Review Article

Breakthroughs in Alzheimer's Research: A Path to a More Promising Future?

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Abstract

Background: Alzheimer's disease (AD) is a widespread neurodegenerative disorder with a significant global impact, affecting approximately 50 million individuals, and projections estimate that up to 152 million people will be affected by 2050. AD is characterized by beta-amyloid plaques and tau tangles in the brain, leading to cognitive decline.

Summary: Recent research on AD has made significant strides, including the development of an "amyloid clock" biomarker that tracks AD progression through positron emission tomography (PET) scans. Surf4 and other genes have been discovered to play a role in regulating beta-amyloid toxicity, while inhibiting the enzyme hexokinase-2 has shown positive results in preclinical studies. New brain mapping techniques have identified early brain-based causes of cognitive changes in AD, and biomarkers such as neuronal pentraxin protein Nptx2 and astrocytic 7-subunit of the nicotinic acetylcholine receptors (7nAChRs) show potential for early detection. Other approaches, such as replenishing the enzyme Tip60, selectively degrading the modified protein p-p38 with PRZ-18002, and targeting the protein voltage-dependent anion channel-1 (VDAC1), have shown promise in enhancing cognitive function and preventing pathophysiological alterations linked to AD. Baseline blood samples and other biomarkers such as urine formic acid, p-tau 198, microRNAs, and glial fibrillary acidic protein (GFAP) have also been discovered for early detection and intervention of AD. Additionally, recent FDA approvals for medications such as aducanumab and lecanemab provide options for reducing AD symptoms and improving function, while clinical trials for dementia vaccines show promise for the nasal and beta-amyloid 40 vaccines as well as vaccinations targeting tau.

Key Messages: These advancements in AD research, including biomarker discovery and the development of disease-modifying treatments, are crucial steps towards improving the lives of those affected by AD and finding a cure for this debilitating disease.

Keywords

Alzheimer's disease (AD), positron emission tomography (PET), surf4, hexokinase-2, Nptx2, astrocytes, biomarkers, aducanumab, lecanemab, VDAC1

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Introduction

In 1906, Alois Alzheimer, a German psychiatrist, and colleague of Emil Kraepelin, first referred to Alzheimer's disease (AD) as "presenile dementia."[1] At least 50 million people worldwide suffer from dementias like Alzheimer's. By 2050, this figure could reach up to 152 million if there is a lack of effective treatment and diagnostic discoveries.[2] In 2022, 6.5 million Americans 65 and older are expected to have Alzheimer's, and deaths by Alzheimer's continue to rise and have more than doubled between 2000 and 2019.[3] The aggregation of beta-amyloid plaques and neurofibrillary tau tangles is the hallmark of AD, followed by neurodegeneration and a steady loss in cognitive function.[4] The disease progresses through a protracted "preclinical" stage, during which AD's pathology builds up prior to the appearance of clinical symptoms.[5]

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The Emergence of an "Amyloid Clock"

AD progression may be predicted by determining how long beta-amyloid plaques have been accumulating in a person's brain. In a recent study, the research team created and evaluated three distinct algorithms that use positron emission tomography (PET) brain scans to simulate the development of amyloid and its impact on disease progression. The Alzheimer's Disease Neuroimaging Initiative, the Baltimore Longitudinal Study of Aging, and the Wisconsin Registry for Alzheimer's Prevention are three different cohort studies to which the team's algorithms were used. They evaluated the three approaches' propensity to forecast the development of amyloid and, in a smaller sample, the course of the disease. In all three trials, all three techniques could forecast the emergence of amyloid, establishing the concept of an "amyloid clock" for tracking the development of illness.[6–9] It is feasible to predict how far along the disease is and when symptoms may start to show by determining the age at which amyloid buildup first appears. This data can aid researchers in determining the most effective timing for interventions and alternative therapies.[10] This advancement may enable researchers to understand better the timing of disease onset and progression, which could help determine optimal interventions and alternative therapies. It represents a significant step towards improved diagnosis, monitoring, and treatment strategies for AD.

New AD-regulating Genes Discovered: Implications for Therapeutic Targets

New genes were discovered that regulate the toxicity of the protein amyloid, which is the cause of AD. In yeast, which has a genome similar to that of humans, the study used molecular biology, genomics, and bioinformatics methods to pinpoint 238 genes that control AD. Among the identified genes, 157 are protective against amyloid toxicity, while 81 increase its toxicity. Most genes involve protein synthesis, mitochondrial activity, and intracellular calcium regulation. However, the Surf4 gene stands out as a calcium entry regulator that has been shown to increase the toxicity of amyloid protein, a factor in AD.[11] The discovery of Surf4 may lead to the development of new therapeutic targets for treating AD. The study paves the way for additional investigation into figuring out how much Surf4 and other genes contribute to the development of the disease and how those genes might be targeted to stop or slow it down. Overall, the discovery of new genes that regulate the toxicity of the amyloid protein in AD presents several positive aspects, including advancements in understanding, potential for new therapeutic targets, interdisciplinary approaches, focus on critical cellular processes, and potential for personalised medicine. This discovery has the potential to significantly contribute to developing new strategies for treating and managing AD.

Translocator Protein's Essential Role in Microglia Energy Production and Potential of Hexokinase-2

Researchers have found that the translocator protein in the energy-producing regions of immune cells is essential for the brain's microglia cells to produce energy to remove harmful beta-amyloid. AD deteriorates due to the microglia's energy deficit and inability to clear beta-amyloid without the translocator protein. They also discovered that the absence of the translocator protein or exposure to toxic beta-amyloid causes the microglia to activate an enzyme known as hexokinase-2. They created a light-activated tool to "turn off" one of hexokinase-2's functions, which improved energy production and improved removal of beta-amyloid. This represents a potential therapeutic target for medications encouraging microglia to produce energy more effectively and eliminate harmful beta-amyloid proteins, thereby preventing AD.[12] The discovery of the role of translocator protein in microglia energy production and beta-amyloid clearance represents a positive advancement in Alzheimer's research. It provides a new understanding of microglia function and identifies hexokinase-2 as a potential therapeutic target. Using a light-activated tool to improve energy production and beta-amyloid clearance is a novel approach to Alzheimer's treatment. This discovery may contribute to the development of precision medicine strategies and can potentially prevent or slow the progression of AD.

Mapping Brain Function in Early Alzheimer's

A study aimed to better our comprehension of AD and its early stages. The team used an innovative brain mapping method to identify subtle changes in brain function, which are frequently missed by traditional imaging analysis methods. To identify any connections between the two, the researchers built individualised maps of brain function and evaluated cognitive performance. In the early stages of the disease, the team's new method of using unique maps of brain function allowed them to identify potential brain-based causes for very subtle cognitive changes. They used the functional connectome, a highly sensitive image analysis method, to understand how various brain regions communicate.

The researchers used a more recent and highly sensitive image analysis method created by their collaborator Hesheng Liu, PhD, to understand how various brain regions function in different people. They discovered that participants with amyloid-beta buildup or preclinical AD had worse information processing when specific changes in the brain fingerprint were present. According to the study, unique functional connectomes can pick up on subtle variations in brain function that other traditional methods of brain imaging analysis might

miss. It also implies that, even before signs of cognitive decline become apparent, the early stages of amyloid-beta buildup may impact brain networks' functioning. Finally, it shows that changes in connectivity within and between particular brain networks may point to early issues with information processing, which could be a good target for therapies to enhance outcomes for patients with AD.[13] The study used innovative brain mapping techniques to understand better AD and its early stages. By creating unique maps of brain function and utilizing highly sensitive functional connectome analysis, the researchers identified potential brain-based causes for subtle cognitive changes in early AD. The study highlighted the importance of detecting subtle variations in brain function and changes in connectivity as potential targets for therapies to enhance outcomes for AD patients.

Inhibiting C1q Activity with Nptx2 to Prevent Synaptic Loss

Researchers recently discovered the neuronal pentraxin protein Nptx2 as the first recognized regulator of the complement system in the adult brain. When it is overactive, it can harm healthy cells, including those in the brain. Excitatory neurons secrete Nptx2, which is a biomarker for several neurological conditions. Nptx2 levels in the cerebrospinal fluid surrounding the brain and spinal cord are decreased in patients with Alzheimer's, frontotemporal dementia, and schizophrenia. The initiating factor of the complement cascade, C1q, was discovered to be directly and bound explicitly by Nptx2, which inhibits its activity. They observed elevated complement system activity and synapses being destroyed by microglia in an animal model lacking Nptx2. The brain tissue synapses recovered when C1q was removed from these animals via genetic deletion or antibody blocking. Increasing Nptx2 production in specific brain cells reduced complement activity and stopped synaptic loss in an animal model of neurodegeneration characterized by hyperactive microglia and elevated complement activity. Neurodegenerative diseases may be prevented or even treated by therapeutic approaches that target the complement system.[14] The discovery of Nptx2 as a regulator of the complement system in the adult brain presents a positive advancement in understanding the pathogenesis of neurodegenerative diseases. The decreased levels of Nptx2 in patients with Alzheimer's, frontotemporal dementia, and schizophrenia suggest it may serve as a biomarker for these conditions. The inhibition of C1q activity by Nptx2 and the potential for therapeutic approaches targeting the complement system offer promising opportunities to prevent or treat neurodegenerative diseases. This research provides new insights into the role of Nptx2 in synaptic loss and complement system activity, paving the way for further investigations and potential interventions in neurodegenerative disease research.

Astrocytic 7nAChRs as Biomarkers for Alzheimer's and Other Neurodegenerative Diseases

Astrocytes are essential for maintaining brain health and function; in response to injury and disease, they engage in a particular form of defence called reactive astrogliosis. Recent research has demonstrated that amyloid deposition and tau tangles can occur before reactive astrogliosis. To better understand reactive astrogliosis in the course of AD, it is crucial to find new astrocytic biomarkers. The astrocytic 7-subunit of the nicotinic acetylcholine receptors (7nAChRs) has been the research subject for the past two decades. It has provided insight into the pathology and biomarkers of AD. Reactive astrogliosis, cholinergic, and the amyloid cascade hypotheses in AD could all be connected by astrocytic 7nAChRs. They contend that using different imaging PET-tracers to target astrocytic 7nAChRs as a novel early biomarker could revolutionize clinical diagnostic and therapeutic approaches for Alzheimer's.[15] This study will open up new possibilities for locating brand-new biomarkers for early diagnosis of AD and brand-new targets for disease-modifying therapies. These discoveries may have wide-ranging clinical ramifications that affect other neurodegenerative diseases where reactive astrogliosis is also seen. The study offers important new information on the early indicators of AD. It is crucial to comprehend the full scope of the illness and identify those at risk of developing it.

Tip60 Enzyme's Role in Regulating Brain Protein Production Could be Key to Preventing AD

Researchers have identified a novel regulatory system in the brain that is essential for producing the proper kinds of proteins necessary for normal brain function. Dysfunction in this system may be a precursor to the onset of AD. The enzyme Tip60, which binds to specific RNA in the brain to regulate how they are spliced, is part of the mechanism. Disruptions in the splicing process, crucial for producing the variety of protein variants required for learning and memory, have been linked to the progression of AD. The researchers demonstrated that replenishing Tip60 levels in Alzheimer's models restored gene activation and provided protection against splicing errors.[16] This discovery might result in novel drug targets and biomarkers for early detection of AD. The impact of environmental changes on AD and the part Tip60 plays in this process are still being studied. In general, this

finding advances our knowledge of AD and has advantages for drug development, early detection, and a multifaceted strategy for treating the condition.

Limitations of Tau-based Mouse Models in Studying Late-Stage Dementia

Since many potential medications target the tau protein, which is involved in 75% of all dementias, the search for effective treatments for dementia has been disappointing. The tau-based mouse models currently being used in research may not accurately represent tau pathology in late-stage human dementia. According to the study, there are differences in the chemical alterations of tau protein between mouse models and human samples, with phosphorylation serving as the primary alteration in mice and people with early-stage dementia. However, distinct tau modifications, such as ubiquitination and acetylation, were present in late-stage and symptomatic human AD but not in the mouse models. According to the study, these mouse models may help test medications in dementia's early stages but may not accurately reflect symptoms or later stages of the disease. The need for better models that can take lifestyle, genetics, environment, and comorbidities into account in order to better reflect human dementia, which is the result of numerous biological insults sustained over a lifetime.[17] The study emphasises the limitations of the mouse models currently used to study late-stage dementia in humans. However, it offers insightful information about drug testing for early-stage disease and tau protein modifications. The thorough examination of tau protein modifications deepens our comprehension of how tau alters throughout dementia. According to the study, where tau phosphorylation is the main modification, the current mouse models may still help test medications in early-stage disease. The study also highlights the complexity of dementia in humans and the need for improved animal models that more accurately represent human disease. Overall, these findings advance our knowledge of dementia and may guide future investigations and drug development projects.

Targeting VDAC1: A Novel Approach to Treating AD

Voltage-dependent anion channel-1 (VDAC1), a key player in mitochondria-mediated cell death, was the target of a recent study that targeted this protein as the mitochondrial gatekeeper. The scientists created a small molecule called VBIT-4 bound to VDAC1 and showed appreciable improvements in AD mouse models. VBIT-4 prevented pathophysiological alterations linked to AD, including dysfunctional neuro-metabolic processes, neuroinflammation, and neuronal cell death. Additionally, it prevented a decline in cognitive abilities and supported neurons' normal development and function. Interestingly, the protective effects were obtained without significantly lowering Tau or amyloid plaques, refuting the conventional wisdom that these are the primary causes of AD. Targeting VDAC1 in this study represents a novel approach to treating AD, with the potential for preventive treatment.[18] The mitochondrial gatekeeper protein VDAC1, which drug candidates have not previously targeted, is the subject of the study's novel treatment proposal for AD. The study questions the widespread belief that amyloid or tau plaques are the primary causes of AD and raises the possibility of targeting VDAC1 as a preventive measure. The study offers a promising treatment strategy for AD with several positive outcomes, including a novel therapeutic strategy, notable advancements, neuroprotective effects, BBB penetration, challenging pre-existing theories, and the potential for preventive treatment.

Exploring Blood-based and Urine-based Biomarkers for Early Detection of AD

Traditional diagnostic biomarkers and blood-based biomarkers for AD have a strong correlation. These blood-based biomarkers are less invasive and cheaper than conventional biomarkers, and they may make AD diagnosis simpler while cutting costs and the number of tests needed by up to 49%. A study involving 200 patients demonstrates that blood-based biomarkers could be used for widespread AD screening because they can be identified through a straightforward blood test in a doctor's office, hospital, or lab. However, for normality/abnormality thresholds and standards to be applied by laboratories for clinical use, more study is required to define these technical details. Only then can routine clinical use be anticipated. However, using blood-based biomarkers in clinical settings can significantly lower the number of diagnostic tests, produce financial savings, and enhance patient outcomes.[19]

To investigate early detectable biomarkers for AD, researchers in China recently enlisted hundreds of volunteers with normal cognition or dementia. The study's primary subject was urine formic acid, a byproduct of formaldehyde. The researchers measured the formic acid levels in the individuals' urine and discovered that greater levels could indicate cognitive impairment. These findings might result in affordable testing for the early detection of AD.[20] If additional research confirms that urine formic acid may detect cognitive loss, then making this kind of testing (non-invasive and affordable) accessible to the general public would be a game changer in the fight against AD. One study examined the differences between people with and without AD using post-mortem brain tissue from both groups. In contrast to non-AD brain tissue, they discovered several p-tau indicators in AD brains. In separating AD disease from other illnesses that are characterized by abnormal tau protein, p-tau is more valuable than the other indicators. They found an intriguing new

biomarker, p-tau 198, beneficial for spotting abnormal tau protein in the brain at the early stages of AD.[21] Early detection and effective AD treatment may be revolutionized by a simple, affordable, and accurate blood test for p-tau 198. According to a different study, tiny nucleotides that attach to mRNAs can be found in the blood and detect a cellular imbalance in the brain. These nucleotides, known as microRNAs, are easily tested blood proteins that may be able to spot AD risk in their early stages. Targeting these microRNAs for therapy may prevent cellular damage in the brain since they direct mRNAs to protect the brain from inflammation. The most encouraging finding of the study is that the three microRNAs appear to be an appropriate, minimally intrusive biomarker, which is simple enough to measure in standard blood samples, like finger pricks. The results also suggest that this three-microRNA-signature test could be a starting step in identifying people who are at risk.[22] Another study found that 10 years before people develop AD, a molecule called glial fibrillary acidic protein (GFAP) present in the brain can be measured at increased levels in the blood. This protein specifies the incidence of immune cells in the brain, which reflects changes caused by AD even before the accumulation of tau protein. GFAP protein can be measured in a blood sample. Since it is elevated ten years before any symptoms of AD appear, measuring concentrations of this molecule could help in the early detection of AD.[23] Minimally invasive molecular biomarkers, which can be detected in a routine blood test to identify high-risk patients, will help in early intervention and prevention of AD. Recent studies also examined the presence of blood biomarkers in people with mild cognitive loss who later acquire Alzheimer's. The scientists discovered that baseline information derived from blood samples might forecast the development of MCI into Alzheimer's up to 3.5 years before a clinical diagnosis. The researchers concluded that these findings might open the door for further mechanistic studies and better evaluation of disease progression.[24] The findings from these studies highlight the positive potential of blood biomarkers for the early detection and prevention AD. These findings have the potential to significantly impact early intervention and prevention strategies for AD, ultimately improving patient outcomes and advancing our understanding of this devastating disease.

Hypothalamic Supra Mammillary Nucleus as a Target for Deep Brain Stimulation

Restoring cognitive and noncognitive functions in mouse AD models can be accomplished by deep brain stimulation of newly formed neurons in the adult hippocampus. The supra mammillary nucleus (SuM), located in the hypothalamus, was stimulated by the researchers using two mouse models of AD. As a result, new neurons were produced, improving connections with other brain regions. However, only when these enhanced new neurons were chemogenetically activated were the behavioural improvements observed. In addition, the activation of new neurons modified with SuM resulted in activating protein pathways linked to enhanced memory function and removing plaques linked to AD. Using these findings as a foundation, the researchers plan to create potential therapeutics for treating AD and related dementia.[25] The study identifies the hypothalamic SuM as a target for deep brain stimulation. It is suggested that a multi-level enhancement strategy may be required for behavioural recovery. The activation of new neurons modified with SuM is linked to enhanced memory function and removing plaques linked to AD. These findings shed light on potential therapeutic approaches and emphasise the significance of addressing cognitive and noncognitive functions in AD research.

PRZ-18002 to Selectively Induce the Degradation of p-p38

A new method that targets and degrades the post-translationally altered protein known as p-p38, which is closely related to AD, has been discovered by scientists. Such modified proteins are "undruggable," as traditional medications have trouble in effectively focusing on them. However, the team found a substance known as PRZ-18002 to selectively induce the degradation of p-p38 while having no effect on related proteins or its inactivated form. PRZ-18002 enhanced cognitive function and decreased disease-related brain chemistry when tested in AD mouse models.[26] New treatment options may be possible due to recent research on the targeting and degradation of this modified protein linked to AD. This study used a substance that selectively breaks down the target protein, p-p38, which is involved in the onset of AD and is difficult to target with conventional drugs. The drug's action was selective and specific, minimizing off-target effects. This study creates avenues for future research and suggests potential treatments for other diseases involving altered proteins. Overall, it represents a significant step towards discovering effective AD treatments and investigating cutting-edge strategies for taking on difficult protein targets in various diseases.

Aducanumab and Lecanemab the First "Disease-modifying" Medications for Alzheimer's

The Food and Drug Administration has granted accelerated approval to two medications, aducanumab and lecanemab, in July 2021 and January 2023, respectively.[27,28] The majority of AD treatments only reduce symptoms and enable those who are afflicted to function for longer than they would otherwise. These are the first "disease-modifying" medications for

Alzheimer's. They function by removing the beta-amyloid plaques that accumulate in the brains of Alzheimer's patients. Since these plaques obstruct nerve impulse transmission, removing the plaques should enhance the cognitive function of individuals with AD.[27] Lecanemab users showed a 27% slower rate of cognitive decline than lecanemab placebo users after an 18-month follow-up, according to the research.[29] The most frequent adverse reaction to the medication is an infusion-related reaction, which can include momentary symptoms such as flushing, chills, fever, rash, and body aches (26.4% of participants vs 7.4% in the placebo group). Further, 75% of these reactions occurred after the first dose, and 96% were mild to moderate. Amyloid-related imaging abnormalities with edema, or fluid formation on the brain, were another possible side effect of lecanemab. However, 12.6% of trial participants experienced this, compared to 1.7% in the placebo group. "It typically has no symptoms when it happens, but we can see it on MRI scans." Lastly, compared to 9% in the placebo group, 17.3% of trial participants experienced amyloid-related imaging abnormalities with brain bleeding.[29] While the adverse reactions mentioned are essential to be aware of, it is worth noting that most of these reactions were mild to moderate. Additionally, the occurrence of infusion-related reactions after the first dose suggests that subsequent doses may be better tolerated. Furthermore, the fact that the symptoms of amyloid-related imaging abnormalities may not have any noticeable symptoms, but can be detected through MRI scans, indicating that close monitoring and early detection can be possible. It is also worth noting that the percentage of participants who experienced these adverse reactions is relatively small compared to the overall trial participant group. Overall, these adverse reactions are manageable with proper monitoring and care, and most trial participants did not experience severe symptoms.

Advancements in Dementia Vaccines: Promising Results from Ongoing Clinical Trials

Several dementia vaccines are undergoing clinical trials to examine their efficacy and security. In November 2021, Brigham and Women's Hospital in Boston began a phase 1 clinical trial for a nasal vaccination against AD. The vaccine makes use of Protollin, an immune modulator, which activates white blood cells in lymph nodes to clear beta amyloid plaques, a symptom of AD. The trial aims to ascertain the vaccine's safety and tolerability as well as how it affects participants' immune responses. If developed successfully, the vaccine might serve as a nontoxic treatment for AD and other neurodegenerative disorders. An important step towards creating a nasal vaccine for AD has been reached with this clinical trial, raising the prospect of brand-new treatments for this deadly condition.[30] The vaccine from Araclon Biotech, which targets beta-amyloid 40, is now undergoing a phase 2 clinical trial. A total of 24 patients with mild to moderate AD participated in a phase 1 clinical trial to assess the safety and tolerability of ABvac40, the first active vaccine against the C-terminal end of A-40. Depending on the study entry time, patients were divided into three groups and randomly assigned to receive ABvac40 or a placebo. Two half-doses of ABvac40 or a placebo were given to the first group, while two and three full doses of ABvac40 were given to the second and third groups, respectively. Treatments were given subcutaneously at intervals of 4 weeks while keeping patients, caregivers, and researchers in the dark. The main goal was to evaluate the safety and tolerability of ABvac40 by keeping track of adverse events (AEs). In total, 18 patients experienced 71 AEs, of which 11 (69%) occurred in the ABvac40 group and 7 (88%) in the placebo group ($p = 0.6214$). Importantly, during the course of the study, no sulcal effusion, vasogenic edema, or microhemorrhages were found in patients receiving ABvac40, pointing to a good safety profile. Additionally, 11 of 12 patients (or 92%) who received three injections of ABvac40 developed specific anti-A40 antibodies, demonstrating the vaccine's immunogenicity. These findings point to ABvac40 having a favorable safety and tolerability profile, with a low incidence of negative side effects and a predictable immune response in the majority of patients. However, more research is required to confirm these results and examine the clinical efficacy of ABvac40 in the treatment of AD, including a phase II clinical trial.[31] A phase 1B/2A clinical trial for a tau-targeted vaccination against AD is being conducted by the Swiss biopharmaceutical company AC Immune SA. One of the main findings was that anti-pTau IgG titres significantly increased just two weeks after the first injection of the mid-dose of ACI-35.030, and that anti-ePHF IgG titres significantly increased as early as two weeks after the second injection at week eight of the mid-dose. A class switch from IgM to IgG was seen in the immune response, which was shown to last over an initial 26-week period. With no clinically significant safety issues reported to date, the interim safety data further supported ACI-35.030's favorable safety and tolerability profile. ACI-35.030 has been advanced into the late-stage development phase with the addition of a total of 24 AD participants from the mid-dose sub-cohort to the ongoing phase 1b/2a study. By focusing on pathological pTau, a precursor to tau accumulation that can be found using imaging techniques, ACI-35.030 may have the potential to be an early intervention for AD, according to the encouraging results of the interim data.[32] In summary, the ongoing clinical trials for dementia vaccines reflect advancements in research, diverse approaches to targeting dementia, progress in phase 1 and 2 trials involving human participants, collaborative efforts among organizations globally, and the potential for prevention or modification of the disease process. These positive aspects highlight the increasing interest and investment in finding potential treatments for dementia and the efforts to tackle the disease from different approaches.

Conclusion

In conclusion, the findings presented in this manuscript highlight the significant advancements in AD research and treatment, underscoring the importance of understanding the disease at both the individual and community levels. The use of innovative techniques such as PET-based algorithms to simulate amyloid plaque development has revealed the concept of an "amyloid clock," providing valuable insights into AD progression and guiding the timing of interventions and alternative therapies. Moreover, the identification of genes such as Surf4 that regulate beta-amyloid toxicity, and the role of the translocator protein in microglial energy production and beta-amyloid clearance, offer potential therapeutic targets for AD. Additionally, the use of advanced brain mapping methods to detect subtle changes in brain function in the early stages of AD has contributed to our understanding of the disease, with unique functional connectomes associated with amyloid-beta buildup providing insights into early changes in brain connectivity and their impact on cognitive function. The discovery of Nptx2 as a regulator of the complement system in the adult brain also holds significant implications for AD research, with the potential for therapeutic approaches targeting the complement system to prevent or treat neurodegenerative diseases, including AD.

Furthermore, the recent accelerated approvals of aducanumab and lecanemab as disease-modifying medications that target beta-amyloid plaques, along with ongoing clinical trials for dementia vaccines targeting beta-amyloid and tau proteins, offer promising developments in AD treatment. In addition, innovative approaches such as deep brain stimulation of newly formed neurons in the adult hippocampus and targeting VDAC1, a mitochondrial protein, have shown potential in restoring cognitive function in AD mouse models, challenging conventional understanding of the primary causes of AD. These recent advancements in research and treatment offer hope for more effective therapies for AD and related dementias in the future. The multidisciplinary research approaches employed in these studies have enhanced our understanding of AD at both individual and community levels, paving the way for improved diagnostics, interventions, and therapies for this devastating neurodegenerative disease. Continued research in this field has the potential to significantly impact the prevention, diagnosis, and treatment of AD, bringing us closer to effectively managing and ultimately overcoming this challenging condition.

Abbreviations

AD, Alzheimer's disease; PET, positron emission tomography; GFAP, glial fibrillary acidic protein; 7nAChRs, astrocytic 7-subunit of the nicotinic acetylcholine receptors; VDAC1, Voltage-dependent anion channel-1; SuM, supra mammillary nucleus; AEs, adverse events.

Authors' Contribution

The conceptualization was done by HSR and HF. The literature and drafting of the manuscript were conducted by HSR, HF, BSR, MAS, and FR. The editing and supervision were performed by HSR and HF. All authors have read and agreed to the final version of the manuscript.

Statement of Ethics

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