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Neurodegenerative disorders and nanoformulated drug development

Ari Nowacek, **Lisa M Kosloski**, and **Howard E Gendelman**†
Department of Pharmacology, & Experimental Neuroscience, Center for Neurovirology &, Neurodegenerative Disorders, University of Nebraska, Medical Center, Omaha, NE 68198-5880, USA

Abstract

Degenerative and inflammatory diseases of the CNS include, but are not limited to, Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis, stroke, multiple sclerosis and HIV-1-associated neurocognitive disorders. These are common, debilitating and, unfortunately, hold few therapeutic options. In recent years, the application of nanotechnologies as commonly used or developing medicines has served to improve pharmacokinetics and drug delivery specifically to CNS-diseased areas. In addition, nanomedical advances are leading to therapies that target CNS pathobiology and as such, can interrupt disordered protein aggregation, deliver functional neuroprotective proteins and alter the oxidant state of affected neural tissues. This article focuses on the pathobiology of common neurodegenerative disorders with a view towards how nanomedicine may be used to improve the clinical course of neurodegenerative disorders.

Keywords

Alzheimer's disease; amyotrophic lateral sclerosis; fullerene; nanomedicine; nanoparticles; neurodegeneration; neuroregeneration; Parkinson's disease; stroke

A significant challenge for 21st century medicine is to positively affect the clinical outcomes for mind, motor and behavioral abnormalities that follow debilitating CNS conditions linked to aging, infections and degeneration. These include, but are not limited to: Alzheimer's and Parkinson's diseases (AD and PD), stroke, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and HIV-1-associated neurocognitive disorders (HAND) [1–6]. A myriad of factors affect disease onset and progression that include host genetics, lifestyle, environment, behavior, immunity and aging [7].

Unfortunately, with the exception of anti-microbials, few therapies are currently available that can affect disease outcomes. Generally, modern medicine used for treatment of neuro-degenerative disorders is at best palliative and manages only the symptoms [8,9]. Adding another level of difficulty is a paucity of early and accurate detection of biomarkers. This is especially important as most neurodegenerative disorders are difficult to diagnose and disease processes are operative for years before either the patient or physician is clear on a specific diagnosis. Another impediment for diagnosis rests with the underlying pathogenic mechanisms for neurodegenerative disorders that include modification, accumulation and aggregation of host proteins, disruption of blood flow, altered tissue homeostasis, low level infection, and/or

†Author for correspondence:, Department of Pharmacology, & Experimental Neuroscience, Center for Neurovirology &, Neurodegenerative Disorders, University of Nebraska, Medical Center, Omaha, NE 68198-5880, USA, Tel.: +1 402 559 8920;, Fax: +1 402 559 3744; hegendel@unmc.edu.

neuroimmune dysfunction [10–15]. All of these issues could be positively affected if an intervention was made before permanent and long-lasting neural damage ensued. Unfortunately, the translation of promising results from laboratory and animal studies to clinical practice has met with mixed results.

We posit that nanotechnology-directed modalities that can specifically target a damaged CNS hold considerable promise if unwanted side effects and tissue barriers can be overcome [16–18]. Based on this idea, we discuss the basic pathobiology associated with each of the common neurodegenerative disorders and then examine how recent studies in nanomedicine may be used to develop potential therapies or improve disease monitoring for both newly found and well-known targets of human disease.

Alzheimer's disease

Alzheimer's disease, worldwide, is the most prevalent neurodegenerative disorder. Although each individual is uniquely affected by AD, the disease is generally characterized by impairments of memory, cognition and behavior [7]. The earliest symptoms are often erroneously attributed to advancing age or stress. Memory loss certainly predominates and includes problems with recall of life events. Diagnosis is usually confirmed by assessments of behavior and cognition. As the disease progresses, confusion, irritability, aggression, mood swings and withdrawal become commonplace. The disease excludes individuals from maintaining normal life events and in the latter stages of disease often requires long-term care and institutionalization [19].

Pathologically, AD is characterized by loss of cortical, and to a lesser extent, subcortical neurons and synapses. This results in gross atrophy, including degeneration of the temporal and parietal lobes and parts of the frontal cortex and cingulate gyrus [20–22]. There are two types of characteristic lesions: extracellular senile plaques and intracellular neurofibrillary tangles [23,24]. Both are composed of abnormal aggregations of amyloid-β (Aβ). Tangles are composed of aggregates of hyperphosphorylated tau, a microtubule-associated protein [11, 12]. These are the most common histopathologic AD features but alone may not be sufficient to generate the significant and profound neuronal loss that occurs in the disease [25–27].

Alzheimer's disease is highly prevalent and well characterized, with a number of potential therapeutic options but regrettably few currently in clinical practice. These include, but are not limited to, clearance of aggregated Aβ, attenuation of neuroinflammatory activities, modulation of redox responses and oxidative stress, halting the formulation of reactive oxygen species (ROS), cell-, tissue- and/or immune-based neuroregeneration, and/or protection and modulation of known biochemical responses [28–34]. Each of these would be improved substantively if drugs could be delivered specifically to affected brain areas. Direct applications could also improve diagnostics if plaques, tangles and/or neuropathological activities could be seen earlier in the disease course. Thus, in recent years there has been a significant effort researching the use of nanoformulations for diagnosing and treating AD [35]. Most of the new therapeutic modalities are aimed at pathogenic events that are well established and known to directly contribute to neurodegeneration.

Aberrant homeostasis of transition metal ions within the brain has long been linked to Aβ aggregate formation [36–40]. As such, chelating agents that selectively bind, remove and neutralize transition metals are considered potential AD therapies. However, many traditional chelators are neurotoxic and the blood–brain barrier (BBB) limits delivery, thus preventing therapeutic use [41,42]. Importantly, delivery of chelating agents to the brain through nanocarriers can reduce cytotoxicity and allow for specific delivery to the CNS. Therefore, transport of chelators to the brain has been developed for therapeutic benefit. The copper(I)-chelating agent D-penicillamine, covalently conjugated to nano-particles (NPs) [43] through a

disulfide bond, is capable of solubilizing copper-Aβ aggregates in a reduced environment [44]. Moreover, chelators 2-methyl-N-(2-aminoethyl)-3-hydroxyl-4-pyridinone (MAEHP) and deferoxamine conjugated to NPs and coated with polysorbate-80 were able to chelate metal ions from brain sections of AD patients [45]. In addition, these particles bind ApoE and ApoA1 and therefore, can be taken into brain microvessel endothelial cells through the low-density lipoprotein receptor, suggesting a possible mechanism of transport across the BBB. Recent work with carboxylic-functionalized polystyrene NPs conjugated to the iron chelator MAEHP showed that NP delivery of chelators to neurons can effectively inhibit Aβ aggregation and neurotoxicity [46]. Such particles, when used in AD transgenic animal models, will investigate biodistribution and in vivo efficacy. The role of transition metal homeostasis in the process of Aβ aggregation is of considerable therapeutic interest.

In addition to decreasing metal ion content, other studies demonstrated the potential therapeutic benefit of copper supplements [47–49]. Such studies address cellular deficiency of copper. In this regard, functional nanocarriers would increase delivery of copper to the brain. For these works, the particles consist of hyperbranched polyethyleneimine as a core surrounded by organic shells. These NPs encapsulate copper, transport it into neurons and decrease extracellular Aβ levels in vitro [50]. While this is a novel approach to reducing Aβ aggregation, clinical trial data released in 2008 showed that copper intake did not affect AD progression [51]. However, considering recent experiments that promote copper uptake as a disease-modifying approach [52–54], copper supplementation remains a therapeutic option. More recently, zinc has been linked with Aβ aggregate formation [55,56]. The formation of zinc–selenium nano-crystals has been used to detect and confirm the presence of zinc as another metal component of Aβ aggregates [57].

Amyloid-β aggregation is a multistep process that involves several oligomeric intermediates. Thus, new nanotherapies have been designed to inhibit the formation of Aβ aggregates during intermediate steps. Polyamidoamine dendrimers inhibit aggregation of Aβ peptides [58]. Copolymeric N-isopropylacrylamide: N-tert-butylacrylamide NPs quench and temporarily reverse fibrillization of Aβ in vitro [59]. The mechanism of reduction in both of these experiments most likely involves depletion of available monomers and trapping of critical nuclei, thereby preventing aggregation initiation. Fullerenes have also been shown to inhibit Aβ fibrillization. C_{60} fullerenes affected Aβ aggregate assembly. Upon intracerebroventricular injection, C_{60} fullerenes were able to prevent impaired cognitive performance on tasks normally induced by the presence of Aβ [60]. Inhibition of Aβ aggregation has also been accomplished using polyethylene glycol (PEG)-stabilized phospholipid nanomicelles [61]. Since the formation of Aβ aggregates is a multistep process with many opportunities for inhibition, continued exploration in this field is necessary.

Another means to reduce the damage done by Aβ aggregates is to remove them. A therapeutic option in the early stages of development is facilitated removal of Aβ aggregates with the use of sequestering agents. A recent example demonstrating this possibility has been the complete removal of amyloidogenic fibrils from an aqueous phase by binding amyloid fibrils to magnetic iron-oxide (maghemite) NPs and then removing these NP–protein complexes from the solution using a magnetic field [62]. Another potential sequestering agent is sialic acid-conjugated polyamidoamine dendrimers, which were able to attenuate Aβ-induced neurotoxicity in vitro [63]. This work was based on a previous study that demonstrated the relatively high binding affinity of Aβ to sialic acid residues on cell surfaces and that removal of cell-surface sialic acids attenuated Aβ toxicity [64]. Gold (Au) NPs can target and remove Aβ deposits with the application of electromagnetic energy. Au NPs conjugated with fragments of Aβ peptide or coated with a peptide known to interact with Aβ aggregates (e.g., CLPFFD-NH_2) can be incorporated into Aβ fibrils. Stable interaction between Au NP–protein complexes and their target, Aβ aggregates, is a key goal in the application of this technology [65]. Aβ aggregates

that incorporate Au NPs can be selectively ablated by laser exposure [66] or with the application of microwave fields [67]. These provide new avenues for both targeting and then removing Aβ deposits. Microwave radiation is perhaps less invasive while still allowing for selective ablation of Aβ deposits.

The formation of ROS has been linked to neuronal death in AD [33,68–70]. However, research on the reduction of ROS in the brain is generally not specific to AD. Research studying the use of NPs to prevent damage caused by free radicals has focused on decreasing the production of ROS that occurs after acute ischemic injuries and other neurodegenerative disorders. Thus, discussion of this subject will be continued in the stroke section of this paper. Another method to improve clinical outcomes in AD is to increase drug delivery to the brain to target biochemical pathways linked to disease. In order to accomplish this end, tacrine (a reversible cholinesterase inhibitor)-containing magnetic chitosan microparticles were intravenously injected followed by placement of a magnet at the head [71]. This resulted in significantly increased drug delivery to the brain. Another AD medication, huperzine-A (a cholinesterase inhibitor used to improve cognitive function), may be packaged into microspheres of poly (lactic-co-glycolytic acid) (PLGA) and can show sustained release over 12 days when administered intramuscularly to reduce scopolamine-induced memory impairment in mice [72,73].

Advancements in diagnosing AD are being made by nanotechnology. During the last decade, much research has focused on developing cerebrospinal fluid biomarkers for disease. The diagnostic focus included tau protein, the 42-amino acid form of β-amyloid, amyloid precursor protein (APP) and amyloid-β-derived diffusible ligands (ADDL). Cerebrospinal fluid ADDL levels are known to correlate with disease. Measurement of these proteins is facilitated by the use of ADDL-specific monoclonal antibodies in an ultrasensitive, NP-based protein detection strategy referred to as biobarcode amplification. Biobarcode amplification uses NPs as DNA carriers to improve the sensitivity of detection [74]. Another recent advance has been in the use of Au NPs. Fragments of Aβ antibody were conjugated to Au NPs, which binds to Aβ protein. The resulting immunocomplexes could be detected in concentrations as low as 1 fg/ml by the use of scanning tunneling microscopy [75,76]. Another use of Au NP has been in the fabrication of Au-capped NP multispot-localized surface plasmon resonance immunochips that can detect tau at 10 pg/ml [77]. Both of these methods would allow for more accurate diagnosis of AD.

Parkinson’s disease

Parkinson’s disease was first detailed in 1817 in a medical essay published on the subject by London doctor James Parkinson. Symptoms appear gradually and are unique to the affected brain subregion [78]. These include difficulty maintaining balance, problems with ambulation, resting tremors, bradykinesia, and stiffness of the limbs and trunk. Pathologically, PD is defined by the loss of dopaminergic neurons within the substantia nigra pars compacta with subsequent loss of striatal dopaminergic projections to both the caudate and putamen [79]. The exact cause of PD is not known as many factors are involved in disease development, including misfolded proteins, neuroinflammation, glial immune activation, ROS production, toxin exposure, host genetics and aging [10,80–83]. However, it is clear that the disease process starts long before any symptoms appear and autonomic abnormalities and dysfunction may be early symptoms [84,85]. Motor, and ultimately cognitive, deterioration are linked to neuronal damage and the breakdown of the BBB, caused by the release of neurotoxic compounds initiated by immune-activated glia [86]. The loss of BBB integrity during disease progression allows leukocyte entry into the brain, which serves to further enhance and perpetuate the neuroinfammatory cascade [87].

Treatments currently available for PD target symptoms of the disease. These are used to replace lost dopamine, serve as dopamine receptor agonists or act as selective inhibitors of monoamine oxidase. The latter metabolizes dopamine, thereby prolonging the positive affects of dopamine replacements. Other drugs such as amantadine or anticholinergic medicines reduce tremors [88]. However, the focus on using nanomedicine approaches for PD is a balance between halting the disease process and improving delivery of more conventional drugs used in the treatment of symptoms. We provide examples for both.

Recent works have used C_{60} fullerenes in the treatment of PD. C_{60} fullerenes have unique physical and chemical properties and have been researched for their potential biomedical applications [89–92]. C_{60} shows potent antioxidant capabilities and could offer therapeutic benefit through the reduction of free radicals. For example, C_{60}-ascorbic acid NPs protect chromaffin cells against levodopa toxicity. This has led to the idea of combining levodopa with ascorbic acid-functionalized C_{60} [93]. However, a number of reports have raised concern about drug safety. For example, it was shown that pristine C_{60} becomes toxic when exposed to visible light in the presence of oxygen [94]. Cyprinus carpio brain homogenates with added C_{60} produced significantly more lipid hydroperoxides when exposed to light, thus raising concerns that in vivo C_{60} could cause damage when present in photic regions of the brain [95]. Such approaches remain in development. Another example includes the polyhydroxylated fullerene derivative, $C_{60}(OH)_{24}$. This fullerene is able to prevent mitochondrial oxidative damage induced by 1-methyl-4-phenylpyridinium ions in an acute cellular PD model using human neuroblastoma cells [96]. The suggested mechanisms of action include radical scavenging and antioxidant activities. C_{60} fullerenes have unique properties and offer many potential uses for the treatment of neurodegenerative disorders. However, before their successful application can be realized, the issues of toxicity must be resolved.

Decreasing microglia-activated ROS production in the brain regions affected in PD by cell delivery of NP catalase is a new technique that is gaining interest [97]. Catalase can be packaged into a NP consisting of a block copolymer complex with polyethyleneimine– PEG. Mouse bone marrow macrophages were exposed to particles in vitro and then adoptively transferred into a mouse with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD. Cells that contained catalase NPs were able to cross the BBB, increase delivery of catalase and remove microglial hydrogen peroxide at greater levels when compared with ‘free’ catalase [98].

Chronic inflammation has been implicated in many neurodegenerative disorders, including PD, and findings have suggested that modulating neuroinflammation can reduce neuronal death [86,88,99–101]. Specific phospholipids, such as phosphatidylglycerol present on apoptotic cells, and certain pathogens can induce anti-inflammatory responses [102,103]. VP025 (Vasogen Inc., ON, Canada) is a phosphatidylglycerol-based phospholipid NP that interacts with antigen-presenting cells and regulates proinflammatory cytokine production, thus controlling inflammation. The potential therapeutic benefit of VP025 in PD has been explored. The VP025 NP protects neurons in the 6-hydroxydopamine mouse model of PD [104]. The neuroprotective responses are linked to preventing neuronal apoptosis, reducing microglial inflammation and/or affecting the ubiquitin–proteasome system. Failure of the latter to degrade abnormal proteins may underlie the accumulation of α-synuclein and dopaminergic neuronal degeneration. In this manner, a reduction of functional proteasome activity has been implicated in the pathogenesis of PD [105]. The VP025 NP prevents the deficits in motor coordination observed in a proteasome inhibitor rat model of PD. Thus, VP025 may have a therapeutic effect on the impairment of dopaminergic-mediated motor activity induced by proteasome inhibition [106]. This compound has produced promising results, and its continued development is encouraged. The product completed a successful Phase I clinical trial in 2005 and is currently in Phase II clinical development.

Another means for treating PD is to deliver functional proteins to affected cells within the CNS. One major barrier, in addition to the BBB, has been delivery of such proteins across neuronal cell membranes. Polybutylcyanoacrylate NPs were used to transport multiple proteins, such as mouse monoclonal antibodies to α-synuclein (H3C), to primary hippocampal cultures. This was accomplished with maintenance of protein function. In addition, antibody uptake was dependent on the low-density lipoprotein receptor, which had been suggested in previous studies [107]. This recent study demonstrates that NP vehicles can be used to effectively deliver intact proteins across neuronal membranes.

As for AD and other neurodegenerative disorders, increasing delivery of currently used drugs to the brain would greatly improve PD clinical outcomes. In an effort to accomplish this, bromocriptine, one of the original dopamine agonists, has been developed into solid lipid NPs. Bromocriptine crystals were suspended with tristearin/tricaprin lipid combination and coated with poloxamer-188. After using 6-hydroxydopamine to induce nigrostriatal degeneration, bromocriptine NPs were administered by intraperitoneal injection. Bromocriptine NPs improved performance in behavioral tests over the use of free drug [108]. This is but one example of traditional PD medications that can be made into stable NPs capable of sustained release. Obviously, future research should explore other means to deliver drug to the nigrostriatum during the course of disease.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, is a disorder of motor neurons and is a common adult-onset neurodegenerative disease [109]. Symptoms include muscle weakness, tripping, dropping items, abnormal fatigue of the arms and/or legs, slurred speech, muscle cramps and twitches. Eventually, complete neuromuscular failure occurs and death typically results due to compromised respiratory function 3–5 years after the onset of symptoms [110]. The neuropathologic hallmark of ALS is neuronal degeneration and atrophy, confined almost entirely to the upper and lower motor neurons. ALS affects approximately six in every 100,000 adults throughout the world with approximately 95% of cases being of a sporadic nature [111]. The remaining cases are caused by missense mutations on chromosome 21, encoding a copper- or zinc-binding protein called superoxide dismutase (SOD), and have been linked to the familial form of the disease [112,113]. SOD is one of the most important enzymes employed in the defense against oxidative stress and has been implicated in many neurodegenerative diseases.

A number of new approaches for ALS therapy are being developed. They include adaptive immune neuroprotection, vaccines against misfolded protein epitopes, stem cell therapy and nanomedicine [114]. Nanomedicine approaches have focused in part on ROS. Indeed, a significant portion of neuronal loss in ALS is potentially due to damage caused by ROS as a result of dysfunctional SOD. Thus, some research in the field of nanomedicine on ALS has been focused on replenishing functional levels of SOD1 to motor neurons. For example, PLGA NPs containing SOD1 have been used to deliver SOD to neurons and provide protection against hydrogen peroxide-induced oxida-tive stress in vitro [115]. Carboxyfullerene SOD mimetics, molecules with SOD-like activity that have a high reactivity to superoxide radicals and are also cell permeable, have been shown to be neuroprotective in vitro [116]. This study also established a structure–activity relationship between carboxyfullerenes and the amount of inherent SOD mimetic activity.

Acrolein is a highly reactive product of lipid peroxidation that has been identified within motor neurons of patients with ALS and in the brains of patients with AD [117]. Mesoporous silica NPs loaded with hydralazine and coated with PEG were able to ameliorate the damage caused to both cell membranes and mitochondria, induced by exposure to a normally lethal amount

of acrolein in vitro [118]. This is a novel therapeutic target for both ALS and AD. Nanomedicine also offers the potential to improve diagnosis of ALS. Au NPs coated with SOD1 monomer readily interact with SOD1 aggregates and have been used to develop a simple and sensitive colorimetric detection system that could be used to improve the diagnosis of ALS [119].

Multiple sclerosis

Multiple sclerosis takes several forms, with symptoms occurring either in discrete relapsing attacks or accumulating slowly in more progressive forms. Between attacks, symptoms may completely go away and neurological function return to normal, but permanent neurological dysfunction can and often does occur most notably in advanced disease [120,121]. Jean Martin Charcot first described disseminated white matter lesions within the CNS in 1868 [122]. Lesions are known to contain perivascular cell-based inflammation and demyelination [123]. Plaques occur anywhere within the CNS white matter but more frequently in the optic nerves, brainstem, cerebellum and spinal cord. These are commonly linked to clinical symptoms. The presence of plaques in brain regions adjacent to the cortex demonstrates spared subcortical myelinated fibers. Plaques rarely spread into the gray matter [124]. Lesions occur as a consequence of host-generated immune responses against oligodendrocytes and myelin components leading to frank demyelination [125]. This affects the ability of cells in the brain and spinal cord to effectively communicate with each other and leads to a broad range of symptoms including, but not limited to, paresthesia, paresis, bowel and bladder deficits, visual disturbances and cognitive impairments. Treatment of MS has traditionally focused on immune suppression, but disease-modifying agents such as glatiramer acetate and IFN-β have also been used [126,127].

An important determinant of neurologic disability in MS is axonal degeneration. Therefore, one therapeutic approach in the treatment of MS is promoting neuroprotection [128–130]. A NP consisting of a water-soluble fullerene derivative (ABS 75) functionalized with an NMDA receptor antagonist has been designed, combining antioxidant and antiexcitotoxic properties. This particle has shown positive results in reducing MS disease progression in mice immunized with myelin basic protein. The NP was able to decrease oxidative injury, cluster of differentiation molecule 11b (CD11b) infiltration and chemokine (C-C motif) ligand 2 (CCL2) expression without affecting T-cell responses [131]. This complex NP, which combined multiple functions into a single particle, is a good demonstration of how a nanomedical tool can simultaneously affect disease outcomes from different angles. Based on results that identified infection with Helicobacter pylori as a protective factor against the development of MS [132], an interesting suggestion has recently been made for a new therapeutic strategy in MS. H. pylori components could possibly be packaged in NPs, functionalized for neuro-specific targets and delivered by cells to the CNS [133]. This concept has yet to be explored, but the use of nanotechnology would be a good method for packaging and delivering H. pylori proteins.

Inhibition of immune responses remains the traditional treatment for MS [134–136]. However, there are other ways to modulate the immune system besides general inhibition. Fullerenes have been suggested for use in the treatment of AD, PD and ALS; they may also be of use in MS. It was unexpectedly found that C_{60} fullerenes were capable of inhibiting the initiation and propagation of an antigen-driven type I hypersensitivity reaction [137]. This finding suggested a new biological role for fullerenes and a potential new way to modulate the immune system in the treatment of MS.

Several advancements in the treatment of MS with the use of nanotechnology are being made in the field of imaging. A number of particles are being developed that are able to help visualize and detect inflammation before outright pathology is evident. These NPs are being

functionalized so they can allow for direct detection of inflammatory markers. One is a carbohydrate-functionalized NP that can detect the presence of E/P-selectins [138]. Another is an antibody-conjugated microparticle carrying iron oxide that can detect VCAM-1 [139]. Iron-oxide NPs are also being used to label macrophages in order to follow their migration into sites of active lesion formation [140]. This could help to monitor inflammatory events and aid in the guidance of therapeutic interventions.

Stroke

In the USA, stroke is the second most common cause of neurologic disability after AD [141]. Atherosclerosis, heart disease, hypertension, diabetes and lifestyle habits are risk factors correlated with the disease. Unlike most neurodegenerative disorders, many of the risk factors associated with stroke are modifiable. Causes of the disease revolve around disruptions of blood flow to the brain parenchyma which includes vascular occlusion (thrombotic and/or embolytic stroke) or rupture (hemorrhagic stroke). The neuropathological hallmarks of stroke are necrotic infarcts of variable size coupled with inflammatory gliosis. Treatment of stroke in the realm of nanomedicine has focused on reducing the production of ROS and re-establishing blood flow to the ischemic brain region.

Excessive production of ROS, as mentioned before, plays a significant role in many neurodegenerative disorders, occurs after cerebral ischemia and has been implicated in brain damage by a variety of cellular and molecular mechanisms. This is further aggravated by the fact that cellular antioxidant defense systems are impaired under ischemic conditions. For stroke, as in ALS, therapeutic strategies based on exogenous delivery of SOD and other ROS scavengers have been an area of exploration. However, delivery of SOD to the brain is difficult owing to its short half-life and poor permeability across the BBB. SOD encapsulated in PLGA NPs positively affected the rat focal cerebral ischemia-reperfusion injury model of human disease. When SOD NPs were administered through the carotid artery at the time of reperfusion, BBB integrity was maintained, edema was prevented, the level of ROS was reduced and neurons were protected from apoptosis [142]. This indicated that SOD NPs might benefit stroke patients when used in conjunction with thrombolytic agents. Compounds capable of scavenging ROS besides SOD have been explored for their ability to provide neuroprotection and to be packaged into a NP for delivery to the brain. For example, attention has been given to ceria NPs. First, cerium-oxide NPs administered in a vacancy-engineered mixed valence state are potent scavengers of ROS. These particles were shown in vitro to be able to decrease intracellular concentrations of ROS and provide neuroprotection. Therefore, they were suggested to be a potential method to decrease neuronal death in stroke and neurodegenerative conditions [143,144]. More work with ceria NPs followed. Free radical scavenging by auto-catalytic ceria NPs provided protection to adult rat spinal cords from hydrogen-peroxide produced ROS in vitro [145]. The use of nano-ceria and other antioxidants may, in the future, prove beneficial for the in vivo mitigation of ischemic events after spinal cord injury, as well as possibly being a new therapeutic agent for oxidation injury in neurodegenerative disorders.

Restoring blood perfusion to the ischemic brain region is a vital therapy for acute stroke. For example, thrombolytics, such as recombinant tissue plasminogen activator, administered soon after symptom onset can improve outcomes. However, the potential for adverse hemorrhagic events limits their use. Specifically targeting clot-dissolving therapeutics with nanotechnology has the potential to decrease the frequency of complications and increase treatment effectiveness by concentrating the available drug at the desired site. One attempt to accomplish this has been through the development of a fibrin-specific, liquid perfluorocarbon NP with bound plasminogen activator streptokinase [43]. This new NP-based thrombolytic agent was able to provide specific and rapid fibrinolysis in vitro. This and similar particles may have a therapeutic role in early reperfusion during acute ischemic stroke.

Another way to decrease the damage inflicted by a stroke is to deliver oxygen to the ischemic site. Normally, this task would be accomplished by red blood cells (RBCs), but in the case of ischemic stroke, the occluding thrombus prevents passage of RBCs. Thus, it is necessary to find another mechanism of oxygen delivery to the starved site until the blockage is removed or dissolved. One method of accomplishing this uses liposome-encapsulated hemoglobin (LEH). LEH was originally investigated 20 years ago for its potential to carry oxygen in order to sustain life during massive hemorrhagic events [146] but it is now finding use in the treatment of stroke. When used in a rat model, it was shown to significantly reduce the size of cerebral infarcts. LEH is able to prevent extravazation of hemoglobin and the small size allowed for oxygen delivery beyond the obstruction via the flow of plasma to areas where RBCs have difficulty reaching. This greatly reduced the diffusion distance and allowed for oxygen delivery to needed areas [147]. More recent studies have also found that LEH can reduce infarct size and edema associated with ischemic stroke [148,149]. A PET imaging study performed in a rat model demonstrated that while there was nearly absent blood flow to the labeled ischemic region, oxygen-carrying LEH were able to penetrate towards the core of the ischemic zone [150]. The advancements in nanotechnology make it more likely that particles like these could soon be successfully used in the treatment of stroke.

HIV-1-associated neurocognitive disorders

Globally, there are more than 30 million people living with HIV, and many now benefit from antiretroviral therapies. HAND are a spectrum of diseases from subtle asymptomatic infection to more overt cognitive and behavioral abnormalities, called in its severest form, HIV-1 associated dementia [151]. Histopathologically, disease can manifest with little or no neuropathologies to a multinucleated giant cell encephalitis or HIV-1 encephalitis (HIVE). HIVE is characterized by micro- and astrogliosis, myelin pallor, the formation of macrophage-origin giant cells and frank neuronal drop-out [152]. Damaged brain subregions are typically localized to the basal ganglia, brainstem and deep white matter [153,154]. The associations between HIVE and HIV-1 associated dementia are substantive and neuropathology is strongly associated with profound memory loss and abnormalities associated with behavior and gait. HIV-1-infected monocytes readily cross the BBB and accumulate in perivascular macrophages and microglia, leading to a range of neurological disorders classified as HAND [155,156]. The use of antiretroviral therapies, including HIV protease inhibitors and nucleoside, nucleotide and non-nucleoside reverse transcriptase inhibitors, has reduced morbidities and mortalities associated with HIV infection but has failed to eliminate HAND due to incomplete antiretroviral penetration of the BBB, amongst other mechanisms [157]. Moreover, compliance and secondary toxicities of drugs have posed disease-combating limitations. Such issues have spawned the development of nanomedicines for antiretroviral and adjunctive HIV therapies, as addressed more completely in our companion paper [158]. The coupling of available antiretroviral therapies with NP-based delivery systems is briefly discussed. Spherical solid lipid NPs of approximately 167 nm can traverse the BBB and effectively deliver atazanivir to the brain, supporting therapeutic NP benefits [159]. Trans-activating transcriptor peptide-conjugated NPs effectively shield ritonavir from the efflux activity of p-glycoprotein [160]. Stavudine, delavirdine and saquinavir can increase their passage through the BBB by association with polybutylcyanoacrylate, methylmethacrylate-sulfopropylmethacrylate and solid lipid NPs by 12- to 16-fold, three- to sevenfold and four- to 11-fold, respectively [161]. This potential targeting of HAND by the joining of nanotechnology and antiretroviral therapeutics holds beneficial therapeutic strategies.

Conclusion

The development of nanomedicine for the treatment of neurodegenerative diseases targets improved disease outcomes. This reflects the incidence, prevalence, clinical significance, well-

characterized pathogenic mechanisms, availability of animal models and the seriousness of these disorders. However, many of the therapies that are being designed for a specific neurodegenerative disorder could potentially be applied to others. If an efficient way to deliver functional proteins across the BBB and into neurons or an effective method for decreasing the damage caused by ROS can be found, these approaches could be applied to nearly all of the neurodegenerative diseases. Thus, development of nanomedicines that focus on one neurodegenerative disorder will generally benefit them all; rarely is a therapy being developed which applies to only one disease. In the past 5 years, new potential therapies for neurodegenerative disorders have been developed. Many of these therapies focused on treating factors that have been well characterized and are known to directly contribute to the disease process. For a complete list of nanotechnology referenced to specific diseases discussed in this paper, see Table 1. These include disease-specific entities, such as Aβ for AD and α-synuclein for PD as well as processes that are common to all neurodegenerative disorders, such as neuroinflammation and ROS production. Some compounds have been more heavily studied than others. C_{60} fullerenes, for example, have gained much attention because their unique physical and chemical properties allow for easy manipulation and creation of new therapeutic methods. However, there continues to be concerns about the safety of these compounds. While continued development of fullerene-based therapies is of value, it is also necessary to gain a better understanding of the potential dangers associated with their use. Another compound that has attracted much attention has been gold, which has been successfully used to make a variety of NPs with different functions, including increased sensitivity of protein detection, enhanced imaging of the CNS and the ability to specifically remove or ablate protein deposits. Gold is a great material for nanomedical applications for CNS disease therapy because it is versatile and has less safety concerns. The development of improved drug delivery methods to the nervous system combined with improved methods for early detection will certainly change clinical outcomes.

Future perspective

Over the past 10 years, new nanomedicine tools have been developed that have improved diagnosis and therapeutic directives for neurodegenerative disorders. As a result, there has been a dramatic increase in knowledge of CNS disease pathobiology. A picture has been developing that shows many features at the cellular level are common to all neurodegenerative disorders. This has provided targets for nanomedicine interventions and helped to guide drug designs.

We propose three important avenues for disease-combating interventions will be developed through nanomedicine approaches. First, the improvement of site-directed drug delivery in brain regions most affected by disease will be achieved through ‘smart formulations’ and the ability to bypass or engage the BBB, thus improving the outcomes of anti-inflammatory, immunomodulatory and anti-apoptotic compounds. Second, regenerative nanomedicine will provide new agents to specifically repair or modulate disease targets. However, such interventions must not only find their way into affected disease areas of the CNS but also show limited or no toxicities. Third, early disease diagnosis will lead to improved intervention outcomes since treatments are likely to be more effective. Interdictive therapies that can halt or reverse the disease course have been tried but were met with varied degrees of success.

As genomic, proteomic and metabolomic studies begin to better decipher the etiologies of disease, new pathways responsible for initiation and propagation of disease are emerging. Chemotherapeutic, anti-inflammatory and neuroprotective agents have the promise of being effective if they can be delivered to the sites where they are most needed. However, they are currently mired by in vivo limitations that prevent them from becoming viable treatments, including poor pharmacokinetics, toxicity and, most importantly, lack of ability to cross the BBB. Techniques such as disruption of the BBB and direct bypass by injection or implantation

will sidestep this last limitation, but they too have undesired side effects, such as the crossing of unwanted compounds into the brain and a high degree of invasiveness, respectively. We propose that the development of nanoformulations that can reach the site of disease when packaged into particles or micelles that are targeted to cells or diseased tissue areas can overcome such obstacles and ultimately lead to effective treatments where few are currently available.

Executive summary

Alzheimer's disease

- Aberrant homeostasis of transition metals has long been linked with amyloid-β (Aβ) aggregate formation. In order to address this potential cause of Alzheimer's disease (AD), methods for sequestering excess metal ions, such as chelator–nanoparticle (NP) complexes, from as well as ways to supplement metal, such as polyethyleneimine metal-transporting NPs, to the brain are being explored.
- Aβ aggregation is a multistep process involving many oligomeric intermediates. Preventing the process of Aβ fibrilization at any point may provide benefits. Particles such as polyamidoamine dendrimers, C_{60} fullerenes and polyethylene glycol-stabilized phospholipid nanomicelles attempt to inhibit this process by depleting either the number of available monomers or critical nuclei.
- The removal of fully formed Aβ aggregates from the blood and brain can reduce neural damage in AD. Metal NPs that bind Aβ fibrils are being used to selectively ablate, by the application of electromagnetic energy, or remove, by magnetization, Aβ aggregates.
- Advancements in AD treatment are being made in drug delivery with the development of huperzine-packaged poly(lactic-co-glycolytic acid) NPs and in diagnosis with the development of gold NPs complexed with fragments of Aβ antibody or protein for imaging.

Parkinson's disease

- C_{60} fullerenes for treatment of Parkinson's diease (PD) and other neurodegenerative disorders is being explored. Particles such as C_{60}-ascorbic acid and polyhydroxylated C_{60} show potential antioxidant and radical scavenging properties. However, concern has been raised about the toxicity of C_{60} fullerenes and much more must be learned about these particles before they can be used clinically.
- Cell-mediated delivery of catalase-containing NPs to the brain is being developed. This method offers great promise for delivering drugs specifically to areas of the brain that need them, not just for PD but for all neurodegenerative disorders.
- Chronic neuroinflammation has been implicated in causing dopaminergic cell death. Studies with VP025, a phosphatidylglycerol-based phospholipid NP, have been purposed to cause an anti-inflammatory response by interacting with antigen-presenting cells and decreasing cytokine production. Recent studies using animal models of PD have suggested that this particle could improve clinical outcomes for patients with PD.
- Delivery of functional proteins to degenerating neurons is being developed. Polybutylcyanoacrylate NPs may be successfully used to deliver multiple proteins to hippocampal cells in culture.

- Solid lipid NPs of bromocriptine are being developed to improve pharmacokinetics over free drug.

Amyotrophic lateral sclerosis

- Dysfunctional superoxide dismutase (SOD) is linked to the pathogenesis of amyotrophic lateral sclerosis. Nanomedicine approaches were used to improve delivery of functional SOD to degenerating neurons or supplement with carboxyfullerene SOD mimetics.
- The production of endotoxins, such as acrolein, are linked with neuronal death in amyotrophic lateral sclerosis and AD. NPs, such as mesoporous silica NPs loaded with hydralazine and coated with polyethylene glycol, mitigate the damage to mitochondria and cell membranes.

Multiple sclerosis

- Axonal degeneration is linked to multiple sclerosis (MS). NPs consisting of a fullerene derivative functionalized with an NMDA antagonist combines antioxidant and antiexcitotoxicity properties. This multifunctional NP has shown benefit in a mouse model of MS.
- The use of NPs to deliver Helicobacter pylori proteins to the CNS is being developed. This suggestion was based on the finding that *H. pylori* infection had been identified as a protective factor against MS.
- General inhibition of the immune system is a common way to treat MS. It has been discovered that C_{60} fullerenes have the unique ability to selectively inhibit antigen-driven type I hypersensitivity reactions.

Stroke

- Excessive production of reactive oxygen species that follows an ischemic episode plays a significant role in neuronal death. In order to address this, SOD NPs and ceria NPs with antioxidant properties are being developed that could reduce oxidant injury after ischemic events.
- Restoring blood flow to the occluded region is of upmost importance in ischemic stroke. Thrombolytics are able to effectively dissolve clots, but severe side effects limit their clinical use. With the application of nanotechnology, NPs are being developed that could transport thrombolytics and specifically target clots.
- Re-establishing blood flow to occluded regions is a focal point for treatment in ischemic stroke. Liposome-encapsulated hemoglobin is capable of transporting and delivering oxygen. These particles have shown promise in the treatment of ischemic stroke because their small size allows them to bypass clots and reach the oxygen-deprived tissues.

HIV-1-associated neurocognitive disorders

- HIV-1-associated neurocognitive disorders are a spectrum of diseases ranging from subtle asymptomatic infection to more overt cognitive and behavioral abnormalities called in its most severe form, HIV-1-associated dementia.
- The use of antiretroviral therapy has reduced morbidities and mortalities associated with HIV infection but failed to eliminate HIV-1-associated neurocognitive disorders due, in part, to incomplete antiretroviral penetration across the blood–brain barrier.

- Nanomedicine is addressing this issue by developing NPs that transport antiretroviral drugs across the blood–brain barrier amongst other methods.

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Bibliography

1. Minati L, Edginton T, Bruzzone MG, Giaccone G. Current concepts in Alzheimer's disease: a multidisciplinary review. Am.J. Alzheimers Dis. Other Demen 2009;24(2):95–121. [PubMed: 19116299]
2. Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. Orphanet J. Rare Dis 2009;4:3. [PubMed: 19192301]
3. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8(4): 355–369. [PubMed: 19233729]
4. Schrag A, Quinn NP, Ben-Shlomo Y. Heterogeneity of Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 2006;77(2):275–276. [PubMed: 16421140]
5. Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights. Curr. Opin. Neurol 2006;19(3):248–254. [PubMed: 16702830]
6. Flachenecker P. Epidemiology of neuroimmunological diseases. J. Neurol 2006;253:V2–V8. [PubMed: 16998750]
7. Mayeux R. Epidemiology of neurodegeneration. Annu. Rev. Neurosci 2003;26:81–104. [PubMed: 12574495]
8. Robichaud AJ. Approaches to palliative therapies for Alzheimer's disease. Curr. Top. Med. Chem 2006;6(6):553–568. [PubMed: 16712491]
9. Elman LB, Houghton DJ, Wu GF, Hurtig HI, Markowitz CE, McCluskey L. Palliative care in amyotrophic lateral sclerosis, Parkinson's disease, and multiple sclerosis. J. Palliat. Med 2007;10(2): 433–457. [PubMed: 17472516]
10. Corti O, Hampe C, Darios F, Ibanez P, Ruberg M, Brice A. Parkinson's disease: from causes to mechanisms. C. R. Biol 2005;328(2):131–142. [PubMed: 15770999]
11. Nerelius C, Johansson J, Sandegren A. Amyloid β-peptide aggregation. What does it result in and how can it be prevented? Front. Biosci 2009;14:1716–1729. [PubMed: 19273157]
12. Watson D, Castano E, Kokjohn TA, et al. Physicochemical characteristics of soluble oligomeric Aβ and their pathologic role in Alzheimer's disease. Neurol. Res 2005;27(8):869–881. [PubMed: 16354549]
13. Brouns R, De Deyn PP. The complexity of neurobiological processes in acute ischemic stroke. Clin. Neurol. Neurosurg 2009;111(6):483–495. [PubMed: 19446389]
14. Bossy-Wetzel E, Schwarzenbacher R, Lipton SA. Molecular pathways to neurodegeneration. Nat. Med 2004;10:S2–S9. [PubMed: 15272266]
15. Ventruti A, Cuervo AM. Autophagy and neurodegeneration. Curr. Neurol. Neurosci. Rep 2007;7(5): 443–451. [PubMed: 17764636]

16. Collister KA, Albensi BC. Potential therapeutic targets in the NF-κB pathway for Alzheimer's disease. Drug News Perspect 2005;18(10):623–629. [PubMed: 16491164]
17. Bruijn LI, Cudkowicz M. Therapeutic targets for amyotrophic lateral sclerosis: current treatments and prospects for more effective therapies. Expert Rev. Neurother 2006;6(3):417–428. [PubMed: 16533145]
18. Tyler CM, Federoff HJ. CNS gene therapy and a nexus of complexity: systems and biology at a crossroads. Cell Transplant 2006;15(3):267–273. [PubMed: 16719061]
19. Weimer DL, Sager MA. Early identification and treatment of Alzheimer's disease: social and fiscal outcomes. Alzheimers Dement 2009;5(3):215–226. [PubMed: 19362885]
20. Querbes O, Aubry F, Pariente J, et al. Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. Brain. 2009 (Epub ahead of print).
21. Listerud J, Powers C, Moore P, Libon DJ, Grossman M. Neuropsychological patterns in magnetic resonance imaging-defined subgroups of patients with degenerative dementia. J. Int. Neuropsychol. Soc 2009;15(3):459–470. [PubMed: 19402932]
22. Pihlajamaki M, Jauhiainen AM, Soininen H. Structural and functional MRI in mild cognitive impairment. Curr. Alzheimer Res 2009;6(2):179–185. [PubMed: 19355853]
23. Chauvire V, Even C, Thuile J, Rouillon F, Guelfi JD. [Frontotemporal dementia: a review]. Encephale 2007;33(6):933–940. [PubMed: 18789785]
24. Galariotis V, Bodi N, Janka Z, Kalman J. Frontotemporal dementia - Part II. Differential diagnosis, genetics, molecular pathomechanism and pathology. Ideggyogy. Sz 2005;58(7–8):220–224. [PubMed: 16173270]
25. Giannakopoulos P, Gold G, Kovari E, et al. Assessing the cognitive impact of Alzheimer disease pathology and vascular burden in the aging brain: the Geneva experience. Acta Neuropathol 2007;113 (1):1–12. [PubMed: 17036244]
26. Giannakopoulos P, Kovari E, Gold G, von Gunten A, Hof PR, Bouras C. Pathological substrates of cognitive decline in Alzheimer's disease. Front. Neurol. Neurosci 2009;24:20–29. [PubMed: 19182459]
27. Castellani RJ, Zhu X, Lee HG, Smith MA, Perry G. Molecular pathogenesis of Alzheimer's disease: reductionist versus expansionist approaches. Int. J. Mol. Sci 2009;10(3):1386–1406. [PubMed: 19399255]
28. Salloway S, Mintzer J, Weiner MF, Cummings JL. Disease-modifying therapies in Alzheimer's disease. Alzheimers Dement 2008;4(2):65–79. [PubMed: 18631951]
29. Rafii MS, Aisen PS. Recent developments in Alzheimer's disease therapeutics. BMC Med 2009;7:7. [PubMed: 19228370]
30. Golde TE. Disease modifying therapy for AD? J. Neurochem 2006;99(3):689–707.
31. Sigurdsson EM. Immunotherapy targeting pathological tau protein in Alzheimer's disease and related tauopathies. J. Alzheimers Dis 2008;15(2):157–168. [PubMed: 18953105]
32. Gardiner J, Barton D, Overall R, Marc J. Neurotrophic support and oxidative stress: converging effects in the normal and diseased nervous system. Neuroscientist 2009;15(1):47–61. [PubMed: 19218230]
33. Block ML. NADPH oxidase as a therapeutic target in Alzheimer's disease. BMC Neurosci 2008;9:S8. [PubMed: 19090996]
34. Rojo LE, Fernandez JA, Maccioni AA, Jimenez JM, Maccioni RB. Neuroinflammation: implications for the pathogenesis and molecular diagnosis of Alzheimer's disease. Arch. Med. Res 2008;39(1): 1–16. [PubMed: 18067990]
35. Nazem A, Mansoori GA. Nanotechnology solutions for Alzheimer's disease: advances in research tools, diagnostic methods and therapeutic agents. J. Alzheimers Dis 2008;13(2):199–223. [PubMed: 18376062]
36. Lovell MA, Robertson JD, Teesdale WJ, Campbell JL, Markesbery WR. Copper, iron and zinc in Alzheimer's disease senile plaques. J. Neurol. Sci 1998;158(1):47–52. [PubMed: 9667777]
37. Sayre LM, Perry G, Harris PL, Liu Y, Schubert KA, Smith MA. *In situ* oxidative catalysis by neurofibrillary tangles and senile plaques in Alzheimer's disease: a central role for bound transition metals. J. Neurochem 2000;74(1):270–279. [PubMed: 10617129]

38. Sayre LM, Perry G, Smith MA. Redox metals and neurodegenerative disease. Curr. Opin. Chem. Biol 1999;3(2):220–225. [PubMed: 10226049]
39. Bush AI, Pettingell WH, Multhaup G, et al. Rapid induction of Alzheimer Aβ amyloid formation by zinc. Science 1994;265(5177):1464–1467. [PubMed: 8073293]
40. Hesse L, Beher D, Masters CL, Multhaup G. The βA4 amyloid precursor protein binding to copper. FEBS Lett 1994;349(1):109–116. [PubMed: 7913895]
41. Crowe A, Morgan EH. Effects of chelators on iron uptake and release by the brain in the rat. Neurochem. Res 1994;19(1):71–76. [PubMed: 8139766]
42. Hider RC, Epemolu O, Singh S, Porter JB. Iron chelator design. Adv. Exp. Med. Biol 1994;356:343–349. [PubMed: 7887240]
43. Marsh JN, Senpan A, Hu G, et al. Fibrin-targeted perfluorocarbon nanoparticles for targeted thrombolysis. Nanomed 2007;2(4):533–543. [PubMed: 17716136]
44. Cui Z, Lockman PR, Atwood CS, et al. Novel d-penicillamine carrying nanoparticles for metal chelation therapy in Alzheimer's and other CNS diseases. Eur. J. Pharm. Biopharm 2005;59(2):263–272. [PubMed: 15661498]
45. Liu G, Men P, Harris PL, Rolston RK, Perry G, Smith MA. Nanoparticle iron chelators: a new therapeutic approach in Alzheimer disease and other neurologic disorders associated with trace metal imbalance. Neurosci. Lett 2006;406(3):189–193. [PubMed: 16919875]
46. Liu G, Men P, Kudo W, Perry G, Smith MA. Nanoparticle–chelator conjugates as inhibitors of amyloid-β aggregation and neurotoxicity: a novel therapeutic approach for Alzheimer disease. Neurosci. Lett 2009;455(3):187–190. [PubMed: 19429118]
47. Bayer TA, Schafer S, Simons A, et al. Dietary Cu stabilizes brain superoxide dismutase 1 activity and reduces amyloid Aβ production in APP23 transgenic mice. Proc. Natl Acad. Sci. USA 2003;100(24):14187–14192. [PubMed: 14617773]
48. Bellingham SA, Lahiri DK, Maloney B, La Fontaine S, Multhaup G, Camakaris J. Copper depletion down-regulates expression of the Alzheimer's disease amyloid-β precursor protein gene. J. Biol. Chem 2004;279(19):20378–20386. [PubMed: 14985339]
49. Phinney AL, Drisaldi B, Schmidt SD, et al. In vivo reduction of amyloid-β by a mutant copper transporter. Proc. Natl Acad. Sci. USA 2003;100(24):14193–14198. [PubMed: 14617772]
50. Multhaup G, Treiber C, Quadir M, et al. Cellular copper import by nanocarrier systems, intracellular availability and effects on amyloid peptide secretion. Biochemistry 2009;48(20):4273–4284. [PubMed: 19331399]
51. Kessler H, Bayer TA, Bach D, et al. Intake of copper has no effect on cognition in patients with mild Alzheimer's disease: a pilot Phase 2 clinical trial. J. Neural Transm 2008;115(8):1181–1187. [PubMed: 18587525]
52. Adlard PA, Cherny RA, Finkelstein DI, et al. Rapid restoration of cognition in Alzheimer's transgenic mice with 8-hydroxy quinoline analogs is associated with decreased interstitial Aβ. Neuron 2008;59(1):43–55. [PubMed: 18614028]
53. Filomeni G, Cerchiaro G, Da Costa Ferreira AM, et al. Pro-apoptotic activity of novel isatin–Schiff base copper(II) complexes depends on oxidative stress induction and organelle-selective damage. J. Biol. Chem 2007;282(16):12010–12021. [PubMed: 17327230]
54. Lee JY, Friedman JE, Angel I, Kozak A, Koh JY. The lipophilic metal chelator DP-109 reduces amyloid pathology in brains of human β-amyloid precursor protein transgenic mice. Neurobiol. Aging 2004;25(10):1315–1321. [PubMed: 15465629]
55. Strozyk D, Launer LJ, Adlard PA, et al. Zinc and copper modulate Alzheimer Aβ levels in human cerebrospinal fluid. Neurobiol. Aging 2007;30(7):1069–1077. [PubMed: 18068270]
56. Talmard C, Bouzan A, Faller P. Zinc binding to amyloid-β isothermal titration calorimetry and Zn competition experiments with Zn sensors. Biochemistry 2007;46(47):13658–13666. [PubMed: 17983245]
57. Zhang LH, Wang X, Stoltenberg M, Danscher G, Huang L, Wang ZY. Abundant expression of zinc transporters in the amyloid plaques of Alzheimer's disease brain. Brain Res. Bull 2008;77(1):55–60. [PubMed: 18639746]

58. Klajnert B, Cangiotti M, Calici S, et al. EPR study of the interactions between dendrimers and peptides involved in Alzheimer's and prion diseases. Macromol. Biosci 2007;7(8):1065–1074. [PubMed: 17654761]
59. Cabaleiro-Lago C, Quinlan-Pluck F, Lynch I, et al. Inhibition of amyloid β protein fibrillation by polymeric nanoparticles. J. Am. Chem. Soc 2008;130(46):15437–15443. [PubMed: 18954050]
60. Podolski IY, Podlubnaya ZA, Kosenko EA, et al. Effects of hydrated forms of C_{60} fullerene on amyloid 1-peptide fibrillization in vitro and performance of the cognitive task. J. Nanosci. Nanotechnol 2007;7(4–5):1479–1485. [PubMed: 17450915]
61. Pai AS, Rubinstein I, Onyuksel H. PEGylated phospholipid nanomicelles interact with β-amyloid(1–42) and mitigate its β-sheet formation, aggregation and neurotoxicity in vitro. Peptides 2006;27(11): 2858–2866. [PubMed: 16762454]
62. Skaat H, Sorci M, Belfort G, Margel S. Effect of maghemite nanoparticles on insulin amyloid fibril formation: selective labeling, kinetics, and fibril removal by a magnetic field. J. Biomed. Mater. Res. A. 2008 (Epub ahead of print).
63. Patel DA, Henry JE. Good TA: Attenuation of β -amyloid-induced toxicity by sialic-acid-conjugated dendrimers: role of sialic acid attachment. Brain Res 2007;1161:95–105. [PubMed: 17604005]
64. Patel D, Henry J, Good T. Attenuation of β-amyloid induced toxicity by sialic acid-conjugated dendrimeric polymers. Biochim. Biophys. Acta 2006;1760(12):1802–1809. [PubMed: 16982154]
65. Olmedo I, Araya E, Sanz F, et al. How changes in the sequence of the peptide CLPFFD-NH2 can modify the conjugation and stability of gold nanoparticles and their affinity for β-amyloid fibrils. Bioconjug. Chem 2008;19(6):1154–1163. [PubMed: 18510352]
66. Triulzi RC, Dai Q, Zou J, et al. Photothermal ablation of amyloid aggregates by gold nanoparticles. Colloids Surf. B Biointerfaces 2008;63(2):200–208. [PubMed: 18262396]
67. Kogan MJ, Bastus NG, Amigo R, et al. Nanoparticle-mediated local and remote manipulation of protein aggregation. Nano Lett 2006;6(1):110–115. [PubMed: 16402797]
68. Aliev G, Obrenovich ME, et al. Reddy VP : Antioxidant therapy in Alzheimer′s disease: theory and practice. Mini Rev. Med. Chem 2008;8(13):1395–1406. [PubMed: 18991755]
69. Yokoyama H, Kuroiwa H, Yano R, Araki T. Targeting reactive oxygen species, reactive nitrogen species and inflammation in MPTP neurotoxicity and Parkinson's disease. Neurol. Sci 2008;29(5): 293–301. [PubMed: 18941931]
70. Yokoyama H, Takagi S, Watanabe Y, Kato H, Araki T. Role of reactive nitrogen and reactive oxygen species against MPTP neurotoxicity in mice. J. Neural Transm 2008;115(6):831–842. [PubMed: 18235988]
71. Wilson B, Samanta MK, Santhi K, Sampath Kumar KP, Ramasamy M, Suresh B. Significant delivery of tacrine into the brain using magnetic chitosan microparticles for treating Alzheimer's disease. J. Neurosci. Methods 2009;177(2):427–433. [PubMed: 19041670]
72. Chu D, Tian J, Liu W, Li Z, Li Y. Poly(lactic-co-glycolic acid) microspheres for the controlled release of huperzine A:*in vitro and in vivo* studies and the application in the treatment of the impaired memory of mice. Chem. Pharm. Bull. (Tokyo) 2007;55(4):625–628. [PubMed: 17409558]
73. Wang C, Zhang T, Ma H, Liu J, Fu F, Liu K. Prolonged effects of poly(lactic-co-glycolic acid) microsphere-containing huperzine A on mouse memory dysfunction induced by scopolamine. Basic Clin. Pharmacol. Toxicol 2007;100(3):190–195. [PubMed: 17309523]
74. Shinjini Singh MS, Gambhir IS. Nanotechnology for Alzheimer's disease detection. Digest J. Nanomater. Biostruct 2008;3(2):75–79.
75. Lee JH, Kang DY, Kim SU, Yea CH, Oh BK, Choi JW. Electrical detection of β-amyloid (1–40) using scanning tunneling microscopy. Ultramicroscopy. 2009 (Epub ahead of print).
76. Kang DY, Lee JH, Oh BK, Choi JW. Ultra-sensitive immunosensor for β-amyloid (1–42) using scanning tunneling microscopy-based electrical detection. Biosens. Bioelectron 2009;24(5):1431–1436. [PubMed: 18829296]
77. Vestergaard M, Kerman K, Kim DK, Ha MH, Tamiya E. Detection of Alzheimer's tau protein using localised surface plasmon resonance-based immunochip. Talanta 2008;74(4):1038–1042. [PubMed: 18371746]
78. Braak H, Del Tredici K. Neuroanatomy and pathology of sporadic Parkinson's disease. Adv. Anat. Embryol. Cell Biol 2009;201:1–119. [PubMed: 19230552]

79. Dauer W, Przedborski S. Parkinson's mechanisms and models. Neuron 2003;39(6):889–909. [PubMed: 12971891]
80. Zhou C, Huang Y, Przedborski S. Oxidative stress in Parkinson's disease: a mechanism of pathogenic and therapeutic significance. Ann. NY Acad. Sci 2008;1147:93–104. [PubMed: 19076434]
81. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol 2009;8(4):382–397. [PubMed: 19296921]
82. Roodveldt C, Christodoulou J, Dobson CM. Immunological features of α-synuclein in Parkinson's disease. J. Cell Mol. Med 2008;12(5B):1820–1829. [PubMed: 18671754]
83. Lesage S, Brice A. Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum. Mol. Genet 2009;18(R1):R48–R59. [PubMed: 19297401]
84. Dubow JS. Autonomic dysfunction in Parkinson's disease. Dis. Mon 2007;53(5):265–274. [PubMed: 17656188]
85. Magerkurth C, Schnitzer R, Braune S. Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. Clin. Auton. Res 2005;15(2):76–82. [PubMed: 15834763]
86. Reynolds AD, Stone DK, Mosley RL, Gendelman HE. Nitrated α-synuclein-induced alterations in microglial immunity are regulated by $CD4^+$ T cell subsets. J. Immunol 2009;182(7):4137–4149. [PubMed: 19299711]
87. Mosley RL, Benner EJ, Kadiu I, et al. Neuroinflammation, oxidative stress and the pathogenesis of Parkinson's disease. Clin. Neurosci. Res 2006;6(5):261–281. [PubMed: 18060039]
88. Stone DK, Reynolds AD, Mosley RL, Gendelman HE. Innate and adaptive immunity for the pathobiology of Parkinson's disease. Antioxid. Redox Signal. 2009 (Epub ahead of print).
89. Bakry R, Vallant RM, Najam-ul-Haq M, et al. Medicinal applications of fullerenes. Int. J. Nanomedicine 2007;2(4):639–649. [PubMed: 18203430]
90. Markovic Z, Trajkovic V. Biomedical potential of the reactive oxygen species generation and quenching by fullerenes (C_{60}). Biomaterials 2008;29(26):3561–3573. [PubMed: 18534675]
91. Mateo-Alonso A, Guldi DM, Paolucci F, Prato M. Fullerenes: multitask components in molecular machinery. Angew. Chem. Int. Ed. Engl 2007;46(43):8120–8126. [PubMed: 17926311]
92. Krokosz A. [Fullerenes in biology]. Postepy Biochem 2007;53(1):91–96. [PubMed: 17718393]
93. Santos SG, Santana JV, Maia FF Jr, et al. Adsorption of ascorbic acid on the C_{60} fullerene. J. Phys. Chem. B 2008;112(45):14267–14272. [PubMed: 18939786]
94. Kolosnjaj J, Szwarc H, Moussa F. Toxicity studies of fullerenes and derivatives. Adv. Exp. Med. Biol 2007;620:168–180. [PubMed: 18217343]
95. Shinohara N, Matsumoto T, Gamo M, et al. Is lipid peroxidation induced by the aqueous suspension of fullerene C_{60} nanoparticles in the brains of Cyprinus carpio? Environ. Sci. Technol 2009;43(3): 948–953.
96. Cai X, Jia H, Liu Z, et al. Polyhydroxylated fullerene derivative $C_{60}OH_{24}$ prevents mitochondrial dysfunction and oxidative damage in an MPP^+-induced cellular model of Parkinson's disease. J. Neurosci. Res 2008;86(16):3622–3634. [PubMed: 18709653]
97. Kabanov AV, Gendelman HE. Nanomedicine in the diagnosis and therapy of neurodegenerative disorders. Prog. Polym. Sci 2007;32:1054–1082.
98. Batrakova EV, Li S, Reynolds AD, et al. A macrophage-nanozyme delivery system for Parkinson's disease. Bioconjug. Chem 2007;18(5):1498–1506. [PubMed: 17760417]
99. Reynolds AD, Stone DK, Mosley RL, Gendelman HE. Proteomic studies of nitrated α-synuclein microglia regulation by $CD4^+CD25^+$ T cells. J. Proteome Res. 2009 (Epub ahead of print).
100. Reynolds AD, Banerjee R, Liu J, Gendelman HE, Mosley RL. Neuroprotective activities of $CD4^+CD25^+$ regulatory T cells in an animal model of Parkinson's disease. J. Leukoc. Biol 2007;82(5): 1083–1094. [PubMed: 17675560]
101. Huang X, Reynolds AD, Mosley RL, Gendelman HE. $CD4^+$ T cells for the pathobiology of neurodegenerative disorders. J. Neuroimmunol. 2009 (Epub ahead of print).
102. Hashimoto M, Asai Y, Ogawa T. Treponemal phospholipids inhibit innate immune responses induced by pathogen-associated molecular patterns. J. Biol. Chem 2003;278(45):44205–44213. [PubMed: 12947124]

103. Huynh ML, Fadok VA, Henson PM. Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF-β1 secretion and the resolution of inflammation. J. Clin. Invest 2002;109(1):41–50. [PubMed: 11781349]
104. Crotty S, Fitzgerald P, Tuohy E, et al. Neuroprotective effects of novel phosphatidylglycerol-based phospholipids in the 6-hydroxydopamine model of Parkinson's disease. Eur. J. Neurosci 2008;27 (2):294–300. [PubMed: 18190522]
105. Cook C, Petrucelli L. A critical evaluation of the ubiquitin–proteasome system in Parkinson's disease. Biochim. Biophys. Acta. 2009 (Epub ahead of print).
106. Fitzgerald P, Mandel A, Bolton AE, Sullivan AM, Nolan Y. Treatment with phosphotidylglycerol-based nanoparticles prevents motor deficits induced by proteasome inhibition: implications for Parkinson's disease. Behav. Brain Res 2008;195(2):271–274. [PubMed: 18817814]
107. Hasadsri L, Kreuter J, Hattori H, Iwasaki T, George JM. Functional protein delivery into neurons using polymeric nanoparticles. J. Biol. Chem 2009;284(11):6972–6981. [PubMed: 19129199]
108. Esposito E, Fantin M, Marti M, et al. Solid lipid nanoparticles as delivery systems for bromocriptine. Pharm. Res 2008;25(7):1521–1530. [PubMed: 18172580]
109. Zoccolella S, Beghi E, Palagano G, et al. Signs and symptoms at diagnosis of amyotrophic lateral sclerosis: a population-based study in southern Italy. Eur. J. Neurol 2006;13(7):789–792. [PubMed: 16834713]
110. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. Lancet 2007;369(9578):2031–2041. [PubMed: 17574095]
111. Qureshi MM, Hayden D, Urbinelli L, et al. Analysis of factors that modify susceptibility and rate of progression in amyotrophic lateral sclerosis (ALS). Amyotroph. Lateral Scler 2006;7(3):173–182. [PubMed: 16963407]
112. Shaw PJ. Molecular and cellular pathways of neurodegeneration in motor neurone disease. J. Neurol. Neurosurg. Psychiatry 2005;76(8):1046–1057. [PubMed: 16024877]
113. Rothstein JD. Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. Ann. Neurol 2009;65:S3–S9. [PubMed: 19191304]
114. Eisen A. Amyotrophic lateral sclerosis:a 40-year personal perspective. J. Clin. Neurosci 2009;16 (4):505–512. [PubMed: 19231200]
115. Reddy MK, Wu L, Kou W, Ghorpade A, Labhasetwar V. Superoxide dismutase-loaded PLGA nanoparticles protect cultured human neurons under oxidative stress. Appl. Biochem. Biotechnol 2008;151(2–3):565–577. [PubMed: 18509606]
116. Ali SS, Hardt JI, Dugan LL. SOD activity of carboxyfullerenes predicts their neuroprotective efficacy: a structure– activity study. Nanomedicine 2008;4(4):283–294. [PubMed: 18656425]
117. Shibata N, Nagai R, Miyata S, et al. Nonoxidative protein glycation is implicated in familial amyotrophic lateral sclerosis with superoxide dismutase-1 mutation. Acta Neuropathol 2000;100 (3):275–284. [PubMed: 10965797]
118. Cho Y, Shi R, Borgens RB, Ivanisevic A. Functionalized mesoporous silica nanoparticle-based drug delivery system to rescue acrolein-mediated cell death. Nanomed 2008;3(4):507–519. [PubMed: 18694313]
119. Hong S, Choi I, Lee S, Yang YI, Kang T, Yi J. Sensitive and colorimetric detection of the structural evolution of superoxide dismutase with gold nanoparticles. Anal. Chem 2009;81(4):1378–1382. [PubMed: 19170529]
120. Genova HM, Sumowski JF, Chiaravalloti N, Voelbel GT, Deluca J. Cognition in multiple sclerosis: a review of neuropsychological and fMRI research. Front. Biosci 2009;14:1730–1744. [PubMed: 19273158]
121. Wallin MT, Wilken JA, Kane R. Cognitive dysfunction in multiple sclerosis: Assessment, imaging, and risk factors. J. Rehabil. Res. Dev 2006;43(1):63–72. [PubMed: 16847772]
122. Murray J. Prelude to the framing of a disease: multiple sclerosis in the period before Charcots Lecons. Int. MS J 2004;11(3):79–85. [PubMed: 15585165]
123. Lassmann H. Multiple sclerosis pathology: evolution of pathogenetic concepts. Brain Pathol 2005;15 (3):217–222. [PubMed: 16196388]

124. Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann. Neurol 2000;47 (6):707–717. [PubMed: 10852536]
125. Korn T. Pathophysiology of multiple sclerosis. J. Neurol 2008;255:2–6. [PubMed: 19300953]
126. Rojas JI, Romano M, Ciapponi A, Patrucco L, Cristiano E. Interferon β for primary progressive multiple sclerosis. Cochrane Database Syst. Rev 2009;1 CD006643.
127. Clerico M, Faggiano F, Palace J, Rice G, Tintore M, Durelli L. Recombinant interferon β or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. Cochrane Database Syst. Rev 2008;2 CD005278.
128. Stangel M. Neuroprotection and neuroregeneration in multiple sclerosis. J. Neurol 2008;255:77–81. [PubMed: 19300964]
129. Chari DM. Remyelination in multiple sclerosis. Int. Rev. Neurobiol 2007;79:589–620. [PubMed: 17531860]
130. Franklin RJ, Ffrench-Constant C. Remyelination in the CNS: from biology to therapy. Nat. Rev. Neurosci 2008;9(11):839–855. [PubMed: 18931697]
131. Basso AS, Frenkel D, Quintana FJ, et al. Reversal of axonal loss and disability in a mouse model of progressive multiple sclerosis. J. Clin. Invest 2008;118(4):1532–1543. [PubMed: 18340379]
132. Li W, Minohara M, Su JJ, et al. Helicobacter pylori infection is a potential protective factor against conventional multiple sclerosis in the Japanese population. J. Neuroimmunol 2007;184(1–2):227–231. [PubMed: 17296235]
133. Pezeshki MZ, Zarrintan S, Zarrintan MH. Helicobacter pylori nanoparticles as a potential treatment of conventional multiple sclerosis. Med. Hypotheses 2008;70(6):1223. [PubMed: 18242004]
134. Chan A, Stuve O, von Ahsen N. Immunosuppression in clinical practice: approaches to individualized therapy. J. Neurol 2008;255:22–27. [PubMed: 19300956]
135. Neuhaus O, Kieseier BC, Hartung HP. Immunosuppressive agents in multiple sclerosis. Neurotherapeutics 2007;4(4):654–660. [PubMed: 17920546]
136. Boster A, Edan G, Frohman E, et al. Intense immunosuppression in patients with rapidly worsening multiple sclerosis: treatment guidelines for the clinician. Lancet Neurol 2008;7(2):173–183. [PubMed: 18207115]
137. Ryan JJ, Bateman HR, Stover A, et al. Fullerene nanomaterials inhibit the allergic response. J. Immunol 2007;179(1):665–672. [PubMed: 17579089]
138. van Kasteren SI, Campbell SJ, Serres S, Anthony DC, Sibson NR, Davis BG. Glyconanoparticles allow pre-symptomatic in vivo imaging of brain disease. Proc. Natl Acad. Sci. USA 2009;106(1): 18–23. [PubMed: 19106304]
139. McAteer MA, Sibson NR, von Zur Muhlen C, et al. In vivo magnetic resonance imaging of acute brain inflammation using microparticles of iron oxide. Nat. Med 2007;13(10):1253–1258. [PubMed: 17891147]
140. Petry KG, Boiziau C, Dousset V, Brochet B. Magnetic resonance imaging of human brain macrophage infiltration. Neurotherapeutics 2007;4(3):434–442. [PubMed: 17599709]
141. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. Stroke 2006;37(10): 2493–2498. [PubMed: 16931783]
142. Reddy MK, Labhasetwar V. Nanoparticle-mediated delivery of superoxide dismutase to the brain: an effective strategy to reduce ischemia-reperfusion injury. FASEB J 2009;23(5):1384–1395. [PubMed: 19124559]
143. Chen J, Patil S, Seal S, McGinnis JF. Rare earth nanoparticles prevent retinal degeneration induced by intracellular peroxides. Nat. Nanotechnol 2006;1(2):142–150. [PubMed: 18654167]
144. Schubert D, Dargusch R, Raitano J, Chan SW. Cerium and yttrium oxide nanoparticles are neuroprotective. Biochem. Biophys. Res. Commun 2006;342(1):86–91. [PubMed: 16480682]
145. Das M, Patil S, Bhargava N, et al. Auto-catalytic ceria nanoparticles offer neuroprotection to adult rat spinal cord neurons. Biomaterials 2007;28(10):1918–1925. [PubMed: 17222903]
146. Rabinovici R, Rudolph AS, Ligler FS, Yue TL, Feuerstein G. Liposome-encapsulated hemoglobin: an oxygen-carrying fluid. Circ. Shock 1990;32(1):1–17. [PubMed: 2208604]

147. Kawaguchi AT, Fukumoto D, Haida M, Ogata Y, Yamano M, Tsukada H. Liposome-encapsulated hemoglobin reduces the size of cerebral infarction in the rat: evaluation with photochemically induced thrombosis of the middle cerebral artery. Stroke 2007;38(5):1626–1632. [PubMed: 17395856]

148. Fukumoto D, Kawaguchi AT, Haida M, Yamano M, Ogata Y, Tsukada H. Liposome-encapsulated hemoglobin reduces the size of cerebral infarction in rats: effect of oxygen affinity. Artif. Organs 2009;33(2):159–163. [PubMed: 19178461]

149. Kawaguchi AT, Kurita D, Furuya H, Yamano M, Ogata Y, Haida M. Liposome-encapsulated hemoglobin alleviates brain edema after permanent occlusion of the middle cerebral artery in rats. Artif. Organs 2009;33(2):153–158. [PubMed: 19178460]

150. Urakami T, Kawaguchi AT, Akai S, et al. In vivo distribution of liposome-encapsulated hemoglobin determined by positron emission tomography. Artif. Organs 2009;33(2):164–168. [PubMed: 19178462]

151. McArthur JC. HIV dementia: an evolving disease. J. Neuroimmunol 2004;157(1–2):3–10. [PubMed: 15579274]

152. Kadiu I, Glanzer JG, Kipnis J, Gendelman HE, Thomas MP. Mononuclear phagocytes in the pathogenesis of neurodegenerative diseases. Neurotox. Res 2005;8(1–2):25–50. [PubMed: 16260384]

153. Kure K, Llena JF, Lyman WD, et al. Human immunodeficiency virus-1 infection of the nervous system: an autopsy study of 268 adult, pediatric, and fetal brains. Hum. Pathol 1991;22(7):700–710. [PubMed: 2071114]

154. Brew BJ, Rosenblum M, Cronin K, Price RW. AIDS dementia complex and HIV-1 brain infection: clinical–virological correlations. Ann. Neurol 1995;38(4):563–570. [PubMed: 7574452]

155. Kaul M, Zheng J, Okamoto S, Gendelman HE, Lipton SA. HIV-1 infection and AIDS: consequences for the central nervous system. Cell Death Differ 2005;12:878–892. [PubMed: 15832177]

156. Alexaki A, Liu Y, Wigdahl B. Cellular reservoirs of HIV-1 and their role in viral persistence. Curr. HIV Res 2008;6(5):388–400. [PubMed: 18855649]

157. Varatharajan L, Thomas SA. The transport of anti-HIV drugs across blood–CNS interfaces: summary of current knowledge and recommendations for further research. Antiviral Res 2009;82 (2):A99–A109. [PubMed: 19176219]

158. Nowacek A, Gendelman HE. NanoART, NeuroAIDS and CNS drug delivery. Nanomedicine 2009;4 (5):557–574. [PubMed: 19572821]

159. Chattopadhyay N, Zastre J, Wong HL, Wu XY, Bendayan R. Solid lipid nanoparticles enhance the delivery of the HIV protease inhibitor, atazanavir, by a human brain endothelial cell line. Pharm. Res 2008;25(10):2262–2271. [PubMed: 18516666]

160. Rao KS, Reddy MK, Horning JL, Labhasetwar V. TAT-conjugated nanoparticles for the CNS delivery of anti-HIV drugs. Biomaterials 2008;29(33):4429–4438. [PubMed: 18760470]

161. Kuo YC, Su FL. Transport of stavudine, delavirdine, and saquinavir across the blood–brain barrier by polybutylcyanoacrylate, methylmethacrylate-sulfopropylmethacrylate, and solid lipid nanoparticles. Int. J. Pharm 2007;340(1–2):143–152. [PubMed: 17418986]

Table 1

Summarization of neurodegenerative diseases and their developing nanomedicine therapies.

Disease	Therapeutic mechanism	Particle composition	Finding	Ref
Alzheimer's disease				
	Metal chelation	Polystyrene conjugated to MAEHP	Inhibit Aβ aggregation and Aβ aggregate neurotoxicity in AD-fixed brain sections. Bind to ApoE and ApoA1 that could facilitate brain entrance and exit	[44]
	Metal supplementation	Polyethyleneimine (hyperbranched) cores with single or multiple organic shells	Encapsulate copper, transport it to neurons and decrease Aβ aggregates *in vitro*	[49]
	Inhibition of Aβ aggregate formation	*N*-isopropylacrylamide: *N*-tert-butylacrylamide	Quench and temporarily reverse fibrillization of Aβ *in vitro*	[57]
	Aβ aggregate sequestration	Maghemite	Removal of Aβ fibrils from aqueous phase with a magnetic field	[60]
	Aβ aggregate ablation	Au NPs coated with CLPFFD-NH_2 peptide	Selectively ablate Aβ aggregates that contain Au NPs with laser exposure	[64]
	Improve drug delivery	Tacrine-containing magnetic chitosan microparticles	Increased drug delivery to brain with placement of magnet	[66]
Parkinson's disease				
	Antioxidation	Polyhydroxylated fullerene derivative, $C_{60}(OH)_{24}$	Prevent mitochondrial oxidative damage induced by MPTP in human neuroblastoma cells	[86]
	Decrease ROS production	Polyethyleneimine-PEG-containing catalase	Cell-mediated delivery of catalase to brain	[87]
	Reduce neuroinflammation	VP025 (Vasogen Inc.), phosphatidylglycerol-based phospholipid NP	Neuroprotective with pretreatment in a 6-OHDA mouse	[90]
	Delivery of functional proteins	Poly(butyl cyanoacrylate)	Delivery of functional proteins to primary hippocampal cultures. Uptake dependent on LDL receptor.	[93]

Disease	Therapeutic mechanism	Particle composition	Finding	Ref
	Improve drug delivery	Bromocriptine crystals suspended in tristearin/ tricaprin lipid combination and coated with poloxamer-188	mproved pharmacokinetics over free drug	[94]
Amyotrophic lateral sclerosis				
	Replenish SOD	SOD-containing PLGA	Deliver SOD to neurons and protect against oxidative damage *in vitro*	[101]
	Supplement SOD	Carboxyfullerene SOD mimetics	Cross cell membranes and high reactivity to superoxide radicals	[102]
	Endotoxin	Mesoporous silica loaded with hydralazine and coated with PEG	Reduce damage caused to cell membranes and mitochondria induced by acrolein	[104]
Multiple sclerosis				
	Neuroprotection	Fullerene derivative (ABS-75) functionalized with an NMDA receptor antagonist	Reduced disease progression in mouse model	[115]
	Immune inhibition	C_{60} fullerenes	Inhibition of initiation and propagation of antigen-driven type I hypersensitivity reaction	[121]
	Immune modulation	NP-containing *Helicobacter pylori* peptides	Purposed, not yet tested	[117]
Stroke				
	Reduce production of ROS	SOD encapsulated in PLGA	BBB integrity maintained, edema prevented, level of ROS formed reduced and decreased neuronal apoptosis	[126
	Re-establish blood flow	Perfluorocarbon NP with bound plasminogen activator streptokinase	Specific and rapid fibrinolysis *in vitro*	[130]
	Increase oxygen delivery	Liposome-encapsulated hemoglobin	Oxygen delivery beyond thrombotic obstruction Decrease infarct size and edema	[132]
HIV-1-associated neurocognitive disorders				
	Antiretroviral therapy	SLNs with atazanivir	SLN of approximately 167 nm cross BBB	[143]
	Antiretroviral therapy	TAT-peptide-conjugated ritonavir	Shields ritonavir from the efflux activity of p-glycoprotein in BBB	[144]

Disease	Therapeutic mechanism	Particle composition	Finding	Ref
	Antiretroviral therapy	SLNs, PBCA and MMA-SPM associated with stavudine, delavirdine and saquinivir	NP association allows for an increased transport across the BBB	[145]

6-OHDA: 6-hydroxydopamine; Aβ: Amyloid-β; AD: Alzheimer's disease; Au: Gold; BBB: Blood-brain barrier; LDL: Low-density lipoprotein; MAEHP: 2-methyl-N-(2-aminoethyl)-3-hydroxyl-4-pyridinone;MMP-SPM: Methylmethacrylate-sulfopropylmethacrylate; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyhdine; NP: Nanoparticle; PBCA: Polybutylcyanoacrylate; PEG: Polyethylene glycol; PLGA: Poly(lactic-co-glycolyticacid); ROS: Reactive oxygen species; SLN: Solid lipid nanoparticle; SOD: Superoxide dismutase.