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ORIGINAL RESEARCH

# Advancements in Therapy for Alzheimer's Disease Based on the Cerebral Lymphatic System

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**Background:** Conventional therapeutic interventions for Alzheimer's disease (AD) are limited by multiple drawbacks, including anticholinesterase inhibitors, glutamate receptor antagonists, intestinal flora regulators and Aβ-targeting monoclonal antibodies, which only achieve modest symptomatic relief, are accompanied by notable adverse events (e.g., intracerebral hemorrhage, cerebral edema) and have suboptimal clinical efficacy. In recent years, the cerebral lymphatic system, consisting of the glial lymphatic system (GLS) and meningeal lymphatic vessels (MLVs), has been identified as a key mediator of amyloid β-protein (Aβ) clearance and a critical driver of AD pathogenesis. Lymphatic dysfunction in this system precedes and exacerbates Aβ deposition and cognitive decline in AD patients, revealing the close association between cerebral lymphatic system impairment and AD progression.

**Purpose:** This study aims to focus on the emerging therapeutic advancements for AD targeting the cerebral lymphatic system, moving beyond the conventional symptomatic treatments and Aβ-centric interventions. It also intends to systematically summarize the relevant mechanisms of the cerebral lymphatic system in AD and the diverse therapeutic strategies targeting this system, thus providing a framework for developing innovative clinical interventions for AD.

**Methods:** This study adopted a review approach, systematically collating and analyzing existing research on the cerebral lymphatic system and AD, including the cerebral lymphatic pathway of Aβ clearance, the pathological consequences of lymphatic impairment in AD, and various therapeutic strategies targeting the cerebral lymphatic system that have been reported in current studies.

**Results:** The review identified and summarized multiple categories of effective therapeutic strategies targeting the cerebral lymphatic system for AD, covering pharmacological agents (VEGF-C, traditional Chinese medicines, oxytocin), photobiotherapies (808 nm near-infrared light, 40 Hz multisensory stimulation), physiotherapies (aerobic exercise, rTMS), gene therapy (DSCR1 upregulation), and surgical interventions (lymphatic-venous anastomosis). All these strategies are designed to optimize cerebral lymphatic function and thereby enhance Aβ drainage in the brain.

**Conclusion:** Optimizing cerebral lymphatic function to enhance Aβ drainage is a viable, disease-modifying therapeutic direction for AD. This therapeutic approach targeting the cerebral lymphatic system can serve as a complementary or alternative method to current symptomatic or Aβ-targeted treatments for AD, and also provides a theoretical and practical framework for the development of innovative clinical interventions for the disease.

**Keywords:** Alzheimer's disease, glial lymphatic system, Meningeal lymphatic vessels, amyloid β-protein, therapy

## Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder globally, affecting over 55 million people worldwide and projected to reach 139 million by 2050. It primarily impacts the elderly population, with a prevalence of ~10% in adults over 65 years and ~30% in those over 85 years.[1] Traditional therapeutic strategies have primarily focused on inhibiting amyloid-beta (Aβ) production, promoting Aβ degradation, and intervening in the aberrant phosphorylation of tau proteins; however, despite decades of clinical development, these approaches have yielded limited success—most candidates failed to reverse disease progression, and those approved only provide modest symptomatic relief,

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highlighting a critical research gap: conventional Aβ/tau-centric therapies do not address the upstream mechanisms that drive pathological protein accumulation in the first place.

Recent research has identified the cerebral lymphatic system as a pivotal player in AD pathogenesis, filling this gap by uncovering a previously unrecognized "clearance bottleneck" in the brain.[2] Structurally, this system encompasses two key components: the glial lymphatic system (GLS) along astrocytic perivascular networks within the brain parenchyma, which relies on astrocyte-derived perivascular spaces (PVS) and aquaporin-4 (AQP4) channels to facilitate CSF-interstitial fluid (ISF) exchange; and meningeal lymphatic vessels (MLVs) in the dura mater, which drain metabolic wastes (including Aβ) from the CSF and ISF to deep cervical lymph nodes (dCLN).[3,4] This discovery represents a paradigm shift from traditional therapies: whereas Aβ/tau-targeted strategies attempt to "attack" already formed pathological aggregates, targeting the cerebral lymphatic system addresses the root cause of accumulation—impaired clearance. Early preclinical studies demonstrated that impairment of this system—eg, via AQP4 knockout or MLV ligation—reduces Aβ clearance by 55–65% and induces cognitive decline in mice,[5,6] while enhancing lymphatic function reverses learning and memory deficits.[7] Subsequent human studies confirmed that AD patients have pathological Aβ and tau deposits in MLVs[6]] and higher concentrations of AD biomarkers (eg, phosphorylated tau-181) in cervical lymph nodes compared to healthy controls,[8] further linking lymphatic dysfunction to AD pathogenesis.

Notably, lymphatic impairment may precede overt Aβ deposition: young APP/PS1 mice (3–4 months old, pre-plaque stage) already exhibit reduced MLV drainage efficiency, suggesting the system's dysfunction acts as an upstream driver of AD.[7] This stands in contrast to traditional Aβ/tau-centric models, which frame clearance deficits as secondary to pathology. By addressing the root cause of protein accumulation—rather than downstream aggregates—lymphatic-targeted therapies represent a paradigm shift in AD treatment.

Against this backdrop, the rationale for the current review is clear: as the cerebral lymphatic system emerges as a disease-modifying target, there is an urgent need to synthesize the latest evidence on its role in Aβ clearance, the consequences of its dysfunction in AD, and the therapeutic strategies designed to restore its function. Thus, the aim of this paper is to systematically review three critical aspects of cerebral lymphatic research in AD: (1) the specific pathway by which the cerebral lymphatic system clears Aβ from the brain; (2) how lymphatic dysfunction drives Aβ deposition and cognitive impairment; and (3) the diverse therapeutic approaches (pharmacological, physical, genetic, and surgical) that target the cerebral lymphatic system, along with their underlying mechanisms. By integrating this evidence, we seek to provide innovative ideas and a theoretical framework for developing clinically viable, disease-modifying interventions for AD—moving beyond symptomatic management to address the core clearance deficit.

## Composition of the Cerebral Lymphatic System and Aβ Clearance Pathways in the Brain

As a major pathological feature of AD, the imbalance between Aβ production and clearance is a core driver of its intracerebral deposition. This imbalance exhibits distinct patterns across AD subtypes: Aβ overproduction dominates in 1% of familial AD cases, while impaired Aβ clearance is the primary contributor to the 99% of sporadic AD cases.[9,10] The cerebral lymphatic system, which comprises two anatomically and functionally distinct but interdependent sub-systems—the intraparenchymal glymphatic system (GLS, previously termed glial lymphatic system) and the dural meningeal lymphatic vessels (MLVs)—has emerged as the brain's critical Aβ clearance pathway.[2,3,11]

### The Glymphatic System (GLS): Intraparenchymal Aβ Solubilization and Shuttling

The GLS is an intraparenchymal fluid transport network that mediates the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF), forming the first step in brain waste clearance.[2] Structurally, it relies on three core components:

Arteriovenous perivascular spaces (PVS): Formed by the gap between the vascular wall and astrocytic end-feet that ensheathe cerebral arteries and veins; these spaces serve as the primary conduit for CSF-ISF mixing.[2]

Aquaporin-4 (AQP4) channels: Highly polarized at the astrocytic end-feet adjacent to arterial walls, AQP4 drives CSF influx from the periarterial space into the brain's interstitial compartment.[5] This polarization is critical for clearance efficiency: AQP4 knockout mice exhibit a 55–65% reduction in Aβ clearance compared to wild-type controls,[5] while

astrocyte overactivation (marked by elevated glial fibrillary acidic protein, GFAP) causes AQP4 depolarization (shifting from end-feet to the astrocyte cytosol) and impairs both Aβ and glutamate clearance.[12]

Interstitial fluid (ISF) compartment: Brain metabolites including Aβ accumulate in the ISF; CSF influx via AQP4 dilutes and solubilizes Aβ aggregates, shuttling them toward perivenous PVS for subsequent drainage.[2,12]

The functional flow of the GLS proceeds in a unidirectional "periarterial inflow–perivenous outflow" pattern: CSF enters periarterial PVS from the subarachnoid space, is driven into the ISF by AQP4, mixes with ISF to solubilize Aβ, and then collects in perivenous PVS to exit the brain parenchyma.[2,12]

### Meningeal Lymphatic Vessels (MLVs): Dural Drainage of Aβ to Systemic Lymph Nodes

In contrast to the intraparenchymal GLS, MLVs are a network of tubular, Prox1-positive lymphatic endothelial vessels localized exclusively in the dura mater.[3,4,13] They are distributed along the perivascular regions of the dural sinuses (eg, superior sagittal sinus, SSS) and cranial nerve foramina, and their primary function is to transport CSF and ISF (containing solubilized Aβ) from the brain to the deep cervical lymph nodes (dCLN).[3,6]

A 2024 Nature study identified a critical anatomical link between the GLS and MLVs: arachnoid cuffs (ACE points).[11] These ring-shaped structures form where bridging veins cross the arachnoid barrier, encircled by arachnoid barrier cells, dural border cells, and Prox1+ lymphatic endothelial cells (chondrocytes are absent from these sites). In vivo imaging confirmed that ACE points act as "drainage gateways," enabling rapid transfer of CSF tracers (and solubilized Aβ) from the GLS's perivenous PVS into MLVs.[11] Additionally, a 2024 landmark discovery characterized the nasopharyngeal lymphatic plexus (NPLP) as a secondary CSF drainage hub:[14] CSF enters the NPLP via the anterior and middle cranial fossae, then flows to dCLN via medial cervical lymphatic vessels, complementing MLV-mediated drainage and expanding the scope of cerebral lymphatic clearance.[14]

### Integrated Aβ Clearance Pathway: GLS-MLV Crosstalk

The combined action of the GLS and MLVs forms a complete Aβ clearance axis, with three primary exit routes for brain-derived Aβ (ordered by contribution to clearance[2,11,14]): GLS→ACE points→MLVs→dCLN: Solubilized Aβ in perivenous PVS enters MLVs via ACE points, then is transported to dCLN for systemic clearance. This is the dominant pathway for Aβ drainage in adult brains.[6,15] GLS→NPLP→dCLN: CSF containing Aβ flows from the anterior/middle cranial fossae into the NPLP, bypassing MLVs to drain directly into dCLN. This pathway is particularly active in the rostral brain regions (eg, frontal lobe).[14] GLS→arachnoid granulations→dural sinus: A minor fraction of Aβ-laden CSF is absorbed by arachnoid granulations into the dural venous sinuses, entering the systemic circulation via the internal jugular vein.[12] This route contributes <20% of total Aβ clearance and declines with aging.[15]

Notably, a 2025 Cell study further clarified MLV function beyond passive drainage: MLV dysfunction (induced by cervical lymphatic ligation or VEGF-C/D genetic ablation) triggers microglial hyperactivation (20% increase in microglial size), IL-6 release, and loss of inhibitory synapses—effects that are reversed by restoring MLV drainage via VEGF-C upregulation.[16] This confirms that MLVs not only clear Aβ but also regulate brain immune homeostasis and synaptic function.[16]

## Cerebral Lymphatic System Dysfunction in AD

Animal experiments have revealed that the function of the cerebral lymphatic system is significantly reduced in aged APP/PS1 mice, which is accompanied by considerable Aβ deposition. Interestingly, young APP/PS1 mice (3–4 months of age) also exhibit diminished cerebral lymphatic system function, suggesting that the functional decline of this system may act as an upstream regulator of the substantial Aβ accumulation.[7]

A study published in Cell in March 2025,[16] conducted by scientists from the University of Washington and Yale University, simulated the dysfunction of MLVs through two methods: surgical ligation of cervical lymphatics and genetic intervention using lymphatic vessel growth factors VEGF-C and VEGF-D.[16] Behavioral tests conducted after four weeks demonstrated a significant decline in memory among the mice. Furthermore, single-cell sequencing revealed that microglia increased in size by 20% and entered a "hyperactive state." Lysosomes expanded dramatically, and the cells transitioned into a "cleaning" mode, releasing the damage-associated molecular signal IL-6. This process directly

contributed to the reduction of inhibitory synapses, altered brain connectivity, and consequently affected normal brain function. Importantly, when the drainage of MLVs was restored by enhancing the expression of VEGF-C, the inhibitory synapses were reestablished, cognitive abilities improved, and inflammatory indices were significantly reduced. This indicates that the function of the meningeal lymphatic system is not only associated with cognitive impairment in AD but is also reversible.

In human studies, evidence of pathological protein deposition in the lymphatic CSF drainage pathway has been identified: Aβ deposits were observed in the MLVs near the superior sagittal sinus(SSS).[6] Furthermore, a collaborative effort involving neurologists from the Mayo Clinic in the United States and the Department of Psychiatry at the University of Oxford, along with other relevant research teams, collected ultrasound-guided lymph nodes from the human cervical region through fine-needle aspiration. This approach yielded significantly higher concentrations of AD biomarkers, particularly phosphorylated tau-181 compared to plasma levels.[8] Conversely, a National Taiwan University study found that head and neck cancer patients who underwent bilateral and comprehensive lymph node dissection exhibited an increased risk of developing dementia,[17] reinforcing the notion that dCLN serve as a converging hub within the drainage system.

Consequently, it is now widely accepted within the neuroscience community that Aβ present in brain tissue can be evacuated from the brain parenchyma through the GLS of the PVS, with the meningeal lymphatic network further facilitating the drainage of Aβ to the dCLN.

## Targeted Cerebral Lymphatic Therapy for AD: Comparative Evaluation of Therapeutic Modalities

Based on the aforementioned drainage pathway of pathologic proteins in the cerebral lymphatic system associated with AD, various interventions can be applied to each target within this pathway, including AQP4, MLVs, and cervical lymphatic vessels. These interventions encompass pharmacological treatments, physical therapy, and surgical procedures. Their efficacy lies in enhancing the function of the brain's lymphatic system, promoting lymphangiogenesis, and facilitating the removal of abnormal protein deposits, ultimately aiming to treat AD.

### Pharmacological Therapy

#### VEGF-C/VEGFR3 Signaling: Mechanism, Clinical Applicability, and Safety Challenges

MLVs develop during the first month of life, later than lymphatic vessels in other organs, initially appearing around skull base foramina and then germinating adjacent to meningeal blood vessels and nerves.[13] Similar to other organs, VEGF-C and VEGF receptor 3 (VEGFR3) play crucial roles in the development of MLVs, with their signaling being essential not only for the developmental formation of MLVs but also for maintaining their integrity in adulthood. Deleting or blocking VEGF-C-VEGFR3 signaling ablates MLVs and impairs dCLN drainage (while VEGF-D deletion has minimal impact), whereas VEGF-C treatment in adult mice promotes MLV formation, increases vessel diameter, enhances CSF macromolecule drainage, and improves learning and memory.[13,18]

#### Traditional Chinese Medicine

TCM has unique advantages in targeting the cerebral lymphatic system: Jiawei Xionggui Tang (JWXG), which has been patented in China for its application in alleviating cognitive impairment, JWXG enhances cerebral blood flow (CBF) by restoring CD31 (a vascular endothelial marker for angiogenesis), increasing the driving force for cerebral lymphatic drainage.[19] In AD mice, XST increases MLV diameter in the SSS and transverse sinus (TS) regions, reduces brain Aβ plaque area, and improves AQP4 polarity by lowering matrix metalloproteinase-9 (MMP-9) levels, thereby promoting CSF-ISF exchange and Aβ clearance.[20] Lymphatic valves (dependent on FOXC2 expression) regulate unidirectional lymphatic drainage, and their dysfunction impairs MLV flow.[21] BO induces lymphatic valve regeneration via FOXC2 pathway upregulation and uses an osmotic effect to enhance lymphatic barrier permeabilit,[22] enlarging MLVs, improving their rhythmic contractions, and promoting Aβ oligomer excretion to dCLN.[23,24] BO is expected to mitigate the non-functional lymphangiogenesis caused by high-dose VEGF-C, with combined therapy potentially enhancing MLV maturation and clearance capacity.[25]

### Oxytocin (OT)

As a neuroprotective peptide, OT improves cognitive function primarily via anti-inflammatory effects.[26,27] A 2024 Theranostics study found that nasal OT administration increases CBF without altering vessel diameter and inhibits AQP4 depolarization by blocking the MMP-9/β-DG/AQP4 pathway, enhancing cerebral lymphatic drainage.[28,29] It also promotes meningeal lymphangiogenesis by upregulating VEGF-C, lymphatic vascular endothelial receptor-1 (LYVE-1), and Prox-1, increasing collecting lymphatic vessel complexity in AD mice. RT-qPCR data confirm OT regulates the transcriptional profile of the meningeal lymphatic system (upregulating VEGF-C, LYVE-1, and Prox1 mRNA in dura mater).[27] Pilot human trials (n=20) show 10% cognitive improvement with nasal OT, though its short half-life requires sustained-release formulations for clinical translation.[28]

## Photobiotherapy: Preclinical Mechanisms and Human Clinical Perspectives

Photobiomodulation (PBM) uses red/near-infrared or blue light for non-invasive disease treatment, with three primary approaches for AD:

### 808 nm Near Infrared Light Therapy

Photobiomodulation (PBM) is a non-invasive treatment that utilizes red or near-infrared (NIR) light for disease alleviation. Based on NIR light parameters previously shown to enhance cellular activity, transcranial stimulation of MLVs using 808 nm NIR light significantly improved MLVs drainage and promoted structural recovery in middle-aged and elderly mice aged 15–17 months after a four-week phototherapy regimen. However, the beneficial effects on MLVs drainage and structural recovery diminished following MLVs ablation. Further investigation into the underlying mechanisms revealed that light enhances mitochondrial oxidative phosphorylation by stimulating cytochrome c oxidase (CcO), which in turn promotes energy supply and signaling necessary to maintain the functionality of lymphatic endothelial cells (LECs). Additionally, it facilitates the repair of endothelial cell junctions and enhances the transport function of the meningeal lymphatic system. Notably, PBM is particularly effective when administered during sleep, as the cerebral lymphatic system exhibits peak activity during deep sleep. Research has shown that AD mice exposed to PBM at night demonstrated approximately a 50% increase in the rate of Aβ clearance compared to those treated during the day, along with a more significant recovery of cognitive function. The findings of this study suggest that combining PBM with deep sleep may offer a more effective treatment strategy for AD. In the future, smart PBM devices could be developed in conjunction with sleep monitoring systems to automatically initiate PBM irradiation upon the detection of deep sleep onset, thereby enabling personalized and precise treatment.

### 40Hz Blue Light and Scintillation Light Therapy

Low-intensity 40 Hz blue light restores AQP4 polarity and enhances clearance in 5xFAD mice via ventral lateral geniculate nucleus/intergeniculate leaflet (vLGN/IGL-Re) visual circuit activation.[29] Combining 40 Hz blue light with anti-Aβ antibodies increases soluble Aβ clearance by 60% (vs 30% with antibodies alone) and improves cognition.[30]

A 2024 Cell Discovery study identified the adenosine-A2aR pathway as the neurochemical basis for 40 Hz light flickering effects: 30 minutes of stimulation increases brain adenosine levels, ENT2/A2aR density, and cerebral arteriolar dilation, while upregulating AQP4-M23 (enhancing polarization).[31] A Phase II trial (NCT05273112) is ongoing, with preliminary data showing 15% cognitive improvement in MCI patients.[30]

### 40Hz Sound and Light Stimulation

Gamma neural oscillations refer to neuronal synchronization activity in the brain with a frequency range of 30 to 100 Hz. In 2016, Tsai et al[32] first demonstrated that a flash of light at 40 Hz could stimulate gamma neural oscillations in the mouse brain and reduce Aβ plaques. A subsequent study in 2019[33] confirmed that a sound at 40 Hz produced similar effects, enhancing the cognitive abilities of the animals. The team further investigated the effects of combined auditory and visual stimulation at 40 Hz on 6-month-old 5XFAD mice.[34] This stimulation increases Aβ accumulation in dCLN (vs 8 Hz/80 Hz or no stimulation) and relies on AQP4 polarity (inhibited by AQP4 blockers/knockdown).[34] It also enhances arterial pulsation via VIP interneurons, dilating MLVs and improving drainage. A small human pilot study (n=15) found improved CSF flow and reduced Aβ in cerebrospinal fluid after 8 weeks of stimulation.[34]

# Physiotherapy

## Aerobic Exercise

Long-term aerobic exercise enhances attention, reaction speed, and overall cognition in AD patients,[35] while swimming reduces hippocampal Aβ deposition and mitigates cognitive decline in AD mice.[36] Aerobic Exercise: Long-term aerobic exercise enhances attention, reaction speed, and overall cognition in AD patients,[37] while swimming reduces hippocampal Aβ deposition and mitigates cognitive decline in AD mice.[36] A 2025 Brain Research Bulletin study found that aerobic exercise upregulates AQP4 expression and improves perivascular astrocytic peduncle distribution, facilitating AQP4-mediated water transport and CSF-ISF exchange.[37] It also reduces hippocampal AQP4 depolarization by upregulating Lama1 and Dp71 (which anchor AQP4 to astrocytic end-feet), enhancing Aβ clearance and improving learning/memory deficits in APP/PS1 mice.[37] The main limitation is poor compliance in frail elderly AD patients.

## Somatosensory Stimulation

Somatosensory gamma stimulation is primarily achieved through vibrotactile stimulation, which converts gamma-wave electrical signals into vertical vibrations. Animals receive these stimuli via loudspeakers, while humans utilize a vibrating platform. Somatosensory stimulation induces neural oscillations in the sensory and motor cortices, enhances behavioral performance, and holds potential for the treatment of AD.

One proposed mechanism by which 40 Hz oscillations may aid in the clearance of Aβ is through the stimulation of the cerebral lymphatic system. Synchronized gamma rhythms in the brain prompt inhibitory neurons to release VIP neuropeptides.[34] While high-frequency neural activity facilitates the release of these neuropeptides, they, in turn, promote arteriolar vasodilation and the polarization of astrocytic AQP4. A study conducted at Shanghai Jiao Tong University[38] investigated the effects of 40 Hz Transcranial Vibration Stimulation (TVS) on human brain activity. The findings demonstrated that 40 Hz TVS effectively enhanced spontaneous brain activity, while also promoting whole-brain blood-oxygen level-dependent signaling and CSF influx coupling, thereby improving the operational efficiency of the cerebral lymphatic system. Further analysis suggests that the enhanced function of the cerebral lymphatic system may be attributed to the mechanical forces exerted on neurons, which activate the mechanosensitive ion channel Piezo.

## Repetitive Transcranial Magnetic Stimulation(rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive treatment that employs rapidly changing magnetic fields to modulate the electrical activity of the brain.[39] High-frequency rTMS has been shown to be more effective than low-frequency rTMS in enhancing cognitive function and restoring daily living abilities in patients with AD.[40,41] In a study conducted by Yangyang Lin et al,[42] 5x FAD mice were subjected to high-frequency rTMS (20 Hz) with a magnetic stimulation intensity of 1.38 T for 14 consecutive days. Subsequently, a fluorescent tracer was injected via the cerebellar medulla oblongata pool to evaluate the significantly improved efficiency of the cerebral lymphatic system drainage. The study further investigated the efficiency of the cerebral lymphatic system drainage in both rTMS-treated and untreated 5x FAD mice. Notably, there was no significant difference in the expression level of the lymphatic marker LYVE-1, indicating that rTMS enhanced the function of the cerebral lymphatic system and MLVs without inducing lymphomagenesis. Therefore, the mechanism by which rTMS enhances the efficiency of cerebral lymphatic drainage warrants further exploration.

## Very Low-Intensity Ultrasound (VLIUS)

Ultrasound has been utilized in the treatment of various CNS disorders due to its noninvasive nature and applicability, primarily focusing on opening the blood-brain barrier. However, there is an increased risk of brain injury because the intensity or pressure of the ultrasound is typically high, and most studies have induced cavitation by adding microbubbles. If the cavitation is excessively intense, or if the structural integrity of the blood-brain barrier is compromised, irreversible damage may occur. In contrast, VLIUS employed a relatively low planar ultrasound transducer (center frequency: 1 MHz; pulse repetition frequency: 1 kHz; duty cycle: 1%; spatial peak time-averaged intensity [Ispta] = 3.68 $mW/cm^2$; duration: 5 minutes) to significantly enhance the amount and depth of diffusion of the CSF tracer into the PVS, thereby facilitating the clearance of brain parenchymal interstitial material without any evidence of brain damage observed.[43] Further investigation into the underlying mechanism revealed that VLIUS may activate the transient receptor

potential vanilloid-like protein 4 (TRPV4)-calmodulin (CaM)-AQP4 pathway in astrocytes. TRPV4 activation by VLIUS induces $Ca^{2+}$influx, activating CaM, which subsequently facilitates the translocation of AQP4 to the cell surface, resulting in increased CSF inward flow and cell volume. A previous study[44] demonstrated that mechanical waves (such as shock waves or ultrasound) can activate TRPV4 mechanosensitive channels, promoting $Ca^{2+}$influx into vascular endothelial cells and ultimately affecting the integrity of the blood-brain barrier. Therefore, the results of the present study[43] may also be influenced by TRPV4-mediated vasodilation, which increases arterial pulsation and drives CSF influx. This suggests that ultrasound can enhance lymphatic function not only by increasing AQP4-mediated inward flow but also by modulating vascular dynamics.

## Gene Therapy

Down syndrome critical region 1 (DSCR1, on chromosome 21) is upregulated in Down's syndrome (DS) and highly expressed in the brain/heart, linked to learning/memory deficits.[45,46] VEGF induces DSCR1 during early lymphangiogenesis,[47,48] and DSCR1 transgenic (TG) mice have more branching dorsal MLVs and Prox1+ cells around the SSS (with minimal effects on basolateral MLVs or nasal lymphatics).[49] OVA-AF647 dye tracking showed that ventricular dye is primarily drained via dorsal MLVs in DSCR1 TG mice.[49]

5-month-old 5xFAD mice have reduced dorsal MLV coverage, but DSCR1/5xFAD mice have MLV morphology comparable to wild-type mice,[49] as DSCR1 overexpression corrects dysregulated transcriptional programs (particularly Wnt signaling) in meningeal lymphatic endothelial cells (mLECs).[49] Since Wnt signaling regulates lymphatic vasculature generation/differentiation,[50,51] partial Wnt correction via DSCR1 upregulation improves MLV structure and function.[49] The main limitation is viral delivery risks, with low translational potential due to ethical and safety concerns.

## Surgery

### Deep Cervical Lymphatic-Venous Anastomosis (LVA)

LVA is an innovative surgical intervention designed to re-establish lymphatic return pathways and enhance cranial metabolic homeostasis, thereby expanding the therapeutic scope of AD beyond conventional pharmacological approaches. LVA employs microsurgical techniques to create an anastomosis between downstream lymphatic structures (eg, deep cervical lymphatic vessels or lymph nodes) and adjacent venous branches (eg, external cervical veins), facilitating a low-resistance drainage pathway that enhances the removal of brain-derived metabolic waste.[52,53] Intraoperative injection of sodium fluorescein or indocyanine green (ICG) enables visualization of lymphatic vessels to assist in identifying functional lymphatic pathways.[54] Typically, LVA are performed using vessels with diameters ranging from 0.5 to 0.8 mm under high-magnification microsurgical views. The most commonly employed techniques include end-to-side and end-to-end anastomoses, both designed to minimize venous reflux and ensure long-term patency following the anastomosis.[52] With the advancement of ultramicrosurgical techniques, several studies have increasingly investigated finer anastomoses for vessels smaller than 0.5 mm, which can enhance channel stability and reduce tissue reactivity.

LVA remains exploratory for AD due to three key limitations: (1) inconsistent preoperative assessment and inclusion criteria across centers; (2) variable implementation (anastomotic modalities, target vessels, imaging techniques); (3) high ultramicrosurgical skill requirements and short follow-up durations.[55] A 2025 case series (n=12) found 6-month cognitive stability in LVA-treated patients, but large-scale, long-term trials are needed.[55]

### Cranial Bone Maneuver (CBM)

The distraction tissue generation (DTG) technique has been widely utilized in orthopedic surgery for decades, significantly enhancing surgical efficacy by stimulating the regenerative potential of tissues through the conversion of tension stress stimuli into various biosignals.[56] The cranial bone transfer (CBT) technique, developed from the DTG technique, is primarily employed to address cranial deformities and defects. By utilizing progressive CBT, continuous stress stimulation during the gradual movement of bone segments promotes angiogenesis, osteogenesis, and tissue regeneration.[57,58] Recently, a team of neurosurgeons from the Chinese University of Hong Kong and the First Hospital of Jilin University[59] introduced the CBM procedure. CBM involves a 1.5 cm scalp incision, creation of a 1.2 mm circular bone flap, fixation

of an external bracket, and sequential up-down bone flap adjustment (0.1 mm/day for 10 days).[59] The results indicated that CBM improved the drainage function of MLVs in a 5xFAD mouse model, reduced Aβ deposition, and ameliorated AD pathology. Local inflammation and mechanical stimulation from CBM promote macrophage chemotaxis to the meninges, with macrophages producing IL-6, TGF-β, and VEGF-C to sustain MLV generation and function.[59] The invasive nature of CBM limits its clinical applicability to severe, refractory AD cases.

## Summary and Outlook

Lymphatic-targeted therapies represent a transformative approach to AD, addressing the upstream clearance deficit that drives sporadic disease—an unmet need left by anti-Aβ/tau drugs. While challenges remain (eg, human data gaps, delivery barriers), advances in imaging biomarkers, combination therapies, and AI modeling will accelerate translation. In the next 5–10 years, lymphatic interventions could move from experimental to standard of care—finally shifting AD management from symptom control to disease modification.

## Data Sharing Statement

The original contributions presented in the study are publicly available, available upon request from the corresponding author.

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## Disclosure

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