Alzheimer's Disease

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ABSTRACT
Alzheimer's disease (AD) is the most common form of dementia around the world. Although the pathological mechanism of AD is not fully established, the deposition of beta-amyloid plaques, neurofibrillary tangles and inflammation have been characterized to be involved in AD's pathology. Diagnosis of AD has been developed not only based on clinical criteria but also take the advantage of biomarkers imaging and fluid test. Currently, while the treatment of AD only focuses on the symptomatic therapy, more advanced trials that under the guidance of pathology are under development. Here, we will first summary the current hypothesis of AD's pathological mechanism and then review the diagnosis and treatment of AD and those methods developed in progress.

Keywords: *Dementia, neurodegenerative disease, Alzheimer's disease, Amyloid cascade hypothesis, Tau-protein, neuroinflammation*

1. INTRODUCTION

Alzheimer's disease (AD) is a typical neurodegenerative disease. The disease is caused by brain disorder and is usually irreversible and progressive. The typical symptoms the patients can have are memory loss, language problems, and unpredictable behavior. There are more than 50 million people globally suffered from this disease. Alzheimer's disease also brings a huge financial burden to the families that have Alzheimer patients due to the expensive drugs and high payments to the nursing workers. Furthermore, it affects the economics growth of the whole country as part of the government fund need to be used on health insurance [1][2]. Alzheimer's disease was first discovered by a Germany doctor called Alois Alzheimer in 1907 and named by him. According to previous studies, it has been found that the brain of the patients usually shrunk significantly with many abnormal clumps and tangled bundles of fibers deposit in the brain3. The clumps and tangled fibers now are confirmed as amyloid plaques and hyperphosphorylated tau proteins respectively [3]. The deposition of these two proteins is toxic to neuron cells which can lead to neuronal dysfunction and thus cause damage to neurons and breakdown the whole neural network. The hippocampus and the entorhinal cortex, two areas that are associated with memory forming and learning ability are the first place for neuronal dysfunction to take place. Then, the damage is further expanded to additional parts of the brain and eventually results in whole brain shrinking. Recently, it has been found out that amyloid plaques and hyperphosphorylated tau protein can not only play a role directly in the pathology of AD, but also can damages the synapses and neuritis in AD brains resulting in a loss synapses, reactive gliosis, microglial activation, and neuroinflammation [4]. Up to date, the most important hypothesis is: beta-amyloid (Aβ) peptide accumulation, tau hyperphosphorylation and neurofilament accumulation and neuroinflammation.

Traditionally, the diagnosis of AD based on the clinical criteria of the patients. However, the sensitivity and specificity of the traditional diagnosis method is low. In order to address this issue, modern detective method that based on the pathological theories such as position emission tomography (PET) and examination of the content of biomarkers of AD such as Aβ and hyperphosphorylated tau peptide (p-tau) in cerebrospinal fluid (CSF) were developed. Current treatments such as cholinesterase inhibitors and agonist are targeted mostly toward symptoms, but none of them can cure or halt AD progression. Therefore, the development of advanced treatment method is urgent. Based on hypothesis of Aβ and p-tau, more new methods and medicine are developed.

In this literature review, we summarizes the three pathological hypothesis of AD, the current AD treatment and the conventional and modern diagnosis of AD.

2. THE AMYLOID CASCADE HYPOTHESIS

Among all the hypothesis that related to the nosogensis of alzheimer's disease, the extracellular accumulation of Aβ hypothesis is the predominant one that has been emphasized by recent studies and is commonly accepted as a mechanism of AD. Amyloid cascade hypothesis shows that AD is result of a series of pathological disorders, involving the accumulation and deposition of Aβ the formation of amyloid plaques and the synaptic and neuronal dysfunction caused by these plaques.

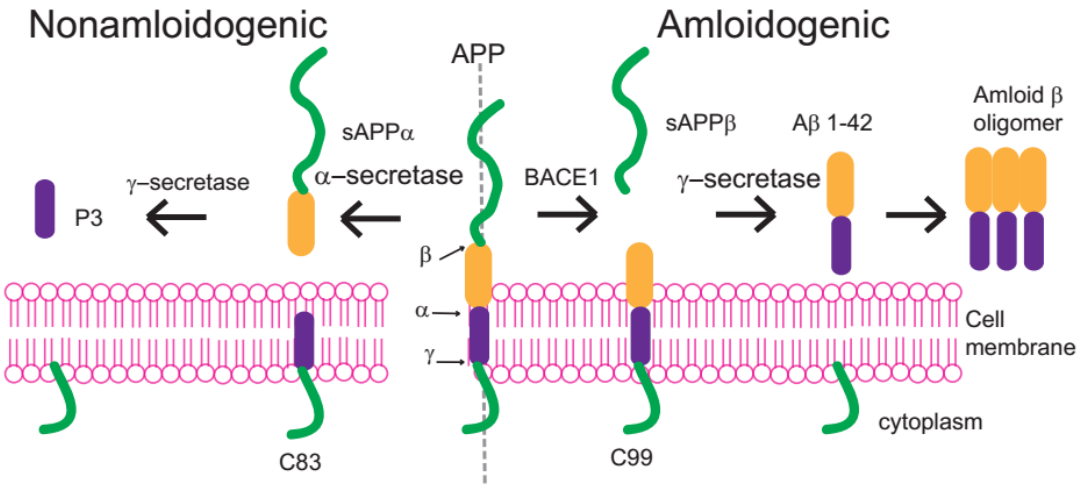

Figure 1 Amyloid Cascade Hypothesis

Figure 1 Schematic representation of APP processing and Aβ accumulation. APP is hydrolyzed by 2 competing pathways, the α-secretase pathway generating sAPPα and C83, and the β-secretase pathway that results in sAPPβ and C99. C99 then is hydrolyzed at γ site producing Aβ. Aβ aggregates into small multimers (dimers, trimers, etc.) known as oligomers.

Aβ is a peptide that is highly insoluble and very hard to undergo proteolytic degradation. Amyloid 1-42 isofroms is considered to have the highest hydrophobicity and the greatest cellular toxicity. Due to its structural properties, it is often presented as aβ-pleated sheet construction, which has high tendency to aggregate and form the core of amyloid plaque [5][6][7][8][9]. The Aβamyloid is generated by the abnormal hydrolysis of amyloid precursor protein (APP) (figure 1), which is a transmembrane glycoprotein found in brain with unclear function. For normal degradation of APP, the APP was breakdown by enzyme called ADAM at its α site, producing an amino terminal peptide called APPsα and a fragment of the carboxyl terminal portion. The carboxyl terminal portion is then breakdown further into p3 and AICD, all the products produced in normal breaking down process are soluble and nontoxic [10][11]. However, in an AD patient brain, the APP is breakdown in a different way at its β site by β-secretase, calledβ-site APP cleaving enzyme (BACE 1), forms a shorter soluble toxic amino terminal portion APPsβ and a longer terminal carboxyl fragment (C99) [12]. The further hydrolysis of APPsβ at γ site produces the β amyloid and AICD. The β-amyloid produced can aggregate into plaques which disrupt the connection between neurons and result a breakdown in neuron network, thus cause AD.

Although it is generally accepted that Aβ plaques play a significant role in AD pathogenesis, the mechanisms are still unclear and need further development and research. Recent studies indicate that the oligomers also damage nervous cells in different ways such as affecting the nucleus and ribosomes as well as mitochondria causing damage in genome information, perforating cell membrane resulting the abnormal outflow and inflow of ions thus causing an imbalance membrane potential. Further studies also show that Aβ aggregation are proven to activate microglial cells and lead to the production of inflammatory mediators which promote neuronal death, suggesting that Aβ accumulation may activate the inflammatory systems and cause inflammation in brain.

3. TAU PROTEIN

Besides Ab plaques, neurofibrillary tangles (NFTs) also contribute to the progression of Alzheimer's disease. These tangles are formed from an aggregation of hyperphosphorylated tau proteins inside the cell and cause the decrease of microtubules stability and disrupt cells' normal function thus improve the progression of AD [13][14].

The tau proteins are highly soluble protein and responsible for stabilizing the microtubules and maintain its function under normal conditions. These microtubules provide support for structural changes, axonal transport, and neuronal growth in cell [15][16]. However, the hyperphosphorylated tau proteins are produced in AD patients' brain due to a dysfuction in phosphorylation processes. The hyperphoshorylated tau protein produced have low affinity with microtubules, which lead to aggregation of free tau protein and cause damages to microtubules and cytoskeletons. The loss in microtubule stability leads to pathological defects in the normal structure and function of the cytoskeleton it supports, therefore resulting in compromise in axonal transport, dysfunction in synapses, and neurodegeneration. Furthermore, burden on immune system can caused by NETs.

4. NEURONINFLAMMATION

Recent study has suggested that Aβ plaque and hyperphosphorylated tau protein could not only be toxic to nerve cells, but also be able to cause inflammation in brain through activing inflammatory cells such microglia and astrocytes to secret different kinds of inflammatory mediators which might contribute to the pathology of AD. Inflammation is a biological and molecular response of immune system to pathogens and damaged cells. Nueroinflammation is defined as the inflammatory responses in the brain. In AD paitents' brain, Nueroinflammation consist of activation of microglia and astrocytes triggered by Aβ plaque or NFTs and releasing of inflammatory mediators such as cytokines, chemokines, neurotransmitters and ROS [17]. These mediators are able to recruit monocytes and lymphocytes through the blood brain barrier (BBB) [18][19] and activate resting microglia cells to release more inflammatory factors, which could accelerate the pathology of AD.

Microglia is the main immune cell in the central nervous system, supporting and protecting normal neuronal functions. Microglia are activated through the receptor for advanced glycation end products (RAGE) and macrophage colony-stimulating factor (M-CSF) [20]. These receptors can be triggered by Aβ and leading to accumulation of microglia around Aβ plaque and releasing different kinds of proinflammatory mediators such as cytokines IL-1□, IL-6, and TNF-a, the chemokines IL-8, macrophage inflammatory protein-1α (MIP-1a), and monocyte chemoattractant protein-1 [20][21]. These mediators will active a series of microglia activities starting with microglial chemotaxis, proliferation, increased macrophage scavenger receptor expression, and finally resulting in enhancing the clearance of Aβ plaque [20][22]. However, not like normal immune responses, these mediators will continuously activate resting microglia and keeping releasing toxic factors such as ROS, which results in further damage on nerve cell and cause neuroinflammation.

Astrocytes are the richest cells in human brain and spinal cord. They are star-shaped glia cells with functions of supplying nervous tissue, maintenance of extracellular ion balance, and healing the brain and spinal cord following traumatic injury. Triggered by Aβ, activated astrocytes cluster around Aβ deposits and secret various mediators such as ILs, prostaglandins, leukotrienes, thromboxanes, coagulation factors, complement factors, proteases, and protease inhibitors, which in return contribute to the reactivation of more astrocytes. In addition, activated astrocytes produce chemokines, cytokines, and ROS that may result in neuronal damage.

Recent study also suggests that the activation of microglia and astrocytes can affect each other interdependently. Influenced by IL-1 mediator released by activated microglia, astrocytes were found to over-express the cytokine S100B, which will lead to the AD-like pathology in the Tg2576 mouse model of AD27. The chemokines released by activated astrocytes were able to attract microglia to further express proinflammatory products that can increase the neuronal damage in the pathologies of AD. Though microglia and astrocytes have the intrinsic functions of Aβ degradation and clearance, their tendency to release proinflammatory molecules are considered to stimulated and contribute to the progress of AD.

5. TREATMENT

Currently, there are two available ways to treat AD: the cholinesterase inhibitors, such as donepezil, galantamine, rivastigmine and the agonist, such as memantine, huperzine. The cholinesterase inhibitors functioned by inhibiting the enzyme that degrade the neurotransmitter, such as acetycholine enabling them to remain in synpase for longer time and keep the extent of stimulation at a relative high level. Memantine works actively as both dopamine and non-competitive N-methyl-D-aspartate receptor antagonists, which can inhibit the inflow of calcium ion (Ca2+) to decrease the noise when electrical impulse transfer along neurone and increase the strength of electric stimulation. All the five drugs are approved to have good effect on ease the symptoms of AD. Donepezil, galantamine, and rivastigmine, are more effective and recommended for AD patients of all stages and Parkinson patients [23]. The Memantine has been approved for AD patients who are in their moderate to severe stages but have difficulty in keeping attentive and alert [24]. Nutraceutical huperzine A can benefit the patients from both memory functioning and daily living activities. However, huperzine A medication is not approved by US

government or on the list of US Food and Drug Administration [25].

More study shows that a health problem that most AD patients have among all stages of AD progression is deficiency in vitamin D, so the nourishment that are rich in vitamin D are always recommended to AD patient [26]. Also, some recent studies show that omega-3 fatty acid supplements (including fish oil) are able to improve the memory function of AD patient [27][28]. Another suggestion is to use non-steroidal anti-inflammatory drugs, which can reduce the risk of AD, alluding to inflammatory contribution in AD progression [29]. However, AD patients who took these medications showed no difference in cognitive conditions. On the aspect for preventing AD, it is indicated in recent systematic reviews that people who have Mediterranean diet are far less likely to develop AD or cognitive impairment than the others due to their emphasis on meals which contain fresh product, legumes, olive oil, seafood, and whole grains while limiting consumption of dairy and poultry products as well as rejecting processed food, red meat, and sweets [30][31]. Meanwhile, keeping regular aerobic exercise is also useful to prevent AD, as the aerobic exercise can protect brain from neurodegeneration and reduces the beuropsychiatric symptoms of AD and eases caregivers' burden [32][33].

All the drugs approved by FDA such as memantine can only ease the symptoms but the patients can't recover to their normal mental and physical condition. Therefore, the future development of AD therapy is aimed to address this issue and fully cure the patient. With the guidance of the pathological hypothesis, there are several Aβ and tau based therapies have been developed.

The first one is anti- Aβ therapy. According to the amyloid cascade hypothesis that ab plaque can cause neuron death and affect the nerve net-work connection in brain eventually resulting in the neuron dysfunction [34]. This therapy requires injecting antibodies that targets Aβ deposition and help to remove it from the brain. The first two monoclonal antibodies were developed in 2014 [35][36], however, none of them showed cognitive improvement in patients with mild to moderate AD and only be effective for taken in early MCI and mild dementia stages.

Apart from cleaning Aβ plaques, another treatment focusing on inhibiting the production of Aβ peptide by targeting the precursor of Aβ, a protein called amyloid precursor protein (APP), is developed. Presently, several drugs are being designed to target b-site APP cleaving enzyme 1 (BACE1), which plays a vital role in Aβ peptide production [37]. A 40-fold reduction of Aβ levels in rodents' and primates' brains has been reported in an early human trials, which has demonstrated good safety profile when using the novel agent verubecestat [38]. Furthermore, when BACE1 inhibitor and a monoclonal antibody were combined, the results showed that the amount of Aβ was significantly reduced in AD mice [39]. Currently, this combination therapy has not been used in human trials, but many experts believe that this approach to eliminate Aβ will lead to successful treatment finally.

Another main category is anti tau therapy [40]. This kind of treatment is invented on the base of tau-protein hypothesis that hyperphosphorylation of tau protein can cause an instability of microtubules and can aggregate together to form neurofibrillary tangles thus damage neurone. Now, researchers have developed many safe and efficacious tau vaccines. Recently, in a small study, an anti-tau drug was examined and showed qualified safety profile. In human AD cases, it also triggered a positive response in the immune system[41]. One kind of anti-tau is proofed to have a good effect on monkey but only little effect on human beings.

The γ oscillation is a high-frequency brainwave rhythm which is correlated with communication among neurons in the brain. Researchers at the Massachusetts Institute of Technology recently find that induction of □ oscillation reduced aggregates of Aβ and led to cognitive improvement in an AD mouse model. They used a 40 Hz photic stimulator to achieve the frequency they desired in the brain cortex of the mouse [42][43]. In human cases, the application of this method is in early phase trails and uses both visual and auditory stimulation.

6. DIAGNOSIS

Among AD patients, there are three stages of symptom from moderate, mild to severe. During the moderate stage, patients can experience memory loss and may not able to recognize their friends or family, they may have problems when carry out multistep tasks. At mild stage, the symptoms are strength with greater memory loss and cognitive difficulties are experienced, the personality and behavior of the patient also changes. Most patients are diagnosed in this stage. During the severe stage, people lose the ability to walk or talk.

The conventional methods used on diagnosing AD were developed based on the symptom observation among the three stages, involving asking or conducting test which based on clinical criteria to patient. The clinical criteria for the diagnosis different stage of dementia caused by AD was fully recorded and developed by the National Institute on Aging-Alzheimer's Association(NIA-AA) in 2011 based on the original 1984 diagnostic criteria [44][45][46].

There are three clinical criteria on diagnosing AD. Firstly, its symptoms should be insidious which means the symptoms is gradual onset over months to years. Secondly, an evident history of worsening of cognition

need to be reported or observed. Thirdly, the initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: amnestic presentation which is also the most common syndromic presentation of AD dementia. The deficits should basically include impairment in learning and recall of recently learned information. The second category is about nonamnestic presentations such as language presentation, visuospatial presentation and executive dysfunction. But there are some cases that the diagnosis of probable AD dementia should not be applied at following situations： (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

However, the conventional method has limitations in terms of accuracy as the accurate result largely depends on the experienced doctors. Also, the symptoms in AD at early stage are very similar to memory loss that due to normal aging, which means more difficulties in identification. In order to address these two issues, modern diagnosis method with higher accuracy are developed.

Positron emission tomography (PET) is a newly developed diagnosis method with high accuracy and non-invasiveness. PET involving injection of a radiolabeled tracer agent which can bind to Aβ in brain. Following the injection, patients undergo a PET scan which will detect the position and relative amount of Aβ plaque in brain. This method is proofed to be extremely accurate and shows a huge development potential in future. In 2012, the sensitivity and specificity of this diagnosis method was 96% and 100% respectively. In 2013, PET showed similar accuracy when diagnosis milder disease patients [47]. Up to now, US Food and Drug Administration have approved several amyloid-specific PET reagent that can be used in PET examination, including florbetaben, flutemetamol and florbetapi. However, the amyloid PET imaging is still limited in practice due to its high cost that beyond many people's income. This test was accepted to most patient as part of clinical trials.

Another examing method involving the analysis of cerebrospinal fluid (CSF) which is less costly but more-invasive method. This method is able to detect the content of Aβ– 42 and hyperphosphorylated tau protein, and total tau protein in CSF. The CSF analysis has slightly lower accuracy compared to PET scan, about 85%-90%. Recently, a head to head comparison showed that the difference in accuracy between PET and CSF is zero. But, the patient who take CSF analysis do need to take more risk and suffer more from inconvenient due to a lumbar puncture procedure and the lack of specific equipment for fluid analysis.

7. CONCLUSION

The molecular mechanism underlying AD has been studied deeply over last decades. Currently it has been acknowledged that there are several theories and hypothesis that can partially explain the pathology of AD, including Aβ, tau protein and neuroinlfammasion. However, none of them alone is able to reveal the whole aspect of molecular mechanism and pathological pathway of AD. Therefore, further studies are urgently required.

In this review we also summarized the current development of AD diagnosis and treatment. Compared with conventional AD clinical criteria, modern imaging and scan technologies as well as advanced CSF fluids analysis provide us with more precise and convincing evidences to aid the diagnosis of AD. As for the treatment aspect, while current drugs that approved by FDA can improve AD patients' memory and alertness, the overall AD progression still remained uncured. In order to address this issue, several advanced method based on the Aβ and p-tau theories such as multiple antibody, drugs and vaccines that targets Aβplauqe, ACE1 enzyme and p-tau have been developed. Given the growing number of AD patients and global healthcare cost due to dementia, the development of more repaid and low cost diagnosis and treatment method such as blood fluid test as well as gene therapy have also been in progress.

REFERENCES

[1] Blennow, K.; de Leon, M. J.; Zetterberg, H. Alzheimer's Disease. Lancet 2006, 368 (9533), 387–403. https://doi.org/10.1016/S0140-6736(06)69113-7.

[2] Prince, M.; Jackson, J. World Alzheimer Report 2009. Alzheimer's Dis. Int. 2009, 1–96.

[3] Cutler, R. G.; Kelly, J.; Storie, K.; Pedersen, W. A.; Tammara, A.; Hatanpaa, K.; Troncoso, J. C.; Mattson, M. P. Involvement of Oxidative Stress-Induced Abnormalities in Ceramide and Cholesterol Metabolism in Brain Aging and Alzheimer's Disease. Proc. Natl. Acad. Sci. U. S. A. 2004, 101 (7), 2070–2075. https://doi.org/10.1073/pnas.0305799101.

[4] Praticò, D.; Trojanowski, J. Q. Inflammatory Hypotheses: Novel Mechanisms of Alzheimer's Neurodegeneration and New Therapeutic Targets? Neurobiol. Aging 2000, 21 (3), 441–445. https://doi.org/10.1016/S0197-4580(00)00141-X.

[5] Neuner, S. M.; Tcw, J.; Goate, A. M. Neurobiology of Disease Genetic Architecture of Alzheimer ' s Disease. Neurobiol. Dis. 2020, 143 (May), 104976.

[6] Jucker, Mathias; Walker, L. C. Amyloid-β Pathology Induced in Humans Cause Freezing in Clouds. Nature 2015, 3–4.

[7] McGowan, E.; Pickford, F.; Kim, J.; Onstead, L.; Eriksen, J.; Yu, C.; Skipper, L.; Murphy, M. P.; Beard, J.; Das, P.; Jansen, K.; Delucia, M.; Lin, W.; Dolios, G.; Wang, R.; Eckman, C. B.; Dickson, D. W.; Hutton, M.; Hardy, J.; Golde, T. McGowan et Al., 2005 NIH Aβ42 Is Essential for Parenchymal and Vascular Amyloid Deposition in Mice.Pdf. Neuron 2006, 47 (2), 191–199.

[8] Bertram, L.; Tanzi, R. E. Thirty Years of Alzheimer's Disease Genetics: The Implications of Systematic Meta-Analyses. Nat. Rev. Neurosci. 2008, 9 (10), 768–778. https://doi.org/10.1038/nrn2494.

[9] Wu, L. G.; Saggau, P. Presynaptic Inhibition of Elicited Neurotransmitter Release. Trends Neurosci. 1997, 20 (5), 204–212. https://doi.org/10.1016/S0166-2236(96)01015-6.

[10] Sennvik, K.; Fastbom, J.; Blomberg, M.; Wahlund, L. O.; Winblad, B.; Benedikz, E. Levels of α- and β-Secretase Cleaved Amyloid Precursor Protein in the Cerebrospinal Fluid of Alzheimer's Disease Patients. Neurosci. Lett. 2000, 278 (3), 169–172. https://doi.org/10.1016/S0304-3940(99)00929-5.

[11] Puzzo, D.; Privitera, L.; Leznik, E.; Fà, M.; Staniszewski, A.; Palmeri, A.; Arancio, O. Picomolar Amyloid-β Positively Modulates Synaptic Plasticity and Memory in Hippocampus. J. Neurosci. 2008, 28 (53), 14537–14545. https://doi.org/10.1523/JNEUROSCI.2692-08.2008.

[12] Velliquette, R. A.; O'Connor, T.; Vassar, R. Energy Inhibition Elevates β-Secretase Levels and Activity and Is Potentially Amyloidogenic in APP Transgenic Mice: Possible Early Events in Alzheimer's Disease Pathogenesis. J. Neurosci. 2005, 25 (47), 10874–10883. https://doi.org/10.1523/JNEUROSCI.2350-05.2005.

[13] Allen, J. P.; Bacteria, P.; Blankenship, R. E.; Madigan, M. T.; Bauer, C. E.; Holten, D.; Deisenhofer, J.; Norris, J. R.; Diego, S.; Kaiser, W.; Silbey, R. J.; Sumi, H.; Warshel, a; Greenfield, S. R.; Wasielewski, M. R.; Hanson, D. K.; Pearlstein, R. M.; Chu, Z. T.; Parson, W. W.; Marchi, M.; Chandler, D.; Muller, J. D.; Wraight, C. a; Nienhaus, G. U.; Walker, G. C.; Kang, T. J.; Barbara, P. F.; Fonseca, T.; Fleming, G. R.; Oxtoby, D. W.; Marcus, R. a; Sakmar, T. P.; Mourik, F. Van; Zwan, G. Van Der; Haacke, S.; Chergui, M. . . In Addition to This, for Five of the Mutants Studied, It Was Possible to Perform an Independent Check of the DDG. Biochemistry 2007, 316 (May), 750–754.

[14] Fuentes G, P.; Slachevsky Ch., A. Enfermedad de Alzheimer: Actualización En Terapia Farmacológica. Rev. Med. Chil. 2005, 133 (2), 224–230. https://doi.org/10.4067/s0034-98872005000200012.

[15] Goedert, M.; Klug, A.; Crowther, R. A. Tau Protein, the Paired Helical Filament and Alzheimer's Disease. J. Alzheimer's Dis. 2006, 9 (SUPPL. 3), 195–207. https://doi.org/10.3233/jad-2006-9s323.

[16] Citron, M. Alzheimer's Disease: Strategies for Disease Modification. Nat. Rev. Drug Discov. 2010, 9 (5), 387–398. https://doi.org/10.1038/nrd2896.

[17] Tansey, M. G.; McCoy, M. K.; Frank-Cannon, T. C. Neuroinflammatory Mechanisms in Parkinson's Disease: Potential Environmental Triggers, Pathways, and Targets for Early Therapeutic Intervention. Exp. Neurol. 2007, 208 (1), 1–25. https://doi.org/10.1016/j.expneurol.2007.07.004.

[18] Lossinsky, A. S.; Shivers, R. R. Structural Pathways for Macromolecular and Cellular Transport across the Blood-Brain Barrier during Inflammatory Conditions. Review. Histol. Histopathol. 2004, 19 (2), 535–564. https://doi.org/10.14670/HH-19.535.

[19] Taupin, P. Adult Neurogenesis, Neuroinflammation and Therapeutic Potential of Adult Neural Stem Cells. Int. J. Med. Sci. 2008, 5 (3), 127–132. https://doi.org/10.7150/ijms.5.127.

[20] Rogers, J.; Lue, L. F. Microglial Chemotaxis, Activation, and Phagocytosis of Amyloid β-Peptide as Linked Phenomena in Alzheimer's Disease. Neurochem. Int. 2001, 39 (5–6), 333–340. https://doi.org/10.1016/S0197-0186(01)00040-7.

[21] Tuppo, E. E.; Arias, H. R. The Role of Inflammation in Alzheimer's Disease. Int. J. Biochem. Cell Biol. 2005, 37 (2), 289–305. https://doi.org/10.1016/j.biocel.2004.07.009.

[22] Tomozawa, Y.; Inoue, T.; Takahashi, M.; Adachi, M.; Satoh, M. Ieuhoscuence Reserrch. 1996, 25, 7–15.

[23] Howard, R.; McShane, R.; Lindesay, J.; Ritchie, C.; Baldwin, A.; Barber, R.; Burns, A.; Dening, T.; Findlay, D.; Holmes, C.; Hughes, A.; Jacoby, R.; Jones, R.; Jones, R.; McKeith, I.; Macharouthu, A.; O'Brien, J.; Passmore, P.; Sheehan, B.; Juszczak, E.; Katona, C.; Hills, R.; Knapp, M.; Ballard, C.; Brown, R.; Banerjee, S.; Onions, C.; Griffin, M.; Adams, J.; Gray, R.; Johnson, T.; Bentham, P.; Phillips, P. Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease. N. Engl. J. Med. 2012, 366 (10), 893–903. https://doi.org/10.1056/NEJMoa1106668.

[24] Grossberg, G. T.; Manes, F.; Allegri, R. F.; Gutiérrez-Robledo, L. M.; Gloger, S.; Xie, L.; Jia, X. D.; Pejović, V.; Miller, M. L.; Perhach, J. L.; Graham, S. M. The Safety, Tolerability, and Efficacy of Once-Daily Memantine (28 Mg): A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients with Moderate-to-Severe Alzheimer's Disease Taking Cholinesterase Inhibitors. CNS Drugs 2013, 27 (6), 469–478. https://doi.org/10.1007/s40263-013-0077-7.

[25] Xing, S. H.; Zhu, C. X.; Zhang, R.; An, L. Huperzine A in the Treatment of Alzheimer's Disease and Vascular Dementia: A Meta-Analysis. Evidence-based Complement. Altern. Med. 2014, 2014. https://doi.org/10.1155/2014/363985.

[26] Littlejohns, T. J.; Henley, W. E.; Lang, I. A.; Annweiler, C.; Beauchet, O.; Chaves, P. H. M.; Fried, L.; Kestenbaum, B. R.; Kuller, L. H.; Langa, K. M.; Lopez, O. L.; Kos, K.; Soni, M.; Llewellyn, D. J. Vitamin D and the Risk of Dementia and Alzheimer Disease. Neurology 2014, 83 (10), 920–928. https://doi.org/10.1212/WNL.0000000000000755.

[27] Lee, L. K.; Shahar, S.; Chin, A. V.; Yusoff, N. A. M. Docosahexaenoic Acid-Concentrated Fish Oil Supplementation in Subjects with Mild Cognitive Impairment (MCI): A 12-Month Randomised, Double-Blind, Placebo-Controlled Trial. Psychopharmacology (Berl). 2013, 225 (3), 605–612. https://doi.org/10.1007/s00213-012-2848-0.

[28] Bo, Y.; Zhang, X.; Wang, Y.; You, J.; Cui, H.; Zhu, Y.; Pang, W.; Liu, W.; Jiang, Y.; Lu, Q. The N-3 Polyunsaturated Fatty Acids Supplementation Improved the Cognitive Function in the Chinese Elderly with Mild Cognitive Impairment: A Double-Blind Randomized Controlled Trial. Nutrients 2017, 9 (1), 1–11. https://doi.org/10.3390/nu9010054.

[29] Gupta, P. P.; Pandey, R. D.; Jha, D.; Shrivastav, V.; Kumar, S. Role of Traditional Nonsteroidal Anti-Inflammatory Drugs in Alzheimer's Disease: A Meta-Analysis of Randomized Clinical Trials. Am. J. Alzheimers. Dis. Other Demen. 2015, 30 (2), 178–182. https://doi.org/10.1177/1533317514542644.

[30] Lourida, I.; Soni, M.; Thompson-Coon, J.; Purandare, N.; Lang, I. A.; Ukoumunne, O. C.; Llewellyn, D. J. Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review. Epidemiology 2013, 24 (4), 479–489. https://doi.org/10.1097/EDE.0b013e3182944410.

[31] Singh, B.; Parsaik, A. K.; Mielke, M. M.; Erwin, P. J.; Knopman, D. S.; Petersen, R. C.; Roberts, R. O. Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis. J. Alzheimer's Dis. 2014, 39 (2), 271–282. https://doi.org/10.3233/JAD-130830.

[32] Stella, F.; Canonici, A. P.; Gobbi, S.; Santos-Galduroz, R. F.; de Castilho Cação, J.; Gobbi, L. T. B. Attenuation of Neuropsychiatric Symptoms and Caregiver Burden in Alzheimer's Disease by Motor Intervention: A Controlled Trial. Clinics 2011, 66 (8), 1353–1360. https://doi.org/10.1590/S1807-59322011000800008.

[33] Dregan, A.; Gulliford, M. C. Leisure-Time Physical Activity over the Life Course and Cognitive Functioning in Late Mid-Adult Years:A Cohort-Based Investigation. Psychol. Med. 2013, 43 (11), 2447–2458. https://doi.org/10.1017/S0033291713000305.

[34] Pooler, A. M.; Polydoro, M.; Wegmann, S.; Nicholls, S. B.; Spires-Jones, T. L.; Hyman, B. T. Propagation of Tau Pathology in Alzheimer's Disease: Identification of Novel Therapeutic Targets. Alzheimer's Res. Ther. 2013, 5 (5), 1. https://doi.org/10.1186/alzrt214.

[35] Doody, R. S.; Thomas, R. G.; Farlow, M.; Iwatsubo, T.; Vellas, B.; Joffe, S.; Kieburtz, K.; Raman, R.; Sun, X.; Aisen, P. S.; Siemers, E.; Liu-Seifert, H.; Mohs, R. Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. N. Engl. J. Med. 2014, 370 (4), 311–321. https://doi.org/10.1056/NEJMoa1312889.

[36] Salloway, S.; Sperling, R.; Fox, N. C.; Blennow, K.; Klunk, W.; Raskind, M.; Sabbagh, M.; Honig, L. S.; Porsteinsson, A. P.; Ferris, S.; Reichert, M.;

Ketter, N.; Nejadnik, B.; Guenzler, V.; Miloslavsky, M.; Wang, D.; Lu, Y.; Lull, J.; Tudor, I. C.; Liu, E.; Grundman, M.; Yuen, E.; Black, R.; Brashear, H. R. Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease. N. Engl. J. Med. 2014, 370 (4), 322–333. https://doi.org/10.1056/NEJMoa1304839.

[37] Vassar, R. BACE1 Inhibitor Drugs in Clinical Trials for Alzheimer's Disease. Alzheimer's Res. Ther. 2014, 6 (9), 1–14. https://doi.org/10.1186/s13195-014-0089-7.

[38] Kennedy, M. E.; Stamford, A. W.; Chen, X.; Cox, K.; Cumming, J. N.; Dockendorf, M. F.; Egan, M.; Ereshefsky, L.; Hodgson, R. A.; Hyde, L. A.; Jhee, S.; Kleijn, H. J.; Kuvelkar, R.; Li, W.; Mattson, B. A.; Mei, H.; Palcza, J.; Scott, J. D.; Tanen, M.; Troyer, M. D.; Tseng, J. L.; Stone, J. A.; Parker, E. M.; Forman, M. S. The BACE1 Inhibitor Verubecestat (MK-8931) Reduces CNS b-Amyloid in Animal Models and in Alzheimer's Disease Patients. Sci. Transl. Med. 2016, 8 (363), 1–14. https://doi.org/10.1126/scitranslmed.aad9704.

[39] Jacobsen, H.; Ozmen, L.; Caruso, A.; Narquizian, R.; Hilpert, H.; Jacobsen, B.; Terwel, D.; Tanghe, A.; Bohrmann, B. Combined Treatment with a BACE Inhibitor and Anti-Aβ Antibody Gantenerumab Enhances Amyloid Reduction in APPLondon Mice. J. Neurosci. 2014, 34 (35), 11621–11630. https://doi.org/10.1523/JNEUROSCI.1405-14.2014.

[40] Pedersen, J. T.; Sigurdsson, E. M. Tau Immunotherapy for Alzheimer's Disease. Trends Mol. Med. 2015, 21 (6), 394–402. https://doi.org/10.1016/j.molmed.2015.03.003.

[41] Novak, P.; Schmidt, R.; Kontsekova, E.; Zilka, N.; Kovacech, B.; Skrabana, R.; Vince-Kazmerova, Z.; Katina, S.; Fialova, L.; Prcina, M.; Parrak, V.; Dal-Bianco, P.; Brunner, M.; Staffen, W.; Rainer, M.; Ondrus, M.; Ropele, S.; Smisek, M.; Sivak, R.; Winblad, B.; Novak, M. Safety and Immunogenicity of the Tau Vaccine AADvac1 in Patients with Alzheimer's Disease: A Randomised, Double-Blind, Placebo-Controlled, Phase 1 Trial. Lancet Neurol. 2017, 16 (2), 123–134. https://doi.org/10.1016/S1474-4422(16)30331-3.

[42] Sederberg, P. B.; Schulze-Bonhage, A.; Madsen, J. R.; Bromfield, E. B.; Litt, B.; Brandt, A.; Kahana, M. J. Gamma Oscillations Distinguish True from False Memories: Research Report. Psychol. Sci. 2007, 18 (11), 927–932. https://doi.org/10.1111/j.1467-9280.2007.02003.x.

[43] Iaccarino, H. F.; Singer, A. C.; Martorell, A. J.; Gao, F.; Gillingham, T. Z.; Mathys, H.; Seo, J.; Abdurrob, F.; Adaikkan, C.; Canter, R. G.; Rueda, R.; Brown, E. N.; Boyden, E. S.; Tsai, L.; Sciences, C.; Sciences, C.; Hospital, G. HHS Public Access. 2017, 540 (7632), 230–235. https://doi.org/10.1038/nature20587.Gamma.

[44] McKhann, G. The Diagnosis of Dementia Due to Alzheimer's Disease. Alzheimers Dement 2012, 7 (3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.The.

[45] Sperling, R. A.; Aisen, P. S.; Beckett, L. A.; Bennett, D. A.; Craft, S.; Fagan, A. M.; Iwatsubo, T.; Jack, C. R.; Kaye, J.; Montine, T. J.; Park, D. C.; Reiman, E. M.; Rowe, C. C.; Siemers, E.; Stern, Y.; Yaffe, K.; Carrillo, M. C.; Thies, B.; Morrison-Bogorad, M.; Wagster, M. V.; Phelps, C. H. Toward Defining the Preclinical Stages of Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease. Alzheimer's Dement. 2011, 7 (3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003.

[46] Albert, M. S.; DeKosky, S. T.; Dickson, D.; Dubois, B.; Feldman, H. H.; Fox, N. C.; Gamst, A.; Holtzman, D. M.; Jagust, W. J.; Petersen, R. C.; Snyder, P. J.; Carrillo, M. C.; Thies, B.; Phelps, C. H. The Diagnosis of Mild Cognitive Impairment Due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease. Focus (Madison). 2013, 11 (1), 96–106. https://doi.org/10.1176/appi.focus.11.1.96.

[47] Saint-Aubert, L.; Barbeau, E. J.; Péran, P.; Nemmi, F.; Vervueren, C.; Mirabel, H.; Payoux, P.; Hitzel, A.; Bonneville, F.; Gramada, R.; Tafani, M.; Vincent, C.; Puel, M.; Dechaumont, S.; Chollet, F.; Pariente, J. Cortical Florbetapir-PET Amyloid Load in Prodromal Alzheimer's Disease Patients. EJNMMI Res. 2013, 3 (1), 1–22. https://doi.org/10.1186/2191-219X-3-43.