus Dr. Y-h. Taguchi of the Department of Physics, Chuo University, Tokyo, Japan, explored the role of aberrant expression of microRNA according to aging in hepatocarcinogenesis. His group conducted a large cohort study that determined that aging was a strong risk factor for liver cancer development (hepatocarcinogenesis) regardless of the stage of liver fibrosis. Several microRNAs (miRNA – short non-coding RNAs that serve as post-translational regulators of gene expression via binding to messenger-RNA – mRNA) emerged as potentially coordinating multiple pathways during aging. Using microarray technology, Dr. Taguchi's group compared hepatic miRNA and mRNA expression profiles between chronic hepatitis C (CHC) and hepatocellular carcinoma (HCC) patients in order to elucidate the difference in the carcinogenetic mechanism according to age. The study identified 13 miRNAs in which p-value (HCC>CHC: miRNA) and p-value (HCC>CHC: mRNA) have negative correlation (the negative correlation is expected insofar as miRNA normally suppress mRNA expression). The bottom p-values of these miRNAs and the top p-values of their target genes (mRNA) appeared at 60 years of age. As Dr. Taguchi described, many cancer-related pathways are enriched by the target genes of the identified 13 miRNAs. In particular, the study identified the significance of 515-3p miRNA and its target gene Cyclin-dependent kinase inhibitor 1A (CDKN1A) for hepatocarcinogenesis. These findings suggested the 13 microRNAs as potential therapeutic targets (for example, using miRNA transfection to regulate the expression of cancer-related target genes). The study also emphasized that the microRNA expression varied with aging, and participated in cancer development in an age-dependent manner.

Even the identification of a single active gene or protein can be determinative for the course and therapy of an age-related disease. As shown by Dr. Nadiya Kazachkova of the Institute for Molecular and Cell Biology (IBMC), at the University of Porto, in Portugal, the variation in the autophagic Beclin-1 (*BECN1*) protein has a potential to modify the onset of the hereditary neurodegenerative Machado-Joseph disease (MJD/SCA3). This is a late-manifesting dominant progressive polyglutamine spinocerebellar ataxia, caused by a Cytosine-Adenosine-Guanine (CAG) tract expansion in the *ATXN3* gene, resulting in abnormal protein accumulation. Autophagy, as a process of lysosomal-dependent intracellular components degradation, can be especially important for such disorders characterized by the accumulation of a mutant protein. Beclin 1 is one of the autophagy-related proteins, whose increase at the site of injury represents enhanced elimination needed to discard injured cells and reduce damage to cells by disposing of injured components, thus exerting neuroprotective effects. Conversely, defects in Beclin 1 were found to be correlated with neurodegenerative diseases. As Dr. Kazachkova described, in the *BECN1* promoter, four previously identified variants (rs60221525, rs116943570, rs34882610 and rs34037822) and one novel variant (c.-933delG) were found in MJD patients and in controls. *BECN1* expression levels were in agreement with the *in silico* predictions, showing decreased and increased expression for rs60221525 and rs116943570 variants, respectively. The variation found in the *BECN1* promoter can modulate the Beclin 1 expression and thus has a potential to improve autophagy and to postpone the age of onset of the disease. Some therapeutic strategies may include induction of Beclin 1 expression or even direct injection of Beclin 1 to stimulate autophagy and neuroprotection.

Protein interactions of particular sub-systems were considered. Thus, Dr. Yukihiro Ohno of the Laboratory of Pharmacology, Osaka University of Pharmacological Sciences, Japan, presented new insights into the therapeutic role of the serotonin-containing (serotonergic) system in Parkinson's disease. While the serotonergic nervous system plays crucial roles in regulating psycho-emotional, cognitive, sensory-motor and autonomic functions, it is now known that multiple serotonin (5-HT) receptors regulate extrapyramidal motor functions, that are particularly impaired in Parkinson's disease and aging. Specifically, stimulation of 5-HT_{1A} receptors and blockade of $5\text{-HT}_{2A/2C}$, 5-HT_{3}, or 5-HT_{6} receptors was shown to improve abnormalities of extrapyramidal motor functions. This recommended 5-HT_{1A} receptors as a novel therapeutic target for the treatment of Parkinson's disease. Indeed, 5-HT_{1A} stimulating agonists could improve the various motor disorders associated with dopaminergic deficits, dyskinesia induced by chronic L-DOPA treatment, mood disturbances (anxiety and depression) and dopamine agonist-induced emesis and cognitive impairment, in aged and Parkinson's patients.

In another proteomic study, Dr. K. Krishna Sharma of the Departments of Ophthalmology and Biochemistry,

School of Medicine, University of Missouri, Columbia, USA, explored the role of small heat-shock proteins in lens aging and cataract (these mechanisms could also be generalized to other manifestations of aging). As Dr. Sharma related, Alpha-crystallin (α-crystallin), belonging to the small heat shock protein family, is the major protein in the lens. Its chaperone protein regulation activity is responsible for maintaining lens transparency. Dr. Sharma tested the hypothesis that, following α-crystallin breakdown and fragmentation, α-crystallin-derived peptides interact with lens crystallins (native and modified by age-related reactions) and the resulting complexes clump together to form light scattering aggregates, which are the hallmarks of cataract lenses. Analysis of the cataract lenses showed that specific peptides (αA66-80 peptide and its truncated forms) associate with water-insoluble proteins fraction, are pro-apoptotic and generate H_2O_2 in the presence of metal ions. Furthermore, it was demonstrated that the αA66-80 peptide interaction with α-crystallin diminishes the chaperone activity of the latter. The preformed complexes of α-crystallin and αA66-80 attract additional crystallin molecules to form light scattering aggregates, thus confirming the hypothesis. Dissolving or preventing the formation of such aggregates can be a powerful line for future therapeutic research to maintain proteostasis and find cures not just to cataract but to a host of other age-related conditions characterized by protein aggregation.

The effectiveness of DNA repair also plays a vital role in aging. Dr. Pei-Chang Wang, of the Medical Laboratory Department, Xuanwu Hospital, Capital Medical University, Beijing, China, explored the changes and function of DNA polymerase δ (DNA polδ), which is responsible for the replication of DNA and DNA damage repair. He suggested that those changes could be among the key determinants of aging. Dr. Wang's group found that the expression of DNA polδ1, both with reference to mRNA and protein, decreased substantially with replicative senescence, which was demonstrated in human lymphocytes at different age stages. Silencing of polδ1 clearly increased the extent of DNA damage, while over-expression of polδ1 mildly protected against oxidative DNA damage, even though there was no statistical significance. These findings suggested that DNA polδ1 may be a potential biomarker of aging, playing an important role in replicative senescence, and may offer yet another therapeutic target designed to enhance the DNA-repair function.

Indeed, the epitome of the genomics and proteomics approaches to the study of aging and longevity is to attempt to find a comprehensive set of genes, proteins and their combinations that are associated with either healthy longevity or degenerative aging, to mimic or stimulate the former or mitigate or suppress the latter. Yet another such attempt was presented by Dr. Rong Yuan and colleagues from the Jackson Laboratory, in Bar Harbor, Maine, USA. They reported a study seeking to identify aging-related genes using mouse genetics**.** They observed significant correlations of both the age of female sexual maturation (FSM) and circulating Insulin-like Growth Factor 1 (IGF1) at 6 months with longevity. The results confirmed the correlation between age of FSM and longevity, and supported the hypothesis that IGF1 plays an important role in regulating the association. Next, using quantitative trait loci (QTL), mapping in conjunction with haplotype and single nucleotide polymorphism (SNP) analyses, they identified candidate genes for aging-related phenotypes, including nuclear receptor interacting protein 1 (*Nrip1*) and proprotein convertase subtilisin/kexin type 2 (*Pcsk2*). Transgenic mice with deletions of *Nrip1* and *Pcsk2* presented significantly reduced IGF1 and delayed age of female sexual maturation. The *Nrip1*-deficient mice had significantly extended longevity, as well as showed reduced cancer incidence and improved metabolism, including increased insulin sensitivity, enhanced mitochondrial function and improved profile of inflammatory cytokines. According to the authors, the discovery of aging-related genes using mouse genetics represents a powerful and effective strategy for uncovering new genes and pathways for validation in human studies. This study showcased yet another incremental advancement in the common effort of translational genomics/proteomics research to piece together weapons against degenerative aging and for healthy life-extension.

Immunotherapy

Notably, in nearly all the studies presented at the conference, the immune system plays some part, whether the main focus is on cell therapy, energy metabolism, toxicology, genomics or proteomics. Yet a series of studies could be considered as immunological studies proper, focusing on the effectors and targets of the immune system. There is again a change of emphasis. Such studies explored methods to modulate the immune function in order to achieve protection against degenerative aging processes and aging-derived diseases. The predominant reference was to modulation of inflammation signaling that appears to play a crucial part in nearly all aging-related conditions.

Thus Dr. Linda J. Van Eldik of the Sanders-Brown Center on Aging, at the University of Kentucky, Lexington, USA, provided an overview for the therapeutic targeting of inflammatory signaling cytokines dysregulation – namely the overproduction of pro-inflammatory cytokines (e.g. Interleukin 1 (IL-1), IL-6, IL-12, IL-23, Tumor Necrosis Factor Alpha – TNFα, etc.)

and underproduction of anti-inflammatory cytokines (IL-4, IL-13, IL-10, Transforming Growth Factor Beta – TGFβ, etc.) – in neurodegenerative age-related disorders, and the related drug discovery process. Much evidence from clinical studies and preclinical animal models suggests that cytokine dysregulation, especially proinflammatory cytokine overproduction from activated glia, is a potential driving force for pathology progression in neurodegenerative conditions such as traumatic brain injury and Alzheimer's disease, and in aging generally. Dr. Van Eldik's group has been developing Central Nervous System (CNS)-active, small molecule experimental therapeutics that selectively restore injury-induced or disease-induced overproduction of proinflammatory cytokines back towards homeostasis, using both molecular target-based and function-based drug discovery approaches. One class of compounds are highly selective inhibitors of p38α MAPK (Mitogen-activated Protein Kinase) – a key protein kinase involved in the pathological up-regulation of proinflammatory cytokines and other neuroinflammatory and dysfunctional responses in activated glia. The other class of compounds are not p38 inhibitors, but act through other signal transduction pathways to selectively suppress stressor-induced glial activation and overproduction of proinflammatory cytokines that contribute to pathology. Both classes of compounds attenuate excessive glial activation and cytokine production, and reduce their pathological consequences. Such compounds represent a paradigmatic approach to therapy of aging-related conditions, as they act on a common early pathophysiologic mechanism responsible for aging and diverse neurodegenerative aging-related disorders.

The importance of modulating the immune function to treat aging conditions is epitomized in the work of Dr. Dong-Ming Su of the Department of Cell Biology and Immunology, University of North Texas Health Science Center, Texas, USA. Dr. Su studies the genetic and epigenetic regulation of T-cell immune system microenvironment aging (focusing on the T-cell producing thymus). Special research focuses include the microenvironment aging-induced immune-senescence, autoimmune predisposition, and age-related chronic inflammatory diseases. Specifically, Dr. Su and his team ascertained causality between age-related deterioration in thymic microenvironment, induced by declined FoxN1 protein expression, and age-related thymic involution. This finding appears to be of major significance. Thymus involution (degeneration), and the subsequent reduction and impairment of naïve T cells, a main line of body defense against pathogens, is primarily responsible for the decline in immune function with aging, and consequently the increased susceptibility of the aged to infectious diseases and their decreased responsiveness to vaccination. Hence the clarification of the molecular mechanisms of the thymus degeneration through FoxN1 expression decline may have paved the way to regeneration of the thymus via increasing FoxN1 expression and thus restoration and rejuvenation of the immune function of the aged. This finding also illuminated the crucial role of degenerative aging processes not only for the emergence of non-communicable diseases, but also for communicable, infectious diseases, and therefore the importance of treating degenerative aging processes to successfully treat both non-communicable and communicable illness. In the current presentation, Dr. Su provided further novel findings regarding immunity mechanisms in aging. Their recent results identified thymic involution and the persistent activation of autoreactive T cells as a source to profoundly participate in the process of age-related chronic inflammation or "inflamm-aging" – a common debilitating process for aging and virtually all age-related diseases, from neurodegeneration to cancer. They found that the self-reactive T cells participate in inflamm-aging due to intrinsically compromised thymic (thymocyte) negative selection, but not defects in regulatory T cells (Tregs) generation in the atrophied thymus. The accumulation of Tregs in the aged peripheral lymph system could be rejuvenated in young microenvironment, suggesting an extrinsic defect, whereas aged thymus-released self-reactive T cells could not be eliminated by the same young microenvironment, showing that they sufficiently induced inflammatory cell infiltration in young mice. These insights may enrich the understanding of inflamm-aging mechanisms and can be potentially used for prevention and treatment of age-related diseases.

Further insight into the possible regeneration of the thymus and subsequent improvement of T cell production and the immune function of the elderly was provided by Dr. Yong Zhao of the Transplantation Biology Research Division, of the Institute of Zoology, Chinese Academy of Sciences, in Beijing. His group found that deficiency of tumor suppressor protein p53-induced phosphatase 1 (Wip1) in mice selectively caused a severe intrinsic deficit in medullary thymic epithelial cells (mTECs) – a key cell type in thymic microenvironment essential for T cell development. Several lines of evidence were provided for the role of Wip1. Among others, the thymus regeneration was significantly less efficient in adult Wip1 Knocked Out mice than in wild-type mice after cyclophosphamide treatment. In the study, Wip1 was shown to positively control mTEC maturation, homeostasis and regeneration through limiting p38 MAPK pathway. These findings also pointed out a possibility of influencing thymic regeneration by enhancing the expression of this protein.

Chronic inflammation (or inflamm-aging) has been widely recognized as a major common cause of aging and

a panoply of aging-related diseases. The dangers and mechanisms, as well as counter-measures for the inflammatory response were further elaborated by Dr. Ruth M. Barrientos of the Department of Psychology and Neuroscience, University of Colorado at Boulder, USA. As she pointed out, healthy aging individuals are more likely to suffer profound memory impairments following an immune challenge than are younger adults. These challenges produce a brain inflammatory response that is exaggerated with age. Sensitized microglia, found in the normal aging brain, are responsible for this amplified response, which in turn interferes with processes involved in memory formation. Dr. Barrientos' group examined the immunoenhancing role of corticosterone (CORT) in microglial sensitization in aged rats. Aged rats exhibited higher CORT levels in the hippocampus, but not in plasma, throughout the daytime, which was associated with increased hippocampal 11β-HSD1 protein expression, the enzyme that catalyzes glucocorticoid formation, and greater hippocampal Glucocorticoid Receptor (GR) activation. A low dose of mifepristone, a GR antagonist, administered intracisternally in the daytime, as well as exercise, were found to be effective at reducing immune-activated proinflammatory responses. These findings strongly suggested that increased Glucocorticoid Receptor activation in the aged hippocampus plays a critical role in sensitizing microglia, and that this activation could be reduced either pharmacologically or through exercise. This provided a proof of principle for a line of potential behavioral and pharmacological therapeutics aimed at reducing aging-associated microglial sensitization

The role of immune signaling for the treatment of age-related brain disorders was also explored by Dr. Jianjing Yang, Dr. Qichuan Zhuge and others of the Department of Neurosurgery, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China. Their study showed that early intra-cerebral injection of the anti-inflammatory cytokine Interleukin-4 (IL-4) promotes the functional recovery after intra-cerebral hemorrhage in rats. The benefits may be due to the induction of a protective inflammatory milieu via inhibiting pro-inflammatory (M1), yet promoting anti-inflammatory (M2) response in microphages/microglia of the brain. This finding is in line with the common approach endeavoring to fight excessive inflammation.

Yet it would be a great mistake to think of the inflammatory response as just and only a bringer of destruction and an enemy of the elderly. Every coin has two sides, and the "dark" and "light" sides often switch places. This was made clear by the presentation of Dr. Changhong Xing, of the Departments of Radiology, Neurology and Pediatrics, at Massachusetts General Hospital, Harvard Medical School, in Charlestown, USA. As Dr. Xing re-emphasized, inflammation is indeed a key part of central nervous system pathophysiology. Yet, recently, it has been increasingly understood that inflammatory factors may have both beneficial and deleterious actions. Dr. Xing's team examined the hypothesis that lipocalin-2, an inflammatory molecule that can be upregulated in the distressed central nervous system, may regulate glial activation and enhance vessel formation (angiogenesis) in brain cells. Their results showed that indeed, in primary glial cell cultures, exposing microglia and astrocytes to lipocalin-2 resulted in glial activation, increased matrigel tube formation and scratch migration, and also elevated levels of iron and reactive oxygen species (ROS). These findings provided in vitro proof-of-concept that lipocalin-2 may contribute to gliovascular recovery aspects of inflammation by activating microglia and astrocytes into potentially pro-recovery phenotypes and promoting angiogenesis via iron and ROS-related pathways. The inflammatory lipocalin-2 thus provided a kind of "Help Me" signal, mobilizing the brain repair mechanisms, protecting the brain against Oxygen and Glucose Deprivation and promoting neuroplasticity. Above all, this study illustrated that inflammation and oxidative stress should not be regarded as "all negative" processes to be battled at all costs, but rather it is important to know under which circumstances and at which doses these processes can produce beneficial or adverse effects.

The above studies emphasized the crucial role impaired immunity plays in aging, and conversely the role immunomodulation can have to counter degenerative aging processes and aging-related diseases. Yet too often the studies of basic aging and aging-related diseases are underappreciated in favor of the studies and treatment of acute infectious diseases that are often perceived to be more urgent, practically significant and even more emotionally engaging. But, in fact, the study of aging is vital also for the understanding and effective treatment of acute infectious diseases. This connection was stressed in the presentation of Dr**.** Hiroshi Saito of the Department of Surgery and Physiology, University of Kentucky, USA. As he emphasized, aging is characterized by reduced tolerance to physiological stressors, including infection and inflammation. Incidence and mortality rate of acute inflammatory diseases, such as sepsis and acute pancreatitis, increase progressively with advancing age. The studies of Dr. Saito's team on the acute inflammatory diseases using aged mice have revealed that dysregulated/prolonged inflammation, increased thrombosis, and increased oxidative damage, are all partly responsible for the elevated mortality. However, dietary intervention could improve the situation. Thus, both mortality rate and inflammatory response after induction of acute inflammatory stresses were significantly reduced

by dietary restriction in aged mice. The study results indicated that age-associated increase in inflammatory gene expression is due not only to increased fat mass, but to changes in the nature of the fat (adipose tissue) by both aging and diet. And generally, it stressed the need to address aging while studying infectious diseases.

The relation between aging and infectious diseases is particularly impressive for the case of HIV/AIDS. In fact, an entire conference session was dedicated to this connection. Yet, the connection could also be made for almost any infectious communicable disease, where aging represents one of the deadliest risk factors. For AIDS the exacerbation by aging is especially prominent, but also conversely, there is a marked ability of the infection to accelerate aging phenotype. This may suggest that the strategies to combat both may not be very different (for example via thymus regeneration and restoration of T-cell supply, whose proofs of feasibility were demonstrated). One of the presentations on the relation of AIDS and Aging was made by Dr**.** Johnny J. He of the Department of Cell Biology and Immunology, University of North Texas Health Science Center, at Fort Worth, USA. As he pointed out, HIV-1 infection of the central nervous system (CNS) often leads to neurological disorders ranging from minor cognitive-motor disorder to HIV-associated dementia, with the effects analogous to those produced by aging. The common hallmarks of HIV-associated neuropathologies include increased blood-brain barrier permeability, microglia activation, astrocytosis, compromised neuronal integrity, and neuronal inflammation. While the combination antiretroviral therapy has increased the life span of HIV-infected individuals, it has failed to provide any protection or relief from HIV-associated neuropathologies. Thus, it is imperative to gain a better understanding of the cellular and molecular mechanisms of HIV-associated neurological disorders. Dr. He's research pointed to HIV-1 Tat protein as one of the viral soluble factors that appears to play important roles in HIV-associated neurotoxicity and neuropathogenesis. Recent studies by Dr. He's team and others, have shown that HIV-1 Tat alone is sufficient to decrease neural progenitor cells (NPC) proliferation and neurogenesis but increase astrogliogenesis. The study results suggested that HIV-1 Tat protein may likely contribute to altered neurogenesis in HIV-infected individuals through Tat interaction with the proliferative Notch signaling pathways. The similarities with "normal" aging processes are so striking that a suspicion may arise whether aging itself is not caused by similar processes of infection and immune deficiency.

The suspicion was confirmed by Dr. Scott Letendre, of the Division of Infectious Diseases at the University of California, in San Diego, USA. He noted that antiretroviral therapy (ART) has improved survival among HIV+ adults and, as a result, HIV disease has become a chronic age-related illness in many. Yet, the enthusiasm over this success has been dampened by the observation that several other medical conditions seem to be more common in older HIV+ adults than in the general population. These conditions include cardiovascular disease, kidney disease, bone loss, and neurocognitive impairment. With regard to neurocognitive impairment, several large studies have now confirmed that HIV-associated neurocognitive disorder (HAND), occurs in a substantial proportion of people living with HIV and have linked the condition to advancing age in addition to worse immune suppression. Using assessments such as neurocognitive testing and neuroimaging, the relationship between HIV, age, and CNS disease does appear to be at least additive, if not cumulative. The possible risk factors for this include immune senescence, persistent inflammation, co-infections (e.g. cytomegalovirus - CMV), metabolic and vascular disorders, and polypharmacy and drug toxicity. As Dr. He concluded, improving understanding of the pathogenesis of premature aging in HIV+ adults should further improve disease outcomes in HIV+ adults and could identify interventions that will improve successful aging in the general population.

The mechanics of this relationship were elaborated by Dr. Anuja Ghorpade, from the Department of Cell Biology and Immunology, University of North Texas Health Science Center, Fort Worth, USA, who explored the role of astrocyte elevated gene 1 (AEG-1) in HIV-associated Neurocognitive Disorder (HAND) and aging. She re-emphasized the progressive loss of cognitive function as a debilitating complication in individuals aging with HIV-1-infection (now the majority of HIV-1 infected individuals are over 50 years old). Many of the mechanisms dysregulated during aging are also contributing to the development of HIV-associated neurocognitive disorders in 20–70% of infected individuals. Among others, the role of AEG-1 mechanism (a well-recognized oncogen) has been unclear. Dr. Ghorpade's studies in primary human astrocytes and astrocytoma cell line U87MG have shown that AEG-1 regulates aspects of reactive astrogliosis, a key pathological feature of HIV-1 CNS disease. HAND-relevant stimuli induced AEG-1 expression and nuclear translocation *via* activation of the NF-kB pathway, indicating that AEG-1 may serve as a novel transcriptional cofactor during neuroinflammation. AEG-1 may mediate protection from oxidative stress through interactions with the master regulator of cellular antioxidant responses – the cytoprotective nuclear erythroid 2-related factor 2, Nrf-2. Interestingly, during oxidative stress and wound healing, despite total AEG-1

levels remaining unchanged, AEG-1 localization in nucleolus increased significantly. Together, these findings indicated that AEG-1 may play a critical role in neurodegenerative mechanisms by regulating astrocyte migration, proliferation, cytokine secretion, excitotoxicity and antioxidant responses during HAND and aging.

The connection between impaired immunity, aging and disease, was illuminated from further unexpected angles. Thus, Dr. Lilia Lens-Pechakova, from HLEB – Healthy Life Expectancy Bulgaria, compared data on autoimmune chronic respiratory diseases (such as asthma) and some other autoimmune diseases (such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes and others) with demographic data on aging in Europe. She found that an increase in the total Sum of autoimmune diseases' rates corresponded to a decrease in the rates of centenarians, CR(50-54), in the same country (the CR is the number of centenarians in the year 2011 divided by the number of people aged 50-54 years in 1961 – a useful indicator of the population longevity). This suggested a correlation between diminished autoimmune diseases and longevity, with potentially similar mechanisms and genes involved, as well as possible common therapeutic approaches against autoimmune and aging-related conditions. Some therapeutic approaches could include anti-inflammatory steroidal or nonsteroidal drugs, natural products, like Vitamins D, A, and B3, green tea, curcumin, omega-3 fatty acids, resveratrol, probiotics, etc. On the basis of that study, Dr. Lens-Pechakova argued that a thorough research on the mechanisms of the aging process may be the most reliable way to develop targeted treatments also for the autoimmune diseases. The presentation published on behalf of Dr. Mladen Davidovic of the Serbian Association of Geriatricians and Gerontologists, in Belgrade, Serbia, also emphasized the association between a higher frequency of auto-antibodies and shorter survival. As it is argued, there is a link between inflammation, intestinal bacteria and the aging process, that can be modulated via life styles and diet changes affecting gut microbiota. According to Dr. Davidovic, longevity privilege can be earned by probiotics effects resulting in the harmonization of the immune system in the elderly, and as a result of "good" bacteria prevalence, which could be designated as "the real Fountain of Youth". Also regarding age-related heart disease, as pointed out by Dr. Bradley S. Fleenor of the Department of Kinesiology and Health Promotion, at the University of Kentucky, in Lexington, USA, translational nutraceutical and functional food interventions may de-stiffen arteries that, in turn, can reduce cardiovascular risk in older adults by ameliorating oxidative stress and inflammation.

All these studies – relating communicable and non-communicable diseases with aging, as well as regarding biological mechanisms at different levels of organization, alongside environmental, lifestyle and cognitive and psychological factors – also emphasized the importance of considering the organism as a whole, stressing the value of systemic and holistic approaches to the study and treatment of aging and disease.

Systemic approaches

As many of the conference presentations illustrated, systemic approaches to the study and treatment of aging and aging-related diseases, promise to provide better understanding and more effective and responsible therapy. Such systemic approaches could combine particular approaches – cell therapy and behavioral therapy, modulation of energy metabolism and immunity, genomics and proteomics – within unified frameworks. They would consider biological mechanisms not as separate modules, but in relation to the organism as a whole and to broader environmental influences. And moreover, they would no longer consider particular diseases and symptoms as stand-alone entities, but would relate them to their underlying root determinants, such as degenerative aging. Several presentations particularly emphasized the need for such systemic approaches, and pointed out further directions for advancement.

In an exemplary way, Dr. Zaven Khachaturian, Chair of the Campaign to Prevent Alzheimer's Disease by 2020 [PAD2020], headquartered in Potomac, Maryland, USA, spoke of the need for a novel conceptual model for complex chronic brain disorders of aging, that needs to be integrative and systemic. The need is urgent. The scale of the pending health-economic crisis, due to the aging population and the associated rise in aging diseases, urgently mandates bold scientific initiatives and massive investments in research on their *prevention.* Thus the essential global scientific challenge is to resolve the question of: *"How to accelerate the discovery-development of cures for chronic brain diseases – such as dementia/Alzheimer's disease?"* According to Dr. Khachaturian, Alzheimer's disease is a paradigmatic case and a good proxy for other chronic brain diseases and other age-related disabilities; the discovery and development of cures need be accelerated for all of them. In spite of remarkable recent advances in the neurobiology of neurodegeneration, there are still no effective treatments for dementia and other neurodegenerative diseases. Still, many believe the prospect of delaying the onset of disabling symptoms within a decade is an attainable goal, provided we can surmount several scientific, administrative, and financial impediments. Among these obstacles the limitations of current conceptual models about the causes (etiologies) of the disease is an important factor. A quantum shift in current approaches to therapy development requires the

adoption of alternative paradigms; such as a *systems failure* model of dementia - based on *general systems theory*. The core premise for such a different approach is to start conceptualizing complex age-related chronic brain disorders in terms of progressive failures in an array of complexly interconnected biological systems and neural networks. The key explanatory concept of this model is that the syndrome is not the linear result of a unitary etiologic factor but rather interaction or failures of several components, thus suggesting the need to consider polygenic etiologies and combined therapies. The same systemic thinking may be needed also for other diseases of aging.

The importance of a systemic approach was also emphasized in the presentation of Dr. Ilia Stambler of the Department of Science, Technology and Society, Bar Ilan University, in Ramat Gan, Israel, together with Dr. David Blokh of CD Technologies, Israel, who presented on the use of information theory for the study of aging, aging related diseases and healthy longevity. The information-theoretical measures, such as entropy and mutual information, may be more adequate for the systemic study of aging and disease processes than statistical measures, as the former take into consideration the non-linear relations in the biological systems. The information-theoretical measures also allow to precisely determine polygenic etiologies by measuring the influence of several combined risk factors (including age) on the emergence of the disease. The authors applied information theory methodology, using measures of entropy and mutual information, to estimate the relation between aging and disease, with specific reference to diagnostic parameters of two major age-related diseases – diabetes and heart disease (though the same methods could be applied to any age-related disease and condition and any parameter). The study estimated entropy changes as a possible measure of the system heterogeneity or variability, which may serve as a proxy measure for the system adaptability, stability and homeostasis. It was shown that both aging and disease are characterized by a decrease of entropy (loss of heterogeneity, variability and adaptability) in the parameters and samples under consideration. This common pattern highlighted a possible formal analogy between aging and aging-related disease with reference to the specific parameters. Furthermore, it was demonstrated that age is a powerful "metamarker" of disease, whose combined consideration with other diagnostic parameters can dramatically improve diagnostic results. It was also shown that the thresholds for the parameters association with disease are strongly related to age, in the parameters and samples studied. It is hoped that further wider use of information-theoretical measures in the systemic study of aging, aging-related diseases and longevity, using a wide array of clinical parameters and large samples, by a greater number of researchers, may provide a useful comprehensive measure to determine physiological age, the degree of organism stability (homeostasis) and its impairment with age and disease, and to estimate the influence of potential anti-aging interventions.

The crucial role of maintaining system stability for healthy longevity was also emphasized in the presentation of Dr. Peter Fedichev of Quantum Pharmaceuticals, Moscow, Russia. His topic was the physics behind the Gompertz law of mortality, aging, and negligible senescence. Some of the questions Dr. Fedichev's systemic approach addresses are: why do we become less fit as we age; why does resistance to a host of stresses decline with age; why does mortality rise exponentially with age, as described by "Gompertz' law"; and how do some species evade senescence, such as the Naked Mole Rat that lives more than 28 years with no increase in mortality or decline in reproduction? Dr. Fedichev's group analyzes network stability, and tests the assumption that most biological organisms inhabit a precarious domain between instability and stability, and strive to maintain that critical balance in the face of environmental perturbations (stresses). From these premises, they derive an equation with both stable and unstable solutions, reflecting negligibly senescent and normally senescing species respectively. The model predicts that all controlled parameters of the organism (transcript levels, epigenetic states, metabolites, etc.) will be maintained close to initial values in stable systems, but will progressively drift away from young levels in species with unstable networks. The model's predictions were demonstrated to be consistent with observations from the transcriptome of aging fruitflies (whether calorically restricted or not), the observed progressive decline in stress resistance with age in senescing species only, and the ability of even unstable (aging) animals to recover from most perturbations with no reduction in longevity. The model clarifies the systemic nature of aging and may help to rationally design the kinds of interventions that could stabilize networks, and extend lifespan of model animals and, hopefully, humans.

The systemic approaches to aging can indeed have direct implications for therapy. This is exemplified by the work of Dr. Judith Campisi of the Buck Institute for Research on Aging at Novato, California, USA. The systemic approach she presents, integrates the genetic, environmental and evolutionary forces that result in aging and age-related diseases, explains why aging is the largest single risk factor for developing age-related degenerative diseases and cancer, and identifies pathways that can be modified to mitigate basic aging processes and consequently alleviate aging-related diseases. Briefly, the systemic approach of Dr. Campisi goes as follows. It focuses on cellular senescence which is a complex stress

response with two main features: a stable, essentially irreversible arrest of cell proliferation (growth), and a multi-faceted senescence-associated secretory phenotype (SASP). The senescence response is likely antagonistically pleiotropic. That is, it is beneficial early in life, but can be deleterious later in life by driving aging phenotypes and age-related disease. The growth arrest suppresses the development of cancer by halting the growth of cells that have experienced potentially oncogenic stress. The SASP can alter the behavior of neighboring cells within tissues and also the quality of the systemic milieu. On the positive side, the SASP can promote tissue repair. In the skin, this benefit is mediated in part by the secretion of a newly identified SASP factor, PDGF-AA, which stimulates the differentiation of dermal fibroblasts into myofibroblasts. On the negative side, the SASP can create a pro-inflammatory tissue environment that can drive the degeneration of the resident tissue. The SASP can also stimulate the growth, migration and invasion of premalignant or weakly malignant cells, and most prominently stimulate the development of cancer metastases. Thus, senescent cells can, ironically, promote the progression of cancer, a major age-related disease. A critical difference between the positive and negative effects of senescent cells is their resident time in vivo. Short, transient residence times appear to be beneficial, which occurs during wound healing. In contrast, chronic resident times, which occur during aging, appear to be deleterious. Therapies aimed at eliminating senescent cells, or suppressing the deleterious components of the SASP, hold promise for treating a spectrum of diseases associated with aging, perhaps even aging itself.

Perhaps one of the most integrative studies was that of Dr. Abbe N. de Vallejo of the Pediatrics and Immunology Department, University of Pittsburgh, and McGowan Institute for Regenerative Medicine, in Pittsburgh, Pennsylvania, USA. The study strives to unravel the physiologic construct of successful aging, focusing on the integral connectivity between immune, physical, and cognitive domains of function. Older adults (defined as over 75 years old) are shown to be highly heterogeneous, ranging from the frail, chronically ill residents of long-term care facilities to elders who are living in the community and remain functionally independent, even beyond a century mark. What determines the difference? Emerging data from biological studies indicate physiologic adaptations or remodeling or plasticity of brain and muscle that contribute to maintenance of function in old age. Because immunity is a determinant of individual fitness, Dr. de Vallejo examined the hypothesis that connectivity of the immune system with physical and cognitive domains of function determines the trajectory of successful aging. In the aging subjects, there were found the predictable age-related declines of classical immune function (involuted thymus, contracted naïve T cell compartment, reduced T-cell receptor (TCR) diversity, irreversible loss of CD28 cells, etc.). Yet surprisingly, Dr. de Vallejo's group found that a unique repertoire of NK-like T cells (including a diversity of markers, such as CD16, CD56, NKG2D, KLRG1, KIRs, etc.) along with objective measures of physical and cognitive function, comprise a signature of successful aging. The novel immune signature was associated with, and predictive of, physical and cognitive resilience, offering new potential targets for immune protection (and perhaps general geroprotection). This presentation demonstrated the need for research paradigm shift from the usual young-vs-old comparison, to the analyses of clinically defined age-matched populations, seeking to identify integrative determinants of truly "successful aging", characterized by prolonged periods of vigorous, robust function and adjustment.

Yet another interesting integration between biological systems was highlighted by Dr. Yanning Cai of the Department of Neurobiology, Xuanwu Hospital of Capital Medical University, Beijing, China. He demonstrated the vital interrelation between the circadian rhythm, molecular clock and the manifestations of aging and aging-related diseases, such as Parkinson's disease (PD). As he pointed out, circadian alterations are tightly associated with Parkinson's disease. Because circadian disruptions may result in sleep problems, oxidative stress and an altered inflammatory response, it has been speculated that circadian disruptions could contribute to the disease pathogenesis. Dr. Cai's group demonstrated that a peripheral molecular clock, as reflected in the dampened expression of the clock gene BMAL1 in total leukocytes, is altered in Parkinson's disease patients. In addition, the relative BMAL1 levels correlated positively with the disease severity, which could provide a molecular basis to help monitor disease progression and response to investigational drugs. Moreover, this work suggested that targeting circadian disruption and the molecular components of the clock may have therapeutic potential, not just against Parkinson's disease, but against a variety of age-related diseases.

A systemic or holistic approach can be well understood through the concept of flow (in particular blood flow) which encompasses the entire organism, not being restricted to any particular "compartment", and whose changes can have profound pathogenic or therapeutic effects for the aging of the organism as a whole. This was the topic of Dr. David A. Greenberg of the Buck Institute for Research on Aging, at Novato, California, USA. As Dr. Greenberg's research shows, the body can respond to interruption of blood supply to the brain (such as due to stroke) by boosting the production

of proteins that help tissues to survive or regenerate. In particular, Dr. Greenberg's lab explored the actions of two protective proteins, neuroglobin and VEGF (vascular endothelial growth factor). As Dr. Greenberg pointed out, vasodegenerative disease, like other so-called diseases of aging, begins decades before it becomes clinically apparent. The main underlying pathologies are atherosclerosis, hypertension, and diabetes, which may also contribute to risk and progression of neurodegenerative disease. Early events in atherogenesis include disturbed blood flow leading to endothelial cell (EC) dysfunction and accumulation of oxidized lipids in the arterial wall. To model these processes, Dr. Greenberg's group cultured *bEnd.3* mouse brain endothelial cells under stationary or flow conditions. Flow induced by orbital rotation altered the expression of key transcription factors and gasotransmitter-synthesizing enzymes, and increased NO production, consistent with an atheroresistant state. Statins and angiotensin receptor blockers reproduced the effect of flow on endothelial nitric oxide synthase (NOS). They further examined the expression of LOX-1, a scavenger receptor facilitating the uptake and toxicity of oxidized low-density lipoprotein (Ox-LDL). The study suggested that LOX-1/Ox-LDL signaling may help to mediate effects of cardiovascular risk factors on neurodegenerative disease. And furthermore the study emphasized the importance of combining molecular-biological considerations with systemic physiological considerations, such as of blood flow and oxygen supply.

Holistic and behavioral therapies

As several conference presentations discussed, effective therapies can be based on systemic or holistic approaches. The best examples are well known, including exercise, moderate diet, and conditioning, that affect the organism as a whole, and that have proven their beneficial effects time and again. Yet novel mechanisms are being discovered to explain and optimize their action.

Thus, Dr. Michael J. Zigmond of the Department of Neurology, Neurobiology, and Psychiatry, University of Pittsburgh, USA, presented on the influence of physical exercise on age-related neurodegeneration, using models of dopamine deficiency. The motor deficits associated with Parkinson's disease (PD) appear due in large part to the loss of dopamine (DA)-containing (dopaminergic) neurons projecting from substantia nigra (SN) to striatum of the brain. There is an analogy with aging. The motor impairments normally associated with aging also appear to involve a dopaminergic deficit. Pharmacological treatments exist that reduce the symptoms of Parkinson's disease. However, they have a limited period of efficacy, often produce side effects, and fail to significantly attenuate the neurodegenerative process. Despite the absence of effective neuroprotective pharmacological interventions (even though there is massive work in progress), several labs have shown that physical exercise can effectively reduce the vulnerability of dopaminergic neurons to neurotoxins in laboratory animals, suggesting that exercise would be useful in slowing the progression of Parkinson's disease and might be useful for general age-related motor dysfunction as well. Furthermore, the impact of exercise seems to be associated with an increase in the concentration of neuroprotective neurotrophic factors (NTFs). Dr. Zigmond concluded that several NTFs are likely to work synergistically to produce their neuroprotective actions and that this involves the activation of the phosphokinases, ERK and Akt, among other intracellular events that retard apoptosis and neurodegeneration.

Another well known holistic therapeutic approach to achieve healthy longevity and mitigate aging-related diseases is through moderate nutrition. This method was practiced by hygienists for centuries, even before the introduction of the Calorie Restriction concept by Clive McCay in the 1930s [7]. Yet, the understanding of the beneficial effects of moderation is yet moderate. Some well-entrenched assumptions regarding Calorie Restriction (CR), and its relation to brain aging and neurodegenerative disease, were challenged by Dr. Michael J. Forster of the University of North Texas Health Science Center (UNTHSC), at Fort Worth, USA. As Dr. Forster pointed out, the observation that a reduction in food intake, or calorie restriction, delays the decline in physiological fitness and extends the life span of organisms of diverse phylogenetic groups, has for some time been considered the primary evidence for a common mechanism of aging and disease. Because CR is presumed to retard such a universal aging process, it has been considered as a valuable tool for elucidating mechanisms of vulnerability in neurodegenerative disease. However, emerging evidence has disputed some of the primary tenets of this conception, suggesting that the CR-related increase in longevity is not shared among different strains of the same species, and that the beneficial effects of CR accrue in proportion to the propensity, under non-restricted feeding, for different genotypes or diets to promote energy imbalance leading to weight gain across the life span. The long-term beneficial effects of CR occurred in direct proportion to the cumulative adult body weight gain associated with each genotype under conditions of non-restricted feeding. When present, the beneficial effects of CR were partially or fully reversible, albeit in an age-dependent manner, following experimentally imposed positive or negative shifts in energy intake. Existing evidence supports the view that CR increases the life span and delays brain aging and

vulnerability to disease, only in those particular genotypes that develop energy imbalance (weight gain) due to non-restricted feeding. Hence, it was suggested that the use of non-restricted controls to study the interaction of aging and disease should be reconsidered. Yet, despite pointing out the complexity of CR effects, the study did not negate, but in fact only reinforced the proof for the beneficial effects of nutritional moderation for healthy longevity.

Another intriguing study from Dr. Kyung Jin Min's lab (together with Drs. Bora Lee and Eun-Ji Lee) explored the parental effects of Dietary (protein) Restriction on the health and longevity of the offspring in Drosophila flies. As Dietary Restriction (alongside Calorie Restriction) is currently one of the best reproducible means for life extension, the examination of parental effects, the ability to pass on the acquired longevity to the offspring, can be trail-blazing. The group found that the offspring of flies fed a protein-restricted diet tended to outlive offspring of flies held on a regular diet, as well as have increased resistance to starvation and oxidative stress, though the results varied among trials. Such parental influences (possibly involving epigenetic effects) need further elaboration.

Another time-tested holistic method of invigoration is conditioning. In general health improvement, conditioning often manifests as "tempering", increasing the resistance to harsh environmental influences. Yet as was shown at the conference, various forms of conditioning could be effectively employed against various aging-related diseases. Thus, Dr. Heng Zhao of the Department of Neurosurgery, Stanford University School of Medicine, Stanford, California, USA, spoke of the significance and mechanisms of ischemic postconditioning against stroke. Ischemic postconditioning (IPostC) must be contrasted with ischemic preconditioning (IPreC). While ischemic preconditioning refers to a sub-lethal, brief ischemia before stroke onset, ischemic postconditioning is a mechanical interruption of reperfusion, as if postconditioning is conducted when the stimulus of preconditioning is removed before stroke onset to after reperfusion. Both ischemic preconditioning and postconditioning protect against brain injury. Nevertheless, as the occurrence of most strokes cannot be predicted, the postconditioning appears as more clinically relevant. In Dr. Zhao's study, the concept of ischemic postconditioning has been expanded from reperfusion interruption to a broad range of interventions, including hypoxic postconditioning, remote postconditioning, and pharmacological postconditioning. The exact therapeutic windows, intensities and the time schedule of conditioning (rapid or delayed) and the underlying protective mechanisms have been investigated. The protective mechanisms of Ischemic Postconditioning apparently involve mitigation of reactive oxygen species (ROS) generation, apoptosis and inflammation, and activation of neuronal survival signaling pathways, such as the Akt/mTOR pathways. The results appear promising and further research is needed.

A different form of conditioning was explored by Dr. Yi-Chung (Clive) Pai of the Departments of Physical Therapy, Biomedical Engineering and Kinesiology and Nutrition, at University of Illinois at Chicago, USA. His group studies neuroplasticity and motor memory retention and improving gait stability for reduction of idiopathic falls among community-dwelling older adults. The problem of falls of the elderly is very acute, and the cumulative effect of falls on older adults and on the healthcare system is enormous, due to debilitating injuries, loss of independence and transfer to an institution. The result of a fall can even be death. Nearly 60% of outdoor falls among community-living adults aged 70 or older come from slips or trips during walking, resulting from their inability to control stability, often coupled with inadequate limb support against gravity during the recovery. Conventional programs rely on improving a person's volitional skills requiring weeks or months of training. Recently emerged perturbation-based motor (implicit) learning involves a (safe) destabilization process to improve both volitional and reactive skills. This trial-and-error (conditioning or learning-from-falling) practice stimulates the central nervous system (CNS) to make adaptive adjustments. The results were impressive. The conditioning training boosted the subjects' resilience to falls by 43.1%. Falls remained low in 6-month (0%), 9-month (8.7%) and 12-month retest (12%); all attributable to the retention of the subjects' significantly improved control of stability, proactive and reactive, acquired from the initial training session. The findings revealed promising functional plasticity of the CNS and outstanding motor memory of such adaptive control of stability, in spite of commonly known age-related sensory motor decay. Furthermore, the study pinpointed the potential effectiveness of conditioning, as a particular holistic (systemic) approach to therapy of aging-related ill health, alongside the need to clarify the biological regulatory mechanisms involved in such a systemic response.

A systemic or holistic approach to the study and treatment of aging-related conditions and diseases would be impossible without a comprehensive collection of data on all systems of the aging organism, and on the widest available population, considered as a collective information-coordinated entity and a potential subject to targeted interventions. This was emphasized by Dr. Xiaoning Wang of the Institute of Geriatrics, at the Chinese People's Liberation Army General Hospital, in Beijing. He emphasized the critical role of the Mobile

Health (mHealth**)** technology for developing efficient ways to manage chronic age-related diseases. The task can be seen as of national importance for China (in fact for any nation). As Dr. Wang emphasized, China has entered the aging society, with a large population of patients suffering from chronic diseases (hypertension, diabetes mellitus, cardiovascular and cerebral vascular disease), which have raised a huge burden of medical care and also consumed huge medical resources. Development of wearable medical equipment and networks based on mHealth applications can provide a new way to manage this kind of diseases. By using mobile wearable devices, it may be possible to remotely monitor the patient's ECG, blood pressure, blood glucose, sleep and many other potential diagnostic parameters. Due to the greatly improved capability for informed medical response, mHealth can provide an efficient management mode for chronic age-related diseases, greatly improving the affordability, access and deployment of high quality medical resources. Yet Dr. Wang also stressed that the application of wearable medical devices must be closely combined with the expertise of clinical teams and researchers, in a new medical care running mode, indeed expanding biomedical research and practice. Wearable medical devices without medical guidance from senior medical personnel, or without connection to extensive research and development programs, could become just fashionable toys of short duration.

Indeed, aging and aging-related diseases must be addressed at the national level. Massive biomedical surveillance of the population, comprising comprehensive collection of data on aging and aging-related diseases, with the explicit aim of discovering and developing therapeutic targets, are critical components for any effort to address the challenge of the aging society. This was pronounced also in the presentation of Dr. Jianping Jia, of the Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, who presented on the current situation and perspectives of mild cognitive impairment (MCI) and dementia in China. As Dr. Jia noted, presently, China has an elderly population, aged 65 years or older, of 130 million, accounting for 9.4% of the total 1.35 billion Chinese population. China is aging and calls for increased anti-dementia research, as one of the foremost manifestations of the aging process. There is an urgent need to know the prevalence of mild cognitive impairment and dementia, and how these conditions are diagnosed and treated in hospitals. For that purpose, Dr. Jia's team performed a population-based cross-sectional survey with a multistage, cluster sampling design, in which residents aged 65 years and older were drawn from urban and rural communities across China. Interventions in several general hospitals infrastructure were performed regarding the drawbacks found and a training program on dementia diagnosis was initiated. Generally, it was found that the rural population had a higher prevalence of overall mild cognitive impairment (23.4% vs. 16.8%, $P < 0.001$). The prevalence of dementia was also significantly higher in rural than in urban areas (6.05% vs. 4.40%, $P <0.001$). The differences in Alzheimer's disease (AD) incidence disappeared when the sample was stratified by educational level. This suggested that the level of education might be an important reason for the urban-rural differences, and the improvement of education may also be a therapeutic target. The infrastructural interventions performed in the course of this study, increased several fold the number of dementia doctors and memory clinics, within the administrative scope of the study, and dramatically raised the rate of dementia detection. Dr. Jia's presentation also stressed the need for policy changes, in health research and care, to address the challenge of the aging population at the national level. (One may add that the policy suggestions made by Dr. Jia for China, and with specific reference to dementia and Alzheimer's disease, could be well applied for any other country, and for any aging-related condition, perhaps with slight modifications.) As Dr. Jia argued, a new dementia management system needs to be organized by the Chinese health administration to improve the current situation with the disease diagnosis and treatment. The specific policy recommendations are as follows: 1) China needs to have more funding to support MCI and Dementia; 2) China needs to set up new outpatient system to increase memory clinics and dementia doctors in hospitals to meet the increasing patients; 3) China needs national efforts to study familial Alzheimer's disease (FAD) since it might be a good way to find the crucial pathogenesis and new drug targets; 4) China needs to have national AD registry for big data to monitor AD in whole China regarding the diagnosis, treatment and care; 5) China needs to set up some neuropsychological assessments which fit Chinese culture for the diagnosis since there are many differences in culture from western countries; 6) China needs to develop compounds from traditional Chinese medicine for anti-dementia, however this needs to be verified by internationally accepted methods to provide evidence.

Substitute any age-related debilitating condition for dementia, and the need for holistic and systemic treatment is emphasized, the need to address the aging organism as a whole, the aging nation as a whole, perhaps even the aging world as a whole.

New policies are needed to promote research of aging and aging-related diseases

Indeed the entire conference demonstrated beyond any doubt that aging-related ill health is a severe problem for

all nations, and governments should invest in the solution. The impressive array of advancements, even breakthroughs, reported at the conference also demonstrated beyond any doubt that aging-related deterioration is not inevitable and could be mitigated, arrested and even reversed, through a wide array or biomedical interventions. Yet, greater efforts and investments will be needed to bring these advances from the stage of basic laboratory research toward effective, safe and universally accessible treatments.

This need was proclaimed in the conference resolution and in the consequent position paper published on behalf of the ISOAD that suggested some necessary policy changes [3,4]. As those documents argued, addressing aging-related debilitating processes through biomedical means should become a new and powerful approach to the prevention of non-communicable diseases which affect most people at the later stages of life. Governments should ensure the following policies to promote research into the biology of aging and aging-related diseases, for improving the health of the global elderly population:

1) Funding: Ensuring a significant increase of governmental and non-governmental funding for goal-directed (translational) research in preventing the degenerative aging processes, and the associated chronic non-communicable diseases and disabilities, and for extending healthy and productive life, during the entire life course.

2) Incentives: Developing and adopting legal and regulatory frameworks that give incentives for goal-directed research and development designed to specifically address the development, registration, administration and accessibility of drugs, medical technologies and other therapies that will ameliorate the aging processes and associated diseases and extend healthy life.

3) Institutions: Establishing and expanding national and international coordination and consultation structures, programs and institutions to steer promotion of research, development and education on the biology of aging and associated diseases and the development of clinical guidelines to modulate the aging processes and associated aging-related diseases and to extend the healthy and productive lifespan for the population.

These measures are designed to reduce the burden of the aging process on the economy and to alleviate the suffering of the aged and the grief of their loved ones. On the positive side, if granted sufficient support, these measures can increase the healthy life expectancy for the elderly, extend their period of productivity and their interaction with society, and enhance their sense of enjoyment, purpose, equality and valuation of life.

The deepest gratitude and appreciation must be expressed to the conference organizers, foremost Dr. Kunlin Jin, Dr. Xunming Ji, Dr. Jian Zhang and Dr. James Simpkins, and to all the participants, for creating such an inspiring and seminal event. The next International Conference on Aging and Disease (ICAD) is planned to take place in 2016 in Stanford, California, USA. There is little doubt that new and exciting research work will be preformed by then. There are strong grounds to hope that the continuation of the current lines of research and the establishment of new ones, supported by the entire society, from the grass roots through the professional to the political level, will help us all reach the declared goal of the conference and the ISOAD motto: "Stop Aging Disease!"

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