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The Landscape of Senolytics in Alzheimer's Disease

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Abstract:
Senolytics are a class of drugs that target and eliminate senescent cells, which are cells that have entered a state of permanent cell cycle arrest and accumulate with age. Alzheimer's disease is characterized by the accumulation of senescent cells in the brain, which contribute to disease progression and cognitive decline. Senolytics therapy has shown promise in preclinical studies as a potential treatment for Alzheimer's disease by reducing senescent cell burden and improving cognitive function. The most well-studied senolytics agents in Alzheimer's disease are dasatinib, quercetin, and fisetin, which have been shown to selectively eliminate senescent cells while sparing healthy cells.

Keywords: Senolytics, Alzheimer's, Dasatinib, Quercetin, Fisetin, Senescent

Introduction
The senolytics in Alzheimer's disease (AD) is fast developing, as many studies investigate the possibility of serological biomarkers to enhance diagnosis, track the course of the illness, and forecast treatment outcome[1]. Protein-based indicators that can be seen in blood serum or plasma are referred to as Senolytics[2]. These biomarkers have the ability to diagnose individuals who are at greater risk of developing AD in addition to track the course of the disease and forecast the extent to which a treatment will be effective. The potential of senolytics to supplement conventional diagnostic techniques[3], like neuroimaging and cognitive testing, which are frequently intrusive, costly, and might fail to detect the disease in its early stages, is the reason why makes these tests of such significance[4].

Hallmark of Alzheimer's disease
The state of senolytics in Alzheimer's disease currently have been found and explored. Amyloid-β (Aβ) is a hallmark of Alzheimer's disease (AD) [5], and its levels in cerebrospinal fluid have been extensively studied, with lower levels found in the serum of AD patients compared to healthy controls despite the invasive nature of cerebrospinal fluid collection.Tau protein is another protein associated with AD pathology, and elevated serum tau levels have been linked to AD diagnosis and severity[6]. Phosphorylated tau (p-tau) is a marker of tau hyper phosphorylation, a characteristic of AD, and elevated serum p-tau levels have been found in AD patients[7]. S100B is a calcium-binding protein involved in neuronal injury and death, and elevated serum S100B levels have been linked to AD diagnosis and cognitive decline[8].Neurofilament light chain (NfL) is a protein involved in neuronal damage and degeneration, and elevated serum NfL levels have been found in AD patients, potentially serving as a biomarker for disease progression[9].YKL-40 is a chitinase-like protein involved in inflammation and tissue remodelling, and elevated serum YKL-40 levels have been linked to AD diagnosis and cognitive decline[10].
Glycated haemoglobin (HbA1c) is a marker of glucose metabolism, and elevated serum HbA1c levels have been linked to AD diagnosis and cognitive decline[11]. Despite the promise of senolytics in AD, several challenges need to be addressed on Standardization of biomarker assays across different laboratories and countries are essential for accurate diagnosis and monitoring[12]. The sensitivity and specificity of senolytics need to be improved to ensure accurate diagnosis and minimize false positives/negatives.
Combination of senolytics with other biomarkers, such as neuroimaging or CSF-based biomarkers, may improve diagnostic accuracy[13]. Large-scale clinical trials are needed to validate the efficacy and safety of senolytics as diagnostic tools or therapeutic targets. In conclusion, the landscape of senolytics in Alzheimer's disease is rapidly evolving, with numerous studies exploring the potential of these biomarkers to improve diagnosis, monitoring, and treatment response[14]. While challenges remain, the development of senolytics has the potential to revolutionize the diagnosis and management of AD[15].

Alzheimer's disease is a devastating condition that impacts millions of individuals globally, leading to substantial cognitive deterioration, memory impairment, and shifts in behaviour[16]. Although there have been notable advancements in research and therapy, Alzheimer's continues to pose a significant public health dilemma[17]. This review is intended to offer an outline of the current state of Alzheimer's disease, encompassing its epidemiology, pathology, diagnosis, and treatment choices[18].

Time-Series Analysis

Alzheimer's disease is responsible for the majority of dementia cases, making up 60-80% of all instances[19]. It impacts around 5.8 million individuals in the United States and more than 50 million people globally[20]. The likelihood of developing Alzheimer's rises with age, with most cases occurring in those aged 65 and older[21]. Additionally, having a family history of the disease, particularly with first-degree relatives (parents or siblings), increases the risk by 2-3 times compared to the general population[22].

The prevalence of Alzheimer's disease has increased steadily over the years, from 2.8 million cases in 1991 to 10.5 million cases in 2024, with a significant jump in the last few years[23]. Meanwhile, the mortality rate from Alzheimer's disease has decreased, from 110.6 deaths per 100,000 populations in 1991 to 70.5 deaths per 100,000 populations in 2024, likely due to improved medical care and treatment options[24]. The incidence rate of Alzheimer's disease has also been increasing, from 133.1 new cases per 100,000 populations in 1991 to 225.7 new cases per 100,000 populations in 2024, likely due to the aging of the population and the increasing prevalence of risk factors such as diabetes and hypertension[25].

Unravelling the Mysteries of Alzheimer's: Aβ and Tau Protein

The accumulation of beta-amyloid (Aβ) and tau proteins characterizes Alzheimer's disease[26]. Aβ peptides are produced by the proteolytic cleavage of amyloid precursor protein (APP) and come together to create insoluble fibrils, which are harmful to neurons[27]. Tau protein is a microtubule-associated protein that undergoes hyper phosphorylation and forms neurofibrillary tangles (NFTs), disrupting regular neuronal function[28].

Neurocognitive diagnosis of Alzheimer's disease

Alzheimer's disease diagnosis presents a challenge due to the absence of definitive tests. Diagnosis usually involves a blend of clinical assessment, medical background, lab examinations, and imaging research[29]. Clinical assessment includes the evaluation of cognitive function, behaviour, and daily functioning. Lab tests might encompass blood assessments to exclude alternative causes of cognitive deterioration, like vitamin deficiencies or infections. Imaging research, such as MRI or PET scans, can be utilized to detect brain atrophy patterns or Aβ accumulation[30].

Multimodal therapy for Alzheimer's disease

Alzheimer's disease currently lacks effective treatments that can halt its progression. Nevertheless, there are multiple medications to address symptoms like memory loss, confusion, and agitation[31]. Cholinesterase inhibitors (Donepezil, Rivastigmine) and Memantine (NMDA receptor antagonist) are frequently prescribed to manage cognitive decline and behavioural disturbances. Additionally, lifestyle adjustments including exercise, social interaction, and cognitive stimulation may offer relief from these symptoms.

Several emerging therapies are being developed to target the underlying pathology of Alzheimer's disease, offering promising new approaches to combat the disease. These therapies include Aβ immunotherapies, which stimulate the immune system to clear Aβ from the brain, as well as tau-targeting therapies that prevent or reverse tau aggregation. Additionally, gene therapies aim to restore normal APP or tau function, while stem cell therapies use stem cells to repair or replace damaged neurons[32]. Furthermore, neuroprotective agents are designed to reduce oxidative stress and inflammation in the brain, providing a multi-faceted approach to tackling the complex disease.

Vulnerability to Alzheimer's disease

As people age, the risk of developing Alzheimer's increases significantly, with the likelihood of developing the disease doubling every 5 years after age 65. Family history also plays a role, as having a first-degree relative with Alzheimer's increases an individual's risk, while certain genetic mutations, such as APOE ε4, can significantly increase the risk[33]. Additionally, lifestyle factors may contribute to an increased risk, including physical inactivity, social isolation and loneliness, a history of cognitive decline or mild cognitive impairment, and medical conditions such as hypertension, diabetes, heart disease, depression, and sleep apnea. However, it's essential to note that many people with one or more of these risk factors do not develop Alzheimer's, and many people without these risk factors do develop the disease[34]. By understanding these risk factors, individuals can take steps to reduce their risk and maintain healthy brain function throughout their lives.

While there are no definitive ways to prevent Alzheimer's disease, several strategies may help reduce the risk. Lifestyle modifications such as regular exercise, social engagement, and cognitive stimulation can help build cognitive reserve and promote brain health[35]. Dietary interventions like consuming omega-3 fatty acids, antioxidants, and following a Mediterranean diet may also help reduce inflammation and oxidative stress, which are associated with the disease. Additionally, engaging in mentally stimulating activities like puzzles, learning new skills, or playing strategy games can help build cognitive reserve and delay cognitive decline[36]. Adequate sleep is also essential for cognitive health, and sleep deprivation can exacerbate cognitive decline. Furthermore, managing stress through relaxation techniques or meditation can help reduce the negative effects of chronic stress on brain health. By incorporating these strategies into daily life, individuals may be able to reduce their risk of developing Alzheimer's disease or slow down its progression[37].

Ongoing research is being conducted on Alzheimer's disease, with several promising areas of investigation for future directions. Researchers are exploring several promising approaches to develop new treatments for neurodegenerative diseases, including biomarkers that can accurately diagnose the condition at its earliest stages, personalized medicine that tailors treatments to an individual patient's unique genetic profile, stem cell therapies that aim to repair or replace damaged neurons, neuroprotective compounds that shield against neuronal damage, and combination therapies that bring together multiple therapeutic approaches to achieve better outcomes.

Alzheimer's disease is a significant public health concern, affecting over 5.8 million people in the United States alone. The disease is characterized by the accumulation of beta-amyloid plaques and tau tangles in the brain, leading to progressive cognitive decline and memory loss[38]. Diagnosis can be challenging, but researchers are developing new diagnostic tools and biomarkers to improve diagnosis and monitor disease progression. While there are no effective treatments yet, emerging therapies show promise, including immunotherapies and approaches that aim to slow down disease progression. Understanding the risk factors, such as age, genetics, and lifestyle factors like physical inactivity and smoking can help reduce risk and delay onset of symptoms. To make progress in treating Alzheimer’s continued research into its underlying causes is crucial, enabling the development of more effective treatments and improving diagnosis and treatment options in the future.

Alzheimer's disease is an advancing neurological condition that predominantly impacts elderly individuals, resulting in a decline in cognitive abilities and loss of memory. It is the primary type of dementia, marked by the gradual decline in brain function. Signs typically start with minor memory gaps and can develop into significant difficulties in communication, logical thinking, and daily activities[39] .

Age, genetics, and lifestyle factors are all risk factors associated with the development of Alzheimer's disease. Although there is no current cure, there are various treatments and interventions available to help manage symptoms and enhance the quality of life for individuals affected[40]. Early diagnosis and support play a crucial role in effectively managing the disease. If you have specific inquiries or require more detailed information, please feel free to ask.

A group of compounds known as senolytics are designed to target and remove senescent cells, which are cells that have ceased dividing and contribute to the process of aging and age-related diseases, such as Alzheimer's disease.

Senolytics Therapy and its implication

Dasatinib, a small molecule kinase inhibitor, has been shown to reduce senescent cell burden in the brain and improve cognitive function in animal models of Alzheimer's disease[41]. Quercetin, a plant-derived polyphenol, has been shown to selectively eliminate senescent cells in the brain and improve cognitive function in animal models of Alzheimer's disease. Fisetin, a flavonoid found in fruits and vegetables, has been shown to reduce senescent cell burden in the brain and improve cognitive function in animal models of Alzheimer's disease[42].

Clinical trials are underway to evaluate the safety and efficacy of senolytics therapy in Alzheimer's disease, with the first human trial having been completed in 2020.The landscape of senolytics in Alzheimer's disease is rapidly evolving, with multiple clinical trials underway to evaluate the potential of these therapies as a treatment for this devastating disease[43]. Overall, senolytics therapy holds significant promise as a potential treatment for Alzheimer's disease, offering a new approach to targeting the underlying biology of the disease.

Senescent cells in Alzheimer's can cause inflammation and interfere with regular cellular communication, which could worsen neurodegeneration[44].Research suggests that the build-up of senescent cells in the brain could contribute to the advancement of Alzheimer's disease. Employing senolytics to eliminate these cells may help diminish inflammation and enhance cognitive abilities. This strategy remains in the research phase, and although preliminary studies indicate potential benefits, additional investigation is required to comprehensively grasp the underlying mechanisms and the possible therapeutic advantages of senolytics within Alzheimer's signalling pathways[45].

Neuropathological studies of Alzheimer's disease

Chronic inflammation in the brain exacerbates neurodegeneration and cognitive decline, while synaptic loss and dysfunction impair communication between neurons[46]. As the disease progresses, brain regions involved in memory and learning undergo atrophy, leading to physical shrinkage of the brain. Changes in neurotransmitter systems, particularly acetylcholine, also contribute to cognitive decline.

The cumulative effects of neurodegeneration, inflammation, and synaptic dysfunction lead to various cognitive impairments, including difficulties with memory, problem-solving, and language[47].

Additionally, individuals with Alzheimer's may experience behavioural and psychological symptoms such as depression, anxiety, and agitation, which can further complicate the management of the disease. Co-occurring neurodegenerative disorders such as Parkinson's disease or vascular dementia can also complicate symptoms and treatment approaches.

The cumulative effects of Alzheimer's on the nervous system can significantly impact an individual's quality of life, including challenges in daily living, social interactions, and emotional well-being[48].

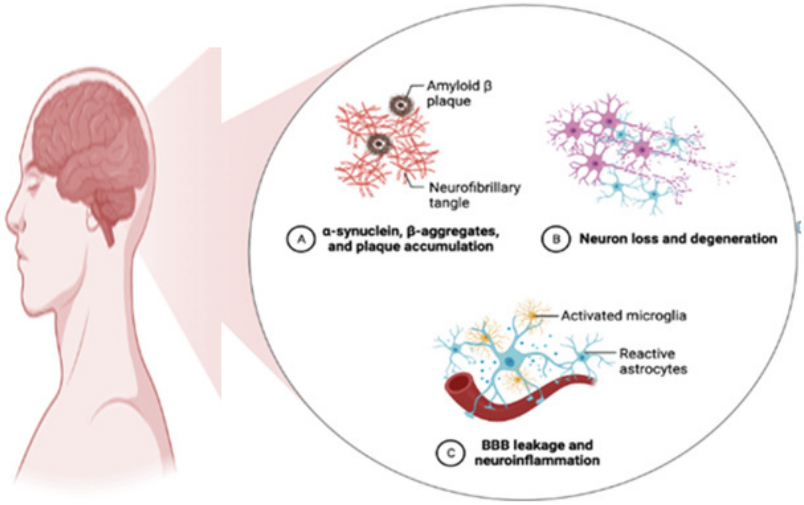


Fig.2. Targeting Beta amyloid plaque with Senolytics

Alzheimer's disease is characterized by the progressive degeneration of neurons in the brain, leading to a decline in cognitive functions such as memory, reasoning, and language skills. This neurodegeneration is accompanied by the accumulation of abnormal protein deposits, including amyloid plaques and tau tangles, which disrupt communication between neurons and contribute to cell death. Additionally, chronic inflammation in the brain exacerbates neurodegeneration and cognitive decline[50].

The disease also affects synapses, the connections between neurons, leading to synaptic dysfunction and impairing communication between neurons[51]. This results in memory loss and other cognitive deficits. Furthermore, Alzheimer's disease is associated with changes in neurotransmitter systems, particularly acetylcholine, which is crucial for memory and learning. The loss of cholinergic neurons contributes to cognitive decline. As the disease progresses, brain regions involved in memory and learning undergo atrophy, leading to physical shrinkage of the brain[52].

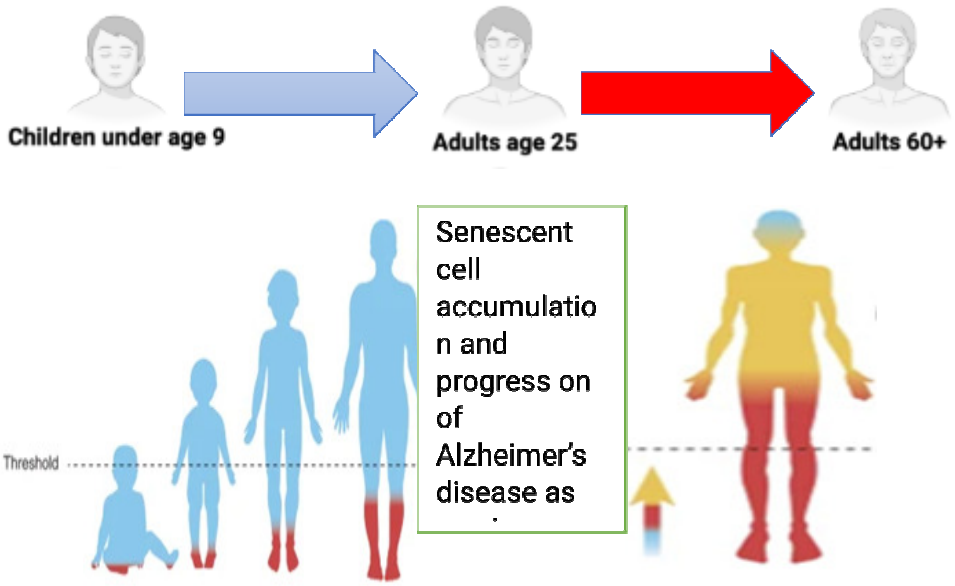
The cumulative effects of Alzheimer's on the nervous system can have significant impacts on an individual's quality of life, including challenges in daily living, social interactions, and emotional well-being. The disease can also coexist with other neurodegenerative disorders, such as Parkinson's disease or vascular dementia, complicating symptoms and treatment approaches[53]. Behavioural and psychological symptoms, such as depression, anxiety, and agitation, are also common in individuals with Alzheimer's disease, further complicating the management of the disease.

The global population of older individuals is on a consistent rise. According to estimates from the World Health Organization (WHO), by the year 2030, approximately 1 in 6 individuals, equating to 2.1 billion people, will be aged 60 or older. Chronological age serves as a primary indicator for the majority of diseases that contribute significantly to morbidity, mortality, and healthcare expenditures across various economic strata, including low-, middle, and high-income nations.

The process of aging unfolds throughout an individual's life and can be particularly pronounced at the etiological sites of numerous acute and chronic illnesses, even in paediatric populations. Notably, fundamental aging processes may commence prior to conception, as evidenced by the association of aged oocytes with conditions such as Down syndrome.

A key aging mechanism that has garnered considerable interest is cellular senescence. The accumulation of senescent cells occurs with aging and is observed at pathological sites associated with various disorders[54]. Following the initial reports of senolytics drugs agents designed to selectively target and eliminate senescent cells in 2015; encouraging outcomes from preclinical investigations have paved the way for early-phase clinical trials assessing the safety and effectiveness of these senolytics, with several studies now published.

Fig.2. Threshold theory of senolytics



Conclusion

Senescent cells have been associated in CNS pathology, according to an expanding body of research[55]. Nevertheless, there are differences over whether multiple cell types or just one specific cell type is at mistake. This could be explained that induce neuropathology using various stressors, as well as various senolytics drugs that have been identified.

References

1. Rinnerthaler, M., & Richter, K. (2018). The Basics of Biogerontology. In *InTech eBooks*. https://doi.org/10.5772/intechopen.76246
2. Golubnitschaja, O., Kapinova, A., Sargheini, N., Bojkova, B., Kapalla, M., Heinrich, L., Gkika, E., & Kubatka, P. (2024). Mini-encyclopedia of mitochondria-relevant nutraceuticals protecting health in primary and secondary care—clinically relevant 3PM innovation. The EPMA Journal, 15(2), 163–205. https://doi.org/10.1007/s13167-024-00358-4
3. Shashi, V., Schoch, K., Spillmann, R., Cope, H., Tan, Q. K., Walley, N., Pena, L., McConkie-Rosell, A., Jiang, Y., Stong, N., Need, A. C., Goldstein, D. B., Adams, D. R., Alejandro, M. E., Allard, P., Ashley, E. A., Azamian, M. S., Bacino, C. A., Balasubramanyam, A., . . . Lau, C. C. (2018). A comprehensive iterative approach is highly effective in diagnosing individuals who are exome negative. Genetics in Medicine, 21(1), 161–172. https://doi.org/10.1038/s41436-018-0044-2
4. Farris, W., Mansourian, S., Chang, Y., Lindsley, L., Eckman, E. A., Frosch, M. P., Eckman, C. B., Tanzi, R. E., Selkoe, D. J., & Guénette, S. (2003). Insulin-degrading enzyme regulates the levels of insulin, amyloid β-protein, and the β-amyloid precursor protein intracellular domain in vivo. Proceedings of the National Academy of Sciences, 100(7), 4162–4167. https://doi.org/10.1073/pnas.0230450100
5. Anamika PK, Muralidharan P. An extensive review on intricacies of autism spectrum disorder and associated pharmacological activity of centella asiatica. European Journal of Molecular and Clinical Medicine. 2021 Jan 15;8(2):662-80.
6. Andreasen, N., Hesse, C., Davidsson, P., Minthon, L., Wallin, A., Winblad, B., Vanderstichele, H., Vanmechelen, E., & Blennow, K. (1999). Cerebrospinal Fluid β-Amyloid(1-42) in Alzheimer Disease. Archives of Neurology, 56(6), 673. https://doi.org/10.1001/archneur.56.6.673
7. Mandel, S. A., Morelli, M., Halperin, I., & Korczyn, A. D. (2010). Biomarkers for prediction and targeted prevention of Alzheimer's and Parkinson's diseases: evaluation of drug clinical efficacy. The EPMA Journal, 1(2), 273–292. https://doi.org/10.1007/s13167-010-0036-z

8. Kofler, B., Brunner, S., Koller, A., Wiesmayr, S., Locker, F., Lang, R., Botz, B., Kemény, À., & Helyes, Z. (2015). Contribution of the galanin system to inflammation. SpringerPlus, 4(S1). https://doi.org/10.1186/2193-1801-4-s1-l57
9. Borreca, A. (2019). Recent Advances in Neurodegeneration. In *IntechOpen eBooks*. https://doi.org/10.5772/intechopen.71995
10. Cohen, J., Mathew, A., Dourvetakis, K. D., Sanchez-Guerrero, E., Pangeni, R. P., Gurusamy, N., Aenlle, K. K., Ravindran, G., Twahir, A., Isler, D., Sosa-Garcia, S. R., Llizo, A., Bested, A. C., Theoharides, T. C., Klimas, N. G., & Kempuraj, D. (2024). Recent Research Trends in Neuroinflammatory and Neurodegenerative Disorders. Cells, 13(6), 511. https://doi.org/10.3390/cells13060511
11. Hjelmesæth, J., Midtvedt, K., Jenssen, T., & Hartmann, A. (2002). Insulin Resistance After Renal Transplantation. Diabetes Care, 25(7), 1260–1261. https://doi.org/10.2337/diacare.25.7.1260
12. Sharma, A. K., Roberts, R. L., Benson, R. D., Pierce, J. L., Yu, K., Hamrick, M. W., & McGee-Lawrence, M. E. (2020). The Senolytic Drug Navitoclax (ABT-263) Causes Trabecular Bone Loss and Impaired Osteoprogenitor Function in Aged Mice. Frontiers in Cell and Developmental Biology, 8. https://doi.org/10.3389/fcell.2020.00354
13. De Vries, L. E., Huitinga, I., Kessels, H. W., Swaab, D. F., & Verhaagen, J. (2024). The concept of resilience to Alzheimer's Disease: current definitions and cellular and molecular mechanisms. Molecular Neurodegeneration, 19(1). https://doi.org/10.1186/s13024-024-00719-7
14. Betz, U. A., Arora, L., Assal, R. A., Azevedo, H., Baldwin, J., Becker, M. S., Bostock, S., Cheng, V., Egle, T., Ferrari, N., Schneider-Futschik, E. K., Gerhardy, S., Hammes, A., Harzheim, A., Herget, T., Jauset, C., Kretschmer, S., Lammie, C., Kloss, N., . . . Zhao, G. (2023b). Game changers in science and technology - now and beyond. Technological Forecasting and Social Change, 193, 122588. https://doi.org/10.1016/j.techfore.2023.122588
15. Costa, A., Pittorru, R., Caocci, G., Migliore, F., Tona, F., Mulas, O., & La Nasa, G. (2023). The Direct and Indirect Effects of Tyrosine Kinase Inhibitors on the Cardiovascular System in Chronic Myeloid Leukemia. Hemato, 4(3), 207–226. https://doi.org/10.3390/hemato4030017
16. Health Reform. (2011). In OECD eBooks. https://doi.org/10.1787/9789264122314-en
17. Wilkinson, S. B. T., Rowe, G., & Lambert, N. (2004). The risks of eating and drinking. EMBO Reports, 5(S1). https://doi.org/10.1038/sj.embor.7400225
18. Grand, J. H., Caspar, S., & Macdonald, S. W. (2011). Clinical features and multidisciplinary approaches to dementia care. Journal of Multidisciplinary Healthcare, 125. https://doi.org/10.2147/jmdh.s17773
19. 2023 Alzheimer's disease facts and figures. (2023). Alzheimer S & Dementia, 19(4), 1598–1695. https://doi.org/10.1002/alz.13016
20. Rosamond, W., Flegal, K., Furie, K., Go, A., Greenlund, K., Haase, N., Hailpern, S. M., Ho, M., Howard, V., Kissela, B., Kittner, S., Lloyd-Jones, D., McDermott, M., Meigs, J., Moy, C., Nichol, G., O'Donnell, C., Roger, V., Sorlie, P., . . . Hong, Y. (2007). Heart Disease and Stroke Statistics—2008 Update. Circulation, 117(4). https://doi.org/10.1161/circulationaha.107.187998
21. Durgan, D. J., & Bryan, R. M. (2012). Cerebrovascular Consequences of Obstructive Sleep Apnea. Journal of the American Heart Association, 1(4). https://doi.org/10.1161/jaha.111.000091
22. McGregor, J. M., Grabczynska, S., Hawk, J. L., Vaughan, R., & Lewis, C. M. (2000). Genetic Modeling of Abnormal Photosensitivity in Families with Polymorphic Light Eruption and Actinic Prurigo. Journal of Investigative Dermatology, 115(3), 471–476. https://doi.org/10.1046/j.1523-1747.2000.00080.x
23. Langener, A. (2024). From Data Streams to Mental Health Predictions: Improving the use of Passive Measures from Digital Devices. https://doi.org/10.33612/diss.1069770227
24. Song, Y., Kim, H., Lee, M., Hong, I., Won, C., Bai, H., Lee, S. S., Lee, S., Chung, B. Y., & Cho, J. (2017). Maysin and Its Flavonoid Derivative from Centipedegrass Attenuates Amyloid Plaques by Inducting Humoral Immune Response with Th2 Skewed Cytokine Response in the Tg (APPswe, PS1dE9) Alzheimer's Mouse Model. PLoS ONE, 12(1), e0169509. https://doi.org/10.1371/journal.pone.0169509
25. Jemal, A., Thomas, A., Murray, T., & Thun, M. (2002). Cancer Statistics, 2002. CA a Cancer Journal for Clinicians, 52(1), 23–47. https://doi.org/10.3322/canjclin.52.1.23
26. Soto, C. (2012). Transmissible Proteins: Expanding the Prion Heresy. *Cell*, *149*(5), 968–977. https://doi.org/10.1016/j.cell.2012.05.007
27. Kerrigan, S., Matthay, Z., Kornblith, L., Balint, B., Pavlovic, M., Todorovic, M., Poddar, M., Banerjee, S., Águila, S., Cuenca-Zamora, E., Martínez, C., Teruel-Montoya, R., Syndrome, B., Mesut, M., Engin, N., Resch, B., Saglanmak, A., Cinar, C., & Gultekin, A. (2020). Platelets. In IntechOpen eBooks. https://doi.org/10.5772/intechopen.77663

28. How does "Protein Corona" Affect the In vivo Efficiency of Polymeric Nanoparticles? State of Art. (2017). In BENTHAM SCIENCE PUBLISHERS eBooks (pp. 199–238). https://doi.org/10.2174/9781681084930117020011
29. Readdick, C., Ballard, S., Settles, B., Boss, P., Macklin, E., Fischer, J., Bailey, S., Letiecq, B., Iglesias, A., Pomelow, M., Viti, N., Coco, C., Readdick, A., Roux, T. L., & Litt, D. (2023). Caring for Each Other: Family Caregiving Across the Generations. https://doi.org/10.3998/mpub.12844648
30. Dagres, N., Chao, T. F., Fenelon, G., Aguinaga, L., Benhayon, D., Benjamin, E. J., Bunch, T. J., Chen, L. Y., Chen, S. A., Darrieux, F., De Paola, A., Fauchier, L., Goette, A., Kalman, J., Kalra, L., Kim, Y. H., Lane, D. A., Lip, G. Y., Lubitz, S. A., . . . Chung, M. K. (2018). European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: What is the best practice? Journal of Arrhythmia, 34(2), 99–123. https://doi.org/10.1002/joa3.12050
31. Tocher, D. R. (2015). Omega-3 long-chain polyunsaturated fatty acids and aquaculture in perspective. *Aquaculture*, *449*, 94–107. https://doi.org/10.1016/j.aquaculture.2015.01.010
32. Torres, M., Busquets, X., & Escribá, P. V. (2016). Brain Lipids in the Pathophysiology and Treatment of Alzheimer's Disease. In InTech eBooks. https://doi.org/10.5772/64757
33. Klinedinst, B. S. (2021). *Investigation and description of the New Brain and New Mind hypotheses*. https://doi.org/10.31274/td-20240329-457
34. Rosamond, W., Flegal, K., Furie, K., Go, A., Greenlund, K., Haase, N., Hailpern, S. M., Ho, M., Howard, V., Kissela, B., Kittner, S., Lloyd-Jones, D., McDermott, M., Meigs, J., Moy, C., Nichol, G., O'Donnell, C., Roger, V., Sorlie, P., . . . Hong, Y. (2007b). Heart Disease and Stroke Statistics—2008 Update. Circulation, 117(4). https://doi.org/10.1161/circulationaha.107.187998
35. Chambers, D., Cantrell, A., Sworn, K., & Booth, A. (2022). Assessment and management pathways of older adults with mild cognitive impairment: descriptive review and critical interpretive synthesis. *Health and Social Care Delivery Research*, *10*(10), 1–150. https://doi.org/10.3310/xluj6074
36. Whitson, J. (2013). Game design by numbers : instrumental play and the quantitative shift in the digital game industry. https://doi.org/10.22215/etd/2013-08579
37. LeRoith, D., Biessels, G. J., Braithwaite, S. S., Casanueva, F. F., Draznin, B., Halter, J. B., Hirsch, I. B., McDonnell, M. E., Molitch, M. E., Murad, M. H., & Sinclair, A. J. (2019). Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, *104*(5), 1520–1574. https://doi.org/10.1210/jc.2019-00198
38. Imbimbo, B. P., Balducci, C., Ippati, S., & Watling, M. (2022). Initial failures of anti-tau antibodies in Alzheimer's disease are reminiscent of the amyloid-β story. Neural Regeneration Research, 18(1), 117. https://doi.org/10.4103/1673-5374.340409
39. Artificial Intelligence in Society. (2019). In *OECD eBooks*. https://doi.org/10.1787/eedfee77-en
40. August, D. A., & Huhmann, M. B. (2009). A.S.P.E.N. Clinical Guidelines: Nutrition Support Therapy During Adult Anticancer Treatment and in Hematopoietic Cell Transplantation. Journal of Parenteral and Enteral Nutrition, 33(5), 472–500. https://doi.org/10.1177/0148607109341804
41. Prasanna, P. G., Citrin, D. E., Hildesheim, J., Ahmed, M. M., Venkatachalam, S., Riscuta, G., Xi, D., Zheng, G., Van Deursen, J., Goronzy, J., Kron, S. J., Anscher, M. S., Sharpless, N. E., Campisi, J., Brown, S. L., Niedernhofer, L. J., O'Loghlen, A., Georgakilas, A. G., Paris, F., . . . Coleman, C. N. (2021). Therapy-Induced Senescence: Opportunities to Improve Anticancer Therapy. JNCI Journal of the National Cancer Institute, 113(10), 1285–1298. https://doi.org/10.1093/jnci/djab064
42. Sip, S., Rosiak, N., Sip, A., Żarowski, M., Hojan, K., & Cielecka-Piontek, J. (2023). A Fisetin Delivery System for Neuroprotection: A Co-Amorphous Dispersion Prepared in Supercritical Carbon Dioxide. Antioxidants, 13(1), 24. https://doi.org/10.3390/antiox13010024
43. Buonfiglio, F., Korb, C. A., Stoffelns, B., Pfeiffer, N., & Gericke, A. (2024). Recent Advances in Our Understanding of Age-Related Macular Degeneration: Mitochondrial Dysfunction, Redox Signaling, and the Complement System. Aging and Disease. https://doi.org/10.14336/ad.2024.0124
44. Vitorakis, N., & Piperi, C. (2023). Insights into the Role of Histone Methylation in Brain Aging and Potential Therapeutic Interventions. *International Journal of Molecular Sciences*, *24*(24), 17339. https://doi.org/10.3390/ijms242417339
45. Liao, P., Yan, B., Wang, C., & Lei, P. (2023). Telomeres: Dysfunction, Maintenance, Aging and Cancer. Aging and Disease. https://doi.org/10.14336/ad.2023.1128

46. Hambright, W. S., Fonseca, R. S., Chen, L., Na, R., & Ran, Q. (2017). Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration. *Redox Biology*, *12*, 8–17. https://doi.org/10.1016/j.redox.2017.01.021
47. Abstracts for the XXIV International Symposium on Morphological Sciences, 2nd-6th September, 2015, Istanbul, Turkey. (2015). Anatomy (International Journal of Experimental and Clinical Anatomy), 9(Suppl 2), S75–S248. https://doi.org/10.2399/ana.15.075s
48. Jones, G. R., Stathokostas, L., Young, B. W., Wister, A. V., Chau, S., Clark, P., Duggan, M., Mitchell, D., & Nordland, P. (2018). Development of a physical literacy model for older adults – a consensus process by the collaborative working group on physical literacy for older Canadians. BMC Geriatrics, 18(1). https://doi.org/10.1186/s12877-017-0687-x
49. Medeiros, R., Kitazawa, M., Passos, G. F., Baglietto-Vargas, D., Cheng, D., Cribbs, D. H., & LaFerla, F. M. (2013). Aspirin-Triggered Lipoxin A4 Stimulates Alternative Activation of Microglia and Reduces Alzheimer Disease–Like Pathology in Mice. *American Journal of Pathology*, *182*(5), 1780–1789. https://doi.org/10.1016/j.ajpath.2013.01.051
50. Kelleher, R. J., & Bear, M. F. (2008). The Autistic Neuron: Troubled Translation? Cell, 135(3), 401–406. https://doi.org/10.1016/j.cell.2008.10.017
51. Phelan, K., & McDermid, H. (2011). The 22q13.3 Deletion Syndrome (Phelan-McDermid Syndrome). *Molecular Syndromology*, *2*(3–5), 186–201. https://doi.org/10.1159/000334260
52. Van Dellen, A., Cordery, P. M., Spires, T. L., Blakemore, C., & Hannan, A. J. (2008). Wheel running from a juvenile age delays onset of specific motor deficits but does not alter protein aggregate density in a mouse model of Huntington's disease. *BMC Neuroscience*, *9*(1). https://doi.org/10.1186/1471-2202-9-34
53. Goyal, A. R., Bergh, S., Engedal, K., Kirkevold, M., & Kirkevold, Ø. (2016). Norwegian version of the rating anxiety in dementia scale (RAID-N): a validity and reliability study. *Aging & Mental Health*, *21*(12), 1256–1261. https://doi.org/10.1080/13607863.2016.1220921
54. Choi, J., Kim, T., & Cho, E. (2024). HIRA vs. DAXX: the two axes shaping the histone H3.3 landscape. *Experimental & Molecular Medicine*, *56*(2), 251–263. https://doi.org/10.1038/s12276-023-01145-3
55. White, T., Bruns, T., Lee, S., & Taylor, J. (1990). AMPLIFICATION AND DIRECT SEQUENCING OF FUNGAL RIBOSOMAL RNA GENES FOR PHYLOGENETICS. In *Elsevier eBooks* (pp. 315–322). https://doi.org/10.1016/b978-0-12-372180-8.50042-1

