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NEUROPROTECTION

GUIDELINE

Preserving cognitive function in patients with Alzheimer's disease: The Alzheimer's disease neuroprotection research initiative (ADNRI)

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Abstract

The global trend toward aging populations has resulted in an increase in the occurrence of Alzheimer's disease (AD) and associated socio-economic burdens. Abnormal metabolism of amyloid-β (Aβ) has been proposed as a significant pathomechanism in AD, supported by results of recent clinical trials using anti-Aβ antibodies. Nonetheless, the cognitive benefits of the current treatments are limited. The etiology of AD is multifactorial, encompassing Aβ and tau accumulation, neuroinflammation, demyelination, vascular dysfunction, and comorbidities, which collectively lead to widespread neurodegeneration in the brain and cognitive impairment. Hence, solely removing Aβ from the brain may be insufficient to combat neurodegeneration and preserve cognition. To attain effective treatment for AD, it is necessary to (1) conduct extensive research on various mechanisms that cause neurodegeneration, including advances in neuroimaging techniques for earlier detection and a more precise characterization of molecular events at scales ranging from

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cellular to the full system level; (2) identify neuroprotective intervention targets against different neurodegeneration mechanisms; and (3) discover novel and optimal combinations of neuroprotective intervention strategies to maintain cognitive function in AD patients. The Alzheimer's Disease Neuroprotection Research Initiative's objective is to facilitate coordinated, multidisciplinary efforts to develop systemic neuroprotective strategies to combat AD. The aim is to achieve mitigation of the full spectrum of pathological processes underlying AD, with the goal of halting or even reversing cognitive decline.

KEYWORDS
Alzheimer's disease, early intervention, neural regeneration, neuroprotection, systematic perspective

1 | INTRODUCTION

Alzheimer's disease (AD), the most common neurodegenerative disorder, is currently posing a threat to the health of approximately 35 million elderly individuals worldwide.[1] It was listed as the seventh-leading cause of death in 2020.[2] The total estimated global socioeconomic burden of AD exceeds $1.3 trillion annually, and it is expected to double by 2030.[3] AD places a tremendous burden on not only individuals but also their families and the healthcare systems. This situation has led to an urgent requirement for efficient interventions against this devastating disease.

Accurate diagnosis and efficient treatment are two of the key aspects for AD intervention. Over the past two decades, several cohort studies have been launched to identify neuroimaging measures and biomarkers for AD diagnosis,[4] such as the Alzheimer's Disease Neuroimaging Initiative, the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing, and the Dominantly Inherited Alzheimer Network. These studies facilitated the development of standardized methods for magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid (CSF) detection of AD biomarkers and promoted the establishment of the A (amyloid-β [Aβ] deposition)—T (pathologic tau)—N (neurodegeneration) framework.[5] They shifted the definition of AD from a syndromic to a biological construct and provided a more reliable and accurate method for monitoring disease progression. Importantly, we are now capable of accurate and early AD diagnosis. Hence, it is now the time to focus our attention on early treatment strategies for patients diagnosed with AD.

2 | CURRENT STATUS AND CHALLENGES OF AD TREATMENTS

The development of new AD therapies has always been challenging with the success rate of new drug development for AD being far below industry average.[6] Currently, approved pharmacological AD treatments are mainly divided into symptomatic drugs and disease-modifying treatment (DMT) interventions. Symptomatic drugs, such as memantine, mainly work by cognitive enhancement or by controlling neuropsychiatric symptoms, without affecting the underlying biological causes of AD. These medications can only temporarily improve or maintain neuronal signaling and function, but they cannot reverse or halt AD progression. Therefore, there is an urgent need for DMT interventions that directly modify the AD-specific pathobiological changes in the brain and exert neuroprotective effects, preventing diffuse neuronal cell loss. Recently, two DMT interventions, aducanumab,[7] and lecanemab,[8] both being monoclonal antibodies targeting brain Aβ plaques, have achieved some clinical success and have been approved by FDA for the treatment of mild cognitive impairment or mild dementia due to AD. Even though the long-term safety and clinical efficacy of these two DMT interventions require further evaluation, their advent may indicate the dawn of a new era in AD therapy.

However, we still need to recognize that the current Aβ-targeting approaches can only slow the progression of AD but cannot reverse or even halt the disease process. Therefore, additional interventions that can rescue cellular and circuit function in both early and advanced AD stages will be crucial for improving the patients' quality of life, and, therefore, should be the ultimate goal of therapeutic developments for AD. It is hence paramount for the global research community to focus attention on disease mechanisms and on how to stop or even reverse cognitive decline.

3 | NEUROIMAGING FROM CELLULAR TO FULL SYSTEM LEVEL IN AD

Accurate diagnosis and efficient treatment are two key aspects of AD intervention with the aim of neuroprotection. Several cohort studies have allowed identification of neuroimaging measures and biomarkers for AD diagnosis,[4] demonstrating the capacity of these techniques for the evaluation of anatomic and functional changes in the brain. Moreover, advances in the field of nanotechnology have allowed extension of the capacities of these techniques, enabling them to become truly molecular imaging tools with which to visualize molecular events at the cellular to the full brain scale, allowing

for a better understanding of AD pathophysiology. Thus, neuroimaging represents an invaluable asset in the development of novel therapies for the treatment of AD.

MRI is, possibly, the most versatile medical imaging technique available both at clinical and preclinical levels. Its noninvasiveness, image quality (in terms of image resolution and contrast generation), and multimodality allow detailed brain imaging at structural, vascular, metabolic, and functional levels.[9] In the field of AD, MRI is used to assess changes in brain structure, allowing the study of brain atrophy,[10] detecting events that may explain nondegenerative cognitive impairment,[11] and providing information about the integrity of white matter and neuronal circuits through all variants of diffusion-weighted imaging (e.g., diffusion-weighted imaging, diffusion tension imaging, diffusion kurtosis imaging, fiber tracking, neurite orientation dispersion, and density imaging, soma and neurite density imaging, etc.[12]). Cerebrovascular alterations assessed through MRI-based cerebral blood flow measurements (CBF-MRI) can be used for the definition of early diagnosis of cognitive impairment,[13] along with magnetic resonance spectroscopy (^{1}H-MRS) or even more advanced spectroscopic approaches such as glutamate-weighted chemical exchange saturation transfer imaging. This enables us to study metabolic alterations associated with AD progression.[14] One of the most valuable MRI modalities in AD is resting-state functional MRI, which has been used to show how AD impairs multiple functional networks across the brain, including the default mode network, the salience network, or the dorsal attention network.[11]

Nuclear imaging techniques such as PET and single photon emission computerized tomography are methods of choice to study important hallmarks of AD by using radioactive tracers that specifically bind to brain metabolites, protein aggregates, or neurotransmitters, or can visualize glucose metabolism, inflammatory events, and other processes involved in the AD pathophysiology. Nuclear medicine imaging techniques are extremely sensitive and can detect AD biomarkers at very early stages. PET is the gold standard technique for tau and Aβ-specific imaging as well as for visualizing glucose metabolism in the brain.[11] Interestingly, PET has been used to show that tau may propagate along functional networks, instead of disseminating locally, but that this is not the case for amyloid.[15] Four different patterns for tau deposition have been described, potentially indicating AD subtypes, with different demographic and cognitive profiles, as well as outcomes.[16] However, these techniques lack the excellent spatial resolution and tissue contrast of MRI.

The recent introduction of powerful hybrid clinical imaging modalities, such as PET-MRI allows us to capitalize on the advantages of each individual imaging modality while at the same overcoming their respective limitations. Using PET-MRI, the A/T/N staging system has been defined, in which AD biomarkers are divided into three binary categories. In this system, A stands for β-amyloid (measured in the brain by PET or alternatively using Aβ42 in CSF), T stands for tau (measured with specific PET tracers), and N stands for neurodegeneration or neuronal injury (determined by FDG-PET and structural MRI).

Each of these three biomarkers is defined as positive or negative, and their combination results in a descriptive system for the categorization of the individual AD stage. These and other imaging-based tools leaning on artificial intelligence, machine learning, deep neuronal networks, and other state-of-the-art computing tools may ultimately advance to automated AD diagnosis and prognosis.[17] Thus, medical imaging applications in AD are a continuously evolving discipline, being of paramount importance.

4 | INTERVENTIONS OF AD FROM THE PERSPECTIVE OF NEUROPROTECTION

Neurons in the AD brain undergo widespread degeneration, which ultimately results in cognitive impairment. Although Aβ deposition is the most important pathological hallmark of AD, the removal of Aβ from the brain through Aβ antibodies can only delay the progression of the disease, as it cannot reverse the neuronal loss (and related symptoms) that has occurred widely in the brain. Various cofactors such as genetics, inflammation, vascular issues, metabolism, and environment can influence neurodegeneration. We believe that only by targeting these pathological changes through different neuroprotective and potentially other therapeutic strategies can the cognitive function of AD patients be truly preserved or even restored (Table 1). Thus, holistic perspectives for neuroprotection strategies, focusing on the brain as well as the periphery, are discussed herein.

4.1 | Central neuroprotective intervention

4.1.1 | Neurotrophic factors (NTFs)

NTFs, such as neurotrophins and brain-derived neurotrophic factor (BDNF), are endogenous soluble proteins supporting neurite outgrowth, neuronal cell differentiation, and survival. The dysregulation of NTFs and their receptors in AD is a key pathological process in the development of sporadic AD.[46–48] Loss in NTFs and their receptors also occurs with normal aging and is associated with normal cognitive decline, which seems to be accelerated in AD. The NTF ability to promote neuronal survival under pathological conditions has driven the idea that direct delivery of NTFs might be beneficial in AD.[49] Indeed, a gene therapy-based approach for nerve growth factor delivery has shown promise in a clinical phase 1 trial in AD patients.[18] Instead of direct NTF delivery, the application of NTF receptor agonists could also exert neuroprotective effects.

TABLE 1 Targets of neuroprotective treatments for AD.

Targets		Evidence	References
Central neuroprotective intervention	NTFs	Gene delivery of NGF into the basal forebrain shows promise in clinical trial in AD patients	[18]
	Antineuroinflammation	Pharmacological activation of microglial Piezo1 channels ameliorate brain Aβ burden and cognitive impairment	[19]
		Replacement of reactive microglia in the aged brain reverses cognitive deficits in mice	[20]
	Astrocytic protection	Selective removal of astrocytic *APOE4* protects against tau-mediated neurodegeneration in PS19/APOE4 mice	[21]
		Inhibition of the astrocytic protein S100B protects CA1 pyramidal neurons in AD mice model	[22]
	Remyelination	Genetically or pharmacologically enhancing myelin renewal reverses cognitive dysfunction in APP/PS1 mice	[23]
		Facilitating oligodendrocytes cholesterol transport increases myelination and improves learning memory in *APOE4*/*4*-TR mice	[24]
	Stem cell therapy and neural regeneration	Transplantation of NSCs increases adult hippocampal neurogenesis, rescues cognitive impairment in AD mice models	[25, 26]
		Overexpression of NeuroD1 in reactive astrocytes of 5xFAD mice successfully converted the reactive astrocytes into functional neurons	[27]
	Glucose metabolism regulation	Administration of GLP-1 agonist prevents memory impairments and synapse loss in APP/PS1 mice	[28]
	Vascular system protection	Blocking RAGE at the BBB effectively reduces Aβ influx into the brain, and improves cognitive performance in APP/PS1 mice	[29]
	Meningeal lymphatic protection	Augmentation of meningeal lymphatic drainage in aged mice improves cognitive function	[30]
	Targeting prion-like proteinopathy	Improving the O-GlcNAcylation of tau prevents the development of tau pathology and functional deficits in PS19 mice	[31]
Peripheral neuroprotective intervention	Peripheral clearance of pathological substances	Enhancing the kidney's Aβ/tau clearing capacity either by peritoneal dialysis or pharmaceutical treatment mitigates cognitive impairment	[32–34]
		Stimulating Aβ uptake and metabolism by blood monocytes alleviates AD-related pathology in APP/PS1 mice	[35]
	Peripheral neuroprotective factors	Exposing aged mice to blood from younger donors enhances hippocampal neurogenesis and boosts memory	[36, 37]
Neuroprotection by lifestyles changes	Physical exercise	Exercise plasma transfusion boosts memory and dampens brain inflammation	[38]
	Food and nutrition	Mediterranean diet and ketogenic diet show beneficial effects in AD patients	[39, 40]
		Vitamin D, DHA, Ω-3/Ω-6, minerals, and phytochemical antioxidants supplementation exhibit neuroprotective effects in preclinical AD models and in clinical trials	[41–45]

Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; BBB, blood–brain barrier; DHA, docosahexaenoic acid; GLP-1, glucagon-like peptide-1; NGF, nerve growth factor; NSCs, neural stem cells; NTF, neurotrophic factor; RAGE, receptor for advanced glycation end products.

For instance, the BDNF mimetic compound 7,8-dihydroxyflavone, a potent small molecular TrkB agonist, displays therapeutic efficacy against AD in mice.[50,51] Thus, the continued development of NTFs for therapy and the determination of whether this potent class of biologically active molecules will maintain the functional state of neurons in the AD brain are important lines of further investigation.

4.1.2 | Antineuroinflammation

Large-scale genome-wide association studies (GWAS) indicate that about half of the AD risk genes are involved in immune processes.[52] This emphasizes the importance of immune dysfunction for AD development. Under physiological conditions, the immune function in the CNS is maintained in a dedicated balance to help the brain to detect and eliminate pathogens and cell debris without causing neuronal death. However, in the context of AD, neuroinflammation tends to be a chronic process that fails to resolve and is thought to accelerate disease progression.[53]

Neuroinflammation is generally characterized by the production of proinflammatory cytokines by immune cells in the brain. The persistent or excessive release of proinflammatory molecules can lead to synaptic dysfunction, neuronal death, and finally cognitive impairment.[54] Therefore, being able to preserve cognitive function in AD will not be possible without controlling neuroinflammation. Currently, the number of clinical trials targeting neuroinflammation exceeds trials focusing on other mechanisms such as targeting Aβ, tau, and neurodegeneration.[55] Most of these trials applied broad-spectrum anti-inflammatory drugs to reduce inflammation, or antibodies to eliminate proinflammatory cytokines. However, none of these approaches targeted key regulators of neuroinflammation, that is, activated or dysregulated immune cells, and so they cannot fundamentally prevent neuroinflammation from occurring. This may be one of the reasons why current trials targeting neuroinflammation have not achieved clinical success.

Immune cells involved in neuroinflammation are mainly microglia and infiltrating monocytes/macrophages. There are also astrocytic contributions to neuroinflammation. In the process of AD, both microglia and astrocytes transit from a neurotrophic state to neurotoxic state,[56] but the underlying mechanism remains to be elucidated.[57] Recently, it was shown that a mechanotransduction ion channel, Piezo1, expressed in microglia orchestrates Aβ clearance by enhancing microglial survival, phagocytosis, and lysosomal activity.[58] Pharmacological activation of microglial Piezo1 ameliorated cerebral Aβ burden and cognitive impairment.[19] Replacement of reactive microglia also exhibited great potential in preserving cognitive function in aged mice.[20]

Future investigations focusing on sensory mechanisms, downstream signaling pathways, and regulatory checkpoints of different immune cells in the brain will greatly advance our understanding of the contribution of neuroinflammation in AD pathogenesis and possibly help in identifying novel therapeutic targets.

4.1.3 | Astrocytic protection

Astrocytes, which are the most abundant cell type in the CNS, play a crucial role in maintaining CNS homeostasis in terms of ion concentration balance, neurotransmitter buffering, synaptogenesis, stabilizing blood–brain barrier (BBB) function, and the secretion of neuroactive agents. In AD, however, astrocytes not only cease neurotrophic support but also secrete neurotoxic factors, which can accelerate disease progression.[56,59] Thus, enhancing the beneficial effects of astrocytes while dampening their negative properties shows great potential for disease modification in AD.

APOE4 is the strongest genetic risk factor for sporadic AD and is mainly expressed by astrocytes.[60] A recent study demonstrated that selective removal of astrocytic *APOE4* strongly protects against tau-mediated neurodegeneration.[21] Additionally, pentamidine, an inhibitor of the astrocytic protein S100B, has been shown to protect CA1 pyramidal neurons in a mouse model of AD by reducing expression of GFAP, S100B, and the receptor for advanced glycation end products (RAGE).[22] Other signaling cascades associated with astrocytes, such as signal transducer and activator of transcription 3, nuclear factor-kappa B, and transforming growth factor beta, have also been implicated in AD pathology[56,61] and should be considered as putative targets for neuroprotection in future studies.

4.1.4 | Remyelination

AD has been mainly considered a gray matter disorder; nevertheless, accumulating evidence emerging from imaging, postmortem, and genetic association studies suggests myelin impairment in AD.[62,63] The myelin sheath is a lipid-rich multilamellar membrane that wraps around neuronal axons and thereby increases the conduction velocity of action potentials. In addition, it offers the necessary trophic support to the wrapped axons. Even though it is not clear whether alterations in myelination are directly involved in AD pathogenesis or just the secondary effect of neurodegeneration, enhancing myelin renewal was able to reverse cognitive dysfunction in AD mouse models.[23] Altered cholesterol localization coincides with reduced myelination in AD brains. Pharmacologically facilitating cholesterol transport has been shown to increase myelination and improve learning and memory in AD mice.[24] Therefore, future efforts to unveil the contribution of myelin dysfunction to AD and developing efficient myelination enhancement strategies require a greater effort in AD research.

4.1.5 | Stem cell therapy and in vivo neural regeneration

Cognitive impairment in AD is due to neuronal degeneration and loss, leading to dysfunction and damage of neural circuits. Therefore, to improve cognitive function,

it is necessary to replace lost neurons and repair damaged neural circuits. Hippocampal neurogenesis persists in the adult brain to maintain learning and memory, but is significantly reduced in AD.[64] Replenishing the exhausted pool of neural stem cells (NSCs) in the brain may help to rebuilt neural circuits and preserve cognitive function. Both in situ and noninvasive transplantation (like intranasal transplantation) of NSCs can increase adult hippocampal neurogenesis and mitigates cognitive impairment in AD mice.[25,26] However, repairing neuronal circuits in the mammalian brain can be challenging due to the absence of anatomical cues that guide brain development during embryogenesis and fetal development. One promising approach is the co-transplantation of NSCs with bioengineered support cells that express target proteins. These support cells have the potential to produce growth factors that enhance the survival and migration of NSCs, eliminating the need for genetical engineering.[65] Several cell populations used in the treatment of neurodegenerative diseases have demonstrated neuroprotective benefits,[66] often referred to as "bystander effects". These cells may also contribute to the prevention of neurodegeneration in AD. Another significant challenge in stem cell-based therapy for AD is the difficulty of delivering stem cells in such a way that they can target all affected brain areas. Direct injection into the brain tissue provides limited coverage,[67] while intravenous administration is not effective with cells lost to filtering organs such as the lungs or liver,[68] and also the likelihood that only a few cells cross the BBB. A promising approach is to use the intra-arterial route, which allows for more widespread and uniform distribution of cells to the targeted brain region. Imaging techniques that enable real-time monitoring of cell distribution are of great interest, as they can increase precision and safety.[69] An alternative approach that is being investigated in preclinical studies is the use of stem cell-derived extracellular vesicles (EVs). Several studies reported that the intranasal administration of mesenchymal stem cells-derived EVs leads to improvements in mouse models of AD.[70,71]

Instead of direct cell transplantation, a new technology has emerged for the regeneration of neurons through in vivo conversion of glial cells.[72,73] Specifically, the overexpression of the neural transcription factor NeuroD1 in reactive astrocytes of 5xFAD mice has successfully converted these astrocytes into functional neurons.[27] In addition to NeuroD1 and the AD mouse model, other transcription factors such as Ngn2, Ascl1, and Sox2 have been reported to convert astrocytes into neurons in various animal models,[74–76] including the first nonhuman primate stroke model.[77] Considering that human brain has 86 billion neurons, the loss of just 1% of neurons in the brain of an AD patient would amount to a loss of 860 million neurons. This extensive neuronal loss may explain why numerous drugs have failed to restore cognitive function in AD patients. Therefore, it may be crucial to combine neuroprotective strategies with in vivo neural regeneration to maximize the benefits for AD patients, particularly those in mid-stage or even late-stage AD.

4.1.6 | Cerebral glucose metabolism regulation

The brain is the most energy-demanding organ in the human body. Even though it constitutes only 2% of the total body weight, it accounts for 20% of an individual's energy expenditure.[78] Insufficient energy supply to the brain swiftly results in irreversible impairment of brain function.[79] The major energy source for the human brain is glucose; unlike in peripheral organs, the brain has a very limited availability of other sources of energy (such as fatty acids). Glucose hypometabolism is one of the earliest pathologic events in AD.[80] Reduced glucose metabolism in the brain may be caused by the decreased expression of glucose transporters,[81] decreased activities of enzymes involved in glucose metabolism,[82] and disrupted insulin/insulin-like growth factor (IGF) signaling pathway.[83] Among them, the insulin/IGF signaling pathway is currently most intensively studied. In addition to participating in cerebral bioenergetics regulation, the insulin/IGF signaling pathway also contributes to Aβ metabolism, tau phosphorylation, and neuroinflammation.[84] Thus, AD is proposed to be type III diabetes, and this concept has emerged as a very promising area of AD research.

An intriguing therapeutic target is the glucagon-like peptide-1 receptor (GLP-1R). Glucagon is an endogenous insulinotropic hormone that participates in the homeostatic regulation of insulin and glucose. The activation of the GLP-1Rs affects neuronal excitability, synaptic plasticity, and memory processes, and GLP-1 analogs have been successfully tested in both preclinical models of neurodegeneration and clinical trials.[28,85] Future efforts should be made to develop more effective approaches to restore cerebral glucose metabolism, thereby offering a therapeutic benefit to AD patients.

4.1.7 | Cerebral blood vessel protection

Cerebral blood vessels and the BBB function as the gatekeepers for the shuttling of ions, molecules, and cells between the blood and the brain, protecting the brain from peripheral toxins and pathogens.[86] They also mediate the clearance of brain-derived neurotoxins such as Aβ and pTau, as well as metabolic waste, into circulation. A recent single-nuclear transcriptome profiling study in human brain vascular and perivascular cells revealed that 30 of the top 45 AD risk genes identified by GWAS analysis are expressed in the cerebral vasculature,[87] which further supports the link between the vascular system and AD. Neuroimaging studies indicate that loss of BBB integrity is an early sign of AD and may contribute to cognitive dysfunction in AD.[88,89] Postmortem studies show that the vast majority of patients diagnosed with AD invariably bear some degree of cerebral vascular pathology, such as cerebral small vessel disease (cSVD).[90] Conditions typically associated with cSVD such as hypertension may increase RAGE expression at the BBB, fostering Aβ influx to the brain, and accelerating cerebral Aβ deposition.[91] Blocking RAGE can effectively reduce Aβ influx and improve cognitive performance in APP/PS1 mice.[29] Altogether,

these pieces of evidence indicate that there is potential in targeting the vascular system for AD treatment. However, even though existing studies in both animal models and patients have confirmed that the BBB plays a key role in AD etiology, it is yet to be explored as a therapeutic target.[92] Thus, future studies focusing on restoring the impaired BBB, targeting the BBB clearance machinery, or eliminating the consequences of BBB breakdown[93] might promote drug research and discovery for AD.

4.1.8 | Meningeal lymphatic protection

The brain has traditionally been regarded as an immune-privileged organ[94] due to the limited entry of immune cells into the healthy brain parenchyma. However, several groups have recently discovered and characterized lymphatic vessels within the meninges.[95,96] It is now widely recognized that meningeal lymphatic vessels play an essential role in maintaining brain homeostasis by draining neurotoxic substances (such as Aβ) from the brain into the cervical lymph nodes,[97] and lymphatic vessel dysfunction may be one of the underlying factors for worsened Aβ pathology and cognitive deficits in AD.[98] Moreover, impaired meningeal lymphatic drainage could exacerbate the microglial inflammatory response in AD.[99,100] In addition, abnormal lymphatic function can affect the effectiveness of immunotherapy targeting Aβ. The ablation of meningeal lymphatic vessels in 5xFAD mice worsened the outcome after treatment with mouse chimeric analogs of aducanumab.[99] The above evidence suggests that lymphatic vessels play an important role in both the pathogenesis and prognosis of AD and represent an important target for AD treatment. Indeed, augmentation of meningeal lymphatic drainage in 5xFAD mice can facilitate the clearance of macromolecules from the brain, resulting in improved cognitive function.[30] Future studies should investigate the mechanisms that drive lymphatic vessel dysfunction, and develop feasible interventions to improve brain lymphatic drainage and ameliorate the progression of AD.

4.1.9 | Targeting prion-like proteinopathy

Tau pathology has been strongly correlated with *ante mortem* cognitive decline in AD patients.[101–103] α-Synuclein (α-syn) pathology is present in 30%–50% of AD patients, and is associated with a more rapid cognitive decline and more severe neuropsychiatric dysfunction.[104,105] Heiko Braak and his colleagues discovered tau and α-syn pathology exhibiting clear progressive and hierarchical spreading patterns in *post-mortem* brains.[106–109] Both clinical and experimental observations support that inoculation with pathologic tau and α-syn can induce substantial prion-like protein aggregation[110–112] resulting in neurodegeneration and cognitive impairment.[113,114] This indicates that prion-like tau and α-syn spreading are both major triggers and drivers. Multiple pathways/mechanisms are involved in the cell-to-cell transmission of pathogenic prion-like seeds, including receptors,[115,116] cell death,[117] inflammation,[118] oxidative stress,[119] aggregation clearance,[120] and strain mediation.[121,122] All of those are potential therapeutic targets.

Uptake of prion-like seeds via receptors is required to initiate subsequent prion propagation and neurotoxicity. Genetic depletion and inhibition of these receptors effectively block cell uptake, prion propagation, neurodegeneration, and behavioral deficits.[115,116,123,124] After uptake, prion-like seeds can induce reactive oxygen species (ROS), activate poly (adenosine 5′-diphosphate-ribose) polymerase-1 (PARP-1), and cause DNA damage. Inhibition of PARP and depletion of PARP-1 can significantly alleviate prion propagation and associated neurodegeneration.[117] Not only neuronal cells but also glial cells play critical roles in these pathological processes. Inhibiting microglial activation induced by seeds can substantially reduce the activation of astrocytes and associated neurotoxicity.[118] Prion-like seeds can induce oxidative stress, which in turn induces further protein aggregation. This vicious circle drives disease progression. Nanozymes can strongly scavenge ROS induced by prion-like seeds, inhibit a feed-forward loop, and block prion-like seed propagation in vivo.[119] Tau and α-syn pathology are observed intracellularly; however, it is challenging to develop agents that can target intracellular pathogenic seeds. Nanobodies capable of specifically recognizing and clearing the fibrillar form of prion-like seeds were developed, and adeno-associated virus-based gene delivery methods provide an attractive approach to inhibit the propagation of prion-like seeds in preclinical models.[31,120] Diverse misfolded aggregates with distinct molecular conformations (strains) are a prion feature that causes a different disease phenotype. The strategies targeting strain mediation, such as inhibiting the strain inducer (i.e., poly adenosine 5′-diphosphate-ribose[117]) or adding strain modulator (i.e., glucocerebrosidase[120]), may provide an effective impact against prion-like propagation and neurotoxicity.

4.2 | Peripheral neuroprotective intervention

As outlined above, the development of AD is not caused by a single factor but involves multisystem and multilevel changes.[125] Many peripheral factors are involved in AD development, such as immune senescence,[126] metabolic[127] and cardiovascular[128] disorders, liver and kidney dysfunction,[32] gut microbiota disturbance,[129] or respiratory and sleep disorders.[130] Therefore, controlling system comorbidity and improving whole-body health will positively impact brain structure and function.

4.2.1 | Peripheral clearance of neurotoxic substances

Aβ and pathological tau have long been considered to be cleared by central metabolic pathways. But in fact, both brain-derived Aβ and tau can be cleared after being transported to peripheral organs and cells,[33,131]

such as the liver,[131] kidney,[32] spleen,[132] and blood monocytes.[133] This suggests that improving peripheral Aβ/tau clearance capacity could be a desirable therapeutic strategy for AD. For instance, enhancing the kidney's Aβ/tau clearing capacity through peritoneal dialysis[33,34] or pharmaceutical treatment[32] has been shown to mitigate cognitive impairment in AD mice. Stimulating monocytic Aβ uptake and metabolism through polysaccharide krestin, a modulator of innate immune signaling, could also alleviate AD-related pathology in AD mouse models.[35] Plasma exchange has shown potential in slowing the rate of cognitive decline in AD patients in clinical trials as well.[134] However, these concepts are still being explored in fundamental research, and future translational and clinical studies are necessary to evaluate the effectiveness and safety of this strategy in AD treatment.

4.2.2 | Systemic neuroprotective factors

Peripheral organs secrete NTFs to boost neurogenesis and reduce neuronal apoptosis, as indicated in heterochronic parabiosis models.[135] The circulatory system integrates signals from all organs and provides a route for crosstalk between peripheral organs/tissues and the brain. For example, exposing aged mice to blood from younger donors enhances hippocampal neurogenesis, induces immediate to early gene activation, increases dendritic spine density, and promotes vascular remodeling.[36,37]

However, due to the potential risks, it is unrealistic to directly apply young plasma transfusion for AD treatment. Hence, the identification of substances in young plasma such as peripheral NTFs that can exert neuroprotective effects is a subject worth further studying. Current research is mainly focused on plasma proteomics and several proteins that promote neurogenesis have been identified, including growth differentiation factor 11, metalloproteinase 2, colony-stimulating factor 2, and osteocalcin.[136,137]

Apart from the identification of neurotrophic proteins, the identification of potential neuroprotective metabolites in youthful plasma is equally important. Moreover, the investigation of exosomes in the plasma is also very promising. Exosomes are membrane-bound, secreted organelles, and are enriched in proteins, metabolites, and nucleic acids, which can reflect their cells of origin. Due to its single-membrane structure, the substances in the exosome are more stable than in plasma. Thus, proteomics, metabolomics, and miRNAomics studies on young plasma exosomes are promising approaches for the identification of new neuroprotective substances.

4.3 | Neuroprotection by lifestyle changes

4.3.1 | Physical exercise

It is now widely accepted that physical exercise can combat neurodegeneration and provide neuroprotection in elderly individuals. Both animal and clinical experiments have demonstrated that physical exercise enhances the proliferation and differentiation of NSCs, promoting NTFs secretion, and finally improving cognitive performance.[138]

However, little is known about the molecular mechanisms of how exercise affects brain health. It has been proposed that "exercise factors," secreted from muscle and other tissues into the blood, mediate this beneficial effect. A recent study found that transfusions of plasma obtained after exercise boosts memory and dampens brain inflammation.[38] Further studies showed that exercise can promote the secretion of myokines from muscles.[139] These myokines were then released into blood and cross the BBB to promote the expression of NTFs in the brain.[140] Animal experiments indicate that peripheral overexpression of myokines is sufficient to promote cognitive function.[141] Furthermore, liver metabolism also changes drastically during exercise. A recent study found that β-hydroxybutyrate produced by the liver during exercise promotes BDNF expression.[142] There is also evidence that exercise can improve cognitive function by promoting cerebral angiogenesis.[143] However, many growth factors need to reach a threshold level of expression to exert beneficial effects. This indicates that conventional behavioral/exercise interventions may not be of benefit as they are too short to trigger a significant increase in growth factors.[144]

In general, research in this area is still in its infancy. Future studies should focus on identifying new "exercise factors" that may improve physical exercise regimens (or exert effects similar to it) for elderly patients with AD and disabilities who cannot perform strenuous exercise.

4.3.2 | Food and nutrition

Nutrition is important for the health and well-being of people living with AD, as weight loss and malnutrition are important complications in AD patients.[145] Thus, maintaining and improving nutritional status in AD patients may help to delay AD development by promoting brain health. Some dietary patterns have been shown to be beneficial in AD, such as the Mediterranean diet[39] and the ketogenic diet.[40] In addition, certain active substances in the diet (for instance, vitamin D,[41] docosahexaenoic acid,[42] omega-3 and omega-6,[43] minerals,[44] and phytochemical antioxidants[45]) were identified as neuroprotective factors. As nutrition-related conditions can occur in all stages of AD, further basic and clinical studies are recommended to elucidate the exact mechanism of malnutrition and weight loss in AD patients and whether nutritional intervention can improve cognitive symptoms.

5 | SUMMARY

Over the last years, several clinical trials were launched trying to overcome AD, and three antibody-based DMT interventions targeting Aβ have achieved limited clinical success by slowing down the pace of AD in early stages. However, merely slowing down the decline of

cognitive function is not sufficient to achieve the clinical goal of AD treatment, which is to preserve the patient's cognitive function. As widespread neurodegeneration in the brain forms the biological basis of the patient's cognitive impairment, developing neuroprotective strategies should become the next important direction of AD treatment after Aβ clearance (Figure 1). However, this field has not garnered sufficient attention thus far, and the progress made has been limited. Furthermore, AD encompasses pathological alterations in numerous facets. Consequently, the objectives of future research lie in the precise classification of AD patients and the application of distinct combinations of intervention strategies tailored to individual patients.

Therefore, we convened a group of experts to jointly issue this initiative to emphasize the importance of neuroprotection research. ADNRI mainly focuses on the prevention of AD, which aims to prevent the loss of

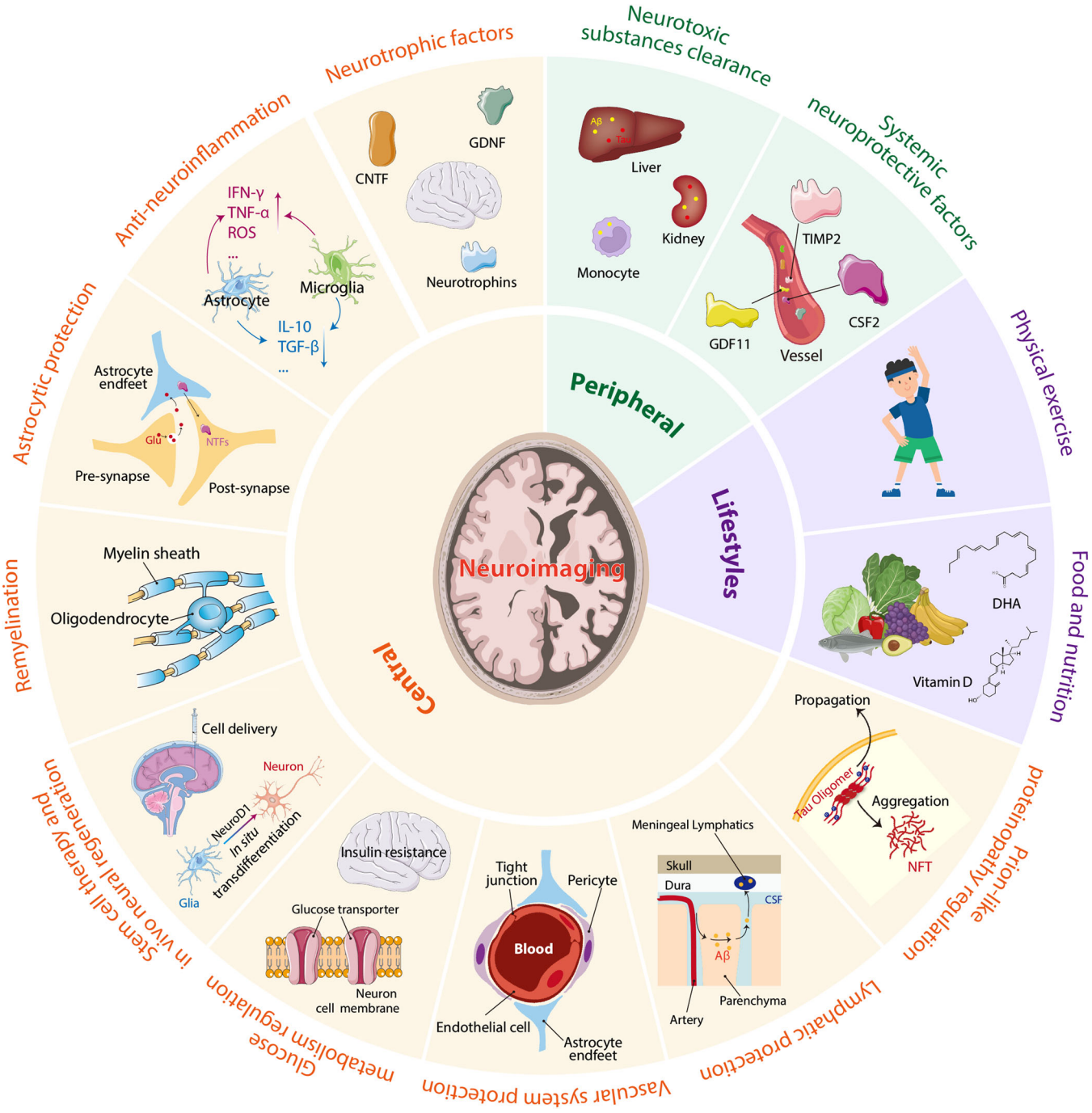

FIGURE 1 Neuroprotective interventions for AD. Main neuroprotective intervention targets for AD, including NTFs, antineuroinflammation, astrocytic protection, remyelination, stem-cell therapy and in vivo neural regeneration, glucose metabolism regulation, vascular system protection, lymphatic protection, prion-like proteinopathy regulation, peripheral neurotoxic substances clearance, systemic NTFs, and physical exercise, as well as food and nutrition. Investigations into advanced neuroimaging techniques for earlier and more precise characterization of molecular events at scales ranging from cellular to full system level are equally important as it is necessary for the evaluation of the beneficial effects of different neuroprotective intervention approaches. AD, Alzheimer's disease; CNTF, ciliary neurotrophic factor; DHA, docosahexaenoic acid; GDF11, growth differentiation factor 11; GDNF, glial cell-derived neurotrophic factor; IFN-γ, interferon-γ; NTFs, neurotrophic factors; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

neurons and the destruction of neural networks in the early stage of the disease through various neuroprotective strategies. We call on our colleagues around the globe to cooperate to reveal the mechanisms of neurological deficits in AD and identify effective neuroprotective targets, to carry out translational research, and to jointly achieve the goal of preserving the cognitive function of AD patients.

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Jie Liu: Resources (equal); writing—original draft (equal). **Heleen van Beusekom**: Conceptualization (equal); writing—review and editing (lead). **Xian-Le Bu**: Conceptualization (equal); writing—review and editing (equal). **Gong Chen**: Conceptualization (equal); writing—review and editing (equal). **Paulo Henrique Rosado de Castro**: Conceptualization (equal); writing—review and editing (equal). **Xiaochun Chen**: Conceptualization (equal); writing—review and editing (equal). **Xiaowei Chen**: Conceptualization (equal); writing—review and editing (equal). **Andrew N. Clarkson**: Conceptualization (equal); writing—review and editing (equal). **Tracy D. Farr**: Conceptualization (equal); writing—review and editing (equal). **Yuhong Fu**: Conceptualization (equal); writing—review and editing (equal). **Jianping Jia**: Conceptualization (equal); writing—review and editing (equal). **Jukka Jolkkonen**: Conceptualization (equal); writing—review and editing (equal). **Woojin Scott Kim**: Conceptualization (equal); writing—review and editing (equal). **Paula Korhonen**: Conceptualization (equal); writing—review and editing (equal). **Shen Li**: Conceptualization (equal); writing—review and editing (equal). **Yajie Liang**: Conceptualization (equal); writing—review and editing (equal). **Guang-Hui Liu**: Conceptualization (equal); writing—review and editing (equal). **Guiyou Liu**: Conceptualization (equal); writing—review and editing (equal). **Yu-Hui Liu**: Conceptualization (equal); writing—review and editing (equal). **Tarja Malm**: Conceptualization (equal); writing—review and editing (equal). **Xiaobo Mao**: Conceptualization (equal); writing—review and editing (equal). **Joaquim Miguel Oliveira**: Conceptualization (equal); writing—review and editing (equal). **Mike M. Modo**: Conceptualization (equal); writing—review and editing (equal). **Pedro Ramos-Cabrer**: Conceptualization (equal); writing—review and editing (equal). **Karsten Ruscher**: Conceptualization (equal); writing—review and editing (equal). **Weihong Song**: Conceptualization (equal); writing—review and editing (equal). **Jun Wang**: Conceptualization (equal); writing—review and editing (equal). **Xuanyue Wang**: Conceptualization (equal); writing—review and editing (equal). **Yun Wang**: Conceptualization (equal); writing—review and editing (equal). **Haitao Wu**: Conceptualization (equal); writing—review and editing (equal). **Lize Xiong**: Conceptualization (equal); writing—review and editing (equal). **Yi Yang**: Conceptualization (equal); writing—review and editing (equal). **Keqiang Ye**: Conceptualization (equal); writing—review and editing (equal). **Jin-Tai Yu**: Conceptualization (equal); writing—review and editing (equal). **Xin-Fu Zhou**: Conceptualization (equal); writing—review and editing (equal). **Marietta Zille**: Conceptualization (equal); writing—review and editing (equal). **Colin L. Masters**: Conceptualization (equal); writing—review and editing (equal). **Piotr Walczak**: Conceptualization (lead); funding acquisition (lead); writing—review and editing (lead). **Johannes Boltze**: Conceptualization (lead); funding acquisition (lead); writing—review and editing (lead). **Xunming Ji**: Conceptualization (lead); funding acquisition (lead); writing—review and editing (lead). **Yan-Jiang Wang**: Conceptualization (lead); funding acquisition (lead); writing—original draft (equal); writing—review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The authors have nothing to report.

ETHICS STATEMENT

The authors have nothing to report.

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