

An Investigative Study into Alzheimer's Disease (AD): Development, Pathway and Progression, and Novel Treatment

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Abstract

The neurodegenerative disorders are typically characterized by the gradual loss of neuronal function and structure, also known as neurodegeneration. They are debilitating conditions that originate from toxic, aggregation-prone proteins. In particular, Alzheimer's disease (AD) is a progressive neurodegenerative disorder, estimated to impact 10 percent of Americans aged 65 years and older, equating to roughly 5.1 million patients. The disease is defined by the buildup and presence of two abnormal structures: Extracellular β -amyloid ($A\beta$) plaques and interneuronal neurofibrillary tangles. Alzheimer's disease (AD) is incurable, whereby current and experimental therapeutic strategies focus largely upon symptomatic treatment. The role of protein aggregation in Alzheimer's disease (AD) therefore mandates the analysis of the ubiquitin-proteasome system (UPS), specifically in the development and drug-targeting aspects of neurodegenerative disease. This systematic review draws upon the existing anti-amyloid and anti-tau therapeutic approaches to propose drug-targeting upon Ub-protein ligase [E3] and, more generally, the ubiquitin-proteasome system (UPS) itself to control the accumulation of ubiquitylated protein substrates.

Keywords: *Alzheimer's disease (AD), β -amyloid ($A\beta$), neurodegenerative disease, Ub-protein ligase [E3], ubiquitin-proteasome system (UPS)*

Introduction

Protein Aggregation and Neurodegenerative Disease

The neurodegenerative disorders are typically characterized by the gradual loss of neuronal function and structure, also known as neurodegeneration. They are debilitating conditions, wherein the degeneration of nervous system cells (known as “neurons”) prompt their abnormal function and demise. Their deterioration ultimately causes many symptoms, ranging from ataxias to dementias.

The neurodegenerative disorders include Alzheimer’s disease, frontotemporal dementia, Huntington’s disease, Lewy body disease, and Parkinson’s disease, among several others (Table 1). The diverse grouping is known to share the common attribute of neuronal damage caused by toxic, aggregation-prone proteins. The mutations in the affected genes therefore cause the “abnormal processing and accumulation of misfolded protein in neuronal inclusions and plaques” [1].

The neurodegenerative disorders progress with virtually identical pathways, thereby indicating the possibility for parallel therapeutic options—based heavily upon an “understanding of the normal cellular mechanisms for disposing of unwanted and potentially noxious proteins” [1].

An incorrect protein conformation or folding is a “major threat to cell function and viability, [whereby] elaborate systems have evolved to protect cells from the deleterious effects of misfolded proteins” [1]. The first safeguard is the molecular chaperone, which attaches itself to the misfolded polypeptide to correct its folding and inhibit harmful interactions. However, the molecular chaperone is unable to precisely target each misfolded protein, thereby requiring the

actions of the ubiquitin–proteasome system (UPS) to eliminate the substantial burden of defective polypeptide [1].

Table I. Features of Neurodegenerative Diseases (Adapted from Taylor et al. 2002)

Disease	Protein Deposits	Toxic Protein
Alzheimer’s Disease	Extracellular Plaques; Intracellular Tangles	β -amyloid
Familial Amyotrophic Lateral Sclerosis (FALS)	Bunina Bodies	Superoxide Dismutase 1 (SOD1)
Parkinson’s Disease	Lewy Bodies	α -Synuclein
Polyglutamine Disease	Nuclear and Cytoplasmic Inclusions	Polyglutamine-containing proteins
Prion Disease	Prion Plaque	Scrapie-associated prion protein (PrP ^{Sc})
Tauopathy	Cytoplasmic Tangles	Tau

That being said, the neurodegenerative diseases are typically related to protein aggregation, which directly results from lack of degradation by the ubiquitin–proteasome system (UPS). It is therefore critical to analyze the role of the ubiquitin–proteasome system (UPS) in the development and drug–targeting aspects of neurodegenerative disease, given its notable role in protein degradation (or lack thereof, in neurodegenerative cases).

Ubiquitin–Proteasome System (UPS)

Ubiquitin is a single–chain polypeptide that exists in eukaryotic cells. It primarily serves to be a regulatory protein that acts to degrade faulty proteins and synthesize other proteins. It also plays a critical role in other processes, including “novel signaling roles in deoxyribonucleic acid (DNA) repair and the activation of protein kinases such as IkappaB kinase” [2].

Its role as the “mark of death” requires polyubiquitination, meaning that the degradation–labeled protein must be tagged by four or more multimers of ubiquitin, which leads to its

recognition by the 26S proteasome (Figure 1). The 26S proteasome is a large, multicatalytic complex that degrades polyubiquitinated proteins to small peptides, thus functioning as the waste disposer of the cell with two 19S caps and 20S catalytic core.

There are three enzymes required to prompt ubiquitination—namely Ub-activating enzyme [E1], Ub-conjugating enzyme [E2], and Ub-protein ligase [E3]. While the Ub-activating enzyme [E1] and Ub-conjugating enzyme [E2] play a critical role in preparing ubiquitin for conjugation, the key enzyme is Ub-protein ligase [E3] due to its role in recognizing its target protein via protein-binding domain to catalyze the attachment of activated ubiquitin.

The process above is termed the ubiquitin-proteasome system (UPS). The dysfunction of the ubiquitin-proteasome system (UPS) yields many human diseases—particularly neurodegenerative disorders, largely “based upon the presence of deposits consisting of ubiquitylated proteins in affected neurons” [3]. Furthermore, it has been theorized that “aggregation-prone proteins associated with [neurodegenerative] disorders, such as α -synuclein, β -amyloid peptide, and polyglutamine proteins, compromise ubiquitin-proteasome system [UPS] function, and delay the degradation of other proteasome substrates” [3].

Alzheimer's Disease

Alzheimer's disease is the most common type of dementia and is estimated to impact 10 percent of Americans aged 65 years and older (roughly 5.1 million individuals). The number of Americans with Alzheimer's disease is projected to grow rapidly by 2050 due to the aging “Baby Boomer” population.

Alzheimer's disease is a progressive neurodegenerative disorder, typically characterized by three groups of symptoms: Phase I (*Cognitive Dysfunction*), which includes executive dysfunction and memory loss; Phase II (*Non-Cognitive Symptoms*), which includes behavioral

disturbances and psychiatric symptoms; and Phase III (*Daily Living*), which includes the inability to perform daily activities like dressing and shopping (Figure 2) [4].

The symptoms of Alzheimer's disease progress from mild to severe dementia and memory loss. The diagnostic evolution of Alzheimer's disease has progressed greatly, from its mid- to late-term diagnosis and management in primary care facilities to early-term diagnosis and investigation with pharmacological symptomatic treatments and psychosocial support [4].

Alzheimer's disease is defined by the buildup and presence of two abnormal structures—namely “extracellular amyloid plaques and intraneuronal neurofibrillary tangles, both of which comprise highly-insoluble, densely-packed filaments” [5]. The respective structures are composed of amyloid- β (A β) peptides for amyloid plaques and tau for neurofibrillary tangles (Table 1). The non-cognitive symptoms of Alzheimer's disease are related to the agglomeration of plaques and tangles, thereby serving as the “direct consequence of the damage and destruction of synapses that mediate memory and cognition” [5]. The ubiquitin-proteasome system (UPS) is associated with early- and late-stages of Alzheimer's disease, thereby characterized by synaptic dysfunction and neurodegeneration, respectively.

The ubiquitin-proteasome system (UPS) is known to play a key role in the regular functioning of synapses. The synaptic dysfunction of early Alzheimer's disease is thus caused by defective proteolysis, which is directly impacted by the ubiquitin-proteasome system (UPS). Moreover, the accumulation of insoluble protein in Alzheimer's patients may be caused by “overload or dysfunction of the ubiquitin-proteasome system (UPS), or by conformational alterations in the protein substrates that prevent their degradation and recognition by the ubiquitin-proteasome system (UPS)” [6].

Furthermore, Sudarshan C. Upadhyaya and Ashok N. Hegde observed that Alzheimer's disease and other chronic neurodegenerative diseases are typically accompanied by inclusion bodies within nerve cells, in conjunction with the abnormal deposition of highly-insoluble protein aggregates. The inclusion bodies depict "ubiquitin immunoreactivity in Alzheimer's disease brains" [7]. However, a more direct relationship between the ubiquitin-proteasome system (UPS) and pathogenesis of Alzheimer's disease has also been established, wherein Alzheimer's disease is characterized by a frameshift mutation in the ubiquitin transcript with twenty additional amino acid residues at its C-terminus, called UBB⁺¹.

UBB⁺¹ is present in Alzheimer's patients. While UBB⁺¹ may serve as the substrate for polyubiquitination (and, in turn, degradation), its polyubiquitin chains cannot be disassembled by deubiquitinating enzymes (DUBs) [7], thus inhibiting the 26S proteasomal unit. The research upon UBB⁺¹ and deubiquitinating enzymes (DUBs) is ongoing, although the inhibitory activity of UBB⁺¹ is a critical determinant of neurotoxicity that likely yields a favorable environment for protein aggregates.

Current Therapeutic Strategies

Alzheimer's disease does not have any functional treatment for suppressing its onset and progression. In previous years, Alzheimer's therapeutic research focused upon the amyloidogenic hypothesis, which hypothesizes that the "β-amyloid (Aβ) peptide is chiefly responsible for cognitive impairment and neuronal death" [8]. The amyloidogenic-based treatments have only been modestly effective, wherein their focus lies upon "reduc[ing] β-amyloid (Aβ) production through the inhibition of β and γ secretase enzymes and promot[ing] dissolution of existing cerebral β-amyloid (Aβ) plaques" [8].

However, the primary obstacle in Alzheimer's research is the sparse insight related to its pathogenesis and pathophysiology. For instance, Alzheimer's disease is known to be multifactorial, with implicated mechanisms including “tangle formation and spread, dysregulated protein degradation pathways, neuroinflammation, and loss of support by neurotrophic factors” [9]. In recent years, Alzheimer's drug development has therefore shifted from amyloid-centric approaches to multi-target approaches.

FDA-Approved Medications

The drug-targeting of Alzheimer's disease is primarily based upon the known features of its pathological cascade: The first step is the accumulation of β -amyloid ($A\beta$), followed by the development of neurofibrillary tangles and neuronal degeneration. The molecular mechanism of β -amyloid ($A\beta$) in Alzheimer's pathogenesis is presently unknown. However, Alzheimer's research has depicted the “presence of crosstalk [among] $A\beta$ /Tau in term of molecular signaling pathways” [10].

In July 2021, the U.S. Food & Drug Administration (FDA) had approved only five drugs for Alzheimer's treatment, which fall into two categories: Acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists (Table II). The drugs provide “symptomatic relief, temporarily improving cognitive function, but are unable to slow the long-term progression of the disorder through a partial amelioration of cholinergic and glutamatergic neurotransmission” [10]. The symptomatic treatment has notable drawbacks and limitations due to the circulatory instability of acetylcholinesterase inhibitors (AChEIs), which directly correlates with an “unpredictable uptake and bioavailability that may cause gastrointestinal complications” [10].

Table II. FDA–Approved Medications (Adapted from Nguyen et al. 2021)

Generic Name	Brand Name	Stage of Alzheimer’s Disease	Principal Target	Side Effects
Donepezil	Aricept	All	Selective Acetylcholinesterase Inhibitor	Increased Frequency of Bowel Movements; Loss of Appetite; Nausea; Vomiting
Galantamine	Razadyne	Mild to Moderate	Acetylcholinesterase and Butyrylcholinesterase Inhibitor	Confusion; Constipation; Dizziness; Headache
Memantine	Namenda	Moderate to Severe	N–methyl–D–aspartate (NMDA) Receptor Antagonist	Increased Frequency of Bowel Movements; Loss of Appetite; Muscle Cramps; Nausea; Vomiting
Rivastigmine	Exelon	Mild to Moderate	Acetylcholinesterase and Butyrylcholinesterase Inhibitor	Increased Frequency of Bowel Movements; Loss of Appetite; Nausea; Vomiting
Memantine & Donepezil	Namzaric	Moderate to Severe	Combined Action	Confusion; Constipation; Dizziness; Headache; Increased Frequency of Bowel Movements; Loss of Appetite; Nausea; Vomiting

Experimental Therapeutic Strategies

Anti-Amyloid Approaches

The anti-amyloid therapy is based heavily upon the amyloidogenic hypothesis, which identifies β -amyloid ($A\beta$) plaques as the “pathological trigger for a cascade that includes neuritic injury, formation of neurofibrillary tangles via tau protein, and cell death” [10]. The recent therapeutic studies have supported the usage of β -amyloid ($A\beta$) targeting in the novel treatments for Alzheimer’s disease and cerebral amyloid angiopathy (CAA), referring to the “cerebrovascular disease directly implicated in Alzheimer’s disease pathogenesis through amyloid- β ($A\beta$) deposition, which may cause the development and progression of dementia” [11].

The pivotal role of β -amyloid ($A\beta$) highlights the necessity of broadened strategies to directly or indirectly attack the plaque buildups and deposits thereof. The current amyloidogenic-based approaches include the following: Antifibrillization Agents; β -Secretase Inhibitors; γ -Secretase Inhibitors; γ -Secretase Modulators; Statins (Inhibitors of Cholesterol Biosynthesis); and Vaccination and Immunization Therapies (Figure 3; Table III) [12].

Monoclonal Antibody Treatment

The amyloidogenic hypothesis recently gained notable traction due to the generation of Aducanumab (or Aduhelm), a “human monoclonal antibody that selectively targets aggregated β -amyloid ($A\beta$)” [13]. The monoclonal antibody’s clinical results have justified its development and usage in Alzheimer’s treatment, given its therapeutic successes in the “transgenic mouse model of Alzheimer’s disease, [where] Aducanumab is shown to enter the brain, bind parenchymal β -amyloid, and reduce soluble and insoluble β -amyloid ($A\beta$) in a dose-dependent manner” [13].

Aduhelm's Phase 3 clinical trials in mild- to moderate-level Alzheimer's patients have revealed the following: "1-year of monthly intravenous infusions of [Aduhelm] reduces brain β -amyloid ($A\beta$) in a dose- and time-dependent manner, [which] is accompanied by a slowing of clinical decline measured by Clinical Dementia Ratings (CDR)—Sum of Boxes and Mini Mental State Examination (MMSE) scores" [13].

The amyloidogenic-directed antibody was approved by the U.S. Food & Drug Administration (FDA) in June 2021. However, the Food & Drug Administration (FDA) was confronted with backlash for its approval of Aduhelm under the accelerated approval pathway. The agency therefore limited the approved patient populace to solely include the following symptoms to better conform with Biogen clinical trials: Mild cognitive impairment (MCI) or mild dementia. Despite its controversies and limitations, Aduhelm is regarded as landmark therapy, whereby the "first-in-class drug will open the door to more efficacious therapies" [14].

Anti-Tau Approaches

The anti-tau therapy is based heavily upon the formation of neurofibrillary tangles and Tau phosphorylation to Alzheimer's pathology [10]. After the many failures of β -amyloid ($A\beta$) drug-targeting, the clinical studies have "enforced to discover treating tauopathy for [Alzheimer's] therapy, targeting prevention of Tau aggregation and improvement of Tau degradation such as methylene blue, curcumin derivatives, N744, rhodanines, and aminothienopyridazines (ATPZs)" [10].

The current tauopathy-based approaches include the following: Caspase Inhibitors; Cholinesterase Inhibitors; Neuroprotective and Neurorestorative Approaches; and Nicotine Acetylcholine (nAChR) Receptor Agonists (Figure 3; Table III) [12].

Table III. Abridged Agents or Drugs in Phase 3 of Alzheimer’s Therapeutic Development

(Adapted from Cummings et al. 2021)

Agent	Mechanism Class	Mechanism of Action	Therapeutic Purpose
Aducanumab*	Amyloid	Monoclonal Antibody for A β Plaques and Oligomers	Disease–Modifying Therapy (DMT)
AGB101 (Low–Dose Levetiracetam)	Synaptic Plasticity; Neuroprotection	SV2A Modulation; Reduction of A β –Induced Neuronal Hyperactivity	Disease–Modifying Therapy (DMT)
Atuzaginstat (COR388)	Inflammation; Infection	Bacterial Protease Inhibitor for Gingipain by <i>P. gingivalis</i> ; Reduction of Neuroinflammation and Hippocampal Degradation	Disease–Modifying Therapy (DMT)
Azeliragon	Amyloid; Inflammation	RAGE Antagonist; Reduction of A β Transport into Brain; Mitigation of Toxic Effects of Oligomers; Reduction of Inflammation	Disease–Modifying Therapy (DMT)
Gantenerumab	Amyloid	Monoclonal Antibody for A β Plaques and Oligomers	Disease–Modifying Therapy (DMT)
Solanezumab	Amyloid	Monoclonal Antibody for A β Monomers	Disease–Modifying Therapy (DMT)
TRx0237	Tau	Tau Protein Aggregation Inhibitor	Disease–Modifying Therapy (DMT)

*See the “Monoclonal Antibody Treatment” sub–section above for more information.

Implications for Future Work

Nanocarrier and Nanoparticle Techniques

The disease–modifying therapies (DMTs) have been unsatisfactory thus far, revealing the necessity for an “optimization of target subjects and monitoring methods” [10]. The difficulty in Alzheimer’s research is attributed to many factors, including the high selectivity of the blood–

brain barrier (BBB), the semipermeable border of “endothelial cells that prevents the solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the central nervous system (CNS) where neurons reside, preventing agent[s] from the blood entering the brain” [10]. The drug-delivering techniques must adapt to effectually traverse the blood-brain barrier (BBB), thereby indicating that strategies like the drug-loaded nanocarrier and surface-modified nanoparticle must be adopted into Alzheimer’s research.

The future trajectory of Alzheimer’s clinical research is gradually moving toward the nanoparticle system, whereby the ultimate hope is to “develop efficient disease-modifying strategies that aim to deliver the nano-based therapeutic drugs to the brain through the blood-brain barrier [and] reduce β -amyloid production, aggregation, and clearance, as well as tau phosphorylation and assembly into neurofibrillary tangles” [10]. The potential and promise of the nano-based drug delivery mechanism is therefore an exciting development for Alzheimer’s treatment.

Ubiquitin-Proteasome System (UPS)

Furthermore, the Alzheimer’s therapeutic strategies must focus upon the ubiquitin-proteasome system (UPS) due to its critical role in promoting highly-insoluble protein aggregation and synaptic dysfunction. The clinical research largely implicates the role of the ubiquitin-proteasome system (UPS) in Alzheimer’s disease, yet “systematic and thorough studies are necessary to pinpoint how each component of the ubiquitin-proteasome system (UPS) could be linked to synaptic dysfunction or neurodegeneration” [7].

The drug-targeting process also necessitates a greater understanding of the role of proteolysis in Alzheimer’s disease. However, the current and experimental targets range from deubiquitinating enzymes (DUBs) to proteasome to Ub-conjugating enzymes [E2]. The largest

focus must continue to be upon Ub–protein ligase [E3] due to its role in deterring substrate specificity. The allosteric modification of Ub–protein ligase [E3] may yield “an increased or decreased affinity towards specific substrates, [which] is one way of controlling accumulation of the ubiquitylated substrate” [7].

The potential of the ubiquitin–proteasome system (UPS) in Alzheimer’s treatment may be illuminated by the “studies [up]on genetic polymorphisms within UPS components, combined with functional validation in animal models” [7]. The continued research upon Ub–protein ligase [E3] and the ubiquitin–proteasome system (UPS) is therefore critical and may benefit from the incorporation of selective engineering and modification techniques.

Conclusion

To conclude, Alzheimer’s disease is debilitating to 10 percent of Americans aged 65 years and older, most notably due to the lack of functional treatment for suppressing its onset and progression. The current and experimental therapeutic strategies are largely symptomatic, thereby unable to inhibit the long–term progression of the progressive neurodegenerative disease.

The promising implementation of Aduhelm has only highlighted the importance of anti–amyloid and anti–tau approaches to Alzheimer’s therapy. The systematic review therefore proposes the necessity for greater insight into the ubiquitin–protease system (UPS) as a possible Alzheimer’s target, whereby Ub–protein ligase [E3] is promising to control the accumulation of ubiquitylated protein substrates. This is particularly notable in Alzheimer’s therapeutics, given that protein accumulation is the key factor in the development of neurodegenerative diseases.

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Appendix

Figure 1. Steps of the Ubiquitin–Proteasome System (UPS) in Substrate Degradation [16]

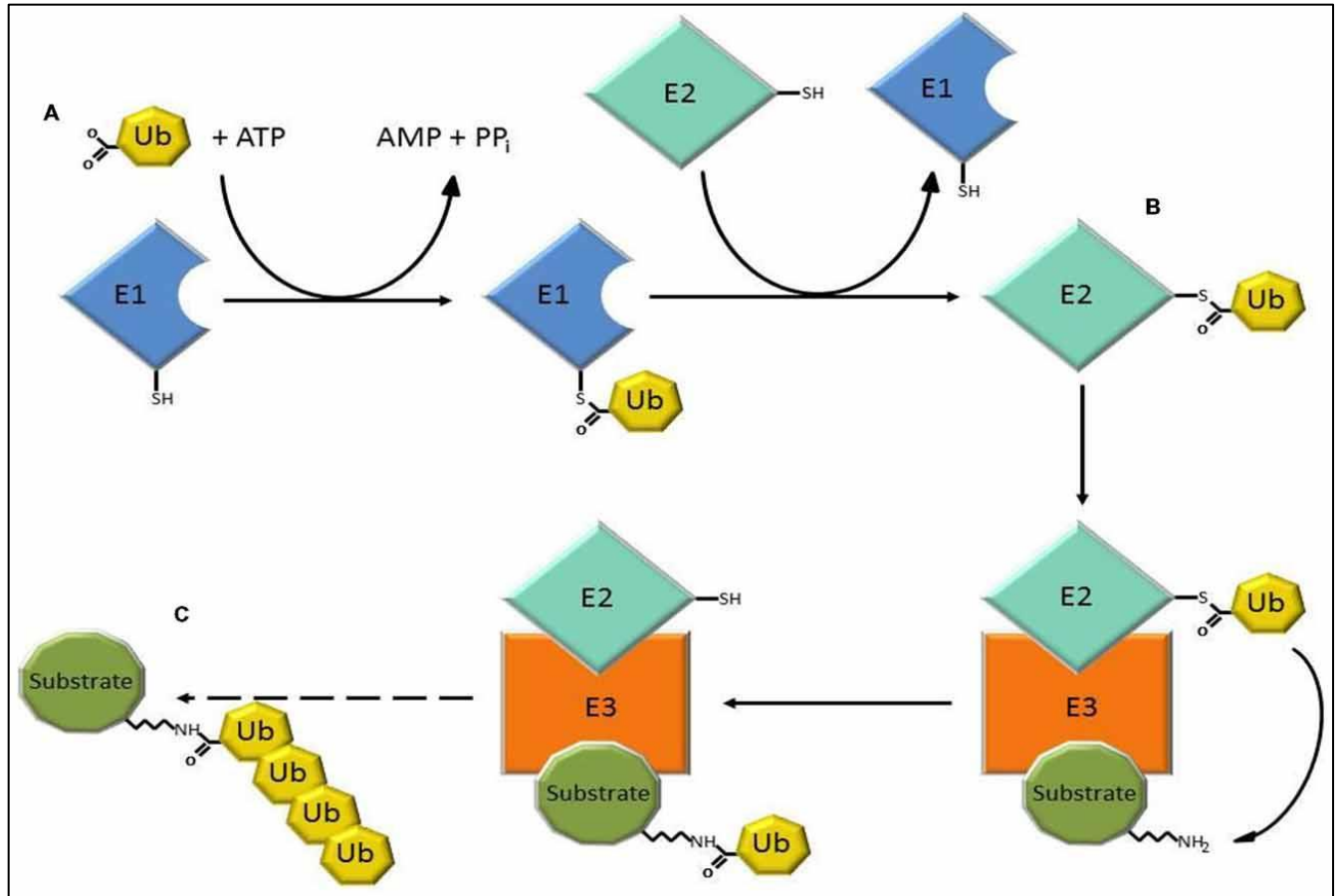


Figure 2. Physiological Structure in Normal versus Alzheimer's Disease (AD) Brain [17]

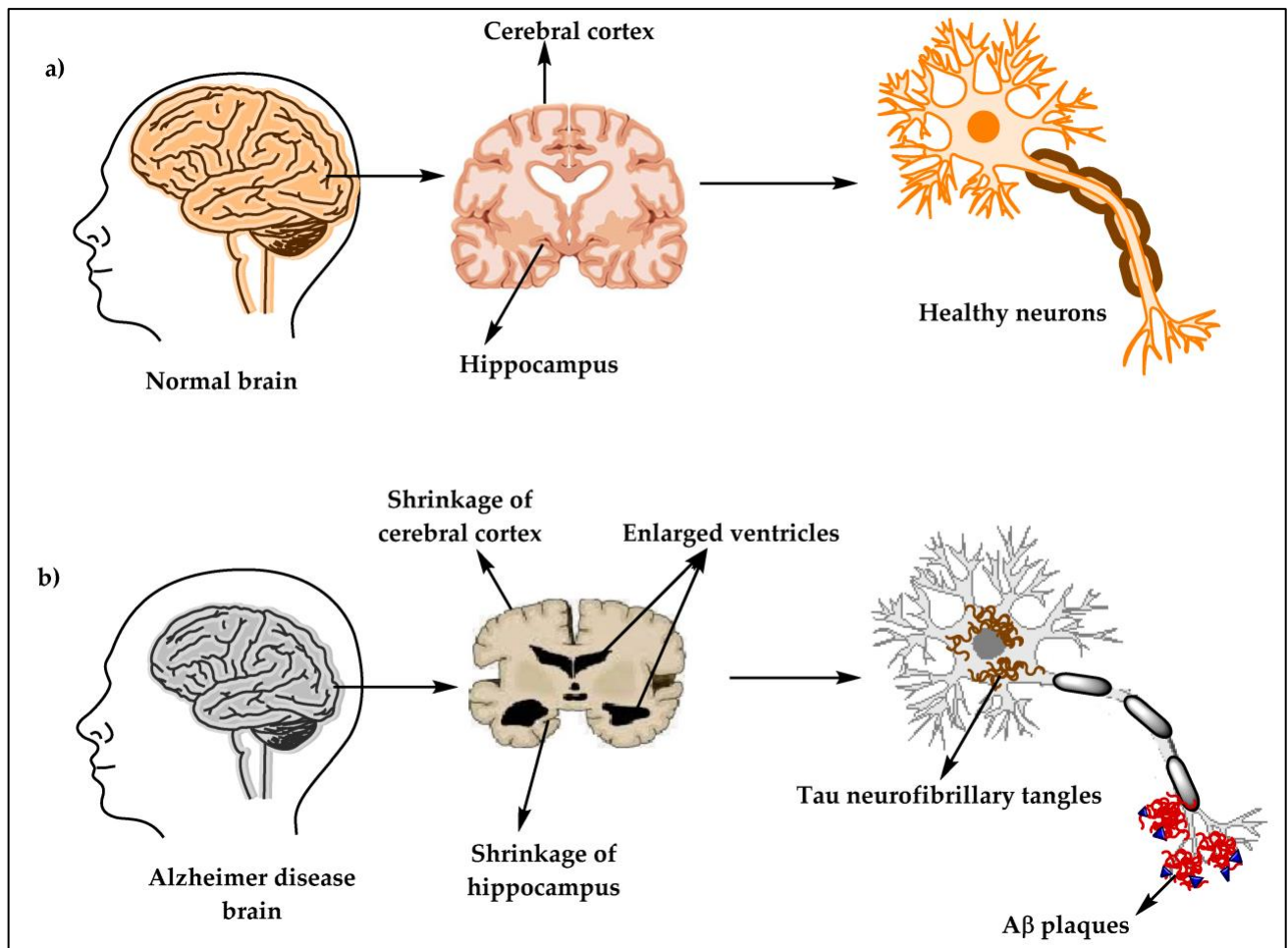
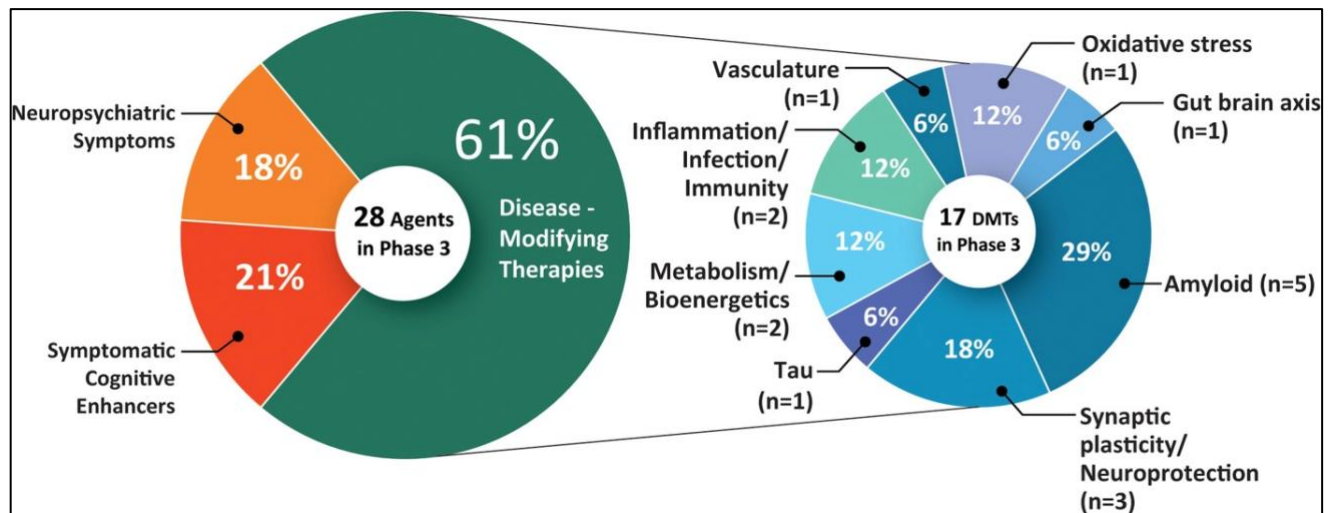


Figure 3. Mechanisms of Action (MOA) of Agents in Phase 3 Clinical Trials [15]



Vita

Aruha Khan is a Chancellor's Honors student dual-majoring in Biological Sciences and Finance (with a Collateral in Economics) at the University of Tennessee, Knoxville. Khan was recently awarded the Torchbearer, the highest student honor conferred by the University. She founded Student Advocates for Medicine in Politics (SAMP) in January 2021, a student organization turned nonprofit that focuses upon amplifying and accelerating the goal of worldwide medical equality. Khan also serves as the Supervisor of Clinical Operations at Shifa Medical Clinic and CORE-in-Training (CIT) at Remote Area Medical. She is presently working as a Clinical Assistant for Genesis Neuroscience Clinic to provide comprehensive community care for patients with cognitive disorders and neurocognitive dementias, which inspired her Honors Capstone upon "An Investigative Study into Alzheimer's Disease (AD): Development, Pathway and Progression, and Novel Treatment." Khan will become their Lead Medical Assistant & Clinical Researcher after graduation, during which her clinical studies will include Aduhelm-based patient outcomes. She ultimately plans to pursue an MD/MBA dual-degree to begin a nonprofit medical practice for low-income and uninsured patients.