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Editorial

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The Second Euro Geroscience Conference: Highlights of the Current Advances and Challenges in the Field of Geroscience

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Geroscience is a recent field of investigation that recognizes aging as the main risk factor for most chronic conditions and functional decline and stipulates that by intervening on biological aging, it is possible to prevent or delay the onset of several clinical conditions (e.g., diseases, geriatric syndromes, declines on function) and reduce their severity during aging. In this context, the second Euro Geroscience Conference took place on the 24th and 25th of March 2022 in Toulouse (France). This conference gathered the world leaders in the field of geroscience who reported and discussed current advances and developments in the field as well as the challenges that the field faces to pursue progress.

To promote knowledge advances in geroscience, it is imperative to understand the interplay in underlying mechanisms in the etiology of biological aging and age-related diseases to be able to implement concrete interventions. Approximately a decade ago, the first paper about the hallmarks of aging (1) paved the way to develop the perspective of biological aging as an actionable target. Since then, unprecedented discoveries have been achieved and the state of the art around geroscience were presented during the conference. For example, regarding the loss of proteostasis, one of the nine identified hallmarks of aging, studies showed that chaperone-mediated autophagy (2), which regulates the oxidized and damaged proteins, necroptosis inhibition in the context of neurodegenerative diseases (3), and plasma proteome (4) are potential effective targets for age-related interventions. New pathways of action to regenerate old stem cells were also revealed, that is through glucose transport for neuronal stem cells (5), and through the enzyme nicotinamide N-methyltransferase for skeletal muscle stem cells. Inflammaging is a well-known alteration associated with intercellular communication and a novel link was illustrated identifying the immune cells as the mediator between oxidation and inflammation (6). Concerning epigenetic alterations, a reprogramming strategy to erase or remodel epigenetic marks was discovered (7), the Alpha-Ketoglutarate compound was found to reduce DNA methylation, and a new layer of biological age dynamics suggested that increasing age caused by stress can be reversed following recovery from stress. Research on cellular senescence has also grown remarkably. Studies successfully identified a set of metabolites that have the ability to impact the senescence phenotype, found the way by which active telomerase can avoid replicative senescence in dysfunctional cells (8), and determined a network of anti-apoptotic regulators (9), a protective mechanism used by the senescent cells, that can be disabled. It has also been found that dysfunctional mitochondria in senescent cells can be a particularly relevant target for killing them. Finally, the discovery of the influence of tissue sex on the regulation of metabolic processes by mTOR could allow the development of sex-optimized therapeutics (10). All of these hallmarks of aging show interconnections and this illustrates the fact that some factors can have a global effect on aging.

Geroscience advances strongly rely on public-private initiatives, with many start-ups pushing the discoveries forward. Firstly, senolytic therapies showed promising results, such as a DRI-peptide-based approach against cancer and chronic diseases. It has also been found that anti-senescence interventions can counteract adverse health effects of radiation exposure (11) and fisetin analogs with improved senolytic activity and lowered toxicity were developed. Secondly, interventions targeting age-related functional decline are currently studied in clinical trials: mesenchymal stem cells showed the potential to improve the clinical outcomes of frailty and cognitive disorders (12), and two other ones, currently in study, have the objective to treat specifically sarcopenia through a drug activating the MAS receptor or the molecule RJx-01. Also, a multi-targeted pharmacology acting on NAD+ and targeting network rather than a single component has been developed.

Besides the development of gerotherapeutics, lifestyle interventions also appear to be relevant strategies as they showed beneficial effects on aging, such as dietary interventions like the Mediterranean diet as investigated in the NU-AGE study (13) and methionine restriction (14), and higher exercise level was found to be associated with better epigenetic and transcriptomic profiles in the human skeletal muscle (15).

One major challenge for the geroscience field is to translate the results obtained in laboratory animal models to humans. In this respect, it is fundamental to demonstrate that the biological mechanisms, as identified by the hallmarks of aging, are truly related to the aging process. There is a critical need for a consensus on the endpoints that should be measured in geroscience trials, and studies evaluating the effect of interventions on these endpoints will also allow the validation of surrogate biomarkers, which is currently missing in the field. The more we can measure, the more accurate and exhaustive the information will be. However, the usual approaches to studying aging biology can be expensive and with limited

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applicability in large clinical trials, limiting their expansion.

A new dimension has grown in the field: machine-learning and artificial intelligence methods may play a major role since they allow researchers to deal with large amounts of diverse data. To date, a machine-learning technique was used to measure efficiently a personalized health status, a novel computational approach allows the analysis of omics, genetic, and molecular data in neurodegenerative diseases, a novel algorithm enables the population scale assessment of epigenetic age, and finally, the first fibrosis therapy was found by an artificial intelligence (16).

The field of geroscience has grown substantially with discoveries both in the understanding of the biology of aging and the development of geroprotectors. However, progress is still to make as challenges remain to fully elucidate the aging process to, in fine, be able to prevent or treat the conditions affecting older adults.

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