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Advancement and Controversies in Alzheimer's Disease: Technological Innovations and the Way Forward

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia worldwide, posing a significant global health burden. Despite decades of research, its precise pathogenesis remains incompletely understood, with emerging evidence pointing to a multifactorial etiology involving amyloid-beta (Aβ) accumulation, hyperphosphorylation, neuroinflammation, oxidative stress, mitochondrial dysfunction, and synaptic loss. Genetic and environmental factors further contribute to disease onset and progression, particularly in sporadic AD. Recent therapeutic advances have focused on targeting Aβ and tau pathology, modulating neuroinflammation, and enhancing neuronal survival. However, most clinical trials have yielded limited success, highlighting the urgent need for multifaceted and personalized therapeutic strategies. This review synthesizes current insights into the molecular mechanisms underlying AD and evaluates recent breakthroughs in drug development, immunotherapy, and lifestyle-based interventions. A deeper understanding of AD pathogenesis may pave the way for more effective diagnostics and therapeutic approaches, ultimately improving patient outcomes and quality of life.

Introduction

Background of Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles from amyloid-β peptide A build-up in the medial temporal lobe and neocortical areas of the brain (Lim et al., 2020). The disease clinically presents with a slow progression of cognitive and behavioral impairment. Approximately 50 million people across the globe suffer from the most common manifestation of the disease dementia and this figure is expected to double every 5 years, with an estimated 152 million cases by the year 2050 (Livingston et al., 2020a; Yiannopoulou & Papageorgiou, 2020).

Clinical diagnostic criteria for the disease were developed in 1984 by the Alzheimer's Disease and Related Disorders Association and the National Institute of Neurological and Communicative Disorders and Stroke study group. The criteria include the following:

Probable Alzheimer's disease: identified by dementia diagnosis through neuropsychological testing, progressive amnesia, and impaired activities of daily living (Neugroschl & Wang, 2016);

Possible Alzheimer's disease: devoid of neurologic and psychiatric disorders, and comorbidities, such as a systemic or brain illness; can also induce dementia, although not the primary cause (Neugroschl & Wang, 2016);

Definite Alzheimer's disease: confirmed by histopathological testing (Neugroschl & Wang, 2016).

THE CHARACTERISTICS OF AD

Prevalence

AD is the principal cause of dementia in older individuals as its prevalence rises with age. In individuals from 65 to 74 years of age, the incidence is about 3%; those between 75 and 84 years of age have a 19% incidence, and those above 84 years of

age have a 47% incidence. Alzheimer's cases are mostly sporadic, with 5%– 10% being hereditary forms, seen at an earlier onset (Eimer et al., 2018).

Mechanism

AD results from the intracranial build-up of two proteins, Aβ and tau, forming extracellular neuritic plaques and intracellular neurofibrillary tangles, respectively. This results in neuronal dysfunction and death, and inflammatory responses. When amyloid precursor protein (APP) is cleaved by β-amyloid-converting enzyme and γ-secretase instead of α-secretase and γ-secretase, it releases Aβ peptides, which culminate in the accumulation of plaques and tangles (Robert-Jiménez et al., 2023).

Risk factors

Multiple loci have been associated with the increased generation and deposition of Aβ protein, such as mutations in components of γ-secretase (encoded by the presenilin 1 or 2 genes), or mutations in the APP gene on chromosome 21. Population with an extra copy of the APP gene, including patients with Down Syndrome or with small interstitial duplications of the gene, present at higher risk (Lim et al., 2020). Moreover, the apolipoprotein E ε4 allele on chromosome 19 is responsible for approximately one fourth of the risk of developing late-onset AD. Despite genetic predisposition, age-related mechanisms are critical for AD development, whereas even in genetically susceptible and immunosuppressed individuals (Uwishema et al., 2022) the illness does not manifest itself until later in life. Other risk factors include hypertension, diabetes, hyperlipidemia, cerebrovascular diseases, family background of dementia, head trauma, female sex, poor education level, and environmental factors such as toxic metals, insecticides or pesticides, industrial or commercial waste, antimicrobial agents, and air impurities (Neugroschl & Wang, 2016).

Epidemiology

Alzheimer disease is characterized by progressive cognitive decline usually beginning with impairment in the ability to form recent memories, but inevitably affecting all intellectual functions and leading to complete dependence for basic functions of daily life, and premature death. The pathological manifestations of Alzheimer disease include diffuse and neuritic extracellular amyloid plaques and intracellular neurofibrillary tangles accompanied by reactive microgliosis, dystrophic neurites, and loss of neurons and synapses (Serrano-Pozo et al., 2011). While these pathological lesions do not fully explain the clinical features of the disease, it has been hypothesized that alterations in the production and processing of amyloid b-protein may be the principal initiating factor (Adelman, 2021). The underlying causes of these multifaceted changes remain unknown, but advancing age, and genetic and nongenetic antecedent factors are thought to play important roles. Alzheimer disease is the most frequent cause of dementia in Western societies. In the US, approximately 5.5 million people are affected, and the prevalence worldwide is estimated to be as high as 24 million. Given that both established and developing nations are rapidly aging, the frequency is expected to double every 20 years until 2040. The magnitude of the impending rise owing to societal aging is considerable and will be a costly public health burden in the years to come.

Incidence and prevalence

In 2018, Alzheimer's Disease International estimated a dementia prevalence of about 50 million people worldwide, projected to triple in 2050, with two-thirds living in low-income and middle-income countries (Prince et al., 2016). The most recent data estimate that dementia prevalence in Europe will double by 2050 (Bezprozvanny &

Communications, 2022). Accumulating evidence suggests that the incidence of dementia is declining in high-income countries, although evidence for a decline in prevalence is less convincing (Mayeda et al., 2017).

Mortality

The relatively stable prevalence despite decreasing incidence could be explained by a long disease duration, although studies on mortality do not support this notion. A US-based study evaluating survival after a dementia diagnosis in almost 60 000 individuals reported survival times of 3–4 years (Vermunt et al., 2019). In an European, memory clinic-based cohort, median survival time was 6 years after a diagnosis of Alzheimer's disease dementia (Jack et al., 2019). This estimate coincides with a multicenter study that provided estimates of duration not only of the dementia stage, but also of the prodromal (mild cognitive impairment) and of preclinical disease stage of Alzheimer's disease (van der Lee et al., 2018). For an individual aged 70 years, duration estimates are 10 years for the preclinical stage, 4 years for the prodromal stage, and 6 years for the dementia stage of Alzheimer's disease, totaling 20 years. A first attempt at estimating prevalence on the basis of a biological (rather than clinical) definition showed that, at the age of 85 years, the prevalence of biologically defined Alzheimer's disease is 3 times higher than that of clinically defined Alzheimer's disease (Babapour Mofrad et al., 2020).

Risk factors for dementia and Alzheimer's disease

The strongest risk factors for Alzheimer's disease are advanced age (older than 65 years, although this is not a fixed definition) and carrying at least one APOE ε4 allele (Livingston et al., 2020b). Moreover, women are more likely to develop Alzheimer's disease than are men, especially after the age of 80 years.20 Women are also more likely to have a higher tau load, despite having a similar amyloid β burden.(Lane et al., 2020). In addition, cardiovascular risk factors and an unhealthy lifestyle have been associated with an increased risk of dementia. The Lancet Commission on Dementia Prevention estimated that 12 modifiable risk factors together account for roughly 40% of the worldwide risk of any type of dementia (Gustavsson et al., 2020). These estimates illustrate that prevention by intervening on modifiable risk factors is of great relevance, even if most of the dementia burden cannot be prevented via a lifestyle-intervention approach (Cantón-Habas et al., 2020). However, evidence suggests that vascular risk factors do not increase the risk of Alzheimer's disease pathology as measured by cerebrospinal fluid biomarkers or PET (Zhang et al., 2024). This evidence implies that lifestyle and vascular risk factors contribute to dementia, but not via the Alzheimer's disease pathway.

Global Burden

Alzheimer's disease (AD) and other dementias are the seventh leading cause of death globally, having affected more than 55 million people. The cost of dementia will rise to exceed $2.8 trillion by 2030 (Livingston et al., 2024). The poor health and high expense of care caused by dementia place significant pressure on families, communities, healthcare systems, and social safety nets (Livingston et al., 2024). Despite substantial progress in the identification and treatment of this disorder, dementia remains incurable. "Prevention is better than cure" is still the primary call to action in the global strategy to address dementia until the healthcare system can universalize access to possible future treatments (Ye et al., 2023). Besides aging, genetics, and family history, as estimated by the Lancet Commission, approximately 45% of dementia cases could be attributed to 14 modifiable risks (Shen et al., 2023). Specific interventions can help prevent or delay cognitive decline and dementia (Wu

et al., 2024). Metabolic disorders, such as obesity and hyperglycemia, are closely related to changes in brain structure, including cortical surface area, thickness, and subcortical volumes. These modifications not only accelerate the process of brain aging but also substantially increase the risk of developing neurodegenerative diseases (Barber et al., 2021). From 2000 to 2021, the number of global all-age disability adjusted life years (DALYs) attributable to metabolic risks increased from 319 million to 476 million, representing a rise of nearly 50%. High fasting plasma glucose (FPG) and high body mass index (BMI) ranked fifth and sixth among the 88 risk factors impacting the global disease burden, accounting for 5.4% and 4.5% of total DALYs, respectively (Cho et al., 2018). Several studies have evidence that the disease burden of dementia is increased by elevated levels of exposure to various metabolic risk factors (Cho et al., 2018). The 2024 report on dementia prevention, intervention, and care research further emphasizes that approximately 3% of dementia cases can be related to obesity and diabetes. Additionally, the metabolic risk distribution differs significantly among populations of varying ages, genders, and regions due to physiological alterations, accumulated lifestyle influences, and disparities in healthcare accessibility. This variance has an indirect impact on the epidemiological trends in the burden of dementia.

Dementia is a syndrome, with the most common type being Alzheimer's disease (Srivastava et al., 2021). Clinically, Alzheimer's disease is mainly characterized by comprehensive dementia, including memory disorder, cognitive disorder, executive dysfunction, and personality and behavior changes, and is accompanied by mental disorder symptoms in most patients (Gao & Liu, 2021).

AD Pathophysiology

Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus. The deposition of tangles follows a defined pattern, starting from the trans-entorhinal cortex; consequently, the entorhinal cortex, the CA1 region of the hippocampus and then the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. The extent and placement of tangle formation correlates well with the severity of dementia, much more so than numbers of amyloid plaques (Kumar & Singh, 2015). The accretion of tau proteins correlates very closely with cognitive decline and brain atrophy, including hippocampal atrophy. In the neuropathology of Alzheimer's disease there is a loss of neurons and atrophy in temporofrontal cortex, which causes inflammation and deposit the amyloid plaques and an abnormal cluster of protein fragments and tangled bundles of fibers due to this there is an increase in the presence of monocytes and macrophages in cerebral cortex and it also activates the microglial cells in the parenchyma (Mishra & Palanivelu, 2008). Summary of pathophysiology of AD are shown in Figure 1.

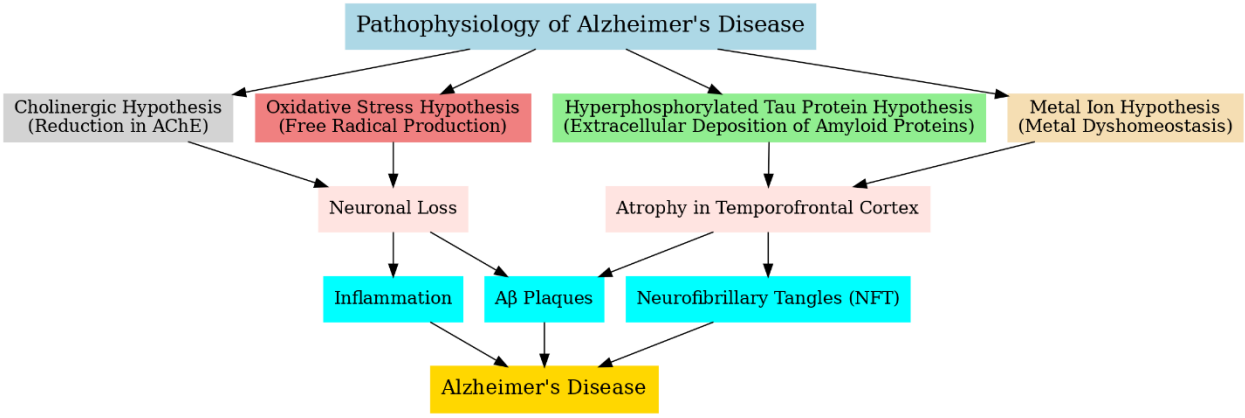

Figure-1: Pathophysiology of Alzheimer's Disease.
Key pathogenic pathways converge to cause neuronal loss, amyloid-β plaques, and neurofibrillary tangles, leading to Alzheimer's disease.

Amyloid Cascade Hypothesis

AD is characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles in the brain." While there may be many causes of Alzheimer's disease (AD), the same pathological sequence of events is likely to occur in all cases. The pathological cascade for the disease process is likely to be beta-amyloid deposition—tau phosphorylation and tangle formation neuronal death. The development of biochemical understanding of this pathological cascade will facilitate the rational design of drugs to intervene in this process" (Järemo et al., 2019). According to the amyloid cascade hypothesis, AD begins in the brain with Aβ peptide accumulation, aggregation, and amyloid formation. Formulated in 1991-1992, the hypothesis has dominated AD research, drug discovery, and clinical trial studies ever since (Selkoe & Hardy, 2016; Hardy, 2017). The hypothesis is supported by the molecular genetics of the early-onset familial forms of AD, caused by inherited dominant mutations in the APP, PS1 or PS2 genes. Some 300 pathogenic mutations have been identified which cause AD at age 22–60, the age of onset depending on the gene and the particular mutation. For example, the PS1 mutation E280A causes AD at the median age of 49. PS1 has the most mutations, which can result in increased, decreased or no Aβ peptide production, or in increased or decreased Aβ42/40 ratio (see below), Aβ42 being the more hydrophobic peptide prone to aggregation and amyloid formation (Karran & De Strooper, 2016; Sun et al., 2017). Several observations and experimental studies are against the hypothesis. The natural history of AD progression does not correlate with brain amyloid formation, therefore amyloid cannot be causally linked to AD (Rosenberg, 2015). Brain amyloid PET scans of cognitively unimpaired people often look the same as the PET scans of people with AD (Mountz et al., 2015). At brain autopsy, 30% of people without AD had typical amyloid formation characteristics of AD brains. In short, as David Snowdon put it in his great 'Nun Study' in 1997: "Brain amyloid is not synonymous with dementia" (Snowdon, 1997). The amyloid cascade hypothesis in Alzheimer's disease is also not supported by the ambiguous, quite controversial results of clinical trials of drugs with β- or γ-secretase inhibitors or with anti-Aβ antibodies, especially clinical trials before the introduction of aducanumab to treatment. Two identical Phase 3 clinical trials, EMERGE and ENGAGE, evaluated the safety and efficacy of aducanumab in the treatment of Alzheimer's disease. The data analysis conclusions at the end of the study at 78 weeks were as follows: In EMERGE, high-dose aducanumab reduced the severity of clinical dementia as measured by dementia severity scales. In the ENGAGE study, aducanumab did not reduce pre-study clinical worsening. Even when the drugs

reduced the production of Aβ peptides and amyloid in the brain, they did not clearly slow cognitive decline, or slowed it only slightly. Worse still, the drugs often harmed the study volunteers, causing serious health problems including infections, skin cancers, cerebral vascular edema, cerebral microhemorrhages, severe cognitive decline, and death (Sevigny et al., 2017; Cummings et al., 2021).

Tau Hypothesis and Neurofibrillary Tangles (NFTs)

Tau is a microtubule associated protein (MAP) encoded by the MAPT gene as part of the MAPT/MAP4/MAP2 gene family. Tau plays important roles in defining the structure and function of the neuronal cytoskeleton and in particular the dynamic properties of microtubules (MT) (Goedert et al., 1988). The structure and function of tau have been studied biochemically with a focus on posttranslational modifications in particular phosphorylation, in cell biology approaches using neuronal cultures that elucidated interactions with MT, axonal growth and transport and by in vivo studies by generating knockout animals. Tau also received intense attention because of its involvement in neurodegenerative disorders related to hyperphosphorylation and mutations leading to aggregation of tau and formation of neurofibrillary tangles (NFTs) (Goedert et al., 1989) which can further propagate (Goedert et al., 1996). The tau hypothesis is that the principle causative substance of AD is tau. In AD brains, 3R and 4R tau is accumulated in a hyperphosphorylated state in the pathological inclusions (Zempel & Mandelkow, 2014). Ultrastructurally, unique twisted fibrils with _80 nm periodicity appearing as paired helical filaments (PHFs) or related straight filaments (SFs) are observed (Braak & Braak, 1991). These pathological inclusions are referred to as neurofibrillary tangles (NFTs) if they are formed in neuronal cell bodies, while they are referred to as threads if they are formed in dendrites or axons. These findings suggested that mis-sorting of tau might induce tau pathology (Bejanin et al., 2017). Neurofibrillary tangles have a lifespan that progresses through three major levels: pretangles, mature tangles, and ghost tangles (Moloney et al., 2021). Pretangles contain diffuse or granular hyperphosphorylated tau in otherwise morphologically normal neurons with perinuclear tau accumulation often observed. Mature tangles are intensely stained bundles of fibers that take the shape of the neuron they occupy. The nucleus may appear shrunken and misplaced toward the cell membrane (Alzheimer et al., 1995). Ghost tangles are the remnants of mature tangles once the neurons have died and are recognized by faintly stained bundles of fibers with no associated nucleus (Alzheimer et al., 1995). We and others have previously provided support that flortaucipir, a tau-PET ligand, recognizes more middling to advanced neurofibrillary tangle maturity levels (mature tangles and ghost tangles) (Lowe et al., 2016; Ono et al., 2017).

Table: Controversies in the Amyloid Hypothesis and Tau Therapies in Alzheimer's Disease

Aspects	Amyloid Hypothesis	Tau Hypothesis
Core idea	Accumulation of β-amyloid (Aβ) plaques triggers AD pathogenesis (Hardy, 2010).	Abnormal, hyper-phosphorylated tau forms intracellular tangles that drive neurodegeneration (Braak et al., 2012).
Supporting evidence	Early Aβ deposition; familial AD genes (APP/PSEN) point to amyloid processing (Hardy, 2010).	Tau tangle burden correlates more closely with disease stage/severity than amyloid plaques (Braak et al., 2012).
Key controversies	Many anti-amyloid antibodies clear plaques but show **modest or inconsistent clinical benefit,** and carry ARIA risks (edema/microbleeds). Also,	Unclear if tau is **a primary trigger** or largely **downstream of amyloid;** major anti-tau antibodies have **not shown robust clinical benefit** to date(Braak et

	some people have high amyloid but **no dementia (Van Dyck et al., 2023).**	al., 2012; Guo et al., 2022).
Current status	Lecanemab and donanemab slowed decline **modestly** vs placebo in early AD, with higher ARIA rates than placebo (Mintun et al., 2023; Van Dyck et al., 2023).	Multiple anti-tau mAbs (e.g., semorinemab, gosuranemab, tilavonemab) have **not met primary clinical endpoints** in Phase 2/3 studies so far (Guo et al., 2022).
Overall debate	Amyloid alone does not fully explain progression; benefit may depend on **very early treatment** and careful risk management (Mintun et al., 2023).	Targeting tau alone may be insufficient; AD is likely **multifactorial,** and **combined or multimodal** approaches are being explored (Guo et al., 2022).

Neuroinflammation and Immune System Dysfunction

The term neuroinflammation is generally used to describe inflammation within neural tissue. A diverse range of cell types and molecular processes characterize neuroinflammation, these include alterations in microglia, astrocytes, cytokines, and chemokines within the central nervous system (CNS). Neuroinflammation can be induced by a number of different modalities ranging from environmental challenges (e.g., diet, toxin exposure), mental and physical health illnesses (e.g., substance use disorders, traumatic brain injury), to genetic predisposition. There is strong evidence linking neuroinflammation to neurodegenerative conditions such as Alzheimer's disease and multiple sclerosis however the focus of this special issue is on the role of neuroinflammation in psychiatric disorders which has been less extensively examined. The primary methods for characterizing neuroinflammation across conditions include the quantification of alterations in the number, morphology and gene expression of glial cells within the CNS and more recent techniques, such as resting state functional connectivity magnetic resonance imaging (rs-fcMRI) to assess inflammation-associated changes in connectivity of large scale networks that lead to cognitive and behavioral changes (Notter et al., 2018). Additionally, the use of novel radio ligand tracers specific for activated microglia in conjunction with positron emission tomography (PET), is becoming more common to image and assess levels of neuroinflammation in neurodegenerative disorders such as Alzheimer's disease (Brohi et al., 2019), and these tools are starting to be used to characterize neuroinflammation in neuropsychiatric disorders such as schizophrenia and substance use disorders (Dobson et al., 2020). Inflammation is universal, beneficial and restorative. However, after major trauma, it can be lethal. As mentioned earlier, the massive release of DAMPs can overwhelm the system and trigger a hyper inflammatory state that, if not resolved in a timely manner, can lead to immune dysfunction, immunosuppression, infection, sepsis and MODS (Efron et al., 2018) (Osuka et al., 2014) . The disruption can lead to pathological interactions between monocyte, macrophage, NK and DCs, T cell dysfunction, and the development of persistent lymphopenia (Mas-Celis et al., 2021) (Manson et al., 2016; Yang et al., 2019) . Persistent lymphopenia carries a high mortality. Brohi's group recently reported a 45%mortality rate in trauma patients when the lymphocyte count was _ 0.5 _ 109/L at 48 h after hospital admission (Campbell et al., 2022). In addition, the type of trauma determines a patient's susceptibility to persistent lymphopenia and infection, with traumatic brain injury (TBI) patients having disproportionally worse outcomes compared to those with burns, polytrauma or major surgery (Wang et al., 2017). A recent study of Campbell et al. reported that 37% ofTBI patients were lymphopenic on hospital admission, and its persistence was associated with increased risk of mortality and pneumonia ((Bonneville et al., 2010). Wang further reported that up to 83% of severe TBI patients contracted a respiratory infection within 3 days following injury (Wang et al.,

2017), (Ruan et al., 2015). The mechanisms responsible for persistent lymphopenia and immunosuppression are not well understood (Campbell et al., 2022) ,(Gabrilovich & Nagaraj, 2009). The difficulty is that immunosuppression is a highly heterogeneous response involving differential T cell loss, T-cell exhaustion, T-helper 1 (Th1) depression, receptor shedding and expansion of myeloid-derived suppressor cells (MDSCs)that have suppressive activity (Müller-Heck et al., 2021), (Mir et al., 2020). Separating the relative contributions of different immune cell subsets to post-traumatic immunosuppression has been a challenge. In a ground-breaking study, Mansen and colleagues examined early changes in circulating lymphocytes and showed that trauma patients who developed MODS within 24 h had nearly 2-fold higher CD56dim NK cells, 80% lower gamma delta (gd)-low T cells and 4-fold higher IFN-g upon hospital admission, compared to patients who did not (Campbell et al., 2022). CD56dim NK cells are potent mediators of natural and antibody-dependent cytotoxicity and only weakly secrete cytokines (Kimbrell & Beutler, 2001). Moreover, the group showed that the patients who developed MODS also developed lymphopenia within 24 h of injury, which if persisted to 48 h led to high mortality (Campbell et al., 2022). The association between lymphopenia, MODS and decreased frequencies and functional responses of innate T cells in trauma patients suggests that early immuno-inflammatory events may "predetermine" late secondary complications. The rise in NK cells and early fall in gd-low T cells seen in patients who developed MODS may be clinically significant and predict risk for late complications.

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress (OS), which occurs when there is an imbalance between oxidant and antioxidant levels in the cell resulting in increased reactive oxygen species (ROS) production, is another important metabolic facet of AD pathology. Specifically, increased levels of ROS cause damage to macromolecules within the cell, and it is this damage of lipids, proteins, and nucleic acids that give rise to pathological consequences (Bains & Shaw, 1997). In the brain, ROS are eliminated by the free radical scavenger glutathione (GSH) through a chemical reaction that converts GSH to its oxidized state (GSSG) (Calabrese et al., 2014). As such higher intracellular GSH levels protect cells from ROS-mediated insults. Given that neurons are particularly sensitive to oxidative damage due to the brain's substantial metabolic requirements alterations in GSH function can have profound effects on brain and cognitive function. Not surprisingly, research now suggests that GSH deficiencies could play a key role in the pathogenesis of various age-related neurodegenerative disorders, including AD (Bradburn et al., 2019). As with OS, microglia-mediated neuro inflammation adversely affects brain function and is now considered a hallmark feature of various neurodegenerative diseases, including AD(Park et al., 2013). Evidence from brain imaging supports the role of neuro inflammation in the progression of dementia. For instance, a recent meta-analysis of positron emission topography (PET) studies found evidence of increased neuro inflammation during the progression of MCI and AD (Fischer et al., 2015). Notably, pro-inflammatory mediator expression is modulated by mitochondrial dynamics in microglial cells (Calabrese et al., 2014). Furthermore, neuro inflammation and OS are linked closely, as neuro inflammation leads to increased OS which, in turn, causes further neuro inflammation (O'Day, 2025). Across the age-related neurodegenerative disorders, progressive decline in neuronal function and loss of neurons (i.e., synapse loss, dendritic pruning, decreased neuronal repair and restoration) are the key biological underpinnings and the most proximal and robust neurobiological events to explain clinical dementia-cognitive impairment.(Harris et al., 2012)Synapses allow for communication and proper brain function, and synapse loss is the strongest correlate of cognitive decline (Hachinski et

al., 2019) Neurons require a constant supply of energy, with the majority spent on synaptic transmission.(Chan, 2006)The brain lacks energy reserves, and neurons rely on continuous cerebral blood flow for delivery of glucose and oxygen for energy metabolism.(Waller et al., 2013)The brain can regulate its energy supply through neurovascular coupling, whereby neurons signal to dilate local blood vessels to increase its oxygen and glucose supply.(Waller et al., 2013) The relationship between the early cerebral blood flow deficits seen in neurodegenerative disorders and decreased neuronal functioning can be explained by the Calcium Hypothesis (Waller et al., 2013)There are various mechanisms that can deprive neurons of energy, and thereby impair neuronal/synaptic function, including, but not limited to cerebral blood flow deficits, increased blood-brain barrier permeability, neurovascu lar uncoupling, glucose transporter protein defects, and mitochondrial dysfunction.(Waller et al., 2013)Mitochondria are highly dynamic, complex organelles that primarily supply energy, but also play a key role in cell death, signaling pathways, apoptosis, reactive oxygen species (ROS) production, and calcium homeostasis—processes that are all perturbed in neurodegeneration.(Swerdlow et al., 2020) Neurons critically rely on mitochondria and are vulnerable to mitochondrial dysfunction owing to their complex morphology and high metabolic demand. Neuronal dysfunction, the core feature of neurodegenerative disorders, is therefore closely linked with mitochondrial dysfunction.

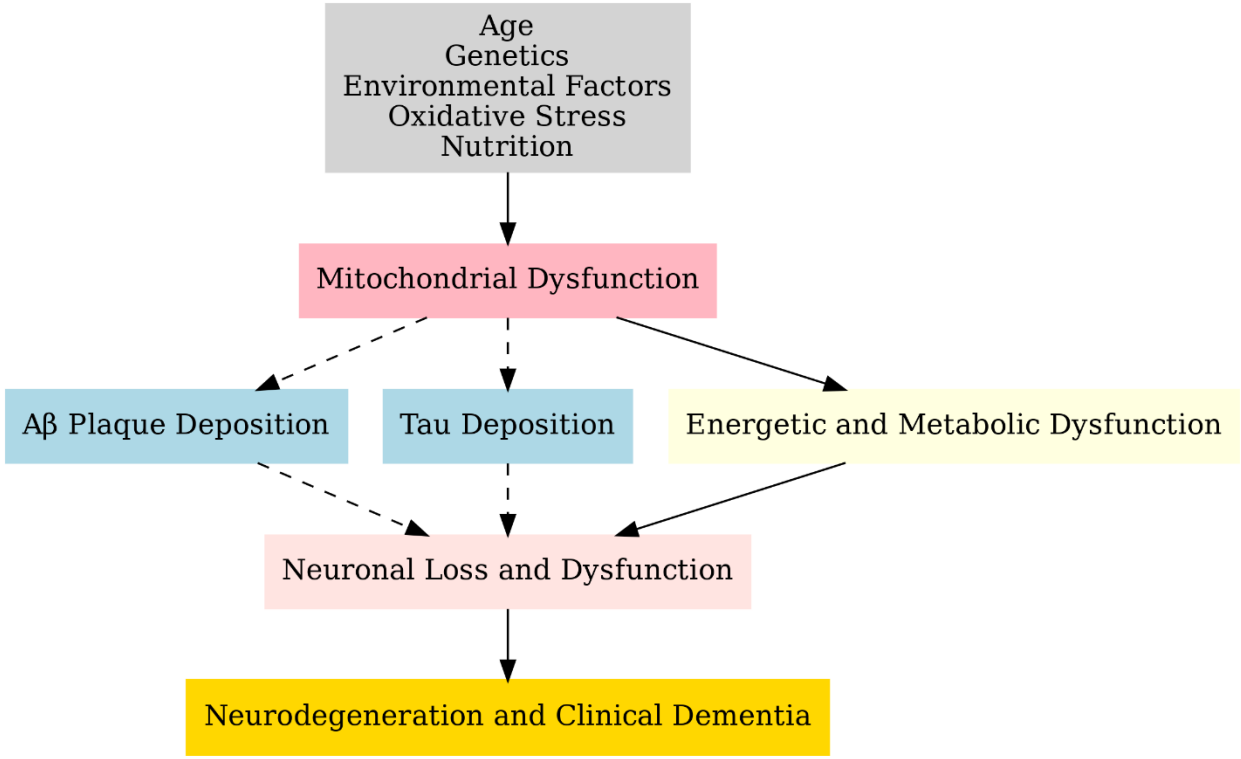

Figure 2. Mitochondrial dysfunction in Alzheimer's disease.
Mitochondrial impairment triggers amyloid and tau pathology, leading to neuronal loss and dementia.

Genetic and Environmental Risk Factors

Alzheimer disease (AD) is the most prevalent neurodegenerative disorder in the human population and underlies 60–70% of the 50 million dementia cases worldwide. Globally, AD is the seventh leading cause of death (Organization, 2020). AD can be classified as early onset AD (EOAD; age of onset ≤60), caused by rare genetic variants of strong effect, or late-onset AD (LOAD; age of onset ≥60), wherein risk is elevated by a spectrum of more common variants, of comparatively small effect (Wingo et al., 2012). EOAD only accounts for 2–10% of all AD cases, which are

highly heritable (92–100%) within families (Wingo et al., 2012; Van Cauwenberghe et al., 2016). These familial cases are most often inherited in an autosomal dominant fashion that can be explained by mutations in the amyloid precursor protein (APP) and presenilin (PSEN1/ PSEN2) genes; however, mutations in these three genes contribute to less than 1% of total AD cases (Van Cauwenberghe et al., 2016). LOAD is responsible for up to 98% of the remaining cases, which are sporadic/multifactorial, as genetic factors account for 53–79% of phenotypic variability. Despite relatively high heritability in both forms of AD, only 30–33% of the phenotypic variance can be attributed to common single nucleotide polymorphisms (SNPs) (Ridge et al., 2016). The strongest known risk variant for both EOAD and LOAD is the ε4 allele of the gene encoding apolipoprotein E (APOE), although the presence of this variant is not sufficient to cause disease. Alone, three common APOE variants (ε2, ε3, and ε4) account for approximately 6% of the genetic contribution to AD risk, and the APOE4 allele contributes 27.3% of the percent attributable fraction (Ridge et al., 2016). Compared to individuals who are homozygous for "wild-type" APOE3, individuals who are heterozygous or homozygous for APOE4 are at threefold or eightfold increased risk for AD, respectively (Avramopoulos, 2009). Those with an APOE2 allele (ε2/ε2 or ε2/ε3 genotypes) have a protective effect against AD compared to other APOE genotypes (ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4) (Avramopoulos, 2009).
The multifactorial nature of AD is highlighted by sex bias in disease incidence, variable age of onset, and variable expressivity of clinical presentation. Hence, in addition to the substantial contribution of genetic factors toward AD risk, disease onset and progression are further modulated by environmental factors. Many early cellular and molecular studies have emphasized the "amyloid cascade hypothesis," suggesting that Aβ deposition marks the pathogenesis of AD. In support of this, certain elements in the human exposome, termed "Alzheimerogens," are thought to promote the production of Aβ plaques; thus, inciting a neuroinflammatory response that results in neurodegeneration (Lafon et al., 2020). For example, pesticides and herbicides have been recognized by epidemiological studies and meta analyses as environmental risk factors for AD/dementia (Gunnarsson & Bodin, 2019).

Current Therapeutic Approaches

A curative treatment of AD remains to be discovered. Currently, the therapeutic armory available focuses on symptom control in milder cases of the disease (Scheltens et al., 2016; Knapskog et al., 2021). Among the pharmacological alternatives available, acetylcholinesterase inhibitors (AChEIs) stand out (Breijyeh & Karaman, 2020). The mechanism of action of AChEIs is based on the inhibition of acetylcholinesterase (AChE) activity, which degrades acetylcholine (ACh), increasing its availability, which is reduced in AD (Rahim et al., 2023; Ullah et al., 2022). Drugs available in this group for the treatment of AD include:

Treatment	Description	References
Donepezil	This drug acts by reversibly binding to AChE, inhibiting ACh hydrolysis, resulting in increased bioavailability of this neurotransmitter at neuronal synapses.	(Breijyeh & Karaman, 2020)
Rivastigmine	This treatment was introduced in 2000 and is indicated for mild and moderate AD. This drug exerts its effect by binding to and inhibiting AChE, increasing ACh levels.	(Breijyeh & Karaman, 2020)

Galantamine	. Its use in mild and moderate AD has been associated with positive evolution of behavior, cognitive performance and development of basic activities of daily living.	(Breijyeh & Karaman, 2020)
Memantine	It is generally well-tolerated and safe as it exerts its effect without altering neuronal synapses.	(Breijyeh & Karaman, 2020)

FDA-Approved Drugs for Symptomatic Treatment

Drug discovery and development is a multi-phase process that takes long years (10–15) of experimenting and optimization with roughly $1–2 billion for every new drug to be approved by Food and Drug Administration (FDA) (Hinkson et al., 2020).Target validation, compound screening, and lead optimization are the first three in silico and in vitro experimentation processes that precede in vivo investigation. Once successfully passed, the drug candidates go into preclinical tests performed on lab animals. This is followed by entry to the three-consecutive clinical trials (phases I–III) which decide the major outcome of the drug in hand. Nevertheless, from drug approval to launch of marketing and distribution, it takes about 1.5 years on average (Dowden & Munro, 2019). For any pharma company or academic institution, the advancement to phase I is an outstanding achievement bypassing rigorous drug optimization stages and preclinical evaluation (Ullah et al., 2020; Hussain et al., 2023). Notably, about 90% of all drugs approval failures are upon phase I advance (Takebe et al., 2018). Such high failure rate is traced to 4 main reasons:

Lack/poor clinical efficacy (accounting for 40–50%),

Unbearable toxicity (30%),

Weak pharmacokinetic and druglikeness properties (10–15%) and

poor financial and management strategy (10%) (Sun et al., 2022).

Given that cancer therapeutics are indispensable, chemotherapy FDA-approvals gradually replace the firstline care products. Indeed, between 2016, and 2021, there were 207 FDA drug approvals in oncology and malignant hematology. Among those, 28 drugs (14%) were standard-care displacing therapeutics (Benjamin et al., 2022). The second most targeted disease was neuropathies (14%) such as amyotrophic lateral sclerosis and polyneuropathy of hereditary transthyretin-mediated amyloidosis. Besides, the list also involved gadopiclenol and hyperpolarized Xe- 129 designed for CNS and pulmonary diagnostic purposes. Surprisingly, the list also included enzyme replacement therapy of sphingomyelinase as well as pyruvate kinase deficiencies. With respect to the drug entity, the newly approved drugs can be grouped into 7 groups as elucidated in Approximately 53% (19 out of 37) of which is small molecules followed by monoclonal antibody (mAb, 25%) and 6% enzymes. This is no surprise as it is evident that 35 years on from the FDA's approval of the first mAb, these biologics represent nearly a fifth of the agency's new drug approvals each year (Mullard, 2021). Notably, this year also witnessed the introduction of short interfering RNA (siRNA) approval to treat polyneuropathy of hereditary transthyretin mediated amyloidosis. After a decade from the first siRNA approval, only few siRNAs got approved by FDA.

Disease-Modifying Therapies

Disease-modifying therapy (DMT) is a major goal of research in Alzheimer's disease (AD) therapeutics. People with or at risk for AD, caregivers and family members, academic scientists, advocacy groups, biopharma industry scientists, the National Institutes of Health and other funders, and regulatory agencies are all stakeholders in

the search for drugs or other interventions that can prevent or defer the onset or slow the decline of AD (Uddin et al., 2020). Putative DMTs build on an increasingly sophisticated neurobiological understanding of AD and intervene in steps thought to be critical to the pathophysiological process leading to cell death and expressing itself clinically as disease progression (Khan et al., 2022; Ullah et al., 2018).

"Disease" includes the preclinical phase of AD when there is evidence of fibrillar amyloid deposition in the brain on amyloid imaging or abnormally low levels of the 42 amino acid amyloid beta protein (AB42) in cerebrospinal fluid (CSF) in a subject who has normal cognition and function; prodromal AD identified by the presence of the same Aβ abnormalities in individuals who have some degree of cognitive impairment but do not meet criteria for dementia; and individuals with biological and clinical evidence of AD dementia. (McKhann et al., 2011),(Dubois et al., 2007). The populations of AD in which DMT development is being pursued. There is a lack of consensus on whether the preclinical phase as described here is properly considered a disease since there are no symptoms, but treatments provided in this stage are aimed at preventing the symptomatic phases of AD and can be considered as DMTs. Preclinical applications of DMTs can include both primary prevention, beginning with individuals who have no evidence of AD pathology, or secondary prevention in individuals who are cognitively normal but have positive amyloid imaging or other biomarker evidence of the presence of AD pathology.

"Modifying" is the key word in the definition of DMT and is considered in more detail throughout this paper. The concept of modification is based on extrapolation from basic science observations that have identified processes in cellular studies, animal models, or human pluripotent stem cells (iPSCs) that result in AD-like changes and that can be altered by treatment (Choi et al., 2014), (Hurtado et al., 2010). For human application, "modification" refers to a change in the underlying disease process that produces an enduring effect on the clinical course of AD. Pathological processes of AD possibly contributing to cell death and representing targets for DMT's include amyloid toxicity, tau-related cytopathy, disruption of membrane integrity, inflammation, oxidation, apoptosis, mitochondrial dysfunction, synaptic loss, cell loss, heavy metal-related facilitation of neuronal injury, demyelination, and possibly other processes yet to be identified.

"Therapy" refers to a structured intervention that might include a pharmacologic agent, device, or nonpharmacologic activity such as exercise(Duara et al., 2009). Disease modification is an inferential concept based on trial-derived data since direct observation of the changes in the brain is not feasible. The data necessary to provide evidence of an enduring clinical effect and disease modification are generated in clinical trials using clinical outcomes and biomarkers. Trial design and analytic strategies are used to optimize the ability to demonstrate drug-placebo differences supportive of disease-modification. The concept of DMT stands in contrast to the idea of "symptomatic" therapy defined as interventions that improve cognition, defer cognitive or functional decline, or ameliorate symptoms such as agitation, depression or delusions without altering the underlying disease processes that comprise AD pathogenesis and without producing enduring changes that persist when the treatment is withdrawn. Symptomatic therapies may be based on disease-related concepts such as a cholinergic deficiency but are not intended to interrupt processes leading to cell death. Symptomatic treatments such as cholinesterase inhibitors have been shown to delay disease progression as measured by cognitive and functional measures (Mohs et al., 2001) delay of symptoms does not constitute proof of disease-modification.

Emerging Therapeutic Strategies

Immunotherapy and Monoclonal Antibodies

Immunotherapy is the medical procedure that uses controlled exposure to known allergens to reduce the severity of allergic disorders. Immunotherapy is usually the final medical modality used in the treatment of allergic rhinitis. When environmental controls and pharmacotherapy are not effective enough or, for whatever reason, are not able to be used, immunotherapy can still offer effective treatment. And, when combined with surgery for nasal obstruction, sinusitis, or nasal polyps, immunotherapy offers the potential of more effective control of nasal symptoms than surgery alone. For these reasons knowledge of immunotherapy is essential for all physicians who treat allergic diseases. immunotherapy began at the dawn of the twentieth century, when immunology was just becoming a recognized scientific discipline. It was known that people could be immunized with bacterial toxins, generating antitoxins in the blood that would then prevent illness. Because it was believed that pollen induced illness was also caused by toxins, attempts were made to immunize for pollen allergy. At least as early as 1900, Curtis ~ tried to immunize people with aqueous extracts of whole weeds. He initially had good success in ameliorating symptoms caused by pollen exposure, and so other physicians began to try immunizing people against various forms of aeroallergens. But shortly after these ma W attempts began, anaphylactic episodes began to be encountered, leading many workers to abandon immunotherapy treatments (Koessler, 1914) Alzheimer's disease (AD) is the most common cause of dementia globally, affecting approximately 36 million people currently and ~115 million by 2050 (Wisniewski & Goni, 2014). Numerous novel therapeutic strategies are being developed to potentially treat AD, with active and passive immunization being among the most advanced approaches (Ozudogru et al., 2012). Active and passive immunotherapies are currently under investigation for AD. While both strive to slow or prevent cognitive decline, each has its own advantages and disadvantages (Selkoe, 2006). Active vaccination, for example, engages the cellular and humoral immune system, including T cells and B cells, to promote the production of anti-antigen antibodies. Typically, an active vaccine is comprised of an antigen (alone or conjugated to a non-self T helper cell epitope) combined with an immune boosting adjuvant to ensure high antibody titers. On one hand, active immunotherapy is attractive because it can induce long-term antibody production in a large population, while being cost-effective and requiring only a few doctor's visits. However, an active vaccine also induces a T cell response that can increase the risk of a deleterious immune response (i.e., release of pro-inflammatory cytokines), especially, if the T cell recognizes the antigen as a self-protein. And, it takes time to "shut off" an active vaccine immune response. An active vaccine leads to a polyclonal antibody response, which means that it generates antibodies recognizing multiple, sometimes overlapping epitopes on the target protein. This may be helpful for broad coverage or, it may be less useful if the goal is to lower a specific form of a protein but not all forms (Lemere & Masliah, 2010). Passive immunotherapy involves the direct injection of monoclonal antibodies without requiring the immune system to generate an antibody response. Several benefits of passive immunotherapy are that it can be stopped immediately if there are any adverse reactions and, that one can target specific epitopes or pathogenic conformations without disturbing the other forms of the protein of interest. On the downside, passive immunization typically requires the production of expensive humanized monoclonal antibodies and monthly injections in a doctor's office, thereby making it less feasible for long-term treatment of a large population compared to active immunization. The Amyloid Hypothesis for Alzheimer's disease (AD) posits that abnormal brain accumulation of amyloid-beta (Aβ) is the key pathogenic event

that triggers a complex cascade leading to tau pathology, neurodegeneration, and cognitive decline (Söderberg et al., 2023). This hypothesis brought focus on the balance between A production and clearance in AD, informing therapeutic strategies aiming to either decrease Aβ production such as β-secretase inhibitors and γ-secretase inhibitors or increase Aβ clearance such as active and passive immunotherapy (Saunders et al., 2023). Of all anti-Aβ approaches, passive immunotherapy using monoclonal antibodies against Aβ has been best tolerated and given its mechanistic selectivity, it has been widely considered as the therapeutic candidate of choice (Franklin et al., 2023). As has been the case with most anti-Aβ approaches, individual trials testing anti-Aβ monoclonal antibodies have largely reported lack of efficacy (Franklin et al., 2023), but newer drugs of this class are still being investigated (Vellas & Aisen, 2021). Recently, investigators of Aducanumab trials reported some relatively promising effects, therefore re-energizing the popularity of the Amyloid Hypotheis and the interest in monoclonal antibodies against Aβ (Schneider, 2020). However, there is controversy regarding Aducanumab's efficacy (Barenholtz Levy, 2022) and at present, FDA is reviewing Aducanumab's data (Barenholtz Levy, 2022). Currently, there is no consensus on the therapeutic potential of monoclonal antibodies against Aβ in AD.

Monoclonal antibodies like Aducanumab and Lecanemab

With advances in understanding AD pathology, diseasemodifying therapies (DMT) targeting Aβ have become a focus of research. Current evidence suggests that the imbalance between Aβ production and clearance, leading to abnormal brain deposition, is a key initiating factor in the AD pathological cascade. Aβ oligomers can induce synaptic toxicity, mitochondrial dysfunction, and bloodbrain barrier damage, ultimately leading to neuronal loss and cognitive impairment (Nakano et al., 2022). In this context, the new anti-Aβ monoclonal antibodies Lecanemab and Donanemab have shown significant therapeutic potential. Lecanemab, a humanized IgG1 monoclonal antibody, exerts its therapeutic effects by specifically binding to soluble Aβ oligomers and protofibrils. Animal studies have shown that Lecanemab significantly reduces the number of pathogenic Aβ plaques in AD models, inhibits Aβ aggregation, and selectively clears Aβ protofibrils from brain tissue and cerebrospinal fluid (Shi et al., 2022). Population pharmacokinetic studies indicate that the drug follows a linear two-compartment model: compared to a 10 mg/kg monthly dosing regimen, biweekly dosing more rapidly reduces amyloid PET standardized uptake value ratios (SUVr) and plasma p-tau181 levels, while significantly increasing the Aβ42/40 ratio. Notably, the half-life of amyloid re-accumulation in the brain after treatment cessation is up to 4 years, while plasma biomarkers (Aβ42/ 40 and p-tau181) recover much faster than brain pathology (Hayato et al., 2022). Donanemab, a recombinant humanized IgG1 monoclonal antibody developed by Eli Lilly, works by specifically recognizing and clearing deposited Aβ plaques. The drug was approved by the FDA in July 2024 for the treatment of early AD (mild NCD or mild dementia stages), making it the first Aβ-targeted therapy that does not require lifelong administration. Its innovative treatment strategy involves periodic dosing to achieve Aβ plaque clearance, and it has not yet entered the Chinese market (Kang, 2024). This study systematically evaluated the clinical efficacy and biological effects of anti-Aβ monoclonal antibodies (Lecanemab/ Donanemab) on patients with early AD through a meta-analysis.

Genomic advancement in understanding AD (e.g., gene editing, CRISPR technology)

Insightful observation of AD and its relevant pathways can be explored through in vitro study and the findings may help to discover potential diagnostic and therapeutic tools in vivo. However, to be optimistic, a newly developed gene editing system called clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 is presenting its great potential to be employed in the study of mutagenesis and neurodegenerative disorders. At present, CRISPR-Cas9 is such a promising gene editing tool that reasonably can be applied as a therapeutic mediator of AD because of the greater capability of this tool to correct a mutation in the genome of brain cells (Rohn et al., 2018). AD model generation with the CRISPR-Cas9 system is gradually proving its acceptability for analyzing disease pathogenesis, phenotypes, and therapies. CRISPR-Cas9 has been used to make a model of the APP and PSEN1 mutations and displayed a precise strategy of genome editing using gRNA synthesis (Paquet et al., 2016). CRISPR-Cas9 can target any gene of different cell lines, tissues, or animal model for modification, and allows a new roadmap for AD research.

MECHANISMS OF CRISPR-CAS9

The CRISPR-Cas9 system was discovered from the adaptive immune system of prokaryotes, basically from that of bacteria and archaea (Barrangou et al., 2007). Type II CRISPR-Cas9 is a commonly used system that consists of three core components: the endonuclease Cas9, CRISPR RNA (crRNA), and trans-activating crRNA (tracrRNA) (Jinek et al., 2012). Among these three components, Cas9 is an enzyme responsible for cleaving the target DNA and consists of six domains: (i) REC I, (ii) REC II, (iii) bridge helix, (iv) protospacer adjacent motif (PAM)-interacting domain, (v) HNH, and (vi) RuvC (Nishimasu et al., 2014). REC I domain helps the guide RNA to bind with the target sequence. The arginineriche bridge helix is critical for initiating cleavage activity upon binding of target DNA and the PAM-interacting domain is subsequently responsible for initiating the binding with target DNA. crRNA–tracrRNA duplex can be fused to form a chimeric single guide RNA (sgRNA) for neering (Nishimasu et al., 2014). The sgRNA consists of a 20-nucleotide guide sequence that is complementary to the target site. When the sgRNA recognizes the target sequence, it binds by Watson–Crick base-pairing and guides Cas9 to cleave the DNA strand and forms a doublestranded break (DSB) at the target site. RuvC and HNH nuclease domains are responsible for cutting the target DNA. Two major repair mechanisms are mainly responsible for repairing the breaks: non-homologous end joining (NHEJ) and homology-directed repair (HDR) (Fig.) (Khan et al., 2020). The HDR repair mechanism uses a donor DNA template to precisely repair DSBs for gene modification with low efficiency, whereas the NHEJ repair mechanism frequently results in genomic insertions or deletions (indels) for gene disruption with higher efficiency. Normally, the NHEJ is error-prone and can directly join the break sequences; it also can introduce random insertions or deletions (indels) at the DSB site. High-efficiency cleavage of any target sequence can easily be achieved by combining the expression of sgRNA and Cas9 (Chen et al., 2019; Tarpley, 2020).

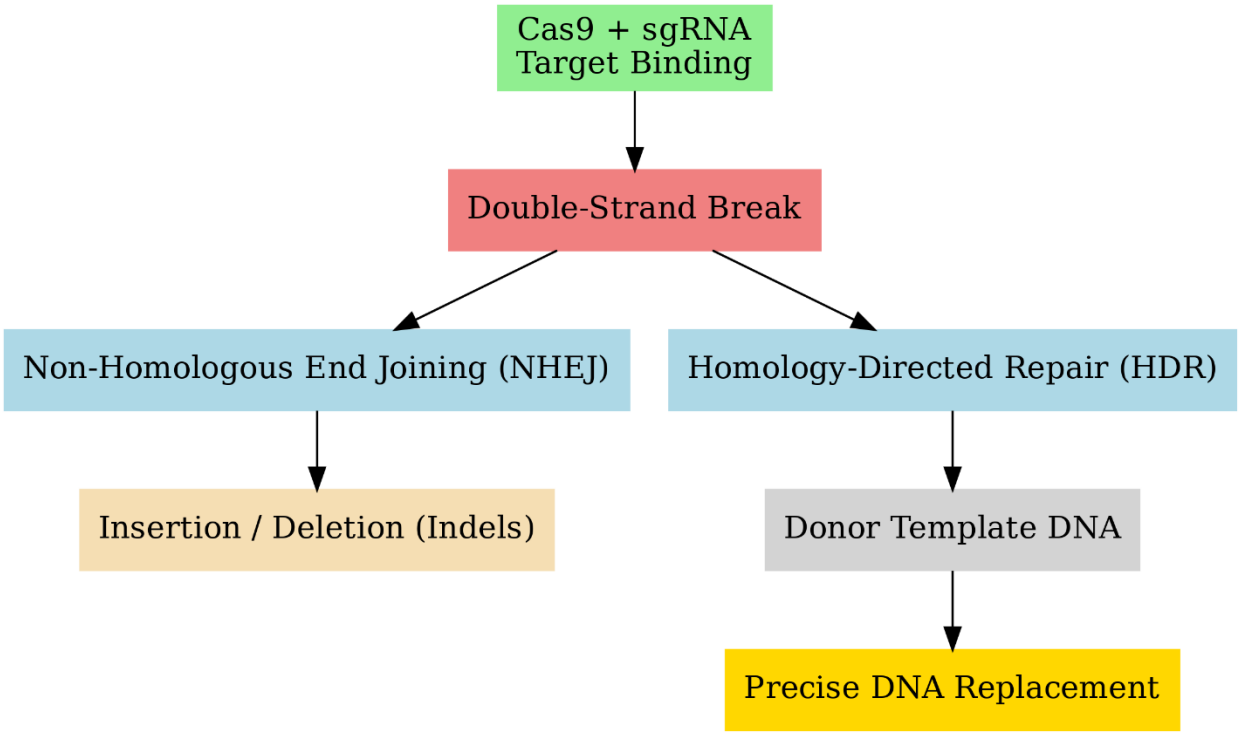

Figure 3. CRISPR-Cas9 genome editing.
Cas9–sgRNA induces a double-strand break repaired by non-homologous end joining (indels) or homology-directed repair (precise replacement with donor DNA).

Sex difference in AD progression

Although Alzheimer disease (AD) is recognized as a public health priority by the WHO1 and is expected to affect 90 million people worldwide by 2050 (Prince et al., 2015), the condition remains incurable and all clinical trials in AD conducted in the past decade have failed. Heterogeneity of disease manifestation and progression among patients has been identified as a critical issue in the current approach to developing new therapies for AD (Husain, 2017). Therefore, characterization of genetic, demographic and phenotypic traits that predict disease onset, prognosis and treatment response is of growing interest in AD research. Phenotypic and genetic factors have been proposed as characteristics that can guide patient selection, stratification and clustering for AD diagnosis and treatment. However, whether demographic variables such as sex should be considered in relation to AD phenotypic variability is unclear (Gamberger et al., 2017).

AD- related cognitive impairment

Sex differences in neuropsychological performance among NCI people have been extensively documented: women score more highly than men in verbal tasks at all ages and exhibit slower cognitive decline, even among the elderly population (average baseline age 64.1–69.7 years24). On the other hand, men score more highly in visuospatial and motor coordination tasks (Laws et al., 2016). Two studies have demonstrated that the higher performance of women than men in the verbal memory domain among the NCI population is maintained in prodromal AD. Both studies demonstrated that verbal memory is preserved in women with amnestic mild cognitive impairment (aMCI) relative to that in men with the same diagnosis, despite comparable hippocampal atrophy and comparable temporal lobe glucose metabolic rates (Sundermann et al., 2016). However, the sex difference in verbal memory tasks observed in NCI and at early stages of AD is not seen among patients with a diagnosis of dementia (Sundermann et al., 2016). The majority of studies in which cognitive

data were stratified by sex in AD dementia indicate that women score lower than men in verbal memory and fluency tasks, particularly confrontation naming tasks, even after controlling for possible demographic and psychological confounders, such as age, education and depression (Benke et al., 2013). In early AD dementia, even a lack of sex differences in memory performance, as observed in one study (Sundermann et al., 2016), could indicate meaningful effects of sex, as this observation deviates from the findings in NCI people for that specific domain.

Gene Therapy and Stem Cell Approaches

Therapies to slow the course of the disease do not exist, and constitute an objective of great medical importance. While amyloid modifying approaches have substantial mechanistic appeal for slowing disease progression, early clinical trial results with amyloid-depleting drugs have been disappointing, leading to the initiation of clinical trials in which amyloid-modifying treatment is initiated in pre-symptomatic or very early stage patients. There remains a great unmet need to identify therapies with the potential to slow disease progression and improve cognitive function in AD. Nervous system growth factors prevent neuronal death in a variety of correlative animal models of AD, including amyloid overexpressing mice, aged rats and primates, and lesioned rats and primates (Zhang et al., 2025). Of the approximately 50 identified nervous system growth factors, two are of particular relevance to AD: Nerve Growth Factor (NGF), and Brain-Derived Neurotrophic Factor (BDNF). NGF specifically prevents the death and stimulates the function of basal forebrain cholinergic neurons that undergo early and prominent degeneration in AD. NGF influences the nervous system in several species, including primates, and is present in the human brain (Tuszynski et al., 2005). Indeed, NGF levels in the basal forebrain region decline in AD. BDNF prevents the death and stimulates the function of cortical neurons, representing a second candidate growth factor treatment for AD (Zhang et al., 2025) (Blurton-Jones et al., 2009). Moreover, NGF induces Schwann cell migration into the brain (Winkler et al., 1997). Ironically, these effects of broad NGF availability in the nervous system reflect its biological potency on mature neurons. Accordingly, growth factor testing in humans requires a long-term delivery method that achieves both central delivery and restricted distribution to only regions of degenerating basal forebrain cholinergic neurons. Gene therapy is one of the few means of achieving this goal. We now report biological responses to NGF in the largest series of brain samples to date of humans that have undergone gene therapy: ten patients with AD. We find that NGF elicits classic “trophic” responses in the AD brain, including neuronal hypertrophy, axonal sprouting and activation of cell signaling. These findings provide evidence that growth factors consistently stimulate the functional state of degenerating neurons in chronic neurodegenerative disorders, constituting a rationale for the continued testing of growth factors as neuroprotective agents in human degenerative nervous system disorders. Stem cell-based therapy is a promising, safe, and effective therapeutic strategy for several neurodegenerative diseases, including AD (Winkler et al., 1997). Stem cell based- approach is still under development but rapid achievements indicate its therapeutic potential for reversing AD-associated neurodegeneration, as well as, improving cellular and structural functions (Lee et al., 2015). This therapeutic potential might be partly attributed to the neurosecretory (paracrine) effect, as several neurotrophic factors are implicated in neuromodulation of various cellular functions that ameliorate the pathological features and neurocognition in AD animal models (Fang et al., 2018). Stem cells are capable of spontaneous self-renewal and subsequent differentiation into specialized cells, such as neurons and glial cells (Eriksson et al., 1998). Based on the differentiation capacity, there are three types of stem cells: totipotent cells that have

the potential to create an organism, pluripotent cells that can be transformed into all cell types, and multipotent cells that can be differentiated into cell types in their own tissues (Yoo et al., 2013). Based on origin, stem cells are divided into embryonic, fetal, and adult types (Takahashi et al., 2008). Choosing the suitable cell source is an important step to develop a stem cell-based therapy (Duncan et al., 2017). The most commonly utilized stem cells in AD-related studies are embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs) and neural stem cells (NSCs) (Takahashi et al., 2008).

Artificial Intelligence and Biomarker Research

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that typically culminates in dementia, predominantly affecting individuals aged 65 and older. Characterized by a gradual onset, its primary clinical manifestations include memory loss, cognitive decline, and a range of physiological and psychological disturbances (Tzioras et al., 2023). Traditional AD diagnosis has relied heavily on post-symptomatic cognitive-mental assessments, with imaging and other diagnostic tools playing more of a complementary role (Malpetti & La Joie, 2022). Unfortunately, by the time clinical symptoms become apparent, the majority of patients have already advanced to moderate or severe stages of AD, at which point no existing treatments can halt disease progression (Iqbal et al., 2013). Hence, early detection and timely intervention have emerged as critical components of AD management, with the potential to enhance patient outcomes and slow the progression of symptoms. Magnetic Resonance Imaging (MRI), with its superior ability to render high-resolution images of brain anatomical structures, is a standout among imaging techniques. It provides precise differentiation between gray and white matter, and clearly depicts changes such as the widening and deepening of cerebral sulci and ventricles as dementia progresses (Martín-Noguerol et al., 2023). Furthermore, MRI's capability to slice brain structures in any direction facilitates accurate measurements of various regions such as the hippocampus and amygdala, which are vital indicators for evaluating brain atrophy in patients (Eickhoff et al., 2018). Structural changes in the hippocampus and the cortex of the olfactory region in the medial temporal lobe areas known to exhibit high concentrations of neurofibrillary tangles and senile plaques in early-stage AD can be measured to enable early diagnosis (Weiskopf et al., 2021). However, despite these advantages, the interpretation of MRI images can be subjective, underscoring the need for advanced techniques such as AI-driven analysis for more accurate and consistent diagnosis. Significant strides in Alzheimer's disease research have been made leveraging Artificial Intelligence (AI), especially machine learning and deep learning algorithms. One noteworthy area of progress pertains to early detection and diagnosis. Researchers are employing these sophisticated AI algorithms to scrutinize MRI scans, enabling the identification of subtle early signs of Alzheimer's disease, often before clinical symptoms manifest. These models are capable of discerning intricate patterns in the brain's structure, potentially indicative of the disease, thereby advancing the prospect of pre-symptomatic diagnosis (Ding et al., 2019; Etminani et al., 2022). Moreover, AI-driven analysis of MRI scans is being utilized to monitor disease progression. By systematically examining sequential scans, these algorithms facilitate tracking of brain atrophy rate and other structural alterations. This technology affords unparalleled insights into the velocity of disease progression at the individual patient level, potentially enhancing tailored therapeutic approaches (Raju et al., 2020). The versatility of AI is further demonstrated in its capacity for predictive modeling. When integrated with other types of data including genetic, cognitive, and lifestyle information AI algorithms can yield predictive models for Alzheimer's disease risk and progression. This multi-dimensional approach

empowers clinicians and caregivers with valuable prognostic information, paving the way for preemptive treatment planning and care management (Yao et al., 2023).
Biomarkers are defined as measurable characteristics that are indicators of biological processes, pathogenic processes, or responses to interventions (Califf, 2018). These can be subtyped by their application, and for this review we focus on indications of susceptibility or risk, diagnostic, and prognostic biomarkers. Improving the clinical management of dementia requires reliable biomarkers that can aid in identifying high-risk populations, early diagnosis, accurate subtyping, and predicting prognosis, drug response, or adverse events (Bayer, 2018). Biomarkers from different biological scales have been investigated in people with dementia, including neuroimaging, electrophysiological, genetic, gene expression, protein, metabolic, gut microbial, sleep, gait, and digital biomarkers (Lin et al., 2019; Soleimani Zakeri et al., 2020; Meghdadi et al., 2021). Biomarkers from cerebrospinal fluid (CSF), as well as minimally invasive collectable biological fluids including blood, saliva, tear, and urine have shown promise in improving dementia diagnosis (Ashton et al., 2019; Teunissen et al., 2022). CSF biomarkers such as CSF amyloid beta (Aβ), total tau (t-tau), and phosphorylated tau (p-tau) have been introduced in some research-based clinical centers and amyloid positron emission tomography (PET) can be used to estimate plaque density using florbetapir, flutemetamol, or florbetaben tracers (Pemberton et al., 2022). Subtype Definition Susceptibility biomarkers Indicate the risk of developing specific diseases in future in those without clinically apparent disease Diagnostic biomarkers Detect or confirm diseases or their subtypes Prognostic biomarkers Indicate the likelihood of disease progression in those who have the disease routine clinical use of dementia biomarkers has not reached most clinical settings, and dementia continues to be diagnosed on the basis of clinical diagnostic criteria (Gaebel et al., 2018; Isaacs & Boenink, 2020). Advancing biomarker research using an interdisciplinary approach is essential for accelerating the discovery of more reliable and clinically adaptable biomarkers for dementia (Chang et al., 2021).

Neuroprotective Agents and Antioxidants

Neuroprotection is a widely studied treatment option for various central nervous system (CNS) disorders including neurodegenerative diseases, stroke and trauma. Cerebral ischemia with a notable cessation of blood supply to the brain tissues leads to necrosis and apoptosis (Lee et al., 2001). It is the third most common cause of mortality and the leading cause of adult neurological disability (Carter et al., 2007). The most important pathological mechanisms in the process of ischemia-induced brain damage include inflammatory reaction, blood-brain barrier (BBB) disruption, oxidative stress, and neuronal apoptosis, all of which have been widely considered to be the four major therapeutic targets for acute ischemic stroke (Rodrigo et al., 2013). Degeneration takes place from a period of hours to days, which offers a window for therapeutic interventions. Antioxidants have a propensity to block or delay apoptosis. Many reports have suggested therapeutic effects of various natural antioxidants against cerebral ischemic damage (Mukherjee et al., 2007). Insufficient levels of antioxidants, or inhibition of antioxidant enzymes, cause oxidative stress which results in damage to cell structure and function and chronic excessive inflammation. Neuroprotective methods often target oxidative stress and excite toxicity, which together with other factors lead to neuronal death and aggravate neurodegeneration. Therefore, glutamate antagonists and antioxidants are successfully used in research and therapy.

Targeting Neuro-inflammation and Microglial Modulation

Inflammation is a response produced towards any injury, trauma or infection to the cells and tissues. It is believed that brain and immune system has a biochemical link. Inflammation that occurs in the brain is known as neuro inflammation. Neuro-inflammation is sometimes beneficial and sometimes destructing to the neuronal cells as over-activation of the inflammatory molecules can cause damage to the cells of the brain (Shabab et al., 2017). Neuroinflammation leads to activation of inflammatory cells in the brain including microglia and astrocytes. The brain is regarded as an "immunological privileged organ" because peripheral immune cells are expected not to enter the blood–brain barrier. Rather, glial cells microglia and astrocytes, are the primary component of the committed neuroimmune system, and interrelate with peripheral immunity but not clearly justified. The glial cells provide favorable and anti-inflammatory actions under normal and pathological conditions, counting phagocytosis, steroid release, free radical depletion, and repairing of cells. Release of cytokines and generation of free radicals can cause neuronal cell death and synaptic dysfunction. So if there is imbalance between the regulations of proinflammatory anti-inflammatory function, it can cause brain injury (Schain et al., 2017) Microglia and astrocytes are the two main constituents of the immune system of brain and they have a key function in the neuroinflammation process. In normal conditions microglia have a phagocytic action which removes damaged neurons thus encourages the repair of tissue at the site of invasion by foreign molecules or pathogens where the immune functions of the cells are initiated. Astrocytes remove the debris from the cerebrospinal fluid and play a neuroprotective role. In Alzheimer's disease there is accretion of these cells around the NFTs and senile plaques. In activated state these cells release cytokines, interleukins and chemokines which act as pro-inflammatory components and potentiate the neuroinflammatory process in the brain contributing to AD(Walters et al., 2016). ApoE is the risk element for Alzheimer disease that possesses immunomodulatory action. This capacity of ApoE is conjugated with triggering receptor expressed on myeloid cells 2 (TREM2), which is mediated by microglia in the CNS (2020). Elevated levels of cytokines in the brain are closely linked with AD. The interleukins and TNF α along with Cox-2 are the major cytokines considered to be involved. Cytokines generation in the brain mediated by Aβ also promotes microglia mediated free radical generation. In general IL-1 is involved in the progression of AD which is released from neurons, astrocytes and microglia. IL-1 enhances the abnormal processing of APP and generates Aβ. There is an increased concentration of IL-1 in the brain of AD patients. Aβ is generally considered to increase the interleukin levels. In contrast, it is seen that interleukins are responsible to generate Aβ from neurons and astrocytes. IL-1 also induces the release of other cytokines and increase NOS activity which results in toxicity of neurons (2021). Microglia are the brain resident macrophages derived from monocyte precursor cells during neurodevelopment. The two significant functional aspects of microglia are immune defense and homeostasis maintenance. Besides, they have an essential role in neurogenesis, the formation of the neuronal circuit, and maintaining neuron health (Araujo & Cotman, 1992; Ginhoux et al., 2013; Ueno et al., 2013). Microglia undergo dynamic changes during the physiological and pathological conditions, exemplified by a change in its morphology from ramified (resting) to amoeboid (active) form (Nimmerjahn et al., 2005). Under normal physiological conditions, the microglia patrol the brain's microenvironment to provide immune surveillance and neuronal survival. Studies have shown that Aβ aggregates induce microglia to acquire a full spectrum of activation by acquiring morphological and molecular changes. This activated form of microglia is referred to as disease-

associated microglia (DAM) and has overexpression of particular receptors, chemokines, cytokines, and other factors (Wolf et al., 2017).

Challenges and Future Directions

Limitations of Current Treatments

Current treatments of PD and AD diseases typically involve administration of drugs in the form of oral caps or pills. However, the systemic delivery of drugs to the CNS is a significant challenge due to their poor access to the brain, extensive first-pass metabolism, reducing their half-life, and possible side effects when reaching non-target peripheral tissues. Indeed, many endogenous proteins and antibody-based biopharmaceutical agent have been proposed and tested for treating neurodegenerative diseases, however, their therapeutic effectiveness still remains inadequate. Recently, antibody-based immunotherapy has obtained successful results in phase 1b clinical trials (Sevigny et al., 2016). The human monoclonal antibody aducanumab has been intravenously administered for 1 year on a monthly basis to patients with prodromal or mild AD and has showed to induce a reduction of Aβ plaques and a slowing of patients' cognitive decline (Sevigny et al., 2016). In case future phase 3 clinical trials are successful, such drug could represent the first valuable strategy to treat AD compared to current treatments that aim at alleviating AD symptoms and/or slowing AD progression. PD and AD are neurodegenerative conditions with the progressive course for which currently disease-modifying treatments are not available. However, selecting a therapeutic plan that is adapted to the patient and limiting adverse effects can ameliorate significantly the quality of life of patients and of their families. The association between L-dopa and carbidopa, a peripheral inhibitor of enzyme DOPA decarboxylase represents the gold standard for the symptomatic treatment of PD (Lees et al., 2009). Carbidopa is involved in the inhibition of the conversion of L-dopa to dopamine peripherally, thus, it guarantees that a higher level of the drug reaches the central nervous system (CNS). Currently, L-dopa represents the most effective treatment in the short-term management of PD. Indeed, even though it is not possible to predict single patient's response to this drug, some motor symptoms, namely bradykinesia, rigidity and postural instability, ameliorate 70% from the first weeks of the treatment (Stamelou et al., 2013). Ldopa is usually well tolerated in the short-term, however, the long-term treatment is associated with the de- velopment of wearing-off phenomena, dyskinesias and neuropsychiatric disorders (e.g. hypomaniacal episodes, depression and delirium) (Lees et al., 2009).

Personalized Medicine and Biomarker Development

As defined by the FDA, precision medicine aims at tailoring disease treatment and prevention for each specific individual accounting for their genetic makeup and lifestyle. In particular, precision medicine seeks to move clinical practice away from the "one therapy fits all" approach taking into account how each patient, or subgroup of patients, might be susceptible to a specific disease or respond to a therapy based on their genetic background, lifestyle and environment (Sperling et al., 2011). In the last few decades, aging-associated, chronic, multifactorial diseases such as cancer, heart disease and dementia have become the biggest challenge to human health. Preclinical and clinical research in the field of cardiovascular disorders and cancer has demonstrated how a single "magic bullet approach" is unlikely to work. A combination of several therapeutics targeting multiple pathogenic pathways is required to treat cardiovascular disorders. For cancer, patient stratification in subgroups based on predisposing risk alleles, such as BRCA1 and BRCA2, has become the most advanced strategy. The AD field is quickly catching up in

characterizing pathogenic mechanisms and predisposing risk factors. Increasing evidence points toward substantial genetic heterogeneity for AD (Arbel-Ornath et al., 2017). Several predisposing risk alleles involved in different pathogenic pathways have been identified. In addition, several lifestyle habits correlate with AD susceptibility. Finally, compelling data from AD clinical trials have shown that the etiopathology and proper staging of disease is fundamental for understanding the best timeline for treatment. In fact, pre-symptomatic intervention seems to be necessary to ensure potential disease-altering effects (Mormino et al., 2016).

Technological progress has been achieved in the genomic, transcriptomic and proteomic fields. GWAS studies and WGS projects provide the means to identify common and rare risk alleles with much greater sensitivity and accuracy. The biomarker field has also progressed rapidly, making new technology for disease stratification available and promising routine AD biomarkers assays in the near future. These accomplishments create an optimal environment to move the AD field toward precision medicine. In fact, the clinician of the near future could be capable of identifying specific predisposing risk alleles in young asymptomatic adults. Moreover, the disease could be diagnosed pre-symptomatically thanks to cutting-edge biomarkers. Biomarker assays could become routinely available and easy to administer, as in the case of P-Tau181 and P-Tau217. Therapeutic approaches could be administered based on genetic background and biomarker profile. Amyloid-targeting therapies could be administered to AD patients before symptoms manifest. Tau therapeutics could be beneficial in combination with Aβ drugs, especially at symptomatic stages of the disease (Martin et al., 2013; Selkoe & Hardy, 2016).

Ethical Issues in Treating Alzheimer's Disease

The ethical implications of preventative treatments begin to arise in the preclinical and mild stages of AD. For example, what clinical measures provide a deterministic rather than probabilistic diagnosis of preclinical disease? At what stage should such interventions occur given the uncertain probability of transition to overt or more significant clinical disease and the possible side effects that may arise? And who should be involved in this decision-making process? Such discussions are of the utmost importance and require careful consideration. This commentary will, however, focus on the ethical issues that arise in late-stage disease.

Ethical decision making in Alzheimer's disease

Individuals living with a dementia diagnosis and/or their caregivers, herein referred to as the primary care team, are currently charged with considering the ethical implications of non-disease modifying interventions, such as the use of enteral intubation to provide nutrition and hydration to individuals who are otherwise unable to consume sufficient food and water (Johnson & Karlawish, 2015). Anecdotally, such interventions are thought to prolong life for individuals with late-stage dementia; however, a growing body of evidence indicates that no significant differences in survival rates occur between those who undergo enteral intubation and those who do not (Goldberg & Altman, 2014; Brooke & Ojo, 2015). By comparison, the administration of a disease-modifying therapeutic would alleviate disease-associated mortality, potentially adding years to an individual's lifespan with little or no subsequent restoration in cognition. While parallels can be drawn between the ethical dilemmas faced in latestage AD and other terminal diseases, such as cancer, HIV/AIDs, or renal disease (Hlongwa, 2016), the confounding impact of the individual's inability to participate in the decision-making progress creates additional challenges when treating dementia. More apt comparisons are perhaps made with the dilemmas arising in the treatment of severe stroke which may involve the

administration of life sustaining treatments, such as mechanical ventilation, in the absence of restorative therapies (Creutzfeldt & Holloway, 2012). Here, despite declining mortality, approximately 40% of patients die within the 12 months following a severe stroke (Eriksson et al., 2016). As in late stage AD, treatment decisions following severe stroke are complex and are often made with incomplete prognostic information.

Multimodal Approaches in AD Treatment

AD and related dementias (ADRDs) are complex and multifactorial, resulting from interactions between non-modifiable (e.g., age, sex, genetics) and modifiable risk factors (e.g., lifestyle, vascular, metabolic). According to the latest estimates, at least 40% of all dementia is attributable to modifiable lifestyle and environmental factors and could, thus, be prevented or delayed. This prevention potential can be even higher in low-middle income countries (LMICs) where dementia burden is increasing very rapidly (Prince et al., 2015). Given the multifactorial etiology of ADRD, a multimodal approach simultaneously targeting several risk factors and mechanisms may be needed for an optimal preventive effect. At the same time, such interventions need to adopt the 'one size does not fit all' paradigm and be adaptable to different populations and individuals across the globe (Stephen et al., 2021). Furthermore, increasing our understanding of the biological mechanisms of multimodal interventions, of their optimal time windows, and target populations is crucial for precision prevention of ADRD. Recent successes in trials of th ree Aβ-targeted monoclonal antibodies (donanemab, lecanemab, and aducanemab) suggest that the first disease modifying therapies (DMTs) may soon be available, at least in the early symptomatic disease stages (Cummings, 2017). However, due to the complex nature of ADRD, targeting a single proteinopathy may not be sufficient to prevent dementia. It is well established that only 10-30% of late onset AD cases have pure AD pathology, with vascular pathology as most common comorbidity (Floris et al., 2013). Various AD profiles and subtypes have been identified and recent advances in biomarkers (fluid biomarkers, neuroimaging) facilitate moving towards precision prevention and targeting the interventions for various at-risk and pathological profiles (Mohanty et al., 2023).

Long term cognitive and socioeconomic impact on AD

Ageing is associated with a dysfunction in a variety of cognitive (e.g., attention, memory, language) and executive (e.g., working memory, inhibition) domains, putatively related to reduced gray matter volume and connectivity among fronto-striatal, temporal, and parietal regions (Cabeza et al., 2018). Evidence also suggests an ageing-associated dysfunction in social cognition abilities, including emotion recognition5 and theory of mind (ToM; the capacity to reason about others' mental sates), which would be mediated by cognitive state and executive functions, partially related with task demands (Bottiroli et al., 2016; Otsuka et al., 2021). In turn, social cognition impairment could affect the experience of complex social emotions (i.e., those that are triggered in the presence of others), such as counter-empathic emotions, since they involve emotion recognition and perspective-taking processes (Jankowski & Takahashi, 2014). Taken together, ageing-associated dysfunction in cognitive and executive processes would reduce social cognition abilities, which would negatively impact social emotions. Socioeconomic status (SES) is a construct that describes the social (e.g., formal education, work prestige) and economic (e.g., material goods, monetary income) resources of an individual, and is one of the main factors from which life outcomes are derived (Farah, 2017). Low-SES older adults have less access to cognitively stimulating environments and cultural resources, which hinders their cognitive (e.g., memory) and executive (e.g., working memory) functioning.

Cognitive and executive functions deteriorate at different rates across the lifespan (i.e., with executive domains showing the earliest and fastest decline, dissociate in early stages of neurodegenerative conditions, and can respond differently to interventions (Meng et al., 2020). Thus, they might be differentially impacted by SES. In support of this claim, recent evidence shows that, while childhood SES disadvantages can negatively impact cognitive functioning in old age, high childhood SES is associated with a faster decline in verbal fluency (an ability closely related to executive functions) (Aartsen et al., 2019). While the SES impact on social cognition has not been formally tested in the elderly, there is evidence of a positive relationship between education (one component of SES) and ToM abilities in this population. Given the strong effect of education on cognitive and executive functions, and the reliance of social cognition on those processes, a mediation effect would be expected. Indeed, low-SES middle-aged adults show preserved or even heightened socioemotional skills such as emotion recognition, empathy, and cooperation, putatively related to its adaptative value in adverse contexts (Varnum et al., 2015). Then, social cognition dysfunction in low-SES older adults could be plausibly explained by primary cognitive and executive impairments. In the same vein, as the experience of social emotions would depend on social cognition processes, SES would affect it indirectly. In sum, it is well established that low-SES negatively affects cognitive state and executive functions in older adults, being its impact on socioemotional processes yet to be determined in this population.

Conclusion

AD represents a multifaceted neurological challenge with significant implications for individuals, families, and society as a whole. Over the past century, extensive research has unraveled the intricate molecular and cellular mechanisms underlying AD pathogenesis, highlighting the roles of beta-amyloid plaques, tau protein pathology, neuroinflammation, and genetic predispositions. Despite these advances, effective disease-modifying treatments remain elusive, underscoring the complexity and heterogeneity of AD. Current diagnostic protocols, incorporating biomarkers and neuroimaging techniques, offer promise in early detection and monitoring of disease progression. However, challenges persist in translating these advancements into routine clinical practice, particularly in resource-limited settings. Furthermore, caregiver burden emerges as a critical issue, necessitating tailored support programs to address the physical, emotional, and social needs of caregivers. While existing pharmacological interventions provide symptomatic relief, ongoing research efforts explore novel therapeutic targets and treatment modalities. From nanoparticles facilitating targeted drug delivery to natural compounds showing potential in preclinical studies, the landscape of AD therapeutics is evolving rapidly. Collaboration among stakeholders, including researchers, healthcare providers, policymakers, and caregivers, is crucial in advancing AD research and improving care outcomes. In the face of uncertainties surrounding recent drug approvals and controversies in gene modification therapies, the quest for effective AD treatments persists. Continued investment in research, coupled with an emphasis on personalized medicine and combination therapies, holds promise in the pursuit of meaningful advancements in AD management. Despite the challenges ahead, the collective efforts of the scientific community offer hope for a future where the burden of AD is alleviated, and individuals affected by this devastating condition can live with dignity and quality of life.

References

Aartsen, M. J., Cheval, B., Sieber, S., Van der Linden, B. W., Gabriel, R., Courvoisier, D. S., Guessous, I., Burton-Jeangros, C., Blane, D., and Ihle, A. (2019). Advantaged socioeconomic conditions in childhood are associated with higher cognitive functioning but stronger cognitive decline in older age. Proceedings of the National Academy of Sciences, 116(12), 5478-5486.

Adelman, M. M. (2021). DEMENTIA AND ALZHEIMER'S DISEASE-WHAT TO KNOW AND REMEMBER. DEMENTIA, 26(2).

Alzheimer, A., Stelzmann, R. A., Schnitzlein, H. N., and Murtagh, F. R. (1995). An English translation of Alzheimer's 1907 paper," Uber eine eigenartige Erkankung der Hirnrinde". Clinical anatomy (New York, NY), 8(6), 429-431.

Araujo, D. M., and Cotman, C. W. J. J. o. N. (1992). Basic FGF in astroglial, microglial, and neuronal cultures: characterization of binding sites and modulation of release by lymphokines and trophic factors. 12(5), 1668-1678.

Arbel-Ornath, M., Hudry, E., Boivin, J. R., Hashimoto, T., Takeda, S., Kuchibhotla, K. V., Hou, S., Lattarulo, C. R., Belcher, A. M., and Shakerdge, N. (2017). Soluble oligomeric amyloid-β induces calcium dyshomeostasis that precedes synapse loss in the living mouse brain. Molecular neurodegeneration, 12, 1-14.

Ashton, N. J., Ide, M., Zetterberg, H., and Blennow, K. (2019). Salivary biomarkers for Alzheimer's disease and related disorders. Neurology and Therapy, 8, 83-94.

Avramopoulos, D. (2009). Genetics of Alzheimer's disease: recent advances. Genome medicine, 1, 1-7.

Babapour Mofrad, R., Tijms, B. M., Scheltens, P., Barkhof, F., van der Flier, W. M., Sikkes, S. A., and Teunissen, C. E. J. N. (2020). Sex differences in CSF biomarkers vary by Alzheimer disease stage and APOE ε4 genotype. 95(17), e2378-e2388.

Bains, J. S., and Shaw, C. A. J. B. r. r. (1997). Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death. 25(3), 335-358.

Barber, T. M., Kyrou, I., Randeva, H. S., and Weickert, M. O. J. I. j. o. m. s. (2021). Mechanisms of insulin resistance at the crossroad of obesity with associated metabolic abnormalities and cognitive dysfunction. 22(2), 546.

Barenholtz Levy, H. J. A. o. P. (2022). Accelerated approval of aducanumab: Where do we stand now? In (Vol. 56, pp. 736-739): SAGE Publications Sage CA: Los Angeles, CA.

Barrangou, R., Fremaux, C., Deveau, H., Richards, M., Boyaval, P., Moineau, S., Romero, D. A., and Horvath, P. (2007). CRISPR provides acquired resistance against viruses in prokaryotes. Science, 315(5819), 1709-1712.

Bayer, A. J. (2018). The role of biomarkers and imaging in the clinical diagnosis of dementia. Age and ageing, 47(5), 641-643.

Bejanin, A., Schonhaut, D. R., La Joie, R., Kramer, J. H., Baker, S. L., Sosa, N., Ayakta, N., Cantwell, A., Janabi, M., and Lauriola, M. J. B. (2017). Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. 140(12), 3286-3300.

Benjamin, D. J., Xu, A., Lythgoe, M. P., and Prasad, V. J. J. N. O. (2022). Cancer drug approvals that displaced existing standard-of-care therapies, 2016-2021. 5(3), e222265-e222265.

Benke, T., Delazer, M., Sanin, G., Schmidt, H., Seiler, S., Ransmayr, G., Dal-Bianco, P., Uranüs, M., Marksteiner, J., and Leblhuber, F. (2013). Cognition, gender, and functional abilities in Alzheimer's disease: how are they related? Journal of Alzheimer's Disease, 35(2), 247-252.

Bezprozvanny, I. J. B., and Communications, B. R. (2022). Alzheimer's disease–Where do we go from here? , 633, 72-76.

Blurton-Jones, M., Kitazawa, M., Martinez-Coria, H., Castello, N. A., Müller, F.-J., Loring, J. F., Yamasaki, T. R., Poon, W. W., Green, K. N., and LaFerla, F. M. J. P. o. t. N. A. o. S. (2009). Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. 106(32), 13594-13599.

Bonneville, M., O'brien, R. L., and Born, W. K. J. N. R. I. (2010). γδ T cell effector functions: a blend of innate programming and acquired plasticity. 10(7), 467-478.

Bottiroli, S., Cavallini, E., Ceccato, I., Vecchi, T., and Lecce, S. (2016). Theory of Mind in aging: Comparing cognitive and affective components in the faux pas test. Archives of Gerontology and Geriatrics, 62, 152-162.

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., and Del Tredici, K. (2012). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta neuropathologica, 112(4), 389-404.

Braak, H., and Braak, E. J. A. n. (1991). Neuropathological stageing of Alzheimer-related changes. 82(4), 239-259.

Bradburn, S., Murgatroyd, C., and Ray, N. J. A. r. r. (2019). Neuroinflammation in mild cognitive impairment and Alzheimer's disease: A meta-analysis. 50, 1-8.

Breijyeh, Z., and Karaman, R. (2020). Comprehensive review on Alzheimer's disease: causes and treatment. Molecules, 25(24), 5789.

Brohi, K., Gruen, R. L., and Holcomb, J. B. J. I. C. M. (2019). Why are bleeding trauma patients still dying? In (Vol. 45, pp. 709-711): Springer.

Brooke, J., and Ojo, O. (2015). Enteral nutrition in dementia: a systematic review. Nutrients, 7(4), 2456-2468.

Cabeza, R., Albert, M., Belleville, S., Craik, F. I., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., and Reuter-Lorenz, P. A. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nature Reviews Neuroscience, 19(11), 701-710.

Calabrese, F., Rossetti, A. C., Racagni, G., Gass, P., Riva, M. A., and Molteni, R. J. F. i. c. n. (2014). Brain-derived neurotrophic factor: a bridge between inflammation and neuroplasticity. 8, 430.

Califf, R. M. (2018). Biomarker definitions and their applications. Experimental biology and medicine, 243(3), 213-221.

Campbell, B., Budreau, D., Williams-Perez, S., Chakravarty, S., Galet, C., and McGonagill, P. J. S. (2022). Admission lymphopenia predicts infectious complications and mortality in traumatic brain injury victims. 57(2), 189-198.

Cantón-Habas, V., Rich-Ruiz, M., Romero-Saldaña, M., and Carrera-Gonzalez, M. d. P. (2020). Depression as a risk factor for dementia and Alzheimer's disease. Biomedicines, 8(11), 457.

Carter, A. M., Catto, A. J., Mansfield, M. W., Bamford, J. M., and Grant, P. J. J. S. (2007). Predictive variables for mortality after acute ischemic stroke. 38(6), 1873-1880.

Chan, D. C. J. C. (2006). Mitochondria: dynamic organelles in disease, aging, and development. 125(7), 1241-1252.

Chang, C.-H., Lin, C.-H., and Lane, H.-Y. (2021). Machine learning and novel biomarkers for the diagnosis of Alzheimer's disease. International journal of molecular sciences, 22(5), 2761.

Chen, M., Mao, A., Xu, M., Weng, Q., Mao, J., and Ji, J. (2019). CRISPR-Cas9 for cancer therapy: Opportunities and challenges. Cancer letters, 447, 48-55.

Cho, K.-C., Kim, J.-J., Jang, C.-K., Hong, C.-K., Joo, J.-Y., and Kim, Y. B. J. J. o. N. (2018). Rete middle cerebral artery anomalies: a unifying name, case series, and literature review. 131(2), 453-461.

Choi, S. H., Kim, Y. H., Hebisch, M., Sliwinski, C., Lee, S., D'Avanzo, C., Chen, H., Hooli, B., Asselin, C., and Muffat, J. J. N. (2014). A three-dimensional human neural cell culture model of Alzheimer's disease. 515(7526), 274-278.

Creutzfeldt, C. J., and Holloway, R. G. (2012). Treatment decisions after severe stroke: uncertainty and biases. Stroke, 43(12), 3405-3408.

Cummings, J. (2017). Lessons learned from Alzheimer disease: clinical trials with negative outcomes. Clinical and translational science, 11(2), 147.

Cummings, J., Aisen, P., Lemere, C., Atri, A., Sabbagh, M., and Salloway, S. (2021). Aducanumab produced a clinically meaningful benefit in association with amyloid lowering. Alzheimer's research & therapy, 13(1), 98.

Ding, Y., Sohn, J. H., Kawczynski, M. G., Trivedi, H., Harnish, R., Jenkins, N. W., Lituiev, D., Copeland, T. P., Aboian, M. S., and Mari Aparici, C. (2019). A deep learning model to predict a diagnosis of Alzheimer disease by using 18F-FDG PET of the brain. Radiology, 290(2), 456-464.

Dobson, G. P., Morris, J. L., Davenport, L. M., and Letson, H. L. (2020). Traumatic-induced coagulopathy as a systems failure: a new window into hemostasis. Seminars in Thrombosis and Hemostasis,

Dowden, H., and Munro, J. J. N. R. D. D. (2019). Trends in clinical success rates and therapeutic focus. 18(7), 495-496.

Duara, R., Barker, W., Loewenstein, D., Bain, L. J. A. s., and dementia. (2009). The basis for disease-modifying treatments for Alzheimer's disease: the Sixth Annual Mild Cognitive Impairment Symposium. 5(1), 66-74.

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., and Jicha, G. J. T. L. N. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. 6(8), 734-746.

Duncan, T., Valenzuela, M. J. S. c. r., and therapy. (2017). Alzheimer's disease, dementia, and stem cell therapy. 8, 1-9.

Efron, P. A., Mohr, A. M., Bihorac, A., Horiguchi, H., Hollen, M. K., Segal, M. S., Baker, H. V., Leeuwenburgh, C., Moldawer, L. L., and Moore, F. A. J. S. (2018). Persistent inflammation, immunosuppression, and catabolism and the development of chronic critical illness after surgery. 164(2), 178-184.

Eickhoff, S. B., Yeo, B. T., and Genon, S. (2018). Imaging-based parcellations of the human brain. Nature Reviews Neuroscience, 19(11), 672-686.

Eimer, W. A., Kumar, D. K. V., Shanmugam, N. K. N., Rodriguez, A. S., Mitchell, T., Washicosky, K. J., György, B., Breakefield, X. O., Tanzi, R. E., and Moir, R. D. (2018). Alzheimer's disease-associated β-amyloid is rapidly seeded by herpesviridae to protect against brain infection. Neuron, 99(1), 56-63. e53.

Eriksson, H., Milberg, A., Hjelm, K., and Friedrichsen, M. (2016). End of life care for patients dying of stroke: a comparative registry study of stroke and cancer. PloS one, 11(2), e0147694.

Eriksson, P. S., Perfilieva, E., Björk-Eriksson, T., Alborn, A.-M., Nordborg, C., Peterson, D. A., and Gage, F. H. J. N. m. (1998). Neurogenesis in the adult human hippocampus. 4(11), 1313-1317.

Etminani, K., Soliman, A., Davidsson, A., Chang, J. R., Martínez-Sanchis, B., Byttner, S., Camacho, V., Bauckneht, M., Stegeran, R., and Ressner, M. (2022). A 3D deep learning model to predict the diagnosis of dementia with Lewy bodies, Alzheimer's disease, and mild cognitive impairment using brain

18F-FDG PET. European journal of nuclear medicine and molecular imaging, 49(2), 563-584.
Fang, Y., Gao, T., Zhang, B., and Pu, J. J. F. i. a. n. (2018). Recent advances: decoding Alzheimer's disease with stem cells. 10, 77.
Farah, M. J. (2017). The neuroscience of socioeconomic status: correlates, causes, and consequences. Neuron, 96(1), 56-71.
Fischer, R., Maier, O. J. O. m., and longevity, c. (2015). Interrelation of oxidative stress and inflammation in neurodegenerative disease: role of TNF. 2015(1), 610813.
Floris, G., Di Stefano, F., Melis, R., Cherchi, M. V., and Marrosu, F. (2013). Isolated bipallidal lesions caused by extrapontine myelinolysis. Neurology, 81(19), 1722-1723.
Franklin, M. E., Franklin, G. A. J. A. o. A. s., and Care, D. (2023). The cost and benefit of targeting amyloid plaques to treat alzheimer's disease. 7(1), 008-013.
Gabrilovich, D. I., and Nagaraj, S. J. N. r. i. (2009). Myeloid-derived suppressor cells as regulators of the immune system. 9(3), 162-174.
Gaebel, W., Jessen, F., and Kanba, S. (2018). Neurocognitive disorders in ICD-11: the debate and its outcome. World Psychiatry, 17(2), 229.
Gamberger, D., Lavrač, N., Srivatsa, S., Tanzi, R. E., and Doraiswamy, P. M. (2017). Identification of clusters of rapid and slow decliners among subjects at risk for Alzheimer's disease. Scientific reports, 7(1), 6763.
Gao, Y., and Liu, X. J. F. i. a. n. (2021). Secular trends in the incidence of and mortality due to Alzheimer's disease and other forms of dementia in China From 1990 to 2019: An age-period-cohort study and joinpoint analysis. 13, 709156.
Ginhoux, F., Lim, S., Hoeffel, G., Low, D., and Huber, T. J. F. i. c. n. (2013). Origin and differentiation of microglia. 7, 45.
Goedert, M., Spillantini, M., Hasegawa, M., Jakes, R., Crowther, R., and Klug, A. (1996). Molecular dissection of the neurofibrillary lesions of Alzheimer's disease. Cold Spring Harbor symposia on quantitative biology,
Goedert, M., Spillantini, M. G., Jakes, R., Rutherford, D., and Crowther, R. J. N. (1989). Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. 3(4), 519-526.
Goedert, M., Wischik, C., Crowther, R., Walker, J., and Klug, A. J. P. o. t. N. A. o. S. (1988). Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau. 85(11), 4051-4055.
Goldberg, L. S., and Altman, K. W. (2014). The role of gastrostomy tube placement in advanced dementia with dysphagia: a critical review. Clinical Interventions in Aging, 1733-1739.
Gunnarsson, L.-G., and Bodin, L. (2019). Occupational exposures and neurodegenerative diseases—a systematic literature review and meta-analyses. International journal of environmental research and public health, 16(3), 337.
Guo, Y., Li, S., Zeng, L.-H., and Tan, J. (2022). Tau-targeting therapy in Alzheimer's disease: critical advances and future opportunities. Ageing and Neurodegenerative Diseases, 2(3), N/A-N/A.
Gustavsson, A. M., Van Westen, D., Stomrud, E., Engström, G., Nägga, K., and Hansson, O. J. A. o. n. (2020). Midlife atherosclerosis and development of Alzheimer or vascular dementia. 87(1), 52-62.

Hachinski, V., Einhäupl, K., Ganten, D., Alladi, S., Brayne, C., Stephan, B. C., Sweeney, M. D., Zlokovic, B., Iturria-Medina, Y., Iadecola, C. J. A. s., and Dementia. (2019). Preventing dementia by preventing stroke: the Berlin Manifesto. 15(7), 961-984.

Hardy, J. (2010). Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. Journal of Alzheimer's Disease, 9(s3), 151-153.

Hardy, J. (2017). The discovery of Alzheimer-causing mutations in the APP gene and the formulation of the "amyloid cascade hypothesis". The FEBS journal, 284(7), 1040-1044.

Harris, J. J., Jolivet, R., and Attwell, D. J. N. (2012). Synaptic energy use and supply. 75(5), 762-777.

Hayato, S., Takenaka, O., Sreerama Reddy, S. H., Landry, I., Reyderman, L., Koyama, A., Swanson, C., Yasuda, S., and Hussein, Z. (2022). Population pharmacokinetic-pharmacodynamic analyses of amyloid positron emission tomography and plasma biomarkers for lecanemab in subjects with early Alzheimer's disease. CPT: Pharmacometrics & Systems Pharmacology, 11(12), 1578-1591.

Hinkson, I. V., Madej, B., and Stahlberg, E. A. J. F. i. p. (2020). Accelerating therapeutics for opportunities in medicine: a paradigm shift in drug discovery. 11, 770.

Hlongwa, P. (2016). Current ethical issues in HIV/AIDS research and HIV/AIDS care. Oral Diseases, 22, 61-65.

Hurtado, D. E., Molina-Porcel, L., Iba, M., Aboagye, A. K., Paul, S. M., Trojanowski, J. Q., and Lee, V. M.-Y. J. T. A. j. o. p. (2010). Aβ accelerates the spatiotemporal progression of tau pathology and augments tau amyloidosis in an Alzheimer mouse model. 177(4), 1977-1988.

Husain, M. (2017). Alzheimer's disease: time to focus on the brain, not just molecules. In (Vol. 140, pp. 251-253): Oxford University Press.

Iqbal, K., Flory, M., and Soininen, H. (2013). Clinical symptoms and symptom signatures of Alzheimer's disease subgroups. Journal of Alzheimer's Disease, 37(3), 475-481.

Isaacs, J. D., and Boenink, M. (2020). Biomarkers for dementia: too soon for routine clinical use. The Lancet Neurology, 19(11), 884-885.

Jack, C. R., Therneau, T. M., Weigand, S. D., Wiste, H. J., Knopman, D. S., Vemuri, P., Lowe, V. J., Mielke, M. M., Roberts, R. O., and Machulda, M. M. J. J. n. (2019). Prevalence of biologically vs clinically defined Alzheimer spectrum entities using the National Institute on Aging–Alzheimer's Association research framework. 76(10), 1174-1183.

Jankowski, K. F., and Takahashi, H. (2014). Cognitive neuroscience of social emotions and implications for psychopathology: examining embarrassment, guilt, envy, and schadenfreude. Psychiatry and clinical neurosciences, 68(5), 319-336.

Järemo, P., Jejcic, A., Jelic, V., Shahnaz, T., Oweling, M., Winblad, B., and Behbahani, H. (2019). Erythrocyte amyloid beta peptide isoform distributions in Alzheimer and mild cognitive impairment. Current Alzheimer Research, 16(11), 1050-1054.

Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., and Charpentier, E. (2012). A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity. Science, 337(6096), 816-821.

Johnson, R. A., and Karlawish, J. (2015). A review of ethical issues in dementia. International psychogeriatrics, 27(10), 1635-1647.

Kang, C. (2024). Donanemab: first approval. Drugs, 84(10), 1313-1318.

Karran, E., and De Strooper, B. (2016). The amyloid cascade hypothesis: are we poised for success or failure? Journal of neurochemistry, 139, 237-252.

Khan, M. N. M., Islam, K. K., Ashraf, A., and Barman, N. C. (2020). A review on genome editing by CRISPR-CAS9 technique for cancer treatment. World Cancer Res J, 7, e1510.

Kimbrell, D. A., and Beutler, B. J. N. R. G. (2001). The evolution and genetics of innate immunity. 2(4), 256-267.

Knapskog, A.-B., Engedal, K., Selbæk, G., and Øksengård, A.-R. (2021). Alzheimer's disease–diagnosis and treatment. Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke, 141(7).

Koessler, K. K. J. I. M. J. (1914). The specific treatment of hayfever by active immunization. 24(120), 32.

Kumar, A., and Singh, A. (2015). A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological reports, 67(2), 195-203.

Lafon, P.-A., Wang, Y., Arango-Lievano, M., Torrent, J., Salvador-Prince, L., Mansuy, M., Mestre-Francès, N., Givalois, L., Liu, J., and Mercader, J. V. (2020). Fungicide residues exposure and β-amyloid aggregation in a mouse model of Alzheimer's disease. Environmental health perspectives, 128(1), 017011.

Lane, C. A., Barnes, J., Nicholas, J. M., Sudre, C. H., Cash, D. M., Malone, I. B., Parker, T. D., Keshavan, A., Buchanan, S. M., and Keuss, S. E. J. J. n. (2020). Associations between vascular risk across adulthood and brain pathology in late life: evidence from a British birth cohort. 77(2), 175-183.

Laws, K. R., Irvine, K., and Gale, T. M. (2016). Sex differences in cognitive impairment in Alzheimer's disease. World journal of psychiatry, 6(1), 54.

Lee, I.-S., Jung, K., Kim, I.-S., Lee, H., Kim, M., Yun, S., Hwang, K., Shin, J. E., and Park, K. I. J. M. n. (2015). Human neural stem cells alleviate Alzheimer-like pathology in a mouse model. 10, 1-16.

Lee, S.-H., Kim, M., Yoon, B.-W., Kim, Y.-J., Ma, S.-J., Roh, J.-K., Lee, J.-S., and Seo, J.-S. J. S. (2001). Targeted hsp70. 1 disruption increases infarction volume after focal cerebral ischemia in mice. 32(12), 2905-2912.

Lees, A. J., Hardy, J., and Revesz, T. (2009). Parkinson's disease. The lancet, 373(9680), 2055-2066.

Lemere, C. A., and Masliah, E. (2010). Can Alzheimer disease be prevented by amyloid-β immunotherapy? Nature Reviews Neurology, 6(2), 108-119.

Lim, C. H., Kaur, P., Teo, E., Lam, V. Y. M., Zhu, F., Kibat, C., Gruber, J., Mathuru, A. S., and Tolwinski, N. S. (2020). Application of optogenetic Amyloid-β distinguishes between metabolic and physical damages in neurodegeneration. Elife, 9, e52589.

Lin, C. N., Huang, C. C., Huang, K. L., Lin, K. J., Yen, T. C., and Kuo, H. C. (2019). A metabolomic approach to identifying biomarkers in blood of Alzheimer's disease. Annals of clinical and translational neurology, 6(3), 537-545.

Livingston, G., Huntley, J., Liu, K. Y., Costafreda, S. G., Selbæk, G., Alladi, S., Ames, D., Banerjee, S., Burns, A., and Brayne, C. J. T. L. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. 404(10452), 572-628.

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., and Cooper, C. (2020a). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The lancet, 396(10248), 413-446.

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., and Cooper, C. J. T. l. (2020b).

Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. 396(10248), 413-446.
Lowe, V. J., Curran, G., Fang, P., Liesinger, A. M., Josephs, K. A., Parisi, J. E., Kantarci, K., Boeve, B. F., Pandey, M. K., and Bruinsma, T. (2016). An autoradiographic evaluation of AV-1451 Tau PET in dementia. Acta neuropathologica communications, 4, 1-19.
Malpetti, M., and La Joie, R. (2022). Imaging Alzheimer's pathology stage by stage. Nature Aging, 2(6), 465-467.
Manson, J., Cole, E., De'Ath, H. D., Vulliamy, P., Meier, U., Pennington, D., and Brohi, K. J. C. C. (2016). Early changes within the lymphocyte population are associated with the development of multiple organ dysfunction syndrome in trauma patients. 20, 1-10.
Martín-Noguerol, T., Casado-Verdugo, O. L., Beltrán, L. S., Aguilar, G., and Luna, A. (2023). Role of advanced MRI techniques for sacroiliitis assessment and quantification. European journal of radiology, 163, 110793.
Martin, L., Latypova, X., Wilson, C. M., Magnaudeix, A., Perrin, M.-L., Yardin, C., and Terro, F. (2013). Tau protein kinases: involvement in Alzheimer's disease. Ageing research reviews, 12(1), 289-309.
Mas-Celis, F., Olea-Lopez, J., and Parroquin-Maldonado, J. A. J. A. o. m. r. (2021). Sepsis in trauma: a deadly complication. 52(8), 808-816.
Mayeda, E. R., Glymour, M. M., Quesenberry, C. P., Johnson, J. K., Pérez-Stable, E. J., Whitmer, R. A. J. A. s., and Dementia. (2017). Survival after dementia diagnosis in five racial/ethnic groups. 13(7), 761-769.
McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R. J. A. s., and dementia. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. 7(3), 263-269.
Meghdadi, A. H., Stevanović Karić, M., McConnell, M., Rupp, G., Richard, C., Hamilton, J., Salat, D., and Berka, C. (2021). Resting state EEG biomarkers of cognitive decline associated with Alzheimer's disease and mild cognitive impairment. PloS one, 16(2), e0244180.
Meng, X., Li, G., Jia, Y., Liu, Y., Shang, B., Liu, P., Bao, X., and Chen, L. (2020). Effects of dance intervention on global cognition, executive function and memory of older adults: a meta-analysis and systematic review. Aging clinical and experimental research, 32(1), 7-19.
Mintun, M., Ritchie, C. W., Solomon, P., Sims, J. R., Salloway, S., Hansson, O., Apostolova, L. G., Zimmer, J. A., Evans, C. D., and Lu, M. (2023). Donanemab in Early Symptomatic Alzheimer's Disease: Efficacy and Safety in TRAILBLAZER-ALZ 2, a Phase 3 Randomized Clinical Trial. Alzheimer's & dementia, 19, e082733.
Mir, M. A., Hamdani, S. S., Mehraj, U., Qayoom, H., Sheikh, B., Nisar, S., and Bhat, B. J. B. F. I. (2020). Antigens and immunogens. 77.
Mishra, S., and Palanivelu, K. (2008). The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Annals of Indian Academy of Neurology, 11(1), 13-19.
Mohanty, R., Ferreira, D., Nordberg, A., Westman, E., and Initiative, A. s. D. N. (2023). Associations between different tau-PET patterns and longitudinal atrophy in the Alzheimer's disease continuum: biological and methodological perspectives from disease heterogeneity. Alzheimer's research & therapy, 15(1), 37.

Mohs, R. C., Doody, R., Morris, J., Ieni, J., Rogers, S., Perdomo, C., Pratt, R., and Neurology, S. G. J. (2001). A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. 57(3), 481-488.

Moloney, C. M., Lowe, V. J., and Murray, M. E. (2021). Visualization of neurofibrillary tangle maturity in Alzheimer's disease: A clinicopathologic perspective for biomarker research. Alzheimer's & dementia, 17(9), 1554-1574.

Mormino, E. C., Sperling, R. A., Holmes, A. J., Buckner, R. L., De Jager, P. L., Smoller, J. W., Sabuncu, M. R., Initiative, A. s. D. N., and Initiative, A. s. D. N. (2016). Polygenic risk of Alzheimer disease is associated with early-and late-life processes. Neurology, 87(5), 481-488.

Mountz, J. M., Laymon, C. M., Cohen, A. D., Zhang, Z., Price, J. C., Boudhar, S., McDade, E., Aizenstein, H. J., Klunk, W. E., and Mathis, C. A. (2015). Comparison of qualitative and quantitative imaging characteristics of [11C] PiB and [18F] flutemetamol in normal control and Alzheimer's subjects. NeuroImage: Clinical, 9, 592-598.

Mukherjee, P. K., Ahamed, K. N., Kumar, V., Mukherjee, K., and Houghton, P. J. J. B. b. r. (2007). Protective effect of biflavones from Araucaria bidwillii Hook in rat cerebral ischemia/reperfusion induced oxidative stress. 178(2), 221-228.

Mullard, A. J. N. r. D. d. (2021). FDA approves 100th monoclonal antibody product. 20(7), 491-495.

Müller-Heck, R. M., Bösken, B., Michiels, I., Dudda, M., Jäger, M., and Flohé, S. B. J. L. (2021). Major surgical trauma impairs the function of natural killer cells but does not affect monocyte cytokine synthesis. 12(1), 13.

Nakano, H., Hamaguchi, T., Ikeda, T., Watanabe-Nakayama, T., Ono, K., and Yamada, M. (2022). Inactivation of seeding activity of amyloid β-protein aggregates in vitro. Journal of neurochemistry, 160(4), 499-516.

Neugroschl, J., and Wang, S. (2016). Alzheimer's disease: diagnosis and treatment across the spectrum of disease severity. Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine, 78(4), 596-612.

Nimmerjahn, A., Kirchhoff, F., and Helmchen, F. J. S. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. 308(5726), 1314-1318.

Nishimasu, H., Ran, F. A., Hsu, P. D., Konermann, S., Shehata, S. I., Dohmae, N., Ishitani, R., Zhang, F., and Nureki, O. (2014). Crystal structure of Cas9 in complex with guide RNA and target DNA. Cell, 156(5), 935-949.

Notter, T., Coughlin, J., Gschwind, T., Weber-Stadlbauer, U., Wang, Y., Kassiou, M., Vernon, A. C., Benke, D., Pomper, M. G., and Sawa, A. J. M. p. (2018). Translational evaluation of translocator protein as a marker of neuroinflammation in schizophrenia. 23(2), 323-334.

O'Day, D. H. J. N. D. M. (2025). The calmodulin hypothesis of neurodegenerative diseases: searching for a common cure. In (pp. 1-3): Taylor & Francis.

Ono, M., Sahara, N., Kumata, K., Ji, B., Ni, R., Koga, S., Dickson, D. W., Trojanowski, J. Q., Lee, V. M., and Yoshida, M. (2017). Distinct binding of PET ligands PBB3 and AV-1451 to tau fibril strains in neurodegenerative tauopathies. Brain, 140(3), 764-780.

Organization, W. H. (2020). WHO technical guidance notes on Sendai framework reporting for ministries of health. World Health Organization.

Osuka, A., Ogura, H., Ueyama, M., Shimazu, T., Lederer, J. A. J. A. M., and Surgery. (2014). Immune response to traumatic injury: harmony and discordance of immune system homeostasis. 1(2), 63-69.

Otsuka, Y., Shizawa, M., Sato, A., and Itakura, S. (2021). The role of executive functions in older adults' affective theory of mind. Archives of Gerontology and Geriatrics, 97, 104513.

Ozudogru, S., Lippa, C. J. A. J. o. A. s. D., and Dementias®, O. (2012). Disease modifying drugs targeting β-amyloid. 27(5), 296-300.

Paquet, D., Kwart, D., Chen, A., Sproul, A., Jacob, S., Teo, S., Olsen, K. M., Gregg, A., Noggle, S., and Tessier-Lavigne, M. (2016). Efficient introduction of specific homozygous and heterozygous mutations using CRISPR/Cas9. Nature, 533(7601), 125-129.

Park, J., Choi, H., Min, J. S., Park, S. J., Kim, J. H., Park, H. J., Kim, B., Chae, J. I., Yim, M., and Lee, D. S. J. J. o. n. (2013). Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells. 127(2), 221-232.

Pemberton, H. G., Collij, L. E., Heeman, F., Bollack, A., Shekari, M., Salvadó, G., Alves, I. L., Garcia, D. V., Battle, M., and Buckley, C. (2022). Quantification of amyloid PET for future clinical use: a state-of-the-art review. European journal of nuclear medicine and molecular imaging, 49(10), 3508-3528.

Prince, M., Ali, G.-C., Guerchet, M., Prina, A. M., Albanese, E., Wu, Y.-T. J. A. s. r., and therapy. (2016). Recent global trends in the prevalence and incidence of dementia, and survival with dementia. 8, 1-13.

Prince, M., Wimo, A., Guerchet, M., Ali, G.-C., Wu, Y.-T., and Prina, M. (2015). World Alzheimer report 2015. The global impact of dementia: an analysis of prevalence, incidence, cost and trends Alzheimer's Disease International].

Raju, M., Gopi, V. P., Anitha, V., and Wahid, K. A. (2020). Multi-class diagnosis of Alzheimer's disease using cascaded three dimensional-convolutional neural network. Physical and Engineering Sciences in Medicine, 43(4), 1219-1228.

Ridge, P. G., Hoyt, K. B., Boehme, K., Mukherjee, S., Crane, P. K., Haines, J. L., Mayeux, R., Farrer, L. A., Pericak-Vance, M. A., and Schellenberg, G. D. (2016). Assessment of the genetic variance of late-onset Alzheimer's disease. Neurobiology of aging, 41, 200. e213-200. e220.

Robert-Jiménez, L., Figueroa-Gerstenmaier, S., Basurto-Islas, G., and Herrera-Velarde, S. (2023). Dinámica molecular de grano grueso de la proteína tau. Revista mexicana de física, 69(3), 0-0.

Rodrigo, R., Fernandez-Gajardo, R., Gutiérrez, R., Manuel Matamala, J., Carrasco, R., Miranda-Merchak, A., Feuerhake, W. J. C., and Targets, N. D.-D. (2013). Oxidative stress and pathophysiology of ischemic stroke: novel therapeutic opportunities. 12(5), 698-714.

Rohn, T. T., Kim, N., Isho, N. F., and Mack, J. M. (2018). The potential of CRISPR/Cas9 gene editing as a treatment strategy for Alzheimer's disease. Journal of Alzheimer's disease & Parkinsonism, 8(3), 439.

Rosenberg, R. N. (2015). Defining amyloid pathology in persons with and without dementia syndromes: making the right diagnosis. JAMA, 313(19), 1913-1914.

Ruan, X., Darwiche, S. S., Cai, C., Scott, M. J., Pape, H.-C., and Billiar, T. R. J. M. o. I. (2015). Anti-HMGB1 monoclonal antibody ameliorates immunosuppression after peripheral tissue trauma: attenuated T-lymphocyte response and increased splenic CD11b+ Gr-1+ myeloid-derived suppressor cells require HMGB1. 2015(1), 458626.

Saunders, T. S., Protsiv, M., Jenkins, N., Solomon, A., Blennow, K., Ritchie, C., and Muniz-Terrera, G. J. T. J. o. P. o. A. s. D. (2023). Association between Longitudinal Cerebrospinal Fluid Alzheimer's Biomarkers and the Lifestyle for Brain Health (LIBRA) Index: Findings from the European Prevention of Alzheimer's Dementia Cohort Study (EPAD LCS). 10(3), 543-550.

Schain, M., Kreisl, W. C. J. C. n., and reports, n. (2017). Neuroinflammation in neurodegenerative disorders—a review. 17, 1-11.
Scheltens, P., Blennow, K., Breteler, M. M., De Strooper, B., Frisoni, G. B., Salloway, S., and Van der Flier, W. M. (2016). Alzheimer's disease. The lancet, 388(10043), 505-517.
Selkoe, D. J. (2006). Alzheimer's disease: genes, proteins, and therapy. Physiological reviews.
Selkoe, D. J., and Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO molecular medicine, 8(6), 595-608.
Serrano-Pozo, A., Frosch, M. P., Masliah, E., and Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. Cold Spring Harbor perspectives in medicine, 1(1), a006189.
Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., and Ling, Y. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature, 537(7618), 50-56.
Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., and Ling, Y. (2017). Addendum: The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature, 546(7659), 564-564.
Shabab, T., Khanabdali, R., Moghadamtousi, S. Z., Kadir, H. A., and Mohan, G. J. I. J. o. N. (2017). Neuroinflammation pathways: a general review. 127(7), 624-633.
Shen, C., Liu, C., and Qiu, A. J. T. p. (2023). Metabolism-related brain morphology accelerates aging and predicts neurodegenerative diseases and stroke: a UK Biobank study. 13(1), 233.
Shi, M., Chu, F., Zhu, F., and Zhu, J. (2022). Impact of anti-amyloid-β monoclonal antibodies on the pathology and clinical profile of Alzheimer's disease: a focus on aducanumab and lecanemab. Frontiers in aging neuroscience, 14, 870517.
Snowdon, D. A. (1997). Aging and Alzheimer's disease: lessons from the Nun Study. The Gerontologist, 37(2), 150-156.
Söderberg, L., Johannesson, M., Nygren, P., Laudon, H., Eriksson, F., Osswald, G., Möller, C., and Lannfelt, L. J. N. (2023). Lecanemab, aducanumab, and gantenerumab—binding profiles to different forms of amyloid-beta might explain efficacy and side effects in clinical trials for Alzheimer's disease. 20(1), 195-206.
Soleimani Zakeri, N. S., Pashazadeh, S., and MotieGhader, H. (2020). Gene biomarker discovery at different stages of Alzheimer using gene co-expression network approach. Scientific reports, 10(1), 12210.
Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack Jr, C. R., Kaye, J., and Montine, T. J. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia, 7(3), 280-292.
Srivastava, S., Ahmad, R., and Khare, S. K. J. E. J. o. M. C. (2021). Alzheimer's disease and its treatment by different approaches: A review. 216, 113320.
Stamelou, M., Quinn, N. P., and Bhatia, K. P. (2013). "Atypical" atypical parkinsonism: new genetic conditions presenting with features of progressive supranuclear palsy, corticobasal degeneration, or multiple system atrophy—a diagnostic guide. Movement Disorders, 28(9), 1184-1199.

Stephen, R., Barbera, M., Peters, R., Ee, N., Zheng, L., Lehtisalo, J., Kulmala, J., Håkansson, K., Chowdhary, N., and Dua, T. (2021). Development of the first WHO guidelines for risk reduction of cognitive decline and dementia: lessons learned and future directions. Frontiers in neurology, 12, 763573.

Sun, D., Gao, W., Hu, H., and Zhou, S. J. A. P. S. B. (2022). Why 90% of clinical drug development fails and how to improve it? , 12(7), 3049-3062.

Sun, L., Zhou, R., Yang, G., and Shi, Y. (2017). Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of Aβ42 and Aβ40 peptides by γ-secretase. Proceedings of the National Academy of Sciences, 114(4), E476-E485.

Sundermann, E. E., Biegon, A., Rubin, L. H., Lipton, R. B., Mowrey, W., Landau, S., Maki, P. M., Initiative, A. s. D. N., Initiative, A. s. D. N., and Weiner, M. (2016). Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. Neurology, 86(15), 1368-1376.

Swerdlow, R. H., Hui, D., Chalise, P., Sharma, P., Wang, X., Andrews, S. J., Pa, J., Mahnken, J. D., Morris, J., Wilkins, H. M. J. A. s., and Dementia. (2020). Exploratory analysis of mtDNA haplogroups in two Alzheimer's longitudinal cohorts. 16(8), 1164-1172.

Takahashi, K., Yasuhara, T., Shingo, T., Muraoka, K., Kameda, M., Takeuchi, A., Yano, A., Kurozumi, K., Agari, T., and Miyoshi, Y. J. B. r. (2008). Embryonic neural stem cells transplanted in middle cerebral artery occlusion model of rats demonstrated potent therapeutic effects, compared to adult neural stem cells. 1234, 172-182.

Takebe, T., Imai, R., Ono, S. J. C., and science, t. (2018). The current status of drug discovery and development as originated in United States academia: the influence of industrial and academic collaboration on drug discovery and development. 11(6), 597-606.

Tarpley, A. J. (2020). CRISPR Technology Cracking into Creation. Journal of Insurance Medicine, 48(2), 144-148.

Teunissen, C. E., Verberk, I. M., Thijssen, E. H., Vermunt, L., Hansson, O., Zetterberg, H., van der Flier, W. M., Mielke, M. M., and Del Campo, M. (2022). Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. The Lancet Neurology, 21(1), 66-77.

Tuszynski, M. H., Thal, L., Pay, M., Salmon, D. P., U, H. S., Bakay, R., Patel, P., Blesch, A., Vahlsing, H. L., and Ho, G. J. N. m. (2005). A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. 11(5), 551-555.

Tzioras, M., McGeachan, R. I., Durrant, C. S., and Spires-Jones, T. L. (2023). Synaptic degeneration in Alzheimer disease. Nature Reviews Neurology, 19(1), 19-38.

Ueno, M., Fujita, Y., Tanaka, T., Nakamura, Y., Kikuta, J., Ishii, M., and Yamashita, T. J. N. n. (2013). Layer V cortical neurons require microglial support for survival during postnatal development. 16(5), 543-551.

Uwishema, O., Ayoub, G., Badri, R., Onyeaka, H., Berjaoui, C., Karabulut, E., Anis, H., Sammour, C., Mohammed Yagoub, F. E., and Chalhoub, E. (2022). Neurological disorders in HIV: hope despite challenges. Immunity, inflammation and disease, 10(3), e591.

Van Cauwenberghe, C., Van Broeckhoven, C., and Sleegers, K. (2016). The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genetics in medicine, 18(5), 421-430.

van der Lee, S. J., Wolters, F. J., Ikram, M. K., Hofman, A., Ikram, M. A., Amin, N., and van Duijn, C. M. J. T. L. N. (2018). The effect of APOE and other

common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. 17(5), 434-444.
Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., and Cohen, S. (2023). Lecanemab in early Alzheimer's disease. New England Journal of Medicine, 388(1), 9-21.
Varnum, M. E., Blais, C., Hampton, R. S., and Brewer, G. A. (2015). Social class affects neural empathic responses. Culture and Brain, 3(2), 122-130.
Vellas, B., and Aisen, P. J. T. J. o. P. o. A. s. D. (2021). New hope for Alzheimer's disease. 8(3), 238-239.
Vermunt, L., Sikkes, S. A., Van Den Hout, A., Handels, R., Bos, I., Van Der Flier, W. M., Kern, S., Ousset, P.-J., Maruff, P., Skoog, I. J. A. s., and Dementia. (2019). Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. 15(7), 888-898.
Waller, A. P., George, M., Kalyanasundaram, A., Kang, C., Periasamy, M., Hu, K., and Lacombe, V. A. J. B. e. B. A.-M. B. o. D. (2013). GLUT12 functions as a basal and insulin-independent glucose transporter in the heart. 1832(1), 121-127.
Walters, A., Phillips, E., Zheng, R., Biju, M., Kuruvilla, T. J. P. i. N., and Psychiatry. (2016). Evidence for neuroinflammation in Alzheimer's disease. 20(5), 25-31.
Wang, J.-W., Li, J.-P., Song, Y.-L., Zhao, Q.-H. J. A. o. C., and Science, L. (2017). Humoral and cellular immunity changed after traumatic brain injury in human patients. 47(1), 10-16.
Weiskopf, N., Edwards, L. J., Helms, G., Mohammadi, S., and Kirilina, E. (2021). Quantitative magnetic resonance imaging of brain anatomy and in vivo histology. Nature Reviews Physics, 3(8), 570-588.
Wingo, T. S., Lah, J. J., Levey, A. I., and Cutler, D. J. (2012). Autosomal recessive causes likely in early-onset Alzheimer disease. Archives of neurology, 69(1), 59-64.
Winkler, J., Ramirez, G. A., Kuhn, H. G., Peterson, D. A., Day-Lollini, P. A., Stewart, G. R., Tuszynski, M. H., Gage, F. H., Thal, L. J. J. A. o. N. O. J. o. t. A. N. A., and Society, t. C. N. (1997). Reversible Schwann cell hyperplasia and sprouting of sensory and sympathetic neurites after intraventricular administration of nerve growth factor. 41(1), 82-93.
Wisniewski, T., and Goni, F. J. B. p. (2014). Immunotherapy for Alzheimer's disease. 88(4), 499-507.
Wolf, S. A., Boddeke, H., and Kettenmann, H. J. A. r. o. p. (2017). Microglia in physiology and disease. 79(1), 619-643.
Wu, Z., Xia, F., Lin, R. J. J. o. H., and Oncology. (2024). Global burden of cancer and associated risk factors in 204 countries and territories, 1980–2021: a systematic analysis for the GBD 2021. 17(1), 119.
Yang, Y., Ye, Y., Chen, C., Kong, C., Su, X., Zhang, X., Bai, W., and He, X. J. N. (2019). Acute traumatic brain injury induces CD4+ and CD8+ T cell functional impairment by upregulating the expression of PD-1 via the activated sympathetic nervous system. 26(1), 43-57.
Yao, Z., Wang, H., Yan, W., Wang, Z., Zhang, W., Wang, Z., and Zhang, G. (2023). Artificial intelligence-based diagnosis of Alzheimer's disease with brain MRI images. European journal of radiology, 165, 110934.
Ye, K. X., Sun, L., Wang, L., Khoo, A. L. Y., Lim, K. X., Lu, G., Yu, L., Li, C., Maier, A. B., Feng, L. J. N., and Reviews, B. (2023). The role of lifestyle factors in cognitive health and dementia in oldest-old: a systematic review. 152, 105286.

Yiannopoulou, K. G., and Papageorgiou, S. G. (2020). Current and future treatments in Alzheimer disease: an update. Journal of central nervous system disease, 12, 1179573520907397.

Yoo, J., Kim, H. S., and Hwang, D. Y. J. J. o. c. b. (2013). Stem cells as promising therapeutic options for neurological disorders. 114(4), 743-753.

Zempel, H., and Mandelkow, E. J. T. i. n. (2014). Lost after translation: missorting of Tau protein and consequences for Alzheimer disease. 37(12), 721-732.

Zhang, B., Chen, S.-L., Teng, X., Han, Q., Wu, T., Yang, Z., Liu, Y., Xiang, K., and Sun, L. J. N. R. (2025). Function of Brain-Derived Neurotrophic Factor in the Vestibular-Cochlear System. 50(1), 1-9.

Zhang, X., Guo, T., Zhang, Y., Jiao, M., Ji, L., Dong, Z., Li, H., Chen, S., Zheng, W., and Jing, Q. J. B. p. (2024). Global burden of Alzheimer's disease and other dementias attributed to metabolic risks from 1990 to 2021: results from the global burden of disease study 2021. 24(1), 910.

Rahim, F., Ullah, H., Taha, M., Hussain, R., Sarfraz, M., Iqbal, R., ... & Khan, K. M. (2022). Synthesis of new triazole-based thiosemicarbazone derivatives as anti-Alzheimer's disease candidates: Evidence-based in vitro study. Molecules, 28(1), 21.

Ullah, H., Khan, S., Rahim, F., Taha, M., Iqbal, R., Sarfraz, M., ... & Jafri, I. (2022). Benzimidazole bearing thiosemicarbazone derivatives act as potent α-amylase and α-glucosidase inhibitors; synthesis, bioactivity screening and molecular docking study. Molecules, 27(20), 6921.

Ullah, H., Rahim, F., Taha, M., Hussain, R., Wadood, A., Nawaz, M., ... & Khan, K. M. (2020). Synthesis, in vitro α-glucosidase inhibitory potential and molecular docking studies of 2-amino-1, 3, 4-oxadiazole derivatives. Medicinal Chemistry, 16(6), 724-734.

Hussain, R., Khan, S., Ullah, H., Ali, F., Khan, Y., Sardar, A., ... & Batiha, G. E. S. (2023). Benzimidazole-based schiff base hybrid scaffolds: a promising approach to develop multi-target drugs for alzheimer's disease. Pharmaceuticals, 16(9), 1278.

Ullah, H., Fayyaz, F., Hussain, A., Rahim, F., Hayat, S., Uddin, I., ... & Khan, K. M. (2022). New oxadiazole bearing thiosemicarbazide analogues: Synthesis, anti-alzheimer inhibitory potential and their molecular docking study. Chemical Data Collections, 41, 100915.

Khan, S., Ullah, H., Rahim, F., Taha, M., Hussain, R., Khan, M. S., ... & Khan, K. M. (2022). New thiazole-based thiazolidinone derivatives: synthesis, in vitro α-amyl

ase, α-glucosidase activities and silico molecular docking study. Chemical Data Collections, 42, 100967.

Ullah, H., Rahim, F., Taha, M., Uddin, I., Wadood, A., Shah, S. A. A., ... & Khan, K. M. (2018). Synthesis, molecular docking study and in vitro thymidine phosphorylase inhibitory potential of oxadiazole derivatives. Bioorganic Chemistry, 78, 58-67.

Uddin, I., Ullah, H., Bibi, A., Taha, M., Khan, F., Rahim, F., ... & Khan, K. M. (2020). Synthesis, in vitro alpha glucosidase, urease activities and molecular docking study of bis-indole bearing Schiff base analogs. Chemical Data Collections, 28, 100396.