WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 5, 1562-1581. Review Article ISSN 2277–7105

ROAD MAP AHEAD FOR THE TREATMENT AND MANAGEMENT OF NEURODEGENERATIVE DISORDERS: A REVIEW

B. Lakshmi Bhargavi[1] and Sandur V. Rajendra[*2]

[1]Research Scholar, Mallige College of Pharmacy, Bangalore.

[2]Professor and Principal, Department of Pharmacology, Mallige College of Pharmacy, Bangalore, India.

Article Received on
18 Jan 2025,

Revised on 07 Feb. 2025,
Accepted on 27 Feb. 2025

DOI: 10.20959/wjpr20255-35833

***Corresponding Author**
Sandur V. Rajendra
Professor and Principal, Department of Pharmacology, Mallige college of Pharmacy, Bangalore, India.

ABSTRACT

Neurological conditions are defined by the progressive degeneration of neurones in the brain as well as spinal cord, resulting in cognitive and movement deficits. These include Alzheimer's, Parkinson's, Huntington's, Amyotrophic Lateral Sclerosis, and Frontotemporal Dementia. Monogenic illnesses, such as HD and Spinal Muscular Atrophy (SMA), feature single-gene abnormalities, making gene therapy an appealing treatment option. Polygenic illnesses, such as Alzheimer's and Parkinson's disease, have complicated genetic and environmental variables that make therapy difficult. Advanced therapeutics like as genetic modification, stem cell transplantation, and exosome delivery have the potential to target NDDs'. Antioxidant therapy using stem cells aimed at oxidative stress and brain repair, as well as CRISPR/Cas9 interventions, are examples of advancements for Alzheimer's disease. Antioxidant chemicals, dopaminergic medications, and stem-cell-derived models treat neurodegeneration in Parkinson's disease. HD research focusses on astrocyte regeneration and gene-editing methods to reduce genetic mutations. Gene therapy for ALS and SMA uses adeno-associated carriers plus stem-cell-derived exosomes to prevent motor neurone degeneration. While these developments provide optimism, issues about delivery efficacy, ethics, and long-term life prolonging of an individual. Additional studies and investigations are required to convert these promising therapeutics into efficient therapies for patients struggling with debilitating NDDs.

KEYWORDS: Alzheimer’s disease (AD), Parkinsons disease (PD), Huntington's disease

(HD), Amyotrophic lateral sclerosis (ALS), Spinal muscular atrophy (SMA), Neurodegenerative Disorders (NDDS).

INTRODUCTION

Most brain-related disorders are characterised by neurodegeneration as their principle pathophysiological change.[1] Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD), Spinal muscular atrophy (SMA) are neurological illnesses that result in the gradual loss of neurones in the brain or spinal cord.[2] The prognosis for these illnesses is usually poor and there is no cure, which results in increasing disability and a shorter life expectancy.[3] There are two types of genetically determined NDDs.[4] Described below.

Monogenic diseases: Mutations in a single gene create monogenic neurodegenerative disorders, which have a distinct, predictable pattern of inheritance and make gene therapy interventions easier to target. As opposed to polygenic illnesses, where several environmental and genetic factors both have a role in the development of disease, but monogenic disorders present special chances for treatment approaches that target the underlying genetic flaw directly. Both Huntington's disease (HD) and spinal muscular atrophy (SMA), two of the most researched monogenic neurodegenerative illnesses, have thoroughly described inherited reasons. Because of their severe clinical effects, the availability of reliable animal models, and the most recent developments in gene treatments, these conditions were selected as the main focus of this review.[5-16]

Polygenic diseases: Polygenic neurodegenerative illnesses are challenging to treat due to intricate interactions between genes and environmental variables. In contrast to monogenic disorders, polygenic disorders do not have distinct pattern of inheritance and may be caused by changes in multiple genes, each with a minor impact on susceptibility. Polygenic neurodegenerative illnesses, such as AD (Alzheimer's disease), PD (Parkinson's disease), and ALS (amyotrophic lateral sclerosis) are caused by a combination of hereditary and environmental factors. This review focused on illnesses with high prevalence, large societal effect, and advances in understanding genetic contributions, despite hurdles due to polygenic nature.[17-37]

Alzheimer’s Disease (AD)

Dementia is most commonly caused by Alzheimer's disease (AD).[24] Death usually happens 5–12 years after diagnosis, and memory loss and cognitive decline are linked to the buildup of hyperphosphorylated tau tangles with β-amyloid plaques.[38]

Traditional AD drugs

- AChEIs : Rivastigmine , galantamine, Tacrine , donepezil
- NMDA receptor antagonists: memantine.[39]

Table 1. Pipeline drugs for AD.[40]

Substance	Therapeutic use	Targeted site	Action	Commencing Date	Estimated completion date
ACP-204	Symptom of neurological psychology	Receptors for Neurotransmitters	Serotonin receptor subtype 2A is an inverse agonist and a selective Antagonist of 5-hydroxytryptamine.	Nov 2023	Jan 2028
AR1001	Small molecules that alter disease	Neurotransmitter receptors	In animal models of AD, a PDE5 inhibitor lowers inflammation and amyloid formation.	Dec 2022	Dec 2025
Donanemab	Disease- modifying biologic	Amyloid beta	Pyroglutamate plaque Anti- amyloid monoclonal antibody related to amyloid	Oct 2022	Apr 2027
E2814	Disease- modifying biologic	Tau	Anti-tau monoclonal antibody	Dec 2012	Oct 2027
Gantenerumab	Minormolecules that alter disease	Amyloid beta	Anti-amyloid monoclonal antibody	Dec 2012	Oct 2027
ABBV-916	Novel molecules that impact disease	Amyloid beta	Anti-amyloid antibody	Aug 2022	Jan 2030
ALZN002	Tiny particles that affect disease	Amyloid beta	Autologous Dendritic Cells Pulsed by Beta-Amyloid Mutant Peptides	Jul 2023	Mar 2028

Stem cell Therapy: Stem cells are a type of cell that may differentiate in multiple directions and self-renew. They come from a variety of tissues, including the placenta, adipose tissue, and tooth pulp. They may be applied to a number of beneficial purposes, including the regeneration of tissues and organs and the treatment of illnesses, particularly serious ones. The development of human cellular models produced from patients is a vital use of regenerative cells in AD research. These include assembled spheroids and organoids, which are representations of several cells composed of brain cells. These models can be used to assess novel genetic

engineering and genome editing approaches to decipher the pathophysiology of AD as well as the effects of genetic, chemical, and environmental variables.[41]

Table 2. Exosomes produced from stem cells for the treatment of AD.

AD strategy	EV culture or medication administration technique	Duration	Results at the molecular level
produced pups by crossing WT male C57BL/6 mice with female APP/PS1 mice.	Injection into the tail vein	4 months	SphK1 and S1P1 appearance was markedly elevated; the Morris water maze experiment showed that the APP/PS1 + exosome group had a significantly shorter escape latency; and the mouse brain and hippocampus (DG region)
			showed markedly elevated NeuN expression.[43]
6-week-old male C57BL/6 mice and 9-month-old female APP/PS1 mice	Intranasal drug delivery	2 weeks	Enkephalin, neuroplasmin, and eIF5A were among the proteins in EV that stimulated synaptic development; BAD was deregulated and PCLO, TENM1, and NEXMIF were upregulated.[44]
Aβ is given bilaterally to 7–8-week-old C57BL/6 mice in the dentate gyrus.	Intracortical injection	2 weeks And 28 days	Increased cell immune response and improved SVZ regeneration.[45]
APPswe /PS1dE9 AD mice	Intracortical injection	25 days/month	reduced expression levels of Alix AGO2, HSP70, TSG101, CD63, and CD9; less Smi31-32 positive regions surrounding ThT-positive plaques.[46]

Gene Therapy

Application of CRISPR/Cas9 in Alzheimer's disease: The application of CRISPR/Cas9 technology is becoming more and more common in AD research. The CRISPR/Cas9 system's effectiveness in correcting mutations linked to cancer has a lot of evidence. The application of the CRISPR/Cas9 system has been broadened from AD assessment to therapy with the same idea in mind. The development of illness models, the detection of mutated genes by examination and the application of focused gene therapy treatments currently make extensive use of this technology.[47]

Table 3. Alzheimer's disease interventional research using CRISPR/Cas9.

Pires et al.[48]	PSEN1	Induced transgenic stem cell line with gene correction generation through
		substitution of the wild-type sequence for the point mutation
Sun et al.[49]	PSEN1	When N2a cells' PSEN1 genes break down, the γ-secretase background that is naturally present.
Konstantinidis et al.[50]	PSEN1	disturbance of human cells' PSEN1 allele, which lowers extracellular Aβ42/40 ratios
Ortiz-Virumbrales et al.[51]	PSEN1	Reversing the PSEN2 point mutation in generated mesenchymal stem cell-derived basal frontal lobe sensory neurons will restore the electrophysiological defect.
György et al.[52]	APP	Fibroblasts' decreased Aβ levels following the removal of Swedish APP mutations
Guyon et al.[53]	APP	decrease of Aβ peptide accumulation in HEK293T cells with the insertion of the A673T mutation

Parkinson's disease (PD)[54]

About 30 million people worldwide suffer from Parkinson's disease (PD), the second most prevalent neurological illness. It impacts the elderly and results in significant disability and suffering, much like Alzheimer's disease (AD).

Pipeline drugs for PD: As of January 31 2024, 136 Phase 1–3 trials were currently underway assessing medication treatments for PD listed on ClinicalTrials.gov that satisfied selection requirements. Since some the website Clinical Trials lacks listings of clinical studies this data set is not an exhaustive list of trials that are now underway.

Table 4. Pipeline drugs for PD.

	Phase1	**Phase 2**	**Phase3**	**The sum**
ST	19	44	13	76
DMT	22	35	3	60
The sum	41	79	16	136

Table 5. Antioxidant Therapy.[55-56]

Treatment with Antioxidants	**Mechanisms of Protection**	**Result of Protective Mechanisms**
Quercetin	↓IFNγ, ↓IL6, ↓IL-1β, ↓TNFα, ↑SOD, ↑GSH	↓DNA oxidation, ↓Lipid peroxidation, ↓protein carbonylation, ↓α-synuclein
Curcumin	↑GSH, ↑LC3-II, ↑SIRT1, ↑SOD	↑cell viability, ↓αsynuclein, ↓lipid peroxidation, ↓DNA oxidation

Metal chelators	↑SOD, ↑catalase, ↓iron in the CNS and periphery	↑cell viability, ↓ Caspase activation, ↑TH, ↑Bcl-2
VA, TFA+ PCA	↑SOD, ↑Fox03a, ↑catalase,↑SIRT1, ↑PGC1α, ↑Nrf2	↑cell viability, ↓ROS, ↑Bcl-2
Sinapic acid	↑PGC1α, ↑Nrf2, ↑SOD, ↑catalase	↑cell viability, ↓ Caspase activation, ↓ROS, ↓DNA oxidation
17β-Estradiol	↑SIRT1, ↑PGC1α, ↑Nrf2, ↑Fox03a, ↓IL-1β, ↓TNFα	↓DNA oxidation, ↓ROS, ↓Glia activation, ↓Aβ
Vitamin A	↑α-synuclein, ↑Aβ, ↑pTau	↑cell viability

Stem cell Therapy: Research on Parkinson's disease has undergone a revolution thanks to stem cell-based disease models. These models offer a platform for researching the disorder underlying mechanisms which aid in the creation of new drugs. For example, the success of Cooper et al.[57] fully developed hESCs into mDA neurones, demonstrating that a possible contributing cause to Parkinson's disease pathogenesis is deregulation of the WNT signalling pathway. Using hESC-derived mDA neurones, Byers et al.[58] illustrated the role of endoplas and the unfolded protein response. These studies demonstrate how well hESC-based models work to investigate disease causes and find new therapeutic targets. HiPSCs have been used to imitate Parkinson's disease (PD) with a noticeable increase in recent years. An important focus in the field of hiPSC models is the investigation of α-syn (SNCA) mutations and gene multiplications linked to Parkinson's disease. Particularly, mDA neurones generated from hiPSCs from people with SNCA mutations showed increased α-syn levels and the detrimental effects that followed including ER stress and oxidative stress.[59-62] Moreover, in hiPSC-derived DA neurones, α-syn oligomers have been found to interfere with axonal transport, mitochondrial activity, and synaptic connection.[63,64]

Table 6. Gene Therapy.

Gene	Phenotype in DA neurons	Treatment	Effect of treatment
SNCA	Mitochondrial malfunction, increased protein nitration and intraneuronal nitric oxide	Isoxazole (which activates MEFC2) and L-NAME (an inhibitor of nitric oxide synthase)	Increased MEFC2 activity and decreased nitric oxide.[65]
SNCA	elevated levels of α-synuclein	Stearoyl CoA desaturase	decreased α-synuclein levels.[66]
SNCA, GBA, PARK9	Reduced neuronal vitality, Amyloidogenic α-	NCGC758	Improved GCase activity and reduced α-synuclein levels.[67]
	synuclein, and α- synuclein		

	accumulation		
GBA-84GG, LRRK2, DJ-1, PARKIN	ER stress, lysosomal and autophagic disruption, and Extracellular α- synuclein	S-181	Increased WT GBA activity restored lysosomal activity, decreased α-synuclein, oxidized dopamine, and glucosylceramide buildup.[68]
PARKIN	Microtubules with defects in the ubiquitin system	Taxol	Normalized morphology of Neurons stabilization of microtubules[69]

Huntington's disease (HD)

HD is a rare, inherited, neurodegenerative condition that is brought on by a trinucleotide CAG-repeat expansion of ≥36 in the Huntington's gene.[70] And characterised by a wide range of symptoms, including as cognitive decline, neuropsychiatric disorders, and motor abnormalities.[71] While chorea is the primary HD motor symptom, postural problems and dystonia are also frequently described. Patients' psychiatric symptoms differ greatly from one another. Although agitation, anger, anxiety, hallucinations and delusions accompany HD as well making HD a complex multisymptomatic disorder.[72,73]

Stem cell Therapy: Multipotent cells are present in adipose tissue, bone marrow, spleen, and the umbilical cord. They can differentiate into a variety of cell types including muscle, bone, fat, and cartilage cells.[74] Because MSCs can self-renew without losing their multipotency, they hold great promise for use in cell therapy for neurodegenerative diseases.

Astrocyte Reprogramming in Huntington's Disease: Glial cells, which are non-neuronal cells that can be classified into four main categories, including astrocytes, oligodendrocytes, microglia, and ependymal cells, are among the most prevalent parts of the mammalian nervous system. It has been claimed that astrocytes can self-renew in a manner akin to that of stem cells, generating additional immature progenitors and neuroblasts.[75,76] Following this discovery, researchers attempted to take charge of the process by evaluating the potential for reprogramming astrocytes into neurons using activated transcription factors and medications, both in vitro and in vivo, as a novel regenerative strategy in the context of neurodegenerative diseases like HD. However a solid pre clinical evidence id needed.

Gene Therapy: Rapid advancements are being made in Genome therapy for HD investigation. The main objective of treatment is to address the single gene mutation that causes the condition is to reduce the effect of CAG repeat expansion at the mHTT gene's origin.[77]

Table 7. Gene therapy for HD.

Editing genes	Distribution	DNA or RNA targeting	Allele selectivity	Effective toexon1 protein	Main outcome	Status
mZFKRAB[78]	ICV	DNA	Yes	Yes	Long-term inhibition of brain expression of mutant HTT	Pre-clinical
ZFP-TF[79]	ICV	DNA	Yes	Yes	mHTT gene expression is decreased.	Pre-clinical
TALENs[80]	ICV	DNA	Yes	Yes	Deterioration of the Huntington allele mutant	Pre-clinical
CRISPR/ Cas9[81-89]	ICV	DNA	Yes	Yes	reduced or corrected the mHTT gene's appearance	Pre-clinical
CRISPR/ Cas13[90]	ICV	RNA	Yes	Yes	mHTT mRNA appearance is decreased.	Pre-clinical

Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis is characterised by selective motor neurone loss in the brain and spinal cord, which leads to muscle weakness, paralysis, and ultimately death.[91] Only a few ALS treatments are now available, and they mostly focus on symptom management and supportive care.[92] Reducing neuroinflammation, repairing injured motor neurones, and providing neuroprotection are the objectives of ALS stem cell-based treatments.[93]

Stem cell Therapy: The safety and viability of regenerative cell treatments in ALS patients have examined in a number of early-stage clinical trials. Foetal spinal cord transplantation intra spinal cord-derived NSCs are safe, well-tolerated, and may be effective in delaying the course of ALS in certain cases.[94,95] ALS patients have also been studied using autologous MSCs.[96,97] Although these preliminary studies have demonstrated the viability of grafting stem cells in ALS, larger randomised controlled trials are required to determine the effectiveness of these strategies. Gene editing technologies could be used in future stem cell therapy for ALS to fix ALS-causing genes in patient-specific iPSCs, which could subsequently develop into transplantable, healthy motor neurons.[98]

Gene Therapy: Hsin-Hsiung Chen et al conducted an experiment that is Forced NRIP

expression in SOD1 G93A mice via AAV-mediated gene therapy and they observed SOD1 G93A mice's Skeletal muscles and the spinal cord showed low levels of NRIP expression. NRIP expression was successfully restored in skeletal muscles and retroactively transduced in the spinal cord by intramuscular injection of AAV-NRIP. Significantly, in ALS animals, AAV-NRIP gene therapy improved α-motor neuron (α-MN) survival, axon terminal input at the neuromuscular junction (NMJ), and the number of NMJs. The increase in NMJ transmission that resulted from these advancements eventually helped to improve motor activity. In both familial and sporadic ALS, there is muscular atrophy, NMJ degradation, and motor neuron degeneration. Consequently, AAV-NRIP may help SOD1 G93A mice and possibly lessen other forms of ALS as well. In order to maximize therapeutic benefits and reduce potential side effects, future research will concentrate on improving the injection method, timing therapeutic administration, and using tissue-specific promoters to stimulate NRIP gene expression. To sum up, NRIP shows promise as a gene therapy option for ALS.[99]

Frontotemporal dementia (FTD)

A group of related neurodegenerative diseases known as frontotemporal dementia (FTD) are characterized by behavioral or linguistic impairments in addition to cognitive and neurological changes.[100]

Table 8. Biomarkers in frontotemporal dementia.

Biomarker	Clinical finding	iPSC cell type	Finding
NfL[101]	Prior to the onset of symptoms, there is acorrelation between the degree of white matter atrophy and an increase in CSF and blood levels that can be distinguished from healthy controls.	Motor neurons with hexanucleotide repeat expansion C9orf72	Electrical overexcitability and disrupted neurite structure are linked to accumulated NfL.
Complement proteins[102]	Blood C3 levels rise as C1s and C7 levels fall.	CHMP2BG/C31449 astrocytes	C3protein, IL-6, and IL-8 levels rise, resulting in the reactive gliosis phenotype. Deficits in metabolism and autophagy
Tau[103]	Elevate blood t- and p-tau and blood p-tau. Plasma t- and p-tau are not greater in carriers of MAPT mutations than in	MAPTN279Kneurons MAPTV337Mneurons	Positive neurons, tau fragmentation, and oxidative stress are all increased when p-tau levels rise.

	non-MAPT-driven FTD.		

Gene Therapy

Progranulin AAV gene therapy for frontotemporal dementia: Progranulin haploinsufficiency, which is brought on by GRN mutations, ultimately results in frontotemporal dementia (FTD-GRN). The granulin gene (GRN) is delivered using the experimental gene therapy PR006 via an adeno-associated vector of virus serotype 9 (AAV9). In non-clinical research, PR006 transduced neurons from induced pluripotent stem cells of FTD-GRN improved lipofuscin, lysosomal, and neuroinflammation pathologies in Grn-knockout mice and produced progranulin expression. In non-human primates, the transduced neurons were well tolerated, with the exception of mild, asymptomatic dorsal root ganglionopathy.[104]

Spinal muscular atrophy (SMA)

The severe neuromuscular genetic condition known as spinal muscular atrophy (SMA) is caused by a mutation or deletion of survival motor neuron gene (SMN1).[105] It is the most common hereditary cause of infant mortality, occurring 1 in 14,848 infants.[106]

Survival Motor Neuron (SMN)-Targeted Therapies: Spinraza, Valproic acid, Olesoxime are the therapy development has so far mostly concentrated on strategies that seek to raise full-length SMN protein levels because it has been known that significantly decreased amounts of SMN are the cause of SMA.[107]

Gene therapy: A mutation in the SMN1 gene results in spinal muscular atrophy (SMA), which is characterised by muscle weakness, atrophy, and loss of motor neurones. It is still very difficult to completely eliminate the endogenous mutations and symptoms of SMA, even if new treatment techniques, like small chemicals or viral vectors, have shown promise in improving motor function and survival.

Fumiyuki Hatanaka et al used SMA mice as a disease model, the work concludes by showing that HITI-mediated gene editing can successfully repair the genetic flaw in SMA mice, producing short-term phenotypic changes like higher body weight, greater mobility, and improved survival when compared to untreated controls. Although the medication effectively alleviates symptoms associated with SMA, the effects are transient, as treated mice do not survive for more than three weeks. This demonstrates that although HITI provides a potential

method for gene repair, additional modification is required to produce a sustained therapeutic outcome because it is now insufficient as a long-term treatment strategy for SMA. The study concludes by highlighting the benefits of using the modified AAV-PHP.eB capsid for gene delivery, namely in focusing on spinal motor neurons, which is crucial for successful treatment outcomes in SMA. Superior transduction effectiveness was shown in important tissues such as the brain and spinal cord, particularly in motor neurons, which are essential for the therapy of SMA, when AAV-PHP.eB and AAV9 were compared. Additionally, the effectiveness of this approach for in vivo genome editing in non-dividing cells, such as neurons, is confirmed by the successful demonstration of HITI-mediated gene knock-in in the spinal cord of Ai14-Cas9 mice. These results highlight the potential of AAV-PHP.eB in gene therapy applications, providing a viable path toward accurate genome editing in SMA and associated conditions.[108]

Stem cell Therapy: Virla et al conducted experiment with ASC-EVs strategy which improves the disease progression in SMA mice and concluded that when ASC-EV therapy was given to SMNΔ7 mice, a model of SMA type II, it may have a neuroprotective impact at the neural level and in terms of rescuing motor performances. Given their similar neuroprotective benefits, this could help establish an ASC-EVs-based therapy as a legitimate substitute for MSC use. Additionally, in the realm of neurodegenerative illnesses and other pathological situations, the EVs-based strategy may be a safer and more convenient choice.[109]

CONCLUSION AND FUTURE PROSPECTIVES

Neurodegenerative illnesses continue to provide a serious medical challenge, with existing treatments offering minimal relief. However, current developments in therapeutic techniques provide a promising path for treating these disorders. Gene and stem cell therapies, combined with emerging anti-oxidants and targeted treatment techniques such as CRISPR/Cas9, have shown promise in addressing the underlying causes of diseases such as AD, PD, HD, ALS, and SMA. The combination of stem cell-derived models and exosome-based techniques improves our ability to research disease mechanisms and identify therapeutic targets. Despite the potential problems like as delivery systems, immune response modulation, and cost limitations remain. Addressing these difficulties will necessitate multidisciplinary collaboration, rigorous clinical studies, and ethical concerns. However, the emergence of breakthrough technology and a better understanding of genetic and molecular processes signals a turning point in neurodegenerative disease care. Advancements in these domains are expected to enhance patient outcomes and offer hope for overcoming the severe consequences of these condition.

REFERENCES

1. Merelli, A.; Czornyj, L.; Lazarowski, A. Erythropoietin: A neuroprotective agent in cerebral hypoxia, neurodegeneration, and epilepsy. Curr. Pharm., Des. 2013; 19: 6791–6801.
2. De Gioia, R et.al; Neural Stem Cell Transplantation for Neurodegenerative Diseases. Int. J. Mol. Sci., 2020; 21: 3103.
3. Pauwels, E.K.J.; Boer, G.J. Parkinson's Disease; a Tale of Many Players. Med. Princ. Pract., 2023; 32: 155–165.
4. Fischell, J.M.; Fishman, P.S. A Multifaceted Approach to Optimizing AAV Delivery to the Brain for the Treatment of Neurodegenerative Diseases. Front. Neurosci., 2021; 15: 747726.
5. Wenceslau, CV et.al; Restoration of BDNF, DARPP32, and D2R Expression Following Intravenous Infusion of Human Immature Dental Pulp Stem Cells in Huntington's Disease 3- NP Rat Model. Cells, 2022; 11: 1664.
6. Macedo, J.; Pagani, E.; Wenceslau, C.V.; Ferrara, L.; Kerkis, I. A Phase I clinical trial on intravenous administration of immature humandental pulp stem cells (Nestacell HDTM) to Huntington's Disease patients. Cytotherapy, 2021; 23: 1.
7. Kotowska-Zimmer et.al; A CAG repeat targeting artificial miRNA lowers the mutant huntingtin level in the YAC128 model of Huntington's disease. Mol. Ther.-Nucleic Acids, 2022; 28: 702–715.
8. Ferlazzo, G.M et.al; Genome-wide screening in pluripotent cells identifies Mtf1 as a suppressor of mutant huntingtin toxicity. Nat. Commun., 2023; 14: 3962.
9. Mendell, J.R. et.al; Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy. JAMA Neurol., 2021; 78: 834–841.
10. Strauss, K.A.; et.al; Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: The Phase III SPR1NT trial. Nat. Med., 2022; 28: 1381.
11. Stettner, G.M .et.al; Treatment of spinal muscular atrophy with Onasemnogene Abeparvovec in Switzerland: A prospective observational case series study. BMC Neurol., 2023; 23: 88.
12. Pane, M. et.al; Nusinersen efficacy data for 24-month in type 2 and 3 spinal muscular atrophy. Ann. Clin. Transl. Neurol., 2022; 9: 404–409.

13. Pane, M.; et.al; Onasemno gene abeparvovec in spinal muscular atrophy: Predictors of efficacy and safety in naive patients with spinal muscular atrophy and following switch from other therapies. EClinicalMedicine, 2023; 59: 101997.
14. Chand, D.H.; et.al; Research Paper Safety of Onasemnogene Abeparvovec for Patients With Spinal Muscular Atrophy 8.5 kg or Heavier in a Global Managed Access Program. Pediatr. Neurol., 2022; 132: 27–32.
15. Besse, A. et.al; M.G. AAV9 Mediated Expression of SMN Restricted to Neurons Does Not Rescue the Spinal Muscular Atrophy Phenotype in Mice. Mol. Ther., 2020; 28: 1887–1901.
16. Rich, K.A.et.al; Premature delivery in the domestic sow in response to in utero delivery of AAV9 to fetal piglets. Gene Ther., 2022; 29: 513–519.
17. Jeon, M.T. et.al; Neurotrophic interactions between neurons and astrocytes following AAV1- Rheb (S16H) transduction in the hippocampus in vivo. Br. J. Pharmacol., 2020; 177: 668–686.
18. Capsoni, S.; Cattaneo, A. Getting Into the Brain: The Intranasal Approach to Enhance the Delivery of Nerve Growth Factor and Its Painless Derivative in Alzheimer's Disease and Down Syndrome. Front. Neurosci., 2022; 16: 773347.
19. Mishra, P. et.al; Rescue of Alzheimer's disease phenotype in a mouse model by transplantation of wild-type hematopoietic stem and progenitor cells. Cell Rep., 2023; 42: 112956.
20. Rocco, M.T. et.al; Long-term safety of MRI-guided administration of AAV2-GDNF and gadoteridol in the putamen of individuals with Parkinson's disease. Mol. Therapy, 2022; 30: 3632–3638.
21. Onuki, Y. et.al; Dopaminergic restoration of prefrontal cortico-putaminal network in gene therapy for aromatic l-amino acid decarboxylase deficiency. Brain Commun., 2021; 3: 078.
22. Tai, C.H.; et.al; Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. Mol. Ther., 2022; 30: 509–518.
23. Chen,C.; et.al; Non toxic HSC Transplantation-Based Macrophage/Microglia-Mediated GDNF Delivery for Parkinson's Disease. Mol. Ther.-Methods Clin. Dev., 2020; 17: 83–98.
24. Gupta, R.; et. Al; In Vivo Assessment of Cell Death and Nigrostriatal Pathway Integrity Following Continuous Expression of C3 Transferase. Neuroscience, 2020; 442: 183–192.
25. Wang, F.; et.al; Treatment of Parkinson's disease using focused ultrasound with GDNF

retrovirus-loaded microbubbles to open the blood-brain barrier. Open Chem., 2020; 18: 882– 889.

26. Cui, K.; et.al; Restoration of Noradrenergic Function in Parkinson's Disease Model Mice. ASN Neuro, 2021; 13: 17590914211009730.
27. Fernandez-Parrilla, M.A.; et.al; Cerebral dopamine neurotrophic factor transfection in dopamine neurons using neurotensin-polyplex nanoparticles reverses 6-hydroxydopamine- induced nigrostriatal neurodegeneration. Neural Regen. Res., 2022; 17: 854.
28. Kip, E.; Bentall, L.; Underwood, C.F.; Hughes, S.M.; Parr-Brownlie, L.C. Patterned Stimulation of the Chrimson Opsin in Glutamatergic Motor Thalamus Neurons Improves Forelimb Akinesia in Parkinsonian Rats. Neuroscience, 2022; 507: 64–78.
29. Li, J.; et.al; Genetically engineered mesenchymal stem cells with dopamine synthesis for Parkinson's disease in animal models. NPJ Park. Dis., 2022; 8: 175.
30. Azevedo, M.D.; et.al; Oxidative stress induced by sustained supraphysiological intrastriatal GDNF delivery is prevented by dose regulation. Mol. Ther.-Methods Clin. Dev., 2023; 31: 101106.
31. Narvaez-Perez, L.F.; et.al; CRISPR/sgRNA directed synergistic activation mediator (SAM) as a therapeutic tool for Parkinson′s disease. Gene Ther., 2023; 31: 31–44.
32. Miller, T.; et.al; Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N. Engl. J. Med., 2020; 383: 109–119.
33. Mueller, C.; et.al; SOD1 Suppression with Adeno-Associated Virus and MicroRNA in Familial ALS. N. Engl. J. Med., 2020; 383: 151–158.
34. Lim,C.K.W.; et.al; Treatment of a Mouse Model of ALSbyInVivo Base Editing. Mol. Ther., 2020; 28: 1177–1189.
35. Nizzardo, M.; et.al.; Synaptotagmin 13 is neuroprotective across motor neuron diseases. Acta Neuropathol., 2020; 139: 837–853.
36. Wang, S.; et. al; Subpial delivery of adeno-associated virus 9-synapsin- caveolin-1 (AAV9- SynCavl) preserves motor neuron and neuromuscular junction morphology, motor function, delays disease onset, and extends survival in hSOD1G93A mice. Theranostics, 2022; 12: 5389– 5403.
37. Tejwani, L.; et.al; Reduction of nemo-like kinase increases lysosome biogenesis and ameliorates TDP-43-related neurodegeneration. J. Clin. Investig., 2023; 133: 138207.
38. Zeng, L.; Jiang, H.L.; Ashraf, G.M.; Li, Z.R.; Liu, R. MicroRNA and mRNA profiling of cerebral cortex in a transgenic mouse model of Alzheimer's disease by RNA sequencing.

Neural Regen. Res. 2021; 16: 2099. [PubMed]

39. Galimberti, D. & Scarpini, E. Old and new acetylcholinesterase inhibitors for Alzheimer's disease. Expert Opin. Investig. Drugs, 2016; 25: 1181–1187.
40. Cummings J; et.al; Alzheimer's diseasedrugdevelopmentpipeline: 2024 Alzheimer's Dement., 2024; 10: 12465.
41. Brody H. Alzheimer's disease. Nature, 2011; 475: 1.
42. Yang L, Zhai Y, Hao Y, Zhu Z, Cheng G. The regulatory functionality of exosomes derived from hUMSCs in 3D culture for Alzheimer's disease therapy. Small, 2020; 16: 1906273.
43. Wang X, Yang G. Bone marrow mesenchymal stem cells-derived exosomes reduce Aβ deposition and improve cognitive function recovery in mice with Alzheimer's disease by activating sphingosine kinase/sphingosine-1-phosphate signaling pathway. Cell Biol Int., 2021; 45: 775–84.
44. Ma X, et.al; ADSCs-derived extracellular vesicles alleviate neuronal damage, promote neurogenesis and rescue memory loss in mice with Alzheimer's disease. J Control Release, 2020; 327: 688–702.
45. Reza-Zaldivar EE, et.al; Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. Neural Regen Res., 2019; 14: 1626–34.
46. Elia CA, et.al; Intracerebral injection of extracellular vesicles from mesenchymal stem cells exerts reduced Aβ plaque burden in early stages of a preclinical model of Alzheimer's disease. Cells, 2019; 8: 1059.
47. Lu L, et.al; Application of CRISPR/Cas9 in Alzheimer's disease. Front Neurosci., 2021; 15: 803894.
48. Pires C, et.al; Generation of a gene-corrected isogenic control cell line from an Alzheimer's disease patient iPSC line carrying a A79V mutation in PSEN1. Stem Cell Res., 2016; 17: 285–8.
49. Sun L, et.al; Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of Aβ42 and Aβ40 peptides by γsecretase. Proc Natl Acad Sci USA., 2017; 114: 476–85.
50. Konstantinidis E, et.al; CRISPR-Cas9 treatment partially restores amyloid-β 42/40 in human fibroblasts with the Alzheimer's disease PSEN 1 M146L mutation. Mol Ther Nucleic Acids, 2022; 28: 450–61.
51. Ortiz-Virumbrales M, et.al; CRISPR/Cas9- correctable mutation-related molecular and

physiological phenotypes in iPSC-derived Alzheimer's PSEN2 (N141I) neurons. Acta Neuropathol Commun., 2017; 5: 77.

52. György B, et.al; CRISPR/Cas9 mediated disruption of the Swedish APP allele as a therapeutic approach for earlyonset Alzheimer's disease. Mol Ther Nucleic Acids, 2018; 11: 429–40.
53. Guyon A, et.al; Base editing strategy for insertion of the A673T mutation in the APP gene to prevent the development of AD in vitro. Mol Ther Nucleic Acids, 2021; 24: 253–63.
54. Kevin McFarthinga, et.al; Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update Journal of Parkinson's Disease, 2024; 14: 899–912.
55. Kaokaen, P et.al; Enhancing Neurological Competence of Nanoencapsulated Cordyceps/Turmeric Extracts in Human Neuroblastoma SH-SY5Y Cells. Cell Mol. Bioeng., 2023; 16: 81–93.
56. Lee, M. et.al; Quercetin, Not Caffeine, Is a Major Neuroprotective Component in Coffee. Neurobiol. Aging., 2016; 46: 113–123.
57. Cooper O, et.al; Pharmacological rescue of mitochondrial deficits in iPSC-derived neural cells from patients with familial Parkinson's disease. Sci Transl Med., 2012; 4: 141ra90.
58. Byers B, et.al; SNCA triplication Parkinson's patient's iPSC-derived DA neurons accumulate α-synuclein and are susceptible to oxidative stress. PLoS One., 2011; 6: 26159.
59. Shulman JM, De Jager PL, Feany MB. Parkinson's disease: genetics and pathogenesis. Annu Rev Pathol., 2011; 6: 193-222.
60. Devine MJ, et.al; Parkinson's disease induced pluripotent stem cells with triplication of the α- synuclein locus. Nat Commun., 2011; 2: 440.
61. Heman-Ackah SM, et.al; Alpha-synuclein induces the unfolded protein response in Parkinson's disease SNCA triplication iPSC-derived neurons. Hum Mol Genet., 2017; 26: 4441- 4450.
62. Stojkovska I, et.al; Rescue of α-syn uclein aggregation in Parkinson's patient neurons by syner gistic enhancement of ER proteostasis and protein traffi cking. Neuron, 2022; 110: 436-451.e11.
63. Prots I, et.al; α-Synuclein oligom ers induce early axonal dysfunction in human iPSC-based models of synucleinopathies. Proc Natl Acad Sci U S A., 2018; 115: 7813-7818.
64. . Ludtmann MHR, et.al; α- Synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson's disease. Nat Commun., 2018; 9: 2293.
65. Ryan SD, et.al; Isogenic human iPSC Parkinson's model shows nitrosative stress-induced

dysfunction in MEF2-PGC1α transcription. Cell, 2013; 155: 1351-1364.

66. Kouroupi G, et.al; Defective syn aptic connectivity and axonal neuropathology in a human iPSC-based model of familial Parkinson's disease. Proc Natl Acad Sci U S A., 2017; 114: 3679- 3688.
67. Mazzulli JR, et.al; Activation of β- glucocerebrosidase reduces pathological α-synuclein and restores lysosomal function in Parkinson's patient midbrain neurons. J Neurosci., 2016; 36: 7693- 7706.
68. Burbulla LF, et.al; A modulator of wild-type glucocerebrosidase im proves pathogenic phenotypes in dopaminergic neuronal models of Parkinson's disease. Sci Transl Med., 2019; 11: 6870.
69. Ren Y, et.al; Parkin mutations reduce the complexity of neuronal processes in iPSC-derived human neurons. Stem Cells, 2015; 33: 68-78.
70. Kremer B, et.al; A worldwide study of the Huntington's disease mutation. The sensitivity and specificity of measur ing CAG repeats. N Engl J Med., 1994; 330: 1401–1406. https://doi.org/ 10.1056/nejm199405193302001
71. Martin JB, Gusella JF. Huntington's disease. Pathogenesis and manage ment. N Engl J Med., 1986; 315: 1267–1276. https://doi.org/10.1056/ nejm198611133152006
72. van Duijn E, et.al; Cross-sectional study on prevalences of psychiatric disorders in mutation carriers of Huntington's disease com pared with mutation-negative first-degree relatives. J Clin Psychiatry, 2008; 69: 1804–1810. https://doi.org/10.4088/jcp.v69n1116.
73. Kirkwood SC, et.al; Progression of symptoms in the early and middle stages of Huntington disease. Arch Neurol., 2001; 58: 273 278. https://doi.org/10.1001/archneur.58.2.273
74. Andrzejewska A, Lukomska B, Janowski M. Mesenchymal stem cells: from roots to boost. Stem Cells, 37: 855-864.
75. Doetsch F, García-Verdugo JM, Alvarez-Buylla A. Cellular composition and three dimensional organization of the subventricular germinal zone in the adult mammalian brain. J Neurosci., 17: 5046-5061.
76. Goldman S . Glia as neural progenitor cells. Trends Neurosci., 26: 590-596.
77. Tabrizi SJ, et.al; Huntington disease: New insights into molecular pathogenesis and therapeutic opportunities. Nat Rev Neurol., 2020; 16: 529-546.
78. Agustín-Pavón C, et.al; Deimmunization for gene therapy: host matching of synthetic zinc fnger constructs enables long-term mutant Huntingtin repression in mice. Mol Neurodegener, 2016; 11: 64.

79. Zeitler B, et.al; Allele-selective transcriptional repression of mutant HTT for the treatment of Huntington's disease. Nat Med., 2019; 25: 1131–1142.
80. Fink KD, et.al; Allele-specifc reduction of the mutant Huntingtin allele using transcription activator-like effectors in human Huntington's disease fbroblasts. Cell Transplant, 2016; 25: 677–686.
81. Dabrowska M, et.al; Precise excision of the CAG tract from the Huntingtin gene by Cas9 Nickases. Front Neurosci., 2018; 12: 75.
82. Ekman FK, et.al; CRISPR-Cas9-mediated genome editing increases lifespan and improves motor defcits in a Huntington's Disease Mouse Model. Mol Ther Nucleic Acids, 2019; 17: 829– 839.
83. Lopes C, et.al; Mitochondrial and redox modifcations in Huntington disease induced pluripotent stem cells rescued by CRISPR/Cas9 CAGs targeting. Front Cell Dev Biol., 2020; 8: 576592.
84. Monteys AM, et.al; CRISPR/Cas9 editing of the mutant Huntingtin allele in vitro and in vivo. Mol Ther., 2017; 25: 12–23.
85. Oikemus SR, et.al; Allele-specifc knockdown of mutant Huntingtin protein via editing at coding region single nucleotide polymorphism heterozygosities. Hum Gene Ther., 2022; 33: 25– 36.
86. Shin JW, et.al; Permanent inactivation of Huntington's disease mutation by personalized allele-specifc CRISPR/Cas9. Hum Mol Genet., 2016; 25: 4566–4576.
87. Xu X, et.al; Reversal of phenotypic abnormalities by CRISPR/Cas9-mediated gene correction in Huntington disease patient-derived induced pluripotent stem cells. Stem Cell Rep., 2017; 8: 619–633.
88. Yan S, et.al; Cas9-mediated replacement of expanded CAG repeats in a pig model of Huntington's disease. Nat Biomed Eng., 2023; 7: 629–646.
89. Yang S, et.al; CRISPR/Cas9-mediated gene editing ameliorates neurotoxicity in mouse model of Huntington's disease. J Clin Invest, 2017; 127: 2719–2724.
90. Morelli KH, et.al; An RNA-targeting CRISPR-Cas13d system alleviates disease-related phenotypes in Huntington's disease models. Nat Neurosci., 2023; 26: 27–38.
91. Mazzini L, et.al; Advances in stem cell therapy for amyotrophic lateral sclerosis. Expert Opin Biol Ther., 2018; 18(8): 865–81.
92. Kondo T, et.al; Focal transplantation of human iPSC-derived glial-rich neural progenitors improves lifespan of ALS mice. Stem Cell Rep., 2014; 3(2): 242–9.
93. Das MM, et.al; Human neural progenitors differentiate into astrocytes and protect motor

neurons in aging rats. Exp Neurol., 2016; 1(280): 41–9.

94. Cho BC, et.al; Tiragolumab plus atezolizumab versus placebo plus atezolizumab as a first-line treatment for PD-L1-selected non-small-cell lung cancer (CITYSCAPE): primary and follow- up analyses of a randomised, double-blind, phase 2 study. Lancet Oncol., 2022; 23(6): 781–92.
95. Je G, Keyhanian K, Ghasemi M. Overview of stem cells therapy in amyotrophic lateral sclerosis. Neurol Res., 2021; 43(8): 616–32.
96. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol., 2020; 27(10): 1918–29.
97. Liu B, Li M, Zhang L, Chen Z, Lu P. Motor neuron replacement therapy for amyotrophic lateral sclerosis. Neural Regen Res., 2022; 17(8): 1633–9.
98. Cheng Y, Zhang Y, Li P. Co-transplantation of autologous treg cells: a groundbreaking cell therapy for brain diseases. J Cereb Blood Flow Meta. 2024. https://doi.org/10.1177/0271678X241245633
99. Hsin-Hsiung Chen et.al; AAV-NRIP gene therapy ameliorates motor neuron degeneration and muscle atrophy in ALS model mice https://doi.org/10.1186/s13395-024-00349-z
100. Weder ND, Aziz R, Wilkins K, Tampi RR. Frontotemporal dementias: a review. Ann Gen Psychiatry, 2007; 6: 15.
101. Lefebvre-Omar C, et.al; Neurofilament accumulations in amyotrophic lat eral sclerosis patients' motor neurons impair axonal initial segment integrity. Cell Mol Life Sci., 2023; 80(6): 150.
102. Chandrasekaran A, et.al; Astrocytic reactivity trig gered by defective autophagy and metabolic failure causes neuro toxicity in frontotemporal dementia type 3. Stem Cell Reports., 2021; 16(11): 2736–51.
103. Ehrlich M, et.al; Distinct neurodegenerative changes in an induced pluripotent stem cell model of frontotemporal dementia linked to mutant TAU protein. Stem Cell Report, 2015; 5(1): 83–96.
104. B.M.S., S.A.S. and E.D.L Progranulin AAV gene therapy for frontotemporal dementia: translational studies and phase 1/2 trial interim results nature medicine https://doi.org/10.1038/s41591-024-02973-0
105. Chaytow, H., et.al; The role of survival motor neuron protein(SMN)inproteinhomeostasis. Cell Mol. Life Sci., 2018; 75: 3877–3894.
106. Aragon-Gawinska, K., Mouraux, C., Dangouloff, T. & Servais, L. Spinal Muscular Atrophy Treatment in Patients Identified by New born Screening—

ASystematicReview.Genes., 2023; 14: 1377.

107. Hannah K. Shorrock, Thomas H. Gillingwater, Ewout J. N. Groen Overview of Current Drugs and Molecules in Development for Spinal Muscular Atrophy Therapy Drugs, 2018; 78: 293–305. https://doi.org/10.1007/s40265-018-0868-8.
108. Fumiyuki Hatanaka, et.al; Therapeutic strategy for spinal muscular atrophybycombininggene supplementation and genome editing https://doi.org/10.1038/s41467-024-50095-5.
109. Federica Virla, Administration of adipose-derived stem cells extracellular vesicles in a murine model of spinal muscular atrophy: effects of a new potential therapeutic strategy. Stem Cell Research & Therapy, 2024; 15: 94.