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= **REVIEWS** =

Longevity Nation—Enhancing Research, Development and Education for Healthy Longevity

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Abstract—On October 28–31, 2024, there took place the international conference, "Longevity Nation 2024— Enhancing Research, Development and Education for Healthy Longevity" in Bar-Ilan University, Ramat Gan, Israel (http://www.longevitynation.org/). This conference explored the challenges that rise from population aging, from interdisciplinary perspectives that reflect new science and technology, and many social, cultural, political, economic and philosophical concerns that aging raises. By bringing together leading Israeli and international voices in the longevity space—researchers, developers, investors, educators, decision makers and public figures—the Longevity Nation conference aimed to contribute to increasing the synergy of science, technology and aging society, and help advance ethical scientific and technological solutions for healthy longevity for the benefit of the entire society. As the conference emphasized, in this period of conflict in Israel and the Middle East, it is especially important to build up international collaboration as a basis for future positive development.

Keywords: healthy longevity medicine, geroscience, longevity research, longevity advocacy, health policy, longevity industry ecosystem

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ENHANCING THE LONGEVITY ECOSYSTEM FOR ISRAEL AND INTERNATIONAL COLLABORATION

On October 28–31, 2024, there took place the international conference, "Longevity Nation 2024— Enhancing Research, Development and Education for Healthy Longevity" in Bar-Ilan University, Ramat Gan (Tel Aviv district), Israel (http://www.longevi-tynation.org/).

This conference explored the challenges that rise from population aging, from interdisciplinary perspectives that reflect new science and technology, and also the many social, cultural, political, economic and philosophical concerns that aging raises. By bringing together leading Israeli and international voices in the longevity space-researchers, developers, investors, educators, decision makers and public figures-the Longevity Nation conference aimed to contribute to increasing the synergy of science, technology and aging society, and help advance ethical scientific and technological solutions for healthy longevity for the benefit of the entire society. Building on Israel's strengths in this area, this conference aimed to help further develop the longevity ecosystem in Israel. boost the prominence of the field in Israel and enhance Israel's international standing and cooperation in the Longevity Field. Thus, beside the primary purpose of advancing the vital subjects of research, development and education for healthy longevity for all, this conference also aimed to bolster support and appreciation for long term national and international development, for a positive vision of the future.

In case there were any doubts whether, in this difficult period, people should be thinking about the preservation of health in old age, the prevention of aging-related diseases, and the extension of healthy longevity, the conference participants unequivocally emphasized that we should indeed continue to think about and work for healthy longevity even now, to improve national resilience that will help overcome the present adversity and maintain the basis for positive development in the future. Wars between human groups start and end, but the entire humanity's war against aging-related ill health continues, and hopefully there will be victories.

The conference participants, including leading voices in the global longevity space, presented cutting edge research and developments promising to advance healthy longevity and prevention of multiple agingrelated chronic diseases. The main conference topics included: enhancing the longevity ecosystem for Israel and international collaboration: breakthroughs in the science of aging; our sources of hope for intervening in fundamental aging mechanisms to extend healthy lifespan: the promises and challenges of the science of healthy longevity; measures and countermeasures of degenerative aging; advancements in healthy longevity medicine-showcasing treatments that can be offered now and in the near future; economic investments and dividends in the longevity industry; visions and directions for the future of healthy human longevity, including ethics and policies. Research fields that were discussed in relation to healthy longevity promotion included AI for early diagnosis and drug discovery, biomarkers of aging and aging-related diseases, regenerative medicine, geroprotective drugs and other therapies, including senescent cell elimination, DNA stability enhancement, mitochondrial replacement therapy, epigenetic modulation, and many other approaches.

Beside the high value scientific exchange, the conference explicitly aimed to raise academic, public and governmental awareness and support for the goals of healthy longevity promotion via enhancing research, development and education, and international cooperation in those areas. The conference is testament to the power of collaboration for a better future of humanity. In this period of conflict and hardship in Israel, many organizations from Israel and from abroad joined forces for the common humanitarian goal of preventing aging-related diseases and extending healthy longevity for all. These organizations include Vetek (Seniority) Association-the Movement for Longevity of Life, Graduate Program in Science, Technology and Society of Bar-Ilan University, American Federation for Aging Research (AFAR), Shlomo Tyran Foundation, Sagol Network, British Council, Britain-Israel Research and Academic Exchange Partnership on Ageing (BIRAX Ageing), Biogerontology Research Foundation (BGRF), International longevity Alliance (ILA) and many other organizations. Together they work to create communication and exchange platforms and grant support programs for research on healthy longevity, in Israel and via international cooperation with Israel, such as the emerging TABILI program-the American British Israeli Longevity Initiative.

Indeed, a leitmotif throughout the conference was that Israel can and should be an important agent for the international enhancement of research, development and education for healthy longevity [1]. This point was emphasized by the conference chairman Dr. Ilia Stambler of Vetek (Seniority) Association and the Graduate Program in Science. Technology and Society of Bar-Ilan University, Israel, He spoke about enhancing longevity ecosystems, focusing on developing Israel's longevity ecosystem and promoting international cooperation, leveraging Israel's strengths in science and technology to enhance its global standing in the field. This ecosystem should be based on cutting-edge research and innovations, including breakthroughs in aging science, geroprotective treatments, regenerative medicine, advancements in longevity medicine. Yet when developing the healthy longevity ecosystem, it is vital to address ethical and societal concerns, including the need for interdisciplinary approaches, the importance of public and governmental support, and the broad public entitlement and distribution of healthy longevity therapies.

The imperative of international collaboration was also emphasized by Prof. Richard Faragher, a board member of the American Federation for Aging Research (AFAR) and head of the UK MRC– BBSRC Ageing Networks who, together with Ilia Stambler and the AFAR CEO Stephanie Lederman, were among the chief initiators of this conference. He stressed that the imperative of collaboration is determined by the fact that all of us have a common problem and a common enemy, namely the degenerative aging process which is the largest risk factor of disease and disability. He pointed out several fundamental areas of aging research to preferentially target, including medications, such as rapalogues, senolytics and senomorphics, the need for new research models and other areas that are promising to bring tangible benefits for the health of older persons. According to Prof. Faragher, what is needed for the longevity field to produce these benefits are focused collaborations between countries (bilateral, trilateral or multilateral), mechanisms of knowledge exchange across and between disciplines, and the reinforcement of organizations willing to bear the administrative burden of facilitating these initiatives (such as VETEK, AFAR, and others). As he emphasized, "a better world for older people is a better world for everyone."

Indeed, a direct outcome of this conference, as a part of more general advocacy efforts, was the encouraging and contributing to the formulation of calls for research proposals on aging in Israel, by the Israel Ministry of Innovation, Science and Technology, and internationally, altogether enhancing the interest, involvement and cooperation in the aging and longevity field (https://www.longevityisrael.org/news/).

The conference presenters spanned the entire multidisciplinary range of the healthy longevity field fundamental science, industry and commercialization, clinical longevity medicine, longevity education, longevity ethics and policies. Over 100 speakers presented at the conference. Below is a selection of some of the topics and points that were discussed.

ENHANCING FUNDAMENTAL AGING AND LONGEVITY RESEARCH

A large part of talks at the conference considered fundamental research of aging mechanisms and the possibility of intervention into these mechanisms as a way toward prevention of multiple aging-related diseases and extension of healthy longevity. Various aspects of such intervention were discussed, from the general theoretical rationales for such interventions to more specific aging mechanisms for which intervention was proven feasible and capable of forming a basis for clinical translation into tangible healthy longevity therapies.

Thus, concerning the general rationale for geroscience-based interventions into aging, Prof. S. Jay Olshansky (School of Public Health at the University of Illinois at Chicago, US) in his talk "Implausibility of radical life extension in humans in the 21st century" emphasized that life extension without health extension would be harmful should it come to pass—unfortunately our current medical model of treating one disease at a time is heading us all in that direction. The solution is to attack the underlying risk factor for all fatal and disabling diseases-the biological process of aging; yielding a new form of primary prevention in the 21st century. Over the course of the 20th century, human life expectancy at birth rose in developed nations by around 30 years, largely driven by advances in public health and medicine. Mortality reduction observed initially at an early age, continued into middle and older ages. However, it was unclear whether this phenomenon and the resulting accelerated rise in life expectancy would continue into the 21st century. Here, using demographic survivorship metrics from national vital statistics in the nine longest-lived populations and the U.S. from 1990 to 2019, Prof. Olshansky's group explored recent trends in death rates and life expectancy [2]. They found that since 1990, improvements overall in life expectancy have decelerated during a time when dramatic advances in lifeextending technologies occurred. These advances should have accelerated the rise in life expectancybut they did not-illustrating the phenomenon of entropy that Olshansky and his colleagues identified decades earlier as a barrier to radical life extension. Their analysis also revealed that resistance to improvements in life expectancy increased, while lifespan inequality declined, and mortality compression occurred. Their analysis suggested that survival to age 100 is unlikely to exceed 15 percent for females and 5 percent for males, altogether suggesting that unless the processes of biological aging can be markedly slowed, radical human life extension is implausible in this century. The implication of these findings is that the only way out of this longevity corner that humanity has painted itself into, is through successful efforts to modulate the biological rate of aging, necessitating enhanced further research, development and education in the field of healthy longevity extension.

Considering the fundamental mechanisms of aging that could form the basis for interventions, Prof. Haim Cohen's team (Bar-Ilan University, Israel) explored maintaining healthy longevity by the enzyme SIRT6. Prof. Cohen's group earlier developed mice overexpressing SIRT6 (MOSES mice) that have extended lifespan along with significant improvement of their healthspan. Aging-related frailty typically manifests as a syndrome of a constellation of weakness, slowness, reduced activity, low energy and unintended weight loss. The group described the mechanisms underlying SIRT6 positive effects on healthy aging primarily by providing the required energy at old age and slowing aging-related frailty. In the current presentation, Prof. Haim Cohen introduced a new aspect of their research, namely the mammalian longevity-associated acetylome, or more broadly the post-translational modifications (PTM) and their association with longevity.

Prof. Björn Schumacher of the Institute for Genome Stability in Aging and Disease, CECAD Research Center, Faculty of Medicine, University of

Cologne, Germany, spoke about genome stability in aging, its mechanisms and interventions. He reemphasized that amid the demographic change, agerelated diseases are posing a major burden on society, where aging is the predominant risk factor for diseases ranging from dementia to cancer. The future of medicine requires a shift from treating diseases to prevention and health maintenance. Targeting aging as the root cause for age-related diseases requires the understanding of the mechanisms of aging. Human aging is greatly accelerated when DNA repair mechanisms are dysfunctional. The daily infliction of DNA damage in the nuclear genome requires constant repair. When DNA damage accumulates during aging, essential cellular processes such as transcription and replication are compromised, cellular function declines and cells increasingly undergo apoptosis and senescence. DNA damage is thus a root cause of aging. Prof. Schumacher's group uncovered the first master regulator of DNA repair capacities and proposed that by boosting overall DNA repair they could target the aging process at its fundamental root cause.

Prof. Susan Greenfield (Neuro-Bio, UK) presented a novel mechanism underlying aging. The new conceptualization has the following components. T14 is a peptide derived from acetylcholinesterase, but independently bioactive of it. It promotes cell growth and renewal in a wide range of in vitro preparations. It declines with normal aging as detected in brain, keratinocytes, sebum, blood, saliva, and nasal secretions. It acts selectively via an allosteric site on the alpha-7 receptor, which then triggers specific activation of the mTORC1 pathway. This process, if aberrantly activated, can lead to neurodegeneration, cancer and arguably conditions such as psoriasis and eczema, depending on the site. The action of T14 can be blocked by a cyclated variant NBP14. According to this concept, a balance is needed to promote antiaging levels of T14, where excessive levels would be offset by NBP14.

Prof. Valery Krizhanovsky (Department of Molecular Cell Biology. Weizmann Institute of Science. Israel), in his talk "Senescent cells: where to find them and how to deal with them" recapitulated that senescent cells accumulate in the body with age and cellular senescence has a key role in the aging process. Senescence appears to be a homeostatic mechanism that enables the tissue to heal when wounded, but becomes harmful when senescent cells accumulate in excess. This mechanism might be broadly relevant to agerelated pathologies involving tissue damage, such as diseases of the liver, lung, skin, pancreas, kidney, prostate, and the cardiovascular system. Prof. Krizhanovsky's group has recently discovered a mechanism that brings about an increase in senescent cells in old age. Previous studies showed that the body has a selfdefense mechanism for clearing senescent cells using the immune system. The study from Prof. Krizhanovsky lab revealed the complexity of senescent cells in aging lungs and in the lung with chronic inflammation. They discovered that senescent cells that arise from multiple origins, including the immune system itself, can contribute to chronic inflammation. Moreover, they showed that the expression of a central marker of senescence, p16, is mechanistically linked to the expression of immune checkpoint protein, thus limiting immune clearance of senescent cells [3]. This study reveals for the first time a mechanism that allows senescent cells to evade immune surveillance and remain in tissues. It might explain how senescent cells accumulate and how we can target this accumulation by new therapeutic approaches.

An additional crucial fundamental mechanism of aging was explored by Dr. Myriam Grunewald (Department of Developmental Biology and Cancer Research and the Hadassah Organoid Center, Israel) in her presentation "Undoing loss of microvascular homeostasis promotes healthy aging." She emphasized that aging is a complex process characterized by the gradual decline of physiological function and the onset of chronic diseases, driven by both cellular and systemic mechanisms. Among these, the vasculature plays a crucial role as more than just a passive conduit for blood, it is now recognized as an active gatekeeper of organ function and homeostasis. The vascular theory of aging posits that vascular dysfunction is a primary driver of systemic aging, as the vascular network is integral to maintaining tissue health. Dr. Grunewald's study provided direct evidence supporting this theory by demonstrating that maintaining Vascular Endothelial Growth Factor (VEGF) signaling in aged mice preserves vascular integrity and delays the onset of age-associated diseases across multiple organ systems. By sustaining VEGF signaling, their group observed improvements in hallmark features of aging, including alleviation of inflammaging, sarcopenia, osteoporosis, and metabolic dysfunction, as well as a reduction in tumor burden, likely mediated by enhanced immune function including thymic and peripheral immunity maintenance. These benefits led to significant extensions in healthspan and lifespan [4]. This comprehensive geroprotective effect underscores the vasculature's pivotal role in organismal aging and highlights the VEGF pathway as a promising therapeutic target for promoting healthy aging and mitigating age-associated diseases.

ENHANCING HEALTHY LONGEVITY RESEARCH AND DEVELOPMENT TOWARD CLINICAL TRANSLATION

Several talks emphasized developments close to the translational stage, yet still requiring a profound elaboration of aging mechanisms.

Considering the more practical translational aspects, Prof. Nir Barzilai (Albert Einstein College of Medicine, US), in his presentation "How to die young at a very old age?" described the scoring that was

developed by basic and clinical geroscientists for FDA-approved drugs in terms of their gerotherapeutic potential [5]. This work was further updated recently [6]. On a Scale of 12 (6 preclinical and 6 clinical points), the drug classes were ranked. The highest ranks of 10-12 were achieved by SGLT2 inhibitors (12), Metformin (11), Bisphosphonates (11), GLP1 receptor agonists (10). In each case, a clinical study has demonstrated that while each medication was officially approved for only one disease, data exists demonstrating ability to prevent other disease conditions, as well as overall mortality. Prof. Barzilai emphasized that while conventional wisdom has generally assumed that supplements are better and safer than approved drugs, this point must be challenged. In the absence of regulatory requirements, most supplements have never been shown to be safe and effective. Moreover, combinations of nutraceuticals may be even more harmful. In contrast, FDA-approved drugs have past safety and efficacy and have been out for many years (metformin for about 8 decades). Furthermore, SGLT-1 inhibitors, metformin and GLP1 receptor agonists have all been repurposed. For example, metformin has previously been repurposed (without FDA approval) for obesity, PCOS, prediabetes, and acute COVID-19. Repurposing is legal when prescribed by a licensed physician to a fully informed patient. Given growing evidence that these licensed and widely prescribed drugs exert pleiotropic effects attenuating varied biological hallmarks of aging, Prof. Barzilai proposed that physicians can consider prescribing gerotherapeutics as secondary prevention for older adults.

Dr. Efstathios S. Gonos (National Hellenic Research Foundation, Greece) spoke about the "development of personalized anti-ageing treatments." In particular, he reported the discovery of natural compounds that delay aging and importantly alleviate telomeres' integrity loss in a telomerase independent pathway, and spoke on the development of personalized anti-aging protocols and treatments. In particular, he presented data on the compounds 18 alpha-glycyrrhetinic acid (18alpha-GA) and omega-3 fatty acids (n3-FAs) as potentially powerful pharmacological activators of proteasome, capable of antiaging effects, in particular alleviating Alzheimer's disease pathology. Also, the positive effects of Alpha-terpineol on biomarkers of aging, such as telomere length, were reported.

Yaky Yanay (Pluri Biotech, Israel), in the talk "From Birth to Renewal: The Therapeutic Potential of Placental Cells to Promote Healthy Longevity," highlighted Pluri's work since 2003. The company has perfected methods to expand a single placental cell into billions of distinct cells, driving the development of advanced cell-based therapies for various medical indications. Yanay presented phase II and phase III clinical evidence of placental cells enhancing angiogenesis in limb ischemia, promoting muscle regeneration, supporting hematological recovery, and modulating immune function. These functions are crucial to healthy aging, highlighting the therapies' potential in longevity. He further discussed using allogeneic cell therapies as preventative treatments for age-related deterioration. Pluri's placenta-derived, allogeneic products, which do not require genetic or tissue matching, can be delivered in diverse clinical settings, aiming to restore the body's functions and provide preventive care against aging.

Dr. Natalie Yivgi-Ohana (CEO Minovia Therapeutics, Israel) spoke on revitalizing the immune system with young mitochondria. She believes aging is not a general disease, but it is predominantly a mitochondrial disease. In her talk, she shared insights into how their team measured mitochondrial dysfunction in different populations and correlated it with agerelated disease. Adding mitochondrial dysfunction as one of the mechanisms of age-related diseases can open the door to new therapeutic modalities. For example, their group showed that in myelodysplastic syndrome, an age-related bone marrow failure disorder, patients are suffering from mitochondrial dysfunction as measured using a novel Mito-Index scoring system developed by their group, and that treating with Mitochondrial Augmentation Technology (MAT) can improve disease outcomes.

ENHANCING THE MODELING AND MEASURING OF AGING AND LONGEVITY

A set of talks concerned general questions of aging modeling and measuring. Thus, Prof. Gil Atzmon (Faculty of Natural Sciences, University of Haifa, Israel) in his talk "Non-traditional approaches to longevity models" emphasized the point that the efforts invested in studying the aging process are immense; however, due to its complexity and lengthy duration, the acquired knowledge is far from complete. This is partly due to the lack of an accurate translatable shortlived human model capable of simulating the aging process in a short period of time. Animal models, accelerated aging diseases, and longevity, all have advantages and disadvantages in terms of becoming a realistic, translatable, short-lived human model capable of replicating the aging process in a short period of time. To overcome these obstacles (disadvantage), Prof. Atzmon's group proposed pregnancy as a translatable, short-term, and natural new human model for aging which demonstrates several similar physiological and cellular degradation mechanisms. They evaluated any similar processes between aging and pregnancy by comparing common biomarkers, pathologies, genetic and epigenetic effects, to establish the pregnant body as a model for aging. Introducing epigenetic and genetic signature to animal model and centenarians, they demonstrated the response of the pregnant body changes to the growing fetus that are similar to the aging process. They illuminated unique areas of potential study to advance our knowledge of the maladies relating to aging and pregnancy, and an avenue for solutions. Thus, Prof. Atzmon proposed pregnancy as an improved and more effective aging model that may help us comprehend the complicated features of a healthy lifetime. An additional outcome of this model is that, since postpartum recovery aids in the completion of reversal mechanisms, these mechanisms may be applicable to aging treatment, delaying the aging phenotype while also reversing aging processes.

Dr. Daniel Zvi Bar (The Faculty of Medicine, Tel Aviv University, Israel) reported their findings on epigenetic information loss as a common feature of multiple diseases and aging. The information theory of aging suggests that the loss of epigenetic information drives the aging process. While age-related epigenetic changes are well documented, their causal relationship with disease development remains poorly understood. Dr. Zvi Bar's group demonstrated that tissue-unique DNA methylation patterns degrade in multiple diseases, reverting toward patterns observed in other tissues. They interpret this regression to the mean as a loss of epigenetic information that defines tissue identity. This phenomenon extends beyond disease states similar erosion of unique methylation patterns occurs with natural aging in specific tissues and cells, though notably, some cell types show the opposite trend, diverging from mean methylation levels. Environmental stressors can trigger comparable changes in methvlation patterns. By analyzing these tissue-unique methylation sites, we can reliably distinguish between healthy and diseased states across various pathologies. These findings establish the loss of epigenetic information as a fundamental feature shared across multiple diseases, providing new insights into the relationship between aging and disease progression.

The importance of advanced modeling of aging, also from a physics perspective, combining mathematical modeling with big data analysis and experimentation was emphasized by Prof. Uri Alon of Weizmann Institute of Science, Israel, in his presentation on "A circuit approach to understand aging." Prof. Alon presented the saturating removal model of aging that explains the production and removal of damage (such as senescent and damaged cells) in aging. The model predicts that changes of the rate of damage production may increase the lifespan as well as the sickspan, while changes of the rate of damage removal that steepen the survival curve reduce the sickspan and correspondingly improve the healthspan. In accordance with the model, the geroprotective interventions that make the survival curve steeper (improve the healthspan) include senolytics, ketogenic diet and pro-vasculature interventions.

During the conference, more emphasis was added on the importance of big data analysis and mathematical modeling as being critical areas of aging research and geroprotective therapy development and implementation. Generally, Israel's strong sides in the international longevity field include advanced computational capabilities and unique access to massive longitudinal health data [1]. These capabilities were further exemplified by the presentation of Prof. Shai Shen-Orr of the Technion–Israel Institute of Technology. entitled "Exposed to Life-Getting at the Immunological Clock." He reported their group's longitudinal study which tracked healthy individuals across many years, revealing a high-dimensional, high-resolution trajectory that captures the dynamics of immunosenescence. This work led to the development of "IMM-AGE"-a single-score metric that comprehensively describes the age and state of an individual's immune system and predicts disease risk and all-cause mortality. The metric evaluates the state of a patient's immune system during the life-course in its relation to aging-differentiated clinical outcomes following therapeutic interventions, such as vaccinations.

ENHANCING THE PRACTICE OF LONGEVITY MEDICINE

A series of approaches to defining and improving practices of healthy longevity medicine were discussed. Thus, Prof. Evelyne Bischof and Prof. Tzipi Strauss (Sheba Longevity Center, Israel) shared their insights about managing a clinical longevity department, utilizing a multidisciplinary approach to advancing longevity medicine. The presentations focused on the development and management of a clinical longevity department, presenting it as a model for integrating cutting-edge science, clinical practice, and education. Central to this initiative was the establishment of a longitudinal cohort of healthy individuals, with a rigorous protocol for collecting and analyzing over 400 biomarkers of aging. This dataset, encompassing genetic, epigenetic, metabolic, and functional biomarkers, forms the foundation for understanding health trajectories and guiding individualized interventions. Key highlights included the department's dual focus on advancing the science of longevity medicine while ensuring its practical application. The integration of advanced predictive algorithms for health trajectory identification was emphasized. These algorithms utilize the longitudinal data to not only predict health outcomes but also provide precise targets for intervention, enabling the design of personalized therapeutic strategies. The use of biological aging clocks to monitor intervention efficacy and refine treatment plans was highlighted as a critical component of this approach. The presentation also detailed the role of the department as a hub for multidisciplinary collaboration. By fostering partnerships with other hospital disciplines, the department enables a holistic approach to longevity care, addressing the complex interplay of systems biology in aging.

Patient care pathways were designed to be dynamic, integrating insights from ongoing biomarker analyses to continually optimize health outcomes. Education and training were presented as integral to the department's mission. The program trains students, junior and senior physicians, and a dedicated team of longevity therapists. This effort ensures the dissemination of best practices and fosters a culture of innovation in the longevity field. The department's efforts in shaping the field of longevity medicine were underscored by its commitment to creating a platform for knowledge exchange, fostering research collaborations, and driving public and professional awareness of aging science. In conclusion, the presentation illustrated how the clinical longevity department combines datadriven precision medicine with interdisciplinary collaboration and robust educational initiatives. This comprehensive model not only advances the science of aging but also establishes a framework for practical, individualized longevity care, setting a benchmark for future developments in the field.

Dr. Natasha Vita-More (GCLS, Switzerland), in her presentation "The Art of Healthy Longevity: Commit, don't quit!" emphasized the need for wellinformed, practice-based approaches in building personalized longevity routines. These approaches are a multidimensional pursuit that includes healthspan and life expectancy through everyday practices that affect the body's ability to regulate cellular breakdown and vulnerabilities and primary for neuroplasticity. According to her exposition, human culture has long been shaped by mental constructs of caution and fear that no longer resonate with our modern aspirations for longer, healthier lives. These fear-based themes persist in society and reinforce a sense of powerlessness in the face of disease. Yet, amid the noise, there are tested and reliable paths forward for those willing to commit to healthy longevity. In her talk, she shared personal approaches to a healthy lifestyle, including 3.5 years at the Yoga College of India, 6000 hours weight training, 50 years practicing Transcendental Meditation, daily cognitive fitness, high-intensity sports, and slow-burn athletics. The research breaks new ground by integrating multi-levels of body and brain exercise into a cohesive framework.

Prof. Vittorio Calabrese (Department of Biomedical and Biotechnological Sciences, University of Catania, Italy) and Prof. Anzhela B. Kozhokaru (Department of Clinical Neurophysiology and Neurofunctional Diagnostics, of The Federal Medical-Biological Agency, Russia), though presenting separately, combined their insights under the common heading of "Sleep, Longevity and Healthy Ageing Medicine." They emphasized that ensuring healthy sleep and improving quality of life during aging is an important issue, as age-related pathologies have a much greater impact on healthcare systems in all nations of the world. The importance of sleep regularity and duration, the relationship of sleep/breathing disorders during sleep with cognitive impairment and cognitive reserve, the role of intermittent hypoxia in cognitive impairment, cardiovascular disease and carbohydrate metabolism disorders and the therapeutic relevance of dietary polyphenols are emerging areas of intense research interest. Modulation of endogenous cellular defense mechanisms via the stress response signaling represents an innovative approach to therapeutic intervention in diseases causing chronic tissue damage, such as neurodegeneration and cancer. Under optimal conditions long-term health protection is accomplished by a highly complex network of molecular interactions that by balancing and efficiently optimizing maintenance and repair processes involved in stress resistance, assure survival mechanisms. This is accomplished by a complex network of the so-called longevity assurance processes, composed of several genes termed vitagenes. The term vitagenes refers to a group of genes which are strictly involved in preserving cellular homeostasis during stressful conditions. Over the past decade there has been a remarkable increase of interest in hormesis as a result of more significance being given to low dose effects and the use of more powerful study designs which have enabled the researchers to identify rational approaches to detect hormetic biphasic dose responses in the low dose zone. The hormetic dose-response, challenging longstanding beliefs about the nature of the dose-response in a low zone, has the potential to affect significantly the design of pre-clinical studies and clinical trials as well as strategies for optimal patient dosing in the treatment of numerous diseases, including oxidant disorders. Given the broad cytoprotective properties of the Nrf2-dependent Vitagene network, there is now strong interest in discovering and developing pharmacological agents capable of inducing stress responses and cellular resilience. At present, many experimental and clinical studies aimed at studying sleep and longevity are being conducted, investigating the Nrf2/vitagene pathway as a target to improve sleep. Knowledge of the pathogenetic mechanisms offers significant potential diagnostic and therapeutic opportunities to improve sleep and promote healthy brain aging [7].

Dr. Marios Kyriazis (National Gerontology Centre, Cyprus) also considered the phenomena of hormesis for practical healthy longevity extension, presenting on the relation of intermittent fasting, hormesis, and adaptive responses. According to his presentation, the main biological purpose of dietary restriction protocols is to cause mild positive stress and so to repair any cell damage that exists. One such dietary restriction intervention is Intermittent Fasting, which creates a situation of positive nutritional stress and forces our organism to adapt and improve. In this way, health is maintained and any age-related damage is repaired. The phenomenon of hormesis was presented to be more general, explaining many of the effects of anti-aging interventions.

ENHANCING THE LONGEVITY INDUSTRY

A series of talks concerned the development of the multifaceted healthy longevity industry, facilitating the transition from fundamental aging research toward the commercialization and dissemination of longevity therapies and technologies.

Thus, Dmitry Kaminskiy (Deep Knowledge Group, Biogerontology Research Foundation, Longevity Industry Analytics, UK) stressed the importance of developing the global healthy longevity industry, including research, development and education aspects. The presentation emphasized that we stand on the cusp of a significant transition from Longevity Industry 1.0 to 2.0. The past decade has seen Longevity grow from a fringe science to a well-funded industry and veritable global mega-trend on-boarded by the highest echelons of science, finance and industry. In the coming decade, venture capital, which has been the primary driver of Longevity's industrialization, will be supplemented and potentially surpassed by entirely new driving forces of Longevity Industrialization. One of the most critical shifts will be the widespread rise of Health as the New Wealth and the emergence of new financial infrastructures, including Longevity Investment Banks, Stock Exchanges as well as health and Longevity-tied financial instruments and derivatives-de-risked and high-liquidity systems that will facilitate the Financial Commoditization of Longevity and its emergence as a new asset class. This will bridge the gap between the conservative investment community and the industry, unlocking trillions in previously inaccessible capital. Another fundamental change will be the rise of Longevity Politics, where Longevity becomes a central theme in national policies and international relations. Governments worldwide will begin to recognize the universal appeal of extending healthy life spans, fostering global cooperation, and making it a central pillar of their national agendas, and a major determinant of elections. Amid the rise of the Longevity Financial Industry and Longevity Politics as two new primary pillars driving the near future of Longevity Industrialization, the need for sophisticated analytical systems and approaches to define hype vs. reality and optimize strategic decision making within the unprecedentedly complex, multidimensional, cross-domain and technologically intersectional realm of Longevity will be more critical than ever before. Practical Longevity will also come into true fruition, bringing Longevity interventions into everyday life. This shift will distinguish hype from reality, as consumer-grade, accessible technologies take precedence over traditional clinical biomedicine. One of the most promising advancements in this space is the emergence of practically-oriented mitochondrial medicine technologies. These will represent a significant breakthrough in delivering actionable, consumer-focused health interventions that directly contribute to extending healthspan. Artificial Intelligence will continue to play a pivotal role in this transition, providing the tools needed to navigate the complex intersections of Longevity science, biomarkers, and individual health strategies, and making it possible to offer personalized, real-time interventions to consumers. Longevity is arguably the only truly universal cause that transcends race, creed, and geopolitical divisions. This is why the group created platforms like "Longevity.International" and have engaged in long-term cooperation with organizations such as the International Longevity Alliance, which began formally in 2018 via the successful joint project to add a World Health Organization-approved disease extension code for 'ageing related' (XT9T) during ICD-11, marking a significant step towards classifying aging as a treatable condition. In Israel, the group's collaboration with VETEK Association on the Longevity in Israel Ecosystem platform reflects the commitment to these principles, and the dedicated efforts to help foster a more globally inclusive Longevity industry, and make extended healthspans a universally accessible reality.

Fiona Miller (QuadraScope Venture Fund, US), in her talk, "Following the data: update on the longevity science and market" argued that longevity healthcare is emerging as a massive new industry that will change the world forever. In her talk, she reviewed current scientific developments on longevity and looked at examples of new ventures advancing the quest of human rejuvenation. She covered several examples of companies in the longevity field. These included Immunis with their novel approach to obesity treatment: strengthening the immune system to reduce chronic inflammation, which in turn builds muscle, which in turn burns fat. Immunis, according to the presentation, has unique technology that consists of hundreds of signaling proteins comprising the immune system secretome. Another company, Turn Bio, Fiona Miller anticipated, may soon be the first to market with epigenetic reprogramming therapy, which may be a promising longevity technology with the potential to rejuvenate any tissue or organs. Turn's first product will be for skin rejuvenation in partnership with a major esthetics company. She also reviewed the Israeli company BioChange which is already in the market with a veterinary product to regenerate bone and gum tissue to save dog's teeth from falling out. This technology is expected to be soon in human trials for tissue regeneration including receding gums, breast reconstruction, wound healing and other such treatments.

ENHANCING LONGEVITY EDUCATION

The importance of enhancing longevity education was emphasized by the presentation of new books in the longevity field, communities' and students' involvement in the conference.

Thus Dr. Arseniy Trukhanov (European Society of Preventive, Regenerative and Anti-Aging Medicine-ESAAM, Austria) presented the new book *Handbook* on Longevity Medicine: The Road Map recently published by ESAAM [8]. This handbook provides the basics of practical longevity medicine protocols and concepts for longevity medicine development in the future. Leading specialists in regenerative and longevity medicine presented their recommendations and opinions. Special attention was paid to the fundamental principles of the longevity clinic, as well as practical instructions on which of the existing protocols are the most effective from the point of view of international experts. The materials cover major fields of longevity medicine and science, including: immune ageing, hormetic nutrients, measurements of aging, policies for healthy longevity, the fundamentals of Mayr medicine in longevity, how sexuality and eroticism promote healthy ageing, protocols of regeneration technologies for the longevity medicine, holistic approaches to healthy longevity, international collaboration in longevity, cell and molecular therapies.

Prof. Vadim Fraifeld (Ben-Gurion University of the Negev, Israel) presented the book Rejuvenation and Longevity: Introduction to Rejuvenology. This book (Muradian, K.K. and Fraifeld, V.E., 2024) [9] is the first attempt to comprehensively analyze what rejuvenation is and its relationships with aging, longevity, origin of life, and the existence of life as is. The authors assert that, over the past decade, the study of rejuvenation has acquired a realistic shape and become a subject of scientific analysis. It would not be an overstatement to suggest that right now a new science is emerging-Rejuvenology. The book covers a wide spectrum of issues, from the evolutionary aspects of the origin of life, rejuvenation, immortality, and aging, to the analysis of species with extreme longevity (Species Exceeding Human Longevity, SEHL) and the evidence indicating that biological time could be reversible. Adding to the optimistic view is the fact that human knowledge and technological capabilities continue to grow exponentially, while the complexity of aging and rejuvenation remains relatively stable. This is a good reason to believe that, sooner or later, humanity will possess the tools to solve any biomedical problem, including those related to anti-aging and rejuvenation.

An intrinsic part of longevity education is building the healthy longevity support community. In this relation, Dr. José Luis Cordeiro (The Millennium Project, US, and HealthGevity Nation, Spain) spoke about the nascent Longevity movement in Latin America and the Middle East. He presented the HealthGevity Nation, a new international initiative to connect more people interested in longevity from the bottom-up. The HealthGevity Nation, Dr. Cordeiro reported, is growing with Ambassadors in many countries around the world, starting with Latin America and the Middle East. The fundamental need for education, the essential requirement for international knowledge exchange for the development of the healthy longevity field was stressed by Prof. Richard Faragher, representing the position of the American Federation for Aging Research, UK MRC–BBSRC Ageing Networks, and other groups.

Longevity education, or more precisely education needed to advance healthy longevity research, development and application, was additionally promoted at the conference via the Longevity Aspiration Prize. Young Israeli longevity researchers and research students who participated in the prize competition presented their works on the main themes of the conference, namely advancing research for enhancing healthy longevity and prevention of aging-related diseases, within diverse and intersecting areas of the healthy longevity field, from biology of aging, to application of medical longevity treatments, to social determinants and implications of geroscience. A special track in the competition was dedicated to presentations focusing on application of computational methods for early detection and prediction of aging-related ill-health [10] and evaluation of the effectiveness and safety of longevity and healthspan-improving treatments. The track was dedicated to the memory of Joseph Gitarts, an aspiring young longevity researcher, focusing on these topics, who fell in battle in Gaza in December 2023, at the age of 25. Great promise and great achievements were killed with his death, as many dreams were destroyed or harmed by the present war. But the conference organizers hope that the dream and drive will live on in the work of other aspiring longevity researchers. Indeed, the conference's main aim was to help maintain and encourage the drive of healthy longevity research, development and education, even under the present difficult conditions, so it can be reinforced in the future when the conditions hopefully improve.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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