Crossing the blood–brain barrier: emerging therapeutic strategies for neurological disease

Josephine H Pedder, Adam M Sonabend, Michael D Cearns, Benedict D Michael, Rasheed Zakaria, Amy B Heimberger, Michael D Jenkinson, David Dickens

Lancet Neurol 2025; 24: 246–60

Published Online January 22, 2025 https://doi.org/10.1016/S1474-4422(24)00476-9

See Comment page 185

Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK (D Dickens PhD, J H Pedder MRes, M D Cearns MRCS, R Zakaria PhD, Prof M D Jenkinson FRCSEd); **Department of Neurological Surgery, Malnati Brain Tumor Institute of the Robert H Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA** (A M Sonabend MD, Prof A B Heimberger MD); **Department of Clinical Infection, Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK** (Prof B D Michael PhD); **Department of Neurology** (Prof B D Michael) **and**

The blood–brain barrier is a physiological barrier that can prevent both small and complex drugs from reaching the brain to exert a pharmacological effect. For treatment of neurological diseases, drug concentrations at the target site are a fundamental parameter for therapeutic effect; thus, the blood–brain barrier is a major obstacle to overcome. Novel strategies have been developed to circumvent the blood–brain barrier, including CSF delivery, intracranial delivery, ultrasound-based methods, membrane transporters, receptor-mediated transcytosis, and nanotherapeutics. These approaches each have their advantages and disadvantages. CSF delivery and intracranial delivery are direct but invasive techniques that have not yet shown efficacy in clinical trials, although development of novel delivery devices might improve these approaches. Ultrasound-based disruption has shown some efficacy in clinical trials, but it can require invasive procedures. Approaches using membrane transporters and receptor-mediated transcytosis are less invasive than are other techniques, but they can have off-target effects. Nanotherapeutics have shown promise, but these strategies are in early stages of development. Advancements in drug delivery across the blood–brain barrier will require appropriately designed and powered clinical studies, with a focus on the timing of treatment, demographic and genetic considerations, head-to-head comparison with other treatment strategies (rather than a placebo), and relevant primary and secondary outcome measures.

Introduction

The blood–brain barrier is a protective semipermeable border between the CNS and the circulatory system, which prevents substances in the blood from reaching the brain. The presence of this barrier poses a challenge for the delivery of drugs to the brain for the treatment of neurological disorders. Early strategies to transport drugs across the blood–brain barrier included intrathecal or intracranial injection, but over the past 5 years, approaches have evolved to incorporate unique pharmacological agents and innovative devices. Based on robust preclinical data, drug-delivery strategies involving ultrasound, nanotherapeutics, and pharmacological targeting of membrane transporters and receptor-mediated transcytosis are now being used in clinical trials.

In this Personal View, we discuss the difficulties surrounding therapeutic delivery to the brain and the challenges of developing new drugs for neurological conditions, particularly brain tumours and neurodegenerative diseases. We describe novel strategies to enhance penetration of the blood–brain barrier focused on those that have been developed over the past 5 years and have advanced into clinical trials. The order of strategies presented is from the oldest first to the newest last. Finally, we provide insights into the future implementation of these innovative approaches into clinical practice. Some potential strategies have been excluded due to a paucity of clinical evidence, such as for intranasal delivery, which had difficulties in clinical trials due to anatomical differences in olfaction between mice and humans.

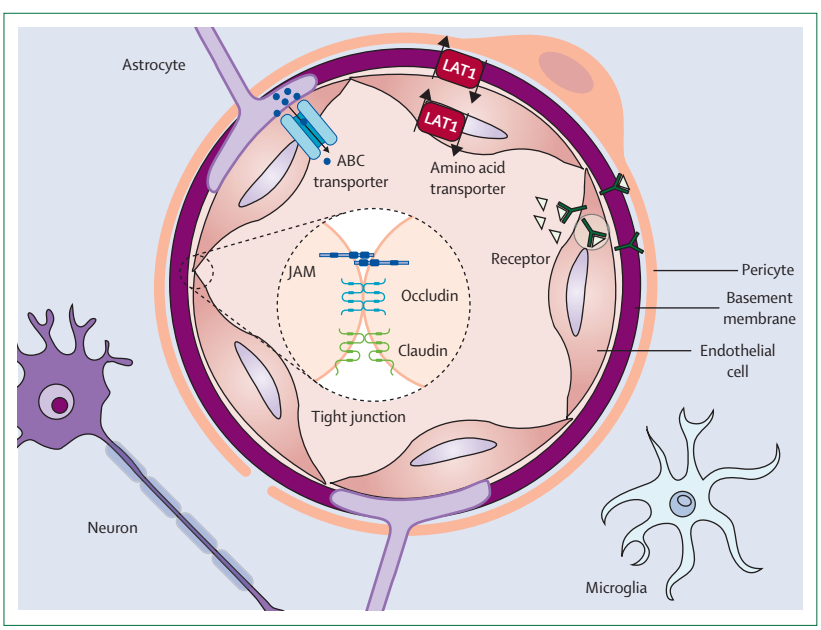

Figure 1: **Structure of the blood–brain barrier neurovascular unit**
ABC=ATP-binding cassette transporter. JAM=junction adhesion molecule. LAT1=L-type amino acid transporter 1.

Structure of the blood–brain barrier and challenges for treatment

The blood–brain barrier is postulated to prevent more than 98% of small compound drugs and nearly 100% of large molecule therapeutics from penetrating the brain sufficiently to have a pharmacological effect.[1] Passive diffusion of lipid-soluble drugs across the blood–brain barrier is possible via a strict selective interface of tight junctions along the basement membrane, which are formed from non-fenestrated brain endothelial cells (figure 1).[1–4] The tight junctions have various proteins to provide structural stability and signalling, including junctional adhesion molecules and membrane-spanning occludin and claudin proteins. Membrane transporters on brain endothelial cells—such as the ABCB1

transporter or the LAT1 amino acid transporter (SLC7A5)—permit active or carrier-mediated movement of selected molecules across the blood–brain barrier. The presence of tight junctions, low permeability, and expression of various transporters means that brain endothelial cells are physiologically distinct from peripheral endothelial cells. Pericytes, astrocytes, microglia, and neurons interact at the the blood–brain barrier, creating the neurovascular unit (figure 1). Components of the neurovascular unit can help to maintain the integrity and protective capacity of the blood–brain barrier (eg, astrocytes and pericytes)[1,2,5,6] or release factors to increase the permeability of the barrier (microglia).[7]

The complex structure and selective nature of the blood–brain barrier imposes clinical challenges for the treatment of neurological and neurodegenerative disorders. Moreover, the blood–brain barrier can be affected in different ways depending on the neurological disease (panel),[8–22] such as alterations in permeability, integrity, transporter expression, infiltration of inflammatory cells, and vascular wall components. Changes in the blood–brain barrier during disease progression are neither well understood nor well characterised and could alter the effectiveness of therapies at different stages of disease. Some therapeutic agents (eg, antibodies) can have very low concentrations in the brain (0·01–0·1% of circulating concentrations), which limits pharmacological effects. Understanding the cellular architecture, transport mechanisms, and potential off-target interactions at the blood–brain barrier is required to attempt novel drug design and delivery.

Department of Neurosurgery (M D Cearns, R Zakaria, M D Jenkinson), **The Walton Centre NHS Foundation Trust, Liverpool, UK**

Correspondence to:
Dr David Dickens, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool L69 7ZX, UK
david.dickens@liverpool.ac.uk

Strategies to overcome the blood–brain barrier

The heterogeneity of blood–brain barrier permeability, particularly changes to endothelial cells across different neurological disorders, highlights the challenges of drug delivery to the CNS. Over the past 5 years, advances in therapeutic strategies to cross the blood–brain barrier have been made (table 1). These strategies can be categorised into CSF delivery, intracranial delivery, ultrasound-based methods, membrane transporters, receptor-mediated transcytosis, and nanotherapeutics.

Panel: Blood–brain barrier disruption in neurological disease

Alzheimer's disease[8–10]
- Permeability of the blood–brain barrier is increased
- Brain endothelial cells express genes associated with Alzheimer's disease susceptibility (eg, *APOE4, CD2AP*, *CASS4, USP6NL*, *INPP5D*, and *ACE*)
- Increased amyloid β impairs blood–brain barrier function through disruption of tight junctions (thereby increasing permeability) and promotes neoangiogenesis of abnormal and leaky vessels
- Inflammatory activation is increased
- Neurovascular dysfunction is observed with downregulation of the ABCB1 transporter in brain endothelial cells

Amyotrophic lateral sclerosis[11–13]
- The ARPC3 subunit of the actin-related protein complex is downregulated in motor cortex brain endothelial cells, leading to mislocalisation of tight junctions
- Reduced HLA-E protein expression leads to blood–brain barrier breakdown mediated by natural killer cells
- Permeability of the blood–brain barrier is increased

Brain metastasis[14,15]
- Proteins associated with vascular permeability are enriched (eg, CD200, LGALS9, and TDO2)
- Astrocytes open gap junctions in the presence of tumour cells, facilitating disease progression

Glioblastoma[16,17]
- Expression of transporters is deregulated (eg, upregulation of solute carrier family transporters, such as SLC4A3, SLC4A8, and SLC9A5)
- The blood–brain barrier has heterogeneous areas of permeability
- Expression is upregulated of laminins, collagens, nidogens, and integrins, as well as genes encoding collagen in blood vessels surrounding the tumour (eg, *LOXL2*)
- Various subtypes of brain endothelial cells show activation or breakdown due to abnormal angiogenesis, resulting in blood–brain barrier impairment and dysregulation

Multiple sclerosis[18]
- Damage to the blood–brain barrier is caused by inflammation and immune cell infiltration
- Dysfunction of brain endothelial cells reduces surface expression of tight junction proteins
- Integrity of the blood–brain barrier is reduced

Parkinson's disease[19,20]
- High K^{trans} values (ie, volume transfer constant) in people with Parkinson's disease, compared with those without the disease, indicate increased diffusion and potential leakage of the blood–brain barrier, although choline PET and gadolinium diffusion do not show changes in integrity of the blood–brain barrier
- In people with Parkinson's disease, the blood–brain barrier shows pathological changes compared with age-matched controls

Epilepsy[21,22]
- Increased permeability of the blood–brain barrier is due to inflammation, oxidative stress, and tight junction alterations
- Increased expression of efflux transporters is seen, particularly ABCB1 and ABCG2 transporters

	Study design and phase	Inclusion criteria	Intervention	Outcomes	Study status and results
CSF delivery					
NCT02623699[23]	Three-part study (randomised, quadruple masked, parallel assignment) across a 12-week period; phase 3	50 patients with amyotrophic lateral sclerosis due to *SOD1* mutation (age ≥18 years years; both sexes)	Antisense oligonucleotide targeting *SOD1*	Incidence of adverse events and serious adverse events; vital signs and physical and neurological abnormalities; pharmacokinetic analysis of antisense oligonucleotides	Completed July 7, 2021; CSF SOD1 concentrations were decreased but no effect reported for clinical endpoints; associated with adverse events
NCT03186989[24,25]	Randomised, double-blind, placebo-controlled study, across 100 weeks; phase 1/2	464 patients with mild Alzheimer's disease (age 50–74 years; both sexes)	Antisense oligonucleotide targeting MAPT	Incidence and severity of adverse events that are related to treatment; CSF total tau protein concentration	Completed May 13, 2022; reduced key tau biomarkers associated with cognitive decline; no serious adverse events reported
Kingwell (2021)[26]	Multicentre, randomised, double-blind, placebo-controlled; phase 1b/2a study	NCT03225846: 88 patients with early manifestations of Huntington's disease (age 25–65 years; both sexes); NCT03225833: 61 patients with early manifestations of Huntington's disease (age 25–65 years; both sexes)	Antisense oligonucleotide targeting a single nucleotide polymorphism on the same allele as the pathogenic CAG expansion	Safety and tolerability, clinical effects, and total functional capacity	Discontinued May 10, 2021 (NCT03225846), and May 11, 2021 (NCT03225833), due to failure to significantly reduce mutant HTT concentrations in the CSF and disease progression was in line with natural history outcomes; no adverse events reported
NCT02899611[27]	Phase 1/2 interventional study	Six patients with medically refractory focal epilepsy (age 18–65; both sexes)	Valproate, intracerebroventricular administration (escalated stepwise from 3 mg/day to 60 mg/day, up to day 64)	Maximum tolerated dose and safety, determined through the incidence of adverse events and changes in the number of seizures	Completed June 1, 2021; seizure activity reduced by >50% in four patients; procedure, implantation, and intra-cerebroventricular valproate were well tolerated by all subjects; nine serious device-related events were resolved after intervention
NCT04153175	Phase 2 interventional study	30 patients with focal seizures (age 18–70 years; both sexes)	Intracardiovascular delivery of CT-010 (reformulation of valproate) or a placebo via an implantable pump and a cranial port and a dual lumen catheter	Frequency of total monthly seizures compared with baseline	Discontinued March 3, 2021, due to poor efficacy
Direct intracranial injection					
NCT04802733	Phase 1 interventional study	12 patients with Parkinson's disease (age 50–78 years; both sexes)	MSK-DA01, with cell delivery device	Safety and tolerability, measured by the incidence of serious adverse events at 1 year after transplant; evidence of cell survival (measured through change in ^{18}F-DOPA uptake using PET); changes in motor function	Completed May 10, 2024; well tolerated and exploratory clinical endpoints showed improved motor and non-motor outcomes
NCT00390299[28]	Phase 1 interventional study	23 patients with recurrent glioblastoma multiforme (age ≥18 years; both sexes)	Carcinoembryonic antigen-expressing measles virus via intratumoural and resection cavity administration	Safety and toxicity; maximum tolerated dose	Completed Nov 30, 2019 ; well tolerated with no dose-limiting toxicity
NCT01811992[29]	Phase 1 interventional study	19 patients with primary malignant glioma (age 18–75 years; both sexes)	Dose escalation of Ad-hCMV-TK and Ad-hCMV-Flt3L(adenoviral vectors expressing herpes simplex virus 1 TK and FlT3L, respectively)	Maximum tolerated dose (measured by adverse events)	Completed January, 2021; safe; combining two vectors was feasible
NCT02026271[30]	Phase 1 interventional study	40 patients with recurrent, progressive glioblastoma or grade 3 malignant glioma (age 18–75 years; both sexes)	Inducible adenoviral vector engineered to express human IL-12 in the presence of the activator ligand veledimex	Safety and tolerability of varying doses of the intervention (measured by incidence and severity of adverse events)	Completed August, 2019; safe; possible immunological anti-tumour effect

(Table 1 continues on next page)

(Continued from previous page)

	Study design and phase	Inclusion criteria	Intervention	Outcomes	Study status and results
Convection enhanced delivery					
Whone et al (2019)[31]	Randomised trial	Six pilot-stage and 35 primary stage patients with Parkinson's disease for ≥5 years (age 35–75 years; both sexes)	GDNF *vs* placebo (dilutant artificial CSF)	Percentage change from baseline in motor score after 40 weeks (based on 6 pilot-stage patients)	Reported March 1, 2019; putamen-wide sustained delivery of GDNF
NCT03566199[32]	Phase 1 interventional study	Seven patients with diffuse midline glioma (age 2–21 years; both sexes)	Panobinostat (MTX-110)	Tolerability and efficacy (measured by proportion of grade 3 or higher and treatment-related adverse events)	Completed March 31, 2021; repeated administration was tolerable and showed a median overall survival of 26 months
NCT04264143	Phase 1 interventional study	Nine patients with newly diagnosed diffuse midline gliomas (age 3–18 years; both sexes)	Infusate with MTX-110 and gadolinium	Incidence of adverse effects and maximum tolerated dose	Completed Nov 22, 2023; treatment was well tolerated
NCT01502917[33]	Phase 1	46 patients with non-progressive diffuse pontine gliomas (age 2–17 years; both sexes)	Radioactive iodine-labelled monoclonal antibody omburtamab	Maximum tolerated dose; safety; and toxicity over 2 years	Completed January, 2022; treatment considered safe
Focused ultrasound					
NCT03321487[34]	First-in-human	Four patients with amyotrophic lateral sclerosis (age 56–70 years; both sexes)	Transcranial MRgFUS combined with intravenous ultrasound contrast (perflutren lipid microbubbles)	Feasibility and safety of transient blood–brain barrier permeabilisation (measured through gadolinium leakage)	Completed Dec 30, 2022; transient blood–brain barrier opening in the primary motor cortex and treatment well tolerated
NCT03714243[35]	Prospective phase 1, single-arm, open-label study	Four patients with HER2-positive breast cancer and brain metastases (age 31–56 years; female)	MRgFUS plus trastuzumab-based therapy	Characterisation of treatment-related adverse events through clinical neurological examinations and neuroimaging studies	Completed March, 2023; increased entrance and concentration of monoclonal antibodies in the brain
Rezai et al (2024)[36]	Prospective, open-label, single-group, single-institution, proof-of-concept trial	Three individuals with Alzheimer's disease (mild cognitive impairment; age 50–85 years; both sexes)	Aducanumab infusion (1 mg/kg of bodyweight for 2 months, followed by 3 mg/kg for 2 months and 6 mg/kg for 2 months)	Amyloid removal (measured by standard uptake value ratio)	Completed Jan 3, 2024; amyloid β concentrations reduced by 32% and few adverse events
NCT03608553[37]	Pilot study (part of a prospective, single-arm, non-randomised phase 1 clinical trial)	Three participants with Parkinson's disease (age 60–80 years; both sexes)	MRgFUS	Safety and blood–brain barrier opening efficacy (measured by ^{18}F-choline-PET uptake)	Completed Dec 31, 2021; enhanced ^{18}F-choline-PET uptake was observed in the targeted brain regions with serious adverse events; no severe clinical or neuroimaging adverse events in any patient
Low-intensity pulsed ultrasound with microbubbles					
Sonabend et al (2023)[38]	Phase 1 dose-escalation study	17 patients (age ≥18 years; both sexes)	Albumin-bound paclitaxel	Pharmacokinetics	Completed May, 2023; 3·7-times increase in the mean brain parenchymal concentrations of albumin-bound paclitaxel
NCT03744026[39]	Phase 1/2	33 patients with recurrent de novo glioblastoma (age ≥18 years; both sexes)	Carboplatin	Dose-limiting toxicity; safety; and efficacy	Completed June 30, 2022; 5·9-fold increase in parenchymal concentrations of carboplatin; procedure-related adverse events consisted of presyncope, fatigue, wound infection, and pain at time of device connection; no serious (grade 4) adverse events reported
NCT03119961[40]	Phase 1/2	Ten people with mild Alzheimer's disease (age 50–85 years; both sexes)	1 MHz ultrasound only	Safety; efficacy of blood–brain barrier opening; and clearance of amyloid and tau	Completed July 10, 2020; safe and effective blood–brain barrier disruption

(Table 1 continues on next page)

	Study design and phase	Inclusion criteria	Intervention	Outcomes	Study status and results
(Continued from previous page)					
Membrane transporters					
NCT04430842	Phase 1 dose-escalation trial	15 patients with advanced or metastatic cancers with high LAT1 signature (age ≥18–years; both sexes)	QBS10072S (QBS72S; a cytotoxic compound that is transported by LAT1)	Determination of the maximum tolerated dose, as indicated by the incidence of adverse events and their severity	Completed Dec 22, 2022; safe and has led to further trials
NCT04268784[41]	Phase 1	96 healthy volunteers (age 18–50 years; both sexes)	DNL343 and placebo (single and repeating oral doses; not a substrate of ABCB1 transporter)	Safety (incidence of adverse events); tolerability; pharmacokinetics; and pharmacodynamics	Completed Aug 3, 2021; DNL343 safe and showed CSF penetrance
NCT05006352[41]	Phase 1b	29 patients with a diagnosis of sporadic or familial amyotrophic lateral sclerosis (age 18–80; both sexes)	DNL343 and placebo (oral repeating dose; not a substrate of ABCB1 transporter)	Safety (incidence of adverse events), pharmacokinetics, and pharmacodynamics	Completed June 5, 2024; DNL343 safe and showed CSF distribution
Receptor-mediated transcytosis					
Kumthekar et al (2020)[42]	Phase 2	72 patients with recurrent brain metastases from breast cancer (age 26–76 years; female) subset of 28 patients with leptomeningeal carcinomatosis	ANG1005 (paclitaxel linked to angiopep-2), 600 mg/m^2 intravenously every 3 weeks	Intracranial response rate, measured by central independent radiology facility review	Completed June 15, 2020; CNS and systemic treatment effects observed
Nanotherapeutics					
NCT03020017[43]	First-in-human, phase 0	8 participants with recurrent glioblastoma (age ≥18 years; both sexes)	RNA interference–based spherical nucleic acid with a gold nanoparticle core, intravenously administered	Safety (incidence of adverse events)	Completed Aug 19, 2020; nanoparticle passed through the blood–brain barrier and accumulated in the tumour; no serious adverse events (grade 4 or 5) reported

Studies were identified by searching PubMed or ClinicalTrials.gov. ^{18}F-DOPA=^{18}fluorine-labelled levodopa. GDNF=glial cell-derived neurotrophic factor. MRgFUS=magnetic resonance-guided focused ultrasound.

Table 1: **Completed clinical studies of strategies to cross or open the blood–brain barrier**

CSF delivery

Intraventricular and intrathecal routes of administration, including with small implantable devices, have been utilised as routes for direct drug delivery to the CSF. The blood–brain barrier and the blood–CSF barrier consist of distinct membranes. The blood–CSF barrier is composed of choroid plexus epithelial cells and tight junctions and does not allow access to the inner brain parenchyma. Although other CNS barriers might allow crossing from the CSF to the brain, the physiologically relevant evidence for this crossing is minimal, perhaps accounting for the poor success with the CSF delivery approach.[44] CSF delivery has been proposed as a strategy for tumours that involve the ependyma or reside in the ventricles.[34] Although this approach might be relevant for leptomeningeal metastases from systemic cancers, most primary tumours are present in the brain parenchyma, and sufficient drug concentrations being achieved by CSF delivery is unlikely.[44] Therapeutic strategies that use CSF delivery should be developed on a case-by-case basis for neurological disorders and brain malignancies.

Antisense oligonucleotides (ASOs) are short, synthetic, single-stranded molecules that can alter RNA and reduce, restore, or modify protein expression through several distinct mechanisms.[45] These large molecules appear to have wide uptake from CSF, and early clinical trials of ASOs for amyotrophic lateral sclerosis to target the *SOD1* gene (NCT02623699),[23] and Alzheimer's disease (NCT03186989) to target the *MAPT* gene,[24,25] have shown promise (figure 2). In the Alzheimer's disease trial, the ASO therapy reduced key tau biomarkers associated with cognitive decline and has been advanced to a phase 2 trial. However, an ASO for Huntington's disease was discontinued (NCT03225846, NCT03225833) because of adverse events and poor efficacy.[26] CSF administration has also been used for delivery of valproate in a clinical trial in people with focal epilepsy (NCT02899611);[27,48] however, a planned phase 2 study was terminated due to low efficacy (NCT04153175).

Intracranial delivery

Injection of agents into a focal target within the brain bypasses the blood–brain barrier and minimises the risk of systemic toxic effects. However, intracranial injection is ideally suited to single treatment protocols, for agents that can diffuse to the target site, or for agents that have a discrete target that can be accessed surgically or stereotactically.

Direct intracranial injection

Direct injection into the putamen of dopamine-producing stem cells (NCT04802733) has progressed to an open-label study in 12 patients with Parkinson's disease and a phase 2 trial is expected. Surgical access for deep brain stimulation is well established for this target and should be possible to do safely, but proof of engraftment and persistent efficacy are needed.

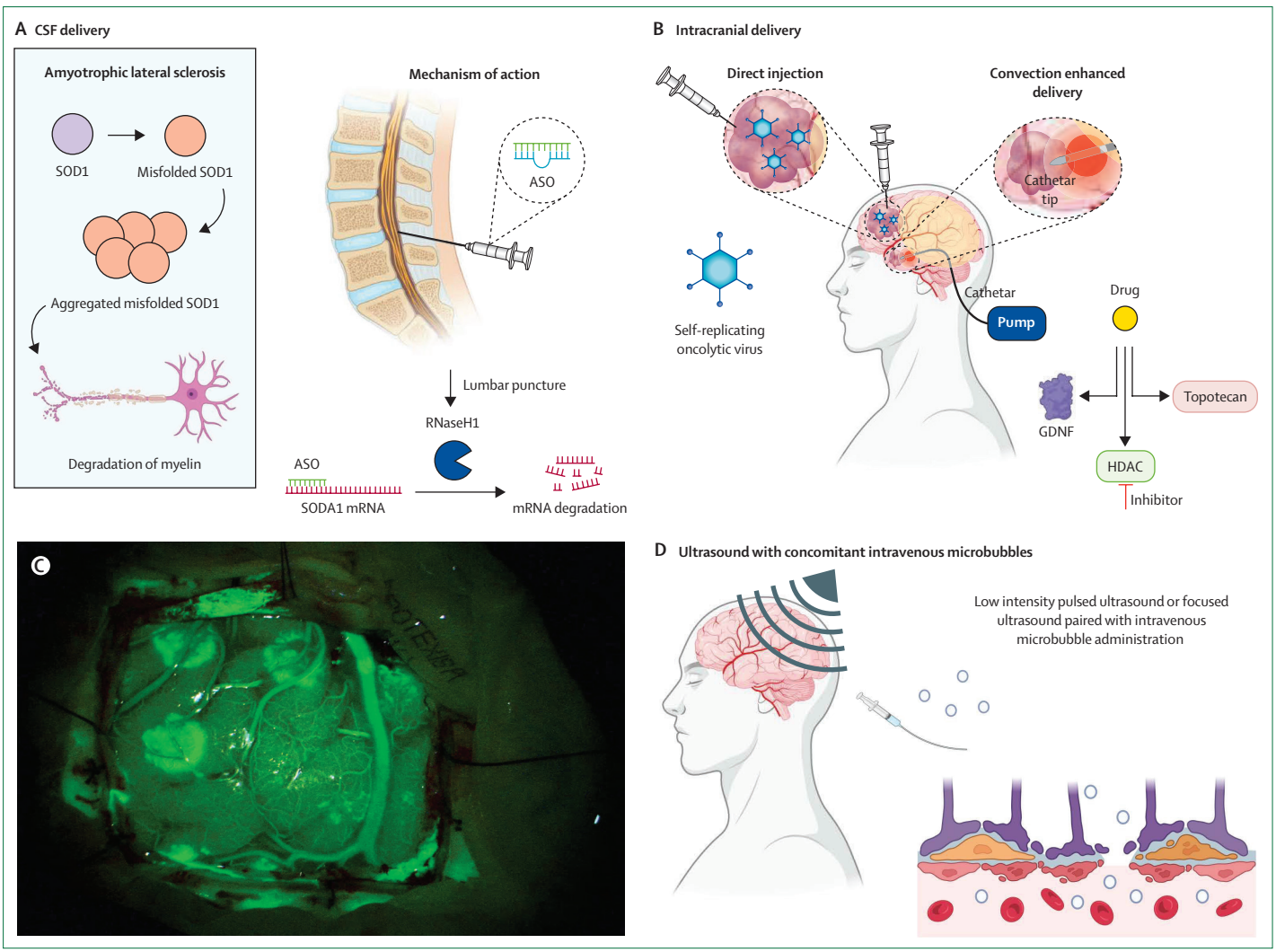

Figure 2: **Methods and measurement strategies for overcoming the blood–brain barrier**
(A) Delivery through the CSF–brain barrier has been targeted by use of ASO therapy in amyotrophic lateral sclerosis. SOD1 misfolding causes neuronal degradation in amyotrophic lateral sclerosis. The ASO will bind the mRNA of SOD1 and initiate mRNA degradation processes, thereby leading to an overall reduction in SOD1 protein.[23,24] (B) Direct injection will deliver therapies such as the oncolytic virus to the target site. Convection-enhanced delivery can be adapted to deliver a range of therapies.[31,46,47] A catheter-pump system creates a positive pressure gradient and allows the diffusion of therapeutics to tissues via bulk flow. (C) Fluorescent microscopy image of the brain of a patient with glioblastoma who underwent intraoperative sonication with intravenous administration of microbubbles, chemotherapy, and fluorescein. This image was taken as part of pharmacokinetic study of the effect of sonication on the concentration of drugs in the peritumoural brain.[38] Cortex regions that underwent sonication show increased fluorescence intensity compared with the surrounding brain. (D) An ultrasound device is used to cavitate circulating microbubbles and increase the permeability of the blood–brain barrier. This technique uses an implanted ultrasound device to deliver low-intensity pulsed ultrasound, which could be used for glioblastoma treatment[38] or for the removal of amyloid plaques in Alzheimer's disease.[36] ASO=antisense oligonucleotide. GDNF=glial cell line derived neurotrophic factor. HDAC=histone deacetylases.

Direct intracranial injection can be appropriate for lesional diseases such as tumours. Viral therapies such as the herpes simplex virus can be engineered to replicate in glioblastoma cells.[49] These viruses are injected into the tumour or peritumoural region, and because viruses are self-replicating, multidosing is not a limitation (figure 2). In a phase 1 trial of 41 patients with recurrent glioblastoma, CAN-3110 (a variant of the herpes simplex virus) enhanced anticancer immune responses (NCT03152318).[50] The therapeutic effect of this viral therapy is mediated partly through the immune system, and therefore efforts have been focused on enhancing these anti-tumour mediated effects. This enhancement includes inducing the expression of an immunological target such as a carcinoembryonic antigen (NCT00390299)[28] or providing immune-stimulatory components such as Flt3L (NCT01811992)[29] or IL-12 (NCT02026271).[30] Robust preclinical animal research is the basis for future trials to investigate enhancing the anti-tumour immune responses by various means with these viruses.[51–54]

Convection-enhanced delivery

For therapeutics that require wider distribution, convection-enhanced delivery can be used instead of a

single stereotactic injection (figure 2). Convection-enhanced delivery relies on a positive pressure gradient generated through a pump that enables large molecules to reach the area of interest that would otherwise struggle due to their size and subsequent diffusion rate.[55] Other advantages of this strategy include a more even and larger distribution area, relative to diffusion-based treatments. Not relying on a steep diffusion gradient also allows a consistent drug concentration to be delivered.[56] Convection-enhanced delivery is most suitable for brain disorders that already require surgical intervention, but the approach has several disadvantages, including a slow infusion rate, geometrical and anatomical constraints that limit delivery, an increased risk of implant infection, and a surgical recovery period.

Convection-enhanced delivery of GDNF as a neurorestorative and neuroprotective therapy has been investigated in Parkinson's disease.[31] Initial trials used intraventricular delivery of GDNF, but this approach led to off-target effects, therefore, convection-enhanced delivery was trialled.[57] The trial randomly assigned 41 people with late-stage Parkinson's disease to receive putamen-wide sustained delivery of GDNF versus placebo and reported that convection-enhanced delivery was an acceptable route for drug delivery.[31] However, poor improvement in motor function and quality of life suggests that either the premise for the role of the growth factor was flawed or patients with early-stage disease, in whom innervation of the striatum with dopaminergic neurons is maintained, need to be enrolled.

Convection-enhanced delivery has also been used in brain tumour clinical trials. MTX-110 is a water-soluble formulation of a histone deacetylase inhibitor (aqueous panobinostat). Treatment with MTX-110 was considered for diffuse midline glioma after it showed efficacy in a rodent xenograft model,[46] which led to a phase 1 clinical trial (NCT03566199).[32] Seven participants received a total of 48 infusions, with three experiencing dose-limited toxic effects. Repeated administration by convection-enhanced delivery was tolerable and the median overall survival of 26 months was similar to historical data. The combined infusions for each participant resulted in tumour coverage of 35–81%.[32] Convection-enhanced delivery of MTX-110 is currently being evaluated for the treatment of recurrent glioblastoma (NCT05324501), diffuse midline glioma (NCT04264143), and medulloblastoma (NCT04315064). Strategies that implant multiple catheters would increase coverage but, to date, only a single flexible catheter has been tested (NCT01502917).[33]

Ultrasound-based methods

Ultrasound is an emerging strategy to enhance blood–brain barrier penetration. This approach uses soundwaves to resonate intravenously administered microbubbles that are co-administered with a drug. The microbubbles open the endothelial junctions around the brain capillaries, enabling penetration of concomitantly administered drugs across the blood–brain barrier. Success of this technique, with a range of chemotherapeutic and immunotherapeutic agents, has been reported in preclinical animal models.[58–61] Translation into the clinic requires that soundwaves either penetrate the human skull (which is considerably denser than in rodent models) or bypass the bone.[62,63] High-energy transcranial ultrasound devices have been developed to penetrate the human skull, incorporating stereotactic guidance and modelling of skull attenuation of soundwaves. Alternatively, bypassing the skull is done with an implantable ultrasound device, of which an array of emitters are positioned epidurally within a skull window. This approach uses low-energy soundwaves and is suitable for multidosing.[38,39,64] Over the past 5 years, both transcranial and skull-implantable ultrasound devices have proven to be safe and feasible as a means of repeated blood–brain barrier opening.

Focused ultrasound

Transcranial magnetic resonance-guided focused ultrasound paired with microbubbles can open the blood–brain barrier in small regions deep within the brain (figure 2). This strategy was evaluated in a first-in-human study of four patients with amyotrophic lateral sclerosis to test feasibility in this neurological disease, without any drug being delivered (NCT03321487).[34] Transient blood–brain barrier opening was observed in the primary motor cortex, shown by the degree of contrast enhancement seen on post-procedure MRI with a gadolinium-based contrast agent, and no major adverse events were reported. Accessing the primary motor cortex has traditionally impeded the development of effective disease-modifying treatments for amyotrophic lateral sclerosis; therefore, a non-invasive strategy, such as magnetic resonance-guided focused ultrasound, has the potential to enable therapeutic access to affected neurons. However, disadvantages of this approach include issues with acoustic pressure, appropriate sonication power, and vessel damage.[65] These technical safety aspects, as well as the possibility that the patient with amyotrophic lateral sclerosis cannot communicate symptoms, should be carefully considered for future studies. To date, no clinical trials are in progress for focused ultrasound for amyotrophic lateral sclerosis. In Alzheimer's disease, blood–brain barrier opening using magnetic resonance-guided focused ultrasound has been achieved in PET studies, but similar to the study in amyotrophic lateral sclerosis, no therapeutic agents were delivered because the study was to test feasibility. The opening of the blood–brain barrier in the default mode network areas did not affect cognitive scores or disease biomarkers (NCT03739905). This opening supports blood–brain barrier modulation using magnetic resonance-guided focused ultrasound as a potential strategy for enhanced therapeutic delivery.[66]

Clinical trials of focused ultrasound to deliver therapeutic monoclonal antibodies in people with brain metastases (NCT03714243)[35] and Alzheimer's disease[36] have shown that this approach facilitates increased entrance and concentrations of the treatment in the brain. In a study of three individuals with Alzheimer's disease, focused ultrasound was applied to one hemisphere of the brain alongside aducanumab infusions once a month for 6 months, with the objective of enhancing amyloid removal.[36] The transient blood–brain barrier disruptions were safe and reduced amyloid β concentrations by 32% (measured by standard uptake value ratio) in the region that received ultrasound compared with the untreated hemisphere of the brain. However, this study did not quantify drug penetration and, therefore, whether focused ultrasound directly enhanced delivery cannot be ascertained definitively, which should be confirmed in future trials. Another monoclonal antibody, lecanemab, is already being similarly applied in an ongoing phase 0 trial (NCT05469009). In a brain metastases study,[35] 20 infusions of trastuzumab were delivered to four patients with HER2-positive breast cancer, indicating that repeated treatment using a focused ultrasound strategy is feasible. Clinical studies using focused ultrasound are also investigating delivery of doxorubicin for paediatric diffuse intrinsic pontine glioma (NCT05630209; NCT05615623).

In patients with Parkinson's disease, focused ablation with ultrasound is becoming established as a therapeutic strategy, but magnetic resonance-guided focused ultrasound has also been used to open the blood–brain barrier in the nigrostriatal region (NCT03608553).[37] In a pilot study with three participants, no adverse events were reported and enhanced [^{18}F]fluorodeoxyglucose-choline-PET uptake was observed in the targeted brain regions. A phase 1/2 study is underway for bilateral putamenal delivery of recombinant glucocerebrosidase in patients with Parkinson's disease (NCT05565443).

A disadvantage of magnetic resonance-guided focused ultrasound is that the patient must be placed into a stereotactic frame for each treatment. Therefore, therapeutics that require frequent dosing would not be suitable for this strategy, from the perspective of patient acceptability and cost.

Low-intensity pulsed ultrasound

With respect to implantable ultrasound devices, brain tumour research has helped with development of low-intensity skull-bypassing ultrasound. Because surgery to resect a brain tumour entails removal of a cranial window, risks of open operation to test an implantable device can be justified. In a phase 1 trial, an ultrasound device (composed of nine 1 MHz ultrasound emitters) was directly implanted in 17 patients with recurrent glioblastoma through a cranial window in the skull. Albumin-bound paclitaxel (a potent chemotherapy drug, that does not cross the blood–brain barrier[67]) was administered immediately after ultrasound. Biopsy specimens of sonicated and non-sonicated peritumoral brain tissue were obtained, and pharmacokinetic analysis showed a 3·7-fold increase in brain parenchymal paclitaxel when compared with non-sonicated samples.[38] A phase 1/2 clinical trial evaluated the safety of the same implantable ultrasound device for delivery of carboplatin in 33 patients with glioblastoma (NCT03744026).[39] Drug delivery across the blood–brain barrier was enhanced, with a 5·9-fold increase in parenchymal concentrations of carboplatin in sonicated brain regions (figure 2).

Low-intensity ultrasound has also been tested in a pilot study of blood–brain barrier disruption to aid in the clearance of amyloid and tau aggregates in people with Alzheimer's disease (NCT03119961).[40] A 1 MHz ultrasound device was implanted in the skull of ten people with mild Alzheimer's disease over the left supramarginal gyrus, which was well tolerated. The risk of open surgical implantation for an older population is not trivial and differs clinically from the risk profile for a patient with an incurable brain tumour such as glioblastoma.

Four other open-label clinical trials are using the low-intensity ultrasound approach, including carboplatin for patients with recurrent glioblastoma (NCT05902169); balstilimab, botensilimab, and liposomal doxorubicin for patients with newly diagnosed glioblastoma (NCT05864534); albumin-bound paclitaxel and carboplatin for patients with recurrent glioblastoma (NCT04528680); and carboplatin for paediatric patients with malignant brain tumour (NCT05293197). A general advantage of a low-intensity ultrasound strategy, compared with focused ultrasound, is the large area that can be covered (eg, in the dominant hemisphere for Alzheimer's disease). For future devices, adjustable direction and coverage could be included.

Membrane transporters

Two types of membrane transporters on brain endothelial cells could be targeted for CNS drug delivery: solute carrier transporters such as LAT1 (SLC7A5; which is a large neutral amino acid transporter); and the ATP-binding cassette (ABC) family of efflux transporters (figure 3). The complexity of membrane transporters with respect to substrate specificity and number has previously made this area challenging for therapeutic approaches, but there is now renewed interest due to an increased understanding of membrane transporters in general at the molecular level. Safety considerations and restriction to transport of small molecules are outstanding areas of challenge for using membrane transporters to enhance drug delivery to the brain.[68,69]

Amino acid transporters

LAT1 is an amino acid transporter that is widely expressed at the luminal and abluminal membranes of the blood–brain barrier and has a large transport capacity.[70,71] Since LAT1 is present on either side of the blood–brain barrier,

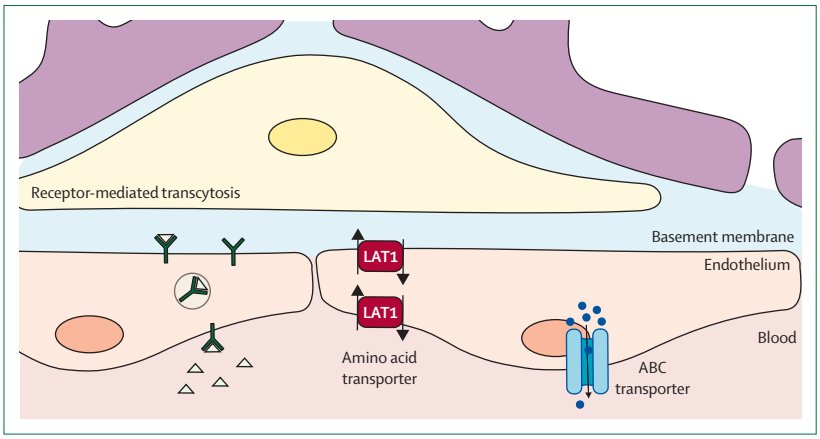

Figure 3: **Transport mechanisms across the blood–brain barrier**
Three different transport systems can be targeted for blood–brain barrier crossing: receptor-mediated transcytosis; the amino acid transporter LAT1; and the ABC transporter (ABCB1 substrate system). Receptor-mediated transport uses the vesicular trafficking system within the brain endothelial cells to allow transcytosis. Ligand-receptor complexes facilitate this system without disruption to the barrier. Amino acid transporters, such as the LAT1 transporter, make use of expression on both the abluminal and luminal sides of the membrane. ABC transporters, such as the ABCB1 transporters, are efflux transporters existing on the luminal side of the membrane. ABC=ATP-binding cassette transporter. LAT1=L-type amino acid transporter 1 (SLC7A5).

transport across the membrane is possible without toxicity to endothelial cells or tight junctions.

A chemotherapeutic agent that bypasses DNA repair mechanisms, designated QBS10072S, has been designed with a chemical moiety that makes it a substrate of LAT1, to enhance blood–brain barrier crossing.[72,73] A dose-escalation trial of QBS10072S has been completed in 15 patients with advanced or metastatic cancers with a high LAT1 expression (NCT04430842). The safety, tolerability, and dose profile has led to the agent now being evaluated for glioblastoma (NCT02977780) and brain metastases (NCT05305365).

4-chlorokynurenine is a prodrug of an NMDA receptor antagonist and is in clinical development for various CNS disorders, including neuropathic pain, major depressive disorder, and levodopa-induced dyskinesia.[74] Preclinical studies indicate that 4-chlorokynurenine crosses the blood–brain barrier via LAT1, after which the active metabolite 7-chlorokynurenic acid leaves the brain extracellular fluid via probenecid-sensitive organic anion transporters. Probenecid could be used to boost the bioavailability of 7-chlorokynurenic acid in the prefrontal cortex by blocking the activity of probenecid-sensitive transporters, which would otherwise have pumped the active metabolite out of the brain.[75,76] Coadministration of probenecid and 4-chlorokynurenineis is being evaluated in a phase 1 trial in healthy volunteers to identify if this boosting strategy can increase the CNS concentration of 7-chlorokynurenic acid (NCT05280054).

ABC transporters

The potential intracranial efficacy of many agents is undermined because of the expression of ABC transporters at the blood–brain barrier, such as ABCB1, which pumps substrates out of the brain. In neurodegenerative diseases, such as amyotrophic lateral sclerosis, activation of EIF2B modulates the integrated stress response that controls protein synthesis, as well as responses to cellular insult, and is a proposed drug target. During early work on EIF2B activators, compounds were assessed for interactions with ABCB1. The therapeutic agent DNL343 was developed, which is not a substrate for the ABCB1 transporter and retains selective EIF2B activation function. DNL343 is CNS-penetrant (NCT04268784; NCT05006352),[41,77] and its efficacy is currently under investigation in the Healey platform trial for amyotrophic lateral sclerosis (NCT05842941).

Some highly effective systemic anticancer drugs, such as paclitaxel and docetaxel, are substrates of the ABCB1 transporter. Inhibition of ABC membrane transporters is problematic because they are expressed elsewhere in the body, leading to toxic effects in organs such as the liver. Instead, molecules designed to overcome the efflux system have shown promise. An example is lorlatinib, a third-generation tyrosine kinase inhibitor designed to avoid being a substrate of the ABCB1 transporter. In a randomised phase 3 trial (NCT03052608) for advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer, 71% of patients with brain metastases who received lorlatinib had an intracranial complete response.[78] Further studies will clarify the rates of CNS progression, but these preliminary results are highly clinically significant because patients with brain metastases are usually excluded from drug trials due to poor intracranial efficacy.[79]

Receptor-mediated transcytosis

Receptor-mediated transcytosis is a non-invasive strategy to cross the blood–brain barrier, which entails binding of a ligand to a receptor on the luminal membrane of the blood–brain barrier (figure 3). Vesicle-mediated endocytosis and subsequent intracellular trafficking to the abluminal blood–brain barrier membrane allows the ligand to cross to the brain parenchyma.[80] An important consideration is the selection of the receptor, because expression can be altered in disease or during ageing. Also, the drug to be transported should avoid lysosomal compartments to prevent degradation.

The LRP1-mediated endocytosis mechanism has been targeted to treat brain metastases in patients with breast cancer.[42] LRP1 is expressed at high concentrations on the blood–brain barrier and on tumour cells, making it an ideal transport system for chemotherapeutic molecules. LRP1 protects the structure of the blood–brain barrier, regulating angiogenesis, clearing toxins, and acting as a diverse endocytic receptor.[81] Expression of LRP1 on tumours induces migration and invasion, inhibits apoptosis, and contributes to metastasis.[82] A synthetic peptide called angiopep-2 can cross the blood–brain barrier via LRP1-mediated endocytosis. A peptide–drug

conjugate called ANG1005, which consists of three paclitaxel molecules linked to angiopep-2, can cross the blood–brain barrier. The paclitaxel is later cleaved from the peptide via lysosomal esterases. A phase 2 study reported benefit for patients with leptomeningeal disease (median overall survival of 8 months [95% CI 5·4–9·4]).[42] A phase 3 trial is underway for leptomeningeal disease and brain metastases from breast cancer (NCT03613181).

Iron transport mechanisms in the brain have been targeted via receptor-mediated transcytosis to facilitate blood–brain barrier penetration for the treatment of mucopolysaccharidosis type II (also known as Hunter syndrome).[83] This lysosomal storage disorder stems from a deficiency in iduronate 2-sulphatase (IDS), an enzyme that impairs various cellular functions. Mucopolysaccharidosis type II causes an accumulation of gangliosides in the brain, which activate microglia and an inflammatory response that triggers neuronal death.[84] DNL310 is a molecule consisting of IDS linked to an antibody fragment that binds the transferrin receptor TFRC. This receptor mediates the uptake of iron-loaded transferrin, which allows the transfer of iron to the brain. Targeting TFRC for blood–brain barrier transport has previously been limited by off-target binding, resulting in anaemia and other downstream effects, as well as sparse delivery into the brain parenchyma.[85] Therefore, the antibody must display a low affinity to TFRC to allow transcytosis and prevent overly strong binding to the endothelial cells. DNL310 has shown activity in mice,[83] and early-stage clinical trials in patients with mucopolysaccharidosis type II are underway (NCT04251026).[86]

A new version of the anti-amyloid agent gantenerumab for treatment of Alzheimer's disease—called trontinemab or brain shuttle gantenerumab—utilises TFRC for enhanced blood–brain barrier crossing.[87] Based on data from a non-human primate model, this receptor-mediated transcytosis approach is predicted to increase brain exposure by 300–700% in humans, which could be especially impactful for Alzheimer's disease because of its diffuse nature.[88] A phase 1b/2a clinical trial is in progress in people with mild-to-moderate Alzheimer's disease to ascertain safety, pharmacokinetics, and pharmacodynamics (NCT04639050).

Nanotherapeutics

Nanosystems can encapsulate, carry, and deliver a variety of therapeutic agents, including drugs and nucleic acids, to the CNS. Nanoparticles are sized between 1–100 nm in diameter and have two distinct categories: organic (eg, lipid and polymeric); and inorganic (eg, metals).[89] No guidelines are available regarding the use of nanoparticles for drug delivery; however, production costs and safety concerns have, thus far, restricted the use of the agents that have reached clinical trials for neurological disease.[90–92] Concerns about nanosystems arise from the inadequate knowledge surrounding their toxic effects, biocompatibility, long-term effects, and regulation, as this technology is very new.

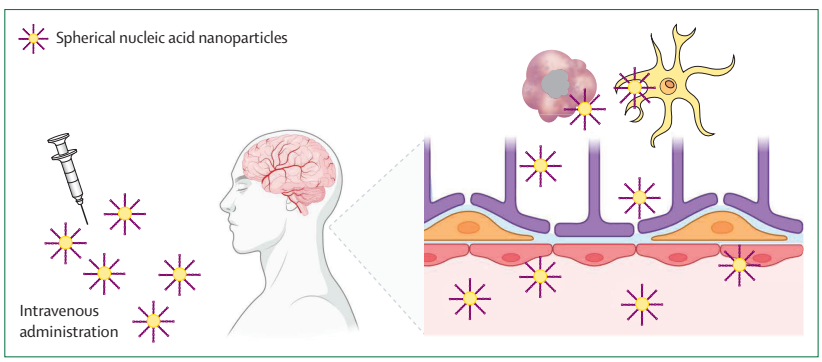

Figure 4: **Therapeutic delivery of drugs with nanoparticles**
A nanoparticle containing a gold core, conjugated with a spherical nucleic acid, could target oncogenes upregulated in patients with glioblastoma. The spherical nucleic acid–nanoparticle conjugates are administered intravenously and will cross the blood–brain barrier through paracellular pathways.

RNA molecules can be engineered to silence genes in genetic disorders, including epilepsy syndromes and Parkinson's disease,[93,94] and oncogenes in cancer.[21] These RNA interference molecules can be attached to an oligonucleotide carrier for therapeutic delivery.[43] In addition to the challenges posed by the blood–brain barrier, unmodified oligonucleotides have a short in vivo half-life, might trigger an immune response, and are not efficient at targeting specific cell populations. Nanoparticles could house small therapeutics such as small interfering RNA (siRNA) and be designed to overcome these issues. Brain-penetrant RNA interference-based spherical nucleic acids (which consist of gold nanoparticle cores covalently conjugated with radially oriented and densely packed siRNA oligonucleotides) were used to target the oncogene *BCL2L12* in glioblastoma patients (figure 4).[43] In a phase 0 first-in-human trial, eight participants were enrolled to identify the safety, pharmacodynamics, and accumulation of these siRNA nanostructures for the treatment of glioblastoma (NCT03020017). Intravenously administered microdoses of the nanoparticle were recorded in endothelial cells, immune cells, and tumour cells, with subsequent reduction of target protein expression. These results showed proof-of-concept of nanoparticle delivery past the blood–brain barrier, but glioblastoma oncogene heterogeneity is a confounder.

Overall nanoparticles have had far less effect than envisaged due to issues such as accumulation, aggregation concerns, and unstable impractical agents to handle and prepare for clinical use. Future studies will need to be directed towards the pharmacokinetics and clearance of nanotherapeutics to inform appropriate safety considerations and schedules.

Towards clinical implementation

The novel treatment approaches that we have described for crossing the blood–brain barrier are in their infancy, and robust clinical trial data will be required to establish

	Study design and phase	Inclusion criteria	Intervention	Outcomes	Study status
Direct intracranial injection					
NCT03152318[50]	Interventional allocated phase 1	Estimated 62 patients (age ≥18 years; both sexes)	Genetically engineered HSV-1 virus (CAN-3110 oncolytic viral vector)	Maximum tolerated dose	Estimated completion December, 2025
Convection enhanced delivery					
NCT05324501	Interventional phase 1	36 patients with recurrent glioblastoma (age ≥18 years; both sexes)	Programmable pump and catheter system with MXT-110	Safety and recommended dose (measured by frequency of serious adverse events and dose-limiting toxicities)	Estimated completion Aug 31, 2028
NCT04315064	Interventional early phase 1	5 patients with recurrent medulloblastoma (age 1–80 years; both sexes)	Infusion of MTX-110 into the fourth ventricle or tumour resection cavity	Neurological adverse events or deaths (grade 3–5) related to the study drug	Estimated completion Dec 30, 2025
Low-intensity pulsed ultrasound with microbubbles					
NCT05293197	Interventional phase 1	24 patients with refractory malignant brain tumours (age 5–17 years; both sexes)	Sonication with a novel transducer device	Dose-limiting toxicity of ultrasound emissions from the device (measured by clinical and radiological evaluation)	Estimated completion October, 2026
NCT05864534	Interventional phase 2	25 patients with newly diagnosed glioblastoma (age ≥18 years; both sexes)	Balstilimab, botensilimab, and liposomal doxorubicin alongside sonication with transducer device	Toxicity rate and landmark survival analysis up to 18 months	Estimated completion August, 2026
NCT04528680	Interventional phase 1 and phase 2	57 patients with recurrent glioblastoma (age ≥18 years; both sexes)	Chemotherapy (albumin-bound paclitaxel for phase 1 and carboplatin for phase 2) alongside sonication with a transducer device	Dose-limiting toxicity (phase 1); 1-year survival rate (phase 2); relationship between overall survival and expression of SSR3 protein (phase 1 and 2)	Estimated completion September, 2025
NCT05902169	Interventional phase 3	560 patients undergoing planned resection for first recurrence glioblastoma (age ≥18 years; both sexes)	Carboplatin, lomustine, or temozolomide alongside sonication with a transducer device	Overall survival measured over 24 months, tumour growth rate, and progression-free survival	Estimated completion July 30, 2028
Focused ultrasound					
NCT03739905	Interventional	30 patients with probable Alzheimer's disease (age 50–85 years; both sexes)	Transcranial MRgFUS	Device and procedure-related adverse events and blood–brain barrier disruption and closure	Estimated completion December, 2024
NCT05630209	Interventional phase 1 and phase 2	10 patients with diffuse intrinsic pontine gliomas (age 5–21 years; both sexes)	MRgFUS in combination with doxorubicin	Adverse events, blood-brain barrier disruption (measured by comparative MRI)	Estimated completion January, 2026
NCT05615623	Interventional phase 1 and phase 2	Three patients with paediatric diffuse intrinsic pontine gliomas (age 5–18 years; both sexes)	MRgFUS with doxorubicin	Safety and feasibility and preliminary efficacy of blood–brain barrier disruption	Estimated completion July 4, 2025
NCT05565443	Interventional phase 1 and phase 2 study	14 patients with Parkinson's disease (age 35–75 years; both sexes)	MRgFUS in combination with recombinant glucocerebrosidase	Incidence of adverse events and feasibility of blood–brain barrier opening for brain delivery	Estimated completion Dec 31, 2025
NCT05469009	Interventional early phase 1	15 patients with mild cognitive impairment or mild Alzheimer's disease (age 50–85 years; both sexes)	Aducanumab or lecanemab alongside blood–brain barrier opening with a focused ultrasound device	Treatment intervention related adverse events up to 5 years after last treatment	Estimated completion July, 2029
Membrane transporters					
NCT02977780[95]	Interventional phase 2	460 patients with glioblastoma (age ≥18 years; both sexes)	Abemaciclib, temozolomide, neratinib, CC115, and QBS10072S (cytotoxic LAT1 substrate)	Overall survival in experimental groups compared with standard therapy	Estimated completion Dec 31, 2025
NCT05305365	Interventional phase 2	40 patients with breast cancer who have developed brain metastases (age ≥18 years; both sexes)	QBS10072S (18 mg/m^2) via intravenous injection once a month	Overall response against intracranial tumour lesions (assessed by mRANO-BM and RECIST criteria)	Estimated completion August, 2026

(Table 2 continues on next page)

their role in routine clinical practice. Each mechanism will require different implementation strategies and resources for education, training, and integrated care models. Moreover, it is important to consider that high-risk invasive strategies will be less favourable for older patients or those with comorbidities. When applied to some neurodegenerative disorders, use of these novel strategies might encounter hesitancy from both patients and health-care providers because, for some disorders (eg, Parkinson's disease), existing therapies are available that improve quality of life (albeit that are not disease-modifying). Ongoing clinical trials of strategies to enhance blood–brain barrier crossing are predominantly in the field of neuro-oncology and for neurological conditions with poor prognosis (table 2). High treatment risks might be more acceptable to patients with diseases with a poor prognosis and few alternative treatments.

Conclusions and future directions

An appreciation that the blood–brain barrier is one of the largest challenges to drug efficacy has prompted development of various novel techniques to overcome this barrier, ranging from direct intracranial approaches to nanotherapeutics. Advances in therapeutic strategies to cross the blood–brain barrier have, to date, been made mostly in the areas of neurodegeneration and neuro-oncology. No singular method of crossing the blood–brain barrier will likely be appropriate for the various neurological disorders, or even for individuals with the same disease. For example, the most effective treatment for a disease as heterogeneous as glioblastoma will differ between patients and possibly even in different regions within the tumour. In neurodegenerative disorders such as Alzheimer's disease, for which surgical intervention is not part of the current standard of care, focused ultrasound to open the blood–brain barrier paired with a therapeutic agent is an exciting therapeutic prospect.

Each of the novel strategies we have described has promise for development into an established standard for enabling blood–brain barrier penetration, which is an exciting step forward for a previously unmet need. Before this advancement can be properly made, appropriately designed and powered clinical studies are needed with a focus on the timing of treatment, demographic and genetic considerations, head-to-head comparison with other treatment strategies (rather than a placebo), and relevant primary and secondary outcome measures. These measures will include imaging of drug delivery, disease modification, and clinical measures of efficacy such as cognition, but should also encompass patient-related and carer-determined parameters, such as quality of life and the ability to drive and work. Looking forward, various preclinical studies show promise but have not progressed to clinical trials, such as the use of nanoparticles to apply deep brain stimulation for the treatment of Parkinson's disease, which is currently showing promise in vivo.

	Study design and phase	Inclusion criteria	Intervention	Outcomes	Study status
(Continued from previous page)					
NCT05280054	Interventional phase 1	24 healthy patients (age 18–55 years; both sexes)	4-chlorokynurenine alone or in combination with probenecid	Plasma and CSF concentrations of 7-chlorokynurenic acid and 4-chlorokynurenine (with and without probenecid)	Estimated completion Nov 1, 2022 (but no results reported to date)
NCT05842941	Interventional phase 2 and phase 3	240 patients with amyotrophic lateral sclerosis (age ≥18 years; both sexes)	DNL343 and matching placebo administered orally once daily for 24 weeks; not a substrate of ABCB1 transporter	Disease progression (measured by change in disease severity against amyotrophic lateral sclerosis functional rating scale-revised and survival)	Estimated completion August, 2025
NCT03052608[78]	Interventional phase 3	296 patients with ALK-positive non-small-cell lung cancer (age ≥18 years; both sexes)	Lorlatinib (not a substrate of ABCB1 transporter) and crizotinib	Progression free survival based on blinded independent central review	Estimated completion Dec 31, 2028; preliminary results show robust intracranial response
Receptor-mediated transcytosis					
NCT03613181	Open-label, interventional phase 3	150 patients with HER2-negative breast cancer with newly diagnosed leptomeningeal carcinomatosis (age ≥18 years; both sexes)	ANG1005 binds to LRP1 to cross the blood–brain barrier	Overall survival (assessed for up to 2 years)	Estimated completion December, 2024
NCT04251026[86]	Interventional phase 1 and phase 2	47 paediatric patients with mucopolysaccharidosis type II (Hunter syndrome; age 1–18 years; male)	DNL310 (tividenofusp alfa), which targets transferrin receptor TFR1 to cross the blood–brain barrier	Incidence and severity of treatment-emergent adverse events and infusion-related reactions, change in baseline in total urine glycosaminoglycan concentrations, and concomitant medications	Estimated completion July, 2027
NCT04639050	Interventional phase 1 and phase 2	285 patients with prodromal, mild, or moderate Alzheimer's disease (age 50–85 years; both sexes)	Trontinemab, which exploits TFR1 for enhanced blood–brain barrier crossing	Percentage of participants with adverse events and change from baseline in brain amyloid load (measured by PET scan)	Estimated completion Dec 31, 2028

Trials were identified by searching PubMed or ClinicalTrials.gov. ALK=anaplastic lymphoma kinase. HSV-1=herpes simplex virus type 1. RECIST=Response Evaluation Criteria in Solid Tumours. MRgFUS=magnetic resonance-guided focused ultrasound. mRANO-BM=modified Response Assessment in Neuro-oncology Brain Metastases.

Table 2: **Ongoing clinical trials of strategies to circumvent the blood–brain barrier**

Search strategy and selection criteria

We searched PubMed, ClinicalTrials.gov, and Google Scholar with the key search terms "blood-brain barrier AND therapeutics", "blood-brain barrier AND clinical trial", and "blood-brain barrier AND crossing". We searched for papers published between March 1, 2019, and Aug 1, 2024, and for publications that were in English. References were selected with respect to originality, impact, and scope. Studies were prioritised if clinical studies had taken place and were primary papers.

Future experimental studies should be directed towards characterising disease alterations of the blood–brain barrier, the development of complex in-vitro models of the blood–brain barrier for rapid screening of strategies, and expansion on the mechanistic understanding of how these strategies enable the blood–brain barrier to be crossed, to more fully optimise their clinical use for diverse groups of patients.

Contributors

JHP and DD searched the literature and wrote the manuscript. JHP, DD, and AMS prepared the figures. All authors reviewed and edited the manuscript.

Declaration of interests

ABH serves on the advisory board of Caris Life Sciences and the WCG Oncology advisory board; owns stock in Caris Life Sciences, a company that conducts molecular profiling of cancer, which is unrelated to the topic of this Personal View; receives royalty and milestone payments from DNAtrix for the licensing of the patent biomarkers and combination therapies using oncolytic virus and immunomodulation (11,065,285); is supported by research grants from Alnylam and AbbVie; and receives consulting fees from Novocure and Istari Oncology. ABH additionally has active granted patents titled miRNA for treating cancer and for use with adoptive immunotherapies (9,675,633) and concurrent chemotherapy and immunotherapy (9,399,662), with a patent pending for low intensity ultrasound combination cancer therapies (international applications PCT/US2022/019435 and US 63/158,642). ABH is also supported by the National Institutes of Health grants CA120813, NS120547, NS12285, NS124594, CA275430, CA221747, and CA272639. MDJ receives consulting fees from Servier and myTomorrows and is supported by the Sir John Fisher Foundation and Royal College of Surgeons of England. AMS is co-author of patents filed by Northwestern University (not licensed) and receives consulting fees from Carthera, Agenus, and Enclear Therapies; has received funding support for trials from Carthera, Bristol Myers Squibb, and Agenus; and is supported by the grants NS110703, CA264338, CA245969, and CA221747. MDC is supported by the Royal College of Surgeons of England, the Gunnar Nilsson Cancer Treatment Trust Fund, and the University of Liverpool Glioblastoma Fund. BDM is supported to conduct neuroscience research by the UK Research and Innovation Medical Research Council (MR/V03605X/1, MC_PC_19059, MR/V007181/1, and MR/T028750/1), the National Institute for Health and Care Research (CO-CIN-01), and Wellcome Trust (ISSF201902/3). DD has received research funding from Vistagen Therapeutics. JHP is funded by a PhD studentship from the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC/X001598/1) awarded to DD. This Personal View was supported by a scheme funded by the Wellcome Trust Institutional Strategic Support Fund (204822/Z/16/Z) and awarded to DD by the Faculty of Health and Life Sciences, University of Liverpool.

References

1 Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. *Signal Transduct Target Ther* 2023; **8:** 217.

2 Knox EG, Aburto MR, Clarke G, Cryan JF, O'Driscoll CM. The blood-brain barrier in aging and neurodegeneration. *Mol Psychiatry* 2022; **27:** 2659–73.

3 Kadry H, Noorani B, Cucullo L. A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids Barriers CNS* 2020; **17:** 69.

4 Schiera G, Di Liegro CM, Schirò G, Sorbello G, Di Liegro I. Involvement of astrocytes in the formation, maintenance, and function of the blood-brain barrier. *Cells* 2024; **13:** 150.

5 Pisani F, Castagnola V, Simone L, Loiacono F, Svelto M, Benfenati F. Role of pericytes in blood-brain barrier preservation during ischemia through tunneling nanotubes. *Cell Death Dis* 2022; **13:** 582.

6 Bhattacharya A, Kaushik DK, Lozinski BM, Yong VW. Beyond barrier functions: Roles of pericytes in homeostasis and regulation of neuroinflammation. *J Neurosci Res* 2020; **98:** 2390–405.

7 Mayer MG, Fischer T. Microglia at the blood brain barrier in health and disease. *Front Cell Neurosci* 2024; **18:** 1360195.

8 Tsartsalis S, Sleven H, Fancy N, et al. A single nuclear transcriptomic characterisation of mechanisms responsible for impaired angiogenesis and blood-brain barrier function in Alzheimer's disease. *Nat Commun* 2024; **15:** 2243.

9 Wang D, Chen F, Han Z, Yin Z, Ge X, Lei P. Relationship between amyloid-β deposition and blood-brain barrier dysfunction in Alzheimer's disease. *Front Cell Neurosci* 2021; **15:** 695479.

10 Sun N, Akay LA, Murdock MH, et al. Single-nucleus multiregion transcriptomic analysis of brain vasculature in Alzheimer's disease. *Nat Neurosci* 2023; **26:** 970–82.

11 Pineda SS, Lee H, Ulloa-Navas MJ, et al. Single-cell dissection of the human motor and prefrontal cortices in ALS and FTLD. *Cell* 2024; **187:** 1971–1989.e16.

12 Pan Y, Nicolazzo JA. Altered blood-brain barrier and blood-spinal cord barrier dynamics in amyotrophic lateral sclerosis: impact on medication efficacy and safety. *Br J Pharmacol* 2022; **179:** 2577–88.

13 Steinruecke M, Lonergan RM, Selvaraj BT, Chandran S, Diaz-Castro B, Stavrou M. Blood-CNS barrier dysfunction in amyotrophic lateral sclerosis: proposed mechanisms and clinical implications. *J Cereb Blood Flow Metab* 2023; **43:** 642–54.

14 Bejarano L, Kauzlaric A, Lamprou E, et al. Interrogation of endothelial and mural cells in brain metastasis reveals key immune-regulatory mechanisms. *Cancer Cell* 2024; **42:** 378–395.e10.

15 Catalano M, Limatola C, Trettel F. Non-neoplastic astrocytes: key players for brain tumor progression. *Front Cell Neurosci* 2024; **17:** 1352130.

16 Schaffenrath J, Wyss T, He L, et al. Blood-brain barrier alterations in human brain tumors revealed by genome-wide transcriptomic profiling. *Neuro-oncol* 2021; **23:** 2095–106.

17 Xie Y, He L, Lugano R, et al. Key molecular alterations in endothelial cells in human glioblastoma uncovered through single-cell RNA sequencing. *JCI Insight* 2021; **6:** e150861.

18 Zierfuss B, Larochelle C, Prat A. Blood-brain barrier dysfunction in multiple sclerosis: causes, consequences, and potential effects of therapies. *Lancet Neurol* 2024; **23:** 95–109.

19 Al-Bachari S, Naish JH, Parker GJM, Emsley HCA, Parkes LM. Blood-brain barrier leakage is increased in Parkinson's disease. *Front Physiol* 2020; **11:** 593026.

20 Elabi O, Gaceb A, Carlsson R, et al. Human α-synuclein overexpression in a mouse model of Parkinson's disease leads to vascular pathology, blood brain barrier leakage and pericyte activation. *Sci Rep* 2021; **11:** 1120.

21 Movahedpour A, Taghvaeefar R, Asadi-Pooya AA, et al. Nano-delivery systems as a promising therapeutic potential for epilepsy: current status and future perspectives. *CNS Neurosci Ther* 2023; **29:** 3150–59.

22 Löscher W, Friedman A. Structural, molecular, and functional alterations of the blood-brain barrier during epileptogenesis and epilepsy: a cause, consequence, or both? *Int J Mol Sci* 2020; **21:** 591.

23 Miller T, Cudkowicz M, Shaw PJ, et al. Phase 1–2 trial of antisense oligonucleotide tofersen for *SOD1* ALS. *N Engl J Med* 2020; **383:** 109–19.

24 Edwards AL, Collins JA, Junge C, et al. Exploratory tau biomarker results from a multiple ascending-dose study of biib080 in Alzheimer disease: a randomized clinical trial. *JAMA Neurol* 2023; **80:** 1344–52.

25 Mummery CJ, Börjesson-Hanson A, Blackburn DJ, et al. Tau-targeting antisense oligonucleotide $MAPT_{Rx}$ in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. *Nat Med* 2023; **29:** 1437–47.

26 Kingwell K. Double setback for ASO trials in Huntington disease. *Nat Rev Drug Discov* 2021; **20:** 412–13.

27 Cook M, Murphy M, Bulluss K, et al. Anti-seizure therapy with a long-term, implanted intra-cerebroventricular delivery system for drug-resistant epilepsy: a first-in-man study. *EClinicalMedicine* 2020; **22:** 100326.

28 Galanis E, Dooley KE, Keith Anderson S, et al. Carcinoembryonic antigen-expressing oncolytic measles virus derivative in recurrent glioblastoma: a phase 1 trial. *Nat Commun* 2024; **15:** 493.

29 Umemura Y, Orringer D, Junck L, et al. Combined cytotoxic and immune-stimulatory gene therapy for primary adult high-grade glioma: a phase 1, first-in-human trial. *Lancet Oncol* 2023; **24:** 1042–52.

30 Chiocca EA, Yu JS, Lukas RV, et al. Regulatable interleukin-12 gene therapy in patients with recurrent high-grade glioma: results of a phase 1 trial. *Sci Transl Med* 2019; **11:** eaaw5680.

31 Whone A, Luz M, Boca M, et al. Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease. *Brain* 2019; **142:** 512–25.

32 Mueller S, Kline C, Stoller S, et al. PNOC015: repeated convection-enhanced delivery of MTX110 (aqueous panobinostat) in children with newly diagnosed diffuse intrinsic pontine glioma. *Neuro-oncol* 2023; **25:** 2074–86.

33 Souweidane MM, Kramer K, Pandit-Taskar N, et al. Phase 1 dose-escalation trial using convection-enhanced delivery of radiolabeled monoclonal antibody for diffuse intrinsic pontine glioma following external radiation therapy. *J Clin Oncol* 2021; **39** (suppl)**:** 2010.

34 Abrahao A, Meng Y, Llinas M, et al. First-in-human trial of blood-brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. *Nat Commun* 2019; **10:** 4373.

35 Meng Y, Reilly RM, Pezo RC, et al. MR-guided focused ultrasound enhances delivery of trastuzumab to Her2-positive brain metastases. *Sci Transl Med* 2021; **13:** eabj4011.

36 Rezai AR, D'Haese P-F, Finomore V, et al. Ultrasound blood-brain barrier opening and aducanumab in Alzheimer's disease. *N Engl J Med* 2024; **390:** 55–62.

37 Gasca-Salas C, Pineda-Pardo JA, Del Álamo M, et al. Nigrostriatal blood-brain barrier opening in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2024; **95:** 1089–82.

38 Sonabend AM, Gould A, Amidei C, et al. Repeated blood-brain barrier opening with an implantable ultrasound device for delivery of albumin-bound paclitaxel in patients with recurrent glioblastoma: a phase 1 trial. *Lancet Oncol* 2023; **24:** 509–22.

39 Carpentier A, Stupp R, Sonabend AM, et al. Repeated blood-brain barrier opening with a nine-emitter implantable ultrasound device in combination with carboplatin in recurrent glioblastoma: a phase I/II clinical trial. *Nat Commun* 2024; **15:** 1650.

40 Epelbaum S, Burgos N, Canney M, et al. Pilot study of repeated blood-brain barrier disruption in patients with mild Alzheimer's disease with an implantable ultrasound device. *Alzheimers Res Ther* 2022; **14:** 40.

41 Sun L, Tsai R, Yulyaningsih E, et al. The integrated stress response is modulated by eIF2B agonist DNL343: results from phase 1 healthy subject and phase 1b ALS patient studies (P8–8·010). *Neurol* 2023; **100** (suppl 2)**:** 3555 (abstr).

42 Kumthekar P, Tang S-C, Brenner AJ, et al. ANG1005, a brain-penetrating peptide-drug conjugate, shows activity in patients with breast cancer with leptomeningeal carcinomatosis and recurrent brain metastases. *Clin Cancer Res* 2020; **26:** 2789–99.

43 Kumthekar P, Ko CH, Paunesku T, et al. A first-in-human phase 0 clinical study of RNA interference-based spherical nucleic acids in patients with recurrent glioblastoma. *Sci Transl Med* 2021; **13:** eabb3945.

44 Cousins O, Hodges A, Schubert J, et al. The blood-CSF-brain route of neurological disease: the indirect pathway into the brain. *Neuropathol Appl Neurobiol* 2022; **48:** e12789.

45 Lauffer MC, van Roon-Mom W, Aartsma-Rus A. Possibilities and limitations of antisense oligonucleotide therapies for the treatment of monogenic disorders. *Commun Med* 2024; **4:** 6.

46 Przystal JM, Park I, Zhang J, et al. Efficacy of convection enhanced delivery of MTX110 (soluble panobinostat) in preclinical diffuse intrinsic pontine glioma models using metabolic hyperpolarized 13C imaging. *EJC Paediatr Oncol* 2023; **2:** 100021.

47 Spinazzi EF, Argenziano MG, Upadhyayula PS, et al. Chronic convection-enhanced delivery of topotecan for patients with recurrent glioblastoma: a first-in-patient, single-centre, single-arm, phase 1b trial. *Lancet Oncol* 2022; **23:** 1409–18.

48 Gernert M, Feja M. Bypassing the blood-brain barrier: direct intracranial drug delivery in epilepsies. *Pharmaceutics* 2020; **12:** 1134.

49 Chiocca EA, Nakashima H, Kasai K, Fernandez SA, Oglesbee M. Preclinical toxicology of rQNestin34.5v.2: an oncolytic herpes virus with transcriptional regulation of the ICP34.5 neurovirulence gene. *Mol Ther Methods Clin Dev* 2020; **17:** 871–93.

50 Ling AL, Solomon IH, Landivar AM, et al. Clinical trial links oncolytic immunoactivation to survival in glioblastoma. *Nature* 2023; **623:** 157–66.

51 von Roemeling CA, Patel JA, Carpenter SL, et al. Adeno-associated virus delivered CXCL9 sensitizes glioblastoma to anti-PD-1 immune checkpoint blockade. *Nat Commun* 2024; **15:** 5871.

52 Bommareddy PK, Wakimoto H, Martuza RL, Kaufman HL, Rabkin SD, Saha D. Oncolytic herpes simplex virus expressing IL-2 controls glioblastoma growth and improves survival. *J Immunother Cancer* 2024; **12:** e008880.

53 Wang S, Yan W, Kong L, et al. Oncolytic viruses engineered to enforce cholesterol efflux restore tumor-associated macrophage phagocytosis and anti-tumor immunity in glioblastoma. *Nat Commun* 2023; **14:** 4367.

54 Tian L, Xu B, Chen Y, et al. Specific targeting of glioblastoma with an oncolytic virus expressing a cetuximab-CCL5 fusion protein via innate and adaptive immunity. *Nat Cancer* 2022; **3:** 1318–35.

55 Sperring CP, Argenziano MG, Savage WM, et al. Convection-enhanced delivery of immunomodulatory therapy for high-grade glioma. *Neurooncol Adv* 2023; **5:** vdad044.

56 D'Amico RS, Aghi MK, Vogelbaum MA, Bruce JN. Convection-enhanced drug delivery for glioblastoma: a review. *J Neurooncol* 2021; **151:** 415–27.

57 Barker RA, Björklund A, Gash DM, et al. GDNF and Parkinson's disease: where next? a summary from a recent workshop. *J Parkinsons Dis* 2020; **10:** 875–91.

58 Dréan A, Lemaire N, Bouchoux G, et al. Temporary blood-brain barrier disruption by low intensity pulsed ultrasound increases carboplatin delivery and efficacy in preclinical models of glioblastoma. *J Neurooncol* 2019; **144:** 33–41.

59 Zhang DY, Dmello C, Chen L, et al. Ultrasound-mediated delivery of paclitaxel for glioma: a comparative study of distribution, toxicity, and efficacy of albumin-bound versus cremophor formulations. *Clin Cancer Res* 2020; **26:** 477–86.

60 Sabbagh A, Beccaria K, Ling X, et al. Opening of the blood-brain barrier using low-intensity pulsed ultrasound enhances responses to immunotherapy in preclinical glioma models. *Clin Cancer Res* 2021; **27:** 4325–37.

61 Wei HJ, Upadhyayula PS, Pouliopoulos AN, et al. Focused ultrasound-mediated blood-brain barrier opening increases delivery and efficacy of etoposide for glioblastoma treatment. *Int J Radiat Oncol Biol Phys* 2021; **110:** 539–50.

62 Sonabend AM, Stupp R. Overcoming the blood-brain barrier with an implantable ultrasound device. *Clin Cancer Res* 2019; **25:** 3750–52.

63 Gould A, Gonzales VAA, Dmello CC, et al. Advances in blood-brain barrier disruption to facilitate drug delivery for infiltrative gliomas. *Adv Oncol* 2023; **3:** 77–86.

64 Asquier N, Bouchoux G, Canney M, et al. Blood-brain barrier disruption in humans using an implantable ultrasound device: quantification with MR images and correlation with local acoustic pressure. *J Neurosurg* 2019; **132:** 875–83.

65 Mungur R, Zheng J, Wang B, Chen X, Zhan R, Tong Y. Low-intensity focused ultrasound technique in glioblastoma multiforme treatment. *Front Oncol* 2022; **12:** 903059.

66 Meng Y, Goubran M, Rabin JS, et al. Blood-brain barrier opening of the default mode network in Alzheimer's disease with magnetic resonance-guided focused ultrasound. *Brain* 2023; **146:** 865–72.

67 Stage TB, Mortensen C, Khalaf S, et al. P-glycoprotein inhibition exacerbates paclitaxel neurotoxicity in neurons and patients with cancer. *Clin Pharmacol Ther* 2020; **108:** 671–80.

68 Puris E, Fricker G, Gynther M. Targeting transporters for drug delivery to the brain: can we do better? *Pharm Res* 2022; **39:** 1415–55.

69 de Gooijer MC, Kemper EM, Buil LCM, et al. ATP-binding cassette transporters restrict drug delivery and efficacy against brain tumors even when blood-brain barrier integrity is lost. *Cell Rep Med* 2021; **2:** 100184.

70 Puris E, Gynther M, Auriola S, Huttunen KM. L-type amino acid transporter 1 as a target for drug delivery. *Pharm Res* 2020; **37:** 88.

71 Lu X. The role of large neutral amino acid transporter (LAT1) in cancer. *Curr Cancer Drug Targets* 2019; **19:** 863–76.

72 Ozawa T, Rodriguez M, Zhao G, et al. A novel blood-brain barrier-permeable chemotherapeutic agent for the treatment of glioblastoma. *Cureus* 2021; **13:** e17595.

73 Deng J, Chernikova SB, Wang Y, et al. A novel brain-permeant chemotherapeutic agent for the treatment of brain metastasis in triple-negative breast cancer. *Mol Cancer Ther* 2021; **20:** 2110–16.

74 Hange N, Poudel S, Ozair S, et al. Managing chronic neuropathic pain: recent advances and new challenges. *Neurol Res Int* 2022; **2022:** 8336561.

75 Patel W, Rimmer L, Smith M, et al. Probenecid Increases the concentration of 7-chlorokynurenic acid derived from the prodrug 4-chlorokynurenine within the prefrontal cortex. *Mol Pharm* 2021; **18:** 113–23.

76 Patel W, Shankar RG, Smith MA, et al. Role of transporters and enzymes in metabolism and distribution of 4-chlorokynurenine (AV-101). *Mol Pharm* 2024; **21:** 550–63.

77 Yulyaningsih E, Suh JH, Fanok MH, et al. DNL343 is an investigational CNS penetrant eIF2B activator that prevents and reverses the effects of neurodegeneration caused by the Integrated Stress Response. *Elife* 2023; **12:** RP92173.

78 Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med* 2020; **383:** 2018–29.

79 Cheng VWT, Heywood R, Zakaria R, et al. BMScope: a scoping review to chart the evolving clinical study landscape in brain and leptomeningeal metastasis. *Neurooncol* 2024; noae140.

80 Terstappen GC, Meyer AH, Bell RD, Zhang W. Strategies for delivering therapeutics across the blood-brain barrier. *Nat Rev Drug Discov* 2021; **20:** 362–83.

81 Nikolakopoulou AM, Wang Y, Ma Q, et al. Endothelial LRP1 protects against neurodegeneration by blocking cyclophilin A. *J Exp Med* 2021; **218:** e20202207.

82 Zhu M, Shen H, Wang B, et al. LRP1 as a promising therapeutic target for gastrointestinal tumors: inhibiting proliferation, invasion and migration of cancer cells. *Oncol Lett* 2023; **26:** 432.

83 Ullman JC, Arguello A, Getz JA, et al. Brain delivery and activity of a lysosomal enzyme using a blood-brain barrier transport vehicle in mice. *Sci Transl Med* 2020; **12:** eaay1163.

84 Zapolnik P, Pyrkosz A. Gene therapy for mucopolysaccharidosis type II—a review of the current possibilities. *Int J Mol Sci* 2021; **22:** 5490.

85 Stocki P, Szary J, Rasmussen CLM, et al. Blood-brain barrier transport using a high affinity, brain-selective VNAR antibody targeting transferrin receptor 1. *FASEB J* 2021; **35:** e21172.

86 Sheridan C. Drugs catch a ride through the blood-brain barrier. *Nat Biotechnol* 2023; **41:** 1182–84.

87 Bateman RJ, Smith J, Donohue MC, et al. Two phase 3 trials of gantenerumab in early Alzheimer's disease. *N Engl J Med* 2023; **389:** 1862–76.

88 Grimm HP, Schumacher V, Schäfer M, et al. Delivery of the Brainshuttle™ amyloid-beta antibody fusion trontinemab to non-human primate brain and projected efficacious dose regimens in humans. *MAbs* 2023; **15:** 2261509.

89 Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *J Nanobiotechnology* 2022; **20:** 262.

90 Liu Y, Liang Y, Yuhong J, et al. Advances in Nanotechnology for enhancing the solubility and bioavailability of poorly soluble drugs. *Drug Des Devel Ther* 2024; **18:** 1469–95.

91 Vashist A, Manickam P, Raymond AD, et al. Recent advances in nanotherapeutics for neurological disorders. *ACS Appl Bio Mater* 2023; **6:** 2614–21.

92 Shah S, Sinha VR, Singh SB, Srivastava S. Roles of nanoparticles in drug discovery and delivery. In: Egbuna C, Găman M-A, and Jeevanandam J, eds. Applications of nanotechnology in drug discovery and delivery. Elsevier, 2022: 3–26.

93 Cai Q, Li X, Xiong H, et al. Optical blood-brain-tumor barrier modulation expands therapeutic options for glioblastoma treatment. *Nat Commun* 2023; **14:** 4934.

94 Kim T, Kim HJ, Choi W, et al. Deep brain stimulation by blood-brain-barrier-crossing piezoelectric nanoparticles generating current and nitric oxide under focused ultrasound. *Nat Biomed Eng* 2023; **7:** 149–63.

95 Rahman R, Trippa L, Lee EQ, et al. Inaugural results of the individualized screening trial of innovative glioblastoma therapy: a phase II platform trial for newly diagnosed glioblastoma using Bayesian adaptive randomization. *J Clinical Oncol* 2023; **41**: 5524–35.