ADDRESSING ALZHEIMER'S DISEASE PATHOLOGY THROUGH COMBINATORIAL THERAPEUTIC INTERVENTIONS

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Abstract:

In recent years, neurodegenerative diseases have become a greater focus area of research due to their significant prevalence and complex pathophysiology. The neurodegenerative disease known as Alzheimer's Disease (AD) is characterized by its variable and progressive symptom expression, which may include memory loss, reduced cognitive function, abnormal behavior, and eventually neuronal cell death. The mechanisms underlying the expression of this disease are continuously being researched, and notable processes that have been implicated in both AD origination and progression include plaque accumulation and neuroinflammation. As a result, a multitude of therapeutic, disease-intervening drugs have been developed to address the different underlying causes of AD. Given the complex pathology of AD and the increasing number of developing therapeutics, combination therapy has become increasingly relevant in neurodegenerative disease research. In this thesis, I examine two neurodegenerative disease treatments with phase III trial data; an anti-amyloid-beta antibody called Lecanemab, and an anti-inflammatory tyrosine kinase inhibitor called Masitinib. I attempt to predict potential outcomes of drug mechanism interaction, as well as overall drug complementarity between these drugs. Furthermore, I outline a theoretical, alternating combinatorial approach for treatment using these drugs–including dosages and dosage periods for each drug. The conclusions drawn from this analysis identify potential synergistic effects between the two drugs, which may increase observable benefits in AD patients greatly, as well as potential areas of concern for antagonism. Additionally, I highlight the need for additional *in vivo* or clinical research into combination therapy, both for these drugs and also for the field as a whole within the context of neurodegenerative disease.

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1. Introduction and Literature Survey

1.1 Symptoms and Diagnosis

Alzheimer's disease (AD) is a debilitating neurodegenerative disease primarily associated with dementia, and has become increasingly prevalent in recent history primarily due to aging populations and increased life expectancies (Mobaderi et al., 2024; Scheltens et al., 2021). It is characterized primarily by the visible degradation of autonomy and cognitive function in affected individuals. This includes loss of memory, as well as issues involving language, comprehension, and judgement, among others. Furthermore, AD symptoms are categorized by insidious onset and variable progression (Lui and Tsao, 2024). AD first becomes noticeable predominantly in individuals age 65 or older, commonly known as late-onset AD (LOAD). More rarely, however, AD symptoms can also appear in individuals younger than 65, which is known as early-onset AD (EOAD). In either case of AD, the first and most commonly noticeable symptom involves the periodic loss of short-term memory. Following this, disease progression may involve the appearance of symptoms such as difficulties involving problem solving or abstract thinking and impaired judgement. Progression into moderate and late stages of AD typically involve the emergence of neuropsychiatric-related symptoms, including wandering, social withdrawal, or psychosis (Lui and Tsao, 2024).

Pathological biomarkers of AD can be detected in individuals many years prior to symptom expression, however, early diagnosis and treatment can be difficult due to a number of factors. Often, affected individuals do not seek treatment until symptom expression becomes severe enough to interfere with daily activities. Furthermore, EOAD symptoms may be dismissed or perceived as effects associated with regular age progression (Porsteinsson et al., 2021). One diagnostic method available to symptom-presenting individuals includes the use of

amyloid-beta (Aβ) binding tracers, which help locate and detect amyloid plaques upon visualization using amyloid PET scans. Another secondary method of detection involves the extraction of cerebro-spinal fluid (CSF) from patients. Upon extraction via lumbar puncture, an indication of AD-associated biomarker presence, as well as overall protein production and clearance can be ascertained (Porsteinsson et al., 2021). While these detection methods allow for proper quantification and diagnosis of AD progression, understanding the underlying mechanisms of AD pathology can help further inform future pathways of AD treatment.

1.2 General Pathology

The pathophysiology of AD, including origination and progression is extremely complex and is constantly being researched and explored. There are a variety of pathological processes that contribute to the progression of AD; notably among these is the accumulation of amyloid-beta (Aβ) and hyperphosphorylation of tau that leads to neurofibrillary tangles (NFTs) (Abdulkhaliq et al., 2026). However, other cellular processes (and cells themselves) can also play a role in AD pathogenesis and disease progression. Two types of cells that have been more recently examined in AD contexts and implicated in AD pathogenesis include astrocytes and oligodendrocytes. Within the CNS, astrocytes are the most commonly found glial cell type and possess a multitude of functions including maintenance of the blood brain barrier, mediating cell-cell interactions, and providing metabolic support across the CNS (Nutma et al., 2020). Discussed by Ziar et al. (2025), recent evidence has connected astrocyte dysfunction to both Aβ and tau accumulation and subsequent neurodegeneration. In relation to Aβ, astrocytes have demonstrated the ability to increase Aβ burden via generation of Aβ, and exposure to Aβ can induce pro-inflammatory states in astrocytes resulting in the production of inflammatory

signaling proteins (i.e., cytokines and chemokines), in turn, furthering chronic neuroinflammation (Ziar et al., 2025).

Oligodendrocytes are myelin-producing cells found exclusively within the CNS, and are also responsible for providing trophic support to neurons. Additionally, oligodendrocytes have been shown to produce immune regulatory factors and communicate with microglia during immune-mediated responses (Nutma et al., 2020). Dysfunction in oligodendrocytes and myelin production has also been shown to increase Aβ burden, and may even act as a driver of AD pathogenesis, rather than a consequence of it (Ziar et al., 2025). Furthermore, oligodendrocyte dysfunction is thought to be caused by high amounts of reactive oxygen species (ROS) within the brain. Several sources have been associated with excessive ROS production and oxidative stress within AD contexts, including accumulation of Aβ and tau, mitochondrial dysfunction, iron accumulation, and disrupted calcium homeostasis (Manoharan et al., 2016). Oxidative stress can be particularly detrimental to oligodendrocyte function, given their elevated mitochondrial activity associated with myelin production. As a result, oxidative stress has been shown to cause oligodendrocyte cell death, impaired oligodendrocyte differentiation, and reduced transcription of myelin-producing proteins (Gruber et al., 2015).

Other significant contributors to the pathogenesis include Lewy bodies (LBs) and TDP-43. LBs are typically more closely associated with another neurodegenerative disease known as Parkinson's disease and in most cases are classified within their own form of dementia, known as Lewy body dementia (Haider et al., 2023). However, LBs have been discovered in over half of sporadic and familial AD cases, indicating a co-pathology between LBs and AD. Such cases have been recognized as the Lewy body variant of AD (LBVAD). These protein aggregates are responsible for generating intraneuronal lesions in several neuronal populations,

including those within the brainstem and neocortex (Kotzbauer et al., 2001). Encoded by the *TARDBP* gene, TDP-43 is a protein heavily involved in RNA processing, including trafficking, stabilization, and splicing. Within AD and other neurodegenerative diseases, truncated forms of TDP-43 have been identified and associated with increased cognitive impairment (compared to TDP-43 absent AD patients) (Meneses et al., 2021). The mechanism underlying these cognitive deficits is thought to be due to co-localization of TDP-43 with NFTs and plaques, resulting in dysfunctional TDP-43 localization and aggregation–leading to altered oxidative stress responses, DNA damage, and impaired mRNA processing (Meneses et al., 2021).

1.3 Amyloid Pathology and Microglia

Aside from the previously discussed contributors to AD pathogenesis, more relevant to this thesis and the therapeutic interventions focused on within it include the pathogenesis of Aβ and microglia within AD. The generation of Aβ plaques in AD patients stems from the abnormal processing of amyloid precursor protein (APP). This transmembrane protein, located primarily at synapses, is involved in many cellular processes including neural plasticity and ion transport, among others (Abdulkhaliq et al., 2026). Processing of APP consists of two main pathways, one which is neuroprotective (non-amyloidogenic) and one which is neurodegenerative (amyloidogenic). In normal, neuroprotective processing, enzymes α-secretase and γ-secretase cleave APP into multiple fragments, in which p3 is the final extracellular product generated by γ-secretase. In neurodegenerative APP processing, however, cleavage of APP by the β-secretase enzyme dysregulates α-secretase and γ-secretase cleavage events, and the resulting final extracellular fragment therefore becomes Aβ (Wilkins and Swerdlow, 2018). Following these cleavage events, the p3 fragment is thought to be largely harmless and does not play a notable role in AD pathogenesis (although recent information may suggest otherwise) (Nhan et al.,

2014). The Aβ fragment, however, is known to form multiple neurotoxic forms of Aβ oligomers, fibrils, proto-fibrils, etc. These structures then aggregate into plaques both intraneuronally and interneuronally, ultimately disrupting synaptic function and causing cell damage (Abdulkhaliq et al., 2026).

Under normal physiological conditions, resident microglial cells respond protectively by clearing Aβ plaques/deposits. In AD, excessive microglial activity has instead demonstrated pro-inflammatory effects, leading to worsening disease progression and neuronal damage (Azmal et al, 2025). This difference in microglial activity is categorized into two types of responses/phenotypes; M1 and M2. The M1 response is characterized by its pro-inflammatory effects, due to the production of inflammatory cytokines and chemokines (i.e., TNF-α, IL-6, IL-1β, etc.) as well as downstream production of species such as nitric oxide and reactive oxygen species (Guo et al., 2022). In contrast, the M2 response is characterized by its anti-inflammatory effects due to the production of anti-inflammatory cytokines (i.e., IL-10, CSF-1, BDNF, etc.) and other neuroprotective proteins and receptors (Guo et al., 2022). In either case, the main mechanism utilized by microglial cells in Aβ plaque removal (or other foreign pathogens) is phagocytosis (Brown et al., 2025). In general, microglia phagocytosis within the central nervous system (CNS) is dependent on the expression of specific receptors on cell surfaces as well as downstream signaling related to particle engulfment. In particular, two main receptor types are relevant in this process, one which binds pathogenic entities and one which binds apoptotic cellular substances (Fu et al., 2014). In the context of AD, it is assumed that the ability of microglial cells to uptake and properly phagocytize Aβ plaques is affected, however studies have shown that the use of antibodies can improve microglial clearance efficacy (Bard et al., 2000).

Similarly, to further address both Aβ and microglial pathology within AD, a variety of medical interventions have been developed, each addressing specific characteristics of these processes.

1.4 Drug Development and Clinical Trials

Advances in the field of molecular biology have allowed for many new possibilities for AD treatments and their pathological targets. Recent studies have provided quantitative data regarding the amount of drugs and trials in the AD pipeline, as well as the diversity in clinical application of the drugs themselves. As of June 2025, there were a total of 182 clinical trials assessing 138 different novel, AD-related drugs in phase I, II, or III trials (Cummings et al., 2025). Illustrated in fig. 1, these drugs can be categorized based on their physical characteristics or intended target effects, with larger categories including disease-targeted small molecule, disease-targeted biologic, cognitive enhancer, etc. Within these categories, many of the drugs possess different mechanisms of action or pathological targets, with some targeting Aβ, tau, neuroinflammation, and oxidative stress, among others (Cummings et al., 2025).

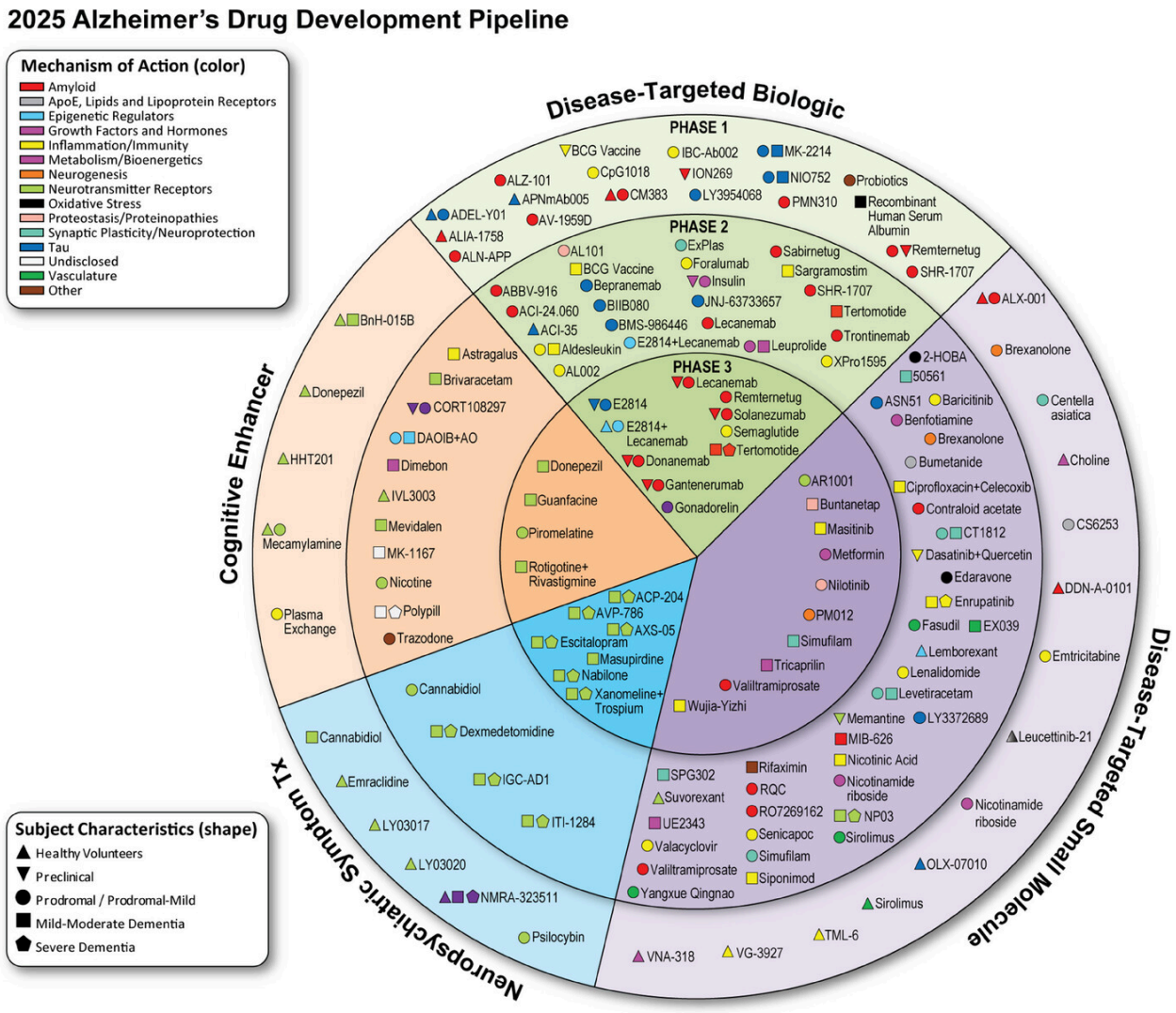

Figure 1. *This figure from Cummings et al., 2025 depicts the variety of novel drugs within the AD pipeline. The figure categorizes drugs based on mode of action, trial phase, as well as subject characteristics.*

Notable drugs within this pipeline are those farther along in clinical trials, particularly those that have demonstrated efficacy in phase III trials or are already FDA approved. These drugs are responsible for a significant portion of the provided AD drug pipeline, with 48 of the 182 trials examined consisting of a phase III drug of some kind (Cummings et al., 2025). A

particular focus on phase III drugs will be utilized in this text, due to the amount of available information regarding their efficacy and molecular mechanism of action.

1.5 Combinatorial Drug Therapy

The concept of utilizing a variety of different drugs in order to target different pathological symptoms or pathways has been employed in many types of disease in recent history, particularly in regards to different types of cancer. With the abundance of pathological processes that contribute to AD progression on a molecular level (Aβ, hyperphosphorylation of tau, glial cell activity, etc.), intervention in many different areas may be necessary to aid in substantial prevention of AD progression. In fact, several existing clinical trials have demonstrated the efficacy of combination therapy within AD. Within these studies, combination therapy was shown to improve specific benchmarks such as cognitive decline and overall functionality (Kabir et al., 2020).

A 2024 publication from Cummings et al. discusses a potential roadmap for how to approach combinatorial drug therapy in AD, covering a continuum of different combinations (based on pathology targets) in relation to disease severity (stage of AD). Furthermore, a list of proposed pharmacodynamic and pharmacokinetic combinations is provided, with some pairings involving existing drugs such as Aducanumab or Rasagline. Most emerging combinatorial drug treatment plans involve the co-development of new drugs, which are required to apply to certain Food and Drug Administration (FDA) guidelines. A more relevant caveat, however, is that certain anti-Aβ and anti-inflammatory agents may be administered independently and also may not require co-development (Cummings et al., 2024). Therefore, for the purposes of this thesis, FDA guidelines associated with co-development and other related factors will not be considered, and independent administration and development of both an anti-Aβ and anti-inflammatory drug

will be assumed. The two drugs of choice that will be examined for their combinatorial potential in this thesis include Lecanemab and Masitinib, chosen based on the following criteria; first, each of these drugs possesses a large amount of significant, published data given their progress in FDA approval and demonstration of effectiveness/safety in phase II and III trials. As a result of the extensive research into their safety and efficacy, they are also among the most practical treatments in terms of near-future usage. Additionally, each of these drugs has distinct, disease-intervening mechanisms of action (e.g., Aβ clearance and anti-inflammation) and therapeutic effects, yet still possess a small amount of overlap, particularly regarding microglial cell regulation (will be explored more in the following sections), that can either enhance or reduce drug efficacy. Finally, these two drugs were chosen due to an absence of published data examining the use of these specific drugs in combination for neurodegenerative disease, which allows for novel insights into drug interaction and the potential for combination therapy within AD.

2. Lecanemab

2.1 Mechanism of Intervention

Lecanemab is a well-researched, FDA approved treatment for early AD that functions as a humanized monoclonal antibody. As an IgG1 antibody, Lecanemab binds to soluble Aβ protofibrils with high affinity to increase efficiency of Aβ plaque clearance and help slow cognitive decline in patients with early to moderate AD (van Dyck et al., 2022). This process is thought to be mediated by the phagocytic properties of cells such as microglia. Other phagocytic cells are also theorized to have some part in antibody-mediated clearance, however contemporary evidence has placed certain microglial cells at the forefront of lecanemab's functionality (Albertini et al., 2026; Chen, 2026). The specific mechanism enacted by these

microglial cells is not certain, but it has been recently demonstrated that fragment crystallizable (Fc) effector pathways as well as transcriptomic changes in microglial cells both contribute to effective Aβ clearance during Lecanemab treatment (Albertini et al., 2026). In contrast, previous studies have demonstrated the detrimental effects of pro-inflammatory pathways associated with Fc-containing antibodies (Sun et al., 2023). However, as previously stated, Lecanemab has also demonstrated an ability to induce transcriptomic changes in microglia via multi-pathway co-activation, resulting in differential gene expression and a mediation of inflammatory responses and synaptophagy previously seen in Fc-containing antibodies (Albertini et al., 2026). Depicted in fig. 2 below, a general overview of Lecanemab's mechanism begins with IgG1 antibodies binding the N-terminus of soluble Aβ protofibrils, forming immune complexes resulting in the recruitment of microglial cells. These microglial cells possess Fcγ receptors (FcγR), which recognize and bind Fc-regions of Lecanemab, resulting in engulfment and phagocytosis of Aβ molecules, activation of intracellular pathways and their downstream effects, and ultimately transcriptome changes to promote Aβ clearance and reduce harmful inflammatory responses (Albertini et al., 2026; Reyes et al., 2025).

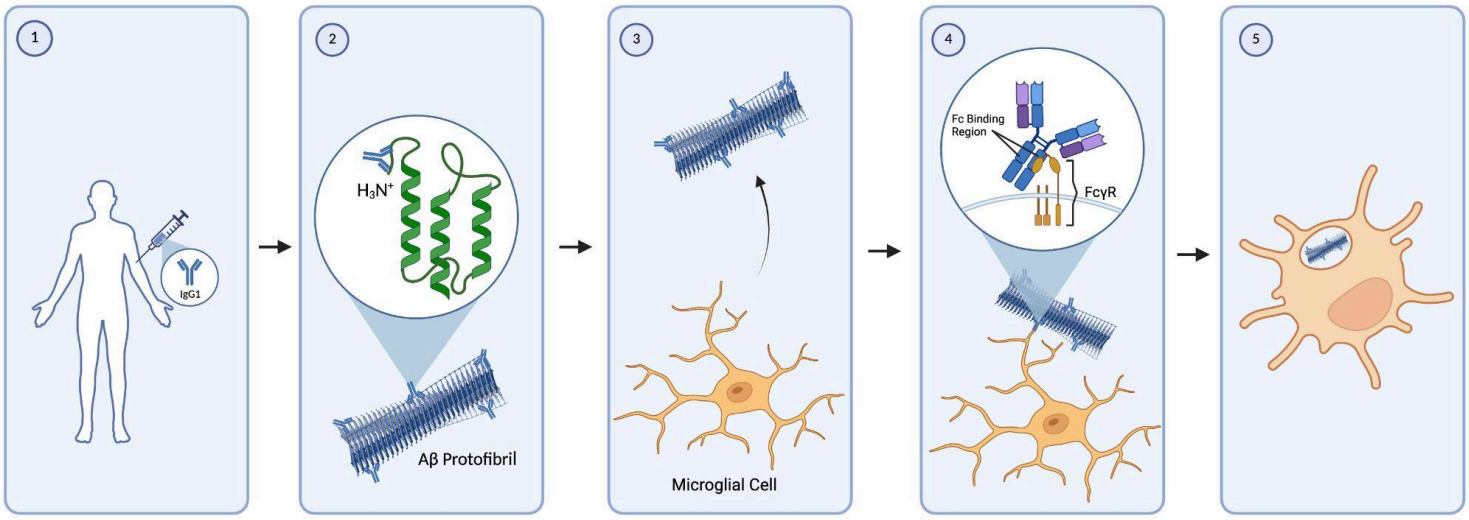

Figure 2. *General steps of Aβ protofibril clearance following Lecanemab administration. The figure illustrates Lecanemab administration (1), N-terminus binding (2), microglial cell recruitment (3), Fc-receptor binding (4), and phagocytosis of protofibrils via microglial cell (5). Created using BioRender.*

2.2 Clinical Findings and Limitations

In addition to how Lecanemab functions, it is important to recognize the efficacy of the drug in clinical trials and other controlled studies. A key phase III study for Lecanemab was published in 2022, in which approximately 1800 individuals with early AD or mild dementia participated in a double-blind, randomized, placebo-controlled trial. The results of the study displayed a statistically significant reduction in Aβ burden (visualized using PET scans), as well as a statistically significant (-0.45 compared to placebo) change from baseline for the Clinical Dementia Rating-Sum of Boxes (CDR-SB) (van Dyck et al., 2022). In a follow-up to the same 2022 phase III trial, quality of life (QOL) measurements (i.e., anxiety/depression, mobility, pain/discomfort, etc.) in patients were also assessed. In terms of health-related quality of life (HRQoL), Lecanemab became statistically relevant at 6 months and reduced the decline of AD-related QOL by approximately 56% (Cohen et al., 2023). Together, these results indicate that Lecanemab can improve Aβ burden and AD progression in observable amounts, on both molecular and clinical levels–serving as a multi-benefit treatment for patients with AD.

While Lecanemab may produce measurable and statistically significant effects in regard to slowing AD progression, it still lacks the ability to prevent or reverse AD. Additionally, the use of Lecanemab was accompanied by certain unintended effects in a small portion of recipients. These reactions seen in Lecanemab-receiving individuals included atrial fibrillations, syncope, and other infusion-related reactions (van Dyck et al., 2022). Perhaps more notably, a small fraction of recipients also experienced amyloid-related imaging abnormalities (ARIA), with a portion also experiencing edema or effusions (ARIA-E) or hemorrhaging (ARIA-H) . Out

of the 1795 individual cohort from the 2022 study, ARIA-E and ARIA-H incidence rates were 12.6% and 17.3%, respectively, and phase II results possessed a similar ARIA profile, with an incidence rate of 9.9% in individuals receiving Lecanemab (van Dyck et al., 2022; Swanson et al., 2021). Additionally, it appeared that individuals possessing either one or two copies of the *APOE*4 allele (genetic risk factor for AD) were at a higher risk for experiencing ARIA-related effects, with incidence of ARIA for non-carriers at 5.4%, heterozygotes at 10.9%, and homozygotes at 32.6% (Cummings et al., 2023).

3. Masitinib

3.1 Mechanism of Intervention

Masitinib is an orally administered tyrosine-kinase inhibitor that has been researched for use in a variety of inflammatory and neurodegenerative disorders, as well as some types of cancers. Specifically, some of the relevant kinases the drug inhibits include Lyn, Fyn, KIT, and MCSFR-1 (Latham et al., 2022). Based on mouse models of AD, Masitinib is thought to act neuroprotectively primarily through mast cell inhibition, reducing detrimental neuroinflammatory responses (Dubois et al., 2023). Lyn kinases are known to contribute to mast cell activation via phosphorylation of FcεRI (receptor for immunoglobulin E) as well as other substrates, while the Fyn kinase also contributes to mast cell responsiveness. Moreover, in the context of kinases, the primary contributor to mast cell homeostasis is KIT, which is heavily involved in the phosphorylation of a multitude of signaling proteins, and is often associated with the survival and proliferation of mast cells (Gilfillan and Rivera, 2010). Therefore, by inhibiting these kinases, Masitinib has demonstrated the ability to reduce cytokine production, degranulation, and migration of mast cells, aiding in the reduction of AD progression (Dubois et al., 2023; Dubreuil et al., 2009). While mast cell inhibition is one of the primary targets for

Masitinib, it also possesses dual targeting effects on microglia and macrophages (Hermine et al., 2025). In the case of microglia, Masitinib has demonstrated the ability to reduce microgliosis (excess accumulation of microglia) in mouse-models largely through inhibition of MCSFR-1 receptors (Elmore et al., 2014). Additionally, other studies have shown that Masitinib does not completely eliminate microglial proliferation (Ketabforoush et al., 2023). Fig. 3 below illustrates a summary of the cellular cascades impacted by Masitinib and their respective consequences on neuroinflammation and neuroprotection.

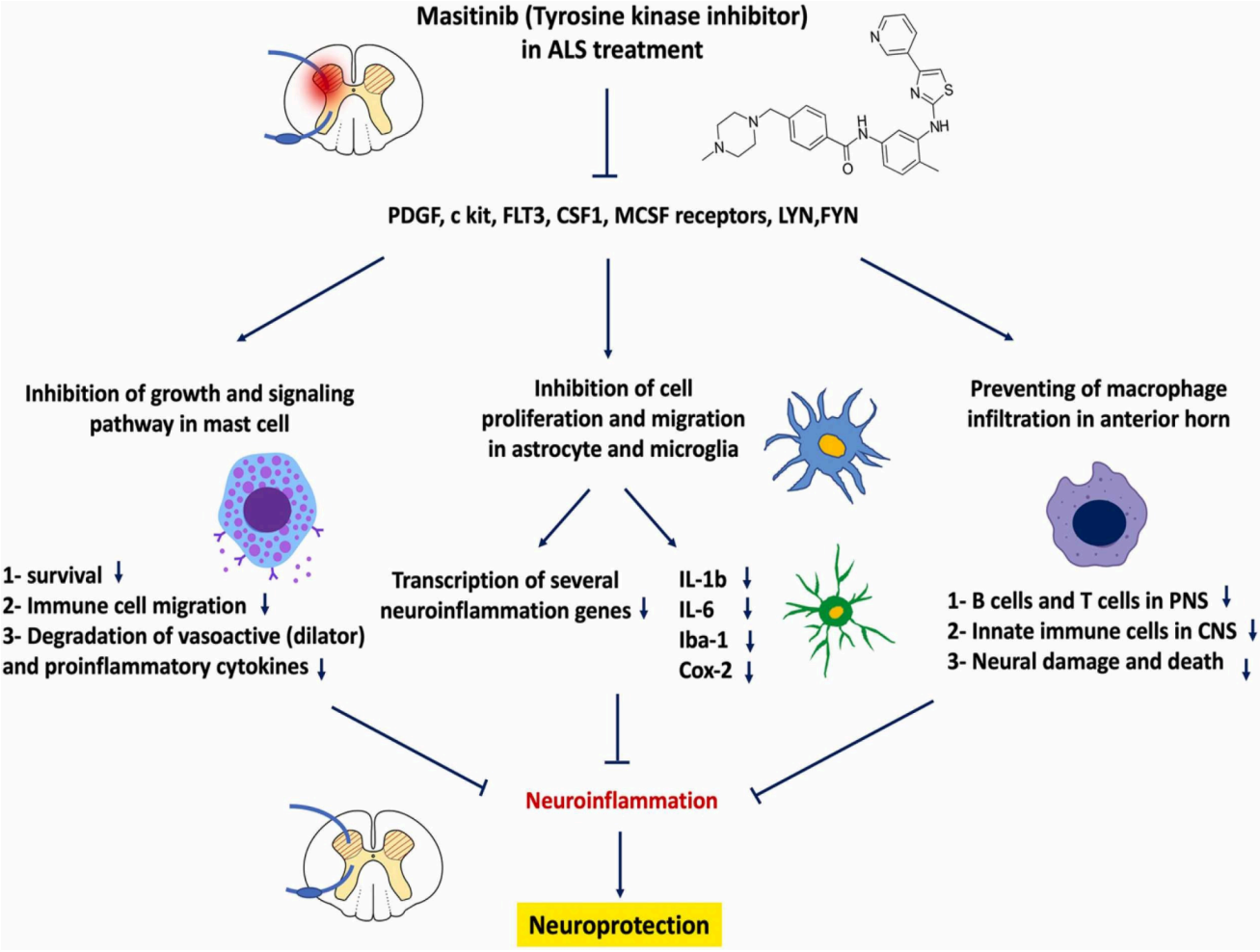

Figure 3. *From Ketabforoush et al., 2023, this figure summarizes the signaling cascade and downstream effects of Masitinib in Amyotrophic Lateral Sclerosis (ALS). This includes Masitinib's effect on mast cells*

(left) as well as microglia (middle) and the downregulation of neuroinflammatory characteristics of these cells.

3.2 Clinical Findings and Limitations

The earliest clinical results for Masitinib in AD comes from a randomized, placebo-controlled, phase II study. Throughout the study, 26 individuals with mild-to-moderate AD were given Masitinib twice daily over the course of 24 weeks as an adjunct to either a cholinesterase inhibitor or memantine. Using the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-Cog) for endpoint measurements, individuals who received Masitinib compared to placebo saw statistically significant improvements in cognitive decline (Piette et al., 2011). More recently, results demonstrating the efficacy of Masitinib in AD were published in a randomized, placebo-controlled, phase 3, clinical trial. This study involved a greater number of patients who received Masitinib with mild-to-moderate AD (182), whilst retaining the drug as an adjunct to a cholinesterase inhibitor or memantine. The results for this study also utilized ADAS-Cog to measure cognitive improvement, as well as the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory scale (ADCS-ADL) to measure overall functionality. Patients that received Masitinib displayed statistically significant improvements in both ADAS-Cog and ADCS-ADL ($p < 0.001$ and $p = 0.038$, respectively) (Dubois et al., 2023).

Similar to Lecanemab and any other currently existing AD therapy, Masitinib is limited in its ability to treat AD and does not possess the capability of preventing progression or AD reversal. Furthermore, additional testing in patients experiencing later, more severe stages of AD may not yield the same results as seen in the phase II and III trials. However, unlike many other disease-modifying AD treatments, Masitinib exhibits a relatively mild safety profile. Phase II trial results reported no fatalities due to Masitinib treatments and few serious adverse effects. Of the reported adverse effects, oedema was the most prominent, followed by a variety of

gastrointestinal-related reactions such as nausea, vomiting, diarrhea, and rash (Piette et al., 2011). Masitinib-related adverse effects observed in the phase III testing of the drug were similar to that of the phase II trial, of which there were no deaths related to Masitinib, and other symptoms observed in treatment-group individuals were consistent with those already previously seen. As a result, the phase III trial reported no new safety signal for Masitinib (Dubois et al., 2023).

4. Drug Combination (Lecanemab + Masitinib)

4.1 Mechanism Complimentarity

Predicting the resulting effect of combining multiple disease-modifying drugs for treating the pathology of a disease as complex as AD is difficult. However, utilizing the known information regarding these drugs' mechanisms and clinical effects can inform how these drugs may be able to act synergistically to make AD more manageable–or at the very least, reveal gaps in knowledge that can be addressed through future research to move toward that goal. It should also be noted that, at the current moment of writing and to the fullest extent of my knowledge, there are no publications discussing the proposed use of Lecanemab and Masitinib together for treating AD. On a broad scale, each of these drugs possess different intended clinical results, with Lecanemab utilizing microglial cells to reduce Aβ aggregation and Masitinib targeting mast cell and microglial activity to prevent recruitment of inflammatory cytokine responses. On a molecular level, it has been discussed that functional Fc receptors on microglia are thought to be required for Aβ clearance at therapeutic concentrations, which raises a concern for how a tyrosine kinase inhibitor such as Masitinib may impact these receptors (Albertini et al., 2026). Current research appears to only implicate Bruton's tyrosine kinase (BTK) inhibitors in microglial functionality, specifically in relation to FcγR activity (Langlois et al., 2024).

Therefore, regarding simultaneous administration and activity of these drugs, Fc receptor functionality in microglia would theoretically not be directly affected by Masitinib. However, despite this hypothetical partial complementarity, simultaneous activity of these drugs could likely face a host of issues (see fig. 4 below for a summary of potential outcomes).

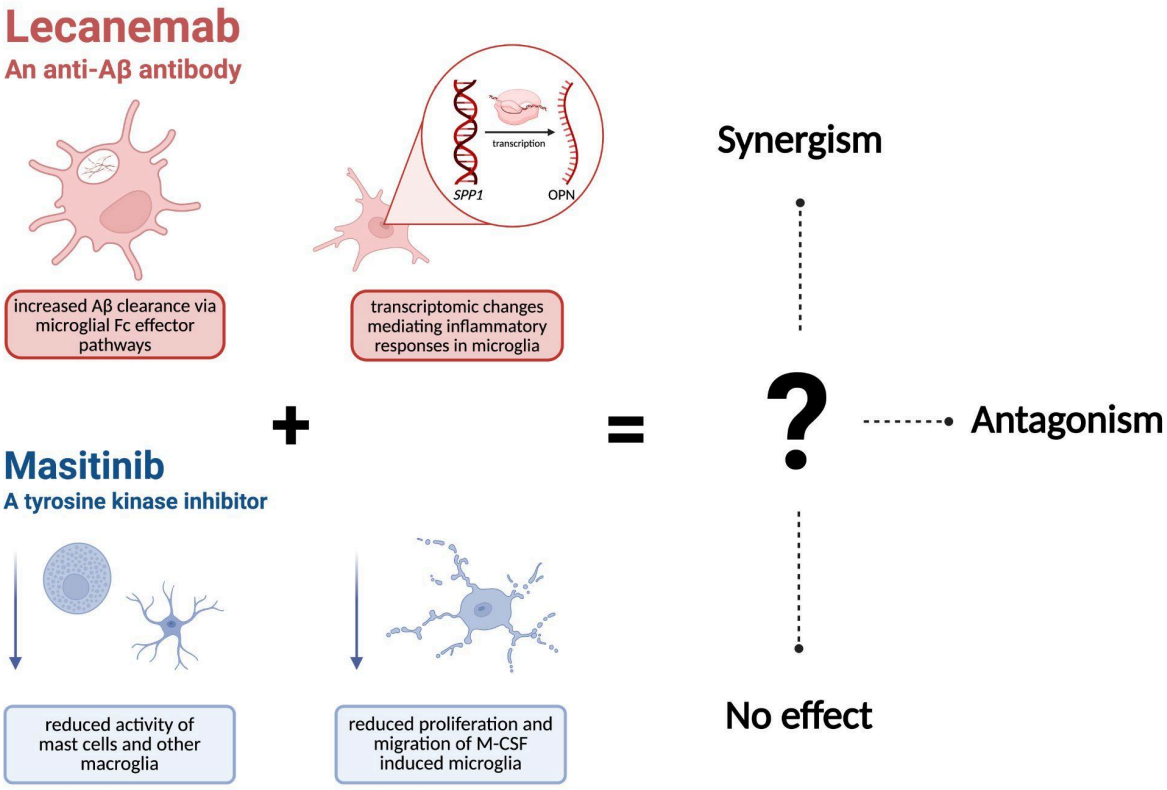

Figure 4. *Summary of the cellular effects of both Lecanemab and Masitinib, as well as a list of potential observable effects following combination therapy. Created using BioRender.*

Due to Masitinib acting on microglial cells to reduce proliferation and activity, there is a concern of conflict with the mechanism of Lecanemab. To maintain therapeutically relevant amounts of Aβ clearance, Lecanemab depends on functioning populations of microglia to phagocyotize Aβ protofibrils. The leading cause of this conflict would be Masitinib's selective inhibition of MSCFR-1 receptors, which are highly expressed by microglia. Therefore, necessary

information for determining the extent of this conflict would be; (1) What is the degree to which Masitinib inhibits microglial cell functionality? and, (2) What is the amount of functional microglia that need to be available for Lecanemab to maintain therapeutic efficacy (or in other words, how much microglial inhibition can be tolerated before Lecanemab loses effectiveness)?

In order to address the first of these two queries, studies analyzing Masitinib's effect on microglia in different disease environments may be of use. First, studies focusing on Amyotrophic Lateral Sclerosis (ALS) have aided in demonstrating the extent of Masitinib inhibition on microglia. At micromolar concentrations, Masitinib was able to reduce microglial transformation into aberrant cell types by over 50%, and lead to significant reductions in spinal cord microglia concentrations (Trias et al., 2016). In contrast, more recent studies investigating the use of Masitinib in AD mouse-models exhibited no change to microglial densities, whilst depleting mast cell concentrations (exhibiting neuro-protective effects) (Li et al., 2020). Therefore, it may be assumed that Masitinib depletion of microglial cells is contextually dependent on disease-specific pathological environments, and baseline microglial states associated with each type of disease. Thus, given the currently available information it is plausible that within AD-specific contexts, Masitinib may not interfere with Lecanemab and microglial functions–however, more research should be conducted to provide a greater understanding of how Masitinib affects microglia in AD environments. Unfortunately, when trying to address the second query, little published data is available for microglial concentration-dependent efficacy of Lecanemab. Available data only suggest that microglial-deficient conditions fail to elicit therapeutic effects when using Lecanemab, rather than providing specific quantitative values for Lecanemab's efficiency given varying microglia populations (Albertini et al., 2026). Therefore, to more accurately predict how Lecanemab's

efficacy may be affected by the presence of Masitinib, research studies should be conducted focused on examining therapeutic Aβ clearance at different microglia concentrations following administration of Lecanemab.

4.2 Therapeutic Application

Mechanistically, there is a possibility that Masitinib and Lecanemab may work synergistically (or at least not conflictingly) to reduce AD progression. Even so, there is also a high likelihood these drugs could act in opposition and reduce overall drug efficacy. Thus, one potential, more promising method of combinatorial therapy could focus on patients receiving individual, alternating periods of treatment of each drug. To determine if this approach could be viable, it is important to understand rates of AD progression following discontinuation of each of these drugs. In the case of Lecanemab, it has been seen that following 12 and 18 month treatment durations, clinical differences between treatment groups and placebo groups can persist for 24 months (on average), however, rates of progression remain similar between treatment and placebo groups during off-drug periods (McDade et al., 2022). In regard to Masitinib, there is unfortunately no available clinical data providing rates of AD progression or re-emergence of symptoms following discontinuation of the drug, so additional research should also be conducted in this area as well.

The length of time (and dosage) required for each drug to reach therapeutic levels should also be accounted for to appropriately structure possible alternating drug treatment. In phase III clinical trials for Lecanemab, statistically significant improvements were measured over an 18 month period with patients receiving 10 mg/kg every two weeks via IV infusion. More importantly, clinical benefits (i.e., cognitive-related improvements) were measured at statistically significant values as early as 6 months into treatment (van Dyck et al., 2022). Phase II clinical

trials of Masitinib demonstrated clinical effectiveness when taken twice daily at 3 or 6 mg/kg/day, with 6 mg/kg/day eliciting a greater therapeutic effect than 3 mg/kg/day compared to placebo. The trial occurred over the course of 24 weeks, however, similar measurable benefits were recorded after 12 weeks of treatment (Piette et al., 2011). It should be noted that to better structure a phase-based treatment plan involving these drugs, dynamics between treatment duration and dosage concentrations could also be explored, perhaps allowing for shorter treatment durations at higher dosages.

Given the immediately discussed parameters for attaining and retaining drug efficacy, a potential phase-based combinatorial approach that retains the therapeutic benefits of both Lecanemab and Masitinib whilst avoiding potential conflicting mechanisms may be possible. First, patients experiencing early or mild-to-moderate AD may begin with 12 weeks of oral Masitinib treatment at 6 mg/kg/day to reduce microgliosis and inflammatory immune cell signaling. Following this 12 week period, Lecanemab treatment at 10 mg/kg every two weeks for 6 months may provide multiple benefits. First, Lecanemab will reduce Aβ aggregation via phagocytosis of Aβ protofibrils. Second, Lecanemab may be able to maintain a healthy microglial environment generated through Masitinib treatment, given its ability to promote neuroprotective microglial phenotypes as demonstrated in mouse-models (Albertini et al., 2026). However, other innate immune cells like mast cells and macrophages are not accounted for in this case, and neuroinflammation should be closely monitored during this phase of treatment. If neuroinflammation does not worsen significantly during the first 6 months of Lecanemab treatment, the duration of treatment should be extended either to 12 or 18 months for greater efficacy and to increase duration of observable benefits while off-drug. Cognitive measurements and quantification of AD biomarkers should be conducted following these treatment periods,

particularly in regard to microglia and neuroinflammation–as it is largely unknown how long Masitinib benefits will persist following cessation of treatment, creating a substantial concern for continued activation of neuroinflammatory responses.

4.3 Gaps in Knowledge and Possible Future Areas of Research

As a whole, research into developing combinatorial therapeutic approaches for AD is becoming increasingly prominent, however, much more empirical evidence is necessary to determine what drugs will work synergistically together to reduce different aspects of AD progression. For the purposes of this thesis and the combination of Lecanemab and Masitinib, phase III clinical trials researching Masitinib in ALS (AB23005) are ongoing, and resulting evidence could greatly inform the biological impacts of the drug, especially over longer timescales. Future research that is not currently being conducted which would be significantly informative, however, is *in vivo* or clinical studies examining the combined treatment of Lecanemab and Masitinib. This should be explored to determine if their mechanisms may act synergistically or antagonistically within a more complex environment, and to determine if alternating/cyclic administration of these drugs is a more promising avenue of treatment. To address other gaps in knowledge previously identified within this text, future studies should focus on measuring the effect of Masitinib on microglial populations within AD, determining how variations in microglia populations impact therapeutic efficiency of Lecanemab, as well as understanding how long therapeutic effects of Masitinib within AD persist following cessation of treatment. Nevertheless, on a more general level, any in-depth studies focused on combinatorial and simultaneous drug treatment to address different pathologies of AD would undoubtedly aid massively in understanding the exceptionally complex and devastating condition of AD.

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