Review
Self-Assembled Nanoscale Materials for Neuronal Regeneration: A Focus on BDNF Protein and Nucleic Acid Biotherapeutic Delivery

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Abstract: Enabling challenging applications of nanomedicine and precision medicine in the treatment of neurodegenerative disorders requires deeper investigations of nanocarrier-mediated biomolecular delivery for neuronal targeting and recovery. The successful use of macromolecular biotherapeutics (recombinant growth factors, antibodies, enzymes, synthetic peptides, cell-penetrating peptide–drug conjugates, and RNAi sequences) in clinical developments for neuronal regeneration should benefit from the recent strategies for enhancement of their bioavailability. We highlight the advances in the development of nanoscale materials for drug delivery in neurodegenerative disorders. The emphasis is placed on nanoformulations for the delivery of brain-derived neurotrophic factor (BDNF) using different types of lipidic nanocarriers (liposomes, liquid crystalline or solid lipid nanoparticles) and polymer-based scaffolds, nanofibers and hydrogels. Self-assembled soft-matter nanoscale materials show favorable neuroprotective characteristics, safety, and efficacy profiles in drug delivery to the central and peripheral nervous systems. The advances summarized here indicate that neuroprotective biomolecule-loaded nanoparticles and injectable hydrogels can improve neuronal survival and reduce tissue injury. Certain recently reported neuronal dysfunctions in long-COVID-19 survivors represent early manifestations of neurodegenerative pathologies. Therefore, BDNF delivery systems may also help in prospective studies on recovery from long-term COVID-19 neurological complications and be considered as promising systems for personalized treatment of neuronal dysfunctions and prevention or retarding of neurodegenerative disorders.

Keywords: neuroprotective assemblies; brain-derived neurotrophic factor (BDNF); nanomedicine for growth factor delivery; lipid nanoparticles; nanocarriers; nanofibers; biotherapeutics

1. Introduction
Neurodegenerative disorders have sophisticated etiology and represent a serious challenge for society [1–6]. Among the various risk factors, oxidative stress and chronic neuroinflammation (which can be due to viral infection or other causes) are involved in the pathogenesis of Parkinson’s disease (PD), Alzheimer’s disease (AD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS) [7]. These pathological conditions comprise the most common incurable neurodegenerative diseases (NDs), whose incidence and prevalence are growing. They are expected to surpass cancer with the second highest mortality rate [2,3]. PD is caused by the deterioration of dopaminergic neurons in the midbrain and is characterized by motor symptoms such as tremor, bradykinesia, and postural instability [4–6]. AD results from slow neuronal degeneration, which begins in
the hippocampus and leads to the progressive loss of memory associated with a variety of neuropsychiatric and behavioral disorders [1].

Improved understanding of the multiple risk factors as well as prospective studies of the cognitive impairments, anxiety, depression, fatigue and sleep behaviour of COVID-19 survivors with new neurological complications (arising several months after long-term hospitalization) may contribute alternative therapeutic options to be developed against the long-term impact of COVID-19. Human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is neuroinvasive and may trigger acute or chronic neurological consequences following inflammation and oxidative stress [7–11]. Accumulating evidence has revealed that COVID-19 can damage not only the respiratory system but also other organs, including the brain and heart [12]. SARS-CoV-2 species have been detected in the cytoplasm of neurons in both the hypothalamus and cortex as well as in the cerebrospinal fluid of patients with COVID-19 [13]. The neuronal loss and damage caused by severe coronavirus infection have increased the number of vulnerable patients who may develop neurodegenerative disorders or long-term neuropsychiatric diseases after hospitalization [14–17]. Some literature reports have suggested that COVID-19 affects the progression of PD [18–20]. Others have emphasized the impact of COVID-19 on Alzheimer’s disease risk [21]. Recent studies have examined whether SARS-CoV-2 infection triggers the stimulation of caspase-2, caspase-3 and caspase-8 enzymes, the increased production of reactive oxygen species (ROS), and the diminishment of neurotrophic factor (e.g., brain-derived neurotrophic factor (BDNF)) levels [9,19,20,22,23].

The existing symptomatic treatments for NDs do not stop the spreading of the neuronal degeneration that is responsible for the progressive impairments in the patients’ daily lives [24,25]. Most of the proposed medications are oral formulations requiring high doses, associated with a subsequent high incidence of side effects. In general, the available medications against NDs only temporarily improve the disease symptoms by increasing the number of neurotransmitters in the brain. In AD, four drugs have been used for the treatment of the dementia phase, namely, the glutamate antagonist memantine and the cholinesterase inhibitors donepezil, rivastigmine, and galantamine [24]. PD patients have often received levodopa combined with a drug that delays the conversion of levodopa into dopamine until it reaches the brain [26]. Anticholinergics and other drugs, which mimic the role of dopamine in the brain, may help control tremor and rigidity. However, none of them stop the process of neuronal damage, which makes the disease ultimately fatal [25]. Currently, drug delivery technologies and alternative treatments that can prevent or delay neurodegeneration and promote neuroregeneration are urgently needed, especially for vulnerable patients in the long-term post-COVID-19 conditions. Studies have been initiated on targeting ND pathogenesis by macromolecular biotherapeutics, including antibodies, growth factors, nucleic acids, and enzymes [27–29]. The designed neuroregenerative strategies aim to repair neuronal damage. However, the major challenge for clinical applications is because the brain is protected by the blood–brain barrier (BBB), through which only specialized small-molecule drugs can pass [30].

In addition to our previous reviews [31,32], in this work, we provide an overview of more recent examples of neurotrophic protein and peptide drug administration as well as of nucleic acid utilization for accelerating the regeneration of damaged neurons. We emphasize the biomimetic assemblies and nanoscale structures, which have shown promise for safe and more efficient drug delivery to the central and peripheral nervous systems. Recent nanotechnology strategies for the delivery of growth factors by liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, hydrogels, or nanofibers are outlined, with a focus on the outcomes of BDNF-loaded nanoparticles and nanofibers in neuronal regeneration trials.

2. Biomolecule Delivery in Neuroregeneration Strategies

The diverse side effects found with conventional ND treatments using small molecule compounds have encouraged research on alternative therapeutic modalities in drug deliv-
ery aimed at neuroregeneration. In principle, regeneration of neurons can be stimulated by either enhancing endogenous neurogenesis upon the administration of growth factors or by the transcription of genes involved in neuronal survival [27,33,34].

2.1. Neuroprotective Biomolecules and Nucleic Acids under Current Investigation

2.1.1. Neurotrophic Factor Protein-Based Therapies

Neurotrophic factors (NTFs) are a family of biomacromolecules (large peptides or small proteins) that support the growth, survival, and differentiation of developing and mature neurons by protecting them from injury and neurotoxins [34,35]. Nerve growth factor (NGF) was the first NTF discovered by Levi-Montalcini [36]. Subsequently, the neuroprotective functions of several other NTFs have been reported over the years [33,37–46]. They have been categorized into three main families: (i) the neurotrophin family, including NGF, BDNF, neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4); (ii) the glial cell line-derived neurotrophic factor (GDNF) family, e.g., GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN); and (iii) the neuroepoietic cytokines, e.g., ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and cardiotrophin (CT-1). Other proteins, such as fibroblast growth factor-1 and -2 (FGF-1 and FGF-2) and platelet-derived growth factor (PDGF), as well as polypeptides, including pituitary adenylate cyclase-activating peptide (PACAP), insulin-like growth factor 1 (IGF-1), human neuropeptide substance P, macrophage colony-stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), can also play a role as NTFs [47–58].

A novel family of unconventional NTFs, cerebral dopamine neurotrophic factor (CDNF) and mesencephalic astrocyte-derived neurotrophic factor (MANF), which are both structurally and mechanistically distinct from the other growth factors, have shown neurorestorative effects in animal models of PD [33]. These biotherapeutics localize to the lumen of the endoplasmic reticulum (ER) and likely modulate the unfolded protein response (UPR) pathway. Intermittent monthly bilateral intraputaminal infusions of CDNF have recently been tested in a randomized placebo-controlled phase I–II clinical trial in PD patients [33].

Studies of an AD rat model with amyloid-β-induced memory loss have demonstrated that granulocyte colony stimulating factor (GCSF), an endogenous neuronal hematopoietic factor protein, improves memory and neurobehavioral functions [39]. GCSF exerted neuroprotective activity associated with significant memory improvements, increased levels of antioxidant enzymes and total RNA expression in the brain, and reduced lipid peroxidation and acetylcholinesterase levels. In addition, GCSF induces neurogenesis, as evidenced by the increased number of progenitor CD34+ cells in the brain [39]. Clinical trials using GCSF for the treatment of AD and stroke have already been carried out [55–57]. The advantages of GCSF, as a good candidate for clinical trials in NDs, also include its capacity for crossing the BBB and its strong anti-apoptotic activity.

Several clinical trials have been conducted to examine the capacity of GDNF, NRTN and PGDF to rescue degenerating dopaminergic neurons in the substantia nigra and their axon terminals in the striatum [44,54]. GDNF has been studied as a candidate in clinical trials of PD considering its neurorestorative effects established in PD animal models [51,58]. The performed in vitro and in vivo studies with PD models have demonstrated the neuroprotective and neurorestorative effects of GDNF on midbrain dopaminergic neurons [51–54]. Unlike GCSF, the penetration of GDNF in the brain is strongly limited. Therefore, various strategies have been undertaken for GDNF delivery to the dopamine-depleted brain, e.g., implantation of microspheres, transfection by viral vectors, or ventricle and intraputaminal infusion of the protein [58–60]. The delivery of BDNF by nanoparticles and other biomimetic nanoscale assemblies will be presented in a separate section below.

2.1.2. siRNA-Based Therapy

Emerging strategies for the prevention or treatment of NDs are being developed based on selective silencing of mutant alleles. This approach aims to directly arrest the
causative mutant genes for neurodegeneration [61]. RNA interference (RNAi) regulates the expression of genes by controlling the synthesis of proteins via a post-transcriptional gene-silencing mechanism. Long double-stranded RNA sequences are cleaved by the cytoplasmic enzyme Dicer into fragments (21–23 nucleotides long) called small interfering RNAs (siRNAs). siRNA is incorporated into a protein complex called the “RNA-induced silencing complex”, and then the sense strand of the siRNA is cleaved. The antisense strand guides the RNA-induced silencing complex to bind with a messenger RNA (mRNA), which is complementary to the antisense strand and degrades it. An important advantage of RNAi over small-molecule and protein therapeutics is that mutant alleles can be targeted with RNAi. In principle, any transcript that encodes a protein that causes or contributes to a disease can be targeted by RNAi [62]. Therefore, a major advantage of sequence-based targeting technologies is the ability to design precisely targeted biotherapeutics for almost any target sequence (coding or noncoding), regardless of the function of the gene product [63].

The therapeutic potential of RNAi in AD has been demonstrated through allele-specific gene silencing by short-hairpin RNA (shRNA) [62]. An anti-APPsw shRNA was delivered by the recombinant adeno-associated virus to the hippocampus of AD transgenic mice (APP/PS1) to selectively suppress mutant APP. No neuronal toxicity was detected in short- and long-term transduction experiments with the viral vector. Intravenously injected rabies virus glycoprotein (RVG)-targeted exosomes have specifically delivered siRNA to neural cells in the mouse brain. Strong mRNA (60%) and protein (62%) knockdown of BACE1 was achieved without noticeable immune stimulation. CBP-1 (acetyltransferase enzyme) has been inhibited by RNAi to evaluate the age-dependent mortality rate for 30 drugs used for protection of mammalian neurons. The genes of interest, which may be more specifically involved in the tau phosphorylation pathways in AD, are DYRK1A and AKAP13 [62].

Several obstacles remain for the clinical development of RNAi-based therapeutics [63]. The delivery issue represents a major challenge, as siRNA should be transferred to specific target sites, and the potential off-target effects should be taken into consideration as well. AD is a multifactor and genetically heterogeneous disorder. It cannot be treated by a single siRNA sequence. Therefore, new strategies should be envisioned to formulate the various RNAi components and successfully deliver them to the target sites.

2.2. Therapeutic Delivery Approaches for Neuroprotective Biomacromolecules
2.2.1. Invasive versus Noninvasive Administration of Carrier-Free Biomolecules

The major reason for the limited effect of therapeutic biomacromolecules (therapeutic peptides or proteins) in clinical trials has been attributed to the presence of the BBB [27,30]. Local delivery to the brain has been suggested via stereotactic cerebral injection or intracerebral infusion [32]. The problem of this approach is the difficulty in determining the most appropriate doses of each compound. For instance, intracerebral neurotrophic factor administration has shown no improvement of motor symptoms in PD (owing to the difficulty for the drug to cross the blood–brain barrier) and thus represents its limited efficacy in clinical trials [64]. Therefore, different approaches for biomolecule delivery are required to increase bioavailability [65–68].

A direct route to reach the brain without going through the BBB is the nasal-to-brain delivery route (Figure 1) [69,70]. Intranasal drug administration avoids hepatic first-pass metabolism and has been considered a safe, noninvasive route [71–73]. In this method, the therapeutic drug, which is applied into the nasal cavity, can penetrate the central nervous system (CNS) via the olfactory and/or trigeminal nerves [73]. Different models have been used to evaluate nasal drug absorption both in vitro and in vivo [70,73–75]. Some biomolecules, such as CNTF, BDNF, and NT-4/5, have been successfully delivered to the hippocampus and cerebral cortex of rats. Quick absorption of BDNF has been observed due to the interaction of BDNF molecules (exposing cationic surface charges) and the nasal mucosa (negatively charged) [75].
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Figure 1. Uptake mechanisms involved in the transport of therapeutic proteins from the nasal cavity directly to the brain via the olfactory nerve pathway (Reprinted with permission from Ref [70]. Copyright 2018 Elsevier).

2.2.2. Gene Delivery

Another strategy to alter local protein expression is based on gene delivery [76,77]. Several clinical trials have been performed to examine the capacity of neurotrophic factors to rescue degenerating neurons by viral vector-mediated gene delivery to the brain [76–80]. A cationic nanocarrier functionalized by dexamethasone and cell-penetrating peptides increased BDNF expression upon BDNF DNA delivery [77]. Many authors have demonstrated the tolerability of gene delivery to PD patients (e.g., intraputaminal injections of adeno-associated virus serotype 2-neurturin (CERE-120)) in a phase I open-label clinical test [78–80]. Although these gene therapy approaches have been shown to be safe, their efficacy in phase II clinical trials has been considered insufficient [80].

2.2.3. Carrier-Mediated Delivery Employing Different Nanoscale Materials

Recent research has focused on the development of neurotrophin delivery systems that can provide a safe and efficient neurotrophic supply over the long term [81–89]. It has been of special interest to combine such systems with implants, i.e., to explore implant-coupled drug delivery [81–83]. An encapsulated cell biodelivery (ECB) device has been demonstrated to be an efficient method to improve NGF levels in AD patients [89]. Other promising approaches have comprised electrode coating materials [82] as well as carrier systems such as hydrogels [83,84], microspheres [85], nanotubes [47], mesoporous silica supraparticles [86], or nanoparticles [87,88].

3. Nanoscale Materials for Stimulation of Neurogenesis and Neuroregeneration

For a long time, the availability of effective treatments against NDs has been restricted not only by the brain structure, which is protected by the BBB, but also by the
high cost of CNS drug development. Extended time periods have been needed to establish whether investigational treatment may truly affect disease progression [90–94]. As most growth factor proteins do not cross the BBB, they must be delivered intracranially [31]. Various reports have emphasized that the efficient diffusion of NTFs in brain tissue is of crucial importance [95–105]. From this perspective, nanoparticles have been largely investigated for neurotrophic factor delivery to improve penetration and diffusion in the brain [32,106,107]. In recent years, different types of nanoparticles [108,109] have been exploited to enhance drug delivery efficacy towards neurogenesis and neuroregeneration, e.g., polymeric nanoparticles, silica nanoparticles, nanofibers, gold nanoparticles, liposomes, cubosomes, and other lipid-based liquid crystalline nanoparticles (Figure 2).

3. Nanoscale Materials for Stimulation of Neurogenesis and Neuroregeneration

3.1. Functionalized Nanoparticles for Brain-Targeted Drug Delivery

Transport of therapeutic biomolecules by nanoparticles through the BBB and cellular membranes can increase the chances for more efficient therapy against NDs [110–123]. The nonselective distribution of drug compounds in the brain hampers the effective treatment of neurodegenerative disorders, as serious side effects may be caused with regard to normal brain function. Functionalized nanoparticles have been intensively studied for improving the permeability of the BBB [124–126]. An important advantage is that the nanosized particles can be functionalized for targeted drug delivery to PD or AD lesions [127] as well as for receptor-mediated transcytosis [128] (Figure 3).

A recent study of SLNs for drug delivery across the BBB explored the chemical modification by borneol (BO) of dioleoyl phosphoethanolamine (DOPE), which is one of the lipid constituents employed [129]. The borneol-modified solid lipid nanoparticles (BO-SLN/CM) displayed lower cytotoxicity, better cellular uptake, and enhanced BBB permeability compared to conventional SLNs. Whereas the control group of nonmodified SLNs accumulated in the lungs, the BO-SLN/CM considerably penetrated the brain. Thus, the synthesized BO-SLN/CM has emerged as a promising lipid-based system for targeted delivery across the
BBB [129]. Other recent in vitro and in vivo reports have investigated dual-functionalized nanocarriers, which have demonstrated brain-targeting effects linked with the use of cholesterol-polyethylene glycol (PEG) and poly(ethylene glycol)-poly(lactide) [130].

![Schematic presentation of the microstructure of the blood–brain barrier (BBB) and possible mechanisms of biomolecule passage to the central nervous system (Reprinted from Ref [128]. MDPI Open Access 2019).](image)

**Figure 3.** Schematic presentation of the microstructure of the blood–brain barrier (BBB) and possible mechanisms of biomolecule passage to the central nervous system (Reprinted from Ref [128]. MDPI Open Access 2019).

PEGylated liposome and cubosome liquid crystalline particles have shown a capacity for delivering different proteins or genetic materials across the BBB [131,132]. Functionalized liposomes and solid lipid nanoparticles, characterized by a high affinity for the amyloid beta (Aβ) neurotoxic peptide, have been broadly considered in AD research [133]. A dual-functionalized nanoparticle-based drug delivery system was designed using a PEGylated poly(lactic acid) (PLA) polymer. Two targeting peptides, TGN and QSH (screened by phage display), have been conjugated to the surface of the nanoparticles. The TGN functionality was suitable for targeting ligands at the BBB, whereas the QSH had a good affinity for the Aβ1-42 sequence, which is a main component of amyloid plaques [134].

3.2. Neuron-Targeted Biomolecule Delivery by Nanocarriers

3.2.1. Nanoparticles for Protein Delivery

Innovative neuron-targeted delivery systems are urgently needed and are being developed based on nanocarriers [135–142]. For the delivery of therapeutic proteins, the designed nanocarriers should enable efficient loading and retention of the entrapped protein biomolecules in the self-assembled nanoscale reservoirs. These carriers should be stable in the biological milieu and ensure suitable release profiles for the functional proteins to interact with their receptors at the sites of action. Notably, surface-modified
nanoparticles may increase the permeability of the BBB [135,136]. Growth factors (GFs) and laminins are two examples of biomolecules involved in regeneration processes [33–36]. GF proteins play an important role in various events, such as cellular proliferation and differentiation. Due to their short half-life, different delivery strategies have been proposed to minimize GF protein degradation in the circulation [137,138]. Polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), and polyglycolic acid (PGA) have been used for growth factor delivery as commonly exploited synthetic biodegradable polymeric matrices in bone regeneration [137,138]. In fact, PLA and PLGA nanoparticle systems have been exploited in experiments for both short- and long-term delivery of biomolecules.

Inorganic mesoporous silica nanoparticles (MSNs), containing immobilized bone growth factors, have been shown to facilitate osteogenic differentiation of human mesenchymal stem cells (hMSCs) [139]. Based on in vitro experiments, Prades et al. reported that gold nanoparticles (AuNPs) conjugated with a CLPFFD peptide (AuNP-CLPFFD) can destroy toxic β-amyloid aggregates (Aβ) [140]. In this case, CLPFFD was chosen as a β-sheet breaker peptide, which recognizes aggregated Aβ. To enhance the permeability in the brain, a second peptide (THR) has been introduced for targeting a receptor present at the neuronal cell membranes. Remarkably, the created AuNP-THR-CLPFFD complex has been established to accumulate in the central nervous system. It should be concluded that AuNPs have the potential to deliver therapeutic peptides or proteins to the brain through certain conjugation strategies [140].

Chitosan nanocarriers have been used for the delivery of an Aβ antigen [141]. Aβ antigen, which was injected into the caudal vein of mice, was subsequently detected in the brain. The obtained results indicated that chitosan nanocarriers can increase the permeability of the BBB and successfully deliver proteins in the mouse brain [141]. Recently, the peptide H102 (HKQLPFFEED), which is another β-sheet breaker, has been found to improve the spatial memory impairments of mice [142]. This finding presents another opportunity for AD treatment. Zhang et al. described the delivery of the H102 peptide to the brain of an AD mouse model by PEG–PLA nanoparticles [142]. Therefore, PEG–PLA nanoparticles may also be considered an opportunity for peptide or protein drug delivery in ND models. Targeted albumin nanoparticles modified by apolipoprotein E have shown strong cellular uptake in the mouse brain [143]. Lipid-based cubosome nanoparticles have been designed for BDNF loading [144]. The multicompartment self-assembled organization of the BDNF-loaded nanocarriers (cubosomes) was revealed by cryo-TEM imaging (Figure 4).

**Figure 4.** Cryo-TEM image of multicompartment cubosome particles loaded with the neurotrophic protein BDNF. (Reprinted with permission from Ref [144]. Copyright 2020 American Chemical Society) BDNF is a water-soluble protein, which interacts with the lipid bilayer, changes the membrane curvature, and induces multiphase domains within the self-assembled lipid membrane particles. L—denotes lamellar phase domain, D—double diamond type cubic phase domain, and G—gyroid type cubic phase domain.
Nanomaterials are promising carriers for the delivery of peptide and protein drugs by intranasal administration [65–69,72–75,91,120,122]. Vasactive intestinal peptide (VIP), which has anti-inflammatory activity, is a 28-amino acid neuropeptide. Its clinical effect is essentially limited due to the rapid degradation of VIP in the blood circulation. Gao et al. encapsulated peptide (VIP) molecules in functionalized PEG-PLA nanoparticles (VIP-NPs) [145]. The uptake of VIP-NP in the brain was achieved by intranasal administration. Subsequently, basic fibroblast growth factor (bFGF) has been entrapped in functionalized polyethylene glycol-poly(lactide-co-glycolide) (PEG-PLGA) nanoparticles [146]. Enhanced spatial learning and cognitive function effects have been reported following the intranasal administration of bFGF-NPs [146].

3.2.2. Nanoparticles for Gene Delivery

Nucleic acid delivery may directly regulate the causative genes of diseases with limited side effects of gene therapy [147–150]. The development of efficient nonviral gene delivery systems remains a key challenge for the clinical application of RNA interference (RNAi) therapeutics in neurological diseases. To deliver siRNAs to brain neuronal cells, nonviral gene carriers are required to cross the BBB and overcome intracellular membrane barriers by avoiding lysosomal degradation. Functionalized nanoparticles have been proposed as a promising strategy to protect RNA from degradation [151]. The nanoparticle surface can be modified by chitosan or by different peptides, which have the ability to interact with brain endothelial cells via the receptor-mediated transcytosis (RMT) mechanism and then target neuronal cells. Sun et al. demonstrated a dual-targeting effect via angiopep-2-modified cationic liposomes (ANG-CLPs), which have been designed for the codelivery of a therapeutic gene encoding human tumor necrosis factor-related apoptosis-inducing ligand (pEGFP-hTRAIL) and paclitaxel (PTX) [152] (Figure 5).

![Figure 5](image_url)

**Figure 5.** Tumor-bearing brain accumulation of ANG-CLP/PTX/pEGFP-hTRAIL liposomes (i.e., Angiopep-2-modified liposome assemblies loaded with pEGFP-hTRAIL and PTX) were visualized by real-time in vivo fluorescence imaging of intracranial U87 MG glioma tumor-bearing nude mice after intravenous injection. (Reprinted with permission from Ref [152]. Copyright 2020 Elsevier).

Park et al. developed a nanoparticle system (R-PEG-PMT/siRNA) composed of siRNA and a nonviral vector, poly(mannitol-co-PEI) gene transporter (PMT), which has been modified by a rabies virus glycoprotein (RVG) peptide fragment [147]. The RVG peptide has been widely investigated in CNS targeting and penetration. The in vitro BBB penetration study confirmed that the internalization of the RVG-PEG-PMT/siRNA complex was enhanced compared to that of the control group (PEG-PMT/siRNA). The intravenously injected RVG-PEG-PMT/siRNA complex reduced BACE1 (beta-site APP cleavage enzyme 1) in
mice. The opportunities to use RVG-PEG-PMT/siRNA assemblies in AD treatment have been outlined considering that BACE1 regulates the levels of the pathogenic amyloid-beta Aβ42 (42-amino acid isoform) [147]. To enhance the biotherapeutic targeting effect, Liu et al. proposed a multifunctional nanoparticle system for BACE1 siRNA delivery [148]. The chosen D-peptide has been proven to decrease tau fibril formation and ameliorate AD symptoms. Both an RVG peptide and a D-peptide have been grafted to a dendrigraft poly-L-lysine (DGL) nanoparticle surface. The penetration and BACE1 silencing effects have been confirmed in vitro and in vivo studies [148]. Another work reported the delivery of BACE1 siRNA to neuronal cells using functionalized PEG-PLGA nanoparticles [151]. Wang et al. synthesized a CGN peptide sequence (d-CGNHPHLAKYNGT) whose targeting capacity has been examined both in vitro and in vivo [151]. The CGN-modified nanocomplexes inhibited 50% of BACE1 expression in PC12 cells and enhanced the learning ability of AD animal models. These results have indicated the potential of the investigated nanosystems for neuron-targeted gene delivery towards AD treatment.

Several recent studies have focused on the delivery of neurotrophic genes to neuronal cells to regulate the local concentration of expressed neurotrophins. Arora et al. reported mannose- and cell-penetrating peptide (RVG)-modified liposomes for transferring the BDNF gene to neuronal cells [149]. BDNF levels in the brain increased after the intravenous injection of the liposome complexes in mice. The recognized efficacy of the p11 gene for depression has been investigated with nanoscale carriers. Gandhi et al. designed a liposome system using synthetic lipids to make gene delivery safer [150]. For targeting purposes, the liposome surface has been modified with an insulin-like growth factor II (IGF-II) monoclonal antibody. As an outcome, the liposomal complex has been characterized by improved stability and distribution in the brain [150].

3.3. Nanomaterials Promote Neuroregeneration by Targeting the Extracellular Environment

Hydrogel nanoscaffolds can facilitate neuronal growth and neuroregeneration by creating an artificial extracellular matrix (ECM). A hyaluronic acid (HA)-based ECM platform, which imitates brain characteristics, has been prepared [153]. A cell-adhesive peptide, arginine-glycine-aspartic acid (RGD), which is the most common peptide motif for cell adhesion in ECM, has been linked to HA hydrogels (Figure 6). Two-photon microscopy images have demonstrated that the modified HA hydrogel promotes neural outgrowth behavior and differentiation [153]. Neural stem cells (NSCs) play an important role in neuroregeneration, which can produce new oligodendrocytes, astrocytes and neurons. It has been established that a hepatocyte growth factor (HGF)-loaded hydrogel can promote NSCs in vitro [154].

3.4. Multifunctional Nanomaterials Promoting Neuroregeneration

The advantages of a combination of nanomaterials for neuronal tissue regeneration and improved control of drug release kinetics have been implemented in peripheral nerve regeneration strategies [155,156]. Nanofibrous scaffolds composed of a natural polymer (SF) and a synthetic polymer (P(LLA-CL)) were fabricated for the encapsulation of NGF [157]. Sustained release of NGF was achieved within 60 days. Peripheral neuroregeneration effects have been observed in rats [157].
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Figure 6. (Top panel) Scheme of the preparation of hyaluronic acid (HA)-based hydrogels functionalized with RGD ligands for central nervous system (CNS) regeneration. (Bottom panel) 3D two-photon microscopy images of neurite outgrowth (β3 tubulin staining) at day 21 after plating hippocampal neural progenitor cells on the surface of hydrogels with a storage modulus of 400 Pa (A) or 800 Pa (B). (Reprinted with permission from Ref [153]. Copyright 2016 American Chemical Society).

3.4. Multifunctional Nanomaterials Promoting Neuroregeneration

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4. BDNF Delivery by Nanocarriers and Nanoscale Materials in Neuronal Diseases

BDNF is a secretory neurotrophic protein that plays a key role in the neurogenesis and survival of neuronal cells [41]. There are 3 different forms of BDNF in mammals: prepro-BDNF, pro-BDNF, and mature BDNF [40]. BDNF is a high-affinity ligand for tropomyosin-related kinase receptor (TrkB). It binds to the receptor and activates the MAPK, PI3K and PLC-γ signaling pathways, which are implicated in neuroprotective and neuroregenerative effects [158]. The BDNF mechanism is used as an emerging targeted strategy in neurorepair [29,158,159]. Figure 7 shows the BDNF-TrkB signaling involved in synaptic transmission. The neurotrophic protein is localized within dense core vesicles, which are responsible for the transport and release of BDNF [158].
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BDNF is a secretory neurotrophic protein that plays a key role in the neurogenesis and survival of neuronal cells [41]. There are 3 different forms of BDNF in mammals: prepro-BDNF, pro-BDNF, and mature BDNF [40]. BDNF is a high-affinity ligand for tropomyosin-related kinase receptor (TrkB). It binds to the receptor and activates the MAPK, PI3K and PLC-γ signaling pathways, which are implicated in neuroprotective and neuroregenerative effects [158]. The BDNF mechanism is used as an emerging targeted strategy in neurorepair [29,158,159]. Figure 7 shows the BDNF-TrkB signaling involved in synaptic transmission. The neurotrophic protein is localized within dense core vesicles, which are responsible for the transport and release of BDNF [158].

Figure 7. Scheme illustrating BDNF transport by dense core vesicles and its release activating neurotrophic BDNF-TrkB signaling, which interplays with glutamate-induced excitotoxicity activities in synapses. (Reprinted from Ref [158]. Frontiers Open Access 2019).

BDNF levels have been established to significantly decrease in several CNS diseases [41,160]. Further to the role of SARS-CoV-2 infection in AD progression associated with oxidative stress and neuroinflammation [21], recent research has confirmed that coronavirus infection may essentially influence BDNF expression levels and thus may impair BDNF/TrkB signaling [161–164]. It has been well documented that decreased BDNF levels present a serious risk factor for neurodegeneration [41,43,164]. Many studies have demonstrated the beneficial effects of neurotrophic BDNF delivery in neuronal pathologies towards the promotion of neural differentiation and survival and the amelioration of memory and learning capacities (among various other features) [31,32,44,45,160]. Therefore, BDNF delivery carriers are receiving increasing interest for the translation of nanomedicine into clinics. In the following, we summarize the recent developments of nanoscale carriers of BDNF, which show potential for exploration also in the research with vulnerable post-COVID-19 patients.

4.1. BDNF Protein Delivery by Nanocarriers to Neurons

Harris et al. performed a polyion complexation of BDNF with PEG(5 kDa)-PGA(9 kDa) diblock copolymer to protect BNDF from rapid degradation in the circulation [165]. The obtained formulation of BDNF nanocomplexes increased BDNF levels in mice and exerted a therapeutic effect on stroke [165]. To improve the stability of BDNF in the presence of serum, BDNF was stabilized by transient hydrogen bonding and cooperative electrostatic interactions using the anionic block copolymer poly(ethylene glycol)-b-poly(l-glutamic acid) (PEG-PLE). This nanoformulation ameliorated the stability of neurotrophin in the circulation without changing the affinity interaction between BDNF and its receptor [166]. Various other hydrogel-based scaffolds have been investigated for BDNF encapsulation and delivery with beneficial outcomes as well [167–171]. PEGylated liposome nanoparticles can serve as efficient nanocarriers to the brain [172]. Xing et al. employed a PEG-conjugated liposomal BDNF vector with a cytomegalovirus promoter (pCMV), which enabled increased BDNF expression [172]. Nanofibers have been widely used as an excellent matrix to help
achieve sustained release of BDNF [173]. A cochlear implant including BDNF-loaded nanoporous silica nanoparticles released BDNF over 80 days [174].

4.2. Nanoparticles Modified by BDNF-Derived Peptides for Drug Delivery to Neurons

The recognition mechanism of BDNF ligands has been used as a targeted strategy to the CNS [175]. Xu et al. demonstrated the internalization of PEG-PCL nanoparticles, whose surface was decorated by a BDNF-derived (IKRG) peptide, into neuronal cells [175]. The tetrapeptide (IKRG) amino acid sequence has been shown to mimic the function of BDNF in targeting TrkB receptors, which are abundant in neurons [175]. Enhanced uptake of peptide-modified PEG-PCL nanoparticles has been observed in TrkB-positive PC12 cells but not in TrkB-negative HeLa cells [175]. Dąbkowska et al. successfully delivered BDNF to neuronal SH-SY5Y cells via PEGylated poly(amidoamine) dendrimer (PAMAM) nanoparticles [176]. The BDNF-loaded nanoparticles were stabilized by electrostatic interactions (Figure 8). The studied BDNF-PAMAM-AF488-PEG nanoparticles have been characterized by slow release of the therapeutic agent and strong interaction with the cell membrane surface [176].

![Figure 8](image-url)  
Figure 8. Scheme of the preparation of PEGylated PAMAM-based nanoparticles containing BDNF and images showing the cellular localization of the nanoparticles in SH-SY5Y cells. The panel on the left presents the control group. The panel on the right presents the cells after 24 h of exposure to BDNF-PAMAM-AF488-PEG. The nanoparticles are observed in green, and the cells are costained with WGA-Texas Red-X (red) and DAPI (blue). (Reprinted with permission from Ref [176]. Copyright 2020 Springer Nature).
A nanofiber hydrogel has been formulated with a mixture of two peptides, one of which is a BDNF mimetic peptide [177]. The purpose has been to promote the remyelination of Schwann cells and the adhesion and proliferation of endothelial cells. RKKA<sub>D</sub>P is a BDNF mimetic peptide that self-assembles in water and forms a hydrogel network [177]. Edelbrock et al. reported that BDNF mimetic peptide can activate BDNF-TrkB signaling as well as other downstream signaling cascades capable of promoting neuronal cell infiltration and functional maturation [178]. The regenerative efficacy, maturation of nerve fibers, and vascularization effect have also been confirmed in vivo.

4.3. BDNF Gene Delivery by Nanocarriers

BDNF gene delivery has been a promising strategy for targeting peripheral neuronal cells. Chitosan-based nanocarriers, which are biodegradable and biocompatible, have been demonstrated as suitable for the condensation and compaction of nucleic acids as well as for preventing BDNF endonuclease degradation [179]. A polymeric nanoparticulate carrier composed of trimethyl chitosan (TMC) has been used for the transfection of therapeutic BDNF plasmid DNA [179]. Significantly increased BDNF levels and subsequent neuronal regeneration have been observed in mice compared to the non-treated group [179]. The performed study demonstrated the role of the targeted nanoparticles in the efficacy of BDNF gene delivery.

4.4. BDNF Delivery by Hybrid Systems and Scaffolds for Tissue Engineering

Tissue engineering has been extensively investigated for the purposes of long-term neurotrophin delivery [180,181]. The local delivery of BDNF using mesenchymal stem cells (MSCs) has provided a continued release of BDNF for 14 days and a recovery of functional activity in an animal spinal cord hemisection [182]. Schwann cell (SC)-seeded alginate hydrogels have been administered to the spinal cord lesion site. The sustained release of BDNF facilitated the axonal growth and pro-regenerative effect of the alginate gels seeded with SCs [183]. A cochlear implant was fabricated for BDNF, GDNF, and laminin delivery using a hydrogel (loaded with fibrin and collagen, which was covered by human adipose-derived stem cells [184]). The expression of BDNF has been detected over a week with a produced quantity (up to 2.59 ng/mL in the supernatant) that has been sufficient for neurotrophic effects [184]. Fibronectin-coated pharmacologically active microcarriers were prepared for the encapsulation of BDNF by nanoprecipitation of poloxamer with glycofurol in NaCl medium (Figure 9). Human mesenchymal marrow-isolated adult multilineage-inducible (MIAMI) stem cells have been attached to the surface of the microcarriers to enhance the secretion of several growth factors, including BDNF. The sustained release of BDNF over 40 days promoted neuronal repair [171].

![Figure 9. Strategy of BDNF delivery using pharmacologically active microcarriers (PAMs) coated with fibronectin and embedded in a hydrogel scaffold. (Reprinted with permission from Ref [171]. Copyright 2017 Elsevier).](image-url)
The therapeutic outcomes observed with recently described neurotrophin carrier systems are summarized in Table 1.

Table 1. Recent examples of nanocarrier-mediated BDNF delivery to the central nervous system.

| Nanoformulation | Disease Indications | Administration Route/Model | Outcomes |
|------------------|---------------------|----------------------------|----------|
| **Lipid-based nanoparticles** | | | |
| Liposomes conjugated with polyethylene glycol (PEG) and transferrin (Tf) as carriers for encapsulated BDNF gene, modified with a glial fibrillary acidic protein promoter (pGFAP) [Tf-pGFAP-BDNF-PEG] or a cytomegalovirus promoter (pCMV) [Tf-pCMV-BDNF-PEG] | Brain injury (degeneration, ischemia, and inflammation) | In vivo tail-vein injection | Tf-pGFAP-BDNF-PEG and Tf-pCMV-BDNF-PEG carriers are able to cross the BBB. Predominant expression of BDNF in the cerebral cortex. The Tf-pGFAP-BDNF-PEG group is promoting more significantly the BDNF expression in the cerebral cortex than the Tf-pCMV-BDNF-PEG group [172]. |
| **Polymeric-based nanoparticles and hydrogels** | | | |
| PEG-PGA nanoparticle polyion complexes with BDNF | Ischemic stroke | In vivo subcutaneous injection in mice | Reduced tissue injury. Behavioral improvements [165]. |
| BDNF mixed in poly(ethylene glycol)-b-poly(l-glutamic acid) (PEG-PLE) copolymer solution | Neurologic diseases | In vivo Intranasal | Protection of BDNF in the circulation. Better distribution than the native protein. Improved BDNF delivery efficiency [166]. |
| BDNF-loaded micropillared poly-c-caprolactone (MP-PCL) or flat PCL (F-PCL) scaffolds | Neuronal lesion | In vitro primary neuronal cultures | Sustained release of BDNF up to 21 days. Increased neuronal survival and synaptic density. Suitable for neural tissue engineering and prosthetics [167]. |
| BDNF in self-assembled IKVAV PA hydrogel | Traumatic spinal cord injuries (TSCI) | Injection, Spinal cord injury induced using clip compression at T7-T8 vertebral segment | Sustained release of BDNF. Axonal preservation. Astrogliosis decreased at 6 weeks post-injury without inflammation. Locomotor functional recovery failed [168]. |
| BDNF encapsulated in hyaluronic acid hydrogel | Stroke | In vivo Stroke models in mouse (strains C57Bl/6, DBA) and non-human primate (chronic stroke) | Distribution of BDNF-loaded hydrogel from the stroke cavity into the peri-infarct tissue up to 3 weeks compared to 1 week for direct BDNF injection in a mouse model. Recovery of motor function. Migration of immature neurons into the peri-infarct cortex and long-term survival. Released BDNF sufficient for functional recovery from stroke in a non-human primate [169]. |
| BDNF dispersed in a hydrogel, consisting of hyaluronan and methylcellulose, with embedded poly(lactic-co-glycolic acid) nanoparticles | Stroke | In vivo stroke lesions; Stroke-injured rat | Unchanged lesion volume compared to a vehicle group. Synaptophysin expression in homotopic contralesional hemisphere. Better plasticity. [170]. |
Table 1. Cont.

| Nanoformulation                                                                 | Disease Indications          | Administration Route/Model | Outcomes                                                                                                                                 |
|---------------------------------------------------------------------------------|-----------------------------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Fibronectin-coated pharmacologically active microcarriers (PAMs) modified with silanized-hydroxypropylmethylcellulose (Si-HPMC) hydrogel for BDNF delivery | Neurological disorders      | Human marrow-isolated adult multilineage-inducible (MIAMI) stem cells | The PAMs Si-HPMC hydrogel facilitated the expression of neuronal differentiation markers in MIAMI cells. Improved secretion of growth factors (e.g., b-NGF, HGF, SCF, LIF, SDF-1α, VEGF-A & D) and chemokines (MIP-1α & β, RANTES, IL-8) [171]. |
| PEGylated PAMAM-based nanoparticles                                              | Neurodegenerative diseases  | In vitro SH-SY5Y cells     | Increased BDNF expression and release for the PEGylated PAMAM nanoparticle group versus the PAMAM-based nanoparticles [176].            |

**BDNF-mimetic peptide nanofiber scaffolds**

| Self-assemble nanoﬁber hydrogel including a BDNF mimetic peptide | Peripheral nerve injury     | In vivo Rat model           | Nerve regeneration and functional recovery observed in a rat model after implantation of nanofiber hydrogels [177]. |
| Nanofibers involving a BDNF mimetic peptide                | CNS injuries and diseases  | Primary cortical neurons    | Neuronal survival and increased functional maturation [178]. |

**Silica nanoparticles**

| BDNF-loaded porous silica nanoparticles (NPSNPs)         | Degeneration of SGNs, inner ear disease | In vitro NIH3T3 fibroblasts, SGNs | Sustained BDNF release from amino-modified nanoparticles over 80 days. Cytocompatibility of the NPSNPs with the fibroblasts. Higher survival rate of SGNs in cell cultures as compared to unloaded control NPSNPs [174]. |

5. Nanoscale Assemblies of Bioactive Lipids Offering Therapeutic Opportunities

Other biometric systems created with bioactive lyotropic lipid self-assembly can also be considered for future studies on neuroprotection and recovery from neuronal damages (Figure 10). For instance, lipid nanoparticles involving bioactive omega-3 polyunsaturated fatty acids (ω-3 PUFAs) have been obtained by self-assembly with the nonlamellar lipid monoollein [185,186]. Multicomponent amphiphilic systems with liquid crystalline self-assembled inner structural organization can serve for the encapsulation of hydrophobic or hydrophilic drugs and natural antiviral compounds for targeting various disease mechanisms as well as pathways favoring recovery from SARS-CoV-2-induced neuronal damage. In examples of multidrug (ω-3 PUFAs, curcumin, and monoglyceride) loading in nanoparticles, curcumin has been considered a drug with antiviral, antioxidant, antimicrobial, anti-proliferative, anti-inflammatory, neuroprotective and cardioprotective properties [159]. Monoglycerides have been indicated to have equal capacity for viral inactivation at 5 to 10 times lower concentrations than their corresponding fatty acids. ω-3 PUFAs are adjunctive therapeutics of strong interest for preventive nanomedicine development [159,185]. Recent experimental data have shown that curcumin-loaded lipid nanoparticles may promote BDNF expression and that the ω-3 PUFA content of the nanoparticles may be beneficial for enhancing BDNF activity [159,186].
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The varying degree of packing and perforation of the bicontinuous lipid membrane yields different types of nano-objects, e.g., small cubosomes, cubosomal intermediates, spongosome particles, swollen sponge-type membranes coexisting with vesicular objects or objects embedding oil-rich domains. The resulting compartmentalized nanocarriers may coencapsulate hydrophobic and hydrophilic guest molecules of interest for combination therapies. (Reprinted from Ref [185]. American Chemical Society Open Access 2018).

In recent years, lipid-based therapies have been suggested as an alternative strategy for slowing neurodegeneration and inhibiting neuroinflammation [187–189]. PUFA-chain ethanolamine plasmalogens have been described as bioactive lipids and can be 100-fold more powerful in stimulating neurorepair than conventional ω-3 PUFA species [187]. By analyzing the results from clinical and in vitro experiments, it has been concluded that certain plasmalogen lipid derivatives may enhance neurotrophic BDNF signaling and thus promote neurogenesis [189].

Based on bioinspiration from biological cubic membranes, self-assembled nanostructures have been designed by mixing synthetic PUFA-chain phospholipids, e.g., plasmenyl phosphoethanolamine (C16:1p-22:5n6 PE), plasmenyl phosphocholine (C16:1p-22:5n6 PC), and DPA-diacyl phosphoinositol (22:5n6-22:5n6 PI) ester, and the nonlamellar lipid monoolein [190]. Various nanoscale object types have been obtained as a result of the structural polymorphism of the investigated lyotropic lipid/DPA-phospholipid mixtures (Figure 11). It has been emphasized that the nanoparticle shape is crucial for drug transport properties. In perspective, further developments should be expected in nanocarrier design for the efficient delivery of CRISPR therapeutics in neurological disorders [191–193] as well as in biogenic metal nanoparticles obtained by self-assembly with template agents of natural biological origin, e.g., biogenic silver nanoparticles (AgNPs) [194].
Figure 11. Cryo-TEM images of lipid nanoparticles obtained by self-assembly of custom-synthesized plasmenyl (ether) and ester phospholipids with long PUFA (22:5 n6) chains and the nonlamellar lipid monooolein. The liquid crystalline nanoparticle topologies and the compartmentalized biomimetic supramolecular architectures comprise vesicles, cubosomal intermediates, cubosomes coexisting with vesicles, multicompartment core-shell cubosomes and hexosomes, multilayer onions; vesicles with joint oil domains, double membrane vesicles, nonlamellar intermediates with HII domains, and dense core (HII) particles hexosomes coexisting with vesicles. (Reprinted from Ref [190]. Frontiers Open Access 2021).

6. Conclusions

Biomimetic self-assembly can yield smart nanocarriers providing reduced side effects in therapeutic delivery strategies. The different topologies of the nanocarriers (elongated or spherical nanoparticles with solid or aqueous cores or with inner liquid crystalline membrane organization, nanofiber scaffolds, or gels) may provide different release profiles for encapsulated molecules as well as different resident times at the biological barriers. In recent years, targeted nanocarriers for recombinant growth factors, therapeutic antibodies, enzymes, synthetic peptides, cell-penetrating peptide-drug conjugates, and RNAi sequences have been successfully developed against NDs. Self-assembled nanoscale materials loaded with biotherapeutics can also be used in emerging neuronal regeneration strategies and considered for potential recovery from long-term COVID-19 neuronal dysfunctions. Sustainable BDNF delivery nanoparticles and polymer-based scaffolds have been reported to facilitate neuronal survival and reduce neuronal tissue injury. Safe drug delivery has been achieved to the central and peripheral nervous systems. Enhanced neurogenesis and neuronal survival have been observed both upon growth factor delivery by nanocarriers as well as by exploring the properties of bioactive lipids such as plasmalogens with long PUFA chains. Towards translation into clinics, further research on nanocarrier-mediated drug delivery will be required in the areas of PUFACP chain phospholipids, growth factor therapies, biogenic metal nanoparticles, mRNA therapies, and CRISPR therapeutics.

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Abbreviations

AD, Alzheimer’s disease; AKAP13, A-kinase anchor protein 13; ApoE, Apolipoprotein E; ALS, amyotrophic lateral sclerosis; ARTN, artemin; BACE1, beta-secretase 1 (beta-site APP cleaving enzyme 1); BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CBP-1, protein cbp-1 acetyltransferase enzyme; CDNF, cerebral dopamine neurotrophic factor; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CSF, cerebrospinal fluid; CT-1, cardiotrophin; DDS, drug delivery system; DYRK1A, dual-specificity tyrosine phosphorylation regulated kinase 1A; ER, endoplasmic reticulum; FGF-1, fibroblast growth factor-1; ER, endoplasmic reticulum; FGF-2, fibroblast growth factor-2; GDNF, glial cell line-derived neurotrophic factor; GCSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; LIF, leukemia inhibitory factor; MANF, mesencephalic astrocyte-derived neurotrophic factor; NDs, neurodegenerative diseases; NGCs, nerve guidance conduits; NGF, nerve growth factor; NP, nanoparticles; NRTN, neurturin; NT-3, neurotrophin-3; NT-4, neurotrophin-4; NTFs, neurotrophic factors; PACAP, pituitary adenylate cyclase-activating peptide; PD, Parkinson disease; PDGF, platelet-derived growth factor; PLA, poly(L-lactide); PLGA, poly(lactic-co-glycolic acid); PSPN, persephin; RGD, arginine-glycine-aspartic acid peptide; RNAi, RNA interference; RVG, rabies virus glycoprotein; shRNA, short-hairpin RNA; siRNA, small interfering RNA; SLNs, solid lipid nanoparticles; TrkB, tropomyosin receptor kinase B; UPR, unfolded protein response.

References

1. Karlawish, J.; Jack, C.R., Jr.; Rocca, W.A.; Snyder, H.M.; Carrillo, M.C. Alzheimer’s Disease: The next frontier—Special report. Alzheimer Dement. 2017, 13, 374–380. [CrossRef] [PubMed]
2. Alzheimer’s Association. 2016 Alzheimer’s disease facts and figures. Alzheimer Dement. 2016, 12, 459–509. [CrossRef] [PubMed]
3. Scheltens, P.; Blennow, K.; Breteler, M.M.; de Strooper, B.; Frisoni, G.B.; Salloway, S.; Van der Flier, W.M. Alzheimer’s disease. Lancet 2016, 388, 505–517. [CrossRef]
4. Aarsland, D.; Creese, B.; Politis, M.; Chaudhuri, K.R.; Ffytche, D.H.; Weitutrub, D.; Ballard, C. Cognitive decline in Parkinson disease. Nat. Rev. Neurol. 2017, 13, 217–231. [CrossRef]
5. Titova, N.; Padmakumar, C.; Lewis, S.J.G.; Chaudhuri, K.R. Parkinson’s: A syndrome rather than a disease? J. Neural Transm. 2017, 124, 907–914. [CrossRef]
6. Balestrino, R.; Schapira, A.H.V. Parkinson disease. Eur. J. Neurol. 2020, 27, 27–42. [CrossRef]
7. Jha, N.K.; Ojha, S.; Jha, S.K.; Dureja, H.; Singh, S.K.; Shukla, S.D.; Chellapan, D.K.; Gupta, G.; Bhardwaj, S.; Kumar, N.; et al. Evidence of coronavirus (CoV) pathogenesis and emerging pathogen SARS-CoV-2 in the nervous system: A review on neurological impairments and manifestations. J. Mol. Neurosci. 2021, 71, 2192–2209. [CrossRef]
8. Liu, J.M.; Tan, B.H.; Wu, S.; Guí, Y.; Suo, J.L.; Li, Y.C. Evidence of central nervous system infection and neuroinvasive routes, as well as neurological involvement, in the lethality of SARS-CoV-2 infection. J. Med. Virol. 2020, 93, 1304–1313. [CrossRef]
9. Tancheva, L.; Petralia, M.C.; Miteva, S.; Dragomanova, S.; Solak, A.; Kalfin, R.; Lazarova, M.; Yarkov, D.; Ciurlleo, R.; Cavalli, E.; et al. Emerging neurological and psychobiological aspects of COVID-19 infection. Brain Sci. 2020, 10, 852. [CrossRef]
10. Nuzzo, D.; Cambula, G.; Bacile, I.; Rizzo, M.; Galia, M.; Mangiapane, P.; Scalisi, L. Long-term brain disorders in post Covid-19 neurological syndrome (PCNS) patient. Brain Sci. 2021, 11, 454. [CrossRef]

11. Jakhmola, S.; Indari, O.; Chatterjee, S.; Jha, H.C. SARS-CoV-2, an underestimated pathogen of the nervous system. SN Compr. Clin. Med. 2020, 2, 2137–2146. [CrossRef] [PubMed]

12. Gu, J.; Gong, E.; Zhang, B.; Zheng, J.; Gao, Z.; Zhong, Y.; Zou, W.; Zhan, J.; Wang, S.; Xie, Z.; et al. Multiple organ infection and the pathogenesis of SARS. J. Exp. Med. 2005, 202, 415–424. [CrossRef] [PubMed]

13. Al Saiegh, F.; Ghosh, R.; Leibold, A.; Avery, M.B.; Schmidt, R.F.; Theofanis, T.; Miuchtouris, N.; Philipp, L.; Peiper, S.C.; Wang, Z.-X. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. J. Neurol. Neurosurg. Psychiatry 2020, 91, 846–848. [CrossRef]

14. Zubair, A.S.; Mcalpine, L.S.; Gardin, T.; Farhadian, S.; Kuruvilla, D.E.; Spudich, S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A review. JAMA Neurol. 2020, 77, 1018–1027. [CrossRef]

15. Nuzzo, D.; Picone, P. Potential neurological effects of severe COVID-19 infection. Neurosci. Res. 2020, 158, 1–5. [CrossRef] [PubMed]

16. Iadecola, C.; Anrather, J.; Kamel, H. Effects of COVID-19 on the nervous system. Cell 2020, 183, 16–27. [CrossRef]

17. Pacheco-Herrero, M.; Soto-Rojas, L.O.; Harrington, C.R.; Flores-Martinez, Y.M.; Villegas-Rojas, M.M.; Leon-Aguilar, A.M.; Martinez-Gomez, P.A.; Campa-Cordoba, B.B.; Apatiga-Perez, R.; Cornel-Tavares, C.N.; et al. Elucidating the neuropathologic mechanisms of SARS-CoV-2 infection. Front. Neurol. 2021, 12, 660087. [CrossRef]

18. Dziedzic, A.; Saluk-Bijak, J.; Miller, E.; Niemcewicz, M.; Bijak, M. The impact of SARS-CoV-2 infection on the development of neurodegeneration in multiple sclerosis. Int. J. Mol. Sci. 2021, 22, 1804. [CrossRef]

19. Chaudhry, Z.L.; Klenja, D.; Janjua, N.; Cami-Kobeci, G.; Ahmed, B.Y. COVID-19 and Parkinson’s disease: Shared inflammatory pathways under oxidative stress. Brain Sci. 2020, 10, 807. [CrossRef]

20. Chana-Cuevas, P.; Salles-Gándara, P.; Rojas-Fernandez, A.; Salinas-Rebolledo, C.; Milán-Solé, A. The potential role of SARS-COV-2 in the pathogenesis of Parkinson’s disease. Front. Neurol. 2020, 11, 1044. [CrossRef]

21. Abate, G.; Memo, M.; Uberti, D. Impact of COVID-19 on Alzheimer’s disease risk: Viewpoint for research action. Healthcare 2020, 8, 30286. [CrossRef] [PubMed]

22. Varahachalam, S.P.; Lahooti, B.; Chamaney, M.; Bagchi, S.; Chhibber, T.; Morris, K.; Bolanos, J.F.; Kim, N.Y.; Kaushik, A. Nanomedicine for the SARS-CoV-2: State-of-the-art and future prospects. Int. J. Nanomed. 2020, 16, 539–560. [CrossRef] [PubMed]

23. Saravanan, M.; Mostafavi, E.; Vincent, S.; Negash, H.; Andavar, R.; Perumal, V.; Barabadi, H. Nanotechnology-based approaches for emerging and re-emerging viruses: Special emphasis on COVID-19. Microb. Pathog. 2021, 156, 104908. [CrossRef]

24. Cummings, J.L.; Morstorf, T.; Zhong, K. Alzheimer’s disease drug-development pipeline: Few candidates, frequent failures. Alzheimer Res. Ther. 2014, 6, 37. [CrossRef]

25. Maiti, P.; Manna, J.; Dunbar, G.L. Current understanding of the molecular mechanisms in Parkinson’s disease: Targets for potential treatments. Transl. Neurodegener. 2017, 6, 28. [CrossRef] [PubMed]

26. Capriotti, T.; Terzakis, K. Parkinson disease. Home Healthc. Now 2016, 34, 300–307. [CrossRef] [PubMed]

27. Asli, S.M.; Ahlawat, J.; Barroso, G.G.; Narayan, M. Nanomaterial based drug delivery systems for the treatment of neurodegenerative diseases. Biomater. Sci. 2020, 8, 4109–4128. [CrossRef]

28. Donaghue, I.E.; Tat, R.; Sefton, M.V.; Shoichet, M.S. Cell and biomolecule delivery for tissue repair and regeneration in the central nervous system. J. Control. Release. 2014, 190, 219–227. [CrossRef]

29. Angelova, A.; Angelov, B. Dual and multi-drug delivery nanoparticles towards neuronal survival and synaptic repair. Neural Regen. Res. 2017, 12, 886–889. [CrossRef] [PubMed]

30. Wong, K.H.; Riaz, M.K.; Xie, Y.; Zhang, X.; Liu, Q.; Chen, H.; Bian, Z.; Chen, X.; Lu, A.; Yang, Z. Review of current strategies for delivering Alzheimer’s disease drugs across the blood-brain barrier. Int. J. Mol. Sci. 2019, 20, 381. [CrossRef]

31. Géral, C.; Angelova, A.; Lesieur, S. From molecular to nanotechnology strategies for delivery of neurotrophins: Emphasis on brain-derived neurotrophic factor (BDNF). Pharmaceutics 2013, 5, 127–167. [CrossRef] [PubMed]

32. Angelova, A.; Angelov, B.; Drechsler, M.; Lesieur, S. Neurotrophin delivery using nanotechnology. Drug Discov. Today 2013, 18, 1263–1271. [CrossRef]

33. Huttunen, H.J.; Saarna, M. CDNF protein therapy in Parkinson’s disease. Cell Transpl. 2019, 28, 349–366. [CrossRef] [PubMed]

34. Subbiah, R.; Guldberg, R.E. Materials science and design principles of growth factor delivery systems in tissue engineering and regenerative medicine. Adv. Healthc. Mater. 2019, 8, e1801000. [CrossRef] [PubMed]

35. Ferenz, K.B.; Gast, R.E.; Rose, K.; Finger, I.E.; Hasche, A.; Kriegstein, J. Nerve growth factor and brain-derived neurotrophic factor but not granulocyte colony-stimulating factor, nimodipine and dizocilpine, require ATP for neuroprotective activity after oxygen–glucose deprivation of primary neurons. Brain Res. 2012, 1448, 20–26. [CrossRef] [PubMed]

36. Levi-Montalcini, R. Growth control of nerve cells by a protein factor and its antiserum: Discovery of this factor may provide new leads to understanding of some neuromuscular processes. Science 1964, 143, 105–110. [CrossRef]

37. Ivanova, L.; Karelsen, M.; Dobchev, D.A. Identification of natural compounds against neurodegenerative diseases using in silico techniques. Molecules 2018, 23, 1847. [CrossRef]

38. Liu, R.; Hudalla, G.A. Using self-assembling peptides to integrate biomolecules into functional supramolecular biomaterials. Molecules 2019, 24, 1450. [CrossRef]
39. Prakash, A.; Medhi, B.; Chopra, K. Granulocyte colony stimulating factor (GCSF) improves memory and neurobehavior in an amyloid-β induced experimental model of Alzheimer’s disease. *Pharm. Biochem Behav.* 2013, 110, 46–57. [CrossRef]

40. Lucini, C.; D’Angelo, L.; Cialli, P.; Palladino, A.; De Girolamo, P. BDNF, brain, and regeneration: Insights from zebrafish. *Int. J. Mol. Sci.* 2018, 19, 3155. [CrossRef]

41. Numakawa, T.; Odaka, H.; Adachi, N. Actions of brain-derived neurotrophin factor in the neurogenesis and neuronal function, and its involvement in the pathophysiology of brain diseases. *Int. J. Mol. Sci.* 2018, 19, 3650. [CrossRef] [PubMed]

42. Runeberg-Roos, P.; Piccinini, E.; Penttinen, A.M.; Mätlik, K.; Heikkinen, H.; Kuure, S.; Bespalov, M.M.; Peränen, J.; Garea-Rodríguez, E.; Fuchs, E.; et al. Developing therapeutically more efficient neurotirin variants for treatment of Parkinson’s disease. *Neurobiol. Dis.* 2016, 96, 335–345. [CrossRef]

43. Fletcher, J.L.; Murray, S.S.; Xiao, J. Brain-derived neurotrophin factor in central nervous system myelination: A New mechanism to promote myelin plasticity and repair. *Int. J. Mol. Sci.* 2018, 19, 4131. [CrossRef] [PubMed]

44. Sullivan, A.M.; Toulouse, A. Neurotrophic factors for the treatment of Parkinson’s disease. *Cytokine Growth Factor Rev.* 2011, 22, 157–165. [CrossRef] [PubMed]

45. Aron, L.; Klein, R. Repairing the parkinsonian brain with neurotrophic factors. *Trends Neurosci.* 2011, 34, 88–100. [CrossRef]

46. Paul, G.; Zachrisson, O.; Varrone, A.; Almqvist, P.; Jerling, M.; Lind, G.; Rehncrona, S.; Linderoth, B.; Bjartmarz, H.; Shafer, L.L.; et al. Safety and tolerability of intracerebroventricular PDGF-BB in Parkinson’s disease patients. *J. Clin. Investig.* 2015, 125, 1339–1346. [CrossRef]

47. Dharmadana, D.; Adamcik, J.; Ryan, T.M.; Appiah Danso, S.; Chong, C.J.H.; Conn, C.E.; Reynolds, N.P.; Mezzenga, R.; Valéry, C. Peptide substance P self-assembles into semi-flexible nanotubes that can be manipulated for nanotechnology. *Nanoscale* 2020, 12, 22680–22687. [CrossRef]

48. Schabitz, W.R.; Krüger, C.; Pitzer, C.; Weber, D.; Laage, R.; Gassler, N.; Aronowski, J.; Mier, W.; Kirsch, F.; Dittgen, T.; et al. A neuroprotective factor for the hematopoietic protein granulocyte-macrophage colony stimulating factor (GM-CSF). *J. Cerebellum, Ataxia* 2008, 28, 29–43. [CrossRef]

49. Bianchi, V.E.; Locatelli, V.; Rizzi, L. Neurotrophic and neuroregenerative effects of GH/IGF1. *Int. J. Mol. Sci.* 2017, 18, 2441. [CrossRef]

50. Pradhan, K.; Das, G.; Gupta, V.; Mondal, P.; Barman, S.; Khan, J.; Ghosh, S. Discovery of neuroregenerative peptide from amphibian neuropeptide that inhibits amyloid-β toxicity and crosses blood-brain barrier. *ACS Chem. Neurosci.* 2019, 10, 1355–1368. [CrossRef]

51. Chernenina, M.; Schouten, P.; Nevalainen, N.; Johansson, F.; Orådd, G.; Strömberg, I. GDNF is important for striatal organization and maintenance of dopamine neurons grown in the presence of the striatum. *Neuroscience* 2014, 270, 1–11. [CrossRef] [PubMed]

52. Gronid, R.; Littrell, O.M.; Zhang, Z.; Ai, Y.; Huettl, P.; Pomerleau, F.; Quintero, J.E.; Andersen, A.H.; Stenslik, M.J.; Bradley, L.H.; et al. Increased brain bio-distribution and chemical stability and decreased immunogenicity of an engineered variant of GDNF. *Nucleic Acids Res.* 2019, 147, 28–36. [CrossRef] [PubMed]

53. Ibáñez, C.F.; Andressoo, J.O. Biology of GDNF and its receptors—Relevance for disorders of the central nervous system. *Neurobiol. Dis.* 2017, 97, 80–89. [CrossRef] [PubMed]

54. Smith, R.C.; O’Bryan, L.M.; Mitchell, P.J.; Leung, D.; Ghneum, M.; Wilson, J.M.; Hanson, J.C.; Sossick, S.; Cooper, J.; Huang, L.; et al. Increased brain bio-distribution and chemical stability and decreased immunogenicity of an engineered variant of GDNF. *Exp. Neurol.* 2015, 267, 165–176. [CrossRef] [PubMed]

55. Tsai, K.J.; Tsai, Y.C.; Shen, C.K. G-CSF rescues the memory impairment of animal models of Alzheimer’s disease. *J. Exp. Med.* 2007, 204, 1273–1280. [CrossRef] [PubMed]

56. Sanchez-Ramos, J.; Song, S.; Sava, V.; Catlow, B.; Lin, X.; Mori, T.; Cao, C.; Arendash, G.W. Granulocyte colony stimulating factor decreases brain amyloid burden and reverses cognitive impairment in Alzheimer’s mice. *Neuroscience* 2009, 163, 55–72. [CrossRef] [PubMed]

57. Schneider, A.; Krüger, C.; Steigleder, T.; Weber, D.; Pitzer, C.; Laage, R.; Aronowski, J.; Maurer, M.H.; Gassler, N.; Mier, W.; et al. The hematopoietic factor G-CSF is a neuronal ligand that counteracts programmed cell death and drives neurogenesis. *J. Clin. Investig.* 2005, 115, 2083–2098. [CrossRef]

58. Nutt, J.G.; Burchiel, K.J.; Comella, C.L.; Jankovic, J.; Lang, A.E.; Laws, E.R.; Lozano, A.M.; Penn, R.D.; Simpson, R.K.; Stacy, M.; et al. Implanted intracerebroventricular Glial cell line-derived neurotrophic factor. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. *Neurology* 2003, 60, 69–73. [CrossRef]

59. Gill, S.S.; Patel, N.K.; Hotton, G.R.; O’Sullivan, K.; McCarter, R.; Bunnage, M.; Brooks, D.J.; Svendsen, C.N.; Heywood, P. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. *Nat. Med.* 2003, 9, 589–595. [CrossRef]

60. Whone, A.; Luz, M.; Boca, M.; Woolley, M.; Mooney, L.; Dharia, S.; Broadfoot, J.; Cronin, D.; Schroers, C.; Barua, N.U.; et al. Randomized trial of intermittent intraputaminal glial cell line derivered neurotrophic factor in Parkinson’s disease. *Brain* 2019, 142, 512–525. [CrossRef]

61. Ramakrishna, S.; Muddashetty, R.S. Emerging role of microRNAs in dementia. *J. Mol. Biol.* 2019, 431, 1743–1762. [CrossRef] [PubMed]

62. Chen, S.; Ge, X.; Chen, Y.; Lv, N.; Liu, Z.; Yuan, W. Advances with RNA interference in Alzheimer’s disease research. *Drug Des. Devel. Ther.* 2013, 7, 117–125. [CrossRef] [PubMed]

63. Miller, V.M.; Gouvion, C.M.; Davidson, B.L.; Paulson, H.L. Targeting Alzheimer’s disease genes with RNA interference: An efficient strategy for silencing mutant alleles. *Nucleic Acids Res.* 2004, 32, 661–668. [CrossRef]
64. Hegarty, S.V.; Lee, D.J.; O’Keeffe, G.W.; Sullivan, A.M. Effects of intracerebral neurotrophic factor application on motor symptoms in Parkinson’s disease: A systematic review and meta-analysis. *Parkinsonism Relat. Disord.* 2017, 38, 19–25. [CrossRef] [PubMed]

65. Wen, Z.; Yan, Z.; He, R.; Fang, Z.; Guo, L.; Qian, Y.; Jiang, X.; Fang, L. Brain targeting and toxicity study of odorranalectin-conjugated nanoparticles following intranasal administration. *Drug Deliv.* 2011, 18, 555–561. [CrossRef]

66. Li, X.; Su, J.; Kamal, Z.; Guo, P.; Wu, X.; Lu, L.; Wu, H.; Qi, M. Odorrana lectin modified PEG-PLGA/PEG-PBLG curcumin-loaded nanoparticle for intranasal administration. *Drug Dev. Ind. Pharm.* 2020, 46, 899–909. [CrossRef]

67. Ahirrao, M.; Shrotriya, S. In vitro and in vivo evaluation of cubosomal in situ nasal gel containing resveratrol for brain targeting. *Drug Dev. Ind. Pharm.* 2017, 43, 1686–1693. [CrossRef]

68. Wu, H.; Li, J.; Zhang, Q.; Yan, X.; Guo, L.; Gao, X.; Qiu, M.; Jiang, X.; Lai, R.; Chen, H. A novel small Odorranalectin-bearing cubosomes: Preparation, brain delivery and pharmacodynamic study on amyloid-β25-35-treated rats following intranasal administration. *Eur. J. Pharm. Biopharm.* 2012, 80, 368–378. [CrossRef]

69. Erdő, F.; Bors, L.A.; Farkas, D.; Bajza, A.; Gizurarson, S. Evaluation of intranasal delivery route of drug administration for brain targeting. *Brain Res. Bull.* 2018, 143, 155–170. [CrossRef]

70. Samaridou, E.; Alonso, M.J. Nose-to-brain peptide delivery—The potential of nanotechnology. *Biorg. Med. Chem.* 2018, 26, 2888–2905. [CrossRef]

71. Sajja, R.K.; Cudic, P.; Cucullo, L. In vitro characterization of odorranalectin for peptide-based drug delivery across the blood-brain barrier. *BMC Neurosci.* 2019, 20, 22. [CrossRef] [PubMed]

72. Fan, Y.; Chen, M.; Zhang, J.; Maincent, P.; Xia, X.; Wu, W. Updated progress of nanocarrier-based intranasal drug delivery systems for treatment of brain diseases. *Crit. Rev. Ther. Drug Cass. Syst.* 2018, 35, 433–467. [CrossRef] [PubMed]

73. Lochhead, J.J.; Thorne, R.G. Intranasal delivery of biologics to the central nervous system. *Adv. Drug Deliv. Rev.* 2012, 64, 614–628. [CrossRef] [PubMed]

74. Lochhead, J.J.; Wolak, D.J.; Pizzo, M.E.; Thorne, R.G. Rapid transport within cerebral perivascular spaces underlies widespread tracer distribution in the brain after intranasal administration. *J. Cereb. Blood Flow Metab.* 2015, 35, 371–381. [CrossRef]

75. Alcalá-Barraza, S.R.; Lee, M.S.; Hanson, L.R.; McDonald, A.A.; Frey, W.H.; McLoon, L.K. Intranasal delivery of neurotrophic factors BDNF, CNTF, EPO, and NT-4 to the CNS. *J. Drug Target.* 2010, 18, 179–190. [CrossRef]

76. Kirik, D.; Cederfjäll, E.; Halliday, G.; Petersen, Å. Gene therapy for Parkinson’s disease: Disease modification by GDNF family of ligands. *Neurobiol. Dis.* 2017, 97 Pt B, 179–188. [CrossRef]

77. Yoon, J.Y.; Yang, K.J.; Park, S.N.; Kim, D.K.; Kim, J.D. The effect of dexamethasone/cell-penetrating peptide nanoparticles on gene delivery for inner ear therapy. *Int. J. Nanomed.* 2016, 11, 6123–6134. [CrossRef]

78. Bartus, R.T.; Baumann, T.L.; Siffert, J.; Herzog, C.D.; Alterman, R.; Boulis, N.; Turner, D.A.; Stacy, M.; Lang, A.E.; Lozano, A.M.; et al. Safety/feasibility of targeting the substantia nigra with AAV2-neurturin in Parkinson patients. *Neurology* 2013, 80, 1698–1701. [CrossRef]

79. Marks, W.J., Jr; Ostrem, J.L.; Verhagen, L.; Starr, P.A.; Larson, P.S.; Bakay, R.A.; Taylor, R.; Cahn-Weiner, D.A.; Stoesz, A.J.; Olanon, C.W.; et al. Safety and tolerability of intratemporal delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson’s disease: An open-label, phase I trial. *Lancet Neurol.* 2008, 7, 400–408. [CrossRef]

80. Marks, W.J., Jr; Bartus, R.T.; Siffert, J.; Davis, C.S.; Lozano, A.; Boulis, N.; Vitek, J.; Stacy, M.; Turner, D.; Verhagen, L.; et al. Gene delivery of AAV2-neurturin for Parkinson’s disease: A double-blind, controlled trial. *Lancet Neurol.* 2010, 9, 1164–1172. [CrossRef]

81. Lavy, T.; De, A.; Shekim, N.; Goldin, T.; Geron, J.; Green, M.; Feldman, D.; Pfeffer, S.; Sussman, A.; Soreq, H.; et al. Polyarylpyrrole-coated electrodes for the delivery of charge and neurotrophins to cochlear neurons. *Biomaterials* 2009, 30, 2614–2624. [CrossRef] [PubMed]

82. Kikkawa, Y.S.; Nakagawa, T.; Ying, L.; Tabata, Y.; Tsubouchi, H.; Ido, A.; Ito, J. Growth factor-eluting cochlear implant electrode: Impact on residual auditory function, insertional trauma, and fibrosis. *J. Transl. Med.* 2014, 12, 280. [CrossRef]

83. Chikar, J.A.; Hendricks, J.L.; Richardson-Burns, S.M.; Raphael, Y.; Pfingst, B.E.; Martin, D.C. The use of a dual PEDOT and RGD-functionalized alginate hydrogel coating to provide sustained drug delivery and improved cochlear implant function. *Biomaterials* 2012, 33, 1982–1990. [CrossRef] [PubMed]

84. Endo, T.; Nakagawa, T.; Kita, T.; Iguchi, F.; Kim, T.S.; Tamura, T.; Iwai, K.; Tabata, Y.; Ito, J. Novel strategy for treatment of inner ears using a biodegradable gel. *Laryngoscope* 2005, 115, 2016–2020. [CrossRef] [PubMed]

85. Madduri, S.; Gander, B. Growth factor delivery systems and repair strategies for damaged peripheral nerves. *J. Control. Release* 2012, 161, 274–282. [CrossRef]

86. Wang, Y.; Wise, A.K.; Tan, J.; Maina, J.W.; Shepherd, R.K.; Caruso, F. Mesoporous silica supraparticles for sustained inner-ear drug delivery. *Small* 2014, 10, 4244–4248. [CrossRef]

87. Li, H.; Edin, F.; Hayashi, H.; Gudjonsson, O.; Danckwardt-Lillieström, N.; Engqvist, H.; Rask-Andersen, H.; Xia, W. Guided growth of auditory neurons: Bioactive particles towards gapless neural-electrode interface. *Biomaterials* 2017, 122, 1–9. [CrossRef]

88. Roy, S.; Glueckert, R.; Johnston, A.H.; Perrier, T.; Bitsche, M.; Newman, T.A.; Saulnier, P.; Schrott-Fischer, A. Strategies for drug delivery to the human inner ear by multifunctional nanoparticles. *Nanomedicine* 2012, 7, 55–63. [CrossRef]

89. Mitra, S.; Bebbahani, H.; Erisksdotter, M. Innovative therapy for Alzheimer’s disease with focus on biodelivery of NGF. *Front. Neurosci.* 2019, 13, 38. [CrossRef]
90. Xi, Y.; Chen, Y.; Jin, Y.; Han, G.; Song, M.; Song, T.; Shi, Y.; Tao, L.; Huang, Z.; Zhou, J.; et al. Versatile nanomaterials for Alzheimer’s disease: Pathogenesis inspired disease-modifying therapy. J. Control. Release. 2022, 345, 38. [CrossRef]

91. Akel, H.; Ismail, R.; Csoka, I. Progress and perspectives of brain-targeting lipid-based nanosystems via the nasal route in Alzheimer’s disease. Eur. J. Pharm. Biopharm. 2020, 148, 38–53. [CrossRef] [PubMed]

92. Babazadeh, A.; Mohammadi Vahed, F.; Jafari, S.M. Nanocarrier-mediated brain delivery of bioactives for treatment/prevention of neurodegenerative diseases. J. Control. Release. 2020, 321, 211–221. [CrossRef] [PubMed]

93. Sonvico, F.; Clementino, A.; Buttini, F.; Colombo, G.; Pescina, S.; Stanisquaski Gutereus, S.; Raffin Pohlmann, A.; Nicoli, S. Surface-modified nanocarriers for nose-to-brain delivery: From biodoshesion to targeting. Pharmaceutics 2018, 10, 34. [CrossRef]

94. Jao, D.; Xue, Y.; Medina, J.; Hu, X. Protein-based drug-delivery materials. Adv. Drug Deliv. Rev. 2019, 148, 146–180. [CrossRef]

95. Teixeira, M.I.; Lopes, C.M.; Amaral, M.H.; Costa, P.C. Current insights on lipid nanocarrier-assisted drug delivery in the treatment of neurodegenerative diseases. Eur. J. Pharm. Biopharm. 2020, 149, 192–217. [CrossRef]

96. Harilal, S.; Jose, J.; Parambi, D.G.T.; Kumar, R.; Mathew, G.E.; Uddin, M.S.; Kim, H.; Mathew, B. Advancements in nanotherapeutics for Alzheimer’s disease: Current perspectives. J. Pharm. Pharmacol. 2019, 71, 1370–1383. [CrossRef]

97. Zorkina, Y.; Abramova, O.; Ushakova, V.; Morozova, A.; Zubkov, E.; Valikov, M.; Melnikov, P.; Majouga, A.; Chekhonin, V. Nano carrier drug delivery systems for the treatment of neuropsychiatric disorders: Advantages and limitations. Molecules 2020, 25, 5294. [CrossRef] [PubMed]

98. Dizaj, S.M.; Eslamifar, M.; Khezri, K.; Saeedi, M.; Babazadeh, A.; Mohammadi Vahed, F.; Jafari, S.M. Nanocarrier-mediated brain delivery of bioactives for treatment/prevention of neurodegenerative diseases. J. Control. Release. 2020, 321, 211–221. [CrossRef] [PubMed]

99. Agrahari, V.; Burnouf, P.A.; Burnouf, T.; Agrahari, V. Nanoformulation properties, characterization, and behavior in complex biological matrices: Challenges and opportunities for brain-targeted drug delivery applications and enhanced translational potential. Adv. Drug Deliv. Rev. 2019, 148, 146–180. [CrossRef]

100. Saeedi, M.; Eslamifar, M.; Khezri, K.; Dizaj, S.M. Applications of nanotechnology in drug delivery to the central nervous system. Adv. Drug Deliv. Rev. 2019, 148, 192–217. [CrossRef] [PubMed]

101. Harilal, S.; Jose, J.; Parambi, D.G.T.; Kumar, R.; Mathew, G.E.; Uddin, M.S.; Kim, H.; Mathew, B. Advancements in nanotherapeutics for Alzheimer’s disease: Current perspectives. J. Pharm. Pharmacol. 2019, 71, 1370–1383. [CrossRef]

102. Liaw, K.; Zhang, Z.; Kannan, S. Neuronanotechnology for brain regeneration. Adv. Drug Deliv. Rev. 2019, 148, 3–18. [CrossRef]

103. Hanafy, A.S. Nanotechnology-based drug delivery systems for Alzheimer’s disease management: Technical, industrial, and clinical challenges. J. Control. Release. 2017, 245, 95–107. [CrossRef] [PubMed]

104. Sahni, J.K.; Dogguri, S.; Ali, J.; Baboota, S.; Rao, L.; Ramassamy, C. Neurotherapeutic applications of nanoparticles in Alzheimer’s disease. J. Control. Release. 2011, 152, 208–231. [CrossRef] [PubMed]

105. Brambilla, D.; Le Droumaguet, B.; Nicolas, J.; Hashemi, S.H.; Wu, L.P.; Moghimi, S.M.; Couvreur, P.; Andrieux, K. Nanotechnologies for Alzheimer’s disease: Diagnosis, therapy, and safety issues. Nanomedicine 2011, 7, 521–540. [CrossRef]

106. Saeedi, M.; Eslamifar, M.; Khezri, K.; Dizaj, S.M. Applications of nanotechnology in drug delivery to the central nervous system. Biomath. 2019, 111, 666–675. [CrossRef] [PubMed]

107. Pires, P.C.; Santos, A.O. Nanosystems in nose-to-brain drug delivery: A review of non-clinical brain targeting studies. J. Control. Release 2018, 270, 89–100. [CrossRef]

108. Geral, C.; Angelova, A.; Angelov, B.; Nicolas, V.; Lesieur, S. Chapter 11: Multicompartment lipidic nanocarriers for targeting of cells expressing brain receptors. In Self-Assembled Supramolecular Architectures: Lyotropic Liquid Crystals; Garti, N., Mezzenga, R., Somasundaran, P., Eds.; John Wiley & Sons, Inc.: New Jersey, NJ, USA, 2012; pp. 319–355. [CrossRef]

109. Liaw, K.; Zhang, Z.; Kannan, S. Neuronanotechnology for brain regeneration. Adv. Drug Deliv. Rev. 2019, 148, 3–18. [CrossRef]

110. Li, Y.; Liu, C. Nanomaterial-based bone regeneration. Nanoscale 2017, 9, 4862–4874. [CrossRef]

111. Bu, M.; Tang, J.; Wei, Y.; Sun, Y.; Wang, X.; Wu, L.; Liu, H. Enhanced bioavailability of nerve growth factor with phytantriol lipid-based crystalline nanoparticles in cochlea. Int. J. Nanomed. 2015, 10, 6879–6889. [CrossRef]

112. Guccione, C.; Oufir, M.; Pizzinini, V.; Eigenmann, D.E.; Jähne, E.A.; Zabela, V.; Faleschini, M.T.; Bergonzi, M.C.; Smiesko, M.; Hamburger, M.; et al. Andrographolide-loaded nanoparticles for brain delivery: Formulation, characterisation and in vitro permeability using hCMEC/D3 cell line. Eur. J. Pharm. Biopharm. 2017, 119, 253–263. [CrossRef]

113. Saraiva, C.; Praça, C.; Ferreira, R.; Santos, T.; Ferreira, L.; Bernardino, L. Nano-particle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. J. Control. Release. 2016, 235, 34–47. [CrossRef]

114. Zhang, T.T.; Li, W.; Meng, G.; Wang, P.; Liao, W. Strategies for transporting nanoparticles across the blood-brain barrier. Biomater. Sci. 2016, 4, 219–229. [CrossRef] [PubMed]

115. Agrawal, M.; Ajazuddin Tripathi, D.K.; Saraf, S.; Saraf, S.; Antimisiaris, S.G.; Mourtas, S.; Hammarlund-Udenaes, M.; Alexander, A. Recent advancements in liposomes targeting strategies to cross blood-brain barrier (BBB) for the treatment of Alzheimer’s disease. J. Control. Release 2017, 260, 61–77. [CrossRef] [PubMed]

116. Sharma, G.; Sharma, A.R.; Lee, S.S.; Bhattacharya, M.; Nam, J.S.; Chakraborty, C. Advances in nanocarriers enabled brain targeted drug delivery across blood brain barrier. Int. J. Pharm. 2019, 559, 360–372. [CrossRef]

117. Kim, J.; Ahn, S.I.; Kim, Y. Nanotherapeutics engineered to cross the blood-brain barrier for advanced drug delivery to the central nervous system. J. Ind. Eng. Chem. 2019, 73, 8–18. [CrossRef] [PubMed]

118. Raj, R.; Wairkar, S.; Sridhar, V.; Gaud, R. Pramipexole dihydrochloride loaded chitosan nanoparticles for nose to brain delivery: Development, characterization, and in vivo anti-Parkinson activity. Int. J. Biol. Macromol. 2018, 109, 27–35. [CrossRef]

119. Eskinazi-Budge, A.; Manickavasagam, D.; Czech, T.; Novak, K.; Kunzler, J.; Owemunw, M.O. Preparation of emulsifying wax/glycerol monooleate nanoparticles and evaluation as a delivery system for repurposing simvastatin in bone regeneration. Drug Dev. Ind. Pharm. 2018, 44, 1583–1590. [CrossRef]
118. El Naggar, Y.S.; Etman, S.M.; Abdelmoneif, D.A.; Abdallah, O.Y. Novel piperine-loaded Tween-integrated monoolene cubosomes as brain-targeted oral nanomedicine in Alzheimer’s disease: Pharmaceutical, biological, and toxicological studies. *Int. J. Nanomed.* **2015**, *10*, 5459–5473. [CrossRef]

119. Li, Y.; Song, H.; Xiong, S.; Tian, T.; Liu, T.; Sun, Y. Chitosan-stabilzed bovine serum albumin nanoparticles having ability to control the release of NELL-1 protein. *Int. J. Biol. Macromol.* **2018**, *109*, 672–680. [CrossRef]

120. Chatterjee, B.; Gorain, B.; Mohanaindu, K.; Sengupta, P.; Mandal, U.K.; Choudhury, H. Targeted drug delivery to the brain via intranasal nanoemulsion: Available proof of concept and existing challenges. *Int. J. Pharm.* **2019**, *565*, 258–268. [CrossRef]

121. Oshiro, J.A.; Sato, M.R.; Scardueli, C.R.; Lopes de Oliveira, G.J.P.; Abucafy, M.P.; Chorilli, M. Bioactive molecule-loaded drug delivery systems to optimize bone tissue repair. *Curr. Protein Pept. Sci.* **2017**, *18*, 850–863. [CrossRef]

122. Chung, E.P.; Cotter, J.D.; Prakapenka, A.V.; Cook, R.L.; DiPerna, D.M.; Sirianni, R.W. Targeting small molecule delivery to the brain and spinal cord via intranasal administration of Rabies Virus Glycoprotein (RVG29)-modified PLGA nanoparticles. *Pharmaceutics* **2020**, *12*, 93. [CrossRef][PubMed]

123. Piazzini, V.; Landucci, E.; D’Ambrosio, M.; Tiozzo Fasiolo, L.; Cinci, L.; Colombo, G.; Pellegrini-Giampietro, D.E.; Bilia, A.R.; Luceri, C.; Bergonzi, M.C. Chitosan coated human serum albumin nanoparticles: A promising strategy for nose-to-brain drug delivery. *Int. J. Biol. Macromol.* **2019**, *129*, 267–280. [CrossRef][PubMed]

124. Yin, T.; Yang, L.; Liu, Y.; Zhou, X.; Sun, J.; Liu, J. Sialic acid (SA)-modified selenium nanoparticles coated with a high blood-brain barrier permeability peptide-B6 peptide for potential use in Alzheimer’s disease. *Acta Biomater.* **2015**, *25*, 172–183. [CrossRef][PubMed]

125. Barnabas, W. Drug targeting strategies into the brain for treating neurological diseases. *J. Neurosci. Methods* **2019**, *311*, 133–146. [CrossRef]

126. Yu, S.; Xu, X.; Feng, J.; Liu, M.; Hu, K. Chitosan and chitosan coating nanoparticles for the treatment of brain disease. *Int. J. Pharm.* **2019**, *560*, 282–293. [CrossRef]

127. Zheng, X.; Zhang, C.; Guo, Q.; Wan, X.; Shao, X.; Liu, Q.; Zhang, Q. Dual-functional nanoparticles for precise drug delivery to Alzheimer’s disease lesions: Targeting mechanisms, pharmacodynamics and safety. *Int. J. Pharm.* **2017**, *525*, 237–248. [CrossRef]

128. Teleau, D.M.; Negut, I.; Grumezescu, V.; Grumezescu, A.M.; Teleau, R.I. Nanomaterials for drug delivery to the central nervous system. *Nanomaterials* **2019**, *9*, 371. [CrossRef]

129. Song, H.; Wei, M.; Zhang, N.; Li, H.; Han, X.; Zhang, Y.; Zheng, W. Enhanced permeability of blood-brain barrier and targeting function of brain via bovine-modified chemically solid lipid nanoparticle. *Int. J. Nanomed.* **2018**, *13*, 1869–1879. [CrossRef]

130. Hu, X.; Yang, F.; Liao, Y.; Li, L.; Zhang, L. Cholesterol-PEG comodified poly (N-butyl) cyanoacrylate nanoparticles for brain delivery: In vitro and in vivo evaluations. *Drug Deliv.* **2017**, *24*, 121–132. [CrossRef]

131. Gajbhiye, K.R.; Pawar, A.; Mahadik, K.R.; Gajbhiye, V. PEGylated nanocarriers: A promising tool for targeted delivery to the brain. *Colloids Surf. B Biointerfaces* **2020**, *187*, 110770. [CrossRef]

132. Azhari, H.; Strauss, M.; Hook, S.; Boyd, B.J.; Rizwan, S.B. Stabilising cubosomes with Tween 80 as a step towards targeting lipid nanocarriers to the blood-brain barrier. *Eur. J. Pharm. Biopharm.* **2016**, *104*, 148–155. [CrossRef][PubMed]

133. Gobbi, M.; Re, F.; Canovi, M.; Beeg, M.; Gregori, M.; Sesana, S.; Sonnino, S.; Brogioli, D.; Musicanti, C.; Gasco, P.; et al. Lipid-based nanoparticles with high binding affinity for amyloid-beta1-42 peptide. *Biomaterials* **2010**, *31*, 6519–6529. [CrossRef][PubMed]

134. Zhang, C.; Wan, X.; Zheng, X.; Shao, X.; Liu, Q.; Zhang, Q.; Qian, Y. Dual-functional nanoparticles targeting amyloid plaques in the brains of Alzheimer’s disease mice. *Biomaterials* **2014**, *35*, 456–465. [CrossRef][PubMed]

135. Aderibigbe, B.A.; Naki, T. Chitosan-based nanocarriers for nose to brain delivery. *Appl. Sci.* **2019**, *9*, 2219. [CrossRef]

136. Ramalho, M.J.; Andrade, S.; Loureiro, J.A.; do Carmo Pereira, M. Nanotechnology to improve the Alzheimer’s disease therapy with natural compounds. *Drug Deliv. Transl. Res.* **2020**, *10*, 380–402. [CrossRef]

137. Prabhath, A.; Vernekar, V.N.; Sanchez, E.; Laurencin, C.T. Growth factor delivery strategies for rotator cuff repair and regeneration. *Int. J. Pharm.* **2018**, *544*, 358–371. [CrossRef]

138. Bayer, E.A.; Gottardi, R.; Fedorchak, M.V.; Little, S.R. The scope and sequence of growth factor delivery for vascularized bone tissue regeneration. *J. Control. Release* **2015**, *197*, 129–140. [CrossRef]

139. Van Rijt, S.; Habibovic, P. Enhancing regenerative approaches with nanoparticles. *J. R. Soc. Interface* **2017**, *14*, 20170093. [CrossRef]

140. Prades, R.; Guerrero, S.; Araya, E.; Molina, C.; Salas, E.; Zurita, E.; Selva, J.; Egea, G.; López-Iglesias, C.; Teixidó, M.; et al. Delivery of gold nanoparticles to the brain by conjugation with a peptide that recognizes the transferrin receptor. *Biomaterials* **2012**, *33*, 7194–7205. [CrossRef]

141. Songjiang, Z.; Lixiang, W. Amyloid-beta associated with chitosan nano-carrier has favorable immunogenicity and permeates the BBB. *AAPS PharmSciTech* **2009**, *10*, 900–905. [CrossRef]

142. Zhang, C.; Zheng, X.; Wan, X.; Shao, X.; Liu, Q.; Zhang, Z.; Zhang, Q. The potential use of H102 peptide-loaded dual-functional nanoparticles in the treatment of Alzheimer’s disease. *J. Control. Release* **2014**, *192*, 317–324. [CrossRef][PubMed]

143. Zenzi, A.; Begley, D.; Pontikis, C.; Legros, C.; Mihoreanu, L.; Wagner, S.; Büchel, C.; von Briesen, H.; Kreuter, J. Albumin nanoparticles targeted with Apo E enter the CNS by transcytosis and are delivered to neurons. *J. Control. Release* **2009**, *137*, 78–86. [CrossRef][PubMed]

144. Angelov, B.; Angelova, A.; Filippov, S.K.; Drechtls, M.; Stépánek, P.; Lesieur, S. Multicompartment lipid cubic nanoparticles with high protein upload: Millisecond dynamics of formation. *ACS Nano* **2014**, *8*, 5216–5226. [CrossRef][PubMed]
145. Gao, X.; Wu, B.; Zhang, Q.; Chen, J.; Zhu, J.; Zhang, W.; Rong, Z.; Chen, H.; Jiang, X. Brain delivery of vasoactive intestinal peptide enhanced with the nanoparticles conjugated with wheat germ agglutinin following intranasal administration. J. Control Release 2007, 121, 156–167. [CrossRef] [PubMed]
146. Zhang, C.; Chen, J.; Feng, C.; Shao, X.; Liu, Q.; Zhang, Q.; Pang, Z.; Jiang, X. Intranasal nanoparticles of basic fibroblast growth factor for brain delivery to treat Alzheimer’s disease. Int. J. Pharm. 2014, 461, 192–202. [CrossRef]
147. Park, T.E.; Singh, B.; Li, H.; Lee, J.Y.; Kang, S.K.; Choi, Y.J.; Cho, C.S. Enhanced BBB permeability of osmotically active poly(mannitol-co-PEI) modified with rabies virus glycoprotein via selective stimulation of caveolar endocytosis for RNAi therapeutics in Alzheimer’s disease. Biomaterials 2015, 38, 61–71. [CrossRef]
148. Liu, Y.; An, S.; Li, J.; Kuang, Y.; He, X.; Guo, Y.; Ma, H.; Zhang, Y.; Ji, B.; Jiang, C. Brain-targeted co-delivery of therapeutic gene and peptide by multifunctional nanoparticles in Alzheimer’s disease mice. Biomaterials 2016, 80, 33–45. [CrossRef]
149. Arora, S.; Sharma, D.; Singh, J. GLUT-1: An effective target to drive brain-derived neurotrophic factor gene across the blood brain barrier. ACS Chem. Neurosci. 2020, 11, 1620–1633. [CrossRef]
150. Gandhi, M.; Bhatt, P.; Chauhan, G.; Gupta, S.; Misra, A.; Mashru, R. IGF-II-conjugated nanocarrier for brain-targeted delivery of p11 gene for depression. AAPS PharmSciTech 2019, 20, 50. [CrossRef]
151. Sun, X.; Pang, Z.; Ye, H.; Qiu, B.; Guo, L.; Li, J.; Ren, J.; Qian, Y.; Zhang, Q.; Chen, J. Co-delivery of PEGFP-hTRAIL and paclitaxel to brain glioma mediated by an angiopoet-conjugated liposome. Biomaterials 2012, 33, 916–924. [CrossRef] [PubMed]
152. Wang, P.; Zheng, X.; Guo, Q.; Yang, P.; Pang, X.; Qian, K.; Lu, W.; Zhang, Q.; Jiang, X. Systemic delivery of BACE1 siRNA through ACE-2 Release and poly(mannitol-co-PEI) modified with rabies virus glycoprotein via selective stimulation of caveolar endocytosis for RNAi therapeutics in Alzheimer’s disease. Biomaterials 2015, 38, 61–71. [CrossRef]
153. Park, T.E.; Singh, B.; Li, H.; Lee, J.Y.; Kang, S.K.; Choi, Y.J.; Cho, C.S. Enhanced BBB permeability of osmotically active poly(mannitol-co-PEI) modified with rabies virus glycoprotein via selective stimulation of caveolar endocytosis for RNAi therapeutics in Alzheimer’s disease. Biomaterials 2015, 38, 61–71. [CrossRef]
154. Park, T.E.; Singh, B.; Li, H.; Lee, J.Y.; Kang, S.K.; Choi, Y.J.; Cho, C.S. Enhanced BBB permeability of osmotically active poly(mannitol-co-PEI) modified with rabies virus glycoprotein via selective stimulation of caveolar endocytosis for RNAi therapeutics in Alzheimer’s disease. Biomaterials 2015, 38, 61–71. [CrossRef]
155. Bae, H.; Chu, H.; Edalat, F.; Cha, J.M.; Sant, S.; Kashyap, A.; Ahari, A.F.; Kwon, C.H.; Nichol, J.W.; Manoucheri, S.; et al. Development of functional biomaterials with micro- and nanoscale technologies for tissue engineering and drug delivery applications. J. Tissue Eng. Regen. Med. 2014, 8, 1–14. [CrossRef]
156. Rakotoarisoa, M.; Angelov, B.; Drechsler, M.; Nicolas, V.; Bizien, T.; Gorshkova, Y.E.; Deng, Y.; Angelova, A. Liquid crystalline lipid nanoparticles for combined delivery of curcumin, fish oil and BDNF. In vitro neuroprotective potential in a cellular model of tunicamycin-induced endoplasmic reticulum stress. Smart Mater. Med. 2022, 55, 380–387. [CrossRef] [PubMed]
157. Prasad, R.; Nokes, P.G.; Bellingham, M.C. The role of altered BDNF/TrkB signaling in Amyotrophic Lateral Sclerosis. Front. Cell Neurosci. 2019, 13, 368. [CrossRef]
158. Minuzzi, L.G.; Seelaender, M.; Silva, B.S.D.A.; Cunha, E.d.B.B.; Deus, M.D.C.; Vasconcellos, F.T.F.; Marqueze, L.F.B.; Gadotti, A.C.; et al. COVID-19 outcome relates with circulating BDNF, according to patient adiposity and age. Front. Nutrit. 2021, 8, 784429. [CrossRef]
159. Potagheinejad, M.; Gholami, M. Possible neurological and mental outcomes of COVID-19 infection: A hypothetical role of ACE-2 Mas/BDNF signaling pathway. Int. J. Prev. Med. 2020, 11, 84. [CrossRef] [PubMed]
160. Nijhawan, A.; Singh, B.; Shukla, A.; Baradari, A.; Pathak, J.; Saxena, A.; et al. Possible neurological and mental outcomes of COVID-19 infection: A hypothetical role of ACE-2 Mas/BDNF signaling pathway. Int. J. Prev. Med. 2020, 11, 84. [CrossRef] [PubMed]
161. Villar, C.; Rivellini, E.; Lavitrano, M.; Combi, R. Can SARS-CoV-2 Infection exacerbate Alzheimer’s disease? An overview of shared risk factors and pathogenetic mechanisms. J. Pers. Med. 2021, 12, 29. [CrossRef] [PubMed]
162. Ng, T.K.S.; Ho, C.S.H.; Tam, W.W.S.; Kua, E.H.; Ho, R.C.M. Decreased serum brain-derived neurotrophic factor (BDNF) levels in patients with Alzheimer’s disease (AD): A systematic review and meta-analysis. Int. J. Mol. Sci. 2019, 20, 257. [CrossRef] [PubMed]
163. Harris, N.M.; Ritzel, R.; Mancini, N.S.; Jiang, Y.; Yi, X.; Manickam, D.S.; Banks, W.A.; Kabanov, A.V.; McCullough, L.D.; Verma, R. Nano-particle delivery of brain derived neurotrophic factor after focal cerebral ischemia reduces tissue injury and enhances behavioral recovery. Pharmacol. Biochem. Behav. 2016, 150–151, 48–56. [CrossRef] [PubMed]
164. Jiang, Y.; Fay, J.M.; Poon, C.D.; Vinod, N.; Zhao, Y.; Bullock, K.; Qin, S.; Manickam, D.S.; Yi, X.; Banks, W.A.; et al. Nanoformulation of brain-derived neurotrophic factor with target receptor-triggered-release in the central nervous system. Adv. Funct. Mater. 2018, 28, 1703982. [CrossRef]
165. Limongi, T.; Rocchi, A.; Cesca, F.; Tan, H.; Miele, E.; Giugni, A.; Orlando, M.; Perrone Donnorso, M.; Perozziello, G.; Benfenati, F.; et al. Delivery of brain-derived neurotrophic factor by 3D biocompatible polycrylamide scaffolds for neural tissue engineering and neuronal regeneration. Mol. Neurobiol. 2018, 55, 8788–8798. [CrossRef]
166. Hassannejad, Z.; Zadegan, S.A.; Vaccaro, A.R.; Rahimi-Moghav, V.; Sabzevari, O. Biofunctionalized peptide-based hydrogel as an injectable scaffold for BDNF delivery can improve regeneration after spinal cord injury. Injury 2019, 50, 278–285. [CrossRef]
169. Cook, D.J.; Nguyen, C.; Chun, H.N.L.; Llorente, I.; Chiu, A.S.; Machnicki, M.; Zarembinski, T.I.; Carmichael, S.T. Hydrogel-delivered brain-derived neurotrophic factor promotes tissue repair and recovery after stroke. J. Cereb. Blood Flow Metab. 2017, 37, 1030–1045. [CrossRef]

170. Obermeyer, J.M.; Tuladhar, A.; Payne, S.L.; Ho, E.; Morshhead, C.M.; Shoichet, M.S. Local delivery of brain-derived neurotrophic factor enables behavioral recovery and tissue repair in stroke-injured rats. Tissue Eng. Part A 2019, 25, 1175–1187. [CrossRef]

171. Kandalam, S.; Sindj, L.; Delcroix, G.J.; Violet, F.; Garric, X.; André, E.M.; Schiller, P.C.; Venier-Julienne, M.C.; des Rieux, A.; Guicheux, J., et al. Pharmacologically active microcarriers delivering BDNF within a hydrogel: Novel strategy for human bone marrow-derived stem cells neural/neuronal differentiation guidance and therapeutic secretome enhancement. Acta Biomater. 2017, 49, 167–180. [CrossRef]

172. Xing, Y.; Wen, C.Y.; Li, S.T.; Xia, Z.X. Non-viral liposome-mediated transfer of brain-derived neurotrophic factor across the blood-brain barrier. Neural Regen. Res. 2016, 11, 617–622. [CrossRef] [PubMed]

173. Low, W.C.; Rujitanaroj, P.O.; Wang, F.; Wang, J.; Chew, S.Y. Nanofiber-mediated release of retinoic acid and brain-derived neurotrophic factor for enhanced neuronal differentiation of neural progenitor cells. Drug Deliv. Transl. Res. 2015, 5, 89–100. [CrossRef] [PubMed]

174. Schmidt, N.; Schulze, J.; Warwas, D.P.; Ehlnert, N.; Lenarz, T.; Warnecke, A.; Behrens, P. Long-term delivery of brain-derived neurotrophic factor (BDNF) from nanoporous silica nanoparticles improves the survival of spiral ganglion neurons in vitro. PLoS ONE 2018, 13, e0194778. [CrossRef] [PubMed]

175. Xu, J.; Chau, Y. Polymeric nanoparticles decorated with BDNF-derived peptide for neuron-targeted delivery of PTEN inhibitor. Eur. J. Pharm. Sci. 2018, 124, 37–45. [CrossRef]

176. Dąbkowska, M.; Łuczewska, K.; Rogińska, D.; Soboś, A.; Wasilewska, M.; Ulariczcyk, Z.; Machaliński, B. Novel design of (PEG-yalted)PAMAM-based nanoparticles for sustained delivery of BDNF to nerve-injured differentiated neuroblastoma cells. J. Nanobiotechnol. 2020, 18, 120. [CrossRef]

177. Lu, J.; Yan, X.; Sun, X.; Shen, X.; Yin, H.; Wang, C.; Liu, Y.; Lu, C.; Fu, H.; Yang, S.; et al. Synergistic effects of dual-presenting VEGF- and BDNF-mimetic peptide epitopes from self-assembling peptide hydrogels on peripheral nerve regeneration. Nanoscale 2019, 11, 19943–19958. [CrossRef]

178. Edelbrock, A.N.; Alvarez, Z.; Simkin, D.; Fyrner, T.; Chin, S.M.; Sato, K.; Kiskinis, E.; Stupp, S.I. Supramolecular nanostructure activates TrkB receptor signaling of neuronal cells by mimicking brain-derived neurotrophic factor. Nano Lett. 2018, 18, 6237–6247. [CrossRef]

179. Lopes, C.D.F.; Gonçalves, N.P.; Gomes, C.P.; Saraiva, M.J.; Pégo, A.P. BDNF gene delivery mediated by neuron-targeted nanoparticles is neuroprotective in peripheral nerve injury. Biomaterials 2017, 121, 83–96. [CrossRef]

180. Wang, B.; Yuan, J.; Chen, X.; Xu, J.; Li, Y.; Dong, P. Functional regeneration of the transected recurrent laryngeal nerve using a collagen scaffold loaded with laminin and laminin-binding BDNF and GDNF. Sci. Rep. 2016, 6, 32292. [CrossRef]

181. Ravina, K.; Briggs, D.I.; Kislal, S.; Warraich, Z.; Nguyen, T.; Lam, R.K.; Zarembinski, T.I.; Shamloo, M. Intracerebral delivery of brain-derived neurotrophic factor using HyStem®-C hydrogel implants improves functional recovery and reduces neuroinflammation in a rat model of ischemic stroke. Int. J. Mol. Sci. 2018, 19, 3782. [CrossRef]

182. Gransee, H.M.; Zhan, W.Z.; Sieck, G.C.; Mantilla, C.B. Localized delivery of brain-derived neurotrophic factor-expressing mesenchymal stem cells enhances functional recovery following cervical spinal cord injury. J. Neurotrauma 2015, 32, 185–193. [CrossRef] [PubMed]

183. Liu, S.; Sandner, B.; Schackel, T.; Nicholson, L.; Chhtarto, A.; Tenenbaum, L.; Puttagunta, R.; Müller, W.; Weidner, N.; Blesch, A. Regulated viral BDNF delivery in combination with Schwann cells promotes axonal regeneration through capillary alginine hydrogels after spinal cord injury. Acta Biomater. 2017, 60, 167–180. [CrossRef] [PubMed]

184. Schendzielorz, P.; Scherzed, A.; Rak, K.; Völker, J.; Hagen, R.; Mlynški, R.; Frölich, K.; Radeloff, A. A hydrogel coating for cochlear implant arrays with encapsulated adipose-derived stem cells allows brain-derived neurotrophic factor delivery. Acta Otolaryngol. 2017, 137, 199–205. [CrossRef]

185. Angelova, A.; Drechsler, M.; Garamus, V.M.; Angelov, B. Liquid crystalline nanostructures as PEGylated reservoirs of omega-3 polyunsaturated fatty acids: Structural insights toward delivery formulations against neurodegenerative disorders. ACS Omega 2020, 2019, 6, 3229–3234. [CrossRef]

186. Guerzoni, L.P.; Nicolas, V.; Angelova, A. In vitro modulation of TrkB receptor signaling upon sequential delivery of curcumin-DHA loaded carriers towards promoting neuronal survival. Pharm. Res. 2017, 34, 492–505. [CrossRef]

187. Fujino, T.; Yamada, T.; Asada, T.; Tsuibo, Y.; Wakana, C.; Mawatari, S.; Kono, S. Efficacy and blood plasmalogen changes by regulating brain-derived neurotrophic factor. Acta Biomater. 2017, 21, 199–205. [CrossRef]

188. Deng, Y.; Angelova, A. Coronavirus-induced host cubic membranes and lipid-related antiviral therapies: A focus on bioactive plasmalogens. Acta Biomater. 2021, 2021, 9, 630242. [CrossRef]

189. Hossain, M.S.; Mawatari, S.; Fujino, T. Plasmalogens, the vinyl ether-linked glycerophospholipids, enhance learning and memory by regulating brain-derived neurotrophic factor. Front. Cell Dev. Biol. 2022, 10, 82828. [CrossRef]

190. Angelova, A.; Angelov, B.; Drechsler, M.; Bizien, T.; Gorshkova, Y.E.; Deng, Y. Plasma-After liquid crystalline multiphase structures involving doxosapentaenoyl derivatives inspired by biological cubic membranes. Front. Cell Dev. Biol. 2021, 9, 627984. [CrossRef]
191. Park, H.; Oh, J.; Shim, G.; Cho, B.; Chang, Y.; Kim, S.; Baek, S.; Kim, H.; Shin, J.; Cho, H.; et al. In vivo neuronal gene editing via CRISPR–Cas9 amphiphilic nanocomplexes alleviates deficits in mouse models of Alzheimer’s disease. *Nat Neurosci.* **2019**, *22*, 524–528. [CrossRef]

192. Kolli, N.; Lu, M.; Maiti, P.; Rossignol, J.; Dunbar, G.L. Application of the gene editing tool, CRISPR-Cas9, for treating neurodegenerative diseases. *Neurochem. Int.* **2018**, *112*, 187–196. [CrossRef] [PubMed]

193. Guan, L.; Han, Y.; Yang, C.; Lu, S.; Du, J.; Li, H.; Lin, J. CRISPR-Cas9-mediated gene therapy in neurological disorders. *Mol. Neurobiol.* **2022**, *59*, 968–982. [CrossRef] [PubMed]

194. Rozhin, A.; Batasheva, S.; Kruychkova, M.; Cherednichenko, Y.; Rozhina, E.; Fakhrullin, R. Biogenic silver nanoparticles: Synthesis and application as antibacterial and antifungal Agents. *Micromachines* **2021**, *12*, 1480. [CrossRef] [PubMed]