Benefits, Pitfalls, and Alternatives to Amyloid-Targeting Alzheimer's Disease Drugs

Vreni Reichard: vreniar@icloud.com

Abstract:

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that leads to a gradual decline in cognitive functions. This condition is primarily characterized by the accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles in the brain, which disrupt neuronal communication and contribute to cognitive impairment. The aggregation of Aβ into plaques is one of the main hallmarks of AD pathology, and understanding this process is crucial for developing effective treatments. Recently, three drugs were approved by the FDA: aducanumab, donanemab, and lecanemab. These drugs target Aβ plaques, aiming to reduce plaque accumulation and help alleviate symptoms. While these treatments represent significant progress, challenges remain in addressing the underlying mechanisms of the disease. In addition to targeting Aβ, there is growing interest in the role of microglia—the brain's immune cells—in the pathology of AD. Microglia play a critical role in clearing amyloid plaques and maintaining brain health. Controlling microglial activity may offer a novel therapeutic approach. This paper aims to provide an overview of the recently approved drugs, evaluate their efficacy and safety, and explore the potential of targeting microglia as a complementary strategy in AD treatment. Through this discussion, we hope to shed light on the evolving landscape of AD treatment and the importance of a multifaceted approach to combating this complex condition.

Introduction:

Alzheimer's disease (AD) is a neurodegenerative disease and one of the leading causes of death in the US. AD affects over 7 million Americans. AD cases are expected to nearly double by 2050 (Alzheimer's Association, 2023). AD causes the death of neurons, the cells in the brain that transmit information through electrical pathways (NINDS, 2024). AD's typical first symptom is the loss of words and memory (Alzheimer's Association, 2023); as the disease progresses symptoms include further memory deficits, the inability to recognize family members, loss of independence, and poor decision making. Age is the largest factor in the progression of AD, and those most affected by AD are typically over 65 years old (Alzheimer's Association, 2023). As people age, parts of the brain start to shrink, particularly in the frontal cortex, which has an impact on crucial abilities such as motoric related abilities, creativity, and judgment (Peters, 2009).

In addition to age, there are many contributing factors to the development of AD. these factors include, but are not limited to, genetics and the presence of the *APOE4* allele. he APOE protein is responsible for regulating the receptors on cells such as neurons and astrocytes that allow specific fats and proteins in and out of the cell (Guojun, 2010). In the setting of the E4 version of *APOE*, there is an increased risk of developing AD due to increased deposition of amyloid beta (Aβ) in the brain parenchyma, one of the molecular hallmarks of AD. Amyloid plaques are formed from the accumulation of Aβ peptides, which result from the improper processing of amyloid precursor protein. These plaques disrupt neuronal connections and promote inflammation, leading to neuronal damage and contribute to the progression of AD. The accumulation of Aβ aggregates and the formation of plaques stimulate inflammation within the brain (Gendron et. al, 2021). In addition to Aβ plaques, aberrant tau is also a molecular hallmark of AD. Tau resides within neurons and is normally crucial for transmitting signals throughout the nervous system. When tau becomes hyperphosphorylated, normal neuronal functions are disrupted resulting in neuronal death. As a consequence, tau accumulates and creates tangles, thus contributing to the pathogenesis of AD (Gendron et al., 2021).

Research published in the last few decades has identified dysfunction in microglial cells as a hallmark of AD pathology in addition to the roles of amyloid beta and tau. Microglia are immune cells within the brain that are important for maintaining homeostasis. When they become dysregulated, this leads to chronic inflammation and cognitive deficits (Casli et al., 2021). Microglia may also cause synapse loss by engulfing them, which subsequently changes the connections between neurons and ultimately negatively affects cognition (Hong et al., 2016).

Despite the prevalence of AD, to date, there have not been any treatments that successfully target the molecular causes of this disease. However, there has been recent advancement in Aβ-targeted drugs, with three drugs, lecanemab, donanemab, and aducanumab, which have received FDA approval. Aducanumab is a therapeutic drug that strives to target aggregated Aβ proteins (Sevigny et al., 2016). It is administered intravenously and binds to the aggregated proteins to decrease the amyloid burden. Lecanemab, otherwise known as Leqembi, is an intravenous therapy aimed at targeting and removing Aβ from the brain. Lecanemab specifically targets protofibrils, a type of soluble Aβ (van Dyck et al., 2023). Donanemab is also an intravenous drug used to target Aβ, and it works by training immune cells to recognize and remove Aβ (Yadollahikhales et al., 2023). While these mechanisms sound relatively straight forward, many factors affect whether these drugs are beneficial to an individual patient.. It remains to be seen if these promising drugs will deliver therapeutic benefits over time. Given that targeting Aβ pathology in AD has historically met with failure (Golde et al., 2011), there remains a need to investigate other therapeutic options. This review will discuss the benefits and potential pitfalls of recently approved Alzheimer's disease drugs targeting Aβ, in addition to considering novel therapeutic options involving microglia (Figure 1).

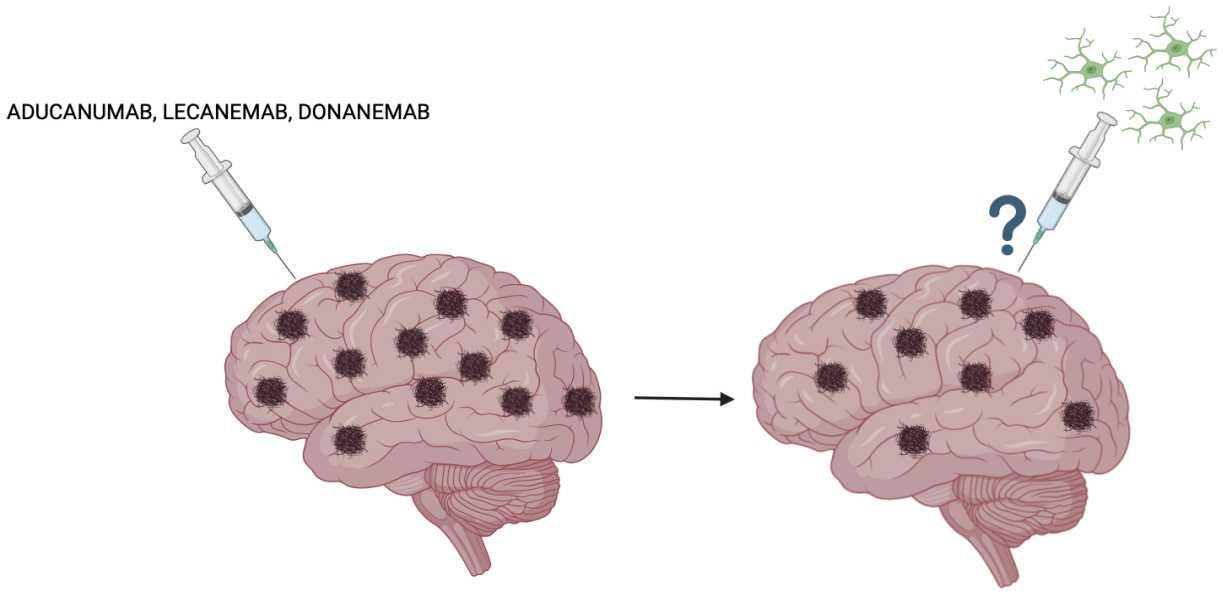

FIGURE 1. A visual schematic of current and potential Alzheimer's disease therapies

Aducanumab:

Aducanemab was first approved by the FDA in 2021 and originated from Neurimmune, a biopharmaceutical company based in Switzerland. Neurimmune originally licensed aducanumab for the treatment and prevention of Alzheimer's disease to Biogen in 2007, and in 2024 Neurimmune regained the rights to the drug.

The first study to assess aducanumab's safety and efficacy was the "PRIME" phase 1B clinical trial. It was a double-blind, randomized trial with a 12-month placebo-controlled period, followed by a long-term extension where all participants who had either prodmal or mild AD received aducanumab or the placebo. The results from the study showed reduced Aβ levels in the treated groups compared to the participants that received the placebo. The trial also demonstrated that there was a dependency on the drug and that the beneficial effects faded upon stopping treatment (Sevigny et al. 2016). Since this sentinel study, subsequent research articles have been published studying aducanumab in the treatment of AD and are discussed below.

As a result of the leading PRIME study, multiple subsequent studies have been performed. Sevigny et al., assessed the continued influence of aducanumab on those with mild Alzheimer's Disease. Their results were in favor of using the drug based on supportive evidence. The study referenced the PRIME study where 165 patients were randomly given the drug. Those who received aducanumab showed reduced Aβ Plaques as measured by fluorine 18 PET imaging. (Sevigny et al., 2023). Another study was done as a continuation of the PRIME study. Over the 48 month period following the PRIME study patients who enrolled were monitored and the results showed slowed cognitive decline and decreased Aβ levels within the brain (Chen et al., 2024).

Cadiz and colleagues investigated the roles of microglia in mediating synaptic loss associated with AD using the APP/PS1 mouse model (Cadiz et al., 2023). They gave either two or four 40 mg/kg doses of aducanumab injections to 10 month old male and female mice. Modest reductions in total amyloid load were observed in mice receiving two or four doses of aducanumab. However, changes in fibrillar plaque load were less notable, and the average plaque size was larger in aducanumab-treated mice. This indicates that aducanumab may be more effective at clearing smaller, diffuse plaques rather than larger, fibrillar ones. The results also suggest similar levels of plaque clearance between the two and four dose groups (Cadiz et al., 2023).

In a study done by Rezai et al. (2024), 3 participants ages 59, 64, 77 who had a diagnosis of mild cognitive impairment due to AD or AD dementia received six monthly aducanumab infusions. These infusions were administered with the hopes that amyloid removal would occur in the selected brian regions. Participant 1 was administered the drug into the right frontal lobe, participant 2 into the left frontal lobe, and participant 3 into the left frontal, parietal, temporal lobes and the hippocampus. The levels of Aβ was measured through fluorine-18 (18F) PET scans along with assessment of behavior and cognitive development. The results show that during the 6 month period there was no cognitive decline observed. However, the 30-180 day follow up period participants 1 and 2 still showed no signs of cognitive decline while on the 30th day participant 3 showed decline in their scores on a cognitive measure (the Repeatable Battery for the Assessment of Neuropsychological Status Line Orientation Test , or RBANS). This was interpreted as a decline in neuropsychological performance, however no neurologic changes were recorded (Rezai et al., 2024). This study suggests that the location of infusion may be of importance for future studies and that the long-term benefits of aducanumab were variable and potentially negligible.

Lecanemab:

Lecanemab received FDA approval in 2022 and was developed by Eisai and Biogen. It is designed for the treatment of AD, specifically targeting Aβ to help reduce plaque accumulation in the brain. The drug's approval represents a significant advancement in Alzheimer's therapy, with ongoing studies exploring its long-term effects and potential benefits for patients in earlier stages of the disease.

Given that individuals that have Down syndrome (DS) have an increased propensity of developing Down syndrome (DS) starting at 40 years of age with a dramatic increase until 53-54 years, Liu and colleagues (Liu et al., 2024) performed a cross-sectional case study of DS syndrome patients with AD by examining brain tissue from the prefrontal cortex, occipital cortex, and hippocampus. Those studied were between the ages of 43 - 68 years old and had significant AD pathology. Their results showed binding of lecanemab to brain blood vessel issues in these patients which clearly posed a safety concern. Therefore, the authors suggested that there should be more thorough testing in clinical trials for Alzheimer's disease within the DS population to evaluate its safety and effectiveness (Liu et al., 2024).

In a clinical trial reported by the New England Journal of Medicine (van Dyke et al., 2022), researchers studied the effects of lecanemab in patients diagnosed with early Alzheimer's disease. The trial included 1,500 patients with just over half receiving the drug and the rest receiving the placebo. The findings revealed that patients receiving lecanemab showed a statistically significant reduction in cognitive decline compared to those on placebo over 18 months. However, the study also noted some adverse effects, including edema and amyloid-related imaging abnormalities in some participants, which highlighted the need for careful monitoring during treatment (van Dyke et al., 2022).

In another double blind randomized clinical trial, Swanson et al. (2021), studied participants that had either mild cognitive impairment due to AD or mild AD dementia. The Bayesian analyses indicated that lecanemab administered at 10 mg/kg biweekly significantly reduced clinical decline at 18 months compared to the placebo. While the 10 mg/kg monthly dose had less of an impact, the treatment was associated with changes in cerebrospinal fluid (CSF) biomarkers, including increased Aβ-42 and decreased p-tau. Additional analysis of these data performed by Alzforum researchers, suggested diminished long term effects upon cessation of lecanemab treatment. The data from this trial showed that despite reduced levels of Aβ, CSF biomarkers remained increased upon drug removal. Similarly, cognition also followed this same pattern as clinical dementia ratings declined at the same rate in the previous treatment and the placebo groups. These data show that the brain develops a dependency on lecanemab for the removal of Aβ plaques, and this includes patients with early AD development and low levels of Aβ plaques (Alzforum, 2023).

Donanemab:

Donanemab was first approved by the FDA in 2024 and is marketed by Eli Lilly and Company and sold under the brand name KISUNLA. It was originally developed for the purpose of targeting the amyloid proteins of AD rather than just the symptoms. In recent years, ongoing research has explored its potential benefits for other neurodegenerative disorders, highlighting its versatility and importance in the field of neurology.

In a press release, Lilly (2023) highlighted the outcomes of the donanemab clinical trial, which involved over 1,500 early symptomatic Alzheimer's patients. The results revealed that

donanemab significantly slowed cognitive and functional decline compared to placebo, with notable improvements in various cognitive scales over a 76-week period. Furthermore, the release indicated that the treatment was generally well tolerated, although some participants experienced amyloid-related imaging abnormalities (ARIA). These findings suggest that donanemab may provide a crucial therapeutic avenue for managing early Alzheimer's disease, particularly by delaying disease progression (Lilly, 2023).

In the TRAILBLAZER-ALZ2 study, Sims et al. (2023) examined the effects of the monoclonal antibody donanemab (antibody against what?) in patients with early symptomatic Alzheimer's disease. The study included 1,736 participants diagnosed with mild cognitive impairment or mild dementia due to Alzheimer's who were 60-85 years old. They received either 700 mg of donanemab for the first 3 doses followed by 1400 mg after, or placebo which was administered intravenously every 4 weeks for up to 72 weeks. However, if patients had amyloid plaque levels below 11 Centiloids, which measures Aβ plaque levels, on any PET scan or between 11 and 25 Centiloids on two consecutive scans, donanemab was switched to placebo with participants being unaware. Final assessments for adverse events and efficacy were conducted at 76 weeks. Additionally, amyloid-related imaging abnormalities were monitored with scheduled MRIs at 4, 12, 24, 52, and 76 weeks, along with unscheduled MRIs as needed. The findings indicated that treatment with donanemab led to a significant slowing of cognitive decline compared to placebo, as measured by the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) and other cognitive assessments, along with amyloid levels (Sims et al., 2023).

Gueorguieva and colleagues subsequently performed a study based on the results of the donanemab phase 1b study and the phase 2 TRAILBLAZER-ALZ study. Participants received donanemab or placebo which were administered via IV injections. In the phase 1 study, participants received single (10, 20, or 40 mg/kg) or multiple (10 or 20 mg/kg) doses of donanemab for up to 72 weeks. In TRAILBLAZER-ALZ, participants received donanemab every 4 weeks for up to 76 weeks (700 mg × 3 followed by 1400 mg doses), with blind dose reductions based on amyloid levels shown on the florbetapir PET (Gueorguieva et. al, 2023a). In another related study based on the same patient population, Gueorguieva and colleagues (2023b) investigated the pharmacokinetics and pharmacodynamics of emerging donanemab in AD patients. The study involved analyzing patient data and pharmacological modeling to understand how this drug behaves in the body. The findings highlighted significant variations in drug metabolism and efficacy based on individual patient characteristics. This clearly informs the importance of personalized treatment approaches in Alzheimer's therapy. They concluded that tailored strategies could enhance therapeutic outcomes and minimize adverse effects in patients with Alzheimer's disease (Gueorguieva et al., 2023b).

Promising Aspects of the Drugs:

Aducanumab, lecanemab, and donanemab are promising therapies targeting Aβ, a hallmark of Alzheimer's disease. These drugs have shown potential in reducing amyloid plaques and slowing cognitive decline in clinical trials, with aducanumab being the first approved amyloid-beta targeted therapy to show any potential benefits to slowing disease in 2021. For instance, lecanemab demonstrated statistically significant cognitive benefits over a period of 18 months in early Alzheimer's patients, suggesting that timely intervention could lead to meaningful improvements in patient outcomes (van Dyck et al., 2022). Similarly, donanemab has also reported positive results, particularly in patients with high amyloid levels, reinforcing the hypothesis that amyloid-targeting therapies can alter disease progression (Lilly, 2023).

Cons and Limitations:

Despite the significant positive impact of these drugs, there are still significant drawbacks. One primary concern is the occurrence of amyloid-related imaging abnormalities (ARIA), particularly ARIA-E, which can induce brain swelling or microhemorrhages. These side effects can lead to severe complications, including headaches, confusion, and in some cases, significant neurological impairment (Sevigny et al., 2016). The risk of ARIA raises questions about the overall safety and long-term effects of these therapies.

In June 2024, two patient deaths occurred after receiving multiple doses of Lecanemab. Both patients were ApoE4 carriers and died from ARIA-E. Two other deaths also occurred. Onene patient showed a microhemorrhage on MRI, but lacked signs of cerebral amyloid angiopathy (CAA), and thus appeared to be an eligible recipient. After the third drug administration, however, the patient developed severe ARIA-E. Five days after this steroid treatment the microhemorrhage dissipated. However, the patient then developed uncontrolled seizures and died. The second patient had a similar experience. The patient was also an *APOE4* carrier who developed inflammatory ARIA-E and died due to seizures. Importantly however, the FDA reported another death of a 79-year-old man who was taking lecanemab and had a hemorrhagic stroke. Thus, it is unclear whether the latter cause of death was a result of the drug (Alzforum, 2024).

Efficacy and Effectiveness:

The overall efficacy and effectiveness of these drugs that target AD remains a controversial topic. While clinical trials suggest some cognitive benefits, many experts argue that there may not be an overall positive impact on patient quality of life. For instance, aducanumab was approved by the FDA based on a surrogate endpoint, but subsequent analyses have indicated that its clinical significance is still under investigation. This has led to debates about the effectiveness of these treatments in routine practice (Salloway et al., 2021).

A notable limitation for individuals with the *APOE4* genotype, a genetic risk factor for Alzheimer's disease, is their reduced responsiveness to these treatments. Due to the low frequency of the *APOE4* allele, this population is often excluded from trials, raising concerns about the generalizability of the results and whether these drugs can effectively benefit all segments of the Alzheimer's population (Ritchie et al., 2022). The age at which treatment begins is also crucial. Most trials have focused on early-stage Alzheimer's patients, and there is insufficient data on the efficacy of these drugs in later stages of the disease. Delaying treatment until the disease is advanced may limit the drugs' effectiveness, thus increasing the need for earlier identification and intervention strategies (Cummings et al., 2021).

Concerns about trial representation are significant as most clinical trials have specific criteria that often exclude individuals with more than one condition or those from diverse backgrounds. This can result in a lack of data on how these drugs perform in a broader spectrum potentially skewing the perceived efficacy and safety profile. Additionally, there is a concern regarding patient dependency on these drugs. Due to the continuous administration that may be required to maintain cognitive benefits, questions about long-term sustainability and whether these therapies truly alter the disease course or merely delay its progression are posed (van der Flier et al., 2023).

There are also multiple logistical challenges that may complicate the administration of these therapies. These include, but are not limited to, the requirement for regular infusions,

receiving the medication intravenously, financial costs, and physician concerns regarding safety. The requirement for regular infusions often limits accessibility for many patients. This aspect is particularly problematic for older adults who may have mobility issues or lack transportation (Antalfy et al., 2023). The intravenous administration method poses additional barriers as patients may experience anxiety regarding injections, and the need for ongoing medical supervision can deter adherence. Oral formulations could improve patient compliance and ease of access (Antalfy et al., 2021). The high cost of these therapies also raises significant concerns. With annual treatment costs often exceeding $50,000, many patients may struggle to afford them, leading to disparities in access (Ross et al., 2022). Additionally, some physicians are hesitant to prescribe these drugs, due to uncertainties about the drugs benefits and potential risks, further complicating the drugs integration into standard Alzheimer's care.

Microglia as an alternative approach to AD that does not involve Aβ:

Targeting Aβ has long been the primary strategy in AD treatment, given its role in plaque formation and neurodegeneration (Schenk et al., 2012). However, emerging research emphasizes the complexity of Alzheimer's pathology, revealing that solely targeting amyloid may not be sufficient for effective treatment. Microglia, the brain's resident immune cells, play a crucial role in maintaining homeostasis and responding to neuroinflammation. These cells not only clear amyloid plaques but also regulate neuroinflammatory processes, making them a promising target for therapeutic intervention. As our understanding of AD evolves, incorporating microglial function into treatment strategies may offer a more holistic approach to managing the disease.

In 2002, Chadareivan and colleagues enhanced the potential for replacing microglia, by developing a version of CSF1R that is resistant to inhibitors. This engineered CSF1R allowed for effective and reliable replacement of microglia, which could lead to an improved treatment option for AD (Chadarevian et al., 2022). In another study led by Chadreivan et al., they found that transplanting induced pluripotent stem cells (iPSC) -derived microglia can both prevent and reverse various neuropathologies in a mouse model of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). The crux of their study relied on developing a xeno-tolerant mouse model that lacks *Csf1r*. This model revealed nearly all the characteristic pathologies associated with ALSP, and, by removing this specific enhancer, they were able to show features that closely mimic those observed in human cases. While not a specific treatment for AD, these findings indicate that iPSC-microglia transplantation might be a promising new treatment strategy for microgliopathies (Chadarevian et al., 2024).

Pros and Cons of Targeting Microglia:

Although microglia-targeted therapies remain under investigation and are far from clinical use, there is a marked increase in interest from the academic field and, as such, new avenues of microglia therapies are being tested at the basic science level and show promise for the future. The therapeutic potential of targeting microglia in AD is valid, as microglial cells can enhance amyloid clearance and regulate inflammation. However, the dual roles of microglia present both opportunities and challenges. While boosting microglial activity may aid in plaque removal, chronic activation can lead to neuroinflammation and exacerbate neurodegeneration. Also, before introducing new cells, one must deplete a patient's immune system which can pose some dangers, given that this typically involves the use of chemotherapy. Therefore, therapeutic strategies must carefully balance microglial activation and potential side effects with any

proposed therapeutic benefits. Integrating microglial modulation into Alzheimer's treatment could represent a more holistic approach, potentially leading to better outcomes for patients.

Conclusion:

With the recent advancements in AD treatment, highlighted by the drugs aducanumab, donanemab, and lecanemab, this review discussed a range of therapeutic options. Each drug has its own benefits and drawbacks; for instance, while aducanumab and lecanemab target amyloid plaques and have shown promise in reducing cognitive decline, they have also faced scrutiny regarding their efficacy and safety profiles. Donanemab, on the other hand, is better-established in improving cognitive function but primarily addresses symptoms rather than underlying disease processes. An alternative strategy gaining attention is the transplantation of microglia, which holds the potential to not only restore normal brain function but also enhance the immune response against neurodegeneration. This approach may offer a more holistic treatment by directly addressing the cellular environment of the brain, however it is still in preclinical studies. Looking to the future, the integration of these drug therapies with innovative strategies like microglial replacement could pave the way for more effective and comprehensive treatments for Alzheimer's disease, potentially improving patient outcomes and quality of life. Continued research and clinical trials will be essential to fully understand the benefits and limitations of these therapies.

Acknowledgements

The author would like to thank Adeline Walsh for her input and mentoring throughout this project. The author also thanks the Polygence Research Program for providing the mentoring platform and resources necessary for the completion of this work.

References:

1. Alzheimer's Association. (2023). *Alzheimer's disease facts and figures*. Alzheimer's Association. Accessed October 30, 2024. https://www.alz.org/facts-and-figures
2. Alzheimer's Association. (2024). *Lecanemab (Leqembi)*. Accessed October 30, 2024. https://www.alz.org/alzheimers-dementia/treatments/lecanemab-leqembi
3. Antalfy, A., et al. (2023). The adherence and outcomes benefits of using a connected, reusable auto-injector for self-injecting biologics: A narrative review. *Advances in Therapy, 40*(11), 4758. https://doi.org/10.1007/s12325-023-02671-2
4. Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: Pathways, pathogenesis and therapy. *Nature Reviews Neuroscience, 10*(5), 333. https://doi.org/10.1038/nrn2620
5. Cadiz, M. P., et al. (2024). Aducanumab anti-amyloid immunotherapy induces sustained microglial and immune alterations. *The Journal of Experimental Medicine, 221*(2), e20231363. https://doi.org/10.1084/jem.20231363
6. Casali, B. T., & Reed-Geaghan, E. G. (2021). Microglial function and regulation during development, homeostasis and Alzheimer's disease. *Cells, 10*(4), 957. https://doi.org/10.3390/cells10040957
7. Chadarevian, J. P., et al. (2022). Engineering an inhibitor-resistant human CSF1R variant for microglia replacement. *The Journal of Experimental Medicine, 220*(3), e20220857. https://doi.org/10.1084/jem.20220857
8. Chadarevian, J. P., et al. (2024). Therapeutic potential of human microglia transplantation in a chimeric model of CSF1R-related leukoencephalopathy. *Neuron*. https://doi.org/10.1016/j.neuron.2024.05.023
9. Cummings, J., et al. (2022). Alzheimer's disease drug development pipeline: 2022. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, 8*(1), e12295. https://doi.org/10.1002/trc2.12295
10. Eli Lilly and Company. (2023, May). Lilly's donanemab significantly slowed cognitive and functional decline in a phase 3 study of early Alzheimer's disease. https://investor.lilly.com/node/48836/pdf
11. Golde, T. E., et al. (2009). Targeting Aβ and tau in Alzheimer's disease, an early interim report. *Experimental Neurology, 223*(2), 252. https://doi.org/10.1016/j.expneurol.2009.07.035
12. Gendron, T. F., & Petrucelli, L. (2009). The role of tau in neurodegeneration. *Molecular Neurodegeneration, 4*, 13. https://doi.org/10.1186/1750-1326-4-13
13. Golde, T. E., et al. (2009). Targeting Aβ and tau in Alzheimer's disease, an early interim report. *Experimental Neurology, 223*(2), 252. https://doi.org/10.1016/j.expneurol.2009.07.035
14. Gueorguieva, I., et al. (2023). Donanemab exposure and efficacy relationship using modeling in Alzheimer's disease. *Alzheimer's & Dementia (New York, N.Y.), 9*(2), e12404. https://doi.org/10.1002/trc2.12404
15. Gueorguieva, I., et al. (2023). Donanemab population pharmacokinetics, amyloid plaque reduction, and safety in participants with Alzheimer's disease. *Clinical Pharmacology & Therapeutics, 113*(6), 1258–1267. https://doi.org/10.1002/cpt.2875
16. Hampel, H., et al. (2021). The amyloid-β pathway in Alzheimer's disease. *Molecular Psychiatry, 26*(10), 5481–5503. https://doi.org/10.1038/s41380-021-01249-0

17. Hong, S., et al. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science, 352*(6286), 712. https://doi.org/10.1126/science.aad8373
18. Liu, L., et al. (2024). Lecanemab and vascular-amyloid deposition in brains of people with Down syndrome. *JAMA Neurology, 81*(10), 1066–1072. https://doi.org/10.1001/jamaneurol.2024.2579
19. National Institute of Neurological Disorders and Stroke. (n.d.). *Brain basics: The life and death of a neuron*. National Institutes of Health. Accessed October 30, 2024. https://www.ninds.nih.gov/health-information/public-education/brain-basics/brain-basics-life-and-death-neuron
20. Peters, R. (2006). Ageing and the brain. *Postgraduate Medical Journal, 82*(964), 84. https://doi.org/10.1136/pgmj.2005.036665
21. Rezai, A. R., et al. (2024). Ultrasound blood–brain barrier opening and aducanumab in Alzheimer's disease. *New England Journal of Medicine, 390*(1), 55–62. https://doi.org/10.1056/NEJMoa2308719
22. Ross, E. L., et al. (2022). Cost-effectiveness of aducanumab and donanemab for early Alzheimer disease in the US. *JAMA Neurology, 79*(5), 478. https://doi.org/10.1001/jamaneurol.2022.0315
23. Salloway, S., et al. (2021). Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurology, 79*(1), 1. https://doi.org/10.1001/jamaneurol.2021.4161
24. Schenk, D., et al. (2012). Treatment strategies targeting amyloid β-protein. *Cold Spring Harbor Perspectives in Medicine, 2*(9), a006387. https://doi.org/10.1101/cshperspect.a006387
25. Sevigny, J., et al. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature, 537*(7618), 50–56. https://doi.org/10.1038/nature19323
26. Sims, J. R., et al. (2023). Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA, 330*(6), 512–527. https://doi.org/10.1001/jama.2023.13239
27. Swanson, C. J., et al. (2021). A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimer's Research & Therapy, 13*(1), 80. https://doi.org/10.1186/s13195-021-00813-8
28. van Dyck, C. H., et al. (2023). Lecanemab in early Alzheimer's disease. *The New England Journal of Medicine, 388*(1), 9–21. https://doi.org/10.1056/NEJMoa2212948
29. van der Flier, W. M., et al. (2023). Towards a future where Alzheimer's disease pathology is stopped before the onset of dementia. *Nature Aging, 3*(5), 494–505. https://doi.org/10.1038/s43587-023-00404-2
30. Yadollahikhales, G., & Rojas, J. C. (2023). Anti-amyloid immunotherapies for Alzheimer's disease: A 2023 clinical update. *Neurotherapeutics, 20*(4), 914. https://doi.org/10.1007/s13311-023-01405-0