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Editorial

THE STATE OF ALZHEIMER'S RESEARCH AND THE PATH FORWARD

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Advances in medicine and public health have resulted in a longer human lifespan worldwide. While this is a remarkable achievement, it has been accompanied by a rise in age-related chronic diseases, such as type 2 diabetes mellitus, cardiovascular disease, cancer, and neurodegenerative disease (1). Morbidity rates for these chronic age-related diseases increase steadily to middle age, then increase sharply, with individuals over 80 experiencing twice the prevalence compared to those aged 60-64, a phenomenon related to the Gompertz curve (2).

Gerontology is the study of aging, a discipline with much history and accumulated knowledge. The term gerontology was coined by Élie Metchnikoff in 1903, and the Journal of Gerontology was initiated in 1946. Within gerontology, geroscience is a multidisciplinary field that examines the relationship between aging biology and age-related chronic diseases. As a research priority for diseases that manifest in later stages of life, geroscience aims to understand the complex interactions between the fundamental processes of aging and the vulnerability to age-related disease (3). A better understanding of these relationships holds the potential to pave the way for more effective clinical interventions that address the diseases and conditions commonly experienced by older adults.

Over the course of almost eight decades of research in geroscience, several common processes that go awry with aging have been identified. These processes include inflammation, vascular dysfunction, aberrant proteostasis and autophagy, mitochondrial oxidative stress, metabolic dysfunction including insulin resistance, cellular senescence and accumulation of senescent cells, and epigenetic dysregulation. These common pathways are all implicated in the development and progression of Alzheimer's disease (AD) (4, 5, 6). Incorporating the principles of geroscience and leveraging the extensive knowledge of biological aging in AD research holds tremendous potential for developing new drugs and more comprehensive and effective treatment strategies. Each of these common biological aging pathways provides a viable therapeutic target to delay or prevent the onset and progression of AD.

In this issue of The Journal of Prevention of Alzheimer's Disease, we present promising therapeutics in development for AD that target biological aging processes. Chronic inflammation, known to contribute to numerous age-related diseases, is linked to reduced brain volume and impaired cognitive function in AD (4, 7). Although broad-spectrum anti-inflammatory drugs have largely failed, targeting specific aspects of inflammation while sparing others have shown promise. In this edition, Dr. Giordano discusses NTRX-07, a selective Cannabinoid Receptor 2 (CB2) agonist that has demonstrated the potential to reduce microglial-mediated neuroinflammation in AD. NTRX-07 is currently in Phase I clinical development and will soon be evaluated in multiple-ascending dose studies in individuals with early AD.

Another age-related process with implications for AD is cellular senescence, where cells evade death and accumulate over time, leading to the release of proinflammatory cytokines and chemokines that induce tissue damage in the brain and other organs (5). Drugs that selectively induce apoptosis of senescent cells are currently in clinical development to explore their efficacy in alleviating the inflammatory burden associated with AD. Dr. Orr presents a Phase II randomized, double-blind, placebo-controlled clinical study in this edition, investigating the safety and efficacy of the combination of two senolytic therapies, dasatinib and quercetin, in older adults with biomarker-confirmed mild cognitive impairment (MCI) or early-stage AD (NCT04685590).

Vascular pathology is also recognized as a contributor to the development of dementias like AD (4, 8). One vascular pathology of interest is vascular breakdown in the brain as a result of blood-brain barrier disruption. Vascular breakdown causes leakage of fibrinogen into the central nervous system, inducing neuroinflammation and formation of insoluble fibrin clots (9). While undetectable in the healthy brain, fibrinogen reaches detectable levels in the AD brain and interacts with amyloid, a hallmark pathological marker of AD, exacerbating clotting, fibrin deposition, and proinflammatory signaling (10, 11, 12). In this edition, Drs. Kantor and Stavenhagen introduce the development of a first in class fibrin-targeting immunotherapy for dementia. 5B8 is an antibody identified in mice that specifically targets fibrin deposits and it has been shown to block fibrin-induced activation of inflammatory cells that lead to neuronal loss, without

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interfering with the beneficial processes of blood clotting (13). 5B8 shows promise as a therapeutic for AD but also an imaging agent for brain vascular damage that could be used to identify early stages of AD.

Autophagy, the cellular process of breaking down and recycling aggregated misfolded and damaged organelles, is disrupted in aging. Aberrant autophagy is thought to contribute to the pathologic buildup of amyloid plaques, tau tangles, and other misfolded proteins in AD (6, 7). Recent clinical studies demonstrate that monoclonal antibodies against amyloid can slow clinical decline by up to 35% (14, 15, 16). Successes of these monoclonal antibodies indicate that misfolded amyloid proteins play a role in AD, but targeting amyloid alone is not sufficient to completely halt the disease progression. AD is often comorbid with pathologies of other misfolded proteins, such as alpha-synuclein, Lewy bodies, and TAR DNA-binding protein 43 (TDP-43) (17). Therefore, therapies that target aberrant autophagy more broadly may provide greater therapeutic benefit. In this edition, Dr. Rosenzweig-Lipson presents a novel class of drugs that activate chaperone-mediated autophagy. Reduced function of chaperone-mediated autophagy is linked to the aggregation of misfolded proteins in AD and other age-related diseases. By enhancing the clearance of misfolded proteins, these drugs hold promise as a therapeutic target for AD.

Mitochondrial dysfunction and oxidative stress increase with aging and are closely associated with neurodegeneration. High metabolic demands along with low levels of antioxidative defense mechanisms make the brain particularly susceptible to oxidative damage (18). Furthermore, shared aging mechanisms underlying AD and other age-related pathologies offer the opportunity to accelerate clinical development by repurposing drugs that have proven safe and efficacious in other disease areas. Edaravone, a free radical scavenger, has been approved for the treatment of stroke and Amyotrophic Lateral Sclerosis (ALS) in Asia and ALS in the US. Previous antioxidant therapies have been unsuccessful in AD, in part due to poor blood-brain barrier penetration (19). Unlike these previously tested agents, edaravone crosses the blood-brain barrier, making it a potential therapeutic strategy for AD. In this edition, investigators at Treeway B.V. introduce a Phase II Study designed to assess the preliminary efficacy and safety of an oral formulation of edaravone (TW001) in individuals with AD.

In addition, Dr. Trushina discusses the development of small molecule modulators of mitochondrial function as a disease-modifying therapy for AD. Mitochondrial dysfunction is detected early in the disease course. Small molecule partial inhibitors of mitochondrial complex I improve mitochondrial function, in part by restoring morphology and communication with other cell organelles and have been shown to be safe and efficacious in AD mice. Thus, these small molecule modulators offer a compelling strategy to modify the disease course at the earliest stages (20).

Synaptic dysfunction and loss of cortical synapses occur with normal aging but become further exacerbated in neurogenerative diseases like AD (21). Postmortem studies have revealed a reduction in synapses in people with MCI, suggesting synaptic alterations precede degeneration and occur early in the disease course (22). Therefore, drugs that promote neuronal and synaptic health may be critical in delaying or preventing degeneration of neurons in AD. In this edition, Dr. Longo introduces LM11A-31-BHS, an orally available small molecule ligand for the p75 neurotrophic receptor (p75NTR). This compound selectively activates p75NTR survival pathways and inhibits apoptosis signaling. LM11A-31-BHS has demonstrated ability to reverse cholinergic neurite degeneration in AD mouse models with mild to severe pathology and was recently tested in a Phase II/III proof-of-concept clinical trial involving patients with mild to moderate AD (NCT03069014). Neuroprotective agents like LM11A-31-BHS have the potential to delay onset of clinical symptoms if administered early in the disease course or to slow progression when administered at later stages.

Metformin and semaglutide, effective drugs against type 2 diabetes, are ideal candidates for repurposing to address the metabolic dysfunction in AD. In this edition, Dr. Luchsinger discusses metformin as a therapeutic strategy for AD prevention. Metformin is thought to regulate age-related metabolic dysfunction in the brain, a known contributor of cognitive decline, by improving brain metabolism and insulin sensitivity (23). Metformin is currently being studied in the Phase II/III Metformin in Alzheimer's Dementia Prevention (MAP) trial. This trial aims to further assess the therapeutic value of metformin as a prevention strategy for AD.

Lifestyle interventions are also being assessed for the prevention of AD. Global, large-scale clinical trials are currently underway to investigate how multidomain lifestyle interventions, alone or combined with certain medications, can reduce the risk of cognitive impairment and dementia. The pivotal FINGER trial, led by Dr. Kivipelto, has yielded critical insights by demonstrating that modifiable lifestyle factors not only slow cognitive decline but may improve cognitive performance in individuals at risk of dementia (24). In this edition, Dr. Kivipelto discusses the next phase of these studies, the MET-FINGER trial. MET-FINGER is a prevention study assessing whether combining healthy lifestyle changes with metformin can reduce the risk of dementia and improve overall health in older adults (NCT05109169). This combined approach may be more effective in reducing the risk of dementia compared to either intervention alone. Trials such as these are paving the way for a precision-medicine approach to prevention by leveraging an individual's modifiable risk factors and unique characteristics to create a personalized prevention strategy.

Furthermore, the edition extensively explores the essential role of biomarkers in advancing the discovery of new therapeutic options for AD. Biomarkers targeting pathology have been instrumental in the success of the recent anti-amyloid antibody therapies, enabling selective recruitment of patients with confirmed pathology, rigorous clinical trial designs, and improved treatment monitoring. Looking to the future, applying this paradigm to the biology of aging will enhance the rigor and efficiency of clinical trials, accelerate the availability of safe and efficacious therapies, and improve the overall patient journey for individuals with AD.

Aging is by far the leading risk factor for AD (25). As biomarkers targeting the biology of aging advance, it will be important to use these tools to identify and monitor one's biological age as opposed to their chronological age. Chronological age refers to the number of years we have been alive, while biological age is determined by assessing the aging of cells and tissues. The imminent ability to measure biological age in both research and clinical settings will deepen our understanding of the complexity of AD and create new opportunities for drug development (26).

The edition concludes by emphasizing the importance of taking a combination therapy approach to the treatment of AD. Such an approach is already the standard of care in other chronic age-related diseases, such as cancer and heart disease. Given that interventions that target one dysregulated system often attenuate others, combination therapies that target multiple age-related dysfunctions have the potential to produce synergistic effects. Recognizing that single-agent approaches may provide only incremental benefits, combination trials are essential to understanding how diverse therapeutic approaches work synergistically to provide meaningful treatment outcomes. Furthermore, combination trials are an integral step toward a precision medicine approach to AD, where a tailored drug cocktail can be recommended based on an individual's specific biomarkers and pathologies.

Conflicts of Interest: HMF receives royalties from the Icahn School of Medicine at Mount Sinai and, in the past 3 years, has received advisory board fees from Alector, Otsuka Lundbeck, LifeWorx, and The Key. BV is an investigator in clinical trials sponsored by Biogen, Eli Lilly, Roche, Eisai, Pfizer, Pierre Fabre, and the Toulouse University Hospital. BV has served on an advisory board for Biogen, Alzheon, Green Valley, Novo Nordisk, Longeveron, and Rejuvenate Biomed and has received honoraria for consulting or serving on an advisory board from Roche, Eli Lilly, Eisai, TauRx, and Cerecin. YH declares there are no conflicts of interest. The Alzheimer's Drug Discovery Foundation has funded or co-funded several projects to develop or clinically test the following drugs that are mentioned in the editorial: NTRX-07, dasatinib + quercetin, 5B8, TW001, LM11A-31-BHS, metformin, and semaglutide.

References

1. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. Cell. 2014;159(4):709-13.
2. Ricklefs RE, Scheuerlein A. Biological implications of the Weibull and Gompertz models of aging. J Gerontol A Biol Sci Med Sci. 2002;57(2):B69-76.
3. Burch JB, Augustine AD, Frieden LA, Hadley E, Howcroft TK, Johnson R, et al. Advances in geroscience: impact on healthspan and chronic disease. J Gerontol A Biol Sci Med Sci. 2014;69 Suppl 1(Suppl 1):S1-3.
4. Hara Y, McKeehan N, Fillit HM. Translating the biology of aging into novel therapeutics for Alzheimer disease. Neurology. 2019;92(2):84-93.
5. Gonzales MM, Garbarino VR, Pollet E, Palavicini JP, Kellogg DL, Jr., Kraig E, et al. Biological aging processes underlying cognitive decline and neurodegenerative disease. J Clin Invest. 2022;132(10).
6. Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. Cell. 2011;146(5):682-95.
7. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69 Suppl 1:S4-9.
8. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011;42(9):2672-713.
9. Bardehle S, Rafalski VA, Akassoglou K. Breaking boundaries-coagulation and fibrinolysis at the neurovascular interface. Front Cell Neurosci. 2015;9:354.
10. Ryu JK, McLarnon JG. A leaky blood-brain barrier, fibrinogen infiltration and microglial reactivity in inflamed Alzheimer's disease brain. J Cell Mol Med. 2009;13(9A):2911-25.
11. van Oijen M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Fibrinogen is associated with an increased risk of Alzheimer disease and vascular dementia. Stroke. 2005;36(12):2637-41.
12. Viggars AP, Wharton SB, Simpson JE, Matthews FE, Brayne C, Savva GM, et al. Alterations in the blood brain barrier in ageing cerebral cortex in relationship to Alzheimer-type pathology: a study in the MRC-CFAS population neuropathology cohort. Neurosci Lett. 2011;505(1):25-30.
13. Mendiola AS, Yan Z, Dixit K, Johnson JR, Bouhaddou M, Meyer-Franke A, et al. Defining blood-induced microglia functions in neurodegeneration through multiomic profiling. Nat Immunol. 2023.
14. Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease. 2023. https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional. Accessed 17 May 2023. [press release].
15. Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis. 2022;9(2):197-210.
16. Igarashi A, Azuma MK, Zhang Q, Ye W, Sardesai A, Folse H, et al. Predicting the Societal Value of Lecanemab in Early Alzheimer's Disease in Japan: A Patient-Level Simulation. Neurol Ther. 2023.
17. Boyle PA, Yang J, Yu L, Leurgans SE, Capuano AW, Schneider JA, et al. Varied effects of age-related neuropathologies on the trajectory of late life cognitive decline. Brain. 2017;140(3):804-12.
18. Jovanović Z. Antioxidative defense mechanisms in the aging brain. Archives of Biological Sciences. 2014;66(1):245-52.
19. Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, et al. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. Arch Neurol. 2012;69(7):836-41.
20. Panes J, Nguyen TKO, Gao H, Christensen TA, Stojakovic A, Trushin S, et al. Partial Inhibition of Complex I Restores Mitochondrial Morphology and Mitochondria-ER Communication in Hippocampus of APP/PS1 Mice. Cells. 2023;12(8).
21. Morrison JH, Baxter MG. The ageing cortical synapse: hallmarks and implications for cognitive decline. Nat Rev Neurosci. 2012;13(4):240-50.
22. Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2006;27(10):1372-84.
23. Lin Y, Wang K, Ma C, Wang X, Gong Z, Zhang R, et al. Evaluation of Metformin on Cognitive Improvement in Patients With Non-dementia Vascular Cognitive Impairment and Abnormal Glucose Metabolism. Front Aging Neurosci. 2018;10:227.
24. Kivipelto M, Solomon A, Ahtiluoto S, Ngandu T, Lehtisalo J, Antikainen R, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. Alzheimers Dement. 2013;9(6):657-65.
25. Association As. 2019 Alzheimer's disease facts and figures. Alzheimers Dement. 2019;15(3):321-87.
26. Ferrucci L, Gonzalez-Freire M, Fabbri E, Simonsick E, Tanaka T, Moore Z, et al. Measuring biological aging in humans: A quest. Aging Cell. 2020;19(2):e13080.

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