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Challenges and opportunities in nanotherapeutics targeted for central nervous system disorders

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Central nervous system (CNS) disorders represent some of the most challenging problems for modern medicine. The complexity of the CNS structure, incomplete understanding of disease, chronic neuroinflammation, and physiological barriers limiting drug delivery all contribute to the difficulty of treating neurological diseases. This review covers the neuroanatomical barriers of the CNS and discusses current treatments, shortcomings of these treatments, recent clinical trials, and opportunities for nanotherapeutic approaches in common CNS disorders. Focus is placed on selected CNS disorders stemming from trauma, neurodegenerative diseases and infectious diseases. The review concludes with a summary and perspectives on the nanotherapeutics development highlighting key challenges and future directions for the field.

Introduction

CNS disorders have an enormous impact on all levels of society, from personal lives, family, and community to broader society. In 2020, it was estimated that 20 800 Australians had spinal cord injuries, with an economic cost to the country of $3.7 billion AUD per year.[1] In the USA, it is estimated that 6.7 million Americans over 65 years of age have Alzheimer's dementia (~1.9% of the population)[2] while it is estimated that 433 350 Australians live with dementia (~1.6% of the population).[3] In 2016, stroke was the second largest cause of death globally.[4] In 2021, it was estimated that 43.1% of the world's population has a condition affecting the nervous system.[5] The additional health and economic impacts of these diseases on families and carers are enormous. As such, therapies that can address these disorders have great potential to drastically improve the lives of many (not just the patients) and may represent a significant market. The development of therapies for these disorders has been hampered by several obstacles – chiefly, the exquisite complexity of the nervous system, difficulty of therapy delivery, imperfect animal models, and an incomplete understanding of the nerve regeneration process. Additionally, similar injuries in patients can lead to considerable variation in functional outcomes and recovery (known as the neuroanatomical-functional paradox).[6] Many clinical trials for different drugs and therapeutic compounds have been published, with some successes. Great strides are being made with the advent of new techniques, more sensitive instrumentation, computational power, and "big data" analytic approaches. Nanoparticles/nanotherapeutics (for the purposes of this review we will use these terms interchangeably) can be defined as constructs in the sub-micron size range capable of delivering a therapeutic product or effect. They can be synthetic or naturally derived but often consist of both synthetic and natural components. In conjunction with nanoparticle geometric properties (such as high surface-area-to-volume ratio and small size), the enormous diversity in nanoparticles and their corresponding functional properties promise to enhance natural recovery processes, but this promise is yet to be fully realized. This great diversity includes composition (*e.g.*, metal, metal oxide, polymer, lipid, hybrids), size (range from nanometers to hundreds of nanometers), shape (spherical, rod, star, dendrimer *etc.*), coatings (functional, stealth), cargo (DNA, RNA, drugs, peptides *etc.*), and many combinations thereof. These have been reviewed extensively,[7] with many creative and amazing variations being published at a high frequency. As such we will mainly focus on specific CNS disorders and the opportunities of nanotherapeutics as treatments for these disorders. Firstly, we briefly discuss the two main physiological barriers for drug delivery to the CNS, particularly in

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relation to nanoparticles, and current strategies to overcome these barriers. Subsequently, we discuss selected CNS disorders, namely: trauma-related brain and spinal cord injury, stroke, neurodegenerative diseases (Huntington's disease (HT), Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD) amyotrophic lateral sclerosis (ALS)), prion-related conditions as well as infectious diseases. In the interest of length, only brief overviews of these CNS disorders will be given, as many excellent in-depth reviews exist for the topics discussed here. Current treatments/interventions and select clinical trials will be discussed for each disorder, followed by opportunities for nanotherapies and some key examples. Psychiatric disorders, pain, and brain cancer related disorders will be excluded from this review, though there may be nanotherapeutic applications for their treatment as well.

Challenges and strategies in CNS drug delivery

The mononuclear phagocyte system (MPS)

The MPS is responsible for the rapid clearing of nanoparticles from the blood stream, preventing accumulation and effective dosage. This is a general phenomenon and not specific to CNS drug delivery. The MPS (formerly known as the reticuloendothelial system)[8,9] consists of the "professional" phagocytic cells of the innate immune system: monocytes of the blood, resident tissue macrophages and dendritic cells. These cells have roles in tissue damage and repair, pathogen detection and phagocytosis. While other cell types can exhibit phagocytosis, these cells particularly specialize in efficient phagocytosis. In the context of nanoparticle drug delivery, they are primarily responsible for the clearance of nanoparticles from the blood and tissues. This clearance is mediated phagocytic receptors present on the cell membrane of these immune cells which recognize opsonins. Opsonins are proteins normally found in the serum which, when bound to a particle or pathogen, mark them for phagocytosis. Opsonins include proteins such as fibronectin, antibodies and complement proteins.[10] Once bound to nanoparticles, these opsonins form part of what is known as the protein corona. The protein corona is the result of spontaneous, non-specific binding of proteins to the surface of nanoparticles upon introduction to biological tissue or fluids. This binding of proteins to nanoparticles is mediated by a variety of forces (*e.g.* hydrogen, hydrophobic *etc.*) highly dependent on the nanoparticle surface chemistry, the specific proteins and the ionic environment. It should be noted that other types of biomolecules (lipids, nucleic acids, sugars) are able to bind to nanoparticles. The ability to predict the protein (or biomolecule) corona composition for a given nanoparticle system, organism and biological fluid type(s) would be a useful tool in designing nanotherapeutics, however at present this is not possible. A 2023 metareview analyzing nanoparticle–protein corona literature between the years 2000–2021 identified the need for robust methodologies in protein corona preparation and analysis, as well as more robust nanoparticle characterization and reporting.[11] Also recommended was utilizing a minimum information reporting checklist such as MIRIBEL (Minimum Information Reporting in Bio-nano Experimental Literature).[12]

Strategies to address the MPS. Much work has been done to identify methods to avoid or mitigate the effects of protein corona; these topics have been reviewed extensively elsewhere.[13–17] As such, we will only briefly mention key strategies, which broadly fall into three categories: non fouling coatings (stealthy), pre-emptive coatings ("don't eat me") and MPS suppression. Non-fouling coatings serve to repel protein adsorption in the first place. Key mechanisms behind this are the neutralization of surface charge and high hydrophilicity, which can be achieved with zwitterionic, fluorinated, polysaccharide or non-ionic surfactant coatings. Important considerations for this strategy are coating density, chain architecture and molecular weight.[13] The most famous example of this is polyethylene glycol (PEG), which while highly effective and widely utilized, cannot completely prevent corona formation. Additionally, there have been reports of adaptive immune responses to PEG-coated treatments which limit the effectiveness of repeated dosing.[18] Pre-emptive coatings involve coating nanoparticles with specific proteins or protein mixtures (*e.g.*, derived from lysed cell membranes) before introduction to the body. Proteins like albumin or apolipoproteins are natural protein transporters within the blood stream and can avoid MPS clearing.[15] Coating with natural protein transporters would likely result in non-specific cellular uptake, which may or may not be acceptable depending on the disease. Strategies involving extracted cell membrane protein mixtures, while providing many "don't eat me" antigens, would suffer from batch-to-batch variability and are usually not characterized in the literature, both of which can lead to quality control issues. Coating nanoparticles with proteins, peptides or aptamers that can bind specific epitopes enable targeted cellular uptake. A commonly employed strategy is to coat nanoparticles with a targeting molecule and "backfill" any empty spaces on the surface with a non-fouling coating. MPS suppression can be achieved by suppressing phagocytic activity with drugs, saturating phagocytic receptors, depleting opsonins in the blood stream or saturating uptake with blocking "decoy" nanoparticles.[17]

Blood-CNS barriers

The other key challenge in drug delivery to the CNS has been the traversal of substances through the blood–brain barrier (BBB) and blood–spinal cord barrier (BSCB). While direct delivery into the brain or spinal cord is possible, less invasive delivery methods are much more practical and financially viable. Central to these efforts are the composition and hierarchical architecture of the BBB and BSCB. Neurons are the primary functional unit of the nervous system. Neurons are supported by several different cell types, including astrocytes, oligodendrocytes, and microglia (Fig. 1a). Oligodendrocytes myelinate axons of multiple neurons and are replaced by oligodendrocyte precursor cells when damaged or dying, while

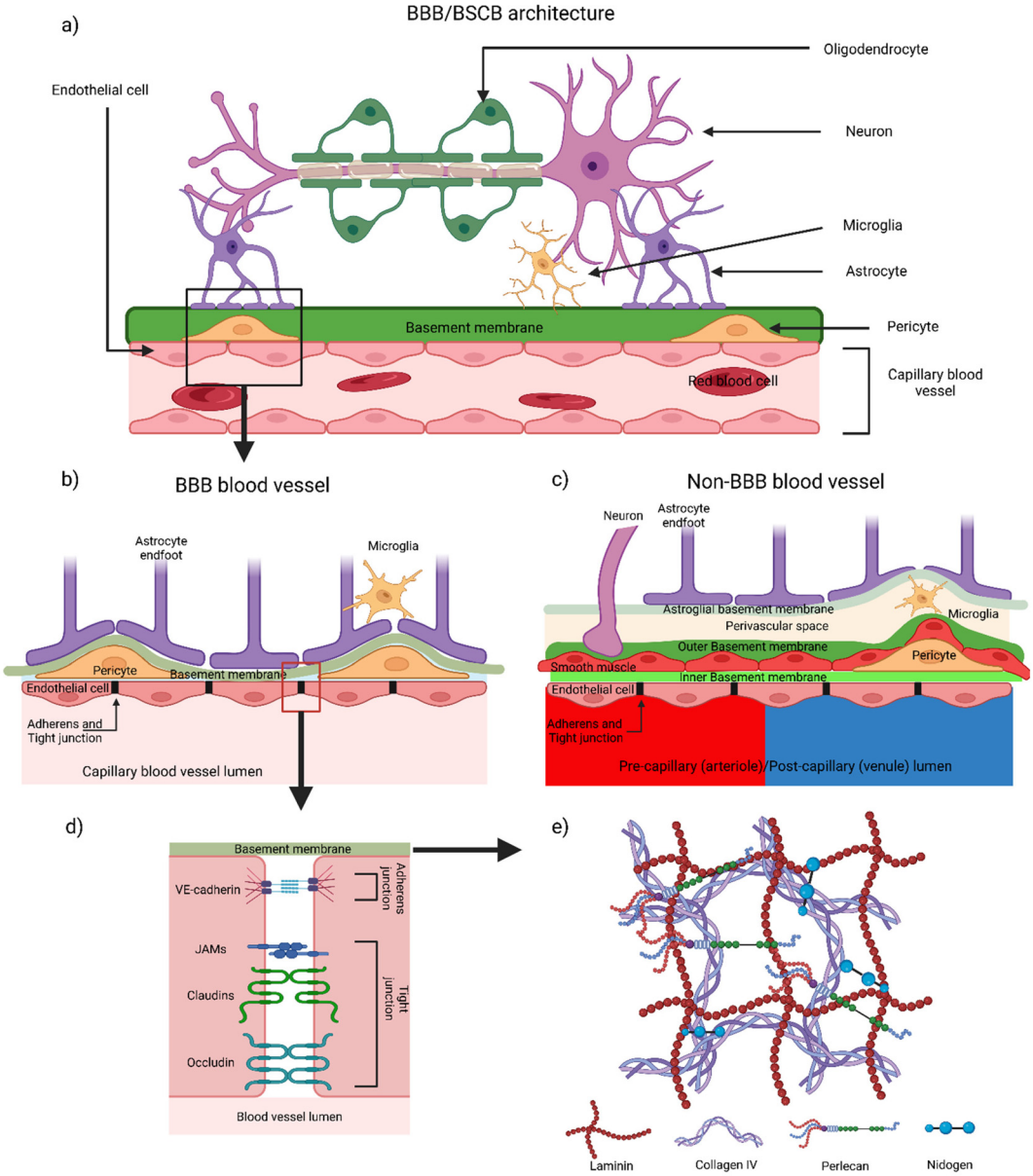

Fig. 1 (a) Neurons in the CNS are supported by oligodendrocytes, microglia and astrocytes, while nutrients and metabolites are exchanged with nearby capillaries; (b) basic schematic of capillary BBB and BSCB architecture: endothelial cells form the lining of blood vessels, and gaps between them are sealed with tight junctions. Pericyte cells partially surround the endothelial cells, and both cell types are surrounded by a specialized basement membrane. Astrocytic foot processes and pericytes maintain the barrier function of the basement membrane and endothelial cells; (c) schematic of pre- and post-capillary (non-BBB) architecture. Endothelial cells are separated from pericytes by the inner BM. Pericytes and smooth muscle cells are covered in an outer BM. Smooth muscle cells are innervated by autonomic nerves controlling vascular tone. A perivascular space exists between the outer BM and the astroglial BM, containing lymph fluid and immune cells; (d) BBB and BSCB specific cell–cell adhesion molecules: adherens junctions are composed of VE-cadherins between endothelial cells and are located basally to the basement membrane. Tight junctions are composed of occludins, the claudin family and junctional adhesion molecules (JAMs) and are located more apically. These are attached to cytoskeletal proteins *via* adaptor proteins; (e) typical BM composition: an intertwined network of laminin, collagen IV, perlecan and nidogen.

astrocytes provide metabolic and structural support to the nervous system by forming connections between the capillaries and neurons, transporting nutrients, metabolites and regulating ion concentrations. Microglia are the resident immune cells of the CNS, phagocytosing debris, presenting antigens to infiltrating immune cells, and pruning dendritic spines.[19] The CNS is a highly regulated and immune-specialized environment. The blood–brain barrier (BBB) and the blood–spinal cord barrier (BSCB) are the major interfaces between the blood and the CNS. The BBB/BSCB consists primarily of the continuous endothelial cell linings of capillaries and the tight junctions that join endothelial cells together, also known as zonula occludens. The primary function of these barriers is homeostatic regulation, including regulation

of ion balance (particularly Na^+ and K^+) and control of traffic into and out of the CNS. This traffic includes macromolecules, metabolites, nutrients, toxins, and immune cells.[20] In the capillaries that form the BBB/BSCB, endothelial cells are supported by a basement membrane (BM), pericytes, astrocytes, and the resident CNS immune cells, microglia (Fig. 1b). The BBB/BSCB capillaries differ from preceding and proceeding blood vessels (arterioles and venules respectively) in several aspects (Fig. 1c). In venules and arterioles, endothelial cells are also supported by smooth muscle cells, which provide vascular tone, sometimes *via* input from innervating neurons. There are three BMs: the endothelial BM (basal lamina), which contacts the basal side of endothelial cells, the outer BM, which covers smooth muscle cells and pericytes, and the astroglial BM, which is formed by astrocytic endfeet.[21] The outer BM and the astroglial BM together are also known as the parenchymal BM. There is a perivascular space surrounding venules and arterioles, whose function is somewhat debated but generally agreed to include fluid drainage and the lymphatic system.[22] These additional layers are not conducive to transport between the blood and CNS. There are two types of cell-to-cell junctions, which together provide the barrier function between cells: the adherens junction and the tight junction (Fig. 1d). During development, the adherens junction is formed first by adhesion between vascular endothelial (VE)-cadherin molecules on opposing cells, without which, tight junctions cannot be formed. Tight junction proteins are concentrated around adherens junctions *via* zonula occludins protein 1 and 2 (ZO1 and ZO2), which become enriched in this region. This concentration allows tight junction proteins on opposing cells to interact with each other and form the functional BBB.[23] Tight junctions consist of three main classes of transmembrane homodimeric proteins: the occludins family, the claudin family, and the junctional adhesion molecule (JAM) family.[24] The claudins create charge selective pores of ~4 Å, while JAMs create size-selective pores of ~60 Å. The precise role of occludins remains unclear.[24] The intracellular regions of these tight junction proteins are associated with ZO1 and ZO2 proteins, which in turn attach to actin cytoskeletal networks and other regulatory proteins.[25] The BMs are specialized extracellular matrices, primarily consisting of perlecan, laminin, type IV collagen, and nidogen (Fig. 1e). Type IV collagen and laminin form independent networks that are bridged by perlecan, nidogen, and other extracellular matrix proteins. Type IV collagen primarily provides structural integrity to the BM, while the laminin network contains many cell signaling regions for adhesion and survival and is the primary contact of cells to the BM.[26] The laminin isoform found in capillary BMs is different from that found in arterioles and venules (and also in different BMs around the body), reflecting their different roles and permeabilities.[27] Perlecan contains various cell binding sites, binding sites for other BM components, and glycosaminoglycan (GAG) chains that are able to interact with growth factors, which are critical for normal development.[28] Nidogen plays a role in BM stability by also providing links between laminin and collagen IV.[29] Knockout studies of BM components result in large structural deformities and embryonic lethality, highlighting their importance.[30] It is important to note that while circulating immune cells cannot enter the CNS at the capillaries of the BBB, under neuroinflammatory or pathological conditions they are able to gain entry to the brain at the post-capillary venules, firstly into the perivascular space and then past the astroglial BM. Immunoglobulins are also able to gain entry to the CNS under pathological conditions, although the entry point is unknown.[21] There is some evidence that transcytosis of immunoglobulins is regulated by pericytes.[31] The BSCB is of a similar structure to the BBB, containing continuous endothelial capillary linings with tight junctions, supported by a BM, pericytes and astrocytes.[32] Some key differences include the presence of glycogen deposits, lower number of pericytes and higher permeability than the BBB,[33] possibly owing to lower expression of tight junction proteins.

Strategies to address blood-CNS barriers. Much research has been devoted to bypassing the blood-CNS barriers in various drug discovery programs. Some key physicochemical design parameters of small molecule drugs include lipophilicity, polar surface area, molecular rigidity, molecular weight, capacity for hydrogen bonding, rotatable bonds, and pK_a.[34] While these design constraints have been rigorously applied to drug discovery programs, reliance on untargeted systemic delivery limits the total dosage able to be applied and the drug efficacy in the CNS. Nanoscience is well positioned to take on this key challenge. Furthermore, applying various approaches, including nanoscience, to aid in BBB and BSCB traversal can expand the scope of drug discovery programs to molecules that may not have been otherwise considered.[35] The two main routes of crossing the BBB/BSCB are paracellular (between cells) (Fig. 2i) and transcellular (through cells) (Fig. 2ii).[36] The paracellular route is regulated by tight junction structures (Fig. 2i). The transcellular routes include passive diffusion, drug efflux pumps, endocytic mechanisms (*e.g.*, receptor- or absorptive-mediated), and solute carriers for small molecules such as glucose, amino acids, and nucleotides (Fig. 2ii). Endocytosed macromolecules and complexes undergo intracellular sorting *via* various Rab proteins and then exocytosis at the abluminal membrane *via* SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) and SNAP (soluble *N*-ethylmaleimide-sensitive factor attachment protein) complexes.[37] Leukocytes are also capable of transcellular migration under inflammatory conditions. Some notable receptors include the transferrin receptor, the apolipoprotein 2 receptor (APOER2), and low-density receptor-related protein (LRP1). A more comprehensive list of substances and their mediators for crossing the BBB are given by Abbott *et al.* (2010).[25]

Various BBB-crossing and BBB-bypass strategies for medicines have been trialed. Intranasal delivery is a safe and non-invasive route, with highly vascularized surfaces that can bypass the BBB. However, the nasal mucosa is home to many enzymes and experiences high clearance rates, leading to low therapy retention. There have been several clinical trials for

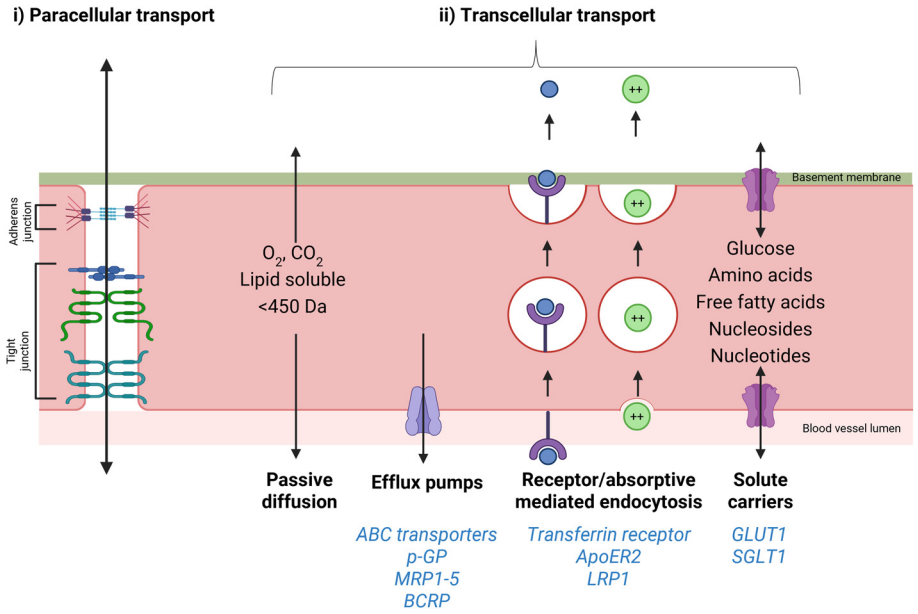

Fig. 2 Transport mechanisms across the BBB: (i) paracellular, between cells, and (ii) transcellular, through cells. Transcellular transport mechanisms include passive diffusion, efflux pumps, receptor or absorptive mediated endocytosis and *via* solute carriers.

delivery of various therapeutic compounds *via* the intranasal route, such as insulin, nerve growth factor, and oxytocin.[38] Nanoparticles and mucoadhesive compounds can increase retention time. In terms of BBB crossing strategies, Tween-(polysorbate) 80, a non-ionic surfactant, has also been shown to be successful, with various proposed mechanisms of action. These include disruption of the drug efflux pump P-glycoprotein[39] and physical adsorption of apolipoproteins B and E, which enhance transcellular transport (transcytosis),[40] although it is unclear whether other receptors are affected by this. Other promising non-invasive approaches involve exploiting transcytosis mechanisms (receptor, carrier or absorptive-mediated). Some examples of these include the transferrin receptor, CD98, GLUT1, and CD147.[41] The transferrin receptor is best characterized for BBB crossing, with the development of RO7126209, a low-affinity bi-specific antibody targeting the transferrin receptor and β-secretase (BACE1), an enzyme involved in the production of amyloid-β in the brain. This was used in a non-human primate model, demonstrating safe and efficient transport into the brain,[42] and is currently undergoing a phase Ib/IIa clinical trial for mild to moderate Alzheimer's disease (NCT04639050). Following this, two fusion proteins have been developed, which consist of the enzyme iduronate-2-sulfatase fused with a transferrin receptor antibody (JR-141), or an engineered Fc fragment of an antibody possessing a high affinity for the transferrin receptor (DNL310), for the treatment of the CNS symptoms associated with mucopolysaccharidosis II (Hunter syndrome). JR-141 has passed a phase I/II clinical trial, showing successful BBB penetration and some CNS efficacy,[43] and is currently undergoing a global phase II/III clinical trial (NCT04573023). DNL310 is still undergoing a phase I/II clinical trial, showing promising interim results (NCT04251026),[44] and is also currently undergoing a phase II/III clinical trial (NCT05371613). There have been some early clinical trials for the use of magnetic resonance-guided focused ultrasound with microbubble contrast agents to temporarily open the BBB,[45–47] showing it to be safe and with some potential benefit in Alzheimer's disease patients. This can be combined with therapeutics that otherwise cannot cross the BBB. It should be noted that it has been reported that the ultrastructure and permeability of the BBB/BSCB can be altered in neurodegenerative disorders, although whether permeability is increased or decreased is unclear and likely to be disease dependent, as reports indicate a reduction in tight junction protein expression while at the same time an increase in drug efflux pump expression (P-glycoprotein and breast cancer resistance protein).[48]

Nervous system disorders

Traumatic brain & spinal cord injuries

Traumatic brain injuries (TBI) and spinal cord injuries (SCI) are major causes of mortality and disability as consequences of motor vehicle incidents, falls, violence and contact sports. These traumatic events have primary and secondary effects, and there is significant overlap between brain and spinal cord injuries. Primary effects typically involve direct damage to neurons, vasculature, and surrounding tissue, as well as BBB/BSCB compromise. Secondary effects occur in the hours and days following the initial event, and include neuroinflammation, axonal degeneration, demyelination, white matter loss, and disruption of axonal transport.[49] Damaged and dying cells release glutamate, damage-associated molecular patterns

(DAMPs), such as cell-free DNA and heat shock proteins, high-mobility group protein 1 (HMGB-1), interleukin-1 (IL-1) family members, and histones. DAMPs, vascular damage, and BBB/BSCB compromise lead to an influx of immune cells, which release pro-inflammatory cytokines such as TNF-α, IL-1α, IL-1β, and IL-6.[50] Neutrophils, macrophages, and microglia release DNA traps known as extracellular traps, which in turn causes reactive astrocytes to overexpress inhibitors of axonal regrowth, such as chondroitin sulfate proteoglycans (CSPGs).[51] Glutamate release results in neuronal excitotoxicity and release of more DAMPs. Vascular damage leads to lack of oxygen, which increases cell stress and inflammation. This inflammatory environment, while important initially, is detrimental to trauma recovery in the long run. Eventually, a glial scar is deposited around the injury site, forming a barrier and inhibiting axonal regeneration. A more in-depth discussion of the pathophysiology of spinal cord injury is given by Ahuja *et al.*[52] and Hausmann *et al.*[53]

Current treatments & clinical trials in TBI & SCI. Current treatment guidelines for traumatic spinal cord injury include maintenance of mean arterial pressure at 85–90 mmHg for adequate spinal cord perfusion, the administration of methylprednisolone sodium succinate, optimally within 8 or 24 hours of acute injury (although this is controversial), and spinal surgery to realign, stabilize, and decompress the spinal column.[52,54–56] Physical rehabilitation training is also an important component for functional recovery.[57] Corticosteroids can act as effective anti-inflammatory therapeutics where inflammation drives cell death.[58] Deep neurostimulation (electrical stimulation of the spinal cord or motor cortex *via* implanted electrodes) is a method to relieve chronic neuropathic pain and essential tremor, with several commercial FDA-approved devices on the market. It is also approved for reduction of seizure events in epilepsy (vagus or cortical nerve implantation).[59] Spinal cord stimulation combined with intense physical therapy has been shown to induce some functional recovery in some paraplegic patients.[60,61] Sometimes spontaneous activation of latent pathways, a form of neuroplasticity, can bypass the scarred area to achieve functional recovery (*e.g.*, the crossed phrenic pathway).[62] There are no pharmacological treatments for TBI despite many clinical trials. Recommendations include head elevations, hyperventilation, prophylactic anti-epileptics, and in extreme cases, cranial surgery to evacuate brain bleeds and cauterize bleeding blood vessels.[63]

Clinical trials for treatment of acute SCI include neuroprotective and regenerative compounds, procedural methods, neurostimulation, stem cell, and bioengineering strategies.[52] Several neuroprotective and regenerative compounds have been tested or are undergoing testing. There has been some interest in using the anti-cancer agent epothilone B, a microtubule-stabilizing compound, for treatment of SCI, because it has been shown to enhance axon outgrowth in rat spinal cord[64] and peripheral nerve[65] injury models. However, this has not progressed past pre-clinical testing. A small lipid-soluble basic fibroblast growth factor (b-FGF/FGF-2) analogue, SUN10387, was tested in a phase II clinical trial involving 65 patients, but was shown to be not clinically effective.[66] A prospective uncontrolled clinical trial for the use of acidic fibroblast growth factor (FGF-1) in a fibrin glue was tested in 60 patients and shown to be safe with significant improvements in function.[67] It is now undergoing phase III clinical trials, with the results expected soon (NCT03229031). Minocycline, an antibacterial compound, has shown promising neuroprotective effects through inhibition of inflammatory pathways in combination with good BBB penetration, being a lipophilic molecule. Several clinical trials have been conducted for minocycline as a treatment for acute SCI and TBI, showing it to be safe within the dosing windows. Some clinical improvements were seen; however, they did not reach statistical significance potentially due to low patient numbers.[68–71] A phase III trial for minocycline treatment for SCI was started in 2013; however, no results have been published (NCT01828203). A randomized, double blinded, placebo controlled clinical trial for a promising neuroprotective agent, the RhoA inhibitor, VX-210/Cethrin, was shown to be well tolerated but not effective and was ended prematurely.[72] Clinical trials involving stem cells for SCI have been summarized in several reviews,[73,74] showing generally good safety and only mild adverse events. While the safety aspect is promising, functional improvement outcomes vary greatly, which is reflective of the early stage of this method as a treatment. A recent clinical trial (approved 2024) is a Phase I/IIa randomized and blinded clinical trial for the use of olfactory ensheathing cells (OEC) transplantation combined with intensive physical rehabilitation for the treatment of spinal cord injury (ACTRN12624000391572). OECs are glial cells of the olfactory system, providing physical guidance to olfactory neurons and phagocytosing debris within the olfactory system.[75]

One of the major contributions to the inhibition of axonal regrowth in SCI is the presence of chondroitin sulfate glycosaminoglycans (CSGAGs) side chains present on chondroitin sulfate proteoglycans (CSPGs) such as NG2/CSPG4, aggrecan, brevican, and phosphocan.[76,77] CSPGs form part of the border of the glial scar, inhibiting axonal regeneration by promoting a pro-inflammatory phenotype in macrophages and microglia *via* activation of cell surface receptors Toll-like receptor 4 (TLR4), leukocyte common antigen-related (LAR), protein tyrosine phosphatase-sigma (PTPσ), and CSPG receptors.[78,79] The enzymatic removal of these CSGAGs with chondroitinase ABC (cABC) is known to enhance axonal regeneration,[80] promote various degrees of functional recovery,[81–83] and has been tested in various animal models.[84,85] A double-blinded randomized clinical trial was conducted for the therapeutic efficacy of heat-stabilized cABC loaded in lipid microtubules for pet dogs with spinal cord injuries (n = 60) and demonstrated a moderate level of functional recovery in treated dogs, with 2 dogs recovering near-normal independent motion.[86] A double blinded, placebo-controlled phase III clinical trial for the use of condoliase (a chondroitinase and hyaluronidase) in human patients with lumbar disc herniation was shown to be safe and reduce pain symptoms.[87]

Transcutaneous stimulation is a nerve stimulation technique, mainly for pain relief, involving delivery of low voltage electrical impulses to peripheral nerves *via* an adhesive pad through the surface of the skin, generally over areas affected by nerve dysfunction. The main benefits are that it is non-invasive, safe, and much simpler to apply. There is currently an ongoing double-blinded randomized controlled trial (eWALK) involving spinal transcutaneous stimulation combined with locomotion training for the improvement of walking ability,[88] and a clinical trial involving transcutaneous spinal stimulation combined with exercise training for the improvement of upper limb and respiratory function in patients with tetraplegia (Get A Grip, Australian and New Zealand Clinical Trials register (ACTRN12623000588695)). Hypothermia is a procedural intervention where the patients are cooled to 33 °C to reduce overall metabolic activity and inflammation. Two clinical trials testing hypothermia for SCI have shown it to be safe with some clinical improvements seen.[89,90] An implantable bioresorbable PLGA tube of 3 mm diameter, named the Neuro-Spinal Scaffold, was tested in two clinical trials for the facilitation of spinal cord repair and shown to be safe with no implant-related adverse side effects. While the first clinical trial showed some promising results, the device was ultimately shown to produce no clinical benefit compared to the control group.[91,92] Further insights into axonal guidance are necessary for advances in bioengineering and nerve scaffold strategies for neuronal regeneration.

Opportunities for nanotherapeutics. We have recently published a review on the potential for using nanomedicine to treat spinal cord injury.[93] In the past, we have utilized the neural tracer, wheat germ agglutinin-horseradish peroxidase (WGA-HRP), conjugated to gold nanoparticles to deliver an adenosine A1 receptor antagonist (dipropylcycloxanthine, DPCPX) to the respiratory center of the brain in a spinal cord injury model (rat) for respiratory paralysis. This work demonstrated a highly efficient drug delivery mechanism bypassing the BBB/BSCB, sustained release of DPCPX and functional respiratory recovery.[94] This strategy of using a neural tracer as a drug delivery mechanism within nerves could potentially be used for any disease or injury where the neuromuscular pathway is damaged, as delivery across both neuromuscular and transsynaptic junctions is possible, while avoiding issues associated with the BBB. Neural tracers are well known to neuroanatomists and have been traditionally used to decipher neural pathways for anatomical studies. We have reviewed known neural tracers and their potential for nervous system drug delivery.[95] These mostly consist of plant lectins, the cell membrane binding components of bacterial toxins, and neurotropic viruses. In general, they are taken up *via* absorptive-mediated endocytic mechanisms.

Superparamagnetic iron oxide nanoparticles have been used to label and track the fates of implanted stem cells in spinal cord injury and cortical photochemical lesion rat models.[96] Using MRI to track labelled cells, this study showed that stem cells implanted or injected intravenously were able to migrate to the lesion site. While no cell toxicity was observed, it is unclear whether the iron oxide nanoparticles influence the stem cell differentiation within the lesion, or what the long-term fate of the nanoparticles is.

PLGA nanoparticles have been loaded with anti-inflammatory compounds methyl prednisolone and minocycline, stabilized with chitosan and coupled with albumin to treat SCI in rats, finding that the albumin-coupled anti-inflammatory nanoparticles reduced lesion volume and improved behavioral activities compared to nanoparticles without albumin.[97] Intranasal delivery of liposomes containing IL-4 has been tested on a controlled cortical impact TBI mouse model. IL-4 is an anti-inflammatory cytokine that directs macrophages and microglia to differentiate to a pro-repair phenotype. Mice treated with these IL-4 liposomes displayed improved cognitive and physiological functions, which were supported by histological assessments.[98] A different study utilized a matrix metalloprotease (MMP-9) activatable cell penetrating peptide to gain access to the BBB, since MMP-9 has been reported to be upregulated at the BBB following TBI. This entry system was utilized to deliver GM1 ganglioside-stabilized liposomes carrying cyclosporin A, a fungus-derived neuroprotective polypeptide, which was able to rescue mitochondrial function after TBI. Intravenous delivery of these liposomes resulted in accumulation and reduced cell death at the lesion site, and improved mouse memory and cognitive functions compared to control-treated mice.[99] A summary of these nanotherapeutic studies for SCI and TBI is given in Table 1.

In the interest of directional nerve guidance for regenerating axons, micro/nanopatterning is a method of generating topological features on materials that drive cells to exhibit certain behaviors or characteristics, such as differentiation or directional growth. These may be achieved by electrospinning, lithography, etching, 3D printing, and focused ion beam milling.[100] Directional growth of neurons has been demonstrated using laminin-coated 3D micropillars etched into glass, finding that axons tend to interact with and align with micropillars within the size range of the neuronal growth cone (~6 μm).[101] Patterned grooves on polycaprolactone-graphene oxide composite surfaces with 1 μm width and 80 nm depths have also been shown to direct neural stem cells to differentiate into neurons and stimulate growth of longer neurites compared to larger grooves.[102]

Stroke due to thrombosis

Strokes are a common cause of death and injury. Stroke is caused by an interruption of blood flow to the brain and is classified as ischemic (deficient oxygen supply) or hemorrhagic (bleeding blood vessels). Thrombotic and embolic strokes are types of ischemic stroke. Thrombotic strokes occur due to atherosclerosis-related plaque buildup within blood vessels, which eventually causes clotting at the plaque site, preventing blood flow. Embolic strokes are caused by other kinds of occluding structures, such as dislodged blood clots or air bubbles. These result in cell stress and necrosis, followed by inflammation, homeostasis disruption and loss of neuronal function. Hemorrhagic strokes are caused by rupture of blood

Table 1 Nanotherapies for spinal cord injury and traumatic brain injury

Disease	Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
SCI-mediated respiratory failure	WGA-HRP coated AuNP	Adenosine receptor antagonist (DPCPX)	Diaphragmatic injection in rats resulted in BBB bypass *via* WGA-mediated retrograde axonal transport delivery to respiratory center of brain with some functional respiratory recovery	Intramuscular delivery, targeted neuronal delivery, sustained drug release	Possibility of AuNP accumulation at injection site, long term fate of AuNPs unknown	94
SCI	Superparamagnetic iron oxide NPs	Stem cells	Intravenous and graft in rats, MRI tracking of injected stem cells in the spinal cord lesion site	Non-invasive tracking of transplanted cells	Effect of NPs on stem cells not assessed, long term fate of NPs unknown	96
SCI	Chitosan and albumin coated PLGA	Methylprednisolone & minocycline	Intravenous injection in rats improved locomotion and resulted in smaller pseudocyst volume at lesion site compared to untreated controls	Improved half-life, higher therapeutic effectiveness ($1/10^{th}$ of conventional dosage) through targeting	No assessment of off-target NP uptake or side effects	97
TBI	Liposome	Interleukin-4	Intranasal delivery in mice improved hippocampal cognitive function	Effective non-invasive intranasal delivery	Only conducted studies on male mice, oversimplified classification of pro- or anti-inflammatory microglia	98
TBI	GM1 peptide coated phosphocholine (lipoprotein NP)	Cyclosporine A	Intravenous injection in mice resulted in CNS targeting through MMP-9 activatable cell penetrating peptide (GM1), causing reduced apoptosis, improved memory and cognitive functions	Delayed treatment (7 days after injury) still showed improvements in memory deficits at $1/16^{th}$ the dose of free drug	Quite complicated system. MMP9 expression is upregulated in tissue damage – if other tissue injuries present may have off target effects	99

vessels within the brain (often by head injury, anticoagulants, or thrombolytic agents), resulting in blood accumulation, an increase in intracranial pressure, release of reactive oxygen species, inflammation, and glutamate excitotoxicity. The areas around the hemorrhage become hypo-oxygenated, causing more cell stress, ultimately leading to cell death. The molecular mechanisms of neurological damage are similar to the secondary effects seen in SCI.

Current treatments & clinical trials. Acute treatments for thrombotic stroke involve administration of intravenous tissue plasminogen activators (t-PA) or urokinase plasminogen activators (u-PA) to dissolve blood clots within 4.5 hours of the event.[103] The faster acting, more stable t-PA, Tenecteplase, has been shown to be safe for use in a 24-hour window.[104] In large vessel blockages, mechanical thrombectomy is also recommended in addition to tenecteplase.[105] Ischemic stroke is treated with anti-clotting agents such as low dose intravenous heparin, warfarin, aspirin and ancrod (a fibrinogenolytic enzyme from snake venom).[106] Neuroprotective agents can also be delivered to minimize the neurological damage. These therapies are well characterized in their pharmacokinetics and adverse effects. The neurological consequences of stroke are difficult to treat at the source of pathology due to its acute onset. However, there is a wide space for aiding patients in recovery, particularly in motor recovery, typically as a supplement to physiotherapy.[107] These can be grouped by the type of neurotransmitters involved in the group of neurons. On the serotonergic side, a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine (Prozac) has shown promise in multiple facets such as mobility, visual acuity, and anti-inflammation,[108–110] although with the latter, the interaction of inflammation with post-stroke depression is still uncertain.[110,111] Similarly to Parkinson's treatment, the activity of dopaminergic neurons can also be addressed in stroke patients by administration of levodopa, which has shown to be a potentially beneficial supplement to physiotherapy, while an exogenous receptor agonist like ropinirole has not shown benefit.[112,113] Minocycline has been tested for stroke in a phase I clinical trial alone and in combination with t-PA, showing it to be safe up to doses of 10 mg kg^{-1} with no cases of intracerebral hemorrhage.[114] Stem cell-based therapies may also be a future treatment option. A 2020 systematic review

and meta-analysis of stem cell-based stroke therapies concluded that stem-cell treatments can improve neurological and activity-based outcomes in stroke patients, however the magnitude of these improvements are limited due to the limited number of participants overall and the early stages of stem-cell-based therapies.[115] As of this writing in 2025, there are 12 stem cell clinical trials for stroke that are active or recruiting, with a wide range of sources of stem cells used.[116]

Opportunities for nanotherapeutics. Nanotherapeutics may provide additional benefits in the delivery of therapeutic compounds for the dissolution or prevention of clots and neuroprotection.[117,118] For acute stroke treatment, nanotherapeutic opportunities likely lie in the economic aspect. Tenecteplase, the gold standard treatment, has excellent thrombolytic activity and a sufficient half-life for a single bolus delivery. However, it is much more expensive than other plasminogen activator (PA) therapies. This is in contrast with earlier generations of PAs (u-PA, streptokinase), which have poor half-lives in the blood, but are much more cost-effective.[119] Therefore, nanoparticles that enhance the activity or prolong the half-life of these could be particularly beneficial, especially for patients living in countries with smaller economies. The other main issue with PA therapies is the risk of intracranial hemorrhage, which is an off-target effect. Nanoparticles designed with a high affinity for thrombi, and designed to release or activate PAs in the vicinity of thrombi would drastically improve acute stroke treatment. One strategy involves liposomal vesicles loaded with streptokinase and decorated with peptides with binding affinities for glycoprotein GPIIb-IIIa and P-selectin, which are markers of activated platelets (which form blood clots). These vesicles demonstrated targeted thrombolysis in a mouse stroke model with minimal systemic bleeding effects.[120] Another study trialed a PEG–u-PA nanogel, which released u-PA at the lowered pH value of ischemic tissue in a rat model, demonstrating less neurological deficits and no systemic side effects compared to u-PA treated rats.[121]

In the medium to long term recovery for stroke, there are opportunities for neuroprotective and neurostimulation strategies. MicroRNA-124, a microRNA which promotes neuronal differentiation, was delivered to neural stem cells *via* calcium-based metal organic frameworks (MOFs) and was shown to accelerate neuronal differentiation and reduce ischemic stroke area in a mouse model,[122] while brain-derived neurotrophic factor (BDNF)-loaded exosomes derived from human neural stem cells were shown to improve neurologic function and reduce infarct volume in a rat model of ischemic stroke.[123] A neuroprotective strategy trialed poly(propylene sulfide) (PPS)–PEG nanoparticles, which were able to reduce neuroinflammatory markers in a mouse model of stroke by scavenging reactive oxygen species (ROS) and nitric oxide species.[124] In a rat ischemic stroke model, transcranial magnetic stimulation was combined with nasally delivered superparamagnetic iron oxide nanoparticles coated with PEG, chitosan and Tat peptide and was shown to enhance neural plasticity, recovery, and reduce ischemic volume.[125] This effect was hypothesized to be due to the neural stimulation *via* generation of electrical current in cell membrane-bound iron oxide nanoparticles due to the oscillating magnetic field. A rather complex system was trialed consisting of PLGA nanoparticles encapsulating the peptide NEP1–40 (a Nogo-66 receptor antagonist), chlorotoxin (a highly specific and high affinity peptide ligand for matrix metalloprotease 2 (MMP2), which is upregulated during ischemia), and lexiscan, a drug known to enhance BBB permeability. Nogo-66 is a receptor that inhibits axonal regeneration when activated by its ligand Nogo; blocking of this receptor encourages axonal regeneration. Intravenous delivery in a mouse stroke model demonstrated targeted delivery to the ischemic region in the brain, with reductions in infarct volume, improved neurological function and enhanced survival.[126] Another strategy utilized redox-active cerium oxide nanoparticles coated in PEG and the peptide Angiopep-2 (ANG). This peptide targets the low-density lipoprotein receptor-related protein, which is highly expressed on BBB endothelial cells. The neuroprotective antioxidant drug Edaravone was loaded within this PEG–ANG coating. This nanoparticle system demonstrated ability to cross the BBB after intravenous injection, a reduction in ischemic infarct volume in the brain and a reduction in ROS levels in the brain while retaining BBB function. However, no functional or cognitive tests were reported. *In vivo* experimental methodology was flawed (inappropriate clinical treatment timeline) and statistical reporting was also lacking.[127] Another study trialed chitosan–modafinil coated AuNPs, delivered daily by oral gavage, combined with injection of mesenchymal stem cells one week after induction of stroke. Results showed a decreased infarct volume and cell death combined with increased neurotrophic factor expression compared to control treatments.[128] A summary of the above-mentioned nanotherapies for stroke is given in Table 2.

Neurodegenerative diseases

Neurodegenerative diseases are a leading cause of disability and death worldwide, with increased prevalence due to increased life expectancy.[5] They are characterized by progressive degeneration of the CNS, which is represented by neuronal cell loss, neuroinflammation and microglia activation, oxidative stress, mitochondrial dysfunction, and abnormal protein aggregation and misfolding.[129] In this section, we discuss the following neurodegenerative diseases: Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), and prion disease, covering an overview of each disease, current therapies and their challenges/limitations, clinical trials,[130,131] and nanomedicine approaches for the particular disease.

Huntington's disease. Characterized by progressive motor dysfunction, cognitive decline, and psychiatric symptoms, HD is an incurable neurodegenerative disease resulting from CAG trinucleotide repeats in the huntingtin (HTT) gene.[132] These repeats encode for an abnormally long polyglutamine (polyQ) strand on the huntingtin protein, which has a propensity to aggregate, eventually leading to atrophy of the caudate

Table 2 Nanotherapies for stroke

Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
Liposomes decorated with GPIIb-IIIa and P-selectin binding peptides	Streptokinase	Jugular vein injection in mice resulted in platelet clot targeting, thrombolysis and enhanced streptokinase stability	Use of two different activated platelet-binding peptides caused reduction in systemic bleeding compared to free streptokinase	Thrombolytic evaluation methodology limited by short experimental window (15 minutes) and clinically unachievable treatment delivery (5 minutes after thrombus induction)	120
PEG nanogel	Urokinase	Intravenous injection in rats, pH-sensitive gel released urokinase near blood clots and decreased severity of ischemic stroke	PEG-urokinase protected BBB integrity and improved clinical score in acute injury phase compared to free urokinase	Long term prognosis of PEG-urokinase treatment not improved compared to free urokinase	121
Calcium MOF	microRNA-124	Stereotactic cerebral injection in mice induced neural stem cell differentiation, improved neurological function and reduced infarct volume	Treatment superior to controls in reduction of infarct volumes and improvements in neurological function	Highly invasive intervention. Testing only in male mice. Unclear if *in vivo* study was adequately powered ($n = 5$ per treatment group)	122
Exosomes from neural stem cells	BDNF	Stereotactic brain insertion in rats induced neural stem cell differentiation and reduced infarct volume	Treatments were given three days after induction of infarct and still showed significant improvement in neurological function and reduction in infarct volume	Highly invasive intervention. Full proteome of exosomes not investigated. Batch-to-batch variations in exosomes could be an issue	123
PPS–PEG	ROS/NO scavenger	Tail vein injection in mice reduced infarct volume, neuronal loss and neuroinflammation, and improved neurological function	Non-invasive intervention, good penetration into the infarct regions of brain. Treatments at clinically relevant timepoints (3 h post infarct) showed improved neurological function	Testing only conducted in male mice. Long term fate of NPs in brain unknown	124
Chitosan, PEG and TAT peptide coated Fe_3O_4 NPs	Transcranial magnetic stimulation	Intranasal delivery in rats combined with non-invasive magnetic neurostimulation resulted in stronger transcranial magnetic stimulation and improved functional outcomes compared to controls	Two non-invasive delivery strategies trialed showing BBB penetration and improvements in neurological function. Use of magnet to improve accumulation brain and transcranial stimulation to improve functional recovery. NPs almost fully cleared from brain in 30 days	Testing only conducted in male rats	125
Chlorotoxin peptide and PEG-coated PLGA NPs	Lexiscan and Nogo-66 receptor antagonist	Tail injection in mice, enhanced BBB permeability with lexiscan. Improved neurological function and survival after stroke	Non-invasive delivery, able to target the infarct area *via* chlorotoxin peptide. Non-invasive fluorescent imaging of NPs through skull *via* infra-red probes	Testing only conducted in male mice. Long term functional recovery (>10 days) not studied	126
PEG and Angiopep-2 coated nanoceria	Edaravone	Intravenous injection in rats enhanced crossing of BBB, reduced infarct volume and reduced BBB damage	Non-invasive delivery, treatment reduced ischemic volume in brain. No acute or long term (30 day) organ toxicity, NP clearance *via* feces	Poor statistical reporting: number of technical and biological repeats not reported. Number of rats per condition not disclosed for any *in vivo* experiments. Sex of rats not reported. No functional testing conducted. Flawed experimental methodology	127
Chitosan-coated AuNP	Modafinil and mesenchymal stem cells	Oral gavage in rats, combination with stem cell treatment reduced infarct volume, prevented neuronal apoptosis and improved behavioral score	Combination therapy superior to single treatments and control	Testing only conducted in male rats. No biodistribution testing. No confirmation of AuNP or stem cells inside brain	128

nucleus, putamen, and external segment of the globus pallidus (GPe).[133] Selective loss of the neurons in the GPe then leads to a decrease in inhibitory control of the motor cortex, resulting in the choreic movements (*i.e.*, involuntary muscle movements) and lack of motor control observed in HD,[133] leading to early death.

Current treatments & clinical trials. Current therapeutic strategies for HD are symptomatic, aiming to alleviate the motor and psychiatric symptoms of the disease. There are two drugs with formal indications for HD, Tetrabenazine and Deutetrabenazine, which have been shown to be effective for treating chorea and dystonia but display concerning adverse effects like parkinsonism and depression.[134,135] In addition, benzodiazepines and SSRIs see frequent usage in treating the psychiatric symptoms of HD, like depression, agitation, and anxiety.[132] Although these treatments are effective in temporarily alleviating symptoms, HD is a progressive disorder, and current available treatments do not stop or reverse the course of the disease. At the moment, there are no existing approved disease-modifying drugs for HD despite many clinical trials,[136] but research into treatments targeting HD pathology is rapidly progressing with the most promising strategies involving suppression of RNA targeting and suppression of mutant huntingtin (mHtt) aggregation.[137,138] Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are two potential treatment pathways, which both interfere with mHtt expression by targeting RNA. In one clinical trial (IONIS-HTT), Tominersen, a non-allele specific ASO, was observed to decrease mHtt expression and wild-type Htt expression following intrathecal administration.[139] However, the treatment requires intrathecal administration 6 times a year for the lifetime of the patient, which could lead to adverse effects in the long term like local infection, post lumbar puncture headaches, arachnoiditis, and radiculopathy.[140] Following a successful Phase I trial, a Phase III clinical trial for Tominersen was undertaken, but discontinued in 2021 due to an unfavorable risk/benefit profile, although a *post hoc* analysis suggested a benefit for younger patients. While mHtt levels were reduced, clinical symptoms were worse than placebo, which was hypothesized to be due to the treatment being outside of the therapeutic window.[141] A Phase II clinical trial is currently underway to determine dosing (NCT05686551). Two other clinical trials using allele-specific ASOs (WVE-120101, WVE-120102) were also discontinued in 2021 due to lack of efficacy in reducing mHtt levels (NCT03225833, NCT03225846). Since then, a third ASO (WVE-003) has completed a phase Ib/IIa clinical trial, with interim reports showing safety and ability to reduce mHtt levels.[142] The negative charge, large size, and high molecular weight of RNA result in low membrane permeability as well as poor ability to bypass the BBB in its naked form necessitate intrathecal delivery, limiting clinical applications and suggesting the need for a delivery vector to overcome these issues.[143] Some less conventional methods have also undergone clinical trials. A phase I clinical trial for treatment of Huntington's utilized human dental pulp stem cells (NestaCell HD) in 6 patients, delivering intravenously once a month for 3 months. No treatment-related serious adverse events were observed, and 5 of the 6 patients observed motor improvement.[144] At the time of writing (2025), phase II and phase III clinical trials for NestaCell HD for the treatment of Huntington's disease are in progress (NCT04219241, NCT06097780). An adeno-associated virus 5 (AAV5)-based gene therapy is currently undergoing a phase I/II trial, utilizing the AAV5 to induce expression of a microRNA which inhibits HTT expression. 10 participants were treated with this *via* 6 injections in the brain striatum. Interim results show good safety and tolerability, with mean mHTT levels in the CSF reduced by 53.8% compared to sham surgery control patients.[145]

Opportunities for nanotherapeutics. With the development of liposome-based RNA delivery methods during the COVID-19 epidemic, the precedent has been set for a liposomal delivery of ASO-based or siRNA-based HTT knockdown, especially with the development of multiple ASOs for Huntington's. With a suitable BBB targeting agent, this would remove the need for intrathecal delivery. Several pre-clinical studies have utilized a similar idea. A polymeric nanoparticle composed of glycosyl-PEG-PLL, targeting glucose-transporter 1 (GLUT-1), which is expressed on brain endothelial cells, was used to deliver ASOs across the BBB. These glucose-modified polymeric nanocarriers demonstrated rapid accumulation in brain tissue 1 hour after intravenous delivery, highlighting the potential for a more efficient and less invasive mode of delivery in treating HD.[146] A modified amphiphilic β-cyclodextrin nanoparticles carrying siRNAs produced sustained knockdown effects on mHtt, alleviated selective motor deficits in a mouse model and exhibited reduced cytotoxicity compared to Lipofectamine 2000, a commercially available cationic transfection reagent.[147] Delivered intranasally, chitosan-based nanoparticles encapsulating anti-Htt siRNA resulted in a greater decrease in mHtt expression compared to that of 'naked' siRNA, demonstrating the possibility for alternate, less invasive routes of administration using nanoparticles.[148] These results confirm that nanoparticles can act as versatile delivery vectors for RNA, capable of improving efficacy whilst retaining a positive safety profile.

As protein misfolding and aggregation are directly linked to neurotoxicity and atrophy, another therapeutic strategy centers around molecules that have been identified to bind to and either inhibit aggregation or dissociate formed protein aggregates.[149] Trehalose is a disaccharide known to have cell-protecting effects and is capable of alleviating polyglutamine aggregation in HD – but only at high doses.[150] Owing to this, poly(trehalose) nanoparticles composed of an iron oxide core and a zwitterionic polymer shell conjugated with trehalose were 1000–10 000 times more effective than their molecular counterparts due to more trehalose particles per nanoparticle binding to the protein, as well as greater endocytic uptake due to the presence of cationic and ionic groups interacting with the cell membrane.[149] Gold nanoparticles (AuNPs) conjugated with an amphiphilic polyglutamine binding peptide (JLD1) were further complexed with polyethyleneimine (PEI) for its

Table 3 Nanotherapeutics for Huntington's disease

Nanomaterial	Therapy	Result	Advantage	Limitation	Ref.
PLL-PEG-glycosyl polyion complex micelle	MALAT 1 ASO	Tail vein injection in mice resulted in targeting of GLUT-1 transporter protein for crossing BBB	Non-invasive delivery, use of well characterized GLUT-1 transporter and glycemic control to trigger BBB crossing	Clearance from brain not investigated. Only female mice used, not tested in disease model, distribution in other organs not tested (GLUT-1 is not exclusively expressed on BBB cells)	146
Cationic amphiphilic cyclodextrin	Knockdown of mHTT gene *via* siRNA	Direct injection into brain transiently improved mice motor function	Gene silencing was effective for a week compared to controls which showed no effect	Highly invasive delivery. Sex of mice not reported	147
Chitosan	Knockdown of mHTT gene *via* siRNA	Intranasal delivery in mice reduced HTT protein expression after 120 h	Non-invasive delivery, moderate interaction between chitosan and siRNA allows release of siRNA for silencing. Use of MRI compatible crosslinking agent	Only female mice used for testing. Functional testing not conducted	148
Poly(trehalose)-coated Fe_3O_4	Polytrehalose prevents mHTT protein aggregation	Intraperitoneal injection, reduced mHTT aggregates in mouse brains, reduced trehalose dosage to achieve effect	Non-invasive delivery, Fe_3O_4 can be imaged easily with MRI	Only female mice used for testing. Functional testing not conducted. NP treatment caused significant weight loss in mice. NP biodistribution in major organs, clearance routes and long-term retention in brain not tested	149
PEI-JLD1 peptide-coated AuNP	mHTT-binding peptide (JLD1)	JLD1 peptide dissociates mHTT amyloids, reduces toxicity, improves locomotion activity in *Drosophila* larva	Determined deca-glutamine sequence in JLD1 peptide responsible for amyloid dissociation and inhibition	Non-mammalian disease model. Treatment duration of larva not reported. Clearance of AuNP from larva brain not assessed	151

transfection properties, resulting in a complex with improved cell-penetrating ability and capable of binding to and preventing mHtt aggregation while also ameliorating cortical damage in Drosophila larvae.[151] A summary of nanotherapies for Huntington's disease is given in Table 3.

Alzheimer's disease. Dementia is caused by a variety of neurodegenerative conditions, affecting over 50 million people globally and this number is expected to triple by 2050.[152,153] Alzheimer's disease (AD) makes up 60–80% of these cases, making it the most common neurodegenerative disease globally.[2] Many of its symptoms are linked to the loss of cholinergic neurons in the basal forebrain. These neurons die due to the formation and accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs).[154–156] These processes are exacerbated by neuroinflammation and oxidative stress.[157,158] AD is infamous for causing memory deficits, often appearing subtle in the initial phases and growing more severe as the disease progresses. However, the specific memory deficits are highly heterogeneous among patients, and many other cognitive functions are also affected, including language, problem-solving, and multi-tasking. AD patients can also present with psychological symptoms such as delusions, hallucinations, depression, and anxiety.[159] 1–5% of cases fall under familial AD, which has an early onset (between 30–65 years old) and rapid progression. These cases are strongly linked with a well-defined collection of autosomal dominant genetic mutations affecting amyloid precursor protein (APP). However, 95–99% of cases are classified as sporadic AD, presenting later (after 65 years old) with more heterogenous pathologies.[156]

Current treatments & clinical trials. No singular neurobiological mechanism has been identified as the primary cause of AD. However, researchers have detailed a few contributing processes that offer promising therapeutic targets. It is worth noting the intimate connection between the legal and scientific pipeline of approval/translation in this case given that anti-amyloids are typically subject to Accelerated Approval, undergirded by the strength of the amyloid cascade hypothesis.[160] Following over 400 therapeutic trials for AD between 2002–2012 and no treatment breakthroughs,[161,162] the amyloid hypothesis came under serious scrutiny and controversy.[163–166] Since then, a number of breakthroughs have been made. To date, there are 65 trials listed for AD on ALZFORUM.[167] The most effective treatments implemented in the clinic are acetylcholinesterase inhibitors such as donepezil, rivastigmine and galantamine.[156,168–170] These drugs prolong otherwise limited endogenous cholinergic activity to provide relief from cognitive symptoms.[171] However, these treatments are not universally effective and can come with side effects.[156] The first of its kind, tacrine was in widespread use for approximately 20 years, particularly due to its efficacy at passing the BBB, prior to its discontinuation in 2013 due to concerns over liver toxicity.[172,173]

Another suggested mode of action to address cognitive decline in patients is through inhibition of Rho kinases.[174,175] While not FDA approved, the Rho kinase inhibitor Fasudil has been clinically approved in China and Japan to treat neurodegenerative memory loss.[176] Fascinatingly, Rho kinases have also been found to be a doubly relevant target for treatment of neurodegenerative diseases through their inhibition of alpha-synuclein aggregation, a key step of Parkinson's disease pathogenesis.[177] Nonsteroidal anti-inflammatory drugs (NSAIDs) have been considered for AD, however no clear benefit has been demonstrated.[178,179] These typically act by inhibiting cyclooxygenase (COX) activity, which is involved in inflammation through the synthesis of prostaglandins. A confounding variable in these studies is the widespread use of aspirin (itself an NSAID) amongst older populations.[180] A different treatment for early AD aims to target metabolic processes seemingly connected with the disease, namely, glucose metabolism. It has been suggested that oxidative stress and alterations in glucose metabolism are more ubiquitous in the onset of cognitive decline during AD than amyloid plaques.[181,182] These interactions can typically be observed in patients both undergoing treatment for AD and for diabetes. To this end, thiamine has been explored as a therapeutic, given its crucial importance in oxidative glucose metabolism in the brain.[183,184] Metabolism is not often considered in CNS conditions but could prove a generalizable therapeutic target.[185] Metabolic conditions have been known for decades to be connected to pathologies of the nervous system, such as Wernicke–Korsakoff syndrome and diabetic neuropathy.[186,187] For the latter, a prodrug of thiamine is already in use, namely, benfotiamine. Further investigation on the connection between glucose metabolism and neurodegenerative diseases includes clinical trials of FDA-approved anti-diabetes drugs such as intranasal insulin, semaglutide (Ozempic), metformin and pioglitazone, which have been found to be more effective than antiamyloids.[188–192] There is a phase III clinical trial ongoing (as of Feb 2025) for the effect of semaglutide on central and peripheral inflammation in patients with AD (NCT05891496). The arrival of newly FDA-approved disease-modifying therapies for AD, including the monoclonal antibodies targeting Aβ plaques, Aducanumab, donanemab and Lecanemab provided great hope for AD treatment. However, they do not stop or reverse the disease and are associated with severe side effects, such as brain swelling and bleeding (ARIA—amyloid-related imaging abnormalities).[193–195] Thus, the evidence for clinical benefit was marginal when weighed against evidence of side effects.[196] It is unclear as to whether the side effects are due to cross-reactivity with anticoagulant medications and current recommendations are to avoid anticoagulants.[197,198] It has been suggested for lecanemab that targeting amyloid "proto-fibrils" is key to clinical success in this mode of action, particularly given how amyloid oligomers are generally considered to be more problematic than plaques. There are also some potential NFT-targeting therapies, however, they are yet to be clinically approved.[199–202] Stem cell treatments also hold promise for treating disease progression through replacement of dead or damaged neurons. Several stem cell clinical trials for AD have taken place. Phase I trials for the intracerebroventricular (N = 9)[203] and stereotactic (N = 9)[204] injection of human umbilical cord stem cells for treatment of AD have been completed, showing safe and well tolerated injections with no serious adverse events. A phase I trial (N = 33) for the intravenous delivery of allogeneic mesenchymal stem cells (Lomecel-B) was also found to be safe with no treatment related adverse events or serious adverse events. Biomarker readings showed an anti-inflammatory, pro-vascular and pro-regenerative effect of Lomecel-B.[205] A Phase IIa double blinded, randomized, and placebo-controlled trial of Lomecel-B for AD (N = 49) showed a good safety and tolerability profile with no treatment related adverse events or death. Testing showed an improvement in cognitive function and a slowing of disease progression compared to placebo.[206] There are currently more clinical trials in progress for AD using different stem cell sources, such as umbilical cord allogeneic mesenchymal stem cells (NCT04040348) and autologous adipose derived stem cells (NCT05667649).

Opportunities for nanotherapeutics. Pre-clinical research into nanomedicines, on the other hand, has provided some promising results that may lead to better treatments for AD. Many of these treatments utilize organic and inorganic nanoparticles as nanocarriers for anti-AD drugs and other therapeutic agents. Solid lipid nanoparticles (SLNs) and liposomes are examples of an organic nanoparticle that has shown to be an effective cross-BBB transporter, improving the bioavailability of insoluble therapeutic agents delivered *via* the nasal route.[207–209] Other types of popular organic nanoparticles are PEG-coated polylactic acid (PLA) or poly(lactic-*co*-glycolic) acid (PLGA) nanoparticles. These have been used for encapsulation of small drugs[210] and functionalization with BBB-crossing peptides.[211] Other types of nanoparticles may have additional antioxidative and anti-inflammatory properties, as well as being nanocarriers. As such, these treatments may be able to affect multiple mechanisms contributing to AD. For example, gold nanoparticles (AuNPs) have shown promise as nanocarriers, allowing for effective transport across the BBB.[212,213] They have also demonstrated anti-inflammatory and antioxidant effects in animal models of AD, reducing both Aβ aggregation and tau phosphorylation (which contributes to NFT formation), along with improving cognitive function.[214,215] Superparamagnetic iron oxide nanoparticles (SPIONs) are similarly effective, as they can also act as nanocarriers[216] and inhibit oxidative stress.[217] Their magnetic properties also make them useful in developing new techniques for Aβ imaging using MRI, which would otherwise require more radiation-intensive PET scans.[218] Still, other approaches are yet more ambitious, such as antioxidative manganese dioxide nanoparticles (MDNPs) loaded with Aβ-inhibiting drugs being encapsulated in 4T1 breast cancer cell membranes to assist in transport to sites of neuroinflammation.[219,220] A summary of nanotherapies for Alzheimer's disease is given in Table 4.

Multiple sclerosis. MS is a prevalent chronic inflammatory, demyelinating, and neurodegenerative disease of the CNS in

Table 4 Nanotherapies for Alzheimer's disease

Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
Chitosan-coated solid lipid nanoparticles	Ferulic acid	Intranasal delivery in rats improved cognitive abilities compared to sham group	Non-invasive delivery, successful delivery of a poorly bioavailable therapeutic agent	Sex of rats not reported. Dosing schedule not reported. NP biodistribution in major organs not determined	207
Solid lipid nanoparticles	Memantine hydrochloride and tramiprosate	Intraperitoneal injection in rats enhanced spatial memory	NP-drug formulations showed longer retention times in blood and better delivery into the brain than controls	Sex of rats not reported. Aβ fibrillation studies showed poor efficacy of therapeutic drugs	208
GLP-R8 peptide coated DSPE liposome	Rivastigmine	Intranasal delivery in rats resulted in BBB crossing	Non-invasive delivery, intranasal delivery was superior to intravenous delivery	Only male rats were tested. Rapid clearance from brain (within 4 hours) – limited therapeutic window may require frequent dosing. Significant levels in kidney and spleen	209
PEG-PLGA	Pioglitazone	Oral delivery in male mice resulted in BBB crossing, reduced β-amyloid in brain and reduction in memory deficit	Oral administration	Only male mice tested. NP biodistribution not determined in major organs. No direct evidence of NPs in brain	210
B6 transferrin peptide and PEG-coated PLA	Neuroprotective peptide (NAPVSIPQ)	Tail vein injection in mice resulted in BBB crossing, reduction in learning impairment and hippocampal neuronal loss	Non-invasive delivery, delivery to the brain occurred within 30 minutes	Only male mice tested. NPs mostly cleared from the brain by 24 hours – limited therapeutic window may require frequent dosing	211
PEG-coated gold nanoparticles	Anthocyanins	Tail vein injection in mice was neuroprotective against memory deficits and reduced neurodegeneration markers	Non-invasive delivery. Simple extraction method of anthocyanins from a cheap and widely available source. Strong biomarker and functional evidence of efficacy	Only male mice tested. Missing NP-only controls. No direct evidence of NPs in brain. Anthocyanin type not characterized. NP biodistribution in major organs not determined	212
Gold nanoparticles	Aβ aggregation inhibitor coating (tungsten-based polyoxometalate and peptide LPFFD)	Intravenous delivery in mice was able to cross BBB, inhibited Aβ aggregation and cytotoxicity *in vitro*	Random distribution of male and female mice	Not tested in mouse disease model. Efficacy only tested *in vitro*	213
Gold nanoparticles	Anti-inflammatory and antioxidant	Intraperitoneal injection in rats decreased Tau phosphorylation and prevented cognitive decline	Non-invasive delivery, simple synthesis method and formulation	Only male rats tested. No NP physical characterization data shown. No direct evidence of NPs in brain. NP biodistribution in major organs not determined	214
Gold nanoparticles	D-glutathione	Intravenous injection in mice resulted in BBB crossing, rescue of memory impairment, improvement of spatial learning and decrease Aβ deposition in brains	Non-invasive delivery, simple synthesis method and formulation. Comprehensive biodistribution analysis	Only male mice tested	215
Superparamagnetic Fe_3O_4	Aβ oligomer-targeting antibody fragment and class A scavenger receptor peptide agonist (XD4)	Tail vein injection in mice reduced neuroinflammation and Aβ burden, increased aβ engulfment and rescued cognitive deficits	Non-invasive delivery. Able to induce Aβ clearing without increasing neuroinflammation	Only male mice tested. NP biodistribution and clearing rate from brain not determined. Fe_3O_4 imaging not conducted – early diagnostic properties not verified	216

Table 4 *(Contd.)*

Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
PEG-coated superparamagnetic Fe_3O_4	Bucladesine co-injection	Low dose intraperitoneal injection in rats improved spatial memory deficits and decreased neuronal oxidative damage	Non-invasive delivery. Dual therapy	Only male rats tested. No direct evidence of NPs in brain. Fe_3O_4 imaging not conducted – early diagnostic properties not verified. NP biodistribution in major organs and clearing rate from brain not determined	217
PLA–PVP–PEG-coated superparamagnetic Fe_3O_4	Curcumin	Intravenous injection in mice for imaging of Aβ plaques. BBB crossing and colocalization with Aβ plaque shown by combination of MRI and fluorescence microscopy	Non-invasive delivery. Clear demonstration of BBB crossing by MRI	Sex of mice not reported. NP biodistribution and clearing rate from brain claimed to be tested but no data shown. No functional testing conducted. Off-target curcumin binding not addressed	218
Cell membrane-coated hollow mesoporous manganese dioxide	Aβ inhibiting peptide (KLVFFC), D-amino acid inhibitor of Tau fibril formation (Dp), ROS scavenging	Intravenous injection in mice caused improvement of learning and memory deficits, inhibition of Aβ aggregation and Tau phosphorylation	Non-invasive delivery. No abnormal histopathological features in major organs	Only male mice tested. NP biodistribution levels in major organs and clearing rate from brain not determined. Cell membrane extract not characterized	219
Manganese dioxide nanoparticles	Aβ antibody and Terpolymer coating (PMMA, polysorbate 80, starch)	Intravenous injection in mice reduced neuroinflammation and hypoxia, and improved brain blood flow and cognitive function	Non-invasive delivery. Random distribution of male and female mice. Investigation of lymph clearance pathway	NP biodistribution levels in major organs and clearing rate from brain not determined	220

young adults, typically starting between the ages of 20 and 40, with a higher incidence in women,[221] and is associated with an increasingly high economic burden.[222] It is a complex, multifactorial, immune-mediated disorder influenced by genetic, environmental, epigenetic, and gene–gene or gene–environment interactions.[223] The clinical presentation and progression of MS vary widely. In the early stages, most patients experience reversible episodes of neurological deficits, known as relapses, typically lasting for days or weeks. This phase is characterized by relapsing-remitting MS (RRMS) in ~85% of patients. As the disease advances, permanent neurological deficits and increasing clinical disability emerge, leading to secondary progressive MS (SPMS). A smaller group of patients (~10–15% of patients) experiences a progressive course from the outset, referred to as primary progressive MS (PPMS).[221]

The primary pathological feature of MS is the formation of demyelinating lesions (focal plaques) in the spinal cord and brain white matter, often accompanied by neuro-axonal damage. Clinical and pre-clinical studies utilizing animal models of MS, such as the commonly used experimental autoimmune encephalomyelitis (EAE), demonstrated that the process of inflammatory demyelination is associated with a breakdown of the BBB, migration and activation of innate and adaptive leukocytes, and both direct and indirect effects of pro-inflammatory cytokines and chemokines produced by endothelial cells, resident immune and glial cells.[224] Although a phase of tissue repair spanning weeks to months occurs, over time, non-resolving inflammation and a failure of compensatory mechanisms like remyelination cause further inflammatory changes in CNS-resident cells (*e.g.*, astrocytes and microglia) and chronic tissue damage as well as neuronal remodelling.[221,225] This process is followed by oligodendrocyte loss, reactive gliosis, and neurodegeneration. Axon damage is already noticeable at early lesion stages, while neuronal loss may begin early but is more noticeable in CNS samples from MS patients with progressive disease.[225]

Current treatments & clinical trials. The treatment of MS includes disease-modifying therapies (DMTs), which aim to reduce inflammatory activity and its long-term clinical manifestations, relapse management, and symptomatic therapies that provide short-term relief from symptoms like fatigue and pain.[221] The DMTs alter the disease course by modulating or suppressing immune function, thus reducing relapse rates, brain lesions, and disability progression. Initial treatments, including interferons and glatiramer acetate, modestly reduced relapse frequency and became widely prescribed. Later, therapies blocking lymphocyte entry into the CNS by blocking adhesion (natalizumab) or trapping lymphocytes in primary lymphoid organs (the sphingosine-1-phosphate [S1P] receptor modulators fingolimod, siponimod, and ozanimod) demonstrated higher efficacy. Anti-inflammatories have been developed to treat MS.[226] Fumarates have been found to be

particularly effective,[227] while teriflunomide and its active metabolite, leflunomide reversibly inhibit pyrimidine synthesis and prevent T and B cell activation and proliferation.[228] Following recognition of the significant role of humoral immunity in MS, B-cell-depleting therapies like rituximab, ocrelizumab, and ofatumumab were developed. These treatments successfully reduce relapses, silent progression in RRMS, and disability progression in PPMS.[229] However, these treatments have significant limitations due to the variable disease course, side effects of DMTs such as increased immunosuppression and susceptibility to infections and malignancies, poor brain penetration of B cell-depleting antibodies, and limited efficacy, especially in patients with progressive MS, which remains an unmet need.[230] A unique challenge of treating MS is comorbidity with other inflammatory conditions.[226] Furthermore, they primarily target immune modulation without directly promoting remyelination or neuroprotection. There are limited human studies and clinical trials of nanotherapeutics in MS patients. For example, a study has shown that a six-month oral administration of nano-curcumin (curcumin encapsulated in nanomicelle) reduced mRNA expression levels of pro-inflammatory cytokines and transcriptional factors in blood samples of MS patients.[231] A phase II clinical trial was carried out to assess the efficacy and safety of CNM–Au8, an orally administered suspension of gold nanocrystals that provide energetic support to CNS cells, as a potential remyelinating treatment for vision-impairing MS lesions in RRMS patients with chronic vision impairment. Despite low participant numbers and early termination due to the COVID-19 pandemic, the study demonstrated safety and favorable energy support.[232] These nanotherapeutics offer promising treatment options for MS.

Opportunities for nanotherapeutics. Numerous *in vitro* and *in vivo* studies in animal models of MS and demyelination have employed various nanocarriers (*e.g.*, organic, inorganic, polymeric and metallic nanoparticles, solid lipid nanoparticles, dendrimers, micelles, liposomes, carbon nanotubes, and quantum dots), and demonstrated their effectiveness in modulating CNS immune responses and suppressing neuroinflammation, mediating neuroprotection, and tolerance induction.[230,233,234] For example, inflammation-targeting biomimetic nano-decoys designed to inhibit immune cell infiltration and deliver glucocorticoids directly to lesions were constructed by coating nanoparticles with neutrophil membranes, leveraging the inflammation-targeting properties of activated neutrophil membranes. They were localized to lesion sites, modulated the inflammatory microenvironment, neutralized cytokines, exhibited antioxidant capabilities, and protected against clinical symptoms of EAE.[235] A pharmaceutical-grade gold nanocrystal formulation (CNM–Au8), synthesized using an electrochemical method without any surface capping ligand, has been utilized as an intracellular catalyst for the conversion of NADH to NAD+ as a mechanism to balance mitochondrial energy homeostasis. This formulation has been tested in a phase II clinical trial for MS and Parkinson's disease,[232] showing an ability to cross the BBB and cause an increase in brain NAD+ levels with a good safety profile. However, due to low patient numbers, no significant clinical benefit was seen. Nano-sized gold clusters (GA, Au29SG27) can significantly alleviate clinical symptoms and prevent demyelination in the EAE mouse model by inhibiting differentiation of T helper (Th)1 and Th17 cells through JAK/STAT signaling, presenting a novel therapeutic approach with relatively low toxicity.[236] The neuroprotective effect of combining rosiglitazone and probiotic-loaded solid lipid nanoparticles in a rat model of MS was demonstrated by improved symptoms through modulation of cellular signaling pathways, surpassing the efficacy of rosiglitazone alone.[237] The potential of myelin-based nanovesicles (MyVes) for treating MS by inducing immune tolerance to myelin-derived antigens was demonstrated. MyVes, produced from bovine brain myelin *via* nanoprecipitation, were non-cytotoxic, hemocompatible, and non-inflammatory. MyVes were specifically taken up *in vitro* by microglial cells, promoting an anti-inflammatory phenotype. Biodistribution studies in rats demonstrated that MyVes can reach the brain *via* intranasal administration.[238] In peripheral blood mononuclear cells isolated from MS patients, MyVes administration induced the production of the anti-inflammatory cytokines IL-10 and IL-4, offering preliminary evidence of the potential of tolerogenic MyVes against MS.[238] A recent scoping review that analyzed 24 studies on nanoparticles for MS highlighted their use in enhancing demyelinating lesion identification and drug delivery, indicating short-term use is relatively safe, necessitating further research on long-term effects.[239] A non-exhaustive list of nanotherapies for MS is given in Table 5. Several more in-depth reviews on nanotherapies for MS are given by Rahiman *et al.*[233,234] and Panghal *et al.*[230]

Parkinson's disease. Parkinson's disease (PD) is a neurodegenerative condition that arises from a loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), reducing dopaminergic input to the striatum. Most patients are diagnosed following the development of motor symptoms, including bradykinesia (slow/halted movement), rigidity and resting tremor. However, non-motor symptoms, such as emotional dysfunction (*e.g.*, depression or anxiety), fatigue, sleep problems, pain, constipation and cognitive problems, may be present up to 10 years pre-diagnosis and persist throughout the disease progression.[240] Globally, 1500 in a million people live with PD, rising to 9300 in a million for those over 60, making it the second most prominent neurodegenerative disease in the world.[241] Ageing and some specific genetic mutations play a role in the development of PD, however, the incidence of PD has been on the rise largely due to environmental factors, such as exposure to pesticides and other forms of pollution.[242]

As with other neurodegenerative conditions, the pathogenesis of PD is complex, with many interconnected mechanisms interacting with one another. α-Synuclein (α-Syn) accumulation is a frequent biomarker of PD, which leads to the formation of Lewy bodies.[243] This accumulation is exacerbated by oxidative stress and ferroptosis, a process by which excess iron ions accumulate in neurons.[244] Additionally, neuroinflammation

Table 5 Nanotherapies for multiple sclerosis

Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
Nanocurcumin	Curcumin	Oral delivery in human clinical trial caused reduced expression of inflammatory markers and improvement in clinical symptoms	Curcumin is known to be a safe product	Missing details of nanocurcumin formulation and physical characterization. No reporting of side effects	231
Gold nanocrystals (CNM–Au8)	Catalytically active gold	Oral delivery in human clinical trial caused a higher NAD+/NADH ratio compared to baseline	No serious adverse events associated with therapy	Low number of participants (n = 13). Crude link between NAD+/NADH ratio and patient functional energy capacity	232
Tannic acid-Pluronic F-68-neutrophil membrane	Methylprednisolone	Intravenous injection in mice, reached lesion sites in brain, decreased expression of pro-inflammatory markers in T-cells, protected against clinical symptoms of EAE	Avoid phagocytosis by immune cells	Only female mice used. Neutrophil membrane profile not investigated	235
Gold nanocluster-glutathione	Inhibits T-cell differentiation *via* JAK binding	Intraperitoneal injection in mice reduced demyelination and inflammation in spinal cord, with functional recovery observed	Histopathology, hematological and blood biochemical indicators showed NPs to be safe. Both prophylactic and therapeutic administration shown to be effective	Only female mice used. Biodistribution shows most of NPs excreted through urine not used in the brain	236
Solid lipid nanoparticles	Rosiglitazone and probiotics	Oral and intraperitoneal delivery in mice, improved locomotor activity and neuromuscular coordination, reduce mTOR and STAT-3 expression	Random distribution of male and female mice. Demonstrated two viable non-invasive routes of administration	Biodistribution in organs not determined. Data for physical characterization of NPs not shown. No details of probiotic bacteria reported	237
Myelin nanovesicles (MyVes)	Promote anti-inflammatory effects	Intranasal delivery in rats, induced expression of anti-inflammatory cytokines IL-4 and IL-10	Rapid on-invasive intranasal delivery to the brain. Tropism for brain white matter	Only male rats used. Low number of rats per treatment group (n = 3). Insufficient proof that MyVes is non-immunogenic. Potential concerns about bovine prion disease. Mass spectrometry results of MyVes protein composition not shown. Clearance from the body in 4 hours – short time to have an effect	238

has been associated with these PD mechanisms through the activation of astrocytes and M1-like (pro-inflammatory) polarization of microglia, as well as *via* the infiltrating proinflammatory T helper cells.[245,246]

Current treatments & clinical trials. Presently, there are no disease-modifying therapies for PD. The most common drug for relieving motor symptoms is levodopa (L-Dopa). This precursor to dopamine readily crosses the BBB and is then converted to dopamine, supplementing the lost input from the SNc.[247] However, despite generally high efficacy, over time patients experience "wearing–off" or "on–off" fluctuations in motor and non-motor (psychiatric, autonomic and sensory) symptoms in response to their medication.[248] After five years of treatment, up to 75% of patients cease to have a positive, predictable response to L-Dopa.[249] Delivery of L-Dopa is generally combined with decarboxylase inhibitors or catechol *O*-methyl transferase inhibitors to provide stability to the molecule while it travels to the brain, without which its potency is greatly reduced.[250] It should also be noted that less direct options, such as a dopamine receptor agonist like ropinirole, can also be prescribed. These solutions can be elaborated on by a controlled release platform such as a L-Dopa/carbidopa intestinal gel, which was delivered by a percutaneous gastrojejunostomy tube and increased "On" time by 4.8 hours.[251] The other major symptomatic treatment for PD, often used in concert with L-Dopa, is deep brain stimulation (DBS). Intracranial electrodes are surgically implanted and deliver stimulation to certain brain regions depending on the stage of the disease and the symptoms of the individual.[252] DBS is highly effective in relieving motor symptoms and can help patients experience a more independent lifestyle, but requires ongoing management, as the progression of disease may

necessitate both surgical and medication adjustments.[253] There have been many clinical trials utilizing different types of stem cells or pre-differentiated dopaminergic neurons from stem cells for the treatment of PD to replace lost dopaminergic neurons, with many still ongoing. Search results from the NIH clinical trials database yield 48 clinical trials, with 20 active or recruiting, indicating a promising future for treatment.[116]

Opportunities for nanotherapeutics. Nanotherapeutics, with their potential to improve specificity and bioavailability, could provide improved outcomes for PD patients. Many approaches currently being developed use nanoparticles (which may be polymeric, organic or metallic) as carriers to improve the delivery and longevity of L-Dopa.[254–258] Other nanoparticles are conjugated to potentially neuroprotective agents that struggle to cross the BBB, such as ropinirole,[259,260] retinoic acid,[261] roflumilast,[262] and Ginkgolide B.[263] Niu *et al.* even used an iron oxide nanoparticle to deliver a gene therapy that limited α-Syn expression in both *in vitro* and *in vivo* models of PD.[264] Nanoparticles can also be engineered to utilize their inherent physical and chemical properties to target certain disease mechanisms, rather than simply acting as carriers for other therapeutic agents. AuNPs have been used for their antioxidant properties and ability to cross the BBB to reduce hallmarks of oxidative stress and relieve behavioral symptoms of PD in mouse models.[265] Another carbon-based nanoparticle design used deferoxamine (DFO)-integrated nanosheets combined with polydopamine and brain-targeting peptides to deliver DFO (an iron chelating agent) to cells affected by PD pathology and directly regulate their iron metabolism to reduce ferroptosis and oxidative stress.[266] Unique organic nanoparticles that mimic the specificity and activity of immune cells are also being developed. For example, Liu *et al.* designed a nanoparticle made from a curcumin liposome that mimicked the membrane of a natural killer (NK) cell. These biomimetic liposomes travel *via* meningeal lymphatic vessels to the affected dopaminergic cells and use the Toll-like receptor 4 (TLR4) on their surface to clear reactive oxygen species (ROS) and absorb excess α-Syn, reducing neuronal death and improving movement in affected mice.[267] A summary of nanotherapies for Parkinson's disease is given in Table 6.

Amyotrophic lateral sclerosis (ALS). ALS is a rare, progressive and invariably fatal CNS neurodegenerative disease, which presents clinically as upper and lower motor neuron dysfunction, leading to progressive weakening of skeletal muscles and eventual loss of movement, difficulty swallowing, speaking and breathing. Cognitive and behavioral changes can also occur, with loss of normal language and executive function. Rapid progression of disease leads to death from respiratory failure and death, with a mean survival of 3–5 years after onset of symptoms.[268] Clinical presentations of ALS are varied, with a range of survival times and include: limb-onset ALS, bulbar-onset ALS, primary lateral sclerosis with pure upper motor neuron involvement, and primary muscular atrophy with pure lower motor neuron involvement.[269] Generally, upper motor neuron disturbance leads to symptoms like spasticity and weakness, whereas lower motor neuron disturbance leads to fasciculations, wasting and weakness.[269] While the onset is typically focal, the disease quickly progresses and subsequently spreads to other regions, with respiratory failure being the primary mode of death for patients.[270] Early diagnosis is important but difficult, as symptoms are often mistaken for other diseases. There are familial and sporadic classifications, of which familial types make up 5–15% of cases.[271,272] More than 40 genes are associated with ALS,[273] the most common and penetrant of which are superoxide dismutase 1 (SOD1), Fused in Sarcoma (FUS), TAR DNA binding protein (TARDBP) and human chromosome 9 open reading frame 72 (C9orf72),[274] with some interesting familial genetic mutation patterns emerging from different ethnicities.[271] While mutations in different genes result in varying disease onset times, phenotypes and disease severities, the unifying pathological feature of ALS is insoluble protein aggregates arising from improper protein degradation,[273] as well as formation of Bunina bodies, which are oval-shaped intraneuronal eosinophilic inclusions that stain positive for cystatin C and transferrin.[275] The significance of these is unknown. Although much progress has been made in recent years, the pathophysiological mechanism of the disease is not completely understood. In general, there are four main mechanisms that contribute to the disease: protein aggregation/misfolding, prion-like mechanisms which accelerate protein aggregation, dysregulated autophagy and disrupted RNA metabolism. Neuroinflammation may also play a role.[276] All of these contribute to premature neuronal cell death.

Current treatments & clinical trials. There are no cures for ALS; treatment focuses on modifying disease and maximizing quality of life. Riluzole and edaravone are commonly used drugs for ALS treatment, however these extend survival by a few months and are only effective in some populations.[271] Riluzole, a sodium channel blocker, is selective for damaged neurons, which has the effect of accelerating glutamate uptake and clearance from synapses, preventing excitotoxicity, thus providing an overall effect of neuronal survival.[277] This same principle has also been translated into SCI treatment.[278] While riluzole is recognized to have neuroprotective properties, it failed clinical trials for Parkinson's and Huntington's disease,[279,280] but passed clinical trials for Alzheimer's treatment.[281] Edavorone, an antioxidant capable of reducing peroxyl radicals and peroxynitrite, has been shown to inhibit motor neuron death. Initially, it failed to demonstrate efficacy in a phase III trial for ALS, but was subsequently shown to be effective in a small subgroup of patients,[282,283] and received FDA approval, although it is not approved worldwide. Other therapeutic compounds have been investigated in clinical trials for ALS. A combination of two compounds, sodium phenylbutyrate and taurursodiol was shown to slow the rate of decline and extend survival time by a median of 6.5 months in a randomized, placebo-controlled phase II clinical trial,[284,285] and received regulatory approval. However, based on the results of a subsequent phase III trial, it was withdrawn from the market by the manufacturer in 2024.[286] A selective tyrosine kinase inhibitor for reduction of

Table 6 Nanotherapies for Parkinson's disease

Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
Zinc oxide nanoparticles	L-Dopa	Oral gavage delivery in mice, reduction in motor impairment, improvement in sensorimotor performance, prevent neuronal damage	Non-invasive delivery	Only used male rats. Lacking NP characterisations – NPs agglomerated, no hydrodynamic diameter measurements, L-Dopa dose per particle not quantified. No direct evidence of NPs in brain. No assessment if zinc oxide can be degraded for zinc ion use in neurons. Biodistribution in major organs not investigated	254
WGA-coated PLGA	L-Dopa	Intranasal delivery in mice, able to bypass BBB, improved locomotor and spontaneous activity	Non-invasive delivery	Only used male rats. Biodistribution in major organs and excretion routes not investigated. WGA has red blood cell agglutinating activity – potentially an issue if NPs can enter blood stream	255
Albumin-coated PLGA	Levodopa	Intraperitoneal injection, BBB crossing *via* albumin, improved motor function, neuroprotective of dopaminergic neurons	Albumin allows for avoidance of clearance by immune cells. Still able to cross BBB despite large size (~500 nm)	Only used male rats. Biodistribution in major organs and excretion routes not investigated. Bovine albumin used instead of rat albumin – possibility for faster clearance from blood. Images of brain slices not shown	256
Chitosan liposomes	Levodopa	Intragastric delivery in rats, significantly decreased abnormal involuntary movement	Positively charged chitosan good for uptake	Only used male rats. Biodistribution in major organs and excretion routes not investigated. Direct evidence of NPs in brain not shown. Physical characterization of NPs not reported	257
Poly(carboxybetaine) and B6 peptide-coated AuNP	Levodopa-quinone, curcumin	Intravenous injection in mice, enhance drug delivery to the brain with transferrin peptide (B6) and targeting dopamine transporter with mazindol, improve motor function, decrease α-syn	Able to track NPs by micro-CT. NPs shown to be cleared from brain. Excretion route by liver and feces	Only used male rats. Very complicated NP system	258
Polysorbate 80-coated chitosan nanoparticles	Ropinirole	Intravenous injection in rats, BBB crossing *via* surfactant coating	Coated particles able to reduce uptake into liver and increase concentration in blood	Sex of rats not reported. Reported NP hydrodynamic radius does not match SEM images. No functional testing. Disease model not used	259
PLGA microparticles	Ropinirole	Intraperitoneal injection, neuroprotective, improved behavioural and motor activity testing	Biodegradable particles	Only male rats used. No biodistribution or pharmacokinetic studies conducted. Very big particles (10–50 μm). Minimal particle characterization. No direct evidence of particles in the brain	260
Dextran-PEI nanoparticles	Retinoic acid	Stereotaxic injection in mice, neuroprotective, enhances neurogenesis, induce expression of neuronal specification and survival markers	Controlled release and improved stability of RA	Only used male rats. Highly invasive delivery. No functional testing, no biodistribution studies. Data for retinoic acid-only control not shown	261

Table 6 *(Contd.)*

Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
Tween 80 and Pluronic 127-coated oleic acid/glycerol monostearate lipid nanoparticles	Roflumilast	Oral administration in rats, attenuated oxidative stress in brain, improved behavioural parameters and dopamine levels in striatum	No morphological signs of toxicity. Equivalent to L-Dopa in changes in behavioral parameters	Only used female rats. No direct evidence of NPs in brain. No biodistribution studies conducted	262
Pluronic F68-coated PEG-PCL	Ginkgolide B	Oral administration in rats and mice, neuroprotective by motor skills assessment and dopamine levels in brain	No organ toxicity observed by histological analysis. Increased systemic circulation time and transport into the brain. Equivalent to selegilin (clinical) treatment in functional testing	Only male rats and mice used. Accumulates in the eyes in a zebrafish model	263
Oleic acid and NGF-coated Fe_3O_4	α-Syn RNAi	Intraperitoneal injection in mice, BBB crossing, improved motor activity, reduction in α-syn expression	No organ toxicity observed by histological analysis. Major clearance organ determined to be the spleen	Only male mice used. Complicated nanoparticle system	264
AuNPs	Intrinsic antioxidant	Intraperitoneal injection in mice, improved motor activity, improved antioxidant activity in brain	Some evidence of ability to prevent brain damage	Only male mice used. Stated nanoparticle size not supported by TEM images. No direct evidence of NPs in brain. No biodistribution studies conducted	265
Polydopamine-coated black phosphorus nanosheet	Deferoxamine, brain targeting peptide RVG29	Intravenous injection in mice, BBB crossing, rescue functional motor impairments, reduce ferroptosis in brain	Comprehensive testing. No organ toxicity observed by histological analysis.	Only male mice used. Only relevant for Parkinson's cases where ferroptosis is the major causative agent	266
Natural killer cell membrane-coated liposome	Curcumin	Subcutaneous injection in mice, improved motor function and behavioural parameters, prevented dopaminergic neuron loss, reduced α-syn expression	Targeting of meningeal lymphatic system for delivery. No organ toxicity observed by histological analysis	Only female mice used. Protein composition of cell membrane not determined	267

neuroinflammation, masitinib (in combination with riluzole), also successfully completed a double blinded placebo-controlled phase 2/3 clinical trial and showed a 27% reduction in the rate of functional decline,[287] with a follow up phase 3 clinical trial currently recruiting (NCT03127267, March 2025). Another clinical trial found that ultra-high doses of methylcobalamin (activated vitamin B12) could slow functional decline in patients who were diagnosed and treated early (≤12 months after symptom onset).[288] Antisense oligonucleotides for SOD1 (toferson), which prevent the synthesis of mutated superoxide dismutase 1 (SOD1) protein, has been proven to be safe, reduce ALS biomarkers and slow disease progression in several clinical trials for SOD1-ALS,[289–292] and was given FDA approval in 2023. Two antisense oligonucleotides (BIIB078 and WVE-004) targeting the C9orf72 gene were trialed in phase 1/2 clinical trials, and while they were deemed safe and well tolerated with a reduction in disease-related biomarkers, no clinical benefit was observed in either trial. As a result, both were discontinued,[293] indicating a need to re-evaluate the pathogenesis of C9orf72-mediated ALS. Another antisense oligonucleotide against calpain-2, a protease associated with neuronal death, is under phase I clinical trials (NCT06665165). A catalytically active gold nanocrystal formulation (CNM-Au8) underwent a phase II, randomized, double-blind, placebo-controlled trial as a disease-modifying treatment for ALS. Delivered orally, it was shown to be safe and well tolerated. The treatment did not show any significant functional improvements, although an analysis of long-term survival showed ~60% reduction in all-cause mortality over 12 months of follow-up[294] and is now undergoing further investigation in an expanded access protocol (NCT05281484). H-151 is a novel (unapproved) inhibitor of the cyclic GMP-AMP synthase (cGAS)/Stimulator of Interferon Genes (STING) pathway, which acts by targeting the pro-inflammatory pathway activated by TDP-43.[295] This novel treatment has been observed to ameliorate neurodegeneration both *in vivo* and *in vitro*.[295] However, frequent high dose intraperitoneal injections were necessitated *in vivo* due to the fast clearance of the molecule from circulation, limiting translatability. Furthermore, the importance of the cGAS/STING pathway in fighting infection suggests that high dose systemic administration of inhibitors may leave patients vulnerable to infection.[296] However, the search for cGAS/STING inhibitors is ongoing, as the role of this pathway in inflammatory and auto-

immune diseases becomes clearer.[297] A comprehensive systematic review of clinical trials in ALS (published 2021) is provided by Wong *et al.* (2021).[298] An interesting finding from clinical trials is that the use of more specific patient inclusion and exclusion criteria has allowed detection of efficacy signals in sample populations smaller than previously used, although care must be taken in the generalizability of these studies.[299] Various stem cell sources have also been trialed as a treatment in many centers around the world, with phase I trials showing good safety profiles and promising clinical benefits.[300–302] A phase II clinical trial using mesenchymal stem cells induced to secrete neurotrophic factors showed an increase in neurotrophic factors and a decrease in inflammatory biomarkers in the CSF but failed to show clinical significance. In a subgroup analysis, some efficacy was seen in patients identified with rapid disease progression.[303] A subsequent phase III trial focusing on this subgroup (NCT03280056) failed to show clinically significant improvements and did not receive FDA approval. A new novel approach utilized exosomes from human umbilical cord blood mesenchymal stem cells delivered *via* nasal drops and is currently under a randomized, double blinded, placebo-controlled, dose-escalation phase I/II clinical trial (NCT06598202). Overall, treatments for ALS currently face issues stemming from off-target adverse effects and poor BBB penetration, highlighting a role for nano-formulations.

Opportunities for nanotherapeutics in ALS. Nano-formulations address issues with more targeted treatments, which allow for higher effective doses, reduce off-target effects and improve penetration of the BBB. Brain-targeted solid lipid nanoparticles (SLNs) based on glyceryl dibehenate containing Riluzole exhibited a higher brain tissue concentration compared to the free drug and a reduction in drug concentration in bloodstream and other organs.[304] These results demonstrate how nano-formulations allow for improved BBB penetration and fewer off-target effects due to reduced systemic concentration. A different study explored the use of a liposome carrier modified with polyethylene glycol (PEG) for co-delivery of Riluzole and Verapamil, the latter inhibiting efflux transporters on the BBB and thus increasing the concentration of Riluzole in brain tissue. The study observed improved uptake of Riluzole, suggesting possibilities for overcoming pharmacoresistance *via* cocktail liposomes.[305] The potential of calcium phosphate (CaP)-lipid nanoparticles as a drug carrier for Tofersen has also been demonstrated in a study which observed an 8× reduction in SOD1 levels compared with the free SOD1 ASO *in vitro*, and demonstrated accumulation around neurons and brain ventricles following direct spinal cord and brain microinjections in zebrafish larvae.[306] As ASOs cannot efficiently cross the BBB, necessitating intrathecal injection, nanoparticles offer possibilities for safer and less invasive routes of administration. To address this, MRI-guided focused ultrasound with microbubbles was used to transiently permeabilize the BBB, at the same time treating mice with these same Tofersen-loaded CaP-lipid nanoparticles. This treatment showed a reduction in SOD1 expression in the brain regions surrounding the focused ultrasound was applied, as well as higher motor neuron counts in the spinal cord as compared to control mice.[307] STING-pathway inhibiting nanoparticles (SPINs) encapsulated with PLGA have also been shown to effectively reduce expression of inflammatory M1 (pro-inflammatory) macrophage markers.[296] The properties of SPINs offer a pathway towards translation by overcoming the need for frequent, high dose systemic administration with off-target effects *via* targeted delivery and sustained release. Retinoic acid signaling has been implicated in neuroprotection against neuronal damage and ALS, however retinoic acid analogues are poorly soluble and rapidly cleared from the blood.[308] By encapsulating Adapalene (a retinoic acid receptor β agonist) in PEG-PLA nanoparticles, it was demonstrated in a mouse SOD-ALS model that intravenously-injected nanoparticles could effectively deliver Adapalene to the brain, activate retinoid signaling and provide neuroprotection and anti-neuroinflammation, significantly increasing the motor function and lifespan of mice.[309] A summary of nanotherapies for ALS is given in Table 7.

Prion diseases. Prion diseases are a group of rare, untreatable neurodegenerative conditions caused by misfolded and aggregated proteins called prions, which possess a distinctive infectious ability.[310] While the incubation period can last for years, the clinical phase usually progresses quickly over weeks to months and is characterized by behavioral changes, motor dysfunction, cognitive decline, and ataxia[311] with an average survival duration of approximately 5 months.[312] Prion diseases affect a wide variety of hosts, including scrapie in ovines, bovine spongiform encephalopathy in bovines, chronic wasting disease in cervids, as well as several human prion diseases. In humans, prion diseases are classified by clinical symptoms and neuropathological features as sporadic, genetic, or acquired.[311] Sporadic cases (~85%) include sporadic Creutzfeldt–Jakob disease (sCJD), hypothesized to result from somatic mutations. Genetic prion diseases, including familial CJD (fCJD), fatal familial insomnia (FFI), and Gerstmann–Sträussler–Scheinker (GSS) disease, are linked to autosomal dominant mutations in the prion gene, *PRNP*, and typically manifest in the 5th or 6th decade of life. Acquired prion diseases, such as kuru and variant CJD (vCJD), result from transmission *via* contaminated grafts, blood transfusions, human growth hormone, prion-contaminated medical instruments, or eating infected beef.[313] Among these forms, CJD is the most prevalent, occurring at a global annual rate of 1–2 cases per million people.[314]

Prion disease is caused by a pathogenic neurotoxic protein, PrP^{Sc}, a misfolded, aggregated form of the cellular prion protein (PrP^{C}). It induces misfolding of the host PrP^{C} in a self-propagating process, resulting in exponential accumulation of PrP^{Sc} in the brain and spinal cord. This ultimately leads to widespread spongiform degeneration and neuronal loss, accompanied by activation of CNS glial cells.[311] At present, there is no efficacious treatment for prion diseases despite considerable research endeavors in this domain. Indeed, research has shown that all anti-infectious agents (viral, bac-

Table 7 Nanotherapies for ALS

Nanomaterial	Therapy	Results	Advantages	Limitations	Ref.
CNM-Au8 gold nanocrystals	Catalytically active gold	Phase II clinical trial in humans was shown to be safe but did not reach primary or secondary endpoints. Reduction in disease progression and all-cause mortality seen in long term follow up	Safe and well tolerated in humans. Long term follow up (120 weeks)	Low patient numbers (n = 23)	294
Solid lipid nanoparticles	Riluzole	Intraperitoneal injection in rats, improved delivery to the brain	NPs delivered to the brain in less than 8 hours.	Only male mice used. NPs cleared from the brain within 16 hours. Low number of rats per treatment group (n = 4)	304
PEG-Liposomes	Riluzole and verapamil	*In vitro* treatment of brain endothelial cells, increased uptake of riluzole	Liposomes stable after 3 months	*In vitro* experiment only	305
Calcium phosphate lipid nanoparticles	SOD1 antisense oligonucleotide	*In vitro* treatment of motor neuron cells, SOD1 knockdown. Accumulation in spinal cord and brain after injection in spinal cord and brain of zebrafish.	NPs stable for at least 20 days	*In vitro* experiment only	306
Calcium phosphate lipid nanoparticles	SOD1 antisense oligonucleotide	Tail vein injection in mice, MRI-guided focused ultrasound with microbubble contrast agents for safe transient BBB opening	Non-invasive delivery, optimized parameters for safe, reversible, transient BBB opening	Only female mice used. No functional studies conducted	307
PLGA	RU.521 and H-151	*In vitro* treatment of murine macrophages, reduction in expression of inflammatory markers	Biodegradable NPs. Convenient macrophage and monocyte cell models with luciferase reporter for IFN-I production	*In vitro* experiment only	296
PEG-PLA	Adapalene	Tail vein injection in mice, lifespan increased and reduction in motor impairment	No signs of NP toxicity in mice. Non-invasive delivery	Only female mice used	309

terial, fungal, and parasitic) are ineffective in modifying the course of prion diseases.[315–317] Although there are emerging technologies for the treatment of prion diseases, such as immunotherapy, gene therapy, drugs for targeted protein degradation, and stem cell therapies,[314] these diseases present several challenges, including unique disease mechanisms of prion protein misfolding and PrP^{Sc} accumulation, prion resistance to proteases, heat and decontamination methods,[318] and drug delivery across the BBB.

Opportunities for nanotherapeutics. Experimental research on nanotherapeutics in prion disease has explored various approaches utilizing nanoparticles to target prion protein misfolding and aggregation, and drug-loaded nanocarriers that cross the BBB. A recent study using mice with prion disease demonstrated that Nanoligomers™ targeting a combination of the NLRP3 inflammasome protein and nuclear factor kappa-B (NFκB) transcription factor protected neurons, reduced glial neuroinflammation and spongiotic change in prion-diseased brains, decreased behavioral and cognitive deficits, and significantly increased life span of treated mice by inhibiting neuroinflammatory pathways.[319] An *in vitro* study showed that carbon nanoparticles, including graphene and carbon nanotubes, can inhibit the fibril formation of prion proteins, highlighting their potential effects on reducing the deposition of pathological PrP^{Sc}.[320] In addition, dendrimers have shown the ability to eliminate protease-resistant PrP^{Sc} in cell culture and in prion-infected brain homogenates in a dose- and time-dependent manner. Specific dendrimers, such as maltose poly (propyleneimine) generation five (mPPIg5), can inhibit the intracellular conversion of PrP^{C} to PrP^{Sc} and alter the conformation of misfolded PrP, enhancing their anti-prion activity *in vitro*.[321] A novel approach to decrease the expression of PrP^{C}, which serves as a substrate for prion replication, was developed using liposome-siRNA-peptide complexes (LSPCs) that effectively cross the BBB to deliver the siRNA. Studies have shown that LSPCs suppressed PrP^{C} expression and eliminated protease-resistant isoforms of PrP^{C} in infected cell cultures. Intravenous injection of LSPCs in mice was able to cross the BBB and deliver the siRNA specifically to PrP^{C}-expressing neurons.[322] Further studies have shown that this approach reduced PrP^{C} expression and subsequent prion replication in the brain, consequently extending survival and improving behavior in prion-infected mice.[323] Gold nanoparticles coated with oppositely charged polyelectrolytes (*e.g.*, polyallylamine hydrochloride and polystyrene sulfonate) were able to interact and reduce the accumulation of PrP^{Sc} in scrapie prion-infected

Table 8 Nanotherapies for prion diseases

Nanomaterial	Therapy	Results	Advantages	Limitations	Ref.
Peptide-nucleic acid coated gold nanoparticle (Nanoligomer)	Synthetic DNA analogues for downregulation of NF-κB and NLRP3	Intraperitoneal and intranasal injection in mice, neuroprotective, rescue of cognitive defects and prolong lifespan in prion-infected mice	Equal number of male and female mice used.	No biodistribution or pharmacokinetic studies conducted	325
Single wall carbon nanotube + graphene	Inhibit prion fibril formation	*In vitro* tests show that π–π stacking inhibits β-sheet formation	Contribution to a mechanistic understanding of prion protein misfolding inhibition by carbon NPs	*In vitro* experiments only	320
Maltose poly (propyleneimine) dendrimer	Inhibit conversion of PrP^{C} to PrP^{Sc} Denaturation of PrP^{Sc}, allowing proteolysis	*In vitro* tests show that a high density of reactive groups destabilize PrP^{Sc}	Contribution to mechanistic understanding of PrP^{Sc} destabilization	*In vitro* experiments only	326
RVG-9r peptide coated liposome	siRNA-peptide for delivery to neurons and knockdown of PrP^{C}	*In vitro*, PrP^{C} expression suppressed. In mice, intravenously delivered siRNA-peptide was delivered to brain and PrP^{C} staining was reduced. Survival was prolonged and cognitive decline was slowed	Both male and female mice used in testing. Limited dosage can still prolong survival and slow cognitive decline. Retention in the brain for at least 10 days, knockdown effective for up to 21 days	Repeated delivery (more than 3 treatments) can generate RVG-9r antibodies which renders treatment ineffective and cause extensive immune activation and death	322 and 323
Polyelectrolyte-coated AuNPs	Delays prion fibril formation	Injection in the brain caused an increased survival time in mice compared to untreated controls	Delayed onset of symptoms compared to untreated control	Sex of mice not reported. Limited applicability of disease model (co-injection of NPs with prion template)	324

cells. Furthermore, treatment with such gold nanoparticles was able to delay the incubation period of prion-infected mice as compared to untreated controls.[324] Thus, these nanotherapeutics that selectively target prion protein misfolding and accumulation and can cross the BBB have an exciting prospect for the treatment of prion diseases. A summary of nanotherapies for prion diseases is given in Table 8.

Infectious disease and the CNS

There is a wide range of organisms that can cause neurological damage in humans. Broadly speaking, this damage can be caused directly by the microorganism or *via* the reaction of the immune system towards these microorganisms, which can be highly damaging to the nervous system, usually through sepsis responses or development of autoimmune responses following contact or infection. An example of indirect damage is the development of an allergy towards red meat (alpha-gal syndrome) after being bitten by the tick *Amblyomma americanum* (although not strictly speaking a microorganism).[327] Lyme disease is caused by bacteria of the *Borrelia* family found in the saliva of ticks, which, if untreated, can infect nerves and cause nerve-related symptoms such as atrioventricular nodal block, meningitis, and paralysis.[328] Another example is bacterial sepsis, a dysregulated systemic immunoinflammatory response to infection which can cause widespread organ damage, CNS damage and death. CNS damage caused by sepsis includes sepsis-associated encephalopathy, BBB damage and neuroinflammation, which leads to cognitive impairment.[329] Focal bacterial infection of the brain (brain abscess) is possible through infection of the inner ear, the sinuses, neurosurgery, TBI or *via* the blood. Some bacteria (*e.g.*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*) can cross the BBB and BSCB and are common causative agents of bacterial meningitis.[330] Fungal infections in the brain are possible in immunosuppressed patients. Direct damage to the nervous system can be caused by bacterial toxins. Some examples of this include the botulinum toxin family, tetanus, Shiga, and cholera toxin. These toxins generally consist of a binding component and an active catalytic component, which causes the main symptoms of the toxin.[331–333] The binding components of these toxins bestow neural tracing properties to the toxins. Viruses able to infect the nervous system (known as neurotropic viruses) include well known examples such as Herpes simplex viruses, human immune-deficiency virus (HIV), rabies virus, Zika and COVID-19.[334] These typically gain entry to nerves by binding to cell surface glycoproteins. There is a moderate level of evidence for an association between infectious diseases and Alzheimer's disease, particularly neurotropic viruses[335] and periodontal bacteria, either by direct infection or inflammation. Some evidence for this is the discovery that Aβ amyloid plaques, the causative agent for Alzheimer's disease,

possess antibacterial properties,[336] and that periodontal bacteria have been detected in post-mortem examination of the brains of Alzheimer's patients,[337] however direct causation has not been confirmed.[338]

Current treatments/clinical trials. Treatment for infectious diseases typically falls under the category of antibiotics and anti-viral drugs, as well as anti-inflammatory drugs to alleviate symptoms. Treatment for sepsis also includes antibiotics and administration of intravenous fluids. Vaccines and neutralizing antibodies are available for many infectious diseases. These treatments have been some of the most successful examples of modern medicinal chemistry and pharmacology, to the point where previously incurable, debilitating, pandemic-level diseases are easily treatable or avoidable (*e.g.*, bubonic plague, cholera, smallpox, polio). However, the rise of antimicrobial resistance, combined with the reduced number of antimicrobial compounds in the development pipeline, presents a serious challenge for healthcare worldwide, with the World Health Organization dubbing this age the "post-antibiotic era", where easily treatable infections once again present a serious threat.[339] Between 2001–2010, AstraZeneca undertook 65 high throughput screens of bacterial targets against their compound library, finding 19 leads.[340] Similarly, between 1995–2001 GlaxoSmithKline undertook 70 high throughput screens of bacterial targets against their compound library, consisting of between 260 000–530 000 compounds, with only 5 lead compounds discovered, at a cost of $1 000 000 USD per screen.[341] In the face of competitive commercial pressures and better returns on investment in other disease areas (based on commercial forecasting), many pharmaceutical companies have ended their antibacterial drug discovery programs, opting instead to generate derivatives of antibiotics for which resistance already exists.[341] As such, interest has turned to other classes of antimicrobials such as antimicrobial peptides (AMPs) and bacteriophages, which were discovered at a similar time to antibiotics, but have been generally underutilized due to the (past) effectiveness of antibiotics and their comparative ease of synthesis and purification. Antimicrobial peptides are generally short, positively charged tryptophan and arginine-rich[342] amino acid sequences (8–50 amino acids) that are found in many organisms (although many synthetic AMPs also exist). Generally, their mechanism of action has been suggested to consist of either non-specific membrane interactions, resulting in pore or micelle formation and ultimately membrane disruption,[342] or direct inhibition of intracellular structures.[343] Their non-specific activity is effective against a wide range of microorganisms, including multi drug-resistant bacterial strains. Currently several are approved for clinical use as alternatives to antibiotics, including nisin, gramicidin, polymyxins, daptomycin and melittin.[344] A database of AMPs (https://dbaasp.org/home) has been collated with detailed information on structural and cytotoxic activity against tested microorganisms,[345] with over 22 000 AMPs banked to date, which will prove useful for future nanotherapeutic applications. Bacteriophages (phages) are a diverse family of viruses that selectively infect bacteria, with many having bactericidal effects only against specific bacteria. For this reason, the majority of phage treatments consist of multiple types of phages, which are selected and customized based on efficacy against bacterial samples taken from patients. They can be broadly classified as lytic (intra-bacterial reproduction of phage leads to bacterial lysis) or lysogenic (phage genome is incorporated into host genome, which leads to phage reproduction and bacterial lysis under optimal conditions). Lysogenic phages pose greater risks due to their ability to transfer genes to bacteria, so most phage therapies consist of lytic phages. First discovered in the early 1900s,[346] interest surged again with the first successful clinical use of intravenous phage therapy in 2017 for the treatment of a multidrug-resistant infection, consisting of a customized cocktail of 8 phages.[347] Since then, phage therapy has been given approval by the FDA for expanded access or compassionate use,[348] although these do not form part of clinical studies and no specific phage products have been approved yet. Interestingly, phages have been shown to inhabit the CNS in the CSF of healthy humans, an area traditionally thought to be sterile,[349] which may suggest they are able to cross the BSCB. While there is a wide range of clinical trials utilizing AMPs and phages for a variety of conditions, we were unable to find any clinical trials utilizing either of these for meningitis or bacterial infections of the brain.

Opportunities for nanotherapeutics. Nanotherapeutic opportunities for infectious disease include drug or vaccine delivery systems and the exploitation of high surface-area-to-volume ratio properties for drug or antibacterial delivery. These have been widely published and reviewed.[350–352] Better success is likely to be found with poorly soluble drugs and those excluded by the BBB/BSCB. Arguably, the most successful nanotherapeutic to date is the Moderna liposomal COVID-19 mRNA vaccine.[353] The success of liposomal RNA delivery has given birth to a dearth of liposomal formulations,[354] with conceivably any RNA able to be packaged within. Indeed, several clinical trials have already taken place using liposomal mRNA-based vaccines for other CNS-related infectious diseases such as rabies virus,[355] zika virus (clinical trial NCT04917861[356]), and cytomegalovirus.[357] For treatment of brain infections, some novel strategies have been employed. For example, PEG–PLGA-based nanoparticles were functionalized with bacitracin A, RVG_{29}, and Pluronic 85 for the treatment of Pneumococcal meningitis. Bacitracin A (BA) is a potent cyclic AMP; RVG_{29} is a peptide derived from the rabies virus glycoprotein known to bind nicotinic acetylcholine receptors on neuronal cells; and Pluronic 85 is known to inhibit the drug efflux pump P-glycoprotein, found on the outward-facing endothelial cells of the BBB. In a mouse model of meningitis, these RVG29–Nano-BA_{P85} nanoparticles were delivered by tail vein injection and shown to bypass the BBB, accumulate in the brain and eliminate bacteria in the brain, with all treated mice surviving 14 days and limited kidney toxicity.[358] Another study utilized amphotericin-encapsulated PEG–PLA micelles functionalized with an anti-transferrin receptor antibody (OX26) for the treatment of a mouse model of intracranial fungal infec-

tion with *Candida glabrata*. Amphotericin is a broad-spectrum antifungal with poor solubility and efficacy. Transferrin receptors are an abundant transcyctotic receptor found on BBB endothelial cells. By targeting the BBB with the OX26 antibody, these nanoparticles were shown to deliver amphotericin into the brain and prevent death from fungal infection, while no liver or kidney toxicity was observed.[359] Given the main issues with bacterial infections are the high adaptability of bacteria to antimicrobial selection pressure and resilience of biofilms, nanotherapeutic compounds should be multifunctional and/or be able to penetrate biofilms. Metal and metal oxide nanoparticles are well known highly potent antibacterial agents,[360] particularly silver,[361] although zinc,[362] copper[363] and gold-based[364] nanoparticles have also been reported, with non-specific mechanisms of action such as reactivity with phosphorus or sulfur-containing molecules (*e.g.*, proteins and nucleic acids) and disruption of ROS balance. One of the important aspects of metal-based antibacterial agents is that due to the fast-acting and non-specific mechanism of action, microbes cannot generate resistance to them. This is especially useful in contexts where elimination of bacterial sources is not possible, such as catheters and dental applications. Nanoparticles also have the potential in treatment of sepsis. Lipid coated calcium phosphate nanoparticles loaded with nicotinamide adenine dinucleotide (NAD^+) were reported to protect mice from LPS-induced sepsis by reducing production of pro-inflammatory cytokines, with 100% of treated mice surviving the septic challenge compared to untreated mice which

Table 9 Nanotherapies for infectious diseases

Disease	Nanomaterial	Therapy	Result	Advantages	Limitations	Ref.
Rabies virus	Lipid nanoparticle CV7202	Rabies virus glycoprotein mRNA vaccine	Two doses of 1–2 μg in humans were safe and resulted in neutralizing titers of antibodies equivalent to current vaccine	Only two doses needed instead of three with the current vaccine	Slightly more moderate adverse events than current vaccine. Current vaccine elicits a faster generation of neutralizing antibody titers	355
Zika virus	Lipid nanoparticle	Pre-membrane and envelope structural protein mRNA vaccines	Two doses of vaccine in humans were safe and generated strong neutralizing antibody responses up to 1 year after vaccination	Shown to be safe and effective – there is no currently approved Zika vaccine	Low ethnic diversity in participants. Congenital Zika syndrome unable to be tested. Unknown cross reactivity with dengue	356
Cytomegalovirus (CMV)	Lipid nanoparticle	CMV glycoprotein B and pentamer mRNA vaccine	Three doses of vaccine in humans were safe and resulted in high neutralizing antibody titers effective against 14 CMV strains up to 1 year after vaccination	Shown to be safe and effective – there is no currently approved CMV vaccine	Low ethnic diversity in participants	357 and 370
Pneumococcal meningitis	PEG, pluronic P85 and RVG29 peptide coated PLGA	Bacitracin A	Tail vein injection in mice resulted in improved survival, reduction in bacterial counts in brain and reduced nephrotoxicity	Preferential delivery to the brain and less in other organs compared to other formulations. Able to treat penicillin resistant bacteria	Only male mice used. Possibility of developing RVG29 antibodies which would limit multiple dosing	358
Intracerebral fungal infection	PEG and transferrin receptor antibody (OX26) coated PLA nanoparticle	Amphotericin B	Tail vein injection in mice resulted in improved survival, reduced fungal detection in brain, reduced kidney and liver damage	NP formulation less toxic to organs and more effective than controls. Extended therapeutic window by increased stability in blood	Sex of mice not reported. Inconsistency in reporting type of electron microscope used	359
LPS mediated sepsis	Lipid coated calcium phosphate	NAD^+	Tail vein injection in mice caused 100% protection from both endotoxin and bacteria-induced septic lethality	Demonstrates intracellular NAD+ as a treatment for sepsis	Only female mice used. Didn't check NP distribution in the brain	365
Histone and LPS mediated sepsis	PEG–hydrogel nanoparticles	Sequestering of histones	Tail vein injection in mice protected from septic lethality	Demonstrates preferential high binding to histones H3 and H4	Only male mice used. Only determined binding to histones, not any other serum components	366

all died within 3 days of the challenge.[365] Another study used synthetic hydrogel nanoparticles composed of four different monomers and selected for their ability to bind to purified histones. These nanoparticles were then used in a mouse model of histone and LPS-mediated sepsis, showing that hydrogel nanoparticle treatment was protective against sepsis and able to sequester histones in the blood stream, reducing their accumulation in the lungs, liver, kidney, and intestines.[366]

A largely unexplored opportunity is the use of neural tracing components from toxins and neurotropic viruses as targeting agents for neural-tracer mediated drug delivery, as mentioned above. For example, cholera toxin subunit B (CTB) has been used since the 1980s as a neural tracing agent[367] and is nontoxic, since it only contains binding properties and no catalytic properties. Rabies virus only contains one surface-exposed protein (rabies virus glycoprotein),[368] through which it gains cellular entry and is transported across neuromuscular and transsynaptic junctions all the way into the brain. Data from various neural tracing studies reveal that different neural tracers can label different types of neurons and have varying abilities for transsynaptic transport, as well as affinities for anterograde (away from the CNS) or retrograde (towards the CNS) directional transport,[95] allowing for targeting of distinct neuronal populations. These are unlikely to be suitable for acute conditions (*e.g.*, stroke), as "fast" axonal transport occurs on the order of ~50–200 mm per day,[369] which is insufficient in humans who contain motor neuron axons in the range of 1 m in length. However, for drug delivery purposes this is viable. Combining neural tracing components with nanotherapeutic compounds would produce true targeting in a way that is not possible with affinity-based "targeting" (*e.g.*, antibodies and aptamers). People with immunity against certain infectious agents may be precluded from these treatments, given that vaccinations exist for protection against some of these infectious diseases (*e.g.*, tetanus and rabies virus). However, in a similar way that botulinum toxin, one of the most potent toxins on earth, has now been adopted for both therapeutic and cosmetic purposes, there is a whole library of plant, microbial, and viral neural tracers which, with care, may be combined with nanotherapeutics for a new generation of truly targeted medicine for the CNS. Higher resolution or more powerful *in vivo* imaging techniques would be required to characterize the transport rate and neural distribution of these. A summary of nanotherapies for infectious diseases concerning the CNS is given in Table 9.

Future perspectives/conclusions

This review has covered several complex diseases, their current state-of-the-art treatments and cutting-edge pharmaceutical and nanotherapeutic research attempting to address these diseases. While this review is not comprehensive, some broader trends are becoming clear. Despite the difficulty of drug delivery to the CNS, there are many reports of nanoparticles of varying composition and sizes that can cross the BBB/BSCB from common delivery routes (intravenous, intraperitoneal, intranasal). From a drug delivery perspective, this is a great opportunity. From a safety perspective, it is important that appropriate safety practices are implemented for people who study or work in industries where aerosolized or airborne nanoparticles are produced. From a scientific reporting standards perspective, a worrying number of reports neglect to provide direct evidence of nanoparticles in the CNS, which should be a key evaluation when reporting on nanoparticle delivery to the CNS. Adhering to a minimum reporting standard would greatly improve the quality of nanotherapeutic research. Nanotherapeutic organ distribution and retention are also generally underreported. These should be a minimal requirement for nanotherapeutic animal studies, especially with nanoparticles containing non-biodegradable or potentially toxic components (*e.g.*, metal ions). This is especially important in the CNS, where there is little to no neuronal cell turnover. Since many nanotherapies are novel and are a combination of synthetic and natural materials, there is scarce historical precedent to draw safety and long-term data from. This, combined with (justified) caution concerning translation of results from rodent models to humans, presents another barrier to use in clinical trials and commercialization. Testing in non-human primate models is an absolute necessary next step in realizing the potential of nanotherapies. However, the cost and ethics requirements are likely to be prohibitive for many research laboratories. Stronger collaborations with clinicians, government and industrial partners are necessary to address these issues. Easily accessible analysis tools and a standardized method of reporting adverse events in animal models may strengthen the results of pre-clinical animal studies. The largest glaring gap in knowledge regarding nanotherapeutics is the potential side effects that they may produce in human patients. Almost all the studies involving nanotherapeutics are conducted on rodent disease models, for which adverse events are rarely noted. Some adverse events typically recorded in human clinical trials which are assessments of internal state (*e.g.*, headache, myalgia, nausea), cannot be extracted from animal models. Others that are observable or able to be inferred (*e.g.*, constipation, diarrhea, respiratory issues, contact dermatitis, behavioral changes) require remote monitoring and event classification, a labor-intensive task which may be well suited for artificial intelligence (AI) tools. The basis for this already exists in the AI software produced by the Canadian company EAIGLE Inc., which was originally produced to monitor human activity in shopping centres,[371] and has additional applications in animal conservation and husbandry.

The main opportunities for nanotherapeutics for the CNS are in encapsulation and delivery of therapeutics which have poor solubility and short circulation lifetimes, and are unable to cross the BBB/BSCB. Targeting ligands for BBB endothelial receptors to enhance transcytosis (enhanced affinity targeting), as well as modulation of drug efflux pumps and transient permeabilization of the BBB may be necessary techniques to enhance delivery to the CNS. However, transcytotic receptors

likely exist in most endothelial compartments around the body (albeit at different expression levels), so dosing must be carefully determined to avoid side effects. Additionally, sex differences in receptor expression must be considered, especially in context of the menstrual cycle. This may become more important with the rising interest in the use of the transferrin receptor for BBB crossing, which is of primary importance in iron uptake and storage. Most *in vivo* studies are conducted on rodents of one sex (usually male). However, it is important to verify the results hold true for both male and female models. Intranasal delivery to the CNS is an effective non-invasive method that is worthy of more study, while the lymphatic system is a major body system which is understudied and underutilized in nanotherapeutic strategies. Neural tracers are a novel and highly promising method of delivery to the CNS that has been largely unexplored. Generally, side effects stem from systemic delivery of therapeutic agents, which impact on various regions of the body, as well as the intended region. By designing more precise delivery methods, side effects may be avoided, and overall dosages can be reduced. Neuroinflammation plays a critical role in many CNS disorders, and effective modulation *via* nanotherapeutics could potentially provide large benefits. Stem cell therapies have been shown to be generally safe, with adverse events mostly associated with the delivery technique. However, the efficacy of stem cell therapies has not yet been clearly demonstrated, indicating that the differentiation process in complex disease and injury environments is poorly understood. One of the key benefits of nanoparticles is the ability to deliver more than one therapeutic compound per particle, *i.e.*, more concentrated, localized drug delivery. A concerted effort to determine optimal BBB/BSCB bypass or penetration strategies would allow for testing of many more treatments, which are naturally excluded from the CNS. There is a huge library of medicinal compounds that have been developed but not approved for clinical use despite showing promising pre-clinical results. Their efficacy can be improved by nanocarriers and targeting strategies.

Author contributions

Dr Joel Yong: writing – original draft, review and editing, project administration. Dr Karen Hakobyan, Sk Al Zaheri Mahmud, Daniel Johnson, Jacob Lee: writing – original draft. Dr Ashish D Diwan: conceptualization, writing – review and editing, supervision. A/Prof. Sophia Gu: writing – review and editing, supervision. A/Prof. Gila Moalem-Taylor: conceptualization, funding acquisition, writing – review and editing, supervision. Prof. Guangzhao Mao: conceptualization, funding acquisition, writing – review and editing, supervision.

Conflicts of interest

The authors declare no conflicts of interest.

Abbreviations

SCI	Spinal cord injury
TBI	Traumatic brain injury
NP	Nanoparticle
BBB	Blood brain barrier
BSCB	Blood spinal cord barrier
BM	Basement membrane
CSPG	Chondroitin sulfate proteoglycan
CNS	Central nervous system
CSF	Cerebrospinal fluid
ALS	Amyotrophic lateral sclerosis
MS	Multiple sclerosis
AD	Alzheimer's disease
ECM	Extracellular matrix
GAGs	Glycosaminoglycans
AMPs	Antimicrobial peptides
ASOs	Anti-sense oligonucleotides
EAE	Experimental auto-immune encephalitis
PEG	Polyethylene glycol
PLA	Poly lactic acid
PLGA	Poly(lactic-*co*-glycolic acid)
AMP	Anti-microbial peptide

Data availability

Data sharing is not applicaple as no primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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