

Next generation in Alzheimer's therapeutic strategies

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**UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE**

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Next Generation in Alzheimer's Therapeutic Strategies

GRADUATE THESIS



Zagreb, 2024

This graduation thesis was completed at the Department of Neurology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb. It was mentored by Associate Professor Marina Boban and submitted for evaluation in the academic year 2023/2024.

List of Abbreviations

A β : Amyloid Beta protein

AChEI: Acetylcholinesterase Inhibitors

AD: Alzheimer's Disease

ADAS-Cog11: Alzheimer's Disease Assessment Scale-Cognitive Subscale 11

ADRD: Alzheimer's Disease Related Dementia

AICD: Amyloid precursor protein Intracellular Domain

ARIA: Amyloid-Related Imaging Abnormalities

ARIA-E: Amyloid-related Imaging Abnormalities with Edema/Effusion

ARIA-H: Amyloid-related Imaging Abnormalities with Hemorrhages

Apo ϵ 2: Apolipoprotein E-2 Allele

Apo ϵ 4: Apolipoprotein E-4 Allele

BALD: Basic Activities of Daily Living

BBB: Blood Brain Barrier

BPSD: Behavioral and Psychological Symptoms of Dementia

CADRO: Common Alzheimer's Disease Research Ontology

DMT: Disease Modifying Therapy

DIAN-TU: Dominantly Inherited Alzheimer Network Trials Unit

EOD: Early-Onset Dementia

EEG: Electroencephalogram

EMA: European Medicine Agency

FAD: Familial Alzheimer's Disease

FDA: Food and Drug Administration

FLNA: Filamin A

ILAD: Instrumental Activities of Daily Living

MABs: Modifying Monoclonal Antibodies

MCI: Mild Cognitive Impairment

MRI: Magnetic Resonance Imaging

PET: Positron Emission Tomography

PSEN1,2: Presenilin 1 or 2 gene

TLR4: Toll-like Receptor 4

WHO: World Health Organization

YOD: Young-Onset Dementia

α 7nAChR: α 7 Nicotinic Acetylcholine Receptor

Table of Contents

SUMMARY

SAŽETAK

1. INTRODUCTION TO THESIS	1
2. UNDERSTANDING ALZHEIMER'S DISEASE	3
3. HYPOTHESIS IN MOLECULAR NEUROPATHY OF AD	8
3.1 Extracellular Aggregation - Amyloid Hypothesis	8
3.2 Intracellular Changes - Neurofibrillary Tangles	11
3.3 The Decline in Cholinergic Function Hypothesis	13
3.4 Additional Emerging Hypotheses in Alzheimer's Disease	13
4. TRADITIONAL ALZHEIMER'S TREATMENTS	14
5. DRIVING PROGRESS IN ALZHEIMER'S THERAPEUTICS	17
5.1 AN-1792 Active Vaccine Targeting Amyloid- Plaques	19
5.2 AADvac1 Active Vaccine Targeting Tau-Tangles	19
5.3 Solanezumab – Targeting Soluble Form of Amyloid	20
5.4 Gantenerumab – Targeting Aggregated Insoluble Amyloid	21
5.5 Simufilam – A Novel Approach Targeting Filamin A	23
6. GROUNDBREAKING TREATMENT FOR AD	25
6.1 Aducanumab	25
6.2 Lecanemab	26
6.3 Donanemab	28
6.4 Limitations of Novel Treatments for Alzheimer's Disease	29
6.5 Sodium Oligomannate	30
DISCUSSION	32
ACKNOWLEDGMENT	34
REFERENCES	36
BIOGRAPHY	40

SUMMARY

Next generation in Alzheimer's therapeutic strategies

Ophir Shenhav

Alzheimer's disease (AD) poses a significant challenge in modern healthcare, demanding urgent solutions and a definitive cure.

As the aging population grows and life expectancy increases, the number of individuals affected by this debilitating condition rises, placing a significant burden on healthcare systems worldwide.

Despite extensive research efforts on a global scale, effective treatments for AD remain elusive. This lack of definitive solutions intensifies the urgency to discover breakthrough therapies, as the race against time to combat AD continues.

In recent times, noteworthy progress has been achieved with the approval of new disease-modifying drugs that employ innovative mechanisms of action, addressing diverse hypotheses concerning the development of AD.

This thesis aims to delve into the foundational aspects of AD, encompassing disease's multifactorial elements and intricate mechanisms. Through this exploration, it seeks to offer a comprehensive insight into recent progress, strategies, and the diverse factors influencing pharmaceutical AD treatment.

Keywords: Alzheimer's disease; Amyloid; Anti amyloid immunotherapy; Drugs; Pharmacological treatments

SAŽETAK

Nova generacija lijekova za Alzheimerovu bolest

Ophir Shenhav

Alzheimerova bolest predstavlja značajan izazov u suvremenom zdravstvu koji zahtijeva hitna rješenja, osobito pronalazak novih farmakoloških mogućnosti. S obzirom na to da populacija stari i produljuje se očekivani životni vijek ljudi, raste i broj pojedinaca pogođenih ovom iscrpljujućom bolesti, što predstavlja značajan teret za zdravstvene sustave diljem svijeta.

Unatoč opsežnim istraživačkim naporima na globalnoj razini, učinkovito liječenje Alzheimerove bolesti je i dalje nedostižno. Nedostatak adekvatne farmakoterapije stavlja imperativ pred znanstvenike za otkrivanjem novih, revolucionarnih lijekova, dok se utrka s vremenom u borbi protiv Alzheimerove bolesti nastavlja.

U posljednje vrijeme postignut je značajan napredak u farmakoterapiji Alzheimerove bolesti s odobravanjem novih lijekova koji mijenjaju tijek bolesti (engl. disease-modifying drugs) time što koriste inovativne mehanizme djelovanja temeljene na različitim hipotezama nastanka Alzheimerove bolesti.

Ovaj diplomski rad ciljano istražuje temeljne aspekte Alzheimerove bolesti, obuhvaćajući multifaktorijalne elemente i komplicirane hipoteze nastanka bolesti.

Ovim istraživanjem nastoji se ponuditi sveobuhvatan uvid u nedavni napredak, strategije i različite čimbenike koji utječu na razvoj lijekova za liječenje Alzheimerove bolesti.

Ključne riječi: Alzheimerova bolest, amiloid, antiamiloidna imunoterapija, lijekovi

1. INTRODUCTION TO THESIS

In 1901, psychiatrist Alois Alzheimer became particularly interested in the case of Auguste Deter, who is now recognized as the first documented patient with Alzheimer's disease (AD) (1). At the relatively young age of 51, Deter exhibited profound memory loss and significant issues with recognition, yet she showed no signs of atherosclerosis, which at the time was widely believed to be the primary cause of dementia in older individuals (1). Following her death, Alzheimer conducted a detailed brain autopsy using a silver staining technique, which allowed him to observe neuritic plaques and neurofibrillary tangles. This groundbreaking discovery led him to propose a connection between these specific brain structures and the pathology of AD, thus laying the foundation for understanding the disease (1).

Over a century of research has significantly advanced the understanding of AD development and progression. Current pharmacological treatments primarily aim to alleviate symptoms and may temporarily delay disease progression; however, they do not reverse, cure, or halt the progression of AD.

Despite the challenges in developing new treatments for AD, recent advancements targeting the amyloid plaque hypothesis offer hope. New Food and Drug Administration (FDA) approved drugs aim to reduce amyloid plaques in the brain and thus potentially slowing disease progression. However, these treatments also face significant challenges. Nonetheless, these advancements represent critical progress in the quest for more effective AD treatments.

AD remains a complex puzzle. Despite significant progress (Figure 1), much about its pathology and progression remains unclear, representing only the tip of the iceberg. This complexity arises from its multifactorial nature, necessitating further research to unravel these complexities and develop effective therapies.

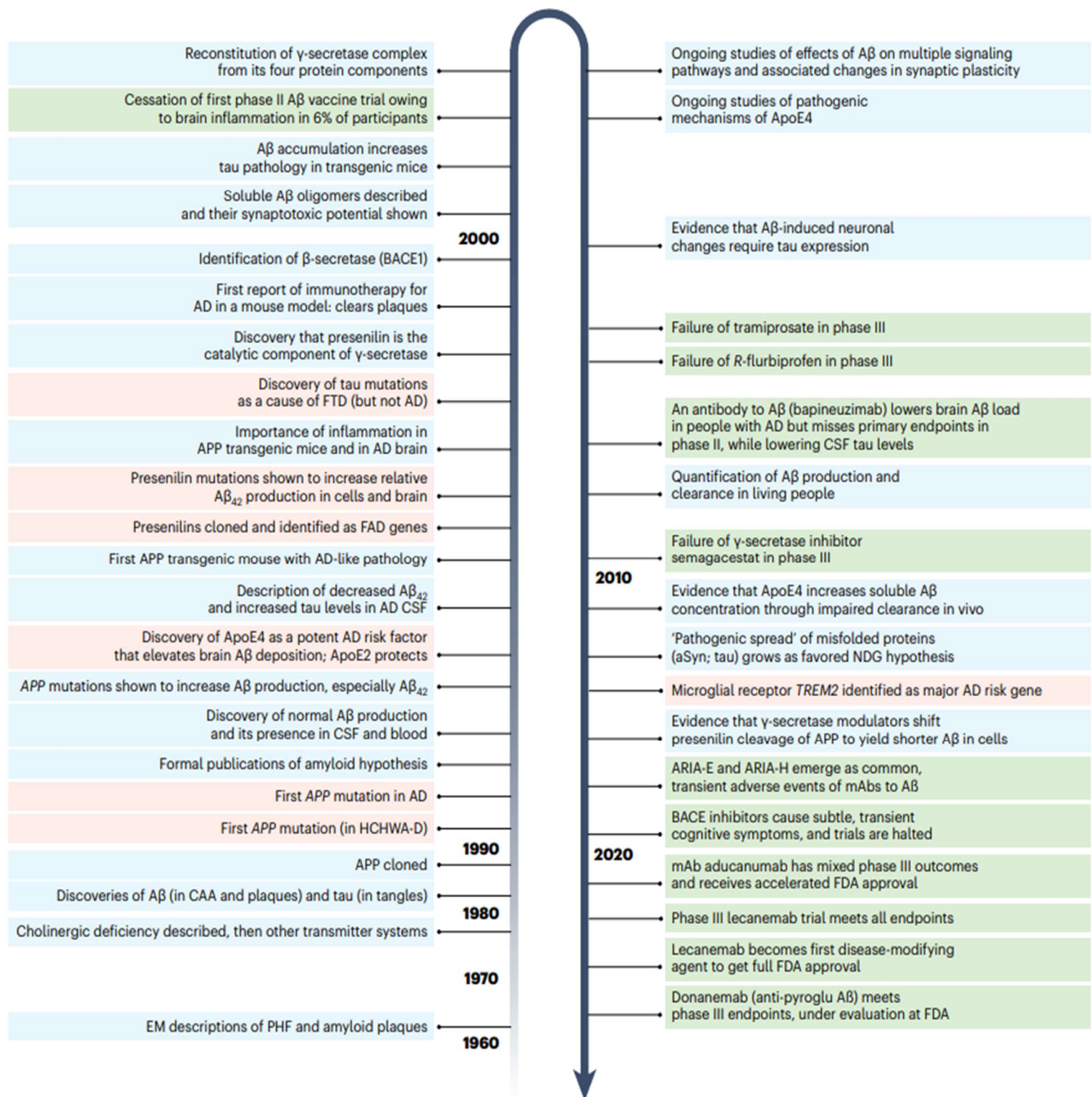


Figure 1. Key Milestones in AD Research.

This timeline highlights significant discoveries in AD research since 1960. It includes milestones considered crucial for the current understanding of AD pathogenesis and the advancement of disease-modifying treatments (2).

2. UNDERSTANDING ALZHEIMER'S DISEASE

AD is a complex multifactorial disease. By enhancing the understanding of high-risk populations, identifying critical risk factors, studying its continuum, and utilizing available diagnostic tools to elucidate underlying mechanisms, researchers can develop targeted therapies with the potential to significantly improve outcomes for those affected by this progressive disease (1,3).

Every 3 seconds, someone in the world develops dementia, with AD responsible for 60-80% of these cases (3). According to the World Health Organization (WHO), more than 10 million new dementia cases occur globally each year. Without effective interventions, especially as the aging population grows in developed nations and due to insufficient attention in developing countries, this figure could almost triple by the year 2050 (3).

AD predominantly affects individuals over 65, also termed late-onset AD (LOAD) (3). However, AD is not limited only to the elderly, and individuals before the age of 65 can also experience early-onset dementia (EOD), including young-onset dementia (YOD) (4), manifesting as early as their 40s-50s. Another aspect of EOD is familial AD (FAD), where genetics play a key factor and anticipation is observed (5). Specific genetic mutations in genes like Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2) genes are associated with FAD (5).

Females are disproportionately affected by Alzheimer's disease (AD), comprising approximately two-thirds of AD patients. This gender imbalance may be influenced by factors such as hormones, genetics, biology, lifestyle, and social aspects, highlighting the need for deeper screening and research to explore and address these underlying causes (6).

AD risk factors encompass both modifiable and non-modifiable elements. Three key non-modifiable risk factors include advancing age, family history, and genetic predisposition (3).

While a family history of AD is not obligatory for AD development, individuals with a first-degree relative with AD have a higher likelihood of developing the disease compared to those without such a family history (3).

Among the various genetic factors associated with an increased risk of developing AD, the Apolipoprotein e-4 allele (APOE- ϵ 4) stands out as having the most significant impact on the risk of LOAD (7). Individuals inheriting two copies of this allele face a significantly higher estimated risk, underscoring the importance of this gene in AD risk (7). Conversely, APOE- ϵ 2 alleles may have a protective effect, reducing the risk of LOAD (7).

There are 12 modifiable risk factors identified for AD (8). These include high blood pressure, cholesterol levels, obesity, and diabetes, which can impact brain health. An inactive lifestyle, smoking, and excessive alcohol consumption also elevate the risk of AD. Furthermore, air pollution and vitamin D levels are contributing factors. Traumatic brain injury, social isolation, depression, and hearing loss are additional risk factors (8). Addressing these modifiable risks could prevent or delay up to 40% of dementia cases globally, making a significant impact, especially in low- and middle-income countries with high dementia rates (8).

Ongoing research indicates a potential link between gut bacterial imbalance and the onset of AD, emphasizing the connection between the gut and the brain. Dysbiosis, characterized by an imbalance or disruption in the normal microbial community, with either overgrowth or underrepresentation of certain microbes, is believed to play a role in the development of AD (9).

Understanding AD continuum is crucial in the quest for a cure, as it provides insights into the disease's progression and clinical features spanning from healthy cognitive states to advanced dementia. The continuum comprises three stages: preclinical AD, mild cognitive impairment (MCI) due to AD, and Alzheimer's disease-related dementia (ADRD) (Figure 2) (3).

Preclinical AD is marked by initial brain changes like amyloid plaques and neurofibrillary tangles, occurring without noticeable symptoms, which complicates diagnosis. This phase offers a critical opportunity for interventions to slow or halt disease progression before symptoms manifest (3).

Following an individualized period, compensatory brain mechanisms become overwhelmed, leading to mild cognitive impairment (MCI) (3). MCI denotes a stage within the AD continuum where observable cognitive decline surpasses what is typically considered normal age-related changes (3). MCI can present challenges related to memory, language, and cognitive functions. Despite this decline, individuals can typically manage daily activities independently, and usually only those in close surroundings can notice these more subtle changes (3).

The time from MCI to ADRD varies, but typically spans two to five years, with some individuals not experiencing further decline. However, all those who develop ADRD initially experience MCI (10).

ADRD is also divided into mild, moderate, and severe stages marked by more profound symptoms impacting memory, language, thinking, or behavior, which can be recognized even in unfamiliar surroundings (3). Initially, instrumental activities of daily living (IADLs) become challenging, requiring complex cognitive and organizational skills for tasks like managing finances, medication, meal preparation, housekeeping, transportation, and communication (3). Subsequently, basic activities of daily living (BADLs) such as bathing, dressing, grooming, eating, and mobility become difficult (3). Behavioral and psychological symptoms of dementia (BPSD) are another significant aspect, encompassing a range of presentations like apathy,

agitation, depression, delusions, hallucinations, sleep disturbances, wandering, and difficulty recognizing loved ones (3).

In the severe stage, individuals heavily rely on caregivers for daily tasks, and verbal communication abilities significantly decline, often necessitating round-the-clock care. This places a substantial burden on both patients and caregivers (3).

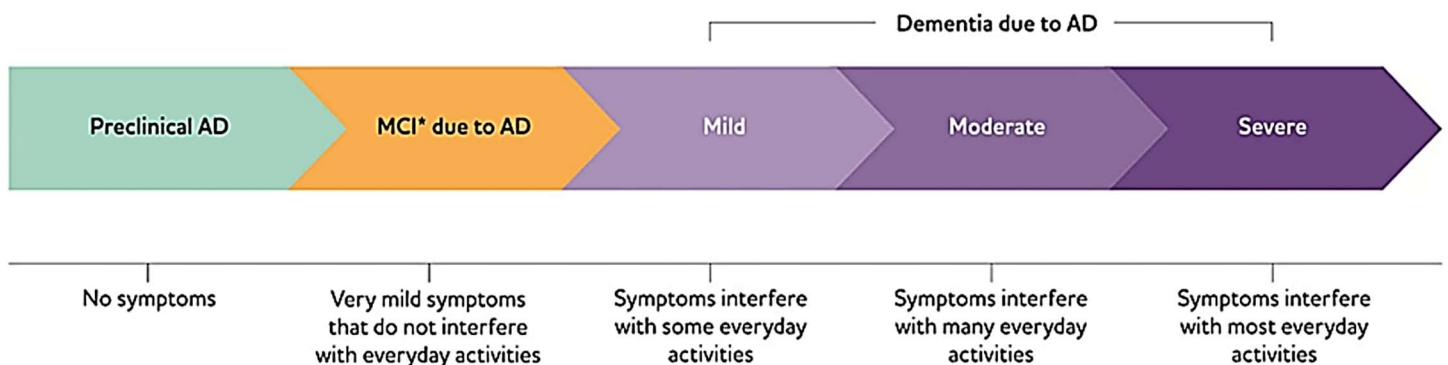


Figure 2. AD continuum (11).

AD diagnosis lacks a definitive gold standard test during a person's lifetime, relying on postmortem pathology for confirmation of diagnosis (12). A systematic diagnostic approach ensures a thorough evaluation, accurately identifying AD while ruling out other causes of cognitive decline (12).

AD diagnosis starts with gathering medical history from reliable sources like family or caregivers, also called hetero anamnesis. This step is crucial for obtaining accurate information about the patient's health background. Following hetero anamnesis, clinical criteria and neuropsychological testing are used to assess cognitive impairment and dementia (13).

Using various imaging and laboratory techniques may also be beneficial. These may involve magnetic resonance imaging (MRI) scans to assess brain structure, positron emission tomography (PET) scans for brain activity and amyloid detection, electroencephalogram (EEG), and genetic testing (3).

AD biomarkers play a critical role in both research and clinical practice, assisting in early detection, differential diagnosis, disease staging, progression monitoring, and treatment evaluation. Key biomarkers include Amyloid beta ($A\beta$) and hyperphosphorylated-Tau protein levels, along with neuroinflammatory markers like various cytokines and chemokines (14).

3. HYPOTHESIS IN MOLECULAR NEUROPATHY OF AD

Numerous hypotheses regarding AD development have been proposed (Figure 3). In this discussion, a few of these hypotheses relevant to the novel treatment will be.

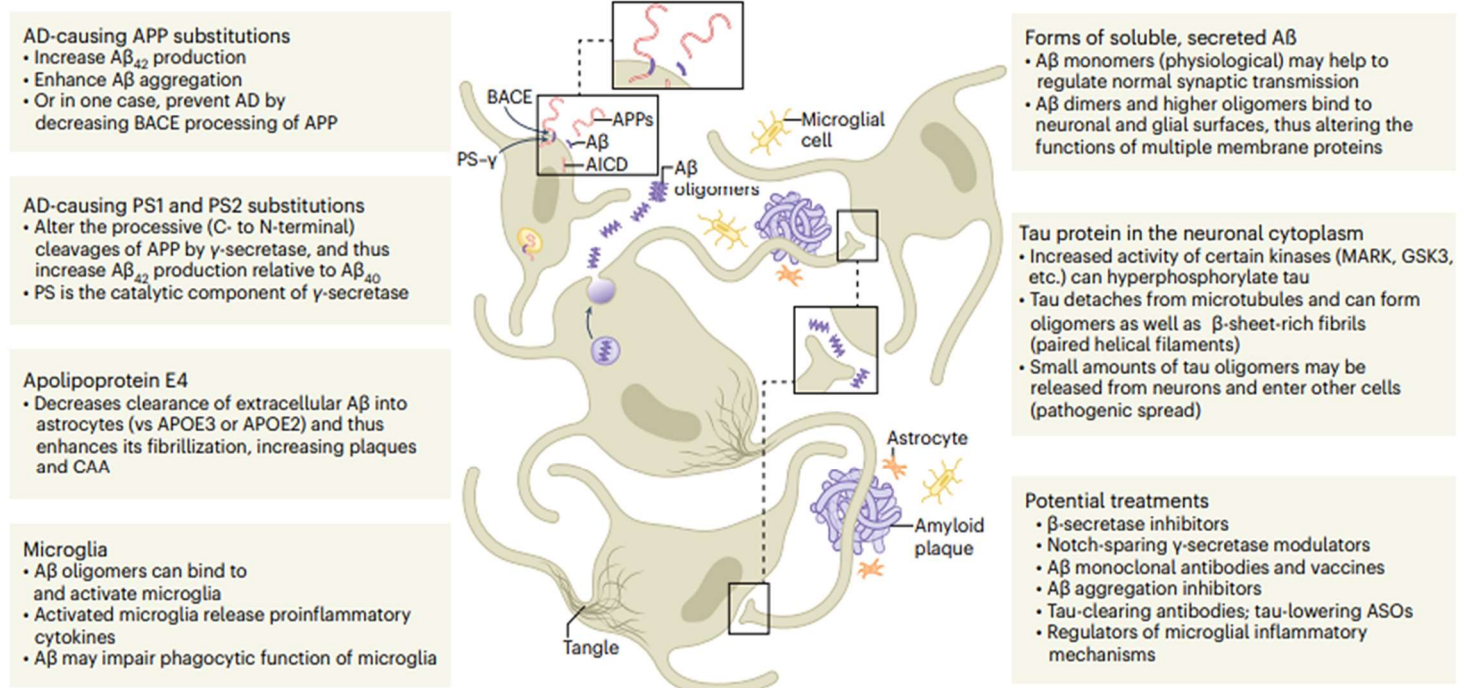


Figure 3. Overview of AD Pathobiology and Therapeutic Targets (2).

3.1 Extracellular Aggregation - Amyloid Hypothesis

Over three decades ago, Hardy and Higgins introduced the amyloid cascade hypothesis, a theory that has since become foundational to the understanding of AD pathophysiology (15). Cellular membranes of neurons in the central nervous system (CNS) feature a transmembrane protein called APP. While its precise function remains elusive, APP is thought to contribute to various cellular processes, including neuronal growth, neuronal repair, and synapse formation (14).

APP can undergo two distinct processing pathways: amyloidogenic pathway and nonamyloidogenic pathways (Figure 4) (14).

The non-amyloidogenic pathway, predominantly active in a healthy brain, is mediated by α -secretase and results in the routine breakdown of APP into soluble fragments that are capable of dissolution and recycling.

Conversely, the amyloidogenic pathway, involving β -secretase, leads to the generation of amyloid-beta ($A\beta$) peptides, particularly $A\beta_{42}$, which aggregate and form insoluble plaques outside neurons (14).

These plaques, also known as amyloid or senile plaques, represent a hallmark pathological finding in AD. The progressive accumulation of these plaques significantly contributes to the development of AD pathology. Notably, a minor amount of $A\beta$ peptides can also be detected in the healthy brain via this pathway (14).

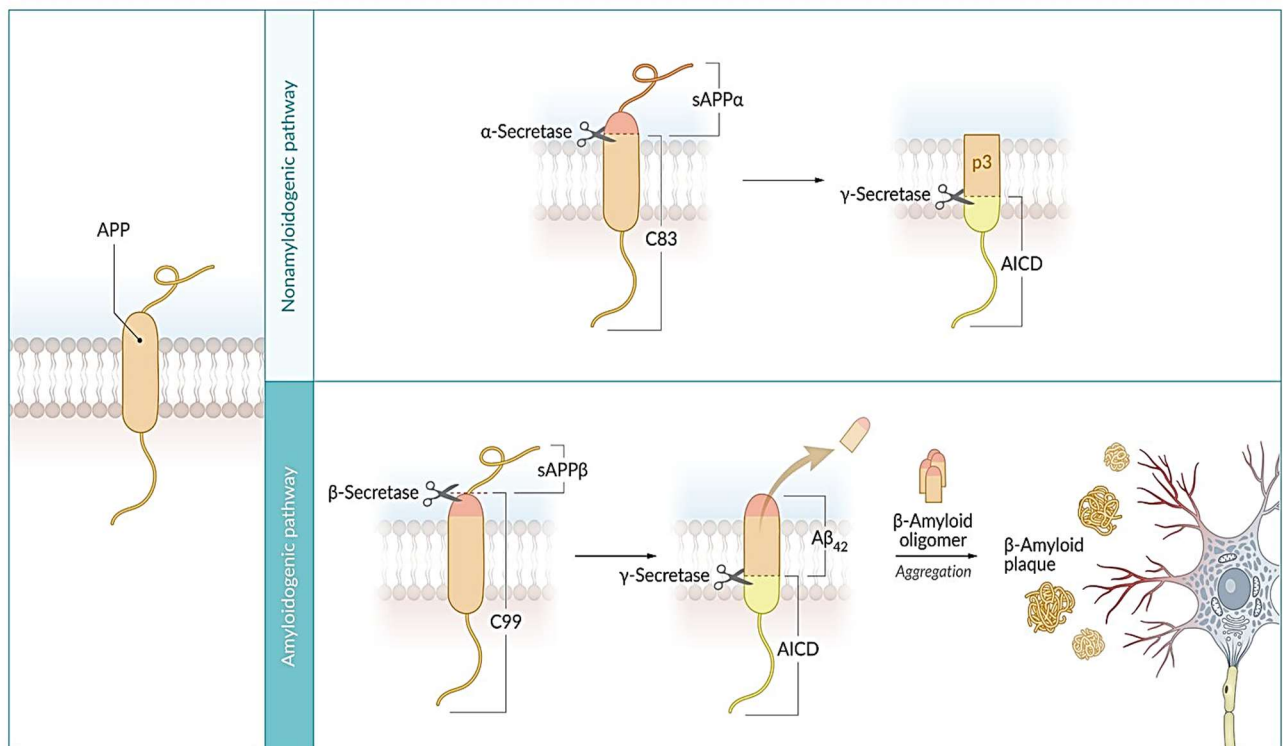


Figure 4. illustrates the two pathways of APP processing: the non-amyloidogenic pathway involving cleavage by α -secretase resulting in a soluble form, and the amyloidogenic pathway involving cleavage by β -secretase leading to aggregation of a non-soluble form, *Amyloid precursor protein intracellular domain (AICD) (16).

A β peptides aggregate through several stages (17) (Figure 5). Initially, these are soluble monomers that can oligomerize into intermediate-sized aggregates called oligomers. Oligomers are toxic to neurons and associated with synaptic dysfunction and damage. Oligomers can then progress to form protofibrils, which are considered precursors to mature fibrils. Protofibrils are also highly toxic and disrupt neuronal activity and synaptic connections. Further aggregation leads to the formation of fibrils, long thread-like structures composed of tightly packed A β peptides. These fibrils can assemble into amyloid plaques, characteristic features of AD pathology. (17)

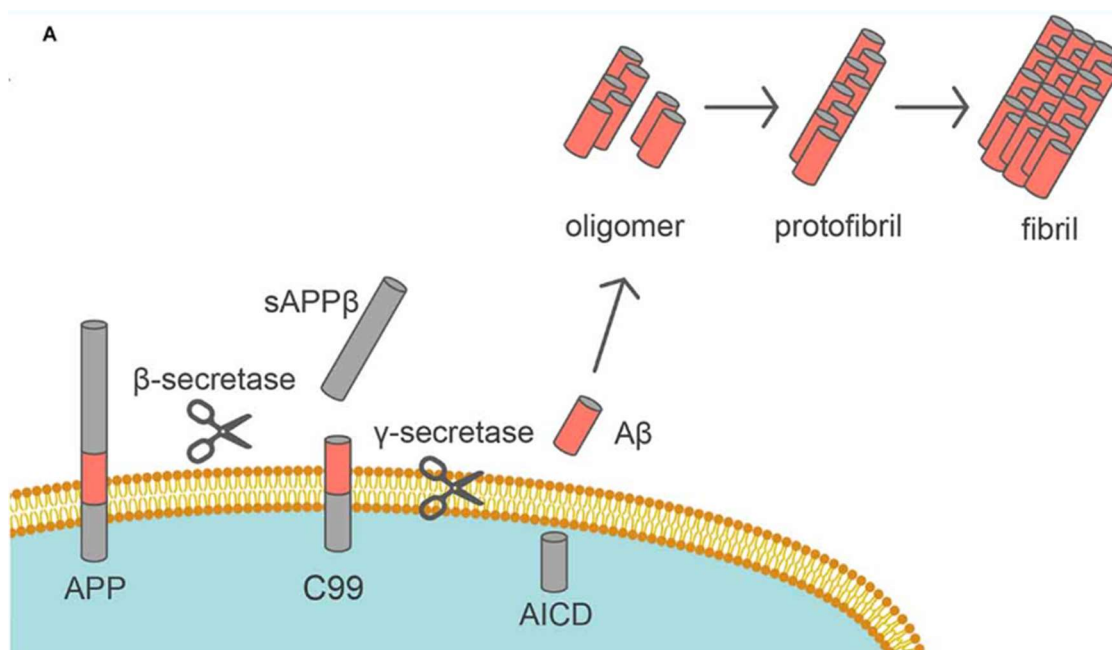


Figure 5. Release of A β into the extracellular space. A β monomers tend to aggregate, forming oligomers, protofibrils, and eventually fibrils (18).

The Amyloid hypothesis is currently paving the way for potential treatment of AD. Novel drugs under development primarily target anti-amyloid plaques, aiming to reduce amyloid formation at various stages from soluble phase to insoluble structure (17).

Individuals with Down syndrome provide persuasive evidence supporting the amyloid plaque hypothesis as the pathological mechanism AD. Due to an additional copy of chromosome 21, which includes the gene that in charge of translation of APP, individuals with Down syndrome produce

excessive A β peptides, particularly the A β 42 variant. It is well-documented that individuals with Down syndrome often develop AD at an earlier age, typically between 40 and 50 years old, further reinforcing this connection (19).

3.2 Intracellular Changes - Neurofibrillary Tangles

Tau proteins play a key role in supporting neuronal microtubules by aiding in their assembly and durability, crucial for preserving neuronal structure and enabling efficient transport within neurons (14).

Upon aggregation of beta amyloid plaques in the extracellular neuronal environment, it is hypothesized to initiate a cascade of events within neurons, including the activation of kinases (Figure 6). These kinases subsequently phosphorylate the Tau protein, resulting in its structural alteration that impairs its ability to support microtubules (20). (20) Another process that can occur is Tau truncation, when the Tau protein undergoes cleavage or fragmentation, resulting in the removal of certain segments of its structure (20).

While Tau typically helps stabilize microtubules, hyperphosphorylated Tau and Tau truncation, which acquiring prion-like properties, create neurofibrillary tangles, disrupt microtubules leading to compromised axoplasmic flow and neuronal connectivity (20).

Tau accumulation and the formation of neurofibrillary tangles is another hallmark of AD (21).

Neurons with neurofibrillary tangles and dysfunctional microtubules have impaired signaling and may undergo apoptosis. As neurons die, the brain undergoes significant changes, including atrophy, narrower gyri, widened sulci, and ventricular enlargement (21). The process of tangle formation is gradual and can occur over many years before symptoms appear (21).

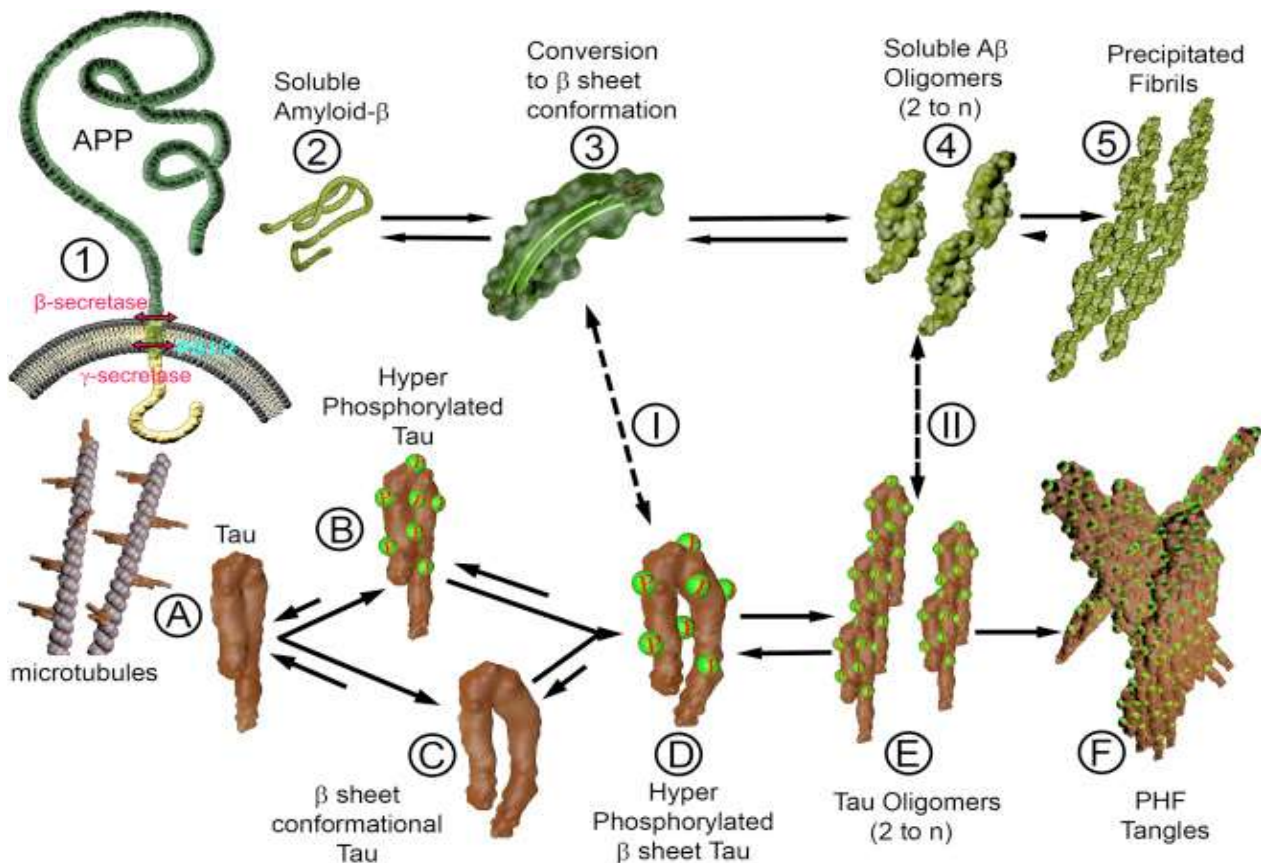


Figure 6. Numbers 1-5 show extracellularly APP is cleaved abnormally by β -secretase, creating soluble A β , the further aggregation of other amyloid forms can be seen – such as oligomers and finally fibrils. Letters A-F show intracellularly Tau protein is abnormally hyperphosphorylated or changed to abnormal conformation (truncated). Tau tangles accumulation can be seen. Arrows I-II represent the suggested connection between extracellular and intracellular processes. The formation of amyloid plaques outside neuronal cells might induce the formation of tau tangles inside neuronal cells (22).

3.3 The Decline in Cholinergic Function Hypothesis

The cholinergic function decline hypothesis connects AD with reduced activity in cholinergic neurons, specifically involving the neurotransmitter acetylcholine. This decline significantly contributes to AD's cognitive and memory impairments. Treatments like acetylcholinesterase inhibitors (AChEIs) aim to boost cholinergic function by increasing acetylcholine levels, aiding in AD symptom management (23).

3.4 Additional Emerging Hypotheses in Alzheimer's Disease

Multiple emerging hypotheses about AD development underscore its intricacy and the need for further research. The neurovascular hypothesis links blood brain barrier (BBB) dysfunction and blood flow regulation to AD, while the mitochondrial cascade hypothesis suggests mitochondrial dysfunction contributes to energy deficits and oxidative stress in AD. Mutational accumulation hypothesis proposes that accumulated genetic mutations over time increase AD risk (24).

According to the inflammatory hypothesis, chronic brain inflammation is a key factor in AD progression, with immune cell activation exacerbating neuronal damage. The autoimmunity hypothesis posits immune dysregulation and autoantibodies targeting neuronal proteins contribute to AD pathology (25). This involves activated microglia releasing inflammatory mediators, which harm neurons and lead to cognitive decline. Systemic inflammation may also impact AD progression (25).

According to this assumption, researchers are exploring the strategy of repurposing anti-inflammatory drugs already in use for different conditions. Using already-approved drugs offers advantages like known safety profiles and established dosing. Further research is needed to assess their efficacy in AD and understand how they affect neuroinflammation and autoimmunity (26).

4. TRADITIONAL ALZHEIMER'S TREATMENTS

Pharmacological interventions, known as traditional or symptomatic therapeutics, have been rigorously studied and are established treatments in clinical settings. They aim to mitigate symptoms, sustain cognitive function, and enhance the overall quality of life for individuals affected by the disease (Figure 7). Symptomatic therapeutic approaches are still pivotal in managing conditions such as AD. These traditional interventions provide essential relief and support to patients and caregivers alike. Nevertheless, it is imperative to acknowledge that while these medications can ameliorate symptoms, they do not impede the progression of the disease (27).

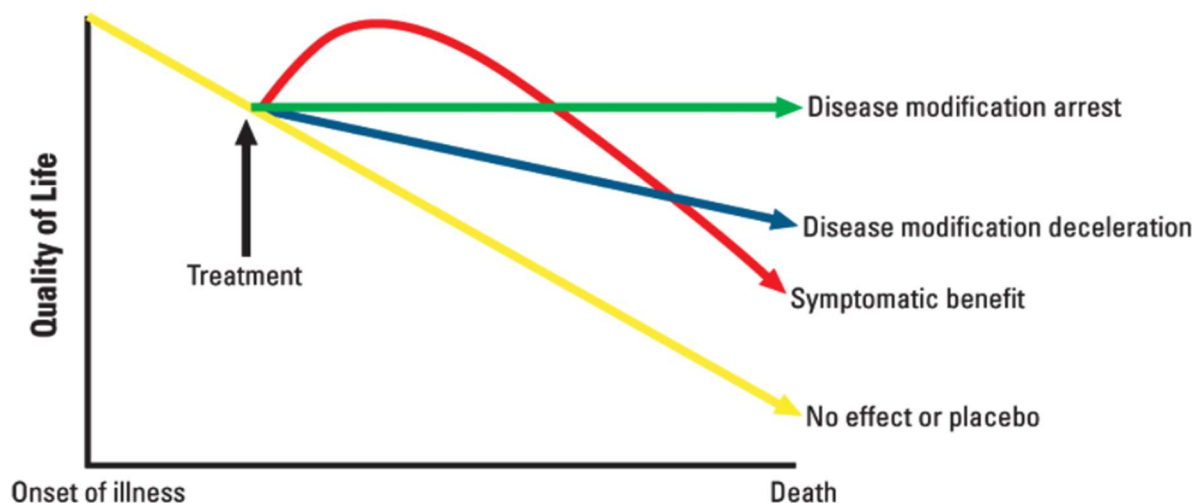


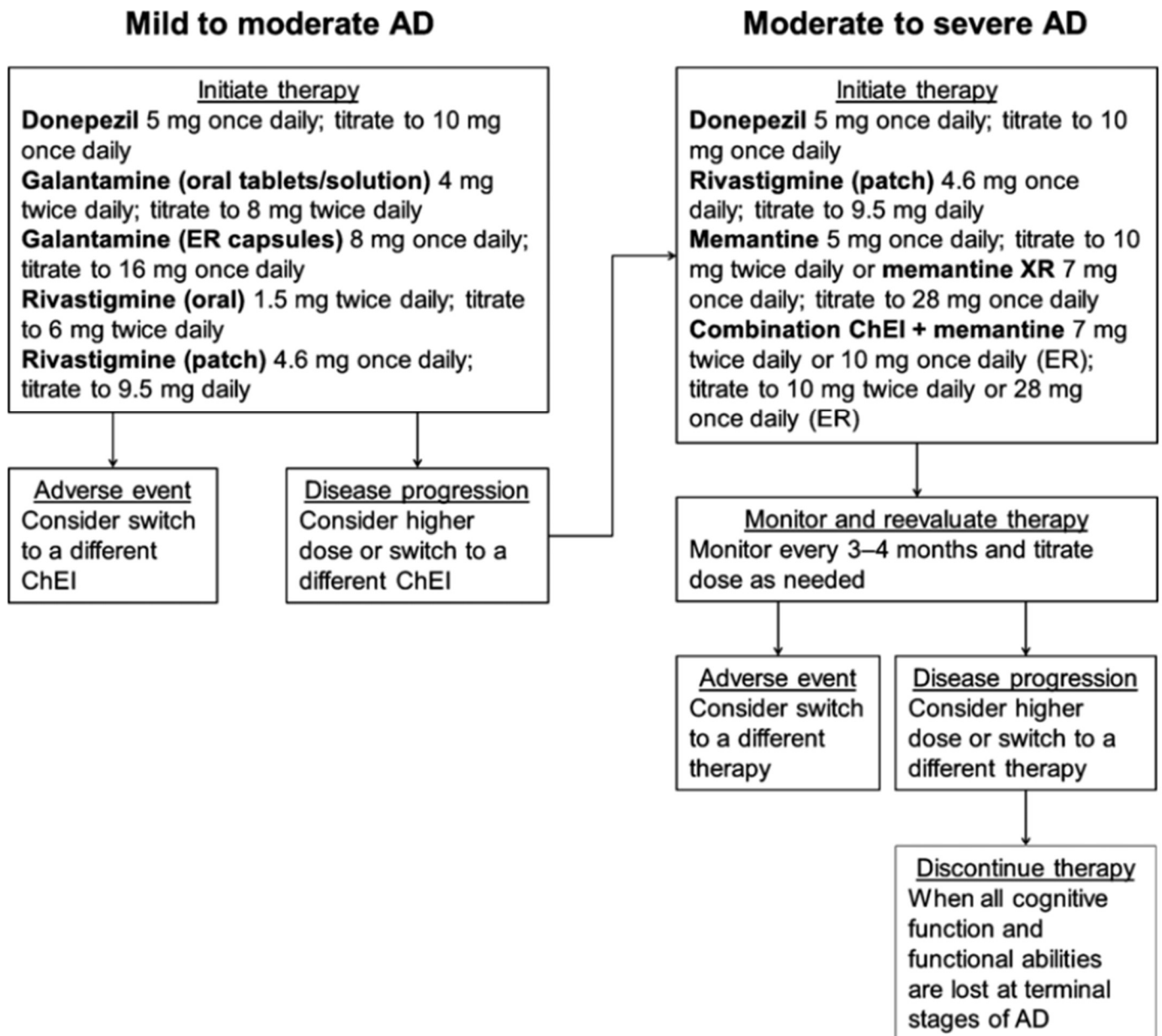
Figure 7. Understanding the spectrum of therapeutic outcomes, from symptomatic relief to disease modification, ranging from managing symptoms to altering disease processes for improved patient outcomes (28).

Donepezil was the first AChEI to receive FDA approval for the treatment of AD in 1996. Followed by rivastigmine, and galantamine (27). AChEIs work by reversibly inhibiting cholinesterase, leading to an increase in acetylcholine concentration at the synaptic gap (27). Their usage stems from the cholinergic hypothesis, aiming to enhance cholinergic neurotransmission, thereby improving cognitive function and managing symptoms (27).

Memantine, which acts through a different mechanism of action compared to AChEIs was approved by the FDA for the treatment of AD in 2003. It is commonly prescribed for moderate to severe stages of AD as indicated in Figure 8. Memantine is an NMDA receptor antagonist, which blocks excessive glutamate activity. Glutamate is an excitatory neurotransmitter that plays a role in cognitive function and memory. In AD, there is an imbalance in glutamate levels, leading to overstimulation of nerve cells and potential cell damage. By blocking excessive glutamate activity, memantine helps regulate neurotransmission and protect nerve cells from excitotoxicity, which is a process that can contribute to neuronal damage and cognitive decline in AD (29).

AChEIs used in AD treatment can lead to side effects like nausea, vomiting, diarrhea, loss of appetite, muscle cramps, and insomnia due to their action of increasing acetylcholine levels (27). On the other hand, memantine, may cause dizziness, headache, confusion, constipation, and increased blood pressure because it blocks excessive glutamate activity (29). These side effects can vary among individuals, and healthcare providers monitor patients closely to manage them effectively and ensure optimal treatment outcomes (29).

Figure 8. Algorithm for administering traditional pharmaceutical treatment for AD based on the stage of the disease (30).



5. DRIVING PROGRESS IN ALZHEIMER'S THERAPEUTICS

Research globally is heavily focused on developing disease-modifying treatments (DMTs) for AD. The goal is to not only slow or halt disease progression but also achieve a complete cure and restore cognitive function (Figure 9). (31) Figure 9 shows the wide array of ongoing research endeavors, highlighting the diverse approaches and strategies being explored to address the complex challenges associated with this neurological condition (31).

2023 Alzheimer's Drug Development Pipeline

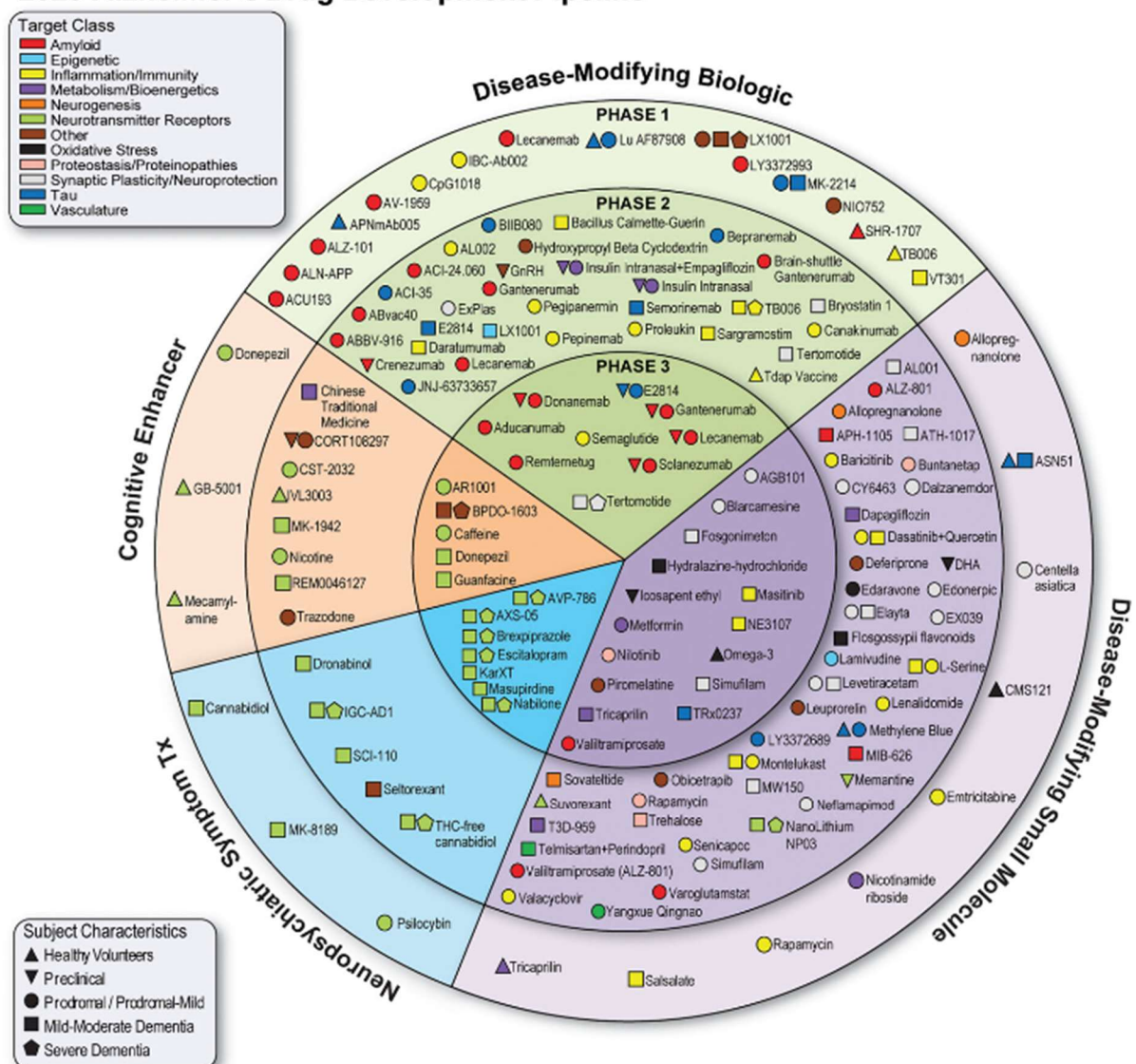


Figure 9. depicts the agents currently under investigation in clinical trials for AD treatment as of 2023.

The diagram categorizes Phase 3 agents in the inner ring, Phase 2 in the middle, and Phase 1 therapies in the outer ring. Disease-modifying biologic treatments are represented by green areas, disease-modifying small molecules by purple, and symptomatic agents (cognitive enhancers) by orange. The shapes of icons denote the trial population, while colors correspond to the Common Alzheimer's Disease Research Ontology (CADRO) -based agent classes (31).

In this literature review, emphasis will be placed on various treatment approaches, prioritizing the most widely recognized methods, considering the extensive scope of ongoing drug development.

The primary focus of current research revolves around therapeutic mechanisms known as immunotherapies, drawing on their functionality as immunoglobulins widely utilized in fields like cancer therapy. These therapies are categorized as immunotherapeutic due to their composition of artificial antibodies specifically designed to target harmful accumulations. Through this targeted approach, they could facilitate the degradation of these accumulations, aiding the immune system in the elimination of unnecessary proteins (32).

Active and passive immunotherapy represent distinct strategies in AD therapeutic management. Active immunotherapy involves administering immunogens along with adjuvants to stimulate the patient's immune system to produce antibodies against accumulated or misfolded A β or Tau proteins. On the other hand, passive immunotherapy involves directly infusing monoclonal antibodies targeted to A β or Tau proteins (21). Both active and passive immunotherapy strategies, though promising, encounter hurdles in clinical application. Active immunization demands precise immunogen and adjuvant selection to balance efficacy and safety, while passive immunotherapy necessitates antibodies with ideal pharmacokinetics and lower immunogenicity. Additionally, questions about treatment duration, patient suitability, and long-term safety profiles require thorough exploration (21).

5.1 AN-1792 Active Vaccine Targeting Amyloid- Plaques

AN-1792, a groundbreaking active immunotherapy for AD developed by Janssen and Pfizer, started clinical trials in 2001 (33). It utilized a formulation with synthetic full-length A β peptide and the QS-21 adjuvant, aiming to trigger an immune response to clear amyloid deposits in the brain (33). Despite robust preclinical evidence, safety concerns emerged during trials, with some participants developing meningoencephalitis post-vaccination (33). This led to trial suspension and raised doubts about the safety and efficacy of A β -targeted active immunotherapy (33). Nonetheless, AN-1792 offered vital insights into AD immunotherapy complexities, guiding ongoing research for safer and more effective treatments.

5.2 AADvac1 Active Vaccine Targeting Tau-Tangles

AADvac1, an active immunotherapy vaccine by AXON Neuroscience, targets abnormal tau proteins, another pathognomonic feature of AD (34). Developed in the early 2000s, it underwent preclinical safety and efficacy assessments before entering clinical trials in the 2010s (34). By stimulating the immune system to produce antibodies against these proteins, AADvac1 aims to reduce tau-related neurotoxicity and slow disease progression.

The effectiveness of AADvac1 was studied in ADAMANT, focusing on AD patients with both amyloid and tau pathology. Results showed promising outcomes for those receiving AADvac1, displaying less cognitive and functional decline compared to the placebo group. Notably, patients with a stronger immune response to AADvac1 had slower cognitive decline and less brain shrinkage, indicating its potential in slowing AD progression, especially in patients with amyloid and tau pathology (34).

However, further large-scale studies are necessary to validate these findings and confirm the efficacy and safety of AADvac1 as a treatment for AD (34).

Despite ongoing research efforts, no tau-directed therapeutic has yet gained FDA approval for treating neurodegenerative diseases or shown substantial impact on clinical measures of disease progression (21). Current therapeutic strategies mainly focus on addressing post-translational modifications of tau, its function or aggregation, or reducing overall tau levels (21).

5.3 Solanezumab – Targeting Soluble Form of Amyloid

The "A4 Study" or Anti-Amyloid Treatment in Asymptomatic Alzheimer's study, aims to evaluate the effects of anti-amyloid antibodies on AD progression, particularly on memory decline (35). This study is a pioneering collaboration between public and private entities and received funding from organizations including the National Institute on Aging, Eli Lilly and Company, Alzheimer's Association, GHR Foundation, and the Foundation for the National Institutes of Health. Led by the Alzheimer's Therapeutic Research Institute at the Keck School of Medicine of USC, and operates under the Alzheimer's Clinical Trials Consortium (35). Collaboration between public and private entities in Alzheimer's research, exemplified by initiatives like the A4 Study, is crucial. It enables resource pooling, diverse expertise, and varied perspectives, leading to faster progress, better translation of research findings, and a more significant impact on understanding and treating the disease (35).

Launched in 2013, the A4 Study was an innovative trial focusing on secondary prevention, with over 1,100 participants aged 65 to 85 (35). Secondary prevention involves intervening in the preclinical phase of a disease, before symptoms manifest, to stop its progression or complications. Participants showed evidence of amyloid plaque buildup in brain PET imaging but lacked clinical symptoms. They were randomly allocated to receive either the investigational immunomodulator solanezumab or a placebo and underwent treatment for about 4.5 years (240 weeks) (35). Participants who completed the initial phase of the study were offered the opportunity to enroll in

the open-label extension phase, during which all participants received solanezumab (35).

Solanezumab, a humanized monoclonal IgG1 antibody, is designed to target the mid-domain of the A β peptide. It specifically recognizes soluble monomeric forms of A β , rather than fibrillar ones. The therapeutic rationale behind solanezumab proposes that it may offer advantages by binding to A β , thereby potentially altering the balance between different forms of A β and eliminating small soluble A β species that can directly impair synaptic function (35).

Despite significant effort and resources allocated in the "A4 Study", the outcomes revealed that endpoints were not achieved. Consequently, the study terminated the clinical advancement of solanezumab, signifying that targeting soluble amyloid beta using this method proves ineffective in this population (35). The "A4 trial" concluded in December 2022. On March 2023, Lilly announced negative top-line results, signaling the end of development for solanezumab (35).

While solanezumab did not meet its objectives in the "A4 Study," the data it provided will be invaluable for shaping future research in AD prevention and treatment strategies.

5.4 Gantenerumab – Targeting Aggregated Insoluble Amyloid

Gantenerumab, developed by Hoffmann-La Roche Pharmaceuticals, is a subcutaneously administered anti-A β IgG1 monoclonal antibody that exhibits high affinity for insoluble aggregated A β and has been evaluated for AD treatment (36).

In phase 3 trials known as GRADUATE I and II, nearly 1000 participants aged 50 to 90 with mild cognitive impairment or mild ADRD and confirmed amyloid plaques on PET or CSF testing were enrolled. These participants were

randomly assigned to receive either gantenerumab or placebo every 2 weeks. The primary endpoint of the trials was the change in clinical dementia in week 116 (36). Phase 3 trials are vital for testing new treatments, assessing their effectiveness and safety, and supporting regulatory approval applications from agencies like the FDA or European Medicine Agency (EMA).

The administration of gantenerumab showed a reduction in amyloid plaque burden on PET imaging, resulting in some participants achieving amyloid-negative status (36). Additionally, gantenerumab recipients exhibited lower levels of CSF phosphorylated tau and higher levels of A β 42 compared to those who received a placebo (36)

Higher levels of A β 42 in the CSF are desirable as they can indicate reduced amyloid plaque burden or clearance, which is beneficial in Alzheimer's treatment (36). However, a significant side effect observed with gantenerumab usage was amyloid-related imaging abnormalities (ARIA). Some participants experienced ARIA-E, which refers to edema in the brain (36).

Hoffmann-La Roche Pharmaceuticals, later on, initiated the SKYLINE trial, a Phase 3 secondary prevention trial, aiming to evaluate gantenerumab in cognitively preclinical individuals with evidence of brain amyloid using CSF or PET imaging (36).

Despite positive trends in plaque reduction and clinical measures, gantenerumab failed to slow cognitive decline in the GRADUATE trials, leading to the cessation of all gantenerumab trials, including SKYLINE, in 2022 (36).

However, Roche continues to supply the antibody for the ongoing Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) study, while subsequent analyses of trial data explore various aspects of disease progression and treatment response.

5.5 Simufilam – A Novel Approach Targeting Filamin A

Simufilam, formerly known as PTI-125, is an investigational novel drug developed by Cassava Sciences, Inc. The primary objective of Simufilam was to evaluate its impact on cognition and its ability to slow cognitive and functional decline in individuals with AD. Secondary objectives included assessing its effects on neuropsychiatric symptoms, caregiver burden, and plasma biomarkers (37).

Differing from conventional approaches that target amyloid plaques, Simufilam introduces an innovative strategy by concentrating on enhancing and strengthening proteins essential for optimal brain function. At the core of this approach is the targeting of Filamin A (FLNA). FLNA is a critical protein involved in regulating the actin cytoskeleton and is believed to be implicated in AD pathology (38). The correlation between the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) and the accumulation of A β 42, a type of amyloid-beta protein associated with AD, is a significant area of investigation.

Research indicates that $\alpha 7$ nAChR activation may help regulate A β 42 levels, potentially reducing its accumulation and the associated brain damage. Understanding this interaction could pave the way for targeted therapies for AD (37). Additionally, Simufilam has demonstrated the ability to mitigate A β -induced inflammatory responses by impeding filamin recruitment to Toll-like Receptor 4 (TLR4), offering a multifaceted approach to addressing the complexities of AD pathology (37).

The Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog11) is a widely used cognitive assessment tool in AD research and clinical trials. It measures various aspects of cognitive function, such as memory, attention, language, and orientation, through a series of tasks and questions (37). In the study mentioned, the results showed that participants receiving Simufilam experienced a decline of 0.9 points on the ADAS-Cog11, while those on placebo had a decline of 1.5 points. This difference, while favoring Simufilam, did not reach statistical significance. This lack of statistical

significance suggests that the observed difference in cognitive decline between the two groups could have been due to chance rather than the effect of Simufilam (37).

Cassava Sciences' development of Simufilam for Alzheimer's treatment has faced controversy and allegations of research misconduct. Retractions of foundational papers due to data irregularities have raised doubts about subsequent studies' reliability. Calls to halt Simufilam trials and conduct an independent data assessment persist. This situation highlights integrity concerns in research, impacting patient trust and investor confidence. Maintaining research integrity is crucial for ensuring reliable scientific findings and patient safety in clinical trials (37).

6. GROUNDBREAKING TREATMENT FOR AD

In response to the urgent need for effective treatments, the FDA has granted approval to two disease monoclonal antibodies (MABs), Aducanumab in 2021 and Lecanemab in 2023 (17). These approvals mark significant advancements in the field of Alzheimer's treatment, offering hope for patients and caregivers alike.

These MABs are designed to target different forms of amyloid and operate via specific pathways. Upon entering the brain, they attach to fibrillar aggregates using their fragment antigen binding sites, which are then recognized by microglia and undergo phagocytosis. Moreover, antibodies can assist in amyloid clearance independently of microglia, dissolving protein aggregates and facilitating their removal from the brain (17).

Despite their ability to target and remove A β from the brain, the clinical benefits of these antibodies in terms of improving cognitive function and slowing the progression of AD have been debated (39). (39)

Thus, while these antibodies hold promise as potential therapies for AD, further research is needed to fully understand their efficacy and to optimize their use in clinical practice.

6.1 Aducanumab

Aducanumab is a recombinant monoclonal antibody specifically engineered to target and bind to A β aggregates associated with AD. By selectively targeting these A β aggregates, aducanumab aims to address the underlying disease biology and potentially slow disease progression. It represents a significant advancement as the first therapy to demonstrate potential in reducing cognitive decline in individuals with early AD, providing hope for preserving independence and memory (40).

While aducanumab is not considered a cure for AD, it is intended for individuals with mild cognitive impairment or mild dementia due to AD, contingent upon confirmation of A β plaques via diagnostic testing. Aducanumab is administered through intravenous infusion every 4 weeks, allowing for convenient delivery in clinical settings (40).

Despite the initial promise, Aducanumab encountered significant regulatory challenges. In November 2020, an FDA advisory committee voted against its approval due to concerns regarding efficacy data. However, in June 2021, the FDA granted accelerated approval to Aducanumab, sparking controversy (40). (40) Safety data from Phase 3 trials revealed risks, including ARIA, particularly among individuals with baseline brain microhemorrhages or Apo ϵ 4 status (40). Further hurdles arose when the EMA rejected its marketing application in December 2021, and Japan's Health Ministry indicated a similar decision (40). In response, in April 2022, the U.S. Centers for Medicare and Medicaid Services restricted Aducanumab coverage to clinical trials. Biogen, the manufacturer, then withdrew its marketing application with the EMA and scaled back marketing efforts, while continuing ongoing clinical studies. The Phase 4 confirmatory trial ENVISION commenced in June 2022, aiming to enroll 1,500 participants with early AD, with a projected completion date of 2026 (40). However, in January 2024, Biogen announced the discontinuation of Aducanumab marketing and termination of the ENVISION trial, with rights reverting to Neurimmune company (40). Nonetheless, research on the treatment effects of Aducanumab persists.

6.2 Lecanemab

Lecanemab, marketed as Leqembi™ and developed by Eisai in partnership with Biogen Inc., received full FDA approval in the summer of 2023 for treating patients with AD in the early stages of mild cognitive impairment or mild dementia (41).

It is a recombinant monoclonal antibody that targets soluble forms of A β , including oligomers and protofibrils, with a high selectivity for protofibrils over fibrils (Figure 10) (41). Administered intravenously at a dose of 10 mg/kg every two weeks, Lecanemab facilitates the clearance of amyloid plaques by binding to both soluble and insoluble forms of A β , thus preventing A β deposition and removing existing plaques. Lecanemab undergoes degradation by proteolytic enzymes like endogenous IgGs and has a half-life ranging from 5 to 7 days (41).

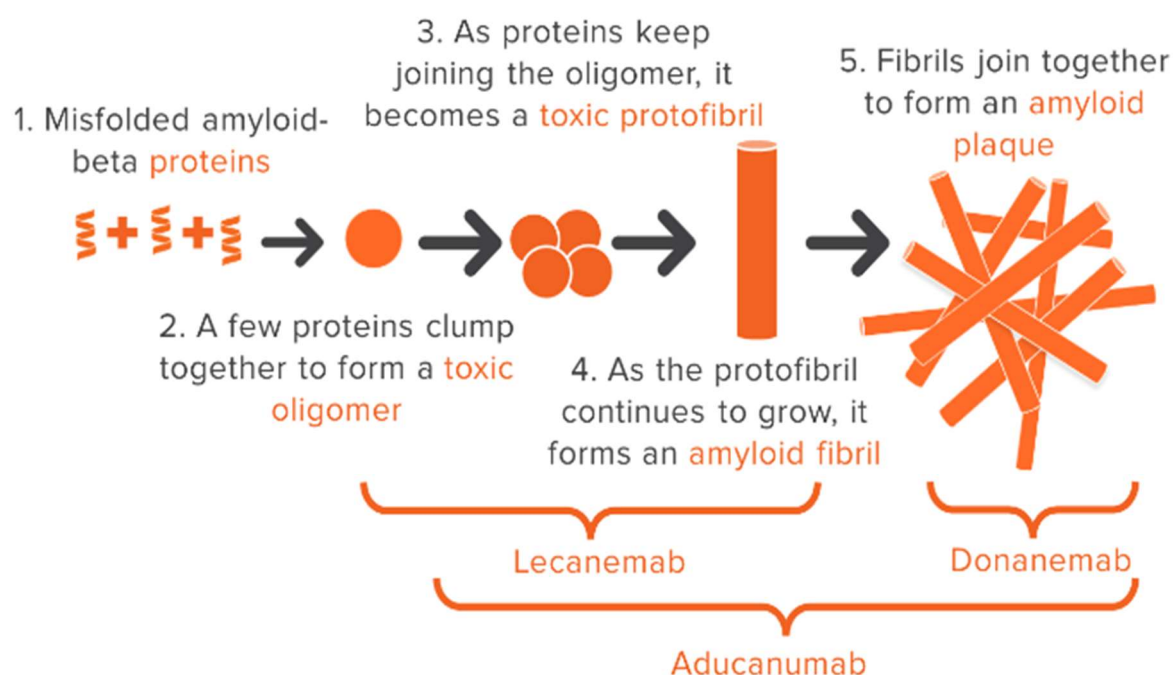


Figure 10. Targeting Various Stages of the Amyloid Plaque Pathway

Lecanemab targets both aggregated soluble and insoluble forms of amyloid beta. Donanemab binds to amyloid plaques after the fibrils have clumped together to form larger buildups or plaques. Aducanumab acts throughout the amyloid aggregation cascade. Provided by Alzheimer's Research UK (42).

Just like Aducanumab, treatment with Lecanemab may also result in adverse events such as ARIA, which can include ARIA-E (edema) and ARIA-H (hemorrhage), which can lead to serious complications such as brain swelling or bleeding. In severe cases, these complications may result in disability or death (41). Dose interruptions may be necessary depending on the severity of

clinical symptoms and MRI results. Patients should be carefully monitored, with baseline brain MRIs obtained before treatment initiation and regular MRIs performed during treatment (41).

Other Adverse effects such as infusion-related reactions, headache, cough, diarrhea, and superficial siderosis of the central nervous system may occur (41).

Patients who are taking antithrombotic medications and those who are ApoE-ε4 homozygotes are particularly at higher risk for severe side effects when undergoing treatment with Lecanemab. Therefore, caution is warranted when initiating treatment in these patient populations (41).

As of 2024, South Korea has become the fourth country to grant approval for Lecanemab, following the United States, Japan, and China. Final approval from the EMA is still pending.

6.3 Donanemab

Donanemab, from Eli Lilly, is a monoclonal antibody targeting amyloid plaques differently than Lecanemab. While Lecanemab addresses both soluble and insoluble amyloid beta, Donanemab acts on amyloid plaques, as can be depicted in Figure 10 (43).

Recent findings from the phase 3 clinical trial, TRAILBLAZER-ALZ 2, spanning 18 months, revealed that donanemab effectively decelerated cognitive and functional decline in individuals experiencing early symptoms of AD (43). Notably, after one year of treatment, 47% of participants receiving donanemab showed no cognitive decline, a significant improvement compared to those who received a placebo (43).

Donanemab like Aducanumab, is administered via intravenous infusion, typically given every four weeks. During clinical trials, common side effects of

this medication included nausea, urinary tract infection, diarrhea, cerebral microhemorrhage, infusion-related reactions, vomiting, and anxiety (43). Significant adverse effect of donanemab, as seen in other drugs mentioned before, is ARIA, which can be observed through MRI scans.

In the TRAILBLAZER-ALZ clinical trial, the incidence of ARIA among patients taking donanemab was 38.9%, whereas only 8% of the placebo group experienced it (43).

The safety profile of Donanemab, particularly regarding ARIA, remains an important consideration in its evaluation and approval process. While preliminary evidence suggests delayed cognitive decline in mild-to-moderate Alzheimer's disease, further trials are needed to determine therapeutic benefits comprehensively (43).

As of now, Donanemab's trial design, which permits patients to discontinue treatment after plaque clearance, and its effectiveness in slowing cognitive decline, are under FDA scrutiny (43). However, the drug has not yet received full approval from the FDA. The agency intends to hold an advisory meeting to evaluate its safety and the design of a crucial clinical trial (43).

6.4 Limitations of Novel Treatments for Alzheimer's Disease

ARIA, in its two forms, ARIA-E and ARIA-H, poses significant concerns for patients on anti-amyloid therapies (17). ARIA-E, characterized by brain edema visible on MRI scans, can lead to symptoms like headaches, dizziness, and seizures. ARIA-H refers to brain micro-hemorrhages, which are also problematic because they can potentially lead to cognitive decline and other neurological complications over time (17). Both changes can remain asymptomatic with only radiologic changes and cumulative clinical effect. These complications emphasize the importance of monitoring and managing ARIA to ensure patient safety. Careful consideration and collaboration among

patients, caregivers, and healthcare providers are essential for informed decision-making and effective management of AD treatments (17).

The financial burden associated with medications like Lecanemab is significant, posing strain on both patients and healthcare systems due to their high costs (44). High costs for medications like Lecanemab can be a burden, particularly for government healthcare programs like Medicare and Medicaid. Eisai Co. estimates an annual cost of \$26,500 per patient, but when considering additional expenses like genetic tests and brain scans, the total cost could reach \$82,500 per patient per year for U.S. taxpayers. Similar pricing challenges are seen in Europe, where Lecanemab treatment costs could exceed 133 billion EUR per year for an estimated 5.4 million eligible individuals (44).

High medication costs can hinder access for some patients, worsening healthcare disparities. To address this, advocating for fair pricing policies and investing in research is crucial. Implementing payment models that address affordability and access disparities is essential for equitable access to Alzheimer's treatments.

6.5 Sodium Oligomannate

Sodium oligomannate, also known as GV-971, is a compound derived from oligosaccharides found in brown algae. Developed by Shanghai Green Valley Pharmaceutical Co., Ltd., studies have shown that these oligosaccharides possess several beneficial effects, including the ability to de-aggregate A β , inhibit astrocyte-mediated inflammatory responses to amyloid plaques, and bind to various proteins inside neurons. Based on these findings, GV-971 has emerged as a potential therapeutic agent for AD (45).

Recent research has investigated GV-971's therapeutic potential in modulating A β amyloidosis and neuroinflammation by targeting the gut microbiome (46). Notably, GV-971 treatment resulted in male-specific reductions in brain A β deposition, alterations in sex-specific microbiota profiles,

and changes in bacterial metabolism, leading to reduced peripheral inflammatory markers (45). Additionally, GV-971 influenced microglial phenotypes, decreasing plaque-associated activated microglia and increasing homeostatic microglia in male mice, along with a reduction in astrocyte reactivity (46).

These findings suggest potential roles for gut microbiota profiles, hormonal differences, and transcriptional outcomes in microglia. Future investigations will focus on elucidating the specific microbial species and metabolites involved in GV-971-mediated alterations in A β amyloidosis and microglial function, as well as determining the levels of GV-971 present in the brain and its interaction with A β species (46). (46)

Shanghai Green Valley Pharmaceuticals has received FDA approval for an international multi-center Phase III clinical trial of GV-971. Additionally, GV-971 received conditional approval in China in 2019. The trial aims to enroll over 2000 patients across global sites, with completion expected by 2024 and a new drug application submission planned for 2025. This trial represents a significant step towards addressing the urgent need for effective treatments for Alzheimer's disease worldwide. (46)

DISCUSSION

The quest for effective treatments and a cure for AD has encountered numerous research failures. Challenges stem from the disease's complex nature, characterized by multifactorial pathology, heterogeneous patient populations, and significant gaps in understanding the complete pathophysiological picture.

The recent FDA approval of Aducanumab and Lecanemab represents a significant milestone forward in AD treatment, igniting hope among patients and caregivers. These monoclonal antibodies, designed to target specific stages in amyloid formation, address a key cause in AD neuropathology. By leveraging distinct mechanisms to facilitate amyloid clearance from the brain, they hold promise for slowing disease progression.

Despite significant progress, ongoing challenges persist, including uncertainties surrounding the efficacy, safety, affordability, and accessibility of these treatments. It is important to note that the targeted patient population, consisting of individuals with mild AD, represents only a subset of those affected by AD. There are uncertainties regarding whether these treatments can effectively address the needs of individuals in advanced stages of AD or serve as preventive measures for those in earlier stages.

Additionally, the possibility of experiencing the severe and hazardous side effects known as ARIA introduces heightened complexity and risk into the deliberation surrounding treatment decisions.

Furthermore, healthcare providers must consider the financial implications for patients and healthcare systems when recommending these therapies, ensuring equitable access to effective treatments while minimizing the risk of adverse events.

Addressing the multifaceted challenges inherent in AD demands a comprehensive and interdisciplinary approach that prioritizes collaboration, innovation, and global cooperation within the scientific community.

Although there has been significant progress, it is vital to note that it is only the beginning of the journey toward effective AD treatments. This calls for a shift in perspective towards innovative and unconventional approaches, urging researchers to delve into new concepts and alternative methods to navigate the complex terrain of AD pathology.

ACKNOWLEDGMENT

I dedicate my thesis work to my beloved grandmother, Lea Danon, who bravely battled Alzheimer's disease until her passing. Born on November 2nd, 1940, in Sofia, Bulgaria, she endured the horrors of the Holocaust as a young girl before moving to Israel with her family. Lea worked as a pediatric nurse known for her professionalism and kindness. Her unwavering love and the values she instilled in me, such as helping others and believing in humanity's goodness, inspired my journey to become a physician. Her enduring love story with my grandfather, spanning 52 years, taught me the importance of companionship and resilience in the face of adversity.

Experiencing firsthand a family member enduring both physical and emotional suffering caused by this devastating illness has heightened the urgency to find a cure for Alzheimer's and to prevent its onset in future generations.

In loving memory of my grandparents, my family contributed to the establishment of Snoezelen® room at 'Dorot' Medical Center for Rehabilitation and Geriatrics, located in Netanya, Israel. The term "Snoezelen®" is a combination of Dutch verbs that mean "to seek and explore" and "to relax." It came into use in the late 1970s, stemming from the innovative work of Dutch therapists Jan Hulsege and Ad Verheul at the DeHartenburg Institute.

A Snoezelen® Multi-Sensory Environment offers diverse benefits, providing education, stimulation, relaxation, calmness, or energy through tailored sensory experiences. These environments adapt by adjusting lighting, atmosphere, sounds, and textures based on individual needs, showcasing exceptional flexibility and extensive applicability across demographics.

A study in the American Journal of Alzheimer's Disease & Other Dementias explored the effectiveness of multisensory environments (MSEs) in enhancing functional performance among individuals with moderate-to-severe

dementia. Results revealed significant improvements in motor and process scores in MSE participants, indicating their potential to reduce cognitive 'noise' and enhance sensory processing and motor response (47). The study advocates personalized activity planning in MSEs but highlights challenges in sample size and funding, emphasizing the need for further research. Overall, the findings support MSEs as a valuable strategy for improving functional performance in dementia (47).

The Snoezelen® room at the 'Dorot' center, active for a year, has shown remarkable success. Guided by the staff occupational therapist, it has become a cherished resource within the department. It effectively stimulates lethargic individuals, prompting responses like opening their eyes, tactile interaction, and verbal communication. Additionally, cognitively alert patients find solace and relaxation in the room. Virtual reality (VR) glasses have gained popularity among patients and families due to their versatility and user-friendly nature.

In the future, there is a willingness to expand the activities of the Snoezelen® room to a wider range of patients, possibly including staff members, beyond the palliative ward.

I'm sincerely grateful to my family and partner for their immense support, as well as to my colleagues who have accompanied me on this journey through medical school.

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BIOGRAPHY

Ophir Shenhav was born in New York City, USA, on December 30th, 1995. She later relocated to Tel Aviv, Israel with her family.

Currently, Ophir is pursuing an M.D. at the University of Zagreb, School of Medicine, with an expected graduation in July 2024.

She earned placement on the Dean's award list for the academic year 2021/2022.

Ophir has gained valuable professional experience through diverse rotations in leading Israeli hospitals, notably "Clalit" hospitals.

She took an active part in CROSS, the Croatian Student Summit, centered on the intersection of neurology and technology's contemporary applications.

Additionally, she gained practical experience in the "Ultrasound as a Stethoscope" elective.

Moreover, she contributed as a demonstrator at the University Hospital Centre Zagreb, Rebro, offering guidance to peers in clinical practice.

Ophir has volunteered in the Heart & Chest Critical Care Unit and NICU at Schneider Children Medical Center, assisting medical personnel and patients with daily tasks.

Furthermore, Ophir served as an Israeli culture instructor at Camp JCC in Washington DC, fostering relationships with children with special needs and promoting Israeli culture globally.

During her service in the Israel Defense Forces as an operations coordinator in the Airforce, Ophir was honored with the Outstanding Soldier Award.

Ophir attended "Lady Davis" High School in Tel-Aviv, Israel, majoring in Biology and Biotechnology. She received an Excellence Award for her exceptional academic achievements and conducted research on the p53 tumor suppressor gene at the Weizmann Institute of Science.