1. INTRODUCTION

The human brain is composed of approximately 100 billion neurons that are interconnected by synapses[1,2]. The synapses facilitate communication between neurons by using neurotransmitters, which are small chemical bursts that transmit information across the synaptic gap[3,4]. They are synthesized in nerve cells (neurons) and stored in vesicles at the end of the neuron's axon[4,5,6]. When an electrical signal, called an action potential, reaches the end of the axon, it triggers the release of neurotransmitters into the synapse, the small gap between the axon and the adjacent neuron[7]. Neurotransmitters bind to receptors on adjacent neurons' dendrites or cell bodies. Depending on the type of neurotransmitter and receptor, this binding can cause either an excitatory or inhibitory response[8]. For example, glutamate is an excitatory neurotransmitter that increases the likelihood of an adjacent neuron firing an action potential, while Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that decreases the likelihood of an action potential. As the brain ages, diseases, illnesses, and injuries can damage or destroy synapses, resulting in weakened connections between neurons that slow down communication[9]. This can lead to normal age-related changes in memory and thinking, but it does not typically cause confusion, disorientation, or other cognitive impairments that interfere with daily life[10].

Dementia is a condition characterized by a decline in cognitive function that interferes with daily activities, caused by the loss of neurons and their connections in the brain[11]. The term comes from the Latin word "dement", meaning "madness"[12]. This loss of neurons can lead to a variety of symptoms, including memory loss, confusion, and changes in behavior and mood[13]. Dementia encompasses several types of neurological disorders, including vascular dementia, Alzheimer's disease, frontotemporal dementia, Lewy body dementia mixed dementia, and less common types such as Parkinson's disease dementia, Huntington's disease dementia, and Creutzfeldt-Jakob disease[1415]. Alzheimer's disease is the most prevalent type, making up approximately 60-80% of all cases[16].

1.1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurological disorder that affects memory, thinking, and behavior[17]. Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, who first described the disease in 1906. Dr. Alzheimer had been treating a patient named Auguste Deter, who was experiencing memory loss, confusion, and other cognitive symptoms. After Deter's death,

Dr. Alzheimer examined her brain and found unusual deposits of beta-amyloid protein and tangled fibers in the brain tissue[18]. The exact cause of AD is not fully understood, but it is believed to be caused by a combination of genetic, environmental, and lifestyle factors. The symptoms of AD usually develop gradually and worsen over time. Symptoms of AD may include memory loss, confusion, difficulty with language and communication, changes in mood and behaviour, and difficulty with daily activities[19].

AD is the most common form of dementia, affecting over 50 million people worldwide. If no cure or preventative measures are found, this number is expected to significantly increase to 152 million by 2050[20]. The prevalence of AD increases with age, with 2-3% of those aged 70-75 years having AD, rising to 20-25% of those aged 85 years or older[21]. It is unclear whether the prevalence of AD is continuing to increase or level off. Women are more likely to develop AD than men, mainly due to age-adjusted risk[22]. Social and economic factors also influence the general prevalence of AD among nations[23].

AD is associated with decreased levels of acetylcholine (ACh) in synapses, extracellular beta-amyloid (Aβ) plaques, and intraneuronal tangles of tau protein[24]. Low ACh levels are thought to be responsible for reasoning and memory impairments. Aβ plaques can disrupt signal transfer from neuron to neuron, leading to cell death, while tau tangles inside neurons block the transport of other important nutrients[25]. Initially, the brain can compensate for these changes, allowing the person to function normally. However, as nerve cells become damaged, the brain's ability to compensate declines, leading to a marked decline in cognitive function. Plaques and tangles are not only found in specific areas of the brain associated with cognitive abilities, but also in other areas[26]. As the disease progresses, people may experience memory loss, confusion, depression, character changes, loss of interest in activities, and eventually, even basic abilities such as swallowing may be affected[27].

The early symptoms of AD can vary from person to person but usually involve problems with memory, such as forgetting recent events or conversations, misplacing objects, or having difficulty completing familiar tasks. As the disease progresses, additional symptoms may include[28–32]:

- **Difficulty with language**: People with AD may have trouble finding the right words or following a conversation.
- **Impaired judgment**: They may make poor decisions, such as giving away money or falling for scams.
- **Confusion and disorientation**: They may become lost in familiar places, forget where they are, or have trouble recognizing people.
- **Changes in mood and behaviour**: They may become irritable, anxious, or depressed, or show sudden shifts in mood or behaviour.
- **Loss of initiative**: They may lose interest in activities they used to enjoy or have difficulty starting new activities.
- **Difficulty with complex tasks**: They may have trouble with tasks that require multiple steps, such as following a recipe or balancing a check book.
- **Problems with spatial orientation**: They may have difficulty with depth perception or distinguishing colours and contrasts.
- **Changes in personality**: They may become more withdrawn or exhibit unusual behaviour, such as speaking incoherently or engaging in repetitive actions.

As AD develops, the symptoms worsen and individuals may require more extensive care and assistance. As the disease progresses, they may experience difficulties with communication, recognizing familiar faces, and performing everyday tasks such as eating, bathing, and getting dressed. The progression of the disease is classified into seven stages, based on how cognitive and functional abilities are affected after the onset of symptoms[33–37]

Stage 1: No cognitive decline

- In this stage, the individual shows no noticeable changes in cognitive function.

Stage 2: Very mild cognitive decline

- The person may notice minor memory problems or difficulty finding words.

Stage 3: Mild cognitive decline

- The person may have trouble concentrating, experience memory lapses, and have difficulty with problem-solving or planning.

Stage 4: Moderate cognitive decline

- Memory loss becomes more apparent, and the person may struggle with basic arithmetic, become disoriented regarding time and place, and have difficulty with complex tasks such as managing finances.

Stage 5: Moderately severe cognitive decline

- The person may have trouble dressing appropriately, may experience confusion about their location or time of day, and may need help with basic activities of daily living such as bathing and grooming.

Stage 6: Severe cognitive decline

- In this stage, memory loss is severe, and the person may have difficulty recognizing loved ones or familiar objects. They may need assistance with toileting, eating, and other basic activities.

Stage 7: Very severe cognitive decline

- This is the final stage of the disease, in which the person loses the ability to communicate, become bedridden, and require constant care.

1.1.1 Causes and pathophysiology

The underlying causes of AD are still unclear[38]. However, several factors have been suggested to contribute to its development, including reduced levels of the neurotransmitter ACh, buildup of the Aβ peptide, accumulation of hyperphosphorylated tau protein, disturbances in biometal homeostasis, oxidative stress, neuroinflammation and mitochondrial dysfunction[39,40]. Based on these factors, several hypotheses have been proposed to explain the pathophysiology of AD.

1.1.1.1.Cholinergic hypothesis

The cholinergic system plays a crucial role in various physiological processes, including attention, learning, memory, stress response, arousal, sleep, and sensory processing[41]. Cognitive and behavioral impairments in AD are thought to be associated with deficits in cholinergic transmission and loss of cholinergic neurons located in the basal forebrain, which can impact cortical and hippocampal functions[42]. Acetylcholine (ACh) is synthesized from acetyl-CoA and choline by the enzyme choline acetyltransferase (CHAT) and is released into the synaptic cleft, where it binds to postsynaptic muscarinic and nicotinic receptors. The availability of ACh at the

synapse is tightly regulated by the enzyme acetylcholinesterase (AChE), which hydrolyzes ACh to acetic acid and choline, which is then recycled by the presynaptic neurons[43, 44](**Figure 1.1**).

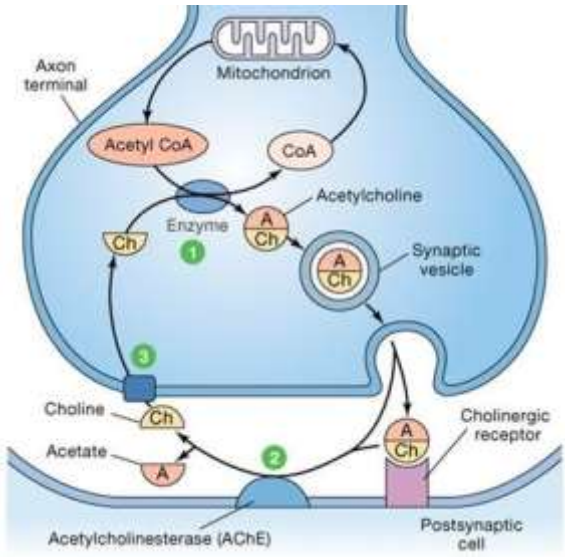

Figure 1.1 Cholinergic hypothesis explaining AD

Two enzymes called AChE and butyrylcholinesterase (BuChE) are important for cholinergic neurotransmission in the central nervous system. They work by breaking down ACh. Even though they are coded by different genes, AChE and BuChE have many similarities, particularly in their active sites[45]. AChE has two binding subsites, the catalytic active site (CAS) and the peripheral anionic site (PAS). The CAS is responsible for maintaining cholinergic neurotransmission, while the PAS is associated with the formation of β-amyloid fibrils that contribute to plaque deposition in AD. In healthy brains, AChE is more active than BuChE and breaks down about 80% of ACh. However, studies have found that as AD progresses, the activity of BuChE increases by 40-90%, while that of AChE decreases in the hippocampus and temporal cortex[46]. This imbalance in cholinergic transmission is thought to play a role in the progression of AD. AChE inhibitors that block both the CAS and PAS of the enzyme can elevate ACh levels and improve cognitive deficits in AD patients, and have also been found to have disease-modifying effects by inhibiting amyloid plaque formation[47].

BuChE has several functions in both neural and non-neural processes. Studies have shown that elevated levels of BuChE in the cortex are linked to major hallmarks of AD, such as the accumulation of the Aβ peptide and hyperphosphorylated tau protein aggregation[48]. Therefore,

there is a need for novel therapies that target both cholinesterases, highlighting their important role. Out of the four FDA-approved drugs for AD treatment, three are AChE inhibitors that function by inhibiting the AChE[49].

1.1.1.2. Amyloid hypothesis

The brains of individuals with AD exhibit two significant pathological features: extracellular Aβ plaques (senile plaques) and intraneuronal tangles of hyperphosphorylated tau protein (neurofibrillary tangles)[50]. These deposits were identified over a century ago, but Aβ was not isolated until 1984 by a pathologist named George Glenner from the University of California. Glenner also discovered that Aβ is produced from a membrane glycoprotein called amyloid precursor protein (APP). APP can be cleaved by proteases through two pathways: the non-amyloidogenic α-pathway and the amyloidogenic β-pathway **(Figure 1.2).**

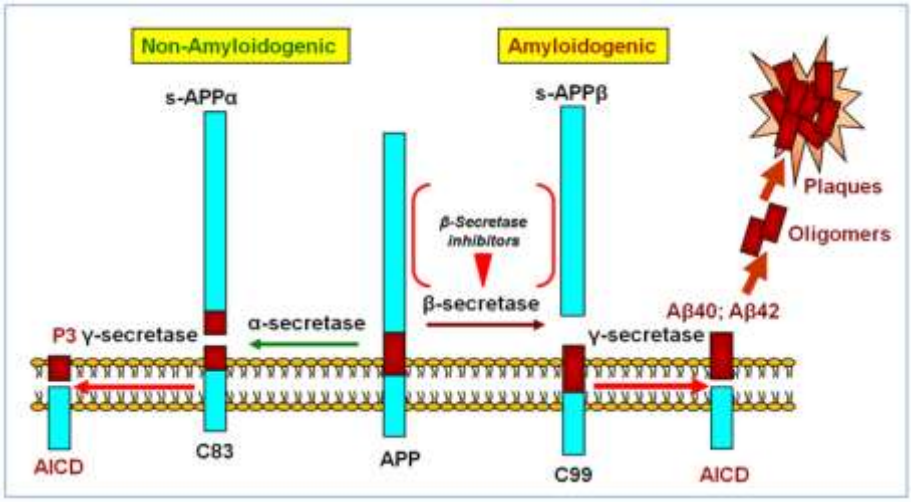

Figure 1.2 Amyloid cascade hypothesis of AD

Normally, APP is cleaved by α- and γ-secretases in the α-pathway, which produces a soluble extracellular APP fragment (sAPPα) and C83 fragment that is further cleaved by γ-secretase to p3 fragment[51]. The physiological role of the p3 fragment is not yet fully understood. The α-pathway is not involved in the production of Aβ, and is therefore considered the non-amyloidogenic pathway. In the β-pathway, APP is initially cleaved by β-secretase (BACE-1) to produce the C-terminal fragment (C99) and a soluble extracellular fragment (sAPPβ). C99 is then cleaved by γ-secretase to produce Aβ peptides containing 38-43 amino acids, including $Aβ_{40}$ and $Aβ_{1-42}$. Aβo is

the primary product of proteolytic cleavage, while $A\beta_{1-42}$ is more fibrillogenic[52]. The Aβ monomers undergo a process of misfolding and aggregation, resulting in the formation of amyloid fibrils and extracellular plaques. These plaques are considered to be neurotoxic and activate inflammatory mediators such as Tumor necrosis factor alpha (TNF-α) and Interleukin (IL-6), while also generating reactive oxygen species (ROS) that negatively affect the normal functions of neurons[53]. The proposed defect in Aβ production or clearance mechanisms in the brain is believed to play a critical role in the development of AD and subsequent neuronal loss.

1.1.1.3. Tau protein hypothesis

Tau protein, a crucial microtubule-associated protein (MAP), plays a vital role in maintaining the stability and dynamics of microtubules (MTs), axonal transport, and neurite outgrowth through its highly soluble form in normal phosphorylation states[54]. However, tau is regulated primarily by post-translational modifications (PTMs), including truncation, phosphorylation, acetylation, glycation, and methylation. Among these PTMs, phosphorylation is the most common[55]. Hyperphosphorylation of tau, which can be induced by the overexpression of GSK-3β, is highly evident in AD brains, leading to around a 3-fold increase compared to normal brains[56]. This hyperphosphorylation results in MT disintegration and filament formation, as illustrated in **Figure 1.3**. Consequently, the abnormal accumulation of paired helical filament (PHF) tangles, consisting of insoluble structures of sequestered normal tau, ubiquitin, MAP-1, and MAP-2, alters cytoplasmic functions, impedes axonal transport, and ultimately causes cell death[57].

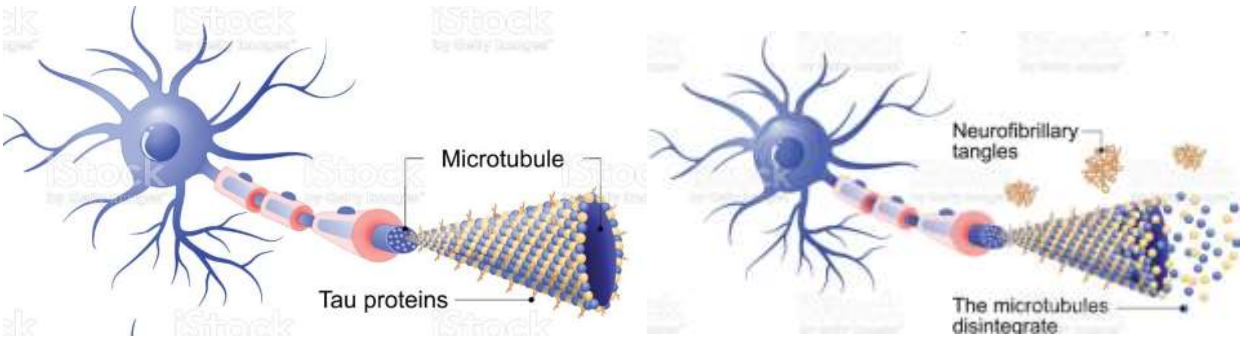

Figure 1.3. Formation of neurofibrillary tangles illustrating tau hypothesis of AD

1.1.1.4.Oxidative stress

Oxidative stress is considered to be an early event in the development of AD, preceding all other pathological hallmarks[58]. Reactive oxygen species (ROS) are produced under normal physiological conditions and are usually kept under control by a delicate balance between their generation and clearance by antioxidant enzymes and compounds such as superoxide dismutase, catalase, ascorbic acid, glutathione, and vitamin E[59]. When this balance is disrupted, either due to increased ROS production or a weakened antioxidant defense system, the redox equilibrium of cells is disturbed, leading to excessive ROS production. In addition, redox-active metal ions such as Fe(II/III) and Cu(III), in combination with Aß, can generate ROS through Fenton-like reactions[60,61]. ROS can damage biomolecules such as proteins, lipids, and nucleic acids, ultimately resulting in tissue damage via necrosis and apoptosis[62].

1.1.1.5. Metal ion hypothesis

Enzymes and intracellular signaling proteins depend on metals for their proper functioning, and the levels of these metals are tightly regulated in healthy individuals[63]. However, in cases of normal aging or neurodegenerative diseases like AD, the homeostasis of these metals is disturbed, leading to dysregulated metal-dependent enzyme functions, mitochondrial dysfunction, and the production of ROS, all of which are associated with AD[64]. The aggregation of Aβ precursor protein (APP) mediated by metals is initiated by Cu^{2+} ion coordination with APP's amino-terminus, leading to the depletion of neuronal Cu^{2+}. The resultant decrease in cellular Cu^{2+} triggers the expression of APP mRNA, leading to the overproduction of $A\beta_{40-42}$[65]. The Aβ protein can bind directly to copper and zinc but not to iron or other metal ions. Low concentrations of Zn^{2+} have been shown to inhibit y-secretase activity, while β-secretase interacts with superoxide dismutase-1 through its C-terminal cytoplasmic domain, which contains a Cu^{2+} binding site. Aβ peptides form complexes with Cu/Zn metals, resulting in neurotoxicity through various mechanisms such as increased Aβ fibrilization, Aβ oligomerization, and ROS generation, all of which contribute to oxidative stress and ultimately lead to cell death[66,67].

Metal-related variations are also observed in the tau protein, which binds to Cu^{2+} in a pH and stoichiometric-dependent manner, resulting in a conformational change in tau. Hyperphosphorylation of tau protein is modulated by Cu through the activation of GSK-3β and

CDK5/p25 complex, both of which play crucial roles in the formation of PHFs, leading to tau protein aggregation and the formation of neurofibrillary tangles[68].(**Figure 1.4**)

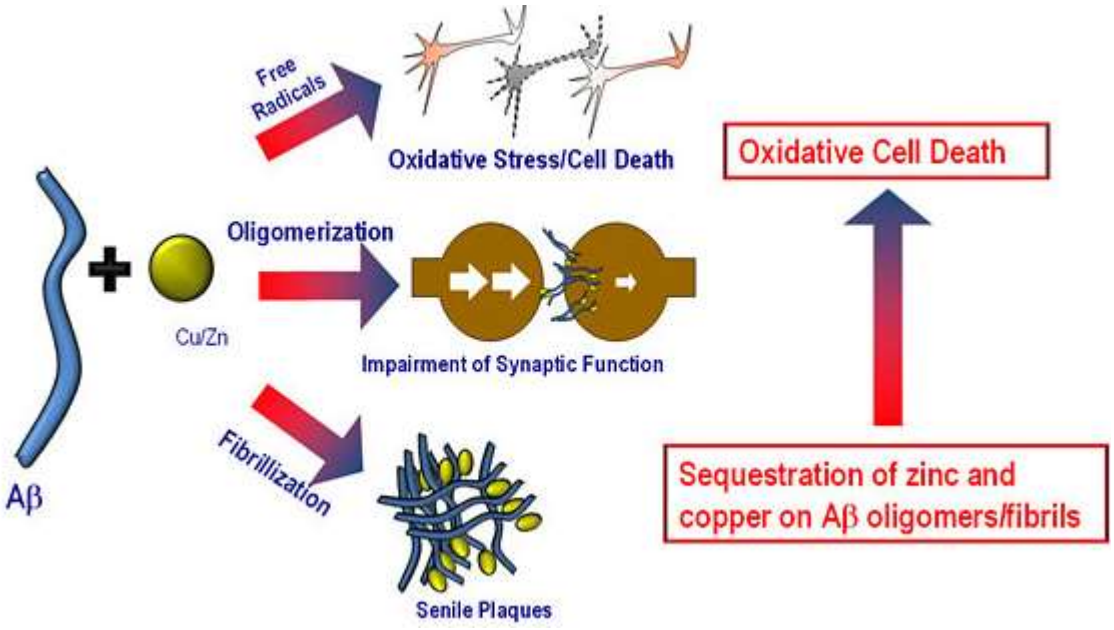

Figure 1.4. Metal mediated toxicity to neuronal cell

1.1.1.6 Monoamine Oxidase hypothesis in AD

Monoamine oxidase (MAO) is an enzyme that breaks down neurotransmitters in the brain, including epinephrine, norepinephrine, dopamine, serotonin, and β-phenylethylamine. There are two types of MAO: MAO-A and MAO-B[69]. MAO-B levels are increased in the brains of AD patients and contribute to oxidative stress, which is a hallmark of the disease. MAO-B inhibitors have been shown to protect against cognitive decline and reduce the accumulation of amyloid-beta and tau proteins in animal models of AD[70]. They may also have potential as disease-modifying agents for AD by reducing neuroinflammation and promoting neuroprotection, although more research is needed to fully understand their role in AD[71,72].

In addition to the cholinergic, Aβ, tau, oxidative stress, metal and MAO hypotheses other factors like excitotoxicity, apoptosis, neuroinflammation, and others are also reported to contribute to the complex pathology of AD[73].

1.2 Recent Advances in AD

Currently, the multi-target drug (MTD) approach is widely used to treat multifactorial diseases like AD[74]. MTDs are designed by combining two or more pharmacophoric structural features of bioactive drugs that act on different targets into a single molecule. While the MTD strategy holds promise as a rational approach, the development of an approved drug that progresses from clinical trials to the market is yet to be achieved[75].

There were over 140 agents with diverse mechanisms of action registered in clinical trials for AD[76] until March, 2022. A search conducted on clinical trials using the term "Alzheimer's" in the disease field and selecting interventional studies revealed that there are currently 111 clinical studies in phase 2/3 and 29 in phase 3 clinical trials[77]. The majority of therapeutic agents in the pipeline target various aspects of AD pathology, including amyloids (such as AChEI and BACE inhibitors), tau proteins, mitochondrial dysfunction, oxidative stress, metal dysregulation, neuroinflammation, and other miscellaneous targets, aiming to reverse the progression of AD.

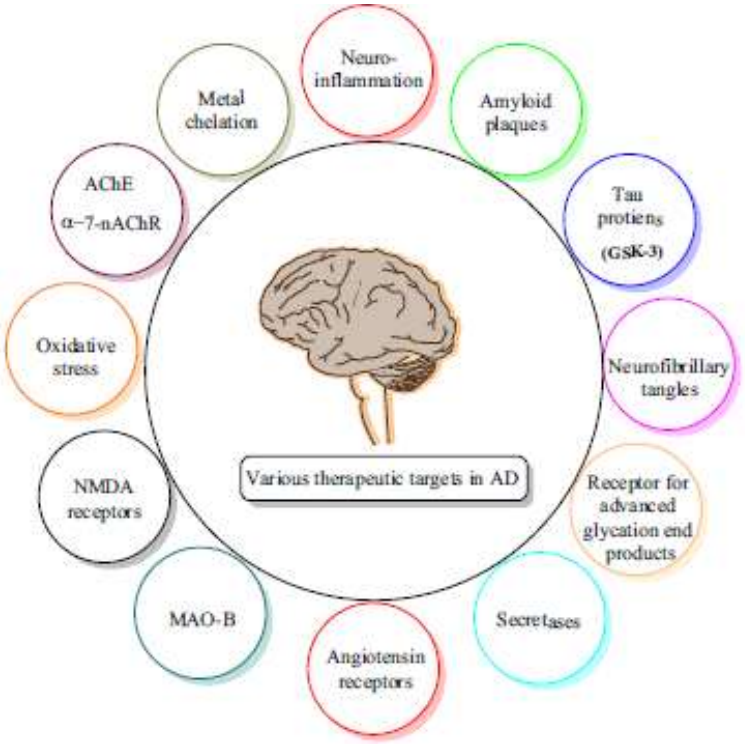

Figure 1.5. Various therapeutic approaches used to develop agents for AD

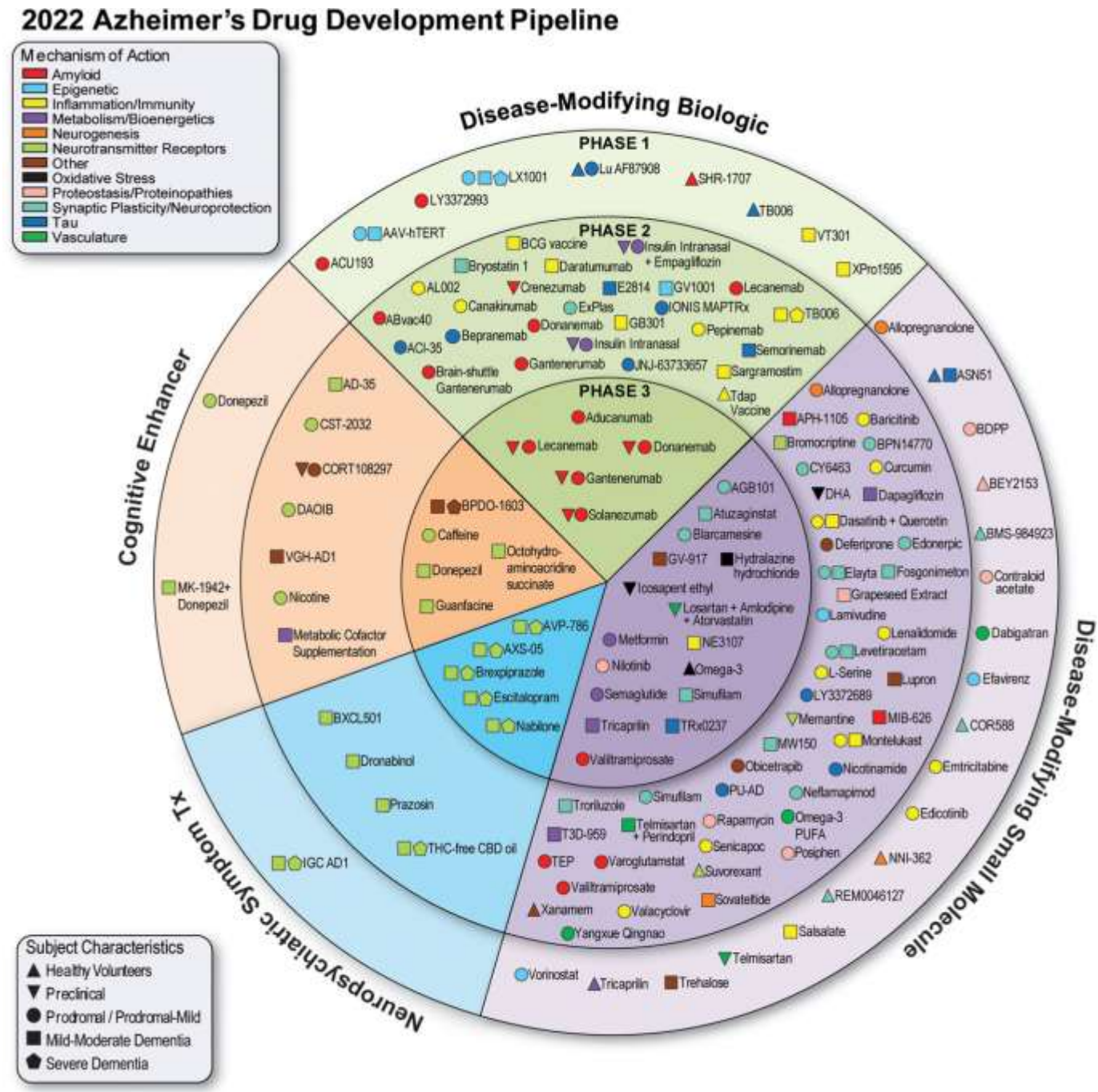

Figure 1.6: Agents in clinical trials for treatment of AD in 2022

Various therapeutic approaches used to develop agents for AD are illustrated in **Figure 1.5** and the status of selected agents tested in clinical trials is presented in **Figure 1.6**. The inner ring shows Phase 3 agents; the middle ring comprises Phase 2 agents; the outer ring presents Phase 1 therapies; agents in green areas are biologics; agents in purple are disease-modifying small

molecules; agents in orange are symptomatic agents addressing cognitive enhancement or behavioral and neuropsychiatric symptoms; the shape of the icon shows the population of the trial; the icon color shows the Common Alzheimer's Disease Research Ontology (CADRO)-based class of the agent[77].

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