

Systematic Overview: AD Pathology and Recent Pharmacological Advances

Tingxi Luo *

Department of Life Science, Imperial College London, SW7 2AZ, London, UK

* Corresponding Author: gabriel.luo20@imperial.ac.uk

Abstract. This systematic review provides a comprehensive analysis of Alzheimer's Disease (AD) pathology and its pharmacological advancements. Population aging over last decades render AD becoming more prevalent, indicating a significant sociological and economic burden. Yet, due to the complexity of the brain structure, the researchers must understand AD's multifactorial pathology and progression mechanisms in order to find an effective treatment. The review will primarily examine the classical amyloid- β hypothesis and tau protein's involvement, exploring their interplay in neuronal degeneration. Additionally, it also examines the emerging theories of neuroinflammation, prion-like proteins and vascular damages as crucial contributors to AD pathology. Recently, several FDA-approved non-curative drugs have been reported to reduce amyloid- β plaque and/or enhance cognitive function. Consequently, beyond analyzing AD's pathological hypotheses, critically assessments on recent pharmacological advances using monoclonal antibodies (Aducanumab), cholinesterase inhibitors (Donepezil) and NMDA antagonists (Memantine) are used as examples to compare their clinical efficacies and controversies. Discussion on other factors including ethical considerations, personalized medicine and the transformation of treatment paradigms are included. By identifying a paradigm shift towards a multi-targeted approach which integrates pharmacological and non-pharmacological interventions, this review underscores the necessities of ethical concerns and patient-centred treatments. Thus, this review aims to present an academic consolidation of current knowledge and stimulate further interdisciplinary research, promoting innovation in AD treatment.

Keywords: Alzheimer's disease; Amyloid- β ; Tau; Aducanumab.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that mainly causes loss of memory and dementia [1]. The first case of AD was documented by a German neuropathologist in 1906 and is affecting more than fifty million people worldwide until 2020. Despite a century has passed, the disease agents that contribute to AD progression remain unknown. There has always been a debate on what really contributes to AD progression, several risk factors such as ageing, random mutations and head injury, have proven to be associated with the disease onset [1]. Additionally, several protein aggregations such as amyloid- β plaque and tau tangle are found excessively abundant in AD patients compared with healthy people, suggesting they may somehow relate to AD development [1].

Due to such poor understanding, there are not any effective treatments to prevent or reverse the process of AD. Currently, there are only two available classes of drugs, cholinesterase enzyme inhibitor and antagonists to N-methyl d-aspartate (NMDA), which can only alleviate AD symptoms but cannot cure the disease [1]. This limitation highlights the urgent need for innovative approaches in drug discovery. Recently, novel drug discovery techniques combined with machine learning algorithms enable researchers not only to explore traditional A β and tau pathways, but also investigate other pathways implicated in AD, such as neuroinflammation and cerebrovascular disturbances. Thus, this review will explore hypothetical pathology pathways in AD using several FDA-approved drugs as proof to promote further researches in this field.

2. Pathological Pathways of AD

AD mainly affects people over sixty and will become more prevalent due to the ageing of the population. However, the scientific community has not agreed on the disease's mechanism. The increasing number of individuals affected by AD, coupled with the socioeconomic burdens it imposes, underscores the importance of exploring various hypotheses that could unravel the complexities of AD. As a consequence, comprehensive research into this neurodegenerative disorder becomes more apparent to mitigate the forthcoming sociological impact.

2.1. Amyloid Beta Hypothesis

This theory hypothesized that accumulation of A β in the brain is the primary factor of AD pathogenesis. As indicated in Fig. 1, when amyloid precursor protein (APP) is cleaved by β and γ secretase, A β with various lengths are formed. Research has shown a clear positive correlation between the length of A β and the likelihood of aggregation, where A β 42 is peculiarly aggregation-prone [2]. The aggregation of A β peptides often leads to the formation of soluble oligomers or fibrils, but insoluble plaques are eventually produced as aggregation proceeds, becoming a hallmark of AD. By adopting neuroimaging equipment, these protein residues' location is confirmed: they deposit in the brain, causing immunoinflammatory responses and therefore suggesting a disrupted cell-to-cell communication and neuro-inflammation [3].

Soluble A β oligomers and insoluble A β plaques are both neurotoxic. However, they differ slightly: High solubility grants A β oligomers an enhanced ability to directly interact with neuronal membranes, which impair synaptic function and lead to neuronal death, contrasting with insoluble A β plaques, which are less directly neurotoxic but contribute to chronic brain inflammation and are thought to sequester toxic oligomers [4].

Having reviewed the pathological pathway of A β , it is also present in normal brains without causing AD [4]. This discrepancy suggests that A β alone may not be sufficient for AD development. Factors like the balance between A β production and clearance, individual brain resilience, and other pathological processes might be crucial in determining whether A β accumulation leads to AD [5]. In terms of genetic factors, they are also crucial in the A β pathway and AD onset. Mutations in the APP gene are linked to early-onset familial AD, while the APOE4 is a significant genetic risk factor for late-onset sporadic AD, associated with increased A β deposition [5].

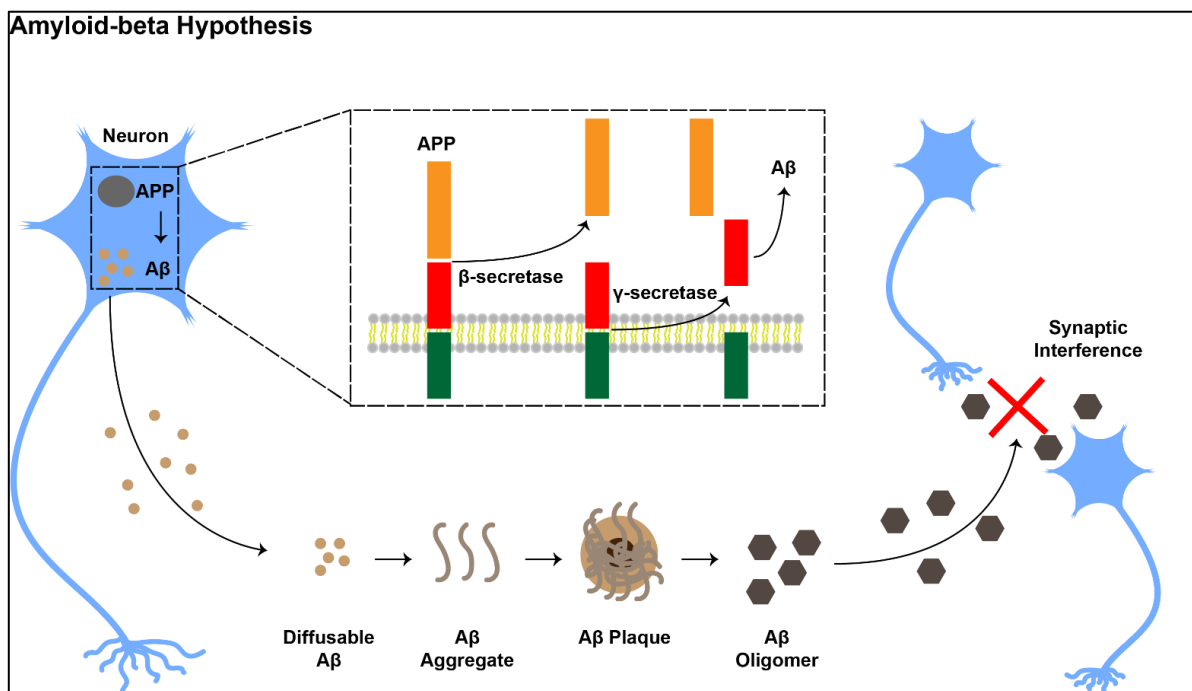


Figure 1. Amyloidopathy

2.2. Tau Protein Hypothesis

Tau hypothesis, complementing A β hypothesis, defines Tau protein as another factor in AD pathogenesis. In healthy neurons, tau protein binds to and stabilises the microtubule in axons, which is crucial for maintaining cellular structure and facilitating intracellular transport [6]. In the context of AD, however, tau proteins usually undergo abnormal hyperphosphorylation (Fig. 2), causing them to detach from the microtubule, aggregate into paired helical filaments and eventually form insoluble neurofibrillary tangles (NFT) [6,7]. The accumulation of NFT prohibits cargo transmission in neurons and contributes to cell death and the progressive cognitive decline. Noteworthy, recent findings suggest that genetic mutations on tau proteins, particularly on tyrosine, can increase the susceptibility to hyperphosphorylation [6]. These mutations are often associated with familial forms of AD and other tauopathies, highlighting a genetic predisposition to the disease.

Similar to A β hypothesis, the scientific community has not completely agreed with Tau hypothesis. There is often a discrepancy between the burden of NFTs and the degree of cognitive impairment. Some individuals with a high NFT load may show fewer clinical symptoms than expected, which imply other factors contribute to the resilience against AD symptoms [8,9]. The distribution and severity of tau tangles, particularly if confined to specific brain areas, might not lead to significant cognitive impairment. Co-occurring pathologies, such as amyloid-beta plaques and vascular changes, also contribute to AD development [8].

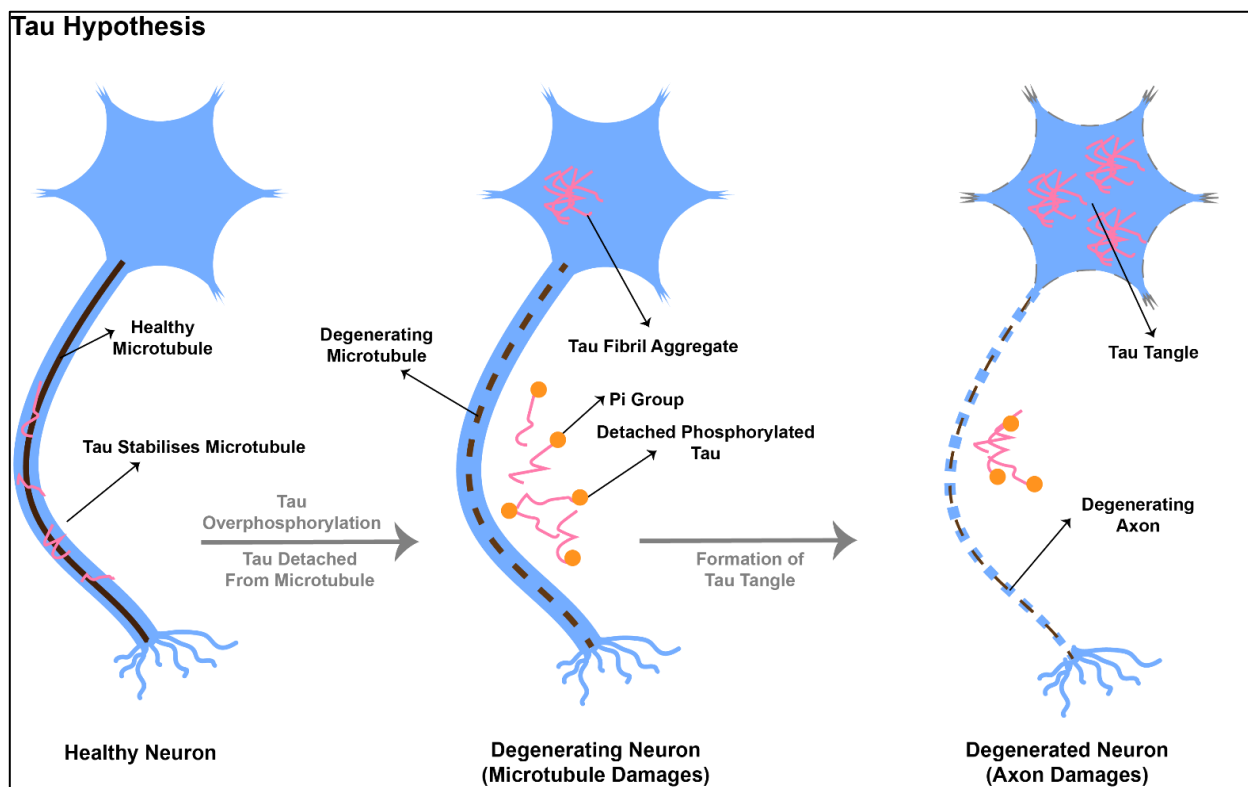


Figure 2. Tauopathy

2.3. Neuroinflammation Hypothesis

Neuroinflammation is often considered a secondary response to the accumulation of A β plaques and tau tangles. The initiation of neuroinflammation in AD is primarily triggered by the accumulation of A β plaques and tau tangles. These protein aggregates are perceived as foreign entities by the brain's immune system, leading to an immune response [10]. Under such circumstance, microglia often respond instantly as the brain's primary immune cells [11]. In the early stage of AD, microglia attempt to clear A β plaques and damaged neurons, but they undergo chronic activation as AD progresses. This may exacerbate neuronal damages when microglia transit from neuroprotective to pro-inflammatory [10]. Although the inflammatory response, under orchestrated supervision, is necessary

to protect against invasion of pathogens, chronic neuroinflammation is toxic to neurons and is postulated to be a trigger for AD progression.

In addition to the involvement of microglia, astrocytes also play a significant role in this inflammatory process. Upon activation, astrocytes release a number of cytokines and chemokines that contribute to the inflammatory environment. These changes in astrocytes affect their ability to support neurons, leading to synaptic dysfunction and neuronal death [12]. The pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6 that are released by activated microglia can also be released by activated astrocytes and also promote inflammation, but they also lead to oxidative stress and synaptic loss [13]. Additionally, the importance of the cytokines and chemokines released by astrocytes and microglia is not even just due to their contribution of their pro-inflammatory roles in the establishment of an inflammatory environment, since formed cytokines perpetuate inflammation by attracting more immune cells across the compromised blood-brain barrier (BBB) and creates an environment where co-stimulatory factors and other signals contribute to affecting the phenotype of neuroinflammatory cells.

2.4. Other Emerging Hypotheses

Along with traditional theories, other concepts, like prion and vascular hypotheses, offer a more comprehensive overview of AD pathogenesis regarding a broader perspective on disease mechanisms and novel treatments. The prion hypothesis is postulated based on the evidence that when A β and tau undergo misfolding processes sporadically or caused by genetic mutation, they behave similarly to prions [14]. Such misfolding behaviour grants A β and tau the ability to aggregate, propagate and transmit across neurons, gradually impairing neuronal communication and eventually resulting in neurodegeneration. Consequently, therapeutic strategies that inhibit misfolding processes can potentially limit aggregation and reduce AD progression.

By contrast, vascular hypothesis introduces a unique insight that highlights the connection between cerebrovascular abnormality and disease progression. Factors including hypertension, blood-brain barrier breakdown, diabetes, vascular damage and reduced blood supply are associated with impaired glymphatic system for waste clearance, consequently leading to A β accumulation. Hence, strategies through target vascular health are of utmost importance in slowing AD progression.

3. Recent FDA-Approved Drugs

Due to the fact that the pathological pathway of AD has not yet been clearly proven by research, this section will use a different approach from the past to verify its pathogenesis hypothesis. The approach is to validate it using several effective drugs that have been approved by the Food and Drug Administration (FDA). Since the drugs are often developed to target specific biomarkers in the disease's progression, researchers can gain valuable insights into the underlying pathological processes they are designed to influence by examining the mechanism of these drugs. Additionally, in clinical trials, the effectiveness of these drugs can provide real-world evidence that either supports or challenges existing hypotheses about the disease. Consequently, this approach can validate theoretical pathways and enhance our understanding of the disease's complexity and multifactorial nature, offering a clearer picture of potential therapeutic strategies.

3.1. Monoclonal Antibody (Aducanumab)

Aducanumab, developed by Biogen and Eisai and accelerated approved by the FDA in June 2021, is a monoclonal antibody specifically targeting A β plaques through intravenous infusion in mild dementia stages of AD [15] (Fig. 3). Despite the drug's benefits in slowing cognitive decline and improving daily functioning, the limitations remain challenging. Aducanumab is administered through monthly infusion, requiring extensive infrastructure and trained technicians, which can be highly inconvenient and expensive (originally expected annual expenses at \$56000 [16]). Besides, the side effects such as amyloid-related imaging abnormalities (ARIA) cause brain swelling or bleeding [15].

Additionally, there has been an ongoing debate on the effectiveness of aducanumab during early clinical trials and two major efficacy studies (EMERGE and ENGAGE). While aducanumab demonstrated the capability of reducing A β plaques in the brain, the drug's impact on enhancing the cognitive functions of patients remains uncertain, which subsequently led to controversy surrounding the FDA's accelerated approval [16]. Some experts believe that the release of aducanumab was premature due to conflicting clinical trial results and the hypothetical nature of the A β pathogenic mechanism in AD, while other researchers are exploring aducanumab's potential in combination with other therapies and its impact on biomarkers associated with AD.

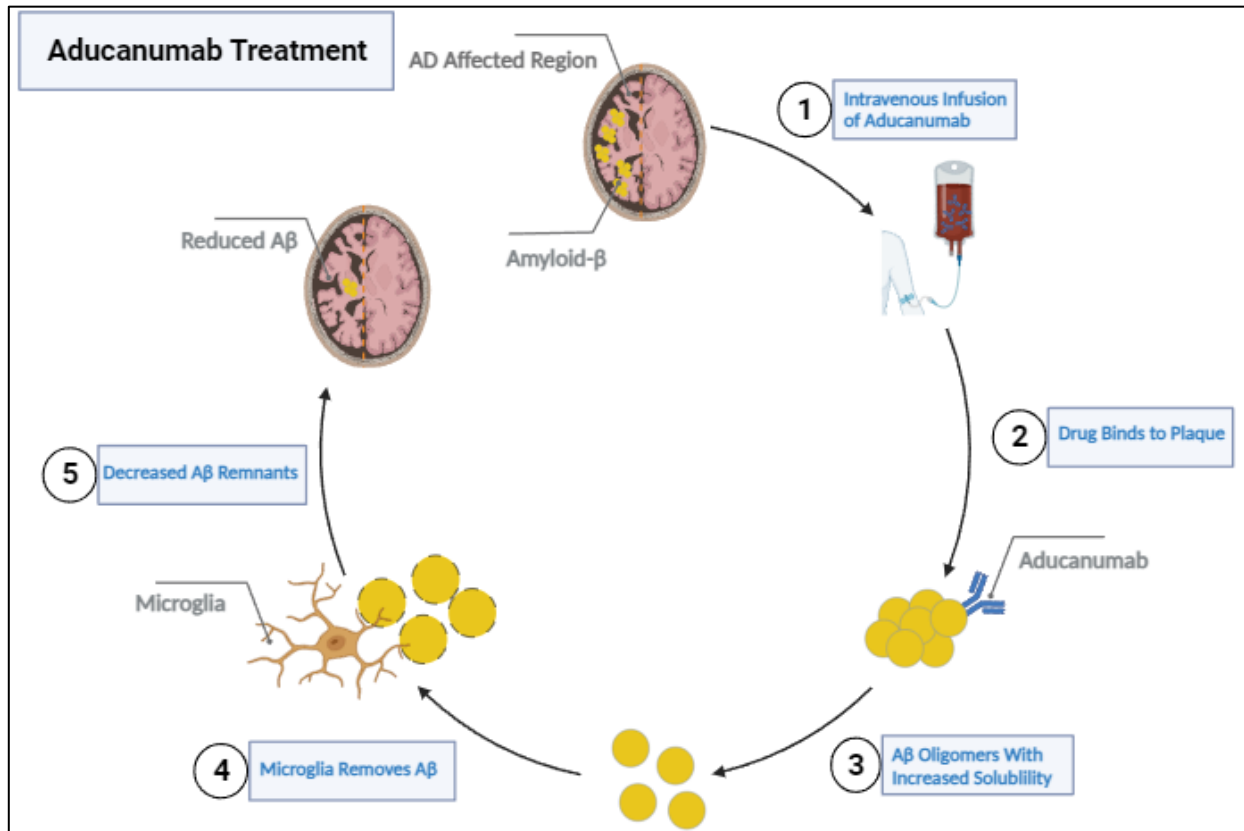


Figure 3. Aducanumab Mechanism of Action

3.2. Other Treatments (Donepezil and Memantine)

Donepezil is a cholinesterase inhibitor, first granted for medical use by FDA in 1996, has demonstrated benefits in enhancing cognitive functions in mild, moderate and severe stages of AD [17]. It acts by inhibiting hydrolysis of acetylcholine, a neurotransmitter believed to enhance cognition, when binding and inactivating cholinesterase [18], thereby relieving AD symptoms. By increasing acetylcholine availability, donepezil addresses the symptomatic aspect of AD, offering cognitive improvement.

The approval of memantine, an NMDA antagonist, provides evidence for glutamatergic hypothesis of AD. This theory suggests that glutamate, a key excitatory neurotransmitter in the brain, is often excessively abundant leading to overstimulation, which contributes to neurotoxicity and neuronal deaths. Memantine moderates the harmful effects of excessive glutamate by selectively blocking NMDA receptors without disrupting their normal physiological functions [18]. This selective blockade helps in reducing neuronal excitotoxicity, potentially slowing the progression of cognitive symptoms in AD patients.

4. Discussion

4.1. Challenges in AD Research

The numerous complexities surrounding AD pathology pose challenges for AD researchers [17]. AD pathology is highly convoluted, involving the interplay of multiple factors such as A β and tau protein accumulation, neuroinflammation, alterations in cerebral vasculature, genetic & environmental influences and synaptic destructions that lead to neuronal loss. This complexity makes determination of specific therapeutic targets difficult. Clinical trials in AD also face significant hurdles: selection of appropriate participants for AD drug trials is a major obstacle, an especially important issue in the earliest stages of disease where treatment may be more effective. Determining sensitive and relevant outcome measures for these trials is another challenge, as cognitive assessments may not fully capture the disease's progression. Additionally, the slow progression of AD necessitates long-term studies, making trials time-consuming and costly. Lastly, a translational gap continues to exist where advances in preclinical models fail to match the same success in clinical trials. Consequently, improved models and new techniques are needed to drive innovation and better represent AD pathology.

4.2. Future Directions in AD Research

Future studies in AD will focus on using multidisciplinary techniques and investigating a variety of possible treatment targets. Emerging targets (aside from A β and tau proteins) include neuroinflammation pathways, synaptic dysfunction and alterations in metabolism and vascular function. This expanded focus acknowledges the complexity of AD and the requirement for therapies that target many aspects of the disease. Furthermore, personalised medicine, which customises treatments to each patient's unique genetic, environmental and lifestyle factors, is becoming increasingly important. These recognise the influence of social and environmental factors on the course of the disease and the quality of life of the patient. They include lifestyle interventions, cognitive therapy, and carer support. It is this comprehensive strategy that combines several therapeutic strategies and customised care to effectively tackle the complexities of the disease.

5. Conclusion

Conclusively, this systematic overview has identified crucial pathways and pharmacological developments in Alzheimer's Disease, highlighting the complexity and dynamism inherent in its pathology and treatment. Despite advances in therapeutic strategies, significant challenges persist, necessitating an integrated, multi-targeted approach. Future research directions point towards the potential of personalised medicine, offering bespoke treatments customised to individual genetic and phenotypic profiles. The importance of ethical considerations in clinical decision-making has been emphasised, advocating for treatments that harmonise efficacy with patient dignity and autonomy. This review underscores the imperative for continued innovation and a collaborative, multi-disciplinary approach to surmount the hurdles in AD research, ultimately aiming to enhance patient outcomes and quality of life. The emergent picture is one of cautious optimism, with the anticipation that ongoing research will yield a more profound understanding of AD and revolutionise current treatment regimes.

References

- [1] Alonso, A.D., Cohen, L.S., Corbo, C., Morozova, V., ElIdrissi, A., Phillips, G. and Kleiman, F.E. Hyperphosphorylation of Tau Associates with Changes in Its Function beyond Microtubule Stability. *Frontiers in Cellular Neuroscience*, 2018, 12.
- [2] Birks, J.S. and Harvey, R.J. Donepezil for Dementia Due to Alzheimer's Disease. *Cochrane Database of Systematic Reviews*, 2018, 2 (6).
- [3] Breijyeh, Z. and Karaman, R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*, 2020, 25 (24), p.5789.

- [4] Chen, G., Xu, T., Yan, Y., Zhou, Y., Jiang, Y., Melcher, K. and Xu, H.E. Amyloid beta: structure, Biology and structure-based Therapeutic Development. *Acta Pharmacologica Sinica*, 2017, 38 (9), pp.1205 – 1235.
- [5] Haddad, H.W., Malone, G.W., Comardelle, N.J., Degueure, A.E., Kaye, A.M. and Kaye, A.D. Aducanumab, a Novel Anti-Amyloid Monoclonal Antibody, for the Treatment of Alzheimer's Disease: A Comprehensive Review. *Health Psychology Research*, 2022, 10 (1).
- [6] Heneka, M.T., Golenbock, D.T. and Latz, E. Innate Immunity in Alzheimer's Disease. *Nature Immunology*, 2015, 16 (3), pp.229 – 236.
- [7] Iqbal, K., Liu, F. and Gong, C.-X. Tau and Neurodegenerative disease: the Story so Far. *Nature Reviews Neurology*, 2015, 12 (1), pp.15 – 27.
- [8] Jack, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C. and Trojanowski, J.Q. Hypothetical model of dynamic Biomarkers of the Alzheimer's pathological cascade. *The Lancet Neurology*, 2010, 9 (1), pp.119 – 128.
- [9] Liddelow, S.A., Guttenplan, K.A., Clarke, L.E., et al. Neurotoxic Reactive Astrocytes Are Induced by Activated Microglia. *Nature*, 2017, 541 (7638), pp.481 – 487.
- [10] McShane, R., Westby, M.J., et al. Memantine for Dementia. *Cochrane Database of Systematic Reviews*, 2019, 3(3).
- [11] Richard, Armstrong.A. Risk Factors for Alzheimer's Disease. *Folia Neuropathologica*, 2019, 57 (2), pp.87 – 105.
- [12] Sierksma, A., Lu, A., Mancuso, R., Fattorelli, N., et al. Novel Alzheimer Risk Genes Determine the Microglia Response to Amyloid- β but Not to TAU Pathology. *EMBO Molecular Medicine*, 2020, 12 (3).
- [13] Vaz, M., Silva, V., Monteiro, C. and Silvestre, S. Role of Aducanumab in the Treatment of Alzheimer's Disease: Challenges and Opportunities. *Clinical Interventions in Aging*, 2022, Volume 17, pp.797 – 810.
- [14] Watts, J.C. and Prusiner, S.B. (7). β -Amyloid Prions and the Pathobiology of Alzheimer's Disease. *Cold Spring Harbor Perspectives in Medicine*, 201, 8 (5), p.a023507.
- [15] Yoon, S.-S. and AhnJo, S.-M. Mechanisms of Amyloid- β Peptide Clearance: Potential Therapeutic Targets for Alzheimer's Disease. *Biomolecules and Therapeutics*, 2012, 20 (3), pp.245 – 255.
- [16] Zenaro, E., Piacentino, G. and Constantin, G. The blood-brain Barrier in Alzheimer's Disease. *Neurobiology of Disease*, 2017, 107, pp.41 – 56.
- [17] Zhang, C., Browne, A., DiVito, J.R., Stevenson, J.A., Romano, D., Dong, Y., Xie, Z. and Tanzi, R.E. Amyloid- β Production via Cleavage of Amyloid- β Protein Precursor Is Modulated by Cell Density. *Journal of Alzheimer's Disease*, 2010, 22 (2), pp.683 – 984.
- [18] Zhang, Y., Thompson, R., Zhang, H. and Xu, H. APP Processing in Alzheimer's Disease. *Molecular Brain*, 2011, 4 (1), p.3.