Title

Drug delivery to the central nervous system.

Journal

Nature Reviews Materials, 7(4)

ISSN

2058-8437

Authors

Nance, Elizabeth
Pun, Suzie
Saigal, Rajiv
et al.

Publication Date

2022-04-01

DOI

10.1038/s41578-021-00394-w

Peer reviewed

Published in final edited form as:

Nat Rev Mater. 2022 April ; 7(4): 314–331. doi:10.1038/s41578-021-00394-w.

Drug delivery to the central nervous system

Elizabeth Nance[1,4,✉], **Suzie H. Pun**[2,4,✉], **Rajiv Saigal**[2,3,4,✉], **Drew L. Sellers**[2,4,✉]

[1]Department of Chemical Engineering, University of Washington, Seattle, WA, USA

[2]Department of Bioengineering, University of Washington, Seattle, WA, USA

[3]Department of Neurological Surgery, University of Washington, Seattle, WA, USA

[4]These authors contributed equally: Elizabeth Nance, Suzie H. Pun, Rajiv Saigal, Drew L. Sellers

Abstract

Despite the rising global incidence of central nervous system (CNS) disorders, CNS drug development remains challenging, with high costs, long pathways to clinical use and high failure rates. The CNS is highly protected by physiological barriers, in particular, the blood–brain barrier and the blood–cerebrospinal fluid barrier, which limit access of most drugs. Biomaterials can be designed to bypass or traverse these barriers, enabling the controlled delivery of drugs into the CNS. In this Review, we first examine the effects of normal and diseased CNS physiology on drug delivery to the brain and spinal cord. We then discuss CNS drug delivery designs and materials that are administered systemically, directly to the CNS, intranasally or peripherally through intramuscular injections. Finally, we highlight important challenges and opportunities for materials design for drug delivery to the CNS and the anticipated clinical impact of CNS drug delivery.

Central nervous system (CNS) disorders are a growing and costly global health problem. Neuropsychiatric disorders are one of the top global health challenges of this century[1]. Added to this are neurological disorders, such as Alzheimer disease (AD) and Parkinson disease (PD), which preferentially affect the growing elderly population. Finally, patients with primary brain tumours or brain metastases have few treatment options, apart from surgical resection, systemic chemotherapy and radiation. However, many major pharmaceutical companies have limited efforts in CNS drug development owing to the high cost, long pathway and low success rate associated with clinical translation[2]. Biomaterial-based delivery systems represent a potential avenue for enabling new CNS therapies. Advances in precision biomaterial synthesis have yielded biomaterials that can be specifically functionalized, engineered to respond to physiological or external triggers and that possess desirable degradation properties.

✉ eanance@uw.edu; spun@uw.edu; rajiv.saigal@ucsf.edu; drewfus@uw.edu.

Author contributions

E.N., S.H.P., R.S. and D.L.S. contributed equally to the literature search, figure preparation, writing and editing of the article.

Competing interests

The authors declare no competing interests.

In this Review, we examine the effect of normal and diseased CNS physiology on drug delivery to the brain and spinal cord. We highlight the pathophysiological changes that complicate drug delivery into the CNS and discuss biomaterials that can be administered systemically, directly to the CNS, intranasally or peripherally through intramuscular injections. The Review concludes with a perspective on the clinical challenges, future directions and anticipated clinical impact of CNS drug delivery.

Barriers to delivery in the normal CNS

Drug delivery challenges to the brain are often attributed to the complex and highly regulated barriers that prevent a drug from reaching its target site in the brain from its point of entry into the body[3] (FIGS 1,2). In particular, two barrier sites between blood and the brain are often considered for drug delivery[4]: the blood–brain barrier (BBB) and the blood–cerebrospinal fluid (CSF) barrier. In addition, independent of the route of administration to the brain, drug delivery systems must penetrate into the brain parenchyma to reach target disease sites.

At the BBB and blood–CSF interfaces, the barrier function is a result of physical, transport and metabolic contributions. Central to the brain's neurovascular unit (NVU), the BBB is a non-fenestrated monolayer of cells and extracellular matrix (ECM), which, on the abluminal side, consists of tightly sealed endothelial cells that form a barrier between the brain tissue and circulating blood (FIGS 1a,2a). The BBB is considered one of the most regulated and exclusive barriers in the human body. At the level of the capillaries, which are spaced, on average, 40 μm apart and contribute to 85% of the 400 miles of blood vessels in the human brain[5], BBB integrity is maintained by pericytes[6–8] and influenced by astrocytes, particularly astrocyte endfeet that surround brain vessels[9,10]. Endothelial cells and pericytes share a stabilizing basement membrane, which represents the non-cellular component of the NVU.

The BBB regulates transport of molecules into and out of the CNS to tightly control the chemical composition required for normal brain function[9]. Oxygen, carbon dioxide and lipophilic molecules smaller than 400 Da passively diffuse across the brain endothelium[11]. The capillary permeability for small, water-soluble molecules (<5 Å in size) is reduced by over two orders of magnitude in the brain compared with other organs; this difference is increased to over seven orders of magnitude for molecules of 50 Å in size[12]. Tight junctions between brain endothelial cells control paracellular transport, and carbohydrates, amino acids and hormones must passage across the BBB using endothelial carrier-mediated transporters[13]. Some macromolecules, including transferrin, insulin and leptin, use endothelial receptor-mediated transport[14]. Endothelial ion transporters and channels are further crucial in controlling ion concentrations in the CNS. Lastly, efflux mechanisms using ATP-binding cassette transporters actively pump drugs and drug conjugates, xenobiotics and endogenous metabolites into the blood, contributing to the barrier function between the blood and the brain.

The blood–CSF interface presents a second barrier to drug penetrance, comprising the choroid plexus epithelium with an estimated surface area of 1.7 m^2 in humans[15]. Compared

with the BBB, the blood–CSF barrier is leaky. Blood capillaries at the blood–CSF interface are fenestrated; therefore, barrier properties are formed by tight junctions between epithelial cells at the CSF-facing surface (apical) of the choroid plexus. Molecules, such as sucrose, inulin and albumin, do not cross the BBB, but can cross the choroid plexus to enter the CSF at a rate inversely proportional to the molecular weight of the substance[16]. To move from the CSF to the brain, drugs can navigate one of three routes. Therapeutics infused into the CSF can move from the CSF into blood and then enter across the BBB to reach brain parenchyma. Diffusion into the brain can occur across the ependyma lining of CSF flow tracts from the CSF into the brain, although this route can be toxic if high concentrations are used to drive diffusion[17,18]. Drugs can also penetrate through bulk flow of CSF along perivascular spaces, as demonstrated by intraventricular infusion of horseradish peroxidase in rats and cats[15,19]. However, the volume of CSF flow within the brain parenchyma is small and 20-fold slower than CSF flow over the surface of the brain[20], limiting penetration from the perivascular space into brain parenchyma.

If therapeutics are able to navigate the BBB or blood–CSF barrier, or if they are locally administered to bypass these barriers, there remains the challenge of tissue penetration from the site of entry into the brain to target cells or regions of interest within the brain. Given the emphasis of the neurotherapeutic field on overcoming the BBB, penetration within the brain parenchyma is an often overlooked but important barrier to drug delivery into the CNS[21]. A small lipophilic substance, which successfully diffused transcellularly across the BBB, faces the additional barrier of partitioning from the lipid environment of the BBB endothelial cell membrane into the aqueous interstitial fluid. Drug distribution by diffusion within the brain extracellular space (ECS) is mediated by blood, the CSF, extracellular fluid movement, pH, the presence of the ECM and the degree of cellularity[22,23]. Diffusion is also limited by the physicochemical properties of the drug or delivery vehicle, such as size, surface charge, shape and molecular weight[24–26]. For example, free drugs only penetrate 1–3 mm into parenchyma, as evidenced by studies measuring drug distribution as a function of distance from the site of intracerebral or intracerebroventricular injection[16,22,27]. Notably, the ECS is heterogeneous and diffusion is anisotropic in many brain regions, further altering net drug distribution. Moreover, many physiological changes associated with disease pathology alter the brain ECS, ECM and NVU microenvironment (FIGS 1,2), affecting the penetration of drug delivery systems within the brain parenchyma; for example, breakdown in vascular function, changes in enzymatic activity, and extracellular and cellular disruption by processes such as inflammation result in alterations in the brain interstitial space.

CNS diseases and drug delivery

Cancer

Glioma is the most common primary brain cancer type. The most aggressive, prevalent subtype of glioma is glioblastoma multiforme (GBM), with a median survival time of only around 1 year[28]. In addition to primary tumours in the brain, an estimated 9–17% of cancers metastasize to the brain. Brain cancer is challenging to treat in large part because the BBB limits drug delivery to the tumour. Physiological changes that occur in brain cancer include

transformations in vascularization, the brain ECM and the local immune composition (FIG. 1b). These disease-associated changes can hinder but can also be exploited for drug delivery.

Glioblastoma can have dysfunctional vasculature, including more irregular vessels and increased permeability compared with healthy brain vasculature. Increased permeability is more associated with high-grade tumours and metastases[29], but can also allow drugs to access brain tumours from the blood circulation, which would otherwise be prohibited by an intact BBB. Vasculature changes also affect brain tumour tissue. Leaky vasculature can lead to cerebral oedema and increased intracranial pressure, and altered distribution of vasculature can generate locations of hypoxia[30]. Glioma cells remodel the local ECM and produce matrix proteins that are not present in normal brain parenchyma[31]. Tumour cells also upregulate protease expression (for example, urokinase plasminogen activator, matrix metalloproteinases (MMPs) and secreted cathepsin B) to facilitate ECM remodelling. Smart materials responsive to the remodelled ECM or upregulated proteases have been designed for tumour-targeted drug delivery[32]. Glioma cells also secrete factors that recruit immune cells into the brain tumours, including tumour-associated macrophages, myeloid-derived suppressor cells and T cells. Immune cell migration from the circulation into the brain has also been exploited for drug delivery.

Trauma

Traumatic brain injury (TBI) affects approximately 2 million and spinal cord injury (SCI) 18,000 US patients per year, with nearly 300,000 patients with SCI dealing with its chronic effects[33–35]. Both types of neurotrauma remain challenging clinical problems, with a complex pathophysiology that evolves over time, adding to the difficulty in finding appropriate treatments (FIG. 1c). In addition to the initial trauma, secondary injury mechanisms, including inflammatory cytokine production, neutrophil infiltration, glutamate excitotoxicity, free radical formation, apoptosis and scar formation, lead to considerable expansion of the injury[36–38], but also offer many potential avenues for intervention[39–41].

A common theme in both TBI and SCI is the role of neuroinflammation and secondary injury. Mitigation of post-TBI neuroinflammation can lead to functional improvements in preclinical rodent models of contusive injury[34,42]. Inflammation is a crucial component of the secondary injury cascade, leading to further cellular damage and death. Tumour necrosis factor is a pro-inflammatory cytokine, present soon after SCI in rodent models, peaking at 1 h post-injury and persisting at detectable levels for 72 h after injury[38]. Therefore, the first 72 h post-injury appear to be the optimal time frame for decreasing inflammation. However, in vivo delivery of anti-inflammatory agents is challenging, owing to adverse side effects. Thus, the American Association of Neurological Surgeons-Central Nervous System Joint Spine section advised against the use of intravenous (iv) methylprednisolone in their 2013 SCI guidelines[43], based on a meta-analysis of systemic adverse effects in published clinical studies. Administration of steroids remains a controversial topic, with patients with SCI[44] and some surgeons in favour[45] of their use within 8 h of injury owing to possible benefits, but a dwindling number of clinicians prescribing them owing to the perceived risk[46]. Although anti-inflammatory drugs may be applicable for the treatment of neurotrauma, targeted delivery methods are required to minimize systemic side effects

(BOX 1). For example, the controversy surrounding steroids could potentially be solved by local and controlled release of an anti-inflammatory agent. This could be achieved by polymer-based approaches, which enable the formation of local drug depots and controlled drug release.

Beyond the acute phase, the chronic phase of SCI offers important opportunities for enhancing recovery through rehabilitation and neuromodulation. For example, advances in epidural electrical stimulation have recently led to some recovery of voluntary motor control and modest, but impaired, overground stepping in a subset of motor-complete patients with SCI[47,48]. Thus, increased tissue sparing right after injury could greatly improve the potential of emerging rehabilitation therapies. These therapies could further be improved using implantable drug delivery technologies.

Neurodegenerative pathophysiology

Evidence of endothelial degeneration and diminished BBB function has been reported for amyotrophic lateral sclerosis, PD and AD, highlighting potential consequences of neurovascular dysfunction in ageing and neurodegenerative diseases[49,50]. The onset of BBB dysfunction occurs with increased gliosis, neurovascular dysfunction, increased neuroinflammation and a progressive loss in neuronal function[51] (FIG. 2b). In patients with chronic psychological disorders or schizophrenia, neurovascular health is also compromised. In these conditions, perivascular microenvironments show a thickened basal lamina, deformation of astrocytic endfeet, microglial activation and chronic neuroinflammation[52].

In addition to challenges related to vascular dysfunction preceding the loss of neuronal function[53,54], drug delivery into the CNS is also complicated by the onset of secondary pathologies, which develop with prolonged BBB dysregulation. The downregulation of tight junction protein expression in the BBB leads to perivascular space expansion and accumulation of toxic proteins (for example, fibrinogen) from the blood[55]. Vascular dysfunction also coincides with increased deposition of heavily sulfated proteoglycans and glial scarring[56] owing to an increase in amyloid protein deposition, which further impacts cellular components (for example, pericytes) of the neurovascular niche[57]. Pericytes have a key function in BBB integrity, and, thus, these progressive angiopathies accelerate vascular degeneration and reduce brain microvasculature[58]. With decreasing vascular function, amyloid and proteoglycan deposition increases, and, thus, material formulations designed to deliver drugs across a healthy BBB face substantial barriers that confound delivery into diseased CNS[49,53,59–62].

Stroke

Stroke refers to vascular brain injuries from either ischaemia and/or haemorrhage, and has high lifetime risk, affecting one in four people[63]. Globally, there are approximately 14 million new stroke cases per year, with 70% ischaemic and 30% haemorrhagic aetiologies[4]. The stroke treatment landscape is rapidly changing. Treatment with tissue plasminogen activator (tPA) has shown survival and functional benefits in several randomized clinical trials[64]; however, tPA must be iv delivered and has a narrow time window for intervention — in the USA, administration is currently only recommended within 4.5 h of stroke onset[65].

As a serine protease, tPA promotes conversion of plasminogen into plasmin, facilitating clot dissolution. Owing to the requirement of systemic delivery, high doses are needed (0.9 mg kg^{-1} iv) and patients may suffer devastating complications from intracerebral and/or subarachnoid haemorrhage. Thus, controlled release systems are needed that achieve functional stroke benefit, while mitigating haemorrhagic risk.

Alternatively, neurointerventional options have been explored for the treatment of ischaemic stroke, for example, the insertion of an intra-arterial catheter (usually in the femoral artery). The catheter is then advanced towards the ischaemic brain vessel to retrieve the offending clot[66–70]. Endovascular thrombectomy has been shown to be an effective treatment up to 24 h post-stroke in a subset of patients with mismatch between clinical severity and infarct volume[71]. Interventional stroke treatments have become more pervasive, and endovascular access also provides a potential route for depositing a drug delivery system to further promote stroke recovery (FIGS 2c,3a).

In addition to acute interventions, subacute and chronic phases of stroke also offer opportunities for controlled drug release, for example, to promote neuroregeneration or neuroplasticity. Multiple biological processes limit the capacity of the CNS to regenerate, including glial scar formation. Chondroitin sulfate proteoglycans are a key component of the glial scar and local delivery of chondroitinase ABC can help degrade this barrier[72]. MMPs are also of therapeutic interest, because they can help remodel the ECM. However, the timing of MMP delivery is crucial; they may be harmful in the acute phase but promote recovery if delivered 1 week post-stroke[73]. Other strategies include neuroprotection (for example, minocycline, natalizumab, uric acid, fingolimod), delivery of growth factors and delivery of microRNAs by depot materials to promote survival and differentiation of stem cells[73–76].

Systemic delivery to the CNS

Drug delivery strategies to the CNS can be implemented by several administration routes: systemic delivery, invasive local delivery, such as intrathecal and intraparenchymal delivery, and alternative administration routes, such as intranasal and peripheral delivery.

Intravenous administration provides a minimally invasive opportunity for drug delivery to the brain but requires passage through the BBB. Consequently, more than 98% of systemically administered small molecules with a molecular weight <500 Da and nearly 100% of molecules with a molecular weight >500 Da are unable to access the brain[77]. Here, we discuss three main approaches to increase drug delivery from the blood circulation into the brain: synthetic formulations that undergo transcytosis across the brain endothelium; biological carriers that traffic to the brain; and drug delivery combined with temporary disruption of the BBB.

Synthetic formulations for transcytosis across the BBB

The brain endothelium closely regulates material transfer between the blood and the brain through transporters, receptors and drug efflux pumps (FIG. 4a). These transporters and receptors can be exploited for drug delivery across the BBB[78–80] (TABLE 1). Of note, the

expression of transporters and receptors at the BBB can be altered in disease, which may affect drug delivery vehicles using these pathways. For example, low-density lipoprotein receptor-related protein expression is reduced, whereas the expression of some drug efflux transporters is increased in AD.

Different brain targeting ligands can be compared using the same material platform. For example, when comparing iv-injected liposomes modified with transferrin (Tf), an anti-transferrin receptor (TfR) antibody, angiopep-2, an ApoE mimetic peptide or a mutated diphtheria toxin, only liposomes functionalized with anti-TfR antibodies show increased brain accumulation, compared with unfunctionalized control liposomes[81]. Similarly, when comparing injection of a 50-kD polyanionic polymer (poly(β-L-malic acid)) conjugated with five different peptide targeting ligands, the angiopep-2-targeted construct exhibits the highest brain accumulation in BALB/c mice when combined with a small peptide for endosomal release[82]. It is important to note that the material design for each targeting approach needs to be optimized based on the specific ligand–receptor interactions and intracellular trafficking pathway.

A case study with TfR

The evolution of materials design driven by increased biological understanding is well illustrated by a series of formulations developed for TfR-mediated blood-to-brain delivery. Three possible outcomes have been reported for TfR trafficking in brain endothelial cells after ligand binding on the apical side: recycling back to the apical side; degradation in lysosomes; or transcytosis to the basolateral side (BOX 2). Successful brain delivery from the circulation requires receptor binding to brain vasculature, transcytosis through brain endothelial cells, diffusion through the basement membrane and penetration through the brain parenchyma, all of which can be impacted by ligand and vehicle properties.

Receptor affinity.—Seminal work by Genentech demonstrated that reducing the affinity of anti-mouse TfR (mTfR) antibodies from 1.7 nM to 111 nM increased brain delivery after iv injection from 0.1% to 0.6% of injected dose (ID)[83]. A follow-up study investigating a series of anti-mTfR antibodies with high (18 nM), moderate (588 nM) and low (100 μM) receptor binding affinities revealed that the antibody with intermediate affinity accumulated with the highest concentration in the brain after iv injection[84]. Several options could explain improved brain delivery with lower-affinity TfR1 binders. Lower-affinity antibodies dissociate more readily from the receptor after transcytosis, improving brain accumulation and distribution[83]. High-affinity, but not low-affinity, anti-mTfR antibodies reduce TfR expression by 50% within 24 h of treatment in the brain cortex, owing to trafficking to lysosomal compartments in endothelial cells[85]. Finally, high-affinity TfR binders may bind non-BBB cells, such as reticulocytes[84] and hepatocytes, reducing BBB targeting. Together, these studies demonstrate the importance of ligand affinity optimization for transcytosis.

Ligand valency and avidity.—Avidity in targeted delivery can be introduced using divalent antibodies or by synthesizing nanoparticles with multivalent ligand display. As observed with high-affinity anti-TfR antibodies, divalent antibodies also increase TfR degradation, compared with monovalent antibodies[86]. Transvascular brain delivery using

targeted nanoparticles can be optimized by fine-tuning ligand valency on the nanoparticles. High-avidity, transferrin-modified nanoparticles remain attached to the brain vasculature, whereas lower-avidity nanoparticles can access the brain parenchyma[87]. For example, more nanoparticles functionalized with low-affinity anti-mTfR antibodies (149 nM) accumulate in the brain parenchyma than nanoparticles functionalized with high-affinity (21 nM) antibodies[88]. Thus, higher ligand valency and avidity are not necessarily better in terms of brain accumulation. Ligand valency effects on receptor binding, receptor trafficking and tissue penetration are complex, and, therefore, optimization may be required for each platform.

pH sensitivity.—The dichotomy in TfR1-mediated transcytosis, that is, high initial binding affinity for cell uptake followed by low-affinity binding to avoid lysosomal trafficking, has galvanized the development of pH-sensitive ligand designs with the following common principle: high receptor binding affinity and avidity at extracellular pH (pH = 7.4) and reduced binding affinity and avidity in early endosomal pH (pH ~6.0). To reduce lysosomal trafficking of multivalent TfR1-targeted nanoparticles, Tf can be linked to nanoparticles by acid-cleavable, diamino ketal or boronate ester linkers, allowing reversible attachment of Tf and higher nanoparticle accumulation in murine brains, compared with formulations with non-cleavable linkers[89,90]. Similarly, the inclusion of an acid-cleavable diamino ketal linker between the T7 TfR1-binding peptide and an electrostatically complexed nanoparticle, composed of an amphiphilic cationic polymer and small interfering RNA (siRNA) against β-secretase 1 (BACE1), increases transcytosis in brain endothelial cell monolayers compared with a control formulation with stably conjugated peptide ligands[91].

Physicochemical and mechanical properties.—The circulation time of nanosized drug carriers is strongly influenced by their physicochemical and mechanical properties, such as size, shape, charge, hydrophilicity and stiffness (FIG. 4b). Prolonged circulation half-life is a prerequisite for systemic and sustained access to the BBB, and, thus, particles should be used that are not immediately cleared after administration, that is, nanoparticles with diameters <100 nm or high aspect ratio, near neutral charge and a protective corona that limits protein adsorption[92]. The vascular basement membrane, a 20–200-nm-thick matrix comprised primarily of glycoproteins, adds an additional charge and size restriction to brain delivery. In addition, size limits within the brain extracellular space accessible for nanoparticle diffusion have been estimated to be <114 nm (REF.[24]). In vivo studies in rodents confirmed that particles <100 nm are best suited for systemic delivery to the brain[87,93]. In a microfluidic in vitro BBB model, rod-shaped particles have been shown to be more efficiently transcytosed than spherical particles of the same volume[94]. The rather underexplored area of particle shape may be a focus of future materials development for brain delivery.

Brain-vasculature-targeted delivery

Despite progress in developing vehicles for BBB transcytosis, overall delivery efficiencies remain low, and most brain-accumulating formulations are associated with the microvasculature endothelium in the brain[88,95]. For example, >90% of brain-associated

anti-TfR antibody, known as OX26, is found in the brain capillaries after iv injection and not in post-capillary compartments[95]. However, endothelial retention and the uniqueness of the brain endothelium also present an opportunity for targeted brain delivery. For example, OX26-functionalized liposomes that associate with brain capillaries without transcytosis can deliver encapsulated oxaliplatin to the brain[96]. The brain vasculature can, therefore, act as an accessible depot site for drug delivery to the brain. Proteins upregulated in inflamed brain vasculature can also be targeted to localize carriers to the cerebral vasculature; for example, anti-vascular cell adhesion molecule 1 antibodies accumulate in the brain vasculature at an impressive 17% ID g^{-1}, compared with 1.5% for anti-TfR antibodies[97]. Localized injection into the carotid artery further increases brain delivery efficiency of liposomes targeted to cellular adhesion molecules by another fivefold[98]. The low level of endocy-tosis in brain endothelial cells compared with peripheral endothelial cells can also be exploited for brain vasculature targeting[99]. Anti-platelet endothelial cell adhesion molecule antibodies bind to endothelial cell surfaces but are less internalized in brain endothelial cells than in the rest of the vasculature. Injection of avidin-functionalized micelles 8 h after injection of biotinylated anti-platelet endothelial cell adhesion molecule antibodies results in selective brain accumulation compared with other organs[99].

Biological carriers.—Red blood cells (RBCs), which can be readily obtained in a clinical setting, can be used as carriers to the brain. For example, conjugating tPA to RBCs leads to reduced hippocampal cell loss in rats with TBI[100]. Injection of RBCs functionalized with nanocarriers into the internal carotid artery, which feeds into the brain, results in 11.5% ID delivered to the brain of healthy mice[101]. Leukocytes from the blood are also able to cross the BBB, with migration rates increasing in response to brain inflammation. For example, macrophages equipped with polymeric backpacks through layer-by-layer deposition of electrolytes can deliver drugs, such as catalase, to the brain[102]. To avoid the complexity associated with cell therapies, liposomes can be functionalized with cyclic RGD peptides to target monocytes and neutrophils[103]. Following iv injection into rats with ischaemia–reperfusion injury, the targeted liposomes associate with 34.5% of circulating monocytes and are carried to the ischaemic brain injury site by these cells[103].

Extracellular vesicles, such as exosomes, are cell-membrane-encapsulated vesicles released by cells. Exosomes participate in intercellular communication by transferring protein and nucleic acid from host to recipient cells. As naturally occurring nanoparticles, exosomes are well tolerated and have minimal non-specific interactions, leading to prolonged circulation time (hours in the blood)[104]. Some exosomes, such as those derived from macrophages, are able to cross the BBB, with approximately fivefold increased passage in inflamed brain compared with healthy brain[105]. To increase BBB targeting, ligands can be attached to exosomes, either through recombinant expression of a fusion protein enriched in exosomal membranes[106] or by direct covalent conjugation[107]. Such engineered exosomes can deliver small-molecule drugs, nucleic acids and proteins[106–108]; for example, exosomes isolated from bone-marrow-derived dendritic cells can be engineered to express a rabies virus glycoprotein-derived peptide, allowing brain endothelial cell targeting and delivery of siRNA against BACE1, resulting in efficient target protein reduction in the mouse brain[106].

Biological carriers are an attractive approach for drug delivery to the brain; however, production costs are high compared with synthetic carriers. Large-scale production and purification, as well as methods for rapid and reproducible characterization of exosomes, remain a bottleneck in the clinical translation of this technology.

Localized disruption to facilitate brain delivery.—The aforementioned approaches focus on navigating the BBB by exploiting innate, non-disruptive pathways. Alternatively, transvascular drug delivery can be achieved through transient disruption of the BBB by osmotic change[109]. However, disrupting the BBB is associated with toxic effects and, thus, this approach requires tight spatial control and temporal transience. Adverse side effects can be reduced by magnetic resonance (MR)-guided[110] optimization of the perfusion area impacted by osmotic agent delivery, combined with temporary occlusion[111].

Focused ultrasound allows precise spatial and temporal control of localized acoustic energy treatment to transiently disrupt the BBB. Combined with MR imaging, MR-guided focused ultrasound (MRgFUS) can improve brain delivery of systemically delivered small-molecule drugs, proteins, antibodies, synthetic nanoparticles, viruses and cells[112–114]. In MRgFUS-mediated brain delivery, drugs are usually co-delivered with microbubbles that respond to ultrasound by expanding and contracting, temporarily increasing neurovascular permeability[115]. Importantly, several recent clinical studies have demonstrated that MRgFUS for brain delivery is well tolerated in patients with AD[116] and brain cancer[117]. Thus, MRgFUS is a promising approach for targeting delivery to specific locations within the brain, However, the approach is complex and requires sophisticated instrumentation.

Invasive local delivery

Local or non-systemic drug delivery routes are often invasive but viable strategies during surgical interventions for resection of malignant tumours, subarachnoid haemorrhage, PD or traumatic injury treatment. For example, extended-release wafers, hydrogel scaffolds, polymer films, microspheres or nanoparticles can be implanted for direct parenchymal administration to the brain (FIG. 5). Intrathecal delivery strategies can further employ biomaterials that can be infused into the CSF. Non-biodegradable polymers, such as silicone rubber, were first explored, which can deliver a range of molecules; however, these materials are not optimal, owing to long-term side effects and reduced drug release rates over time[118]. Improved clinically available polymer delivery systems were composed of hydrophilic matrices that adsorb water and undergo homogeneous degradation; however, homogeneous degradation results in rapid and uncontrolled inactivation of drug agents. Hydrophobic adsorbable polymer sutures were the first clinically used biodegradable polymers, introduced in the 1980s[119], which then inspired the next generation of sustained intraparenchymal delivery strategies.

Intraparenchymal administration

Drug delivery through intraparenchymal (also referred to as intracranial or intracerebral) injection can be achieved using natural or synthetic polymer-based systems, which provide controlled, timed and long-lasting drug delivery as the material degrades. Natural polymers, such as polysaccharides (for example, alginate, hyaluronic acid, dextran and chitosan) and

proteins (for example, collagen, albumin, elastin and gelatin), can form hydrogels through self-assembly or cross-linking. Natural polymers are abundant and generally well tolerated in vivo. Synthetic polymers have the advantage of allowing sophisticated modifications, enabling customization for specific drug release and degradation requirements. Most synthetic polymers used for intraparenchymal depots are composed of polyesters, poly anhydrides, polyamides, polycarbonates and phosphate-based polymers. These polymers are typically hydrophobic and provide a stable platform for water-insoluble drugs. Natural and synthetic polymers have been used in the form of wafers, injectable hydrogels, implantable hydrogel scaffolds, conducting polymers, and microparticles and nanoparticles.

Extended-release wafers.—The most extensively studied intraparenchymal delivery system is the US Food and Drug Administration (FDA)-approved carmustine (BCNU)-loaded polyanhydride wafer (Gliadel), used in the treatment of glioblastoma. This wafer is composed of pol y(carboxyphenoxy-propane-co-sebacic acid anhydride) and is a core technology for the delivery of antitumour agents, including paclitaxel[120], camptothecin[121] and temozolomide[122]. BCNU wafers provide high local drug concentrations while limiting systemic toxicity[123], resulting in modest efficacy in patients with GBM[124]. However, the majority of BCNU is released from the wafers within the first week of implantation and the drug concentration is highest within 1 cm of the implanted wafers[125], which is suboptimal, given the invasive nature of high-grade gliomas. Thus, greater tissue penetrance of therapeutically effective drug concentrations is required to improve outcomes after Gliadel implantation. Although the approval of BCNU wafers was an important step for the drug delivery and biomaterials fields, follow-up clinical trials in patients who were not eligible for the initial clinical trials raised concerns about side effects potentially caused by materials with prolonged polymer degradation[126]. Nonetheless, BCNU wafers provide an exemplary design platform for intraparenchymal drug delivery and can guide the development of alternative polymer depots, such as hydrogels, microspheres and nanoparticle systems. For example, the composition of polymer reservoir systems based on polyester nanofibre composites can be tailored by electrospinning[127].

Injectable hydrogels.—Hydrogels are soft, often shear-thinning materials that can be tuned to degrade over a period of days to weeks, rather than months. Intraparenchymally delivered hydrogels can encapsulate various payloads, including mesenchymal stem cells[128], small-molecule drugs, growth factors[129] and extracellular vesicles[130]. Many hydrogel studies have focused on brain cancer treatment; however, peptide-based and polymer-based hydrogels have also proven effective in delivering trophic factors for the treatment of inflammation and ongoing oxidative injury in stroke, TBI and SCI[73,129,131]. For example, a complement component 7 (C7)-poly(ethylene glycol) (PEG) hydrogel encapsulating vascular endothelial growth factor and MMP9 provided sustained release and improved functional recovery in a preclinical middle cerebral artery occlusion model for stroke[73]. Delivery of vascular endothelial growth factor and MMP9 into the CSF resulted in downregulation of connective tissue growth factor, representative of a purported recovery mechanism shown in preclinical studies on stem cell transplantation[73]. Humans have a larger tissue volume than mice, which may allow better tolerance of microlitre-volume hydrogel injections relative to the smaller spinal cord space. Indeed, brain injections for

convection-enhanced delivery has been demonstrated in humans. An injectable ultraviolet (UV) cross-linked poly(lactic acid)–PEG hydrogel encapsulating neurotrophin 3 (NT3) enabled controlled release of the drug in a dorsal hemisection preclinical model of SCI[132]. Local delivery led to improved functional recovery as measured by standard locomotor tests[132]. Although this is an interesting approach for spinal cord transection, the great majority of human SCI cases are contusive rather than true transections. Injection of a hydrogel is more challenging in this clinical setting because there is no open spinal cord wound in which to place the gel; rather, the surgeon would have to violate the meninges and spinal cord tissue with an injection, potentially causing further injury. Moreover, whether UV polymerization is successful if the pre-polymer is intrathecally injected remains to be shown, because UV light has to pass through an intact dura and subarachnoid space. In situ temperature-based polymerization has been demonstrated with an injectable F-127 hydrogel depot containing poly(lactic-co-glycolic acid) (PLGA) microspheres loaded with thrombin inhibitors, resulting in improved recovery in a mouse SCI model compared with animals injected with CSF or heparin hydrogel controls[133].

Hydrogel delivery of enzymes, which are unstable and challenging to deliver in free form at body temperature, has shown promise for the treatment of neurotrauma. For example, a chondroitinase ABC fusion protein can be stabilized by site-directed mutagenesis and PEGylation when encapsulated in a methylcellulose hydrogel[72]. Following injection, chondroitinase ABC enzymatically degrades chondroitin sulphate proteoglycan, making the post-injury microenvironment more permissive for axonal regrowth and enabling remodelling after neurotrauma or stroke[72]. Sustained release from the hydrogel system reduced chondroitin sulfate proteoglycan levels in a rodent stroke model. A polymeric form of bivaliru-din, a thrombin inhibitor, can be delivered by an injected hyaluronic acid and methylcellulose hydrogel, which reduced gliosis in a rat SCI model[134].

Implantable hydrogel-based scaffolds.—Hydrogel scaffolds can also be employed for controlled CNS drug delivery. Hydrogel scaffolds are structural and compositional mimics of the target tissue environment and may be used to deliver drugs or chemical cues to promote regeneration after stroke or neurotrauma[135], such as trophic factors to promote overall growth, mechanical alignment cues, or attractive and repulsive cues to help regenerative nerve fibres to reach their target. For example, a heparin system encapsulating NT3 in a fibrin gel[136] showed evidence of regenerating fibres in an SCI model without functional assessment. Similarly, poly(ε-caprolactone-co-ethyl) ethylene phosphate can be electrospun into aligned nanofibres and embedded in a collagen hydrogel to enable sustained release of NT3 and microRNAs after implantation in a cervical hemisection model of SCI[137]. In this model, aligned axon regeneration could be achieved; however, behavioural recovery was not assessed, and, thus, it remains unclear whether the hydrogel had a functional effect. In addition, the system may be challenging to implement in humans with non-penetrating SCIs; in the most common human clinical scenario, there is almost never a hemisection gap available in which to implant such a hydrogel and implantation itself may cause injury.

Conductive polymer implants.—Conductive polymer scaffolds offer the possibility to house and stimulate cells that can act as therapeutics for the CNS. For example, neural stem cells can be pre-stimulated on a polypyrrole scaffold prior to implantation in a rat stroke model[138]. Animals treated with electrically preconditioned neural stem cells showed improved functional recovery compared with animals implanted with unstimulated neural stem cells. Combining this approach with controlled drug release by a polymer in vivo may further improve the results. Conductive polymer thin films have been used in various applications for targeted drug delivery. By undergoing oxidation–reduction reactions, conductive polymers can provide a depot for the release of bioactive molecules in the CNS. In particular, polypyrrole has grown in popularity owing to its biocompatibility[139,140]. Additionally, microfabrication techniques can create polymer-covered electrode arrays with any geometry of interest for controlled local drug delivery to the CNS[139–142].

Microscale and nanoscale delivery systems.—Natural and synthetic polymers can be fabricated into microspheres and nanoparticles for intraparenchymal delivery. For example, drug delivery by biodegradable PLGA microspheres has been investigated for high-grade gliomas, pain[143] and spasticity[144]. In a randomized phase II trial, patients with high-grade glioma received multiple injections of PLGA microspheres loaded with 5-fluorouracil following tumour resection, with post-operative fractionated radiotherapy[145]. These patients survived 15.2 months, compared with 13.5 months for patients who only received radiotherapy after surgical resection. PLGA can also provide a depot for nimodipine to treat vasospasm and secondary brain injury after a subarachnoid haemorrhage[146]. Incorporated into PLGA microspheres, nimodipine treatment resulted in a significant reduction of vasospasm with no signs of toxicity[147,148].

Microspheres have high loading capacity and long drug release profiles, but show limited brain parenchyma penetration. By contrast, nanoparticles designed to minimize interactions with the ECM and cellular components of the brain microenvironment are more widely distributed in the parenchyma and show increased retention following intraparenchymal delivery[24,149]. For example, PLGA nanoparticles copolymerized with PEG and loaded with paclitaxel resulted in slowed brain tumour growth after intratumoural injection in a gliosarcoma rat model[150]. Paclitaxel-loaded PLGA particles without PEG were not able to delay tumour growth compared with free drug and no-treatment controls, owing to limited penetrance and distribution of the particles and drug. PLGA nanoparticles in disc rather than spherical form were equally effective at treating glioma, because they achieve high paclitaxel concentrations at >5 mm from the site of injection, demonstrating the potential importance of shape and size in improving drug distribution within the parenchyma[151]. Lipid polymer capsules delivering doxorubicin, paclitaxel or temozolomide also improve glioma outcomes following intracranial administration[152]. Brain tumour models are the most common models for investigating intraparenchymal delivery strategies; however, liposomal nanoparticles loaded with dopamine have also been studied for the treatment of PD. Delivery into the striatum of rats with PD-like symptoms resulted in partial recovery of behavioural deficits and partial amelioration of symptoms[153], and the effects were further improved by altering the dopamine/lipid ratio[154].

Convection-enhanced delivery.—When a substance is administered directly into the parenchyma, transport away from the site of entry is thought to predominantly occur by concentration-gradient-driven diffusion[25]; in general, there is little bulk flow of fluid within the neuropil ECS compared with lower resistant areas, such as the perivascular space[22]. Diffusion can limit the therapeutic relevance of drugs, because the distances over which drugs would have to diffuse to impart a therapeutic effect can be very long. Therefore, other forms of passive delivery, such as convection-enhanced delivery, have been explored. Here, a drug or delivery vehicle solution is infused through a surgically implanted catheter by a pump to allow bulk flow into the brain ECS. Convection-enhanced delivery can increase the volume of drug and nanoparticle distribution up to 15-fold compared with nanoparticle distribution by diffusion alone[155]. For example, the distribution of polymer nanoparticles infused by convection-enhanced delivery is more heterogeneous in the presence of tumours compared with normal brain tissue, although the net volume of distribution remains larger compared with healthy brain[156].

Convection-enhanced delivery of free drugs has been shown to be safe and feasible in clinical trials[157]; however, survival has not been improved for patients with GBM. Combining convection-enhanced delivery with nanocarriers may address the limitations of short half-lives and rapid free drug metabolism after infusion is stopped. Polymer[156] and liposomal[158] nanoparticles administered by convection-enhanced delivery can provide sustained drug release on the order of days and weeks after infusion has ended. The surface properties and size of the nanoparticles influence nanoparticle volume of distribution following convection-enhanced delivery[159]; interestingly, nanotherapeutic distribution could further be increased by altering the osmolality of the infusate used to deliver the nanoparticles[160].

Convection-enhanced delivery is also often used for intracranial gene delivery to the CNS. As of 2020, more than 30 clinical trials have been conducted for intraparenchymal viral vector delivery systems for the treatment of glioblastoma and PD[161], with 90% of these studies using adeno-associated viral vectors (AAVs). For example, studies in non-human primates showed that AAV infusion into the subcortical region results in broader and more robust expression of glial-cell-derived neurotrophic factor, which restored dopaminergic function in parkinsonian monkeys[162]. AAVs have the advantage of being small (25 nm), non-replicative and non-pathogenic viruses, which makes them interesting for local delivery in the brain[161].

Intrathecal administration to the CSF

Different routes of drug administration can lead to absorptive uptake in the CNS. Biomaterials can also be administered directly to the CSF by intrathecal injection to achieve high doses with minimal off-target exposure and toxicity[163] (FIG. 5). Consequently, intrathecal administration may potentially circumvent the shortfalls of systemic delivery of drugs and non-viral gene delivery to treat CNS diseases.

Materials injected directly into the CSF circumvent BBB obstacles; however, ependymal cells of the choroid plexus also act as a barrier, limiting tissue penetrance despite widespread diffusion of biologics throughout the CSF[164]. Therefore, nanoparticles and

polymer formulations are being explored in preclinical studies to improve delivery and brain tissue penetrance[165]. Initially, polyethyleneimine–DNA complexes, cationic liposomes and silica nanoparticles were used for siRNA and non-viral gene delivery in vivo[166]. Since these initial studies, multifunctional polymer materials have been optimized to further increase cargo stability[167] and to enhance endosomal escape[168]. In addition, copolymers have been designed to mimic viruses to increase gene delivery to the brain[169]. Materials engineered to increase tissue penetrance and widespread delivery into cells have the potential to create viable non-viral gene and biologics delivery therapies for the brain. Although biologics delivery remains difficult owing to substantial biological barriers[170], these limitations may be overcome by appropriately designing the size, charge and shape of biomaterials[171]. For example, smart, stimuli-responsive biomaterials or depot delivery polymeric formulations could be used to improve uptake and pharmacokinetics of therapeutics to treat diseases of the CNS[172].

Intranasal and peripheral administration

Intranasal administration

Despite neurovascular changes and loss of BBB integrity associated with neurodegenerative disease, brain-targeted materials show restricted CNS penetrance and premature drug degradation after systemic administration or drug depot implantation[11]. Alternatively, intranasal administration can bypass the BBB and deliver therapeutic drugs into the brain[173]. Similarly, peripheral injection allows uptake and delivery to the CNS and spinal cord by motor neurons and the autonomic nervous system (ANS), as has been demonstrated with model drugs[174]. These alternative routes of administration oiler the potential to increase CNS delivery with minimal systemic drug distribution and without the need to disrupt or damage the BBB[175].

Drug delivery across the nasal epithelium provides two routes for delivery into the CNS. Lipophilic drugs and small biologics can leak through the nasal epithelium and diffuse into the brain and CSF[176], or drugs can be transported through transneuronal pathways along olfactory and trigeminal nerve axons[177]. Consequently, intranasal delivery offers ease of use, reduced systemic exposure, faster drug onset of action and greater bioavailability in a non-invasive manner compared with systemic or local delivery[178].

Despite the potential advantages and clinical efficacy of intranasal administration[179], the approach is limited by the nasal cavity surface area and properties of the nasal mucosa[180], which attenuate effective drug uptake[181]. Surfactants or encapsulation by nanoparticles are being explored to increase delivery[182,183]. For example, alginate or chitosan nanoparticles can prevent active export by BBB receptors (for example, P-glycoproteins) and protect against biological and/or chemical degradation[184]. Nanostructured lipids[185], nanoemulsions[186] and chitosan-coated niosomes[187] can be applied to alter the surface properties of nanoparticles to improve nose-to-brain delivery[188]. Similarly, degradable polymeric materials, such as poly(lactic acid), poly (glycolic acid), PLGA and poly(sebacic anhydride)[185], can encapsulate and increase drug stability for intranasal delivery[189]. Targeting the nasal epithelium for uptake and delivery can further be achieved by

functionalization with lectins, cell-penetrating peptides and proteins, for the treatment of AD and PD[190].

Retrograde delivery from the periphery

CNS delivery can also be achieved after intramuscular injection through retrograde transport along nerve axons that project from the periphery (for example, gastrocnemius) back to the spinal cord and brain[191]. Delivery of viruses and non-viral biomaterials to the CNS by intramuscular injection and retrograde transport has been demonstrated in rodents[192,193] and non-human primates[194,195].

Moreover, administration into multiple muscle groups and neuromuscular endplates was shown to improve delivery to the CNS[192,196]. Viral delivery vehicles conjugated with recombinant protein chimeras, peptide ligands from cholera and tetanus toxin[197], or wheat germ agglutinin increase neuronal uptake and delivery into the brain and spinal cord[198]. In addition, material formulations functionalized with small peptides demonstrate axonal uptake by motor neurons and delivery into the CNS[199,200]. However, access to nerve termini within injectable muscle sites remains limited and, thus, delivery strategies exploiting the ANS are being explored[201,202] as a means for enhancing CNS uptake via sympathetic and parasympathetic neurons. Thus, peptides targeting the ANS could be used in polymer and material formulations to deliver drugs at therapeutically relevant doses[174], which is crucial for treating CNS diseases[203].

Conclusions and perspective

Owing to the tightly controlled BBB, drug delivery to the CNS remains technically and clinically challenging. Neurodegenerative, psychiatric, oncologic and traumatic injuries may all benefit from controlled, responsive and tailored drug release systems. However, there is a disconnect between successes in preclinical studies and the few drug delivery systems that made it into human clinical trials (TABLE 2), owing to the considerable challenges associated with using rodent models to test engineered materials, which may not overcome biological barriers present in human disease.

Perhaps the biggest biological challenge is the complexity and diversity of human pathology. Mammalian models only partially mimic the biological barriers faced by drug delivery vehicles in humans. In vitro monocultures do not have complex multicellular networks or an ECM. By contrast, ex vivo organotypic brain slices retain regional differences, the 3D architecture of cells and the ECM; however, vascular and ventricular flow effects are absent. In vivo models provide the BBB, fluid flow and solute exchange, but it is difficult to perform mechanistic studies in vivo. In addition, no animal model adequately replicates the complexity, heterogeneity and spatial-temporal scale of any CNS disease in humans. For example, the location, severity and pathology of TBI or SCI vary greatly between patients; by contrast, injury patterns are tightly controlled in preclinical animal models. Many failed human pharmaceutical trials may not have achieved statistical significance owing to injury diversity. Additionally, the scale (for example, volume) of injuries can be very large in humans (FIG. 3), emphasizing the need for drug delivery strategies that

can achieve therapeutically relevant distributions throughout the entirety of the injured or diseased tissue.

Biomaterial formulations for CNS delivery have been effective for drug release at the site of action (for example, Gliadel wafer); however, there remains a need for materials that can mediate delivery throughout the CNS. Although materials can deliver past the BBB, the delivery efficiencies remain low. Formulations are required that show increased BBB transport and tissue penetrance at distal targets to promote cellular repair. For example, dynamic materials that transform in response to biological stimuli or environmental cues could overcome serial barriers and facilitate systemic delivery in the pathologic CNS. Furthermore, injectable materials with wide-ranging hydrodynamic modulus and biomimetic properties would improve local delivery. Materials that are biodegradable in relevant timescales are needed to improve biocompatibility and prevent additional neuroinflammation. Similarly, conductive materials could be used to further improve neuronal communication within the diseased CNS[204,205]. Finally, materials that are responsive to biological stimuli and temporal shifts could better respond to the challenges of disease pathology to account for temporal control in acute versus chronic conditions; for applications in SCI or TBI, an ideal material would be anti-inflammatory immediately after injury, but facilitate regeneration at longer time points. Chronic conditions that require sustained drug release over longer periods will also benefit from materials that mitigate immune responses.

The clinical translation of promising CNS drug delivery systems also suffers from a funding gap, given the orders of magnitude cost difference in completing a pre-clinical versus a clinical trial. New funding mechanisms are needed to bridge the gap and to increase the number of CNS drug delivery devices that reach the market and, ultimately, help patients.

Nonetheless, the rapidly growing body of tools for CNS drug delivery will certainly improve treatment options for patients with CNS disease. A detailed understanding of CNS pathophysiology is crucial for the rational design of CNS delivery approaches. Use of transferrin receptors, lipoprotein receptors and choline transporters has led to successful demonstrations of CNS drug delivery, including systemic injection for applications, such as brain cancer, in animal models. Intranasal PLGA delivery devices are promising for neurodegenerative conditions, such as AD and PD. The intrathecal route has proven viable for CNS delivery of DNA, siRNA or nanoparticle complexes. Non-invasive methods to access the brain from systemic administration, especially for biological drugs, would transform care of neurodegenerative diseases that require repeated administration and for metastatic brain cancer. Substantial advances have been made in recent years with antibody and nanoparticle engineering, as well as focused-ultrasound-mediated delivery; however, further improvements in delivery efficiency to the CNS are needed to avoid exacerbating disease pathologies.

New neurosurgical approaches allow greater access to target sites for local delivery strategies; for example, electrode implantation for PD provides access to the diseased basal ganglia; convection-enhanced delivery has been tested in humans with high-grade CNS tumours, facilitating high-volume infusate delivery; endovascular approaches for

clot retrieval after stroke give access to the local vasculature for materials implantation; decompressions after brain injury or SCI enable access to injured neurons and glia; and stereotactic devices have been developed for local implantation in human patients with amyotrophic lateral sclerosis[206]. Hydrogel drug depots that mitigate gliosis, inhibit thrombin or release neurotrophic factors have improved functional recovery in preclinical models of CNS injury. Implantable BCNU wafers have shown modest efficacy in human patients with GBM. Importantly, drug-material formulations for local delivery strategies can be combined with systemic delivery approaches to provide temporal and multifaceted control of treatment approaches for the CNS to further improve outcomes. Taken together, technical challenges in CNS delivery are gradually being overcome and the landscape for continued progress and materials development is bright.

Acknowledgements

The authors are grateful for support from NIH 2R01NS064404 (S.H.P.), U54CA199090 (S.H.P.), R01AG063845 (S.H.P. and D.L.S.), 1R21HD100639 (E.N.), 5R35GM124677 (E.N.), R21NS099654 (D.L.S.), 1R01NS118247 (D.L.S.) and DOD SC130249 (S.H.P.).

References

1. Wittchen H-U et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 655–679 (2011). [PubMed: 21896369]
2. Lindsley CW 2013 Statistics for global prescription medications: CNS therapeutics maintain a leading position among small molecule therapeutics. ACS Chem. Neurosci. 5, 250–251 (2014). [PubMed: 24735159]
3. Helmbrecht H, Joseph A, McKenna M, Zhang M Nance E Governing transport principles for nanotherapeutic application in the brain. Curr. Opin. Chem. Eng 30, 112–119 (2020) [PubMed: 33304774]
4. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18, 439–458 (2019). [PubMed: 30871944]
5. Zlokovic BV Neurovascular mechanisms of Alzheimer's neurodegeneration. Trends Neurosci 28, 202–208 (2005). [PubMed: 15808355]
6. Armulik A et al. Pericytes regulate the blood–brain barrier. Nature 468, 557–561 (2010). [PubMed: 20944627]
7. Bell RD et al. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. Neuron 68, 409–427 (2010). [PubMed: 21040844]
8. Sweeney MD, Ayyadurai S & Zlokovic BV Pericytes of the neurovascular unit: key functions and signaling pathways. Nat. Neurosci 19, 771–783 (2016). [PubMed: 27227366]
9. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR & Begley DJ Structure and function of the blood–brain barrier. Neurobiol. Dis 37, 13–25 (2010). [PubMed: 19664713]
10. Vanlandewijck M et al. A molecular atlas of cell types and zonation in the brain vasculature. Nature 554, 475–480 (2018). [PubMed: 29443965]
11. Pardridge WM Drug transport across the blood–brain barrier. J. Cereb. Blood Flow Metab 32. 1959–1972 (2012). [PubMed: 22929442]
12. Groothuis DR The blood-brain and blood-tumor barriers: a review of strategies for increasing drug delivery. Neuro-Oncology 2, 45–59 (2000). [PubMed: 11302254]
13. Oldendorf WH Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am. J. Physiol 221, 1629–1639 (1971). [PubMed: 5124307]
14. Banks WA Brain meets body: the blood-brain barrier as an endocrine interface. Endocrinology 153, 4111–4119 (2012). [PubMed: 22778219]

15. Pardridge WM CSF, blood-brain barrier, and brain drug delivery. Expert Opin. Drug Deliv 13, 963–975 (2016). [PubMed: 27020469]
16. Pardridge WM Drug transport in brain via the cerebrospinal fluid. Fluids Barriers CNS 8, 7 (2011). [PubMed: 21349155]
17. Yamada K et al. Basic fibroblast growth factor prevents thalamic degeneration after cortical infarction. J. Cereb. Blood Flow Metab 11, 472–478 (1991). [PubMed: 2016355]
18. Day-Lollini PA, Stewart GR, Taylor MJ, Johnson RM & Chellman GJ. Hyperplastic changes within the leptomeninges of the rat and monkey in response to chronic intracerebroventricular infusion of nerve growth factor. Exp. Neurol 145, 24–37 (1997). [PubMed: 9184106]
19. Cserr HF, Cooper DN, Suri PK & Patlak CS Efflux of radiolabeled polyethylene glycols and albumin from rat brain. Am. J. Physiol 240, F319–F328 (1981). [PubMed: 7223889]
20. Szentistvanyi I, Patlak CS, Ellis RA & Cserr HF Drainage of interstitial fluid from different regions of rat brain. Am. J. Physiol 246, F835–F844 (1984). [PubMed: 6742132]
21. Henrich-Noack P et al. The blood–brain barrier and beyond: Nano-based neuropharmacology and the role of extracellular matrix. Nanomedicine 17, 359–379 (2019). [PubMed: 30759369]
22. Wolak DJ & Thorne RG Diffusion of macromolecules in the brain: implications for drug delivery. Mol. Pharm 10, 1492–1504 (2013). [PubMed: 23298378]
23. Sykova E & Nicholson C Diffusion in brain extracellular space. Physiol. Rev 88, 1277–1340 (2008). [PubMed: 18923183]
24. Nance EA et al. A dense poly(ethylene glycol) coating improves penetration of large polymeric nanoparticles within brain tissue. Sci. Transl. Med 4, 149ra119 (2012).
25. Patel T, Zhou J, Piepmeier JM & Saltzman WM Polymeric nanoparticles for drug delivery to the central nervous system. Adv. Drug Deliv. Rev 64, 701–705 (2012). [PubMed: 22210134]
26. Curtis C, Toghani D, Wong B & Nance E Colloidal stability as a determinant of nanoparticle behavior in the brain. Colloids Surf. B Biointerfaces 170, 673–682 (2018). [PubMed: 29986264]
27. Morrison PF & Dedrick RL Transport of cisplatin in rat brain following microinfusion: an analysis. J. Pharm. Sci 75, 120–128 (1986). [PubMed: 3958919]
28. Wen PY & Kesari S Malignant gliomas in adults. N. Engl. J. Med 359, 492–507 (2008). [PubMed: 18669428]
29. Nduom EK, Yang C, Merrill MJ, Zhuang Z, & Lonser RR Characterization of the blood-brain barrier of metastatic and primary malignant neoplasms. J. Neurosurg 119, 427–433 (2013). [PubMed: 23621605]
30. Jain RK Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J. Clin. Oncol 31, 2205–2218 (2013). [PubMed: 23669226]
31. Wiranowska M & Rojiani MV in *Glioma – Exploring Its Biology and Practical Relevance* Ch. 12 (ed. Ghosh A) (IntechOpen, 2011).
32. Yao Q, Kou L, Tu Y & Zhu L MMP-responsive ‘smart’ drug delivery and tumor targeting. Trends Pharmacol. Sci 39, 766–781 (2018). [PubMed: 30032745]
33. National Spinal Cord Injury Statistical Center (NSCISC). Spinal Cord Injury: Facts and Figures at a Glance (University of Alabama at Birmingham, 2021).
34. Lee S et al. A novel antagonist of p75NTR reduces peripheral expansion and CNS trafficking of pro-inflammatory monocytes and spares function after traumatic brain injury. J. Neuroinflammation 13, 88 (2016). [PubMed: 27102880]
35. Centers for Disease Control and Prevention (CDC). Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation (National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention, 2015).
36. Hulsebosch CE Recent advances in pathophysiology and treatment of spinal cord injury. Adv. Physiol. Educ 26, 238–255 (2002). [PubMed: 12443996]
37. Beattie MS Inflammation and apoptosis: linked therapeutic targets in spinal cord injury. Trends Mol. Med 10, 580–583 (2004). [PubMed: 15567326]
38. Wang CX, Nuttin B, Heremans H, Dom R, & Gybels J Production of tumor necrosis factor in spinal cord following traumatic injury in rats. J. Neuroimmunol 69, 151–156 (1996). [PubMed: 8823387]

39. Ramlackhansingh AF et al. Inflammation after trauma: microglial activation and traumatic brain injury. Ann. Neurol 70, 374–383 (2011). [PubMed: 21710619]
40. Kandell RM, Waggoner LE & Kwon EJ Nanomedicine for acute brain injuries: insight from decades of cancer nanomedicine. Mol. Pharmaceutics 10.1021/acs.molpharmaceut.0c00287 (2020).
41. Kudryashev JA et al. An activity-based nanosensor for traumatic brain injury. ACS Sens 5, 686–692 (2020). [PubMed: 32100994]
42. Delbary-Gossart S et al. A novel inhibitor of p75-neurotrophin receptor improves functional outcomes in two models of traumatic brain injury. Brain 139, 1762–1782 (2016). [PubMed: 27084575]
43. Hurlbert RJ et al. Pharmacological therapy for acute spinal cord injury. Neurosurgery 72, 93–105 (2013). [PubMed: 23417182]
44. Bowers CA, Kundu B, Rosenbluth J, & Hawryluk GW Patients with spinal cord injuries favor administration of methylprednisolone. PLoS ONE 11, e0145991 (2016). [PubMed: 26789007]
45. Fehlings MG et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the use of methylprednisolone sodium succinate. Glob. Spine J 7, 203S–211S (2017).
46. Hurlbert RJ & Hamilton MG Methylprednisolone for acute spinal cord injury: 5-year practice reversal. Can. J. Neurol. Sci 35, 41–45 (2008). [PubMed: 18380276]
47. Angeli CA et al. Recovery of over-ground walking after chronic motor complete spinal cord injury. N. Engl. J. Med 379, 1244–1250 (2018). [PubMed: 30247091]
48. Gill ML et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nat. Med 24, 1677–1682 (2018). [PubMed: 30250140]
49. Profaci CP, Munji RN, Pulido RS & Daneman R The blood–brain barrier in health and disease: Important unanswered questions. J. Exp. Med 217, e20190062 (2020). [PubMed: 32211826]
50. Yang AC et al. Physiological blood–brain transport is impaired with age by a shift in transcytosis. Nature 583, 425–430 (2020). [PubMed: 32612231]
51. Montagne A et al. Blood-brain barrier breakdown in the aging human hippocampus. Neuron 85, 296–302 (2015). [PubMed: 25611508]
52. Khandaker GM et al. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2, 258–270 (2015). [PubMed: 26359903]
53. Iturria-Medina Y et al. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat. Commun 7, 11934 (2016). [PubMed: 27327500]
54. Winkler EA et al. Blood–spinal cord barrier disruption contributes to early motor-neuron degeneration in ALS-model mice. Proc. Natl Acad. Sci. USA 111, E1035–E1042 (2014). [PubMed: 24591593]
55. Yamazaki Y et al. Selective loss of cortical endothelial tight junction proteins during Alzheimer's disease progression. Brain 142, 1077–1092 (2019). [PubMed: 30770921]
56. Yamada M & Hamaguchi T The sulfation code for propagation of neurodegeneration. J. Biol. Chem 293, 10841–10842 (2018). [PubMed: 29980653]
57. Blanchard JW et al. Reconstruction of the human blood–brain barrier in vitro reveals a pathogenic mechanism of APOE4 in pericytes. Nat. Med 26, 952–963 (2020). [PubMed: 32514169]
58. Kisler K et al. Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. Nat. Neurosci 20, 406–416 (2017). [PubMed: 28135240]
59. Sweeney MD, Sagare AP & Zlokovic BV Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat. Rev. Neurol 14, 133–150 (2018). [PubMed: 29377008]
60. Zlokovic BV Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat. Rev. Neurosci 12, 723–738 (2011). [PubMed: 22048062]
61. Winkler EA, Sengillo JD, Bell RD, Wang J & Zlokovic BV Blood–spinal cord barrier pericyte reductions contribute to increased capillary permeability. J. Cereb. Blood Flow Metab 32, 1841–1852 (2012). [PubMed: 22850407]

62. Nikolakopoulou AM et al. Pericyte loss leads to circulatory failure and pleiotrophin depletion causing neuron loss. Nat. Neurosci 22, 1089–1098 (2019). [PubMed: 31235908]
63. Campbell BCV & Khatri P Stroke. Lancet 396, 129–142 (2020). [PubMed: 32653056]
64. Wardlaw JM et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet 379, 2364–2372 (2012). [PubMed: 22632907]
65. Davis SM & Donnan GA 4.5 hours: the new time window for tissue plasminogen activator in stroke. Stroke 40, 2266–2267 (2009). [PubMed: 19407232]
66. Berkhemer OA et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N. Engl. J. Med 372, 11–20 (2015). [PubMed: 25517348]
67. Campbell BC et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N. Engl. J. Med 372, 1009–1018 (2015). [PubMed: 25671797]
68. Goyal M et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N. Engl. J. Med 372, 1019–1030 (2015). [PubMed: 25671798]
69. Saver JL et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N. Engl. J. Med 372, 2285–2295 (2015). [PubMed: 25882376]
70. Bracard S et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 15, 1138–1147 (2016). [PubMed: 27567239]
71. Nogueira RG et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N. Engl. J. Med 378, 11–21 (2018). [PubMed: 29129157]
72. Hettiaratchi MH et al. Local delivery of stabilized chondroitinase ABC degrades chondroitin sulfate proteoglycans in stroke-injured rat brains. J. Control. Release 297, 14–25 (2019). [PubMed: 30690102]
73. George PM et al. Engineered stem cell mimics to enhance stroke recovery. Biomaterials 178, 63–72 (2018). [PubMed: 29909038]
74. Bolan F, Louca I, Heal C & Cunningham CJ The potential of biomaterial-based approaches as therapies for ischemic stroke: a systematic review and meta-analysis of pre-clinical studies. Front. Neurol 10, 924 (2019). [PubMed: 31507524]
75. Saraiva C et al. MicroRNA-124-loaded nanoparticles increase survival and neuronal differentiation of neural stem cells in vitro but do not contribute to stroke outcome in vivo. PLoS ONE 13, e0193609 (2018). [PubMed: 29494665]
76. Chamorro A, Dirnagl U, Urra X, & Planas AM Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol 15, 869–881 (2016). [PubMed: 27180033]
77. Pardridge WM Why is the global CNS pharmaceutical market so under-penetrated?. Drug Discov. Today 7, 5–7 (2002). [PubMed: 11790589]
78. Furtado D et al. Overcoming the blood–brain barrier: the role of nanomaterials in treating neurological diseases. Adv. Mater 30, 1801362 (2018).
79. Tang W et al. Emerging blood–brain-barrier-crossing nanotechnology for brain cancer theranostics. Chem. Soc. Rev 48, 2967–3014 (2019). [PubMed: 31089607]
80. Johnsen KB, Burkhart A, Thomsen LB, Andresen TL & Moos T Targeting the transferrin receptor for brain drug delivery. Prog. Neurobiol 181 101665 (2019). [PubMed: 31376426]
81. van Rooy I, Mastrobattista E, Storm G, Hennink WE & Schiffelers RM Comparison of five different targeting ligands to enhance accumulation of liposomes into the brain. J. Control. Release 150, 30–36 (2011). [PubMed: 21087646]
82. Israel LL et al. A combination of tri-leucine and angiopep-2 drives a polyanionic polymalic acid nanodrug platform across the blood–brain barrier. ACS Nano 13, 1253–1271 (2019). [PubMed: 30633492]
83. Yu YJ et al. Boosting brain uptake of a therapeutic antibody by reducing its affinity for a transcytosis target. Sci. Transl. Med 3, 84ra44 (2011).
84. Couch JA et al. Addressing safety liabilities of TfR bispecific antibodies that cross the blood-brain barrier. Sci. Transl. Med 5, 183ra157 (2013).

85. Bien-Ly N et al. Transferrin receptor (TfR) trafficking determines brain uptake of TfR antibody affinity variants. J. Exp. Med 211, 233–244 (2014). [PubMed: 24470444]

86. Lesley J, Schulte R & Woods J Modulation of transferrin receptor expression and function by anti-transferrin receptor antibodies and antibody fragments. Exp. Cell Res 182, 215–233 (1989). [PubMed: 2653853]

87. Wiley DT, Webster P, Gale A & Davis ME Transcytosis and brain uptake of transferrin-containing nanoparticles by tuning avidity to transferrin receptor. Proc. Natl Acad. Sci. USA 110, 8662–8667 (2013). [PubMed: 23650374]

88. Johnsen KB et al. Antibody affinity and valency impact brain uptake of transferrin receptor-targeted gold nanoparticles. Theranostics 8, 3416–3436 (2018). [PubMed: 29930740]

89. Clark AJ & Davis ME Increased brain uptake of targeted nanoparticles by adding an acid-cleavable linkage between transferrin and the nanoparticle core. Proc. Natl Acad. Sci. USA 112, 12486–12491 (2015). [PubMed: 26392563]

90. Wyatt EA & Davis ME Method of establishing breast cancer brain metastases affects brain uptake and efficacy of targeted, therapeutic nanoparticles. Bioeng. Transl. Med 4, 30–37 (2019). [PubMed: 30680316]

91. Cai L et al. Endo/lysosome-escapable delivery depot for improving BBB transcytosis and neuron targeted therapy of Alzheimer's disease. Adv. Fund. Mater 30, 1909999 (2020).

92. Li S-D & Huang L Pharmacokinetics and biodistribution of nanoparticles. Mol. Pharm 5, 496–504 (2008). [PubMed: 18611037]

93. Betzer O et al. The effect of nanoparticle size on the ability to cross the blood–brain barrier: an in vivo study. Nanomedicine 12, 1533–1546 (2017). [PubMed: 28621578]

94. Nowak M, Brown TD, Graham A, Helgeson ME & Mitragotri S Size, shape, and flexibility influence nanoparticle transport across brain endothelium under flow. Bioeng. Transl. Med 5, e10153 (2020). [PubMed: 32440560]

95. Moos T & Morgan EH Restricted transport of anti-transferrin receptor antibody (OX26) through the blood–brain barrier in the rat. J. Neurochem 79, 119–129 (2001). [PubMed: 11595764]

96. Johnsen KB et al. Targeting transferrin receptors at the blood-brain barrier improves the uptake of immunoliposomes and subsequent cargo transport into the brain parenchyma. Sci. Rep 7, 10396 (2017). [PubMed: 28871203]

97. Marcos-Contreras OA et al. Selective targeting of nanomedicine to inflamed cerebral vasculature to enhance the blood–brain barrier. Proc. Natl Acad. Sci. USA 117, 3405–3414 (2020). [PubMed: 32005712]

98. Marcos-Contreras OA et al. Combining vascular targeting and the local first pass provides 100-fold higher uptake of ICAM-1-targeted vs untargeted nanocarriers in the inflamed brain. J. Control. Release 301, 54–61 (2019). [PubMed: 30871995]

99. Gonzalez-Carter D et al. Targeting nanoparticles to the brain by exploiting the blood–brain barrier impermeability to selectively label the brain endothelium. Proc. Natl Acad. Sci. USA 117, 19141–19150 (2020). [PubMed: 32703811]

100. Stein SC et al. Erythrocyte-bound tissue plasminogen activator is neuroprotective in experimental traumatic brain injury. J. Neurotrauma 26, 1585–1592 (2009). [PubMed: 19331516]

101. Brenner JS et al. Red blood cell-hitchhiking boosts delivery of nanocarriers to chosen organs by orders of magnitude. Nat. Commun 9, 2684 (2018). [PubMed: 29992966]

102. Klyachko NL et al. Macrophages with cellular backpacks for targeted drug delivery to the brain. Biomaterials 140, 79–87 (2017). [PubMed: 28633046]

103. Hou J et al. Accessing neuroinflammation sites: Monocyte/neutrophil-mediated drug delivery for cerebral ischemia. Sci. Adv 5, eaau8301 (2019). [PubMed: 31531392]

104. Zheng M, Huang M, Ma X, Chen H & Gao X Harnessing exosomes for the development of brain drug delivery systems. Bioconjug. Chem 30, 994–1005 (2019). [PubMed: 30855944]

105. Yuan D et al. Macrophage exosomes as natural nanocarriers for protein delivery to inflamed brain. Biomaterials 142, 1–12 (2017). [PubMed: 28715655]

106. Alvarez-Erviti L et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat. Biotechnol 29, 341–345 (2011). [PubMed: 21423189]

107. Tian T et al. Surface functionalized exosomes as targeted drug delivery vehicles for cerebral ischemia therapy. Biomaterials 150, 137–149 (2018). [PubMed: 29040874]
108. Haney MJ et al. TPP1 delivery to lysosomes with extracellular vesicles and their enhanced brain distribution in the animal model of batten disease. Adv. Healthc. Mater 8, 1801271 (2019).
109. Rapoport SI, Hori M & Klatzo I Testing of a hypothesis for osmotic opening of the blood-brain barrier. Am. J. Physiol 223, 323–331 (1972). [PubMed: 5046750]
110. Chian RJ et al. IGF-1:tetanus toxin fragment C fusion protein improves delivery of IGF-1 to spinal cord but fails to prolong survival of ALS mice. Brain Res 1287, 1–19 (2009). [PubMed: 19563785]
111. Chu C et al. Optimization of osmotic blood-brain barrier opening to enable intravital microscopy studies on drug delivery in mouse cortex. J. Control. Release 317, 312–321 (2020). [PubMed: 31751635]
112. Karakatsani ME et al. Amelioration of the nigrostriatal pathway facilitated by ultrasound-mediated neurotrophic delivery in early Parkinson's disease. J. Control. Release 303, 289–301 (2019). [PubMed: 30953664]
113. Rich MC et al. Focused ultrasound blood brain barrier opening mediated delivery of MRI-visible albumin nanoclusters to the rat brain for localized drug delivery with temporal control. J. Control. Release 324, 172–180 (2020). [PubMed: 32376461]
114. Thévenot E et al. Targeted delivery of self-complementary adeno-associated virus serotype 9 to the brain, using magnetic resonance imaging-guided focused ultrasound. Hum. Gene Ther 23, 1144–1155 (2012). [PubMed: 22838844]
115. Zhou Y, Yang K, Cui J, Ye J & Deng C Controlled permeation of cell membrane by single bubble acoustic cavitation. J. Control. Release 157, 103–111 (2012). [PubMed: 21945682]
116. Lipsman N et al. Blood–brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nat. Commun 9, 2336 (2018). [PubMed: 30046032]
117. Carpentier A et al. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. Sci. Transl. Med 8, 343re2 (2016).
118. Langer R & Folkman J Polymers for the sustained release of proteins and other macromolecules. Nature 263, 797–800 (1976). [PubMed: 995197]
119. Wang PP, Frazier J & Brem H Local drug delivery to the brain. Adv. Drug Deliv. Rev 54, 987–1013 (2002). [PubMed: 12384318]
120. Walter KA et al. Interstitial taxol delivered from a biodegradable polymer implant against experimental malignant glioma. Cancer Res 54, 2207–2212 (1994). [PubMed: 7909720]
121. Sampath P et al. Camptothecin analogs in malignant gliomas: comparative analysis and characterization. J. Neurosurg 98, 570–577 (2003). [PubMed: 12650430]
122. Brem S et al. Local delivery of temozolomide by biodegradable polymers is superior to oral administration in a rodent glioma model. Cancer Chemother. Pharmacol 60, 643–650 (2007). [PubMed: 17256133]
123. Grossman SA et al. The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers. J. Neurosurg 76, 640–647 (1992). [PubMed: 1545259]
124. Perry J, Chambers A, Spithoff K, & Laperriere N Gliadel wafers in the treatment of malignant glioma: a systematic review. Curr. Oncol 14, 189–194 (2007). [PubMed: 17938702]
125. Fung LK, Shin M, Tyler B, Brem H, & Saltzman WM Chemotherapeutic drugs released from polymers: distribution of 1,3-bis(2-chloroethyl)-l-nitrosourea in the rat brain. Pharm. Res 13, 671–682 (1996). [PubMed: 8860421]
126. Wait SD, Prabhu RS, Burri SH, Atkins TG, & Asher AL Polymeric drug delivery for the treatment of glioblastoma. Neuro-Oncology 17, ii9–ii23 (2015). [PubMed: 25746091]
127. Ramachandran R, et al. Theranostic 3-dimensional nano brain-implant for prolonged and localized treatment of recurrent glioma. Sci. Rep 7, 43271 (2017). [PubMed: 28262735]
128. Lee JH, et al. Collagen gel three-dimensional matrices combined with adhesive proteins stimulate neuronal differentiation of mesenchymal stem cells. J. R. Soc. Interface 8, 998–1010 (2011). [PubMed: 21247946]

129. Jeong DU, et al. Hydrogel-mediated local delivery of dexamethasone reduces neuroinflammation after traumatic brain injury. Biomed. Mater 16, 035002 (2021).
130. Tsintou M, et al. The use of hydrogel-delivered extracellular vesicles in recovery of motor function in stroke: a testable experimental hypothesis for clinical translation including behavioral and neuroimaging assessment approaches. Neural Regen. Res 16, 605–613 (2021). [PubMed: 33063708]
131. Alvarado-Velez M, et al. Immuno-suppressive hydrogels enhance allogeneic MSC survival after transplantation in the injured brain. Biomaterials 266, 120419 (2021). [PubMed: 33038594]
132. Piantino J, Burdick JA, Goldberg D, Langer R, & Benowitz LI An injectable, biodegradable hydrogel for trophic factor delivery enhances axonal rewiring and improves performance after spinal cord injury. Exp. Neurol 201, 359–367 (2006). [PubMed: 16764857]
133. Sellers DL, Kim TH, Mount CW, Pun SH, & Horner PJ Poly(lactic-co-glycolic) acid microspheres encapsulated in Pluronic F-127 prolong hirudin delivery and improve functional recovery from a demyelination lesion. Biomaterials 35, 8895–8902 (2014). [PubMed: 25064804]
134. Chu DS, et al. MMP9-sensitive polymers mediate environmentally-responsive bivalirudin release and thrombin inhibition. Biomater. Sci 3, 41–45 (2015). [PubMed: 25589953]
135. He W, Reaume M, Hennenfent M, Lee BP, & Rajachar R Biomimetic hydrogels with spatial- and temporal-controlled chemical cues for tissue engineering. Biomater. Sci 8, 3248–3269 (2020). [PubMed: 32490441]
136. Taylor SJ, McDonald JW III, & Sakiyama-Elbert SE Controlled release of neurotrophin-3 from fibrin gels for spinal cord injury. J. Control. Release 98, 281–294 (2004). [PubMed: 15262419]
137. Nguyen LH, et al. Three-dimensional aligned nanofibers-hydrogel scaffold for controlled non-viral drug/gene delivery to direct axon regeneration in spinal cord injury treatment. Sci. Rep 7, 42212 (2017). [PubMed: 28169354]
138. George PM, et al. Electrical preconditioning of stem cells with a conductive polymer scaffold enhances stroke recovery. Biomaterials 142, 31–40 (2017). [PubMed: 28719819]
139. Leprince L, Dogimont A, Magnin D, & Demoustier-Champagne S Dexamethasone electrically controlled release from polypyrrole-coated nanostructured electrodes. J. Mater. Sci. Mater. Med 21, 925–930 (2010). [PubMed: 20143134]
140. Gao W, & Borgens RB Remote-controlled eradication of astrogliosis in spinal cord injury via electromagnetically-induced dexamethasone release from “smart” nanowires. J. Control. Release 211, 22–27 (2015). [PubMed: 25979326]
141. Du ZJ, Bi G-Q, & Cui XT Electrically controlled neurochemical release from dual-layer conducting polymer films for precise modulation of neural network activity in rat barrel cortex. Adv. Funct. Mater 28, 1703988 (2018). [PubMed: 30467460]
142. Koch B, Rubino I, Quan FS, Yoo B, & Choi HJ Microfabrication for drug delivery. Materials 9, 646 (2016). [PubMed: 28773770]
143. Tian X, et al. Injectable PLGA-coated ropivacaine produces a long-lasting analgesic effect on incisional pain and neuropathic pain. J. Pain 22, 180–195 (2021). [PubMed: 32739615]
144. Menei P, Montero-Menei C, Venier MC, & Benoit JP Drug delivery into the brain using poly(lactide-co-glycolide) microspheres. Expert Opin. Drug Deliv 2, 363–376 (2005). [PubMed: 16296760]
145. Menei P, et al. Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of malignant glioma: a randomized phase II trial. Neurosurgery 56, 242–248 (2005). discussion 242–248. [PubMed: 15670372]
146. Bege N, et al. In situ forming nimodipine depot system based on microparticles for the treatment of posthemorrhagic cerebral vasospasm. Eur. J. Pharm. Biopharm 84, 99–105 (2013). [PubMed: 23298622]
147. Hanggi D, et al. Dose-related efficacy of a continuous intracisternal nimodipine treatment on cerebral vasospasm in the rat double subarachnoid hemorrhage model. Neurosurgery 64, 1155–1159 (2009). discussion 1159–1161. [PubMed: 19487896]
148. Hanggi D, et al. Local delivery of nimodipine by prolonged-release microparticles — feasibility, effectiveness and dose-finding in experimental subarachnoid hemorrhage. PLoS ONE 7, e42597 (2012). [PubMed: 23049732]

149. Nance E Brain-penetrating nanoparticles for analysis of the brain microenvironment. Methods Mol. Biol 1570, 91–104 (2017). [PubMed: 28238131]

150. Nance E, et al. Brain-penetrating nanoparticles improve paclitaxel efficacy in malignant glioma following local administration. ACS Nano 8, 10655–10664 (2014). [PubMed: 25259648]

151. Ranganath SH, et al. The use of submicron/nanoscale PLGA implants to deliver paclitaxel with enhanced pharmacokinetics and therapeutic efficacy in intracranial glioblastoma in mice. Biomaterials 31 , 5199–5207 (2010). [PubMed: 20350766]

152. El Demerdash N, Kedda J, Ram N, Brem H, & Tyler B Novel therapeutics for brain tumors: current practice and future prospects. Expert Opin. Drug Deliv 17, 9–21 (2020). [PubMed: 31971041]

153. During MJ, et al. Biochemical and behavioral recovery in a rodent model of Parkinson's disease following stereotactic implantation of dopamine-containing liposomes. Exp. Neurol 115, 193–199 (1992). [PubMed: 1735466]

154. Zhigaltsev IV, et al. Liposomes containing dopamine entrapped in response to transmembrane ammonium sulfate gradient as carrier system for dopamine delivery into the brain of parkinsonian mice. J. Liposome Res 11, 55–71 (2001). [PubMed: 19530919]

155. Zhang C, et al. Convection enhanced delivery of cisplatin-loaded brain penetrating nanoparticles cures malignant glioma in rats. J. Control. Release 263, 112–119 (2017). [PubMed: 28279797]

156. Saucier-Sawyer JK, et al. Distribution of polymer nanoparticles by convection-enhanced delivery to brain tumors. J. Control. Release 232, 103–112 (2016). [PubMed: 27063424]

157. Kunwar S, et al. Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. Neuro-Oncology 12, 871–881 (2010). [PubMed: 20511192]

158. Allard E, Passirani C, & Benoit JP Convection-enhanced delivery of nanocarriers for the treatment of brain tumors. Biomaterials 30, 2302–2318 (2009). [PubMed: 19168213]

159. Chen MY, et al. Surface properties, more than size, limiting convective distribution of virus-sized particles and viruses in the central nervous system. J. Neurosurg 103, 311–319 (2005). [PubMed: 16175862]

160. Zhang C, et al. Strategies to enhance the distribution of nanotherapeutics in the brain. J. Control. Release 267, 232–239 (2017). [PubMed: 28739449]

161. Lonser RR, Akhter AS, Zabek M, Elder JB, & Bankiewicz KS Direct convective delivery of adeno-associated virus gene therapy for treatment of neurological disorders. J. Neurosurg 134, 1751–1763 (2020). [PubMed: 32915526]

162. Johnston LC, et al. Clinically relevant effects of convection-enhanced delivery of AAV2-GDNF on the dopaminergic nigrostriatal pathway in aged rhesus monkeys. Hum. Gene Ther 20, 497–510 (2009). [PubMed: 19203243]

163. Papisov MI, Belov VV, & Gannon KS Physiology of the intrathecal bolus: the leptomeningeal route for macromolecule and particle delivery to CNS. Mol. Pharm 10, 1522–1532 (2013). [PubMed: 23316936]

164. Iliff JJ, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci. Transl. Med 4, 147ra111 (2012).

165. Fowler MJ, et al. Intrathecal drug delivery in the era of nanomedicine. Adv. Drug Deliv. Rev 165, 77–95 (2020). [PubMed: 32142739]

166. Tan JY, Sellers DL, Pham B, Pun SH, & Horner PJ Non-viral nucleic acid delivery strategies to the central nervous system. Front. Mol. Neurosci 9, 108 (2016). [PubMed: 27847462]

167. Wei H, et al. Dual responsive, stabilized nanoparticles for efficient in vivo plasmid delivery. Angew. Chem. Int. Ed. Engl 52, 5377–5381 (2013). [PubMed: 23592572]

168. Schellinger JG, et al. Melittin-grafted HPMA-oligolysine based copolymers for gene delivery. Biomaterials 34, 2318–2326 (2013). [PubMed: 23261217]

169. Cheng Y, Yumul RC, & Pun SH Virus-inspired polymer for efficient in vitro and in vivo gene delivery. Angew. Chem. Int. Ed. Engl 55, 12013–12017 (2016). [PubMed: 27538359]

170. Varkouhi AK, Scholte M, Storm G, & Haisma HJ Endosomal escape pathways for delivery of biologicals. J. Control. Release 151, 220–228 (2011). [PubMed: 21078351]

171. Householder KT, Dharmaraj S, Sandberg DI, Wechsler-Reya RJ, & Sirianni RW Fate of nanoparticles in the central nervous system after intrathecal injection in healthy mice. Sci. Rep 9, 12587 (2019). [PubMed: 31467368]

172. Calias P, Banks WA, Begley D, Scarpa M, & Dickson P Intrathecal delivery of protein therapeutics to the brain: A critical reassessment. Pharmacol. Ther 144, 114–122 (2014). [PubMed: 24854599]

173. Khan AR, Liu M, Khan MW, & Zhai G Progress in brain targeting drug delivery system by nasal route. J. Control. Release 268, 364–389 (2017). [PubMed: 28887135]

174. Sellers DL, et al. Targeting ligands deliver model drug cargo into the central nervous system along autonomic neurons. ACS Nano 13, 10961–10971 (2019). [PubMed: 31589023]

175. Poovaiah N, et al. Treatment of neurodegenerative disorders through the blood–brain barrier using nanocarriers. Nanoscale 10, 16962–16983 (2018). [PubMed: 30182106]

176. Yamamoto A, et al. Absorption of water-soluble compounds with different molecular weights and [$Asu^{1,7}$]-eel calcitonin from various mucosal administration sites. J. Control. Release 76, 363–374 (2001). [PubMed: 11578749]

177. Thorne RG, Pronk GJ, Padmanabhan V, & Frey WH Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience 127, 481–496 (2004). [PubMed: 15262337]

178. Miyake MM, & Bleier BS The blood-brain barrier and nasal drug delivery to the central nervous system. Am. J. Rhinol. Allergy 29, 124–127 (2015). [PubMed: 25785753]

179. Shrewsbury SB, et al. The SNAP 101 double-blind, placebo/active-controlled, safety, pharmacokinetic, and pharmacodynamic study of INP105 (nasal olanzapine) in healthy adults. J. Clin. Psychiatry 81, 19m13086 (2020).

180. Van de Bittner GC, et al. Positron emission tomography assessment of the intranasal delivery route for orexin A. ACS Chem. Neurosci 9, 358–368 (2018). [PubMed: 29035509]

181. Lochhead JJ, & Thorne RG Intranasal delivery of biologics to the central nervous system. Adv. Drug Deliv. Rev 64, 614–628 (2012). [PubMed: 22119441]

182. Song Q, et al. Biomimetic ApoE-reconstituted high density lipoprotein nanocarrier for blood–brain barrier penetration and amyloid beta-targeting drug delivery. Mol. Pharm 13, 3976–3987 (2016). [PubMed: 27700119]

183. Bourganis V, Kammona O, Alexopoulos A, & Kiparissides C Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics. Eur. J. Pharm. Biopharm 128, 337–362 (2018). [PubMed: 29733950]

184. Haque S, Md S, Sahni JK, Ali J, & Baboota S Development and evaluation of brain targeted intranasal alginate nanoparticles for treatment of depression. J. Psychiatr. Res 48, 1–12 (2014). [PubMed: 24231512]

185. Zada MH, Kubek M, Khan W, Kumar A, & Domb A Dispersible hydrolytically sensitive nanoparticles for nasal delivery of thyrotropin releasing hormone (TRH). J. Control. Release 295, 278–289 (2019). [PubMed: 30610951]

186. Ahmad E, et al. Evidence of nose-to-brain delivery of nanoemulsions: cargoes but not vehicles. Nanoscale 9, 1174–1183 (2017). [PubMed: 28009915]

187. Rinaldi F, et al. in Pentasomes: An innovative nose-to-brain pentamidine delivery blunts MPTP parkinsonism in mice. J. Control. Release 294, 17–26 (2019). [PubMed: 30529726]

188. Mistry A, Stolnik S, & Illum L Nose-to-brain delivery: investigation of the transport of nanoparticles with different surface characteristics and sizes in excised porcine olfactory epithelium. Mol. Pharm 12, 2755–2766 (2015). [PubMed: 25997083]

189. Sonvico F, et al. Surface-modified nanocarriers for nose-to-brain delivery: from bioadhesion to targeting. Pharmaceutics 10, 34 (2018). [PubMed: 29543755]

190. Kamei N, et al. Effective nose-to-brain delivery of exendin-4 via coadministration with cell-penetrating peptides for improving progressive cognitive dysfunction. Sci. Rep 8, 17641 (2018). [PubMed: 30518944]

191. Tosolini AP, & Sleigh JN Intramuscular delivery of gene therapy for targeting the nervous system. Front. Mol. Neurosci 13, 1047–1016 (2020).

192. Chen Z, Fan G, Li A, Yuan J, & Xu T rAAV2-retro enables extensive and high-efficient transduction of lower motor neurons following intramuscular injection. Mol. Ther. Methods Clin. Dev 17, 21–33 (2020). [PubMed: 31890738]

193. Xu X, et al. Viral vectors for neural circuit mapping and recent advances in trans-synaptic anterograde tracers. Neuron 107, 1029–1047 (2020). [PubMed: 32755550]

194. Towne C, Schneider BL, Kieran D, Redmond DE Jr., & Aebischer P Efficient transduction of non-human primate motor neurons after intramuscular delivery of recombinant AAV serotype 6. Gene Ther 17, 141–146 (2010). [PubMed: 19727139]

195. Davidson BL, & Breakefield XO Viral vectors for gene delivery to the nervous system. Nat. Rev. Neurosci 4, 353–364 (2003). [PubMed: 12728263]

196. Tosolini AP, & Morris R Targeting motor end plates for delivery of adenoviruses: an approach to maximize uptake and transduction of spinal cord motor neurons. Sci. Rep 6, 33058 (2016). [PubMed: 27619631]

197. Francis JW, et al. Tetanus toxin fragment C as a vector to enhance delivery of proteins to the CNS. Brain Res 1011, 7–13 (2004). [PubMed: 15140640]

198. Stoeckel K, Schwab M, & Thoenen H Role of gangliosides in the uptake and retrograde axonal transport of cholera and tetanus toxin as compared to nerve growth factor and wheat germ agglutinin. Brain Res 132, 273–285 (1977). [PubMed: 70259]

199. Li J, et al. Identification of peptide sequences that target to the brain using in vivo phage display. Amino Acids 42, 2373–2381 (2011). [PubMed: 21792566]

200. Sellers DL, et al. Targeted axonal import (TAxI) peptide delivers functional proteins into spinal cord motor neurons after peripheral administration. Proc. Natl Acad. Sci. USA 113, 2514–2519 (2016). [PubMed: 26888285]

201. Kerman IA, Enquist LW, Watson SJ, & Yates BJ,. Brainstem substrates of sympatho-motor circuitry identified using trans-synaptic tracing with pseudorabies virus recombinants. J. Neurosci 23, 4657–4666 (2003). [PubMed: 12805305]

202. Card JP, et al. Neurotropic properties of pseudorabies virus: uptake and transneuronal passage in the rat central nervous system. J. Neurosci 10, 1974–1994 (1990). [PubMed: 2162388]

203. Thorne RG, & Frey WH II Delivery of neurotrophic factors to the central nervous system: pharmacokinetic considerations. Clin. Pharmacokinet 40, 907–946 (2001). [PubMed: 11735609]

204. Lee DC, Sellers DL, Liu F, Boydston AJ, & Pun SH Synthesis and characterization of anionic poly(cyclopentadienylene vinylene) and its use in conductive hydrogels. Angew. Chem. Int. Ed 59, 13430–13436 (2020).

205. Guo B, & Ma PX Conducting polymers for tissue engineering. Biomacromolecules 19, 1764–1782 (2018). [PubMed: 29684268]

206. Mazzini L, et al. Results from phase I clinical trial with intraspinal injection of neural stem cells in amyotrophic lateral sclerosis: a long-term outcome. Stem Cells Transl. Med 8, 887–897 (2019). [PubMed: 31104357]

207. Zhao Y, et al. Dual targeted nanocarrier for brain ischemic stroke treatment. J. Control. Release 233, 64–71 (2016). [PubMed: 27142584]

208. Xia H, Anderson B, Mao Q, & Davidson BL Recombinant human adenovirus: targeting to the human transferrin receptor improves gene transfer to brain microcapillary endothelium. J. Virol 74, 11359–11366 (2000). [PubMed: 11070036]

209. Maier KE, et al. A new transferrin receptor aptamer inhibits new world hemorrhagic fever mammarenavirus entry. Mol. Ther. Nucleic Acids 5, e321 (2016). [PubMed: 27219515]

210. Wu X, et al. Elucidation and structural modeling of CD71 as a molecular target for cell-specific aptamer binding. J. Am. Chem. Soc 141, 10760–10769 (2019). [PubMed: 31185171]

211. Fan K, et al. Ferritin nanocarrier traverses the blood brain barrier and kills glioma. ACS Nano 12, 4105–4115 (2018). [PubMed: 29608290]

212. Kariolis MS, et al. Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys. Sci. Transl. Med 12, eaay1359 (2020). [PubMed: 32461332]

213. Li X, et al. Enhanced in vivo blood–brain barrier penetration by circular Tau–transferrin receptor bifunctional aptamer for tauopathy therapy. J. Am. Chem. Soc 142, 3862–3872 (2020). [PubMed: 31991082]

214. Demeule M, et al. Identification and design of peptides as a new drug delivery system for the brain. J. Pharmacol. Exp. Ther 324, 1064–1072 (2008). [PubMed: 18156463]

215. Dal Magro R, et al. ApoE-modified solid lipid nanoparticles: A feasible strategy to cross the blood-brain barrier. J. Control. Release 249, 103–110 (2017). [PubMed: 28153761]

216. He C, et al. Two-step targeted hybrid nanoconstructs increase brain penetration and efficacy of the therapeutic antibody trastuzumab against brain metastasis of HER2-positive breast cancer.Adv. Funct. Mater 28, 1705668 (2018).

217. Li J, et al. A multifunctional polymeric nanotheranostic system delivers doxorubicin and imaging agents across the blood–brain barrier targeting brain metastases of breast cancer. ACS Nano 8, 9925–9940 (2014). [PubMed: 25307677]

218. Jiang Y, Yang W, Zhang J, Meng F, & Zhong Z Protein toxin chaperoned by LRP-1-targeted virus-mimicking vesicles induces high-efficiency glioblastoma therapy in vivo. Adv. Mater 30, 1800316 (2018).

219. Shi X-X, et al. Angiopep-2 conjugated nanoparticles loaded with doxorubicin for the treatment of primary central nervous system lymphoma. Biomater. Sci 8, 1290–1297 (2020). [PubMed: 31899467]

220. Tao J, et al. Angiopep-2-conjugated “core–shell” hybrid nanovehicles for targeted and pH-triggered delivery of arsenic trioxide into glioma. Mol. Pharm 16, 786–797 (2019). [PubMed: 30620881]

221. Han L, et al. Systemic delivery of monoclonal antibodies to the central nervous system for brain tumor therapy. Adv. Mater 31, e1805697 (2019). [PubMed: 30773720]

222. Meng X, et al. Dual functionalized brain-targeting nanoinhibitors restrain temozolomide-resistant glioma via attenuating EGFR and MET signaling pathways. Nat. Commun 11, 594 (2020). [PubMed: 32001707]

223. Wen J, et al. Sustained delivery and molecular targeting of a therapeutic monoclonal antibody to metastases in the central nervous system of mice. Nat. Biomed. Eng 3, 706–716 (2019). [PubMed: 31384008]

224. Xie J, et al. Dual-sensitive nanomicelles enhancing systemic delivery of therapeutically active antibodies specifically into the brain. ACS Nano 14, 6729–6742 (2020). [PubMed: 32431145]

225. You L, et al. Targeted brain delivery of rabies virus glycoprotein 29-modified deferoxamine-loaded nanoparticles reverses functional deficits in parkinsonian mice. ACS Nano 12, 4123–4139 (2018). [PubMed: 29617109]

226. Guo Q, et al. A dual-ligand fusion peptide improves the brain-neuron targeting of nanocarriers in Alzheimer’s disease mice. J. Control. Release 320, 347–362 (2020). [PubMed: 31978446]

227. Wang P, et al. Systemic delivery of BACE1 siRNA through neuron-targeted nanocomplexes for treatment of Alzheimer’s disease. J. Control. Release 279, 220–233 (2018). [PubMed: 29679667]

228. Burtea C, et al. Magnetic resonance molecular imaging of vascular cell adhesion molecule-1 expression in inflammatory lesions using a peptide-vectorized paramagnetic imaging probe. J. Med. Chem 52, 4725–4742 (2009). [PubMed: 19580288]

229. Lutton EM, et al. Acute administration of catalase targeted to ICAM-1 attenuates neuropathology in experimental traumatic brain injury. Sci. Rep 7, 3846 (2017). [PubMed: 28630485]

230. Fehlings MG, et al. Rho inhibitor VX-210 in acute traumatic subaxial cervical spinal cord injury: design of the SPinal Cord Injury Rho INhibition InvestiGation (SPRING) Clinical Trial. J. Neurotrauma 35, 1049–1056 (2018). [PubMed: 29316845]

231. Dautry-Varsat A, Ciechanover A, & Lodish HF pH and the recycling of transferrin during receptor-mediated endocytosis. Proc. Natl Acad. Sci. USA 80, 2258–2262 (1983). [PubMed: 6300903]

232. Young SP, Bomford A, & Williams R The effect of the iron saturation of transferrin on its binding and uptake by rabbit reticulocytes. Biochem. J 219, 505–510 (1984). [PubMed: 6743230]

Box 1 |

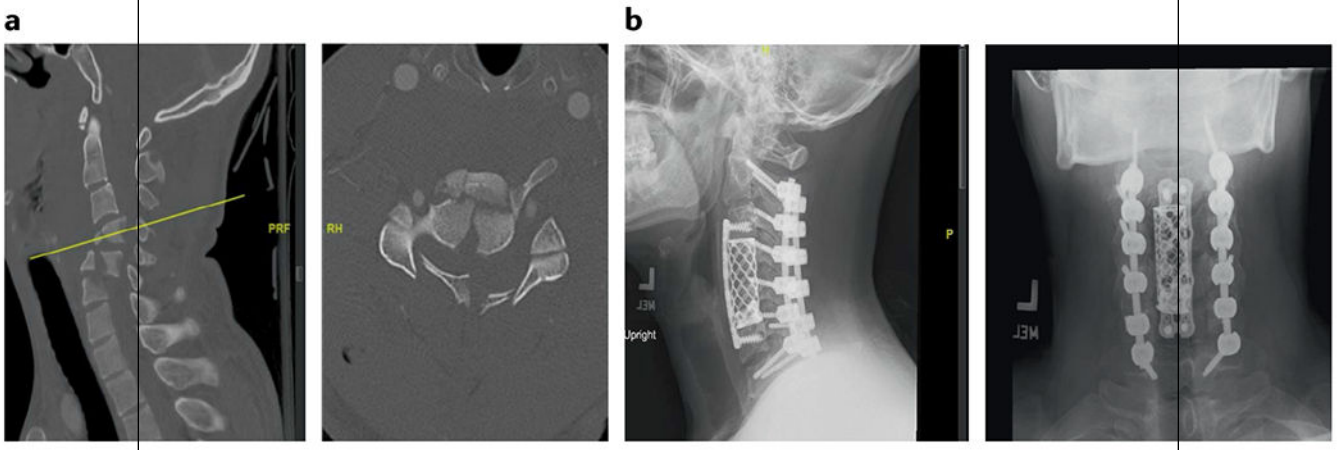
Clinical vignette

A 20-year-old male fell in a mountaineering accident. After the fall, he was able to move his biceps but had no movement in other muscles of the extremities. He had sensation above the clavicles but none below. A computed tomography scan of the cervical spine revealed C4–C5 burst fractures, with bone fragments in the spinal canal (see the figure, panel **a**). He was intravenously (iv) treated with methylprednisolone and emergency surgical decompression and stabilization.

According to the National Acute Spinal Cord injury Study (NASCIS) protocol, patients with spinal cord injury treated with iv methylprednisolone are given a 30 mg kg^{-1} iv loading bolus over 15 min, followed by a 5.4 mg kg^{-1} h^{-1} iv drip over the next 23 h. For an 80-kg patient, this translates to a total dose of 12,300 mg. This high systemic dose may lead to adverse side effects, such as pneumonia, sepsis, gastrointestinal bleeding, myopathy and hyperglycaemia. Thus, administration of iv methylprednisolone is controversial.

This patient underwent a two-stage spine surgery; first, a C4–C5 corpectomy with reconstruction of the vertebral bodies using a titanium cage and, second, C2–C7 posterior spinal fusion with C3–C6 laminectomies (see the figure, panel **b**). In spite of the technically successful spine surgery and early administration of iv steroids, he did not regain any movement or sensation at long-term follow-up.

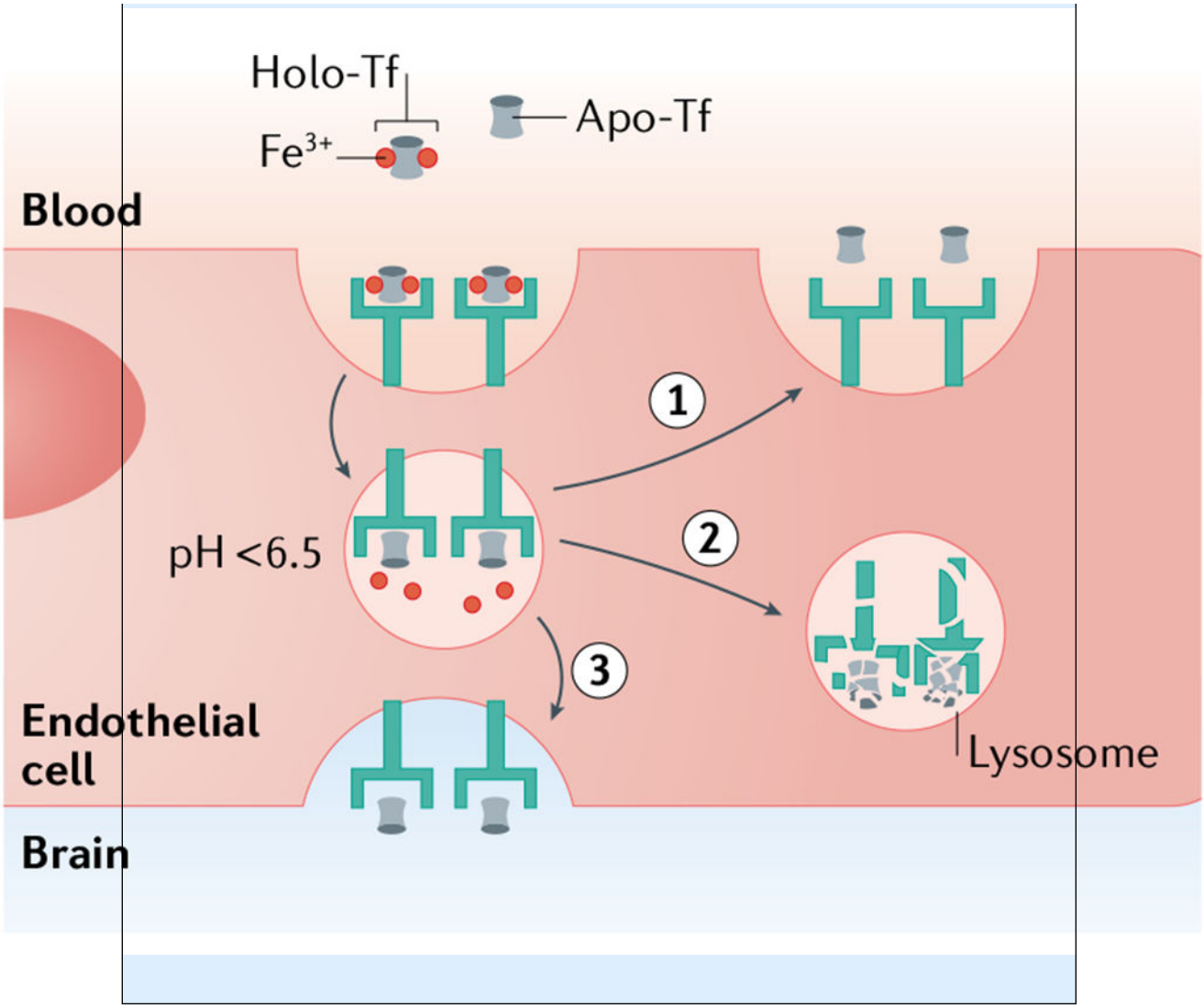
The case would have benefited from a controlled release system for the spinal cord. Multiple preclinical studies have shown promising results with local delivery of anti-inflammatory or pro-regenerative molecules. A human clinical trial was completed for an epidural implantation of a Rho inhibitor encapsulated in a fibrin sealant[230]. Although the trial did not demonstrate functional benefit, it demonstrated a new strategy for controlled release to the spinal cord.



Box 2 |

TfR1-targeted delivery

Transferrin receptor 1 (TfR1) is a transmembrane glycoprotein with two identical subunits, each binding to one transferrin. Holo-transferrin (Holo-Tf), bound to two Fe, binds TfR1 with high affinity (~10 nM) at pH 7.4 (24 times higher affinity than the apo-transferrin (Apo-Tf) form)[231,232]. TfR1 expressed on brain endothelial cells preferentially binds Holo-Tf in blood and is subsequently internalized through clathrin-mediated endocytosis into acidifying endosomes (pH ~6.0). In the endosomes, the affinity between Fe and transferrin is reduced, and Fe is released. However, Apo-Tf binds to TfR1 with higher affinity in acidic environments and can, therefore, remain associated with the receptor during intracellular trafficking[231]. From there, TfR1 can be recycled back to the apical surface by recycling endosomes (1), degraded in lysosomal compartments (2) or transcytosed to the basolateral side for potential cargo delivery to the brain (3). Targeting ligands that preferentially undergo transcytosis in brain endothelial cells are desirable for transvascular brain delivery formulations.



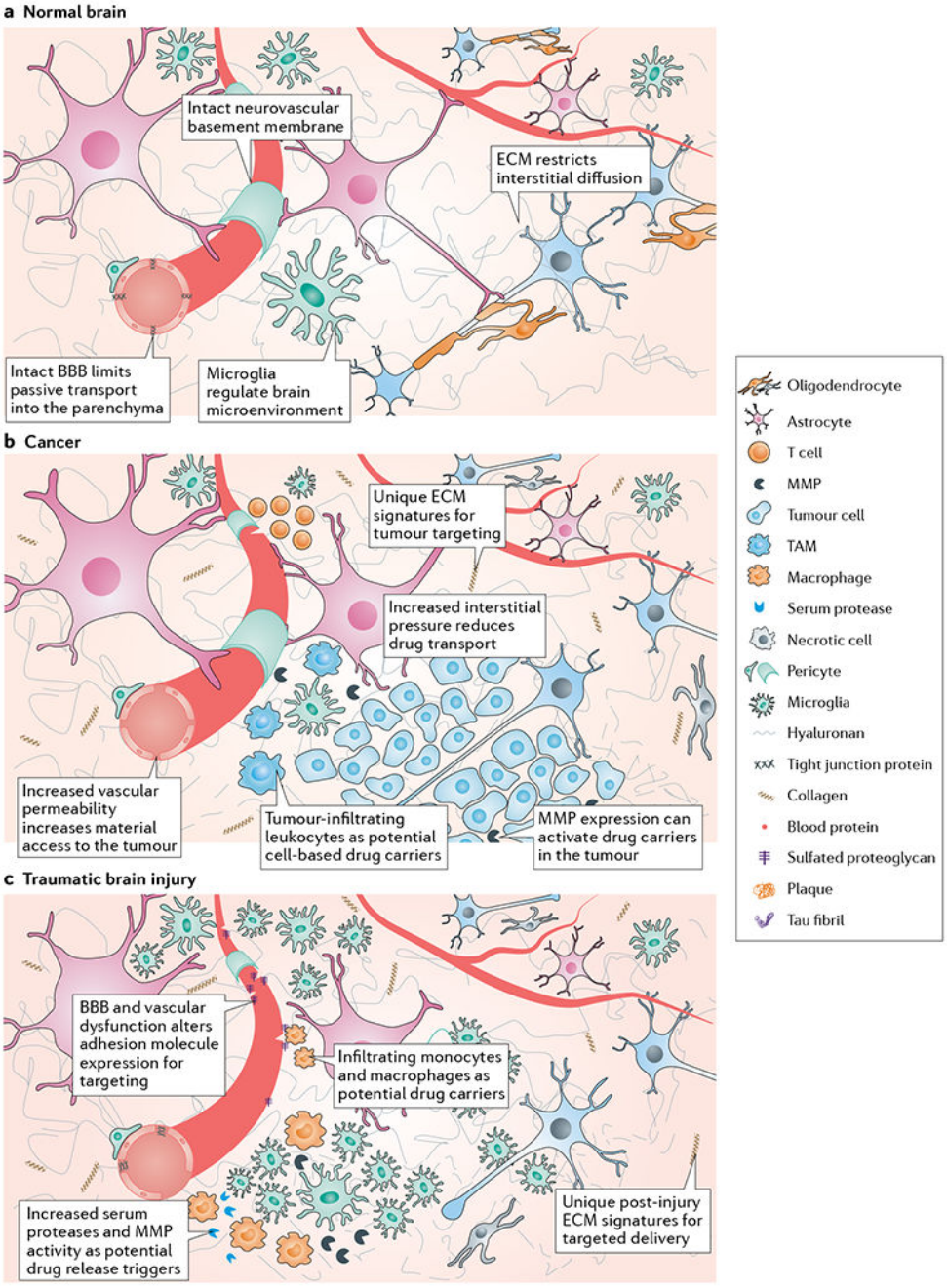


Fig. 1 |. Physiological and pathological changes of the central nervous system in cancer and traumatic brain injury.

The impact of vascular, enzymatic, extracellular, cellular and interstitial barriers on drug delivery is shown in normal brain tissue (panel **a**), cancer (panel **b**) and traumatic brain injury (panel **c**). BBB, blood–brain barrier; ECM, extracellular matrix; MMP, matrix metalloproteinase; TAM, tumour-associated macrophage.

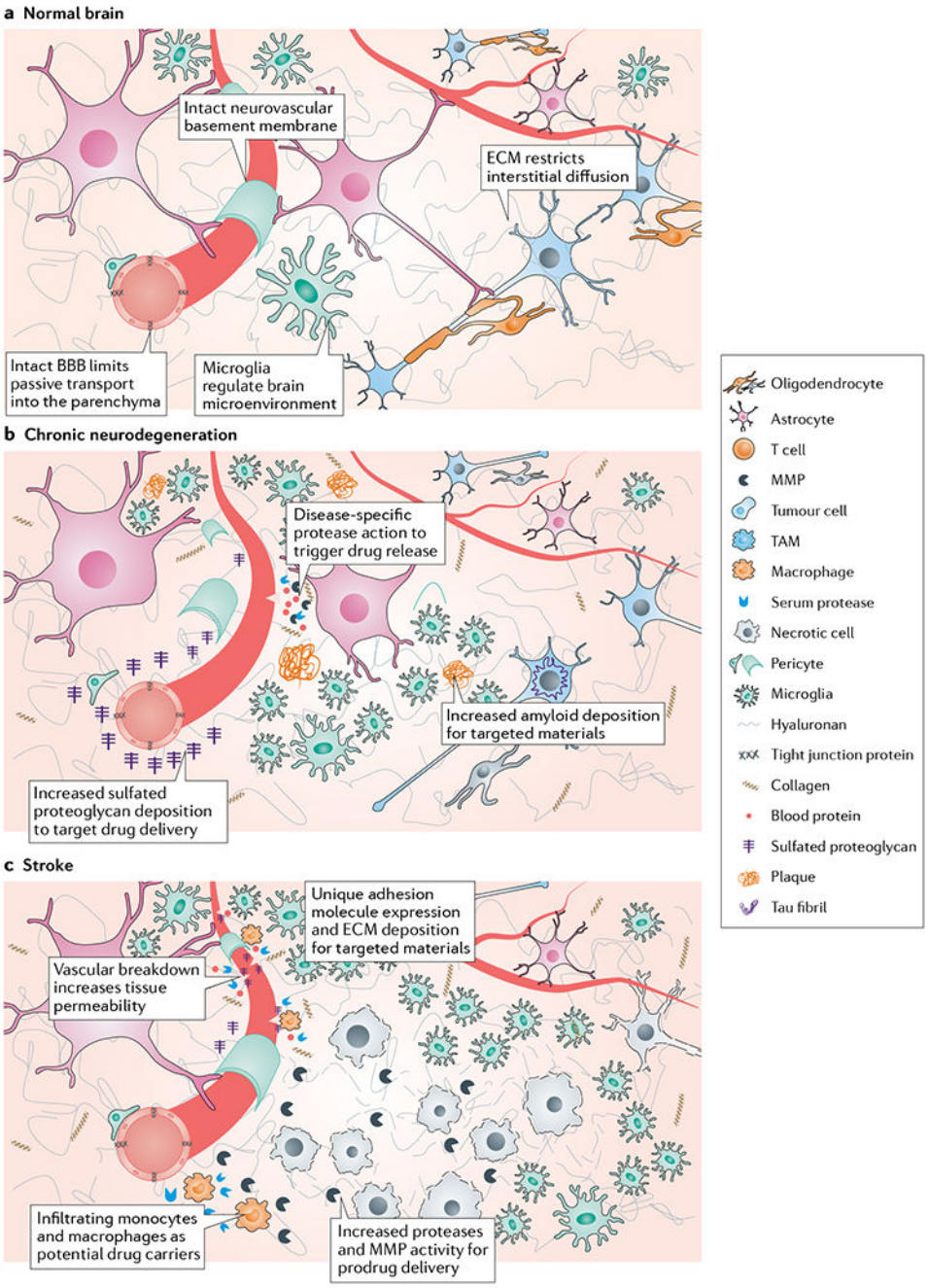


Fig. 2 |. Physiological and pathological changes of the central nervous system in chronic neurodegeneration and stroke.

The impact of vascular, enzymatic, extracellular, cellular and interstitial barriers on drug delivery is shown in normal brain tissue (panel **a**), chronic neurodegeneration (panel **b**) and stroke (panel **c**). BBB, blood–brain barrier; ECM, extracellular matrix; MMP, matrix metalloproteinase; TAM, tumour-associated macrophage.

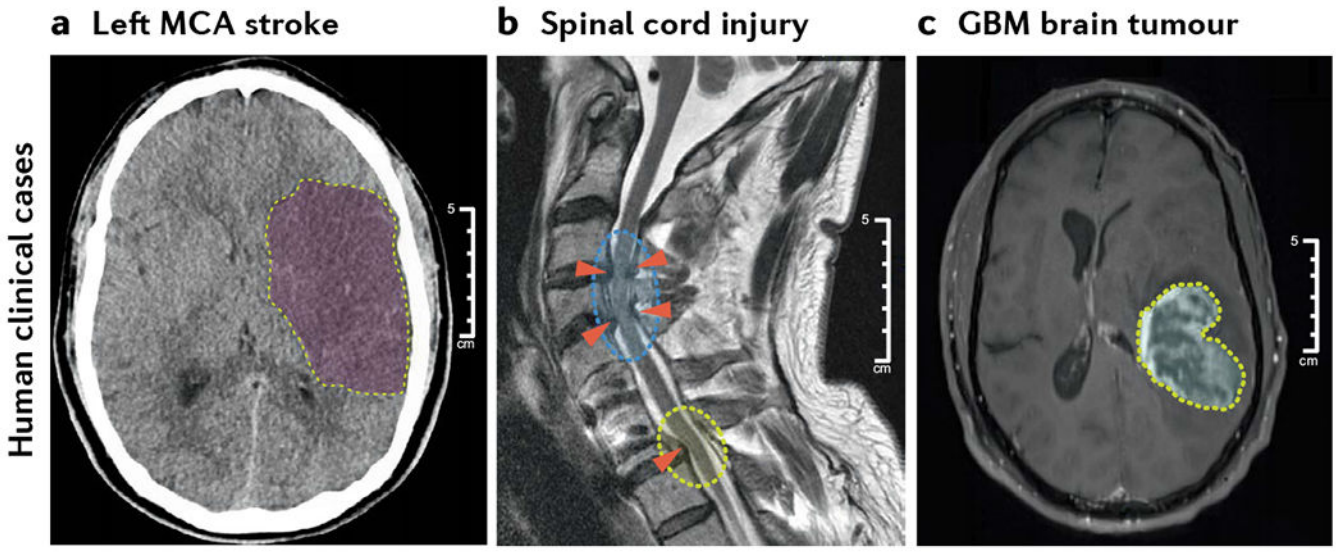


Fig. 3 |. Different human diseases present different central nervous system drug delivery challenges.

a | Computed tomography scan of a malignant middle cerebral artery (MCA) stroke, area outlined in yellow. The highlighted area (magenta) shows injured brain parenchyma occupying much of the left hemisphere, in which drug delivery solutions may be able to salvage tissue in the stroke penumbra that is transiently ischaemic but not yet infarcted or lost owing to cell death. **b** | Magnetic resonance image of a spinal cord injury (blue outline) shows a compressed spinal cord from cervical stenosis. The yellow outline shows a C7–T1 traumatic herniated disc displacing the spinal cord. Thus, two distinct areas (red arrows) of injury would need to receive a drug at therapeutic dose to preserve or recover white matter tracts, which could be accessible during surgery. **c** | Magnetic resonance imaging scan of glioblastoma multiforme (GBM) brain tumour, showing a large mass effect (enhancement within the left temporal lobe, yellow outline) causing mass effect and displacing the brain by over 1 cm from left to right. Resection surgeries for tumour removal (cyan) allow placement of local antineoplastic drug delivery devices. The technical challenge of targeting microscopic tumour cells in the brain beyond the large macroscopic tumour could benefit from materials that facilitate the delivery of therapeutic doses across a large tissue volume. Images obtained by R. Saigal.

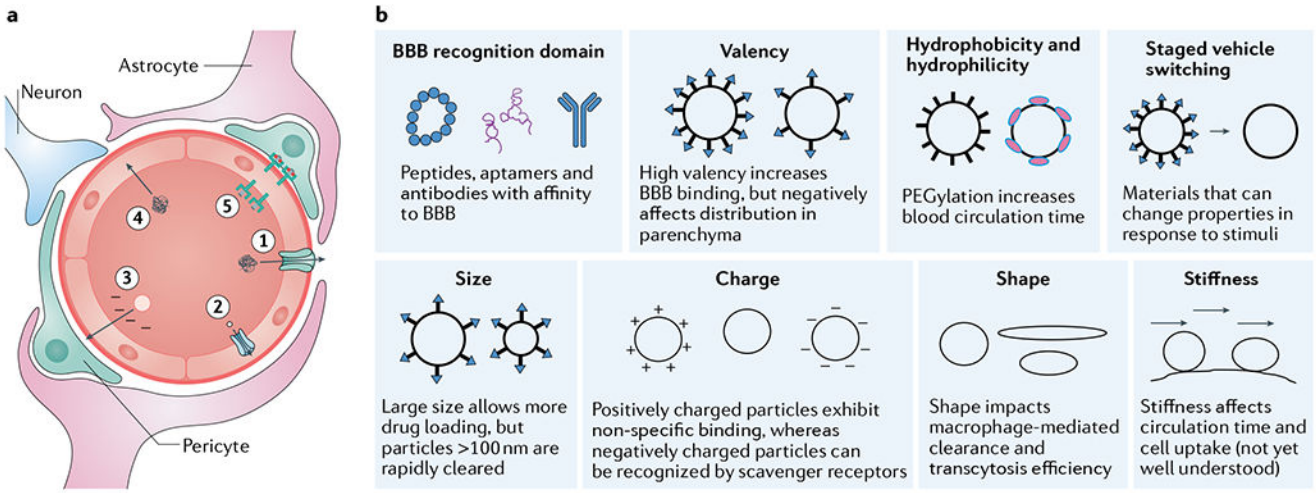


Fig. 4 |. Drug delivery across the blood–brain barrier.

a | Drug delivery systems can take advantage of several transport mechanisms across the blood–brain barrier (BBB)[4]. (1) Paracellular transport can occur for low- molecular-weight hydrophilic molecules; (2) transporters can facilitate movement of specific endogenous small molecules or mimics/derivatives of small molecules[136]; (3) absorptive transcytosis can be driven by charge-based binding and transport of macromolecules and nanoparticles, followed by internalization and transcytosis; (4) transcellular diffusion can occur for low-molecular-weight hydrophobic molecules; and (5) receptor-mediated transcytosis involves receptor-mediated shuttling of ligands and ligand–drug conjugates from the apical to the basolateral side. **b** | Material properties of drug delivery systems can influence adsorption, distribution and clearance of drug delivery systems following systemic administration. PEG, poly(ethylene glycol).

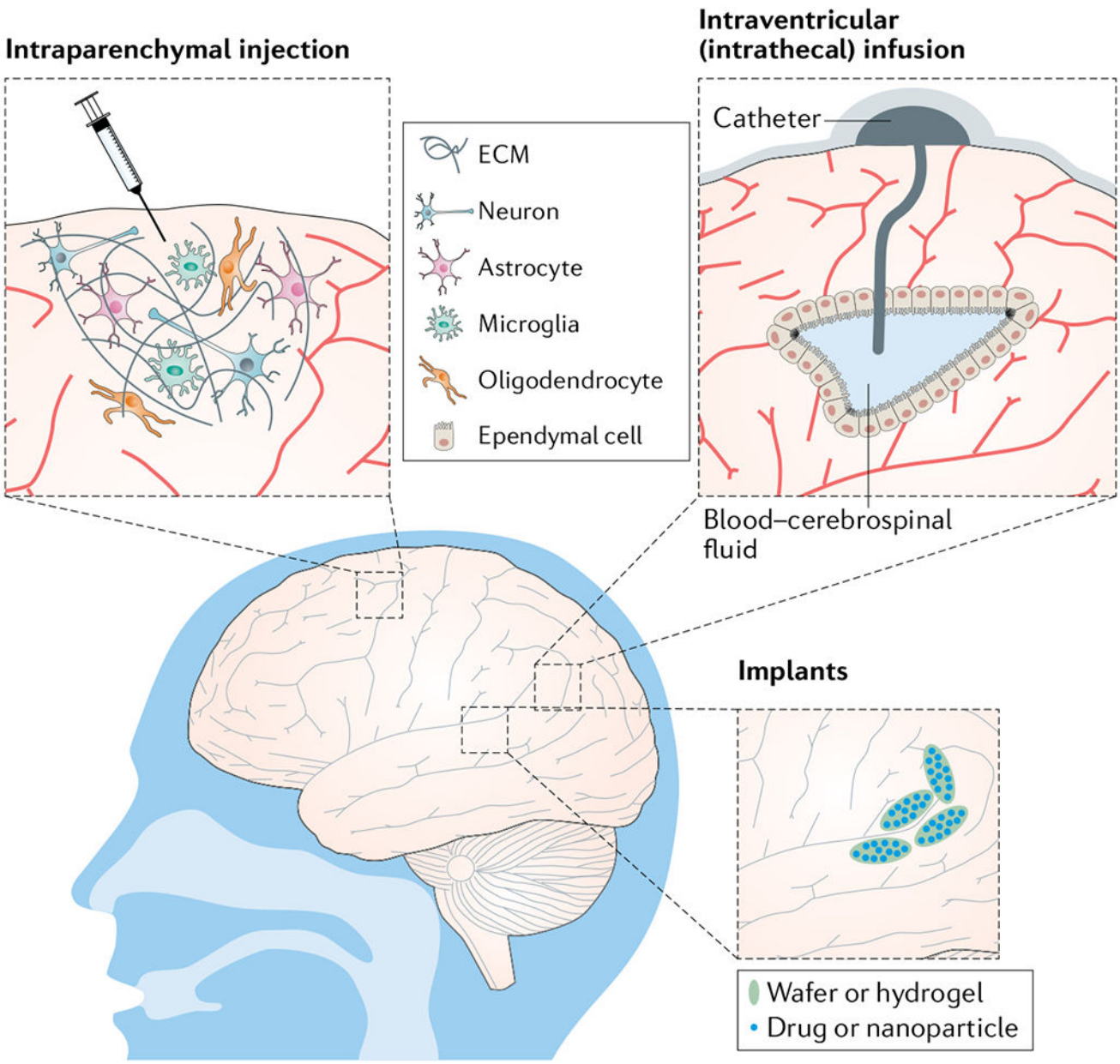


Fig. 5 |. Local central nervous system drug delivery routes.

Direct drug delivery to the central nervous system can be achieved by intraparenchymal injection, intraventricular or intrathecal infusion, or by implants, such as wafers or hydrogels loaded with drug or drug delivery systems. ECM, extracellular matrix.

Table 1 |

Protein targets for delivery to and across the blood–brain barrier

Receptor	Ligands for delivery	Applications
TfR1/CD71	Transferrin Ferritin Anti-TfR1 antibodies T7 peptide (HAIYPRH)[207] B6 peptide (GHKAKGPRK)[208] Anti-TfR1 aptamers[209,210]	Ferritin-based nanocages increase doxorubicin delivery and improve outcome in a murine orthotopic glioma model[211]
		Engineered protein containing a TfR1-binding sequence delivers active anti-β-secretase Fab to the brains of cynomolgus monkeys[212]
		Bifunctional aptamer binding TfR1 and Tau protects against Tau accumulation after TBI in mice[213]
LDL receptor, LDL-receptor-reiated proteins	ApoE Angiopep-2 (REF.[214])	ApoE-modified lipid nanoparticles accumulate in the brain after pulmonary administration[215]
		Polysorbate 80-coated particles bind to ApoE for transport to the brain[216,217]
		Angiopep-2 attached to nanoparticle formulations increases brain delivery in animals compared with controls[218–220]
Choline transporters	MPC	Nanocapsules formed from polymerized MPC deliver antibodies, peptides and proteins past the BBB[221–223]
Glucose transporters (GLUT1)	Glucose	Glucose-functionalized polymeric micelles deliver antibody fragments into the rodent brain, reducing amyloid-β aggregation in an Alzheimer disease model[224]
Possibly nicotinic acetylcholine receptor (under debate)	Rabies virus glycoprotein (RVG) peptides TGN peptide (TGNYKALHPHNG)	RVG peptide conjugated to PLGA nanoparticles increases brain delivery of deferoxamine in a mouse model of Parkinson disease[225]
		Peptide TGN and its retro-inverso isomer deliver small molecules, siRNA and peptides to the brain[226,227]
Cell adhesion molecules[57] (for example, CAM1/PECAM1, ICAM1, VCAM1)	Anti-CAM antibodies VCAM1 binding peptide (R832, CNNSKSHTC)[228]	Anti-ICAM1 antibodies conjugated to catalase deliver enzyme to the BBB after TBI to reduce oxidative stress[229]
		Liposomes functionalized with anti-VCAM1 antibodies deliver mRNA to the inflamed brain[97]

BBB, blood–brain barrier; CAM1, cell adhesion molecule 1; GLUT1, glucose transporter 1; ICAM1, intercellular adhesion molecule 1; LDL, low-density lipoprotein; MPC, 2-methacryloyloxyethyl phosphorylcholine; PECAM1, platelet endothelial cell adhesion molecule 1; PLGA, poly(lactic-co-glycolic acid); TBI, traumatic brain injury; siRNA, small interfering RNA; TfR1, transferrin receptor 1; VCAM1, vascular cell adhesion molecule 1.

Table 2 |

Examples of central nervous system biomaterials in clinical trials

Drug name	Material	Disease	Delivery route	Trial register	Status
MTX110	Panobinostat nanoparticle	Brain cancer	Convection-enhanced delivery	NCT04264143	Recruiting
APH-1105	Nanoparticle	Alzheimer	Intranasal	NCT03806478	Not yet recruiting
DepoCyte	Liposome	Cancer	Intrathecal	NCT00854867	Completed
Cytarabine	Liposome	Cancer	Intrathecal	NCT00992602	Completed
Doxorubicin	Liposome	Cancer	Intrathecal	NCT00019630	Completed
Doxorubicin	PEG-liposome	Cancer	Intrathecal	NCT00944801, NCT00944801	Completed
AGuIX	PoLysiloxane nanoparticle	Cancer	Intravenous	NCT03818386	Recruiting
EnGeneIC EDV	Nanocell	GBM/cancer	Intravenous	NCT02766699	Recruiting
RNA-LP	RNA-loaded DOTAP liposome	High-grade glioma/GBM	Intravenous	NCT04573140	Not yet recruiting
Gliadel	Polymer wafer	Cancer	Parenchymal	NCT00525590	Completed
CNM-Au8	Gold nanoparticle	ALS	Oral	NCT04098406	Recruiting
NU-0129	Spherical nucleic acid	Cancer	Systemic	NCT03020017	Completed
Abraxane	Albumin-stabilized nanoparticle	Cancer	Systemic	NCT00307255	Completed

ALS, amyotrophic lateral sclerosis; DOTAP, 1,2-dioleoyl-3-trimethylammonium propane; GBM, glioblastoma multiforme; PEG, poly(ethylene glycol).