Overview of the results of clinical studies based on stem cell transplantation for patients suffering from nervous system diseases

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OVERVIEW OF THE RESULTS OF CLINICAL STUDIES BASED ON STEM CELL TRANSPLANTATION FOR PATIENTS SUFFERING FROM NERVOUS SYSTEM DISEASES

GRADUATION THESIS

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Summary

Title: Overview of the results of clinical studies based on stem cell transplantation for patients suffering from nervous system diseases

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Keywords: nervous system diseases, stem cell transplantation, mesenchymal stem cells, neural stem cells, clinical trials

Stem cell transplantation (SCT) is a promising strategy in developing new treatments for diseases like Parkinson's, Alzheimer's, multiple sclerosis (MS), stroke and amyotrophic lateral sclerosis (ALS). Stem cells are undifferentiated cells with potential to develop into any needed cell type. They have the ability to regenerate damaged nerve tissue or restore nerve cell functions. Following that, stem cell transplantation has been successfully applied in clinical trials for the treatment of neurological disorders, with varying degrees of progress and success. For example, mesenchymal stem cells have been shown to improve stroke outcomes by restoring blood flow, removing intracranial blood clots and reducing intracranial pressure. On the other hand, human neural stem cells can increase the degree of neuroregeneration, while autologous CD-34 positive hematopoietic stem cells can improve outcomes in patients with MS. Finally, neural stem cells (NSCs) can be used to treat MS by re-establishing functional interactions between neural and glial cells or by activating endogenous neural cells. In addition to positive effects observed in clinical trials, this thesis also reviews possible drawbacks and points towards elements which need to be improved before such protocols become routine part of therapeutic procedures.

Sažetak

Naslov: Overview of the results of clinical studies based on stem cell transplantation for patients suffering from nervous system diseases
Autor: Eun Joo Park
Ključne riječi: bolesti živčanog sustava, transplantacija matičnih stanica, mezenhimalne matične stanice, živčane matične stanice, klinička ispitivanja

Transplantacija matičnih stanica (SCT) je obećavajuća strategija u razvoju novih terapija za bolesti kao što su Parkinsonova bolest, Alzheimerova bolest, multipla skleroza (MS), moždani udar i amiotrofična lateralna skleroza (ALS). Matične stanice su nediferencirane stanice s potencijalom koji im omogućuje razviti se u bilo koju potrebnu vrstu stanica, a imaju sposobnost obnove oštećenog živčanog tkiva koju prati i obnova funkcije živčanih stanica. Transplantacija matičnih stanica uspješno je primijenjena u kliničkim ispitivanjima za liječenje neuroloških poremećaja, s različitim stupnjevima napretka i uspjeha. Na primjer, pokazalo se da mezenhimalne matične stanice poboljšavaju ishode moždanog udara obnavljanjem protoka krvi, uklanjanjem intrakranijalnih krvnih ugrušaka i smanjenjem intrakranijskog tlaka. S druge strane, ljudske živčane matične stanice mogu povećati stupanj obnove tkiva, dok autologne CD-34 pozitivne hematopoetske matične stanice mogu poboljšati ishode kod bolesnika s MS-om. Konačno, živčane matične stanice (NSC) mogu se koristiti za liječenje MS ponovnim uspostavljanjem funkcionalnih interakcija između neurona i glijalnih stanica ili aktiviranjem endogenih stanica. Osim pozitivnih učinaka uočenih u kliničkim ispitivanjima, ovaj rad razmatra i moguće nedostatke te ukazuje na elemente koje je potrebno poboljšati prije nego što takvi protokoli postanu rutinski dio terapijskih postupaka.

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1. Introduction

1.1. Background and the major goals of this study

Within the last two decades, stem cell therapy has become increasingly attractive for patients with neurological disorders. Its major principle is to act towards regenerating injured cells or restoring neuronal function in conditions such as Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and stroke (1). While Parkinson's disease is caused by loss of dopamine-producing nerve cells and mainly causes movement disorders, Alzheimer's disease is characterized by death of neurons and subsequent deterioration in patient's cognitive function due to the accumulation of beta amyloid and tau proteins (2 - 6). In multiple sclerosis, the immune system damages the myelin sheath within the central nervous system, causing damage to neural fibers and various neurological symptoms, depending on the regions of the lesion presentation (7, 8). Contrastingly, amyotrophic lateral sclerosis is a neurodegenerative disease in which both upper and lower motor neurons gradually degenerate and die, leading to fast progressing deteriroration of the motoric function and death occuring on average five years from the establishing diagnosis (9). At the same time, stroke is a neurological condition that results from sudden lack of blood flow (10). Albeit having different etiologies, patterns and courses of development among other related aspects; the toll that nervous system damage takes on medical expenses as well as individual's living standard cannot be underestimated. Consequently, stem cell transplant offers hope for improving patient's lives and may even cut down costs for subsequent treatments.

The main benefit for employing stem cells in regenerative medicine is their ability to continuously renew and divide, coupled with their ability differentiate into various cell types (1). Although most cells proliferate and divide, they have a limited lifespan. Contrastingly, stem cells' ability to differentiate allows them to create specialized cells that can replace other, damaged cells, including muscle, blood, and nerve cells. Therefore, in this paper we discuss stem cells, their use and application in clinical research and present several examples of stem cells showing success in clinical trials with patients suffering from brain diseases.

2. Nervous system

2.1. Basic structure of the nervous system

The nervous system is responsible for orchestrating the activities of our organisms and processing of sensory data by sending and receiving signals (11). Based on the location of the cells, the nervous system can be divided into the peripheral (PNS) and the central nervous system (CNS). The PNS comprises neural projections and ganglia outside of the CNS, while the CNS consists of the brain and spinal cord (Figure 1) (12). Peripheral nervous system consists of the autonomic nervous system (ANS) and the somatic nervous system (SNS). While the SNS is under voluntary control and transmits signals from the brain to various organs, the ANS is not under control of our will (12).

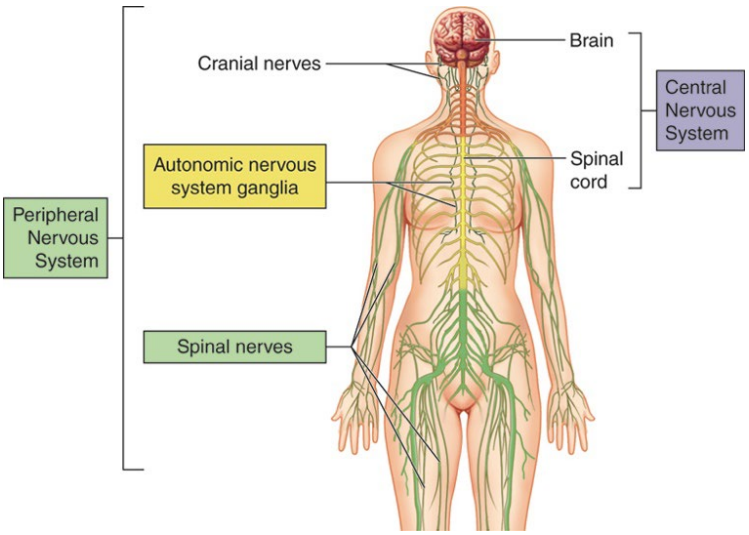

Figure 1. Structure and organisation of the nervous system (12)

Basic building blocks of the nervous system are neurons and glia. While neurons are responsible for conducting impulses, glial cells play a general supportive role. Neurons are specialized cells that transmit nerve impulses. They are the main signaling unit of the nervous system and are composed of the soma, dendrites, axons, axon terminals, and synapses (12). While soma is the cell body that contains the nucleus and other organelles that synthesize neurotransmitters and maintain cell stability and viability, dendrites form branch-like extensions from the cell body and receive signals from other neurons and transmit them toward the cell body through the extensions (13). An axon, whether myelinated or not, is a long projection that carries electrical signals away from the cell body to other neurons or muscle or gland cells. In terms of

size and location, axons that are myelinated have larger diameters and can be found in the CNS, while unmyelinated ones have smaller diameter and are distributed throughout the ANS. This difference in their structure impacts the speed of electrical impulse propagation, with myelinated fibers having significantly faster impulse propagation (Fig 2).

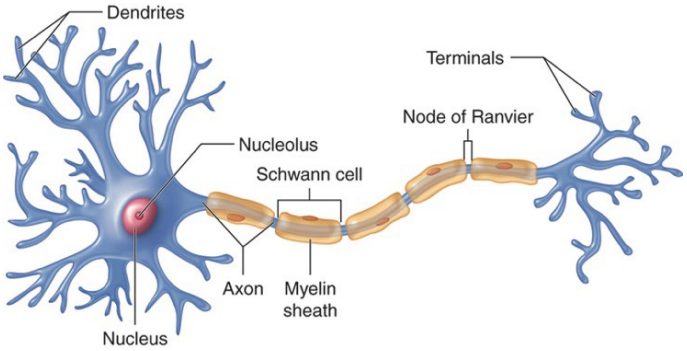

Figure 2. Structure of a neuron (12)

The ends of the axon where neurotransmitters are released, regions called axon terminals or synaptic boutons, transmit signals to other neurons or effector cells through a synapse where the junction between two neurons, or between a neuron and an effector cell, or where neurotransmitter molecules are released to propagate the signal (13). Following the axon terminals is the region known as the synapse, where neuron-to-neuron communication takes place. This synapse is a gap between two neurons, also known as a presynaptic and postsynaptic neurons, where communication is accomplished using specific chemical messenger molecules known as neurotransmitters. These neurotransmitters include serotonin and gamma-amino butyric acid (GABA), which inhibit nerve impulses, while norepinephrine and glutamate serve as excitatory neurotransmitters (13).

Glial cells, also known as neuroglia, provide nutrition and protection to neurons and function as support cells that protect and maintain neuronal homeostasis (14). There are several types of glial cells, including microglia, astrocytes, oligodendrocytes and ependymal cells in the CNS, and satellite and Schwann cells in the PNS (Figure 3). Astrocytes, the most numerous cells of the CNS, are star-shaped cells that provide structural and metabolic support for neurons. They play a role in maintaining the blood-brain barrier and regulate ion concentration in the extracellular space. Moreover, they are the major element in controlling activitiy of the synapses. Myelin, an insulating coating or sheath composed of protein and lipid substances that develops around neuronal projections, is made by cell membranes of oligodendrocytes in the CNS and Schwann

cells in the PNS. Electrical impulses pass trough neurons in a saltatory manner, leaping between the nodes of Ranvier (14). This unique mode of travel is facilitated by the insulating myelin sheath, which envelops the majority of the neuronal fibers, effectively isolating them. Therefore, any damage to the myelin sheath, for example in patients with multiple sclerosis, causes slowing of the impulse propagation and hinders the proper functioning of the nervous system.

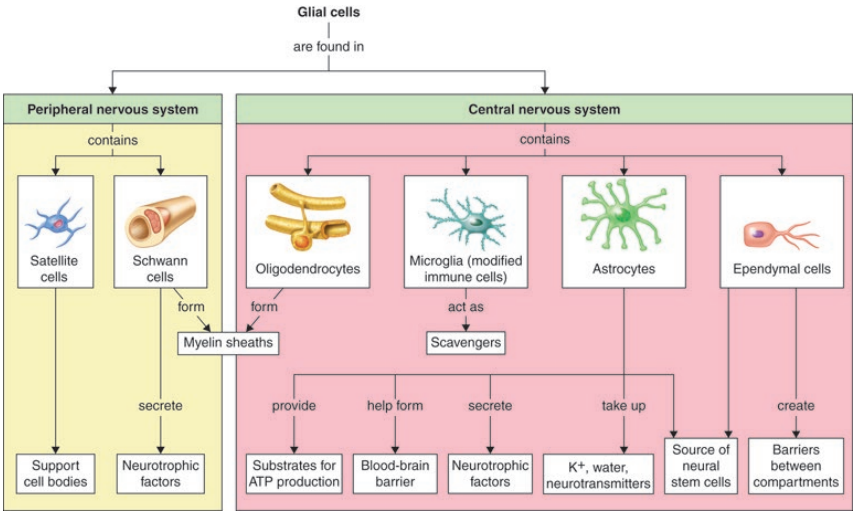

Figure 3. Types, locations and function of glial cells within the nervous system (12)

Besides astrocytes and oligodendrocytes, another type of glial cells within the CNS are microglia. Microglia are the resident immune cells of the CNS, corresponding to 10 – 15% of all brain cells (14). They are responsible for removing external substances that invade the brain or unnecessary substance generated internally and, with that, they regulate the inflammatory response. Since knowledge of the therapeutic targets can improve the efficacy of treatment, many large-scale studies were conducted targeting patients with Alzheimer's disease to determine which genes are different from the general populations (15). It was reported that, following the well-known gene APOE4, a gene called TREM2 has the second most important correlation with the development of Alzheimer's disease. Because TREM2 is a gene that encodes the microglial surface, it may likely suggest that disfunction of microglia might be correlated with Alzheimer's disease. Next, ependymal cells are a type of glial cells found in the CNS that line the ventricles of the brain and the central canal of the spinal cord and produce and circulate the cerebrospinal fluid (CSF) (15). Finally, satellite cells are found in the peripheral nervous system, together with Schwann cells, where their main role is providing general support to neurons.

2.2. Function of the nervous system

Communication between neurons takes place through the nerve impulse conduction mechanism (13). When the cell membrane of a neuron is in a stable state, potassium diffuses out of the cell due to a concentration gradient, and this force creates a negative charge within the cell. This voltage difference is called the resting membrane potential, and -70mV is normal for the nerve cells (Figure 4). When a cell receives appropriate stimulation, the permeability of the cell membrane increases, with sodium, a major cation in the extracellular fluid, being utilized inside the cell, and potassium, a major ion in the intracellular fluid, being pushed out to the cell membrane (13). This creates of flow of electric current. When sufficient stimulation is applied, the positions of the negative and positive electrodes change and move along the entire axon. This is called an action potential. The refractory period is the brief time after a nerve is activated during which it does not react to the subsequent stimulation (13).

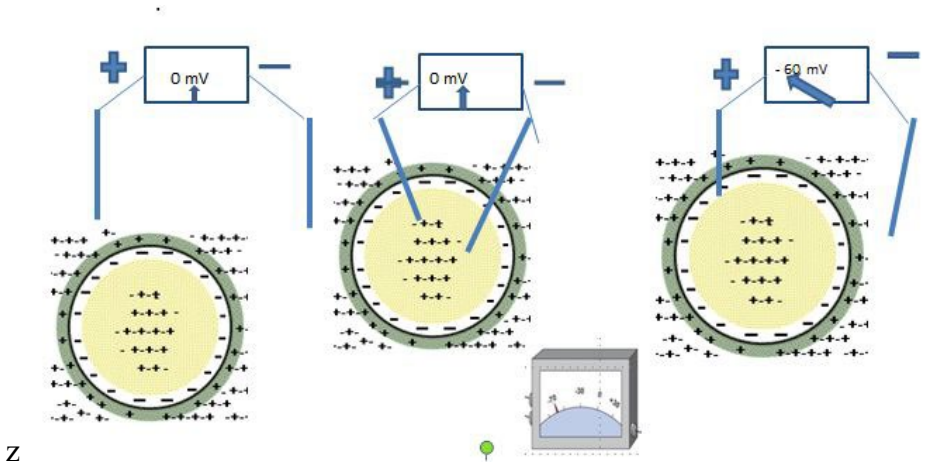

Figure 4. Resting membrane potential (12)

Based on their function, nerves can be classified into sensory, motor, and association nerves (13). Sensory nerves transmit internal and external changes of the body perceived by sensory receptors to the central nervous system. The information from the sensory nerves is collected in the thalamus of the CNS and then transfer to the parietal lobe of the cerebral cortex to integrate perception.

The brain is composed of three main structural divisions: the cerebrum, the cerebellum, and the brainstem (13) (Figure 5).

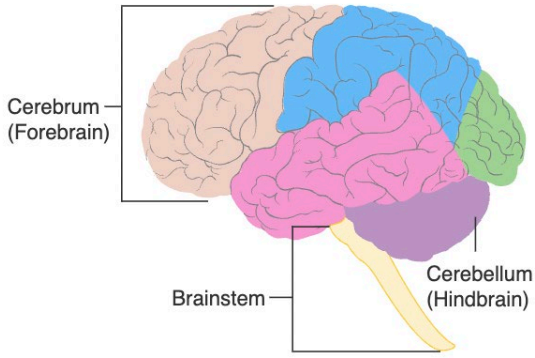

Figure 5. Structural division of the brain (12)

The cerebrum is the upper part of the brain that consists of frontal, parietal, temporal, insular, and occipital lobes (Figure 6). These are responsible for muscle movement, language, and sensory processing. The cerebrum consists of the cerebral cortex with white matter and the wrinkled gray matter forming the gyrus.

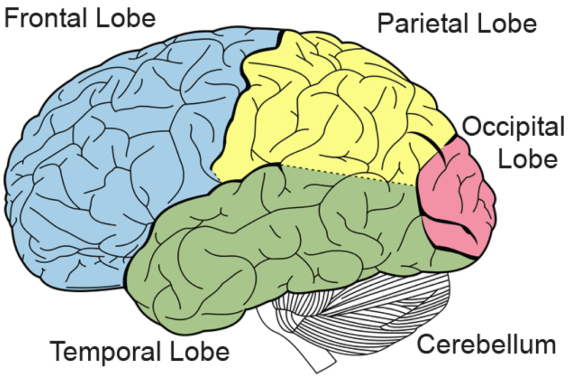

Figure 6. Frontal, parietal, occipital and temporal lobes of the cerebrum (12)

The frontal lobe is dominated by motor neurons, and includes the motor cortex, which is the primary motor area, and the frontal association area, which is responsible for personality, attitude, and high intellectual functions (13). The premotor area has the function of controlling and integrating complex, learning, and unconscious movements, and its fine movements. It also contains Broca's area, a region which governs the movements of the tongue and mouth. Therefore, if this area is damaged for various reasons, motor aphasias may result. Additionally, the frontal lobe is also responsible for controlling behavior based on judgement and foresight, the ability to develop goals, concentration, imagination, and logic.

Contrastingly, the parietal lobe is populated with sensory nerves, responsible for understanding sensation, texture, size, shape, spatial relationships, recognizing body parts and body posture (14). This is also the region where taste is interpreted. On the other hand, the temporal lobe is the center of hearing which interprets sound an regulates the balance of the body. It especially includes the Wernicke area, which is responsible for understanding the meaning of words, and speaking. Therefore, damage to this area can result in sensory aphasia (14). Finally, the occipital lobe comprises the primary visual area and visual association area. It is also involved in visceral activities, including intra-abdominal sensations and visceral movements.

The brainstem has a wide distribution the reticular activating system that controls cognition and arousal and it can result in coma when damaged (13). It is divided into the midbrain, pons, and medulla oblongata. While the pons plays a crucial role in relaying messages between the brain and the body, the medulla oblongata controls vital life-sustaining functions such as heartbeat and breathing. The midbrain, also known as the mesencephalon, is associated with vision, hearing, motor control, sleep and wake cycles, alertness, and temperature regulation.

3. Neurological disorders

3.1. Neurodegenerative disorders

Neurodegenerative diseases refer to diseases in which nerve cells are gradually damaged or die, deteriorating the function of the CNS or the PNS, and resulting in various serious functional deficits (13). These diseases generally have progressive and chronic characteristics and, although they mainly occur in the elderly population, they can also affect population of any age. Major neurodegenerative diseases include Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS, “Lou Gehrig's disease”).

Even though neurodegenerative diseases present with distinct symptoms, several common pathological mechanisms contribute to their development. One such mechanism is the malfunction and accumulation of abnormally folded proteins. For example, beta amyloid and tau proteins build up in Alzheimer's disease, whereas alpha synuclein is the main pathogenic component in Parkinson's disease (16). Another method is oxidative stress, which causes cell damage by overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Furthermore, cell death in neurodegenerative diseases can also be caused by mitochondrial

dysfunction (2). Apart from that, chronic inflammation is another common mechanism among patients with neurodegenerative disorders. In addition, a number of gene mutations have been linked with different types of neurodegenerative diseases. For instance, the APOE4 allele has been associated with Alzheimer's disease (5).

Currently, the main focus in treating neurodegenerative diseases is the relief of symptoms. Therefore, ongoing research aims to identify underlying causes and develop new therapeutic interventions (17). In this process, many different methods are being investigated, including neuroprotection, inhibition of protein accumulation and decrease in inflammation, coupled with innovative treatments like stem cell transplantation (18).

3.1.1. Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by deposition of amyloid-beta plaques (Aβ) and neurofibrillary tangles (NFTs), leading to synaptic dysfunction and neuronal death. It is the most prevalent neurodegenerative disease and, as such, one of the major causes for dementia worldwide. AD is more common in older adults, with a large role in its onset and progression being assigned to family history (5). Previous head injuries may also increase the risk. The primary early sign of AD is diminished short term memory. Over time, the memory worsens, and additional symptoms appear, including difficulty with concentration and simple decision making (4). In the advanced stages of AD, the severe loss of brain function can lead to life-threatening malnutrition, dehydration, and infections.

Nevertheless, recent years have seen a rise in the development and subsequent FDA approval of new anti-amyloid drugs, including Lecanemab and Adunacemab (19). Even though these drugs have the ability to enhance the clearance of amyloid plaques, their impact on patient outcomes has to be evaluated further (19). Another substantial advancement in the field has been the identification of genes that exert a protective effect on the brain, particularly in the context of amyloid accumulation. In this regard, the Laboratory for Stem Cells at University of Zagreb School of Medicine played a role in a large-scale international study which led to the discovery of BACE2, a gene which has been found to exert protection against AD (20).

3.1.2. Parkinson's disease (PD)

Parkinson's disease is a progressive disease of the nervous system characterized by various pathological changes. The main abnormality evident in people with this condition involves the death of their substantia nigra neurons that produce dopamine. Lewy bodies can also be found (3). Still, it is unknown what causes Parkinson's or how it progresses, although some scientists think environmental influences could act together with genetics as triggers for this illness. Symptoms of Parkinson's include trembling of extremities and the face, stiffness is arms and legs, slowed movements, speech difficulty and diminished balance and coordination. Patients that go without treatment may face more outcomes like depression, problems with talking, sleeplessness, inability to hold in urine or feces, and sex-related challenges (3).

The most common drug used to treat Parkinson's disease is Levodopa also known as L-DOPA. Its main function is to increase dopamine in the brain (3). Besides L-DOPA, patients can also be administered with dopamine (DA) agonists such as Ropinirole and Pramipexole (21). These DA agonists work by activating dopamine receptors in the brain, mimicking the role of dopamine. With that, they help relieve the symptoms of PD. Nevertheless, while both L-DOPA and the variety of DA agonists can alleviate motor symptoms, they do not prevent the progressive death of dopaminergic neurons associated with the disease. Aside from pharmaceutical agents, patients with PD also have access to surgical options employing medical devices, one of which is deep brain stimulation (DBS) (21). However, while DBS surgery can improve motor symptoms and enhance the quality of life, some challenges may persist even after stimulation, including negative impact on the patient's gait and postural skills during long-term stimulation (5+ years) (21). Contrastingly, short-term DBS (1-2 years) has been shown to be more beneficial.

3.1.3. Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is characterized by muscle weakness, cramps, and muscle atrophy. These symptoms happen because both upper and lower motor neurons degenerate (17). ALS affects all voluntary muscles and leads to fatal outcome within three to five years after establishing diagnosis (18). ALS is also linked to some genetic mutations, like SOD1 or C9orf72, and environmental factors (17). Besides physical signs, patients may also exhibit mental health issues, including depression. Furthermore, patients may experience changes in cognition and

behavior. In some cases, ALS may be associated with frontotemporal dementia. Interestingly, 90% of amyotrophic lateral sclerosis cases are sporadic.

During treatment of patients with ALS, the main goal is to find a way to slow down the progression of the disease, stop any complications from arising and improve the patients' living standards. Currently, there exist two FDA-approved medications for treatment of ALS – antioxidants Riluzole and Edaravone (17). Riluzole works by blocking the release of glutamate which is an excessive amount that could harm nerve cells, while Edaravone seizes ROS produced during cellular respiration where energy is consumed. In addition to these, people with ALS can also obtain Tofersen, an investigative drug. By reducing the synthesis of the SOD 1 protein, which is harmful to motor neurons, this medication is intended to target a kind of ALS brought on by mutations in the SOD1 gene.

3.2. Neurovascular disorders

Neurovascular disorders refer to a group of diseases that cause neurological damage due to problems with the blood vessels that supply the brain and spinal cord (22). These disorders, can have significant effects on brain function, leading to high morbidity and mortality. The major types of neurovascular disorders include stroke, aneurysm, arteriovenous malformation (AVMs), vasculitis and cerebral venous sinus thrombosis (CVST) (22).

In the realm of neurovascular disorders, the primary objective is to mitigate the causative risk factors as much as feasible. However, achieving this prevention is often a challenging task, presenting a realistic limitation. Stroke necessitates immediate intervention upon onset. Unfortunately, it is frequently detected late in patients, which complicates the situation (22). The harsh reality is that even with prompt treatment, the delay in action often results in unavoidable aftereffects, the severity of which depends on the recovery process.

3.2.1. Stroke

Stroke is a neurological disease that occurs when a cerebral blood vessel becomes blocked or bursts, causing acute neurological damage (23). It is divided into ischemic and hemorrhagic. A blood clot that blocks blood flow within a blood artery is what causes an ischemic stroke (23). It accounts for about 80% of all strokes, resulting in damage to the nervous system. This damage is a direct consequence of the lack of oxygen and nutrients which cannot pass through the blocked

vessels (23). Hemorrhagic stroke, on the other hand, results from a brain blood vessel rupture (24). It accounts for approximately 20% of all strokes, wherein the brain tissue is directly damaged due to cerebral hemorrhage. As the pressure caused by the hemorrhage increases, compressing surrounding brain tissue, it causes brain damage (24). Stroke symptoms depend on the part of the CNS which is affected by ischemia. For example, if it affects motoric cortex or capsula interna, it presents as sudden paralysis or weakness of one side of the face, arm, or leg and speech impediment. It also causes headaches, dizziness, and balance problems. Treatments include control of blood pressure (BP), thrombolytics (tPA) and thrombectomy through intravascular angiography, or surgery to remove the hematoma (23, 24).

3.2.2. Aneurysm

Aneurysm is an abnormal balloon-shaped swelling that occurs when the walls of cerebral blood vessels become weak (24). If it ruptures, it can cause a hemorrhagic stroke. Even though it can, oftentimes, be asymptomatic before rupture, it causes acute headache, vomiting, and loss of consciousness upon rupture. The treatment includes aneurysm ligation and coil embolization.

3.3. Neuroinflammatory disorders

Neuroinflammatory disorders are characterized by the inflammation of the nervous system, including the brain, spinal cord, and peripheral nerves, which can damage nerve tissue and cause a variety of neurological symptoms (25). These disorders result from a variety of causes and can be chronic and progressive. They are also often associated with autoimmune reactions, infections, or other triggers that result in an inappropriate immune response targeting the nervous system. Some of the most common neuroinflammatory disorders include multiple sclerosis (MS), autoimmune encephalitis, and transverse myelitis, among others (25).

3.3.1. Multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic autoimmune disease that reduces nerve transmission by damaging the central myelin sheath, which is a protective covering of nerve fibers (26). This leads to demyelination and axonal damage that affects communication within the nervous system. The types of MS are relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-

progressive MS (PPMS), and progressive-relapsing MS (PRMS), where symptoms occur in different patterns at different times with varying degrees of intensity as they progress. Symptoms of MS include numbness, weakness or tingling, often on one side of body giving rise to unsteady gait; problems with vision; cognitive functions including mood swings; slurred speech together with lack coordination accompanied by fatigue can also happen.

There is no cure for MS, but treatment can manage symptoms and long-term outcomes (27). With that, the treatment for patients with MS commonly includes corticosteroids, beta blockers and glatiramer acitate. Corticosteroids, a class of drugs designed to reduce inflammation while suppressing the immune response, include Methylprednisolone and Prednisone (27). On top of this, beta blockers like Avonex and Rebif can also be employed. These work by blocking the action of interferon beta, a protein responsible for causing inflammation (27). Aside from corticosteroids and interferon beta blockers, patients can also be administered with glatiramer acetate (GA), found in medications like Copaxone and Glatopa. GA is a synthetic protein that simulates myelin basic protein (MBP) and is thought to act by competing with myelin antigens (27). These medications are part of a group known as disease-modifying therapies (DMTs).

4. Stem cells

4.1. Introduction to stem cells

Stem cells are cells which are present during embryonic development where they contribute to development of all the tissues. Aside from embryos, stem cells are also present in adults, where they contribute to regeneration of the tissue after damage (29). The capacity of a cell to proliferate and self-renew typically originates from a single, clonal cell and evolves into various cell types and tissues, functioning as a potent cell. Therefore, stem cells can be utilized to substitute damaged cells or regenerate organs. Furthermore, the establishment of disease-specific cell lines can be used to enhance our understanding of disease development and pathogenesis, offering valuable insights for pharmaceutical development (30).

Stem cells play a crucial role in understanding organogenesis and the body's regenerative processes. Moreover, they are a benchmark in the study of disease pathogenesis and may help researchers understand the pathophysiology of different diseases. In addition, SCs can also serve as useful biological models for testing new drugs. Most importantly, stem cells have the ability to

replace injured tissues or regenerate organs which makes them very important in medical research (31, 32). Stem cells can be divided into four types, according to their differentiation potential: totipotent, pluripotent, multipotent and oligopotent (Figure 7).

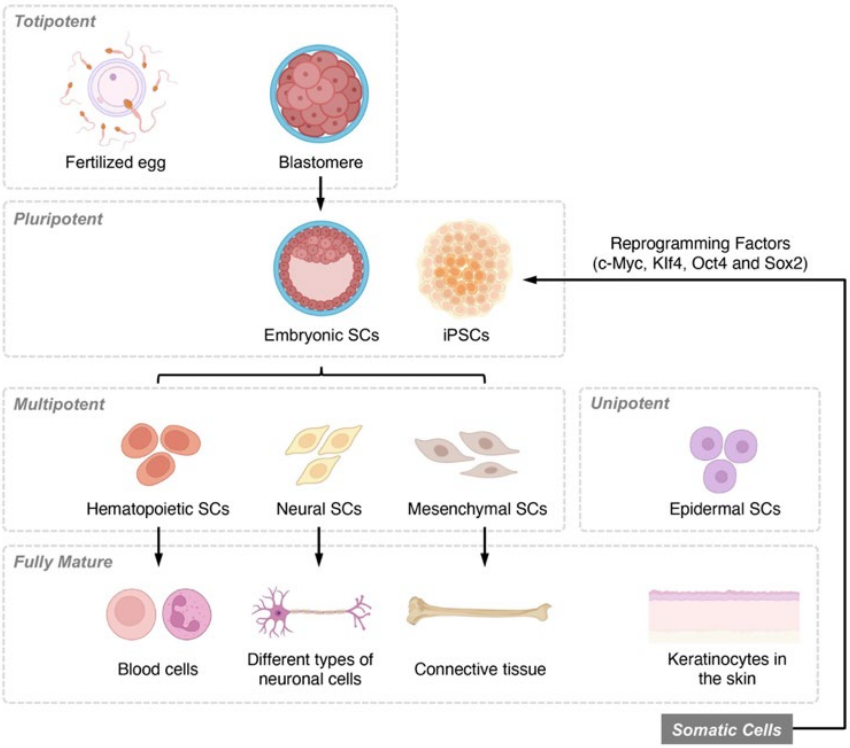

Figure 7. Types of stem cells based on differentiation potential and developmental stages (32)

During the early stages of development, **totipotent cells** are the most undifferentiated. These cells, which include a fertilized oocyte, a zygote, and the cells from the first two divisions, can develop into both embryonic and extra-embryonic tissues. They ultimately form the embryo and placenta. Similarly, the differentiation of **pluripotent stem cells** leads to the formation of the three germ layers: the ectoderm, endoderm, and mesoderm (29). These layers give rise to all tissues and organs. There, and derived from the inner mass of the blastocyst, is where embryonic stem cell (ESCs) are found. On the other hand**, multipotent cells** could be seen in nearly all tissues where they can differentiate into different cell types derived from one germ layer (30**). Oligopotent stem cells**, lastly, are capable of self-renewal and differentiation into several lineages within a particular tissue (30). These cells are further classified as adult or somatic stem cells. Since all of the aforementioned stem cell types have unique properties, they are proving to be an

effective treatment for a wide range of disease, including ALS, Parkinson's, Alzheimer's, cardiovscular, renal, and autoimmune.

4.2. Types of commonly used stem cells in clinical trials and their characteristics

4.2.1. Embryonic Stem Cells (ESCs)

Embryonic stem cells (ESCs) belong to the category of **pluripotent stem cells** and are obtained from the inner cell mass of pre-implantation mammalian embryos (34). Since these cells can develop into any type of cell or tissue, they are of interest to scientists worldwide as they provide an opportunity for studying differentiation and development of any organ system.

4.2.2. Adult stem cells (ACSs)

Adult tissues and organs include a unique subset of cells called adult or somatic stem cells (ASCs). They play a crucial role in the body's ability to renew and repair its tissues (35). Adult stem cells, in contrast to other cells, possess a special capacity for cell division and multiplication. Therefore, since they are multipotent, ASCs can replace cells that are lost due to normal wear and tear, injury, or disease and are, as such, crucial for maintaining proper tissue homeostasis (32).

4.2.3. Induced pluripotent stem cells (iPSCs)

Induced pluripotent stem cells (iPSCs) are a huge step forward for the study of stem cells. They can be made by reprogramming adult cells, like skin cells, to act as though they were ESCs (33). This means that these adult cells may be brought back to a younger state so that they have all the abilities of embryonic ones; this is called „genetic resetting“. Additionally, **pluripotent cells**, as shown by Takahashi and Yamanaka, can also be generated through reprogramming of somatic cells (36, 37). Despite their many similarities with ESCs, there is one main difference between them – the process of their derivation. In particular, iPSCs do not use embryos in their creation, thereby avoiding certain ethical dilemmas surrounding research on these types of cells (34).

4.2.4. Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are non-hematopoietic cells that can be obtained from various sources (38). These include bone marrow (BM-MSC), adipose tissue (AT-MSC), embryonic tissue (E-MSC), cord blood (CB-MSC) and Wharton's jelly (WJ-MSC). Their traditional functions include hematopoiesis support, mesodermal lineage cell production, and immunomodulatory and neurotrophic actions. MSCs have the capacity for self-renewal and are are multipotent (38). This characteristic renders them useful in regenerative medicine, where it has been discovered that MSCs can be transformed into cells of the neural tissue. The term used to describe this phenomenon is trans-differentiation, where a cell from one germ layer (mesoderm) differentiates into a different type of cell belonging to another germ layer (ectoderm) (29).

4.2.5. Neural stem cells (NSCs)

Stem cells obtained from the nervous system, known as neural stem cells (NSCs), can develop into neurons, astrocytes or oligodendrocytes (39). They are mainly distributed throughout the CNS and are important for its growth as well as upkeep. Moreover, and due to their differentiation capacity, NSCs also have significant implications in treating of neurodegenerative disorders or injuries to nerves (40).

4.3. Techniques for isolation and cultivation of stem cells

The first step for clinical use of stem cells is their isolation using tissue biopsy (41, 42). Then, by using various protocols, depending on the cell type, they are separated using enzymes and centrifuged in a density gradient. Immunomagnetic separation is sometimes used to purify the stem cells based on their surface markers (41). Once exposed to a magnetic field, cells that have bound antibodies can be separated from other parts of the sample.

Scientists can also perform further sorting and characterization of these cells through flow cytometry after isolation. In this case, cells start off with specific fluorescent tags which enable researchers to identify different types of stem populations (40). Lastly, culture and expansion of cells involves growing isolated stem cells on a dish where they multiply. At each stage during multiplication more refined collections may be made towards diverse uses (41).

5. Clinical trials

5.1. The basics of clinical trials

All drugs and medical devices must pass a series of clinical trials to be cleared for public use, meeting the necessary regulatory thresholds (43). Therefore, only those treatments which have been shown to work and not cause damage are permitted for general application. Clinical trials primarily fall into two categories: **interventional** and **observational** (43). **Interventional trials** are designed to discover more about treatments by studying various treatment groups, enabling researchers to compare the outcomes. The main goals of early-phase trials are to determine a drug's safety and any potential adverse effects. However, later-stage studies are conducted to ascertain whether the novel treatment is superior to the existing. In day-to-day life, participants are monitored in observational trials which collect data on health outcomes or risk factors (43). These trials differ from standard clinical trials but they do involve observation practices.

Clinical trials typically consist of three key phases: phases 1 through 3 (44**). Phase 1** studies comprise a small cohort of around 20–50 participants. The goals are to ascertain the ideal dosage for the medication, recognize any adverse effects, and comprehend how the medication interacts with the body. Next, a medium-sized sample of about 10 to over 100 individuals participates in **phase 2** trials (44). Verifying the optimal therapy dosage, expanding knowledge regarding adverse effects, and assessing the treatment's efficacy are the main goals. These studies may occasionally be randomized. Lastly, **phase 3** studies, often known as later phase trials, contain hundreds or thousands of participants in sizable groups. The new therapy will be compared to either a placebo or the standard of care. These trials usually employ a randomized design (44). Moreover, some trials also have an earlier phase, phase 0, which tipically involve around 10 – 20 participants. The primary objective is to test a low dose of the treatment to ensure it is not harmful. Finally, if more information on the long-term benefits and side effects of treatment is needed, a phase 4 trial can be conducted. These involve medium to large groups of people and are conducted after a drug has been licensed (44).

Unlike interventional trials, **observational trials** intend to find out what takes place under different conditions through observing participants without influencing their treatment choices or splitting them into treatment groups (44). These include: treatment trials, prevention trials, diagnostic trials, screening trials, quality of life (QoL) trials and other observational studies. Each of these types of trials can occur at different stages, depending on the phase of treatment

development. Treatment trials act as testing grounds for new drugs, procedures or therapies (44). In the early phases (Phase 0 to 3), safety andside effect profile are studied. Contrastingly, later phases of the trial concentrate on whether a new treatment works better than the current one. Next, randomized trials are often used when two or more treatments need to be compared because they provide reliable information about the effectiveness of a new intervention. Prevention trials are designed to prevent certain conditions or diseases (44). They may involve medications alone or in combination with lifestyle changes such as diet modifications. For example, prevention trials can investigate if, among people who do not have cancer, a particular therapy can help prevent cancer from occurring. Therefore, they can be designed for the general population or individuals with increased risk due to genetic predispositions.

On the other hand, diagnostic trials endeavor to improve methods used for diagnosing diseases by employing new imaging techniques or blood tests, among others. Likewise, screening tests aim for early detection of an illnesses, usually before the symptoms appear, so that treatment outcomes may be enhanced. Similar to prevention trials, screening tests could target entire populations or specific high risk groups, e.g those with family history. Quality of life trials seek ways to enhance individuals living standards suffering from chronic ailments. Lastly, observational studies follow up participants throughout their normal daily activities, all while collecting health outcomes data or risk-related factors (44). This holistic approach allows us to obtain knowledge about their efficacy of different treatment modalities and their impact on patients' lives.

5.2. Design and methodology of clinical trials

The process of conducting a clinical trial starts by finding out a promising treatment in the conceptualization stage that could improve the patient outcomes. After that is done, the researchers come up with an organized research plan, also known as a protocol (43). Indicating the study design, eligibility criteria and means of data analysis are what this protocol does. Once it has been created, this document goes through a strict examination before approval. Any trial must be ethical, safe and respect participants' rights so that it may not fail to meet standards set by ethical review boards like the Institutional Review Board or an Ethics Committee (44).

Once the approval has been obtained, the next step is participant recruitment. Possible subjects are located, then checked against eligibility criteria as per the protocol. Every person must

give their informed consent where they understand what they will be subjected to during these trials, i.e. the purpose of trial and procedures followed, among others (43). The last step involves conducting of the trial itself. Different treatments are given to groups of patients according to the design of study. Here, safety and efficiency data are closely monitored by investigators throughout this experiment.

5.3. Ethical considerations in clinical trials

A careful assessment must be made before any treatment, including those that involve stem cells, is tried out (45). This assessment consists of a number of steps. It usually starts with preclinical studies aimed at establishing the safety and efficacy of the stem cells in animals. Then, regulatory agencies, such as the FDA, scrutinize these studies to confirm compliance with ethical standards and protection of participant rights (46). This evaluation is important because it helps to decide whether or not a given stem cell therapy should proceed into clinical trials. If a treatment approach is deemed viable, it progresses into clinical trials. Once there, scientists conducting this trial and regulators overseeing its execution are bound by law to ensure that their conduct meets stringent requirements designed for the safeguarding of human subjects who serve as test objects (46). Additionally, the consent process must balance caution and progress, disclose uncertainties, and define the risks. Among those already mentioned, additional ethical considerations also include obtaining informed consent from donors, establishing appropriate biobanking models, and addressing the ethical issues surrounding the commercialization of stem-cell based treatments (47).

The Helsinki-Tokyo-Venice Declaration is a framework for worldwide standards on human trials. It supports the principle of informed consent and requires an ethics committee or an investigational review board to be involved. Since this general framework must be followed during all clinical trials, some improvement in technical norms, such as those provided by the European Organization for Research and Treatment of Cancer (EORTC), including more specific bioethical criteria and moral norms, should be made (45). As part of the technical aspects of the design and monitoring process, checklists can also be used to help prevent the misinterpretation of clinical data as being in the "most beneficial interests of the patient" (45). Moreover, the use of preclinical animals and computer simulations can also mitigate risks associated with clinical research. Bioethicists, who lay the groundwork for informed consent in medical research, should also be kept informed of all trust and risk-related information. It is the responsibility of review committees

and bioethicists to prioritize clear and educated communication over mere consent (46). Thus, ethical considerations in clinical trials are of paramount importance because they guarantee the protection of the rights, safety and welfare of the participants which, in turn, maintains the honesty and trustworthiness of research done (48, 49).

6. Stem cell therapy in neurological disorders

6.1. Amyotrophic lateral sclerosis

Although the use of Riluzole and Edaravone is authorized by the FDA, they only have a slight impact on slowing down the progression of the disease, and extending the patient's life by several months (9). Moreover, patients in which mutation in SOD1 is the cause of disease since recently are eligible to receive Tofersen, antisense oligonucleotide which reduces quantity of toxic form of SOD1. Therefore, because there is currently no available treatment that can effectively stop or reverse ALS, researches are now focusing on employing new treatment approaches, including stem cell therapy. One of these techniques involves transplanting MSCs which are given via IV and IT routes. This strategy has shown good results in animal models (50) and clinical trials (51, 52, 53) where it notably improved motor functions and prolonged patient's survival.

Beyond preclinical trials, a multitude of clinical trials have surfaced, rigorously examining the efficacy of stem cells in treating ALS. One of these is a 2022 clinical trial conducted by Cudkowics et al. (51). In it, the researchers investigated the use of BM-MSCs engineered to produce elevated levels of NTFs (MSCs-NTFs) as a potential therapeutic approach for ALS. These were shown to favorably modify neuroprotective and neuroinflammatory cerebrospinal fluid (CSF) biomarkers (51). However, it is important to note that this trial was conducted on patients with mild to moderate ALS. Therefore, when ALS reached an advanced stage, particularly with respect to the respiratory subscale, the impact was not significant. Nevertheless, the biomarker data from the study supports a treatment associated with disease progression (51). In general, this clinical trial, among others, provides evidence linking a targeted therapeutic mechanism of action and the prediction of personalized prognosis to the preservation of function in ALS patients, as also demonstrated by Petrou et al. (52, 53).

The study of Petrou et al. in 2016 had the same goal – to observe what would be the clinical effects on patients with ALS brought about by MSC-NTFs. In this phase 1/2 and 2a study, 12 and

14 patients with mild to moderate ALS were enrolled from June 2011 until October 2014 in the Hassadah Medical Center in Israel (52). The treatment was shown to be safe and well-tolerated. The patients in the phase 1/2 clinical trial, who had mild ALS, received MSC-NTFs intramuscularly (IM), while those with more severe cases were administered with an intrathecal (IT) injection. Following treatment, improvement in motor function, muscle strength and respiratory function was observed (52). A similar group of authors, lead by Petrou et al., also performed another phase 2 clinical trial on patients with ALS, the results of which were published in 2021 (53). Likewise, and following 1-4 intrathecal injections of autologous MSCs over 3-6 months, the treatment appeared to be well-tolerated by patients. Out of 19 in total, seven patients even exhibited clinical improvements in their symptoms (53).

With that being said, while current treatments for ALS can only slow the disease's progression, stem cell therapies, particularly those involving MSCs, show promising potential. Clinical trials, such as the ones conducted by Cudkowics et al. and Petrou et al., have demonstrated the ability of MSCs to modify neuroprotective and neuroinflammatory biomarkers, providing a new avenue for treatment.

6.2. Alzheimer's disease

In order to treat and manage AD, numerous clinical trials targeted single patho-mechanisms such as Aβ or Tau, which are in the core of AD (4, 53). Besides Aβ or Tau, recent research has also shown that exosomes, extracellular vesicles that are released by diverse cells in the rest or stress states and contain enhanced lipids, proteins, and nucleic acids, play a significant role in Alzheimer's disease (53). Nevertheless, since AD is a multifaceted disorder, the use of multi-target therapies may be more effective than single-target therapies and may result in a change in clinical course.

While current medications for AD effectively manage symptoms, they do not cure the disease itself. Therefore, stem cells have the potential as a treatment for AD. By this point, NSCs have been used to treat ALS and Parkinson's disease, showing potential for repairing damaged brain circuits and acetylcholine neurons, paving the way for innovative treatments (54). Despite ongoing debates about the role of the brain's defense system (BBB) in clearing Aβ, NSCs may safeguard crucial blood vessels and prevent amyloid angiopathy or angiogenesis in the brain (54). The reduction in Aβ load following neural stem cell transplantation could be attributed to low β-

secretase levels, the presence of NEP, microglial recruitment, and immunological responses. Although the fundamental mechanism remains unclear, transplanted human NSCs have been observed to reduce tau phosphorylation in mouse ventricles (54). NSC transplantation for AD also appears to have an anti-inflammatory effect, thereby reducing molecular markers and pro-inflammatory cytokines. As the disease progresses, neurotrophic and degradative enzymes produced by transplanted NSCs may help slow cognitive decline (54).

Besides NSCs, existing research has utilized both allogenic human adipose MSCs (Aha-MSCs) and human umbilical cord blood MSCs (hUCB-MSCs) to treat patients with mild to moderate Alzheimer's disease at the level of clinical trials (53, 54). Since exosomes have been shown to play a role in AD, MSCs-derived exosomes possess unique advantages over MSCs, including low immunogenicity, avoidance of invasion of MSCs during collection or differentiation, and simplicity in storage (53). Moreover, there is evidence that exosomes can reach the brain and improve cognitive function in animals (53). Particularly, and due to their neuroprotective potential, Aha-MSC exosomes can be used for AD treatment in mice through intranasal administration. These, in turn, trigger neurogenesis and enhance spatial memory. Moreover, MSC-derived exosomes have also proven to be effective for treatment of different degenerative and inflammatory conditions such as lung injury, wound healing, heart disease, liver damage and bone restoration in triple transgenic 3xTg mouse models (53).

In a clinical trial reported by Xie et al., intranasal Aha-MSCS-Exos manufactured by Cellular Biomedicine Group (Shanghai, China) were inspected by transmission electron microscopy (TEM) and their size distribution was analyzed by nanoparticle tracking (53). Two years of phase 1 and phase 2 clinical trials were conducted until 2022. All the patients were over 50-years old with mild to moderate Alzheimer's disease who were prohibited from taking any cognitive enhancing medication. Trial participants were excluded from the study if they suffered from severe and poorly controlled concomitant diseases, severe allergic reactions, or MRI contraindications. On the basis of vital signs and clinical laboratory tests, the outcome of the safety trial was assessed at baseline, 4, 12 and 16 weeks after the first treatment. In order to evaluate the efficacy of the intervention, cognitive function and daily activities were assessed. As part of this study, PET-MRI was used to estimate amyloid, tau, and hippocampal volumes, which are hallmarks of AD pathology (53). The results of the study observed the amount of amyloid and tau deposition, as well as the rate of change in the bilateral hippocampus volumes. Following the first

treatment, cerebral amyloid plaque levels increased about a year after follow-up, whereas tau deposition levels did not change significantly. Moreover, a decrease in the hippocampal volume was observed in patients who received the medium-dose (53).

On the other hand, Kim et al. conducted a clinical trial in South Korea involving hUCB-MSCs to determine the mechanisms and nature of their effects on AD (54). As part of phase 1, nine patients with significant amyloid burden and neuronal degeneration underwent PET-MRI. All patients had mild to moderate AD dementia and received three repeated intracerebroventricular (ICV) injections of hUCB-MSCs (54). A Ommaya reservoir, an intraventricular catheter system that can be used to aspirate CSF or deliver drugs into the CSF, was used to implant MSCs into the lateral ventricle. Once there, MSCs can migrate into the brain parenchyma by adhering initially to the lateral ventricle walls, making the intracerebroventricular route more effective for delivering them to the brain (54).

A 12-week follow-up was conducted on the patients, followed by a 36-month follow-up to determine the success of the trial (54). The most common side effect following hUCB-MSC injection was fever, followed by headache, nausea, and vomiting. Two of the nine participants were hospitalized more than 48 hours after injection, the period for monitoring the side effects. A MRI scan, PiB-PET scan, and florbetaben PET scan were performed following an injection of hUCB-MSCs (54). There were no problems with tolerability among all patients and not a single one of them suffered from cerebral hemorrhage. The fever went down the following day without any antibiotics or anti-viral drugs. MSCs are likely to have caused an inflammatory response by way of injection side effect thus. Furthermore, after each injection, the CSF concentration of white blood cells (WBCs) increased for the first six to twenty-four hours with fever, then normalized after four weeks. Additionally, WBC count increase was shown to be related to lower doses and higher doses, and to repetitions of injections. AD biomarkers such as total Tau, phosphorylated tau, and A*β42,* decreased after the first day of each injection, and then increased to the baseline level after 4 weeks.

Therefore, Kim et al. suggested that the immune response to hUCB-MSC injections was sensitized after the second and third injections (54). Although the inflammatory response was transient, they note that repeated injections of MSCs may cause widespread encephalophathy (54). Researchers did not expect an immune reaction to MSCs that expressed low levels of major histocompatibility complex (MHC) class I and low or negative levels of MHC class II. However,

it is possible that the immune response arose following the injection of MSCs, since a high infiltration of immune cells was observed at the injection site a week after the procedure. As a result, immune cells were evidently expressed pronouncly at the injection site. Nevertheless, since some evidence of improvement in the patient's condition was observed, using MSCs for treatment of AD looks feasible, safe and well tolerated (54).

In summary, the works of Xie et al. and Kim et al. have given us valuable insights into the potential of MSCs and MSC-derived exosomes for treatment of AD. As shown by their clinical trial employing intranasal Aha-MSCS-Exos, Xie et al. achieved good results, witnessing increased neurogenesis. Similarly, Kim et al.'s clinical trial involved the use of hUCB-MSCs and demostrated promising results. Even though both of these studies showed that MSCs could enhance cognitive function and overall brain health, the clinical trials are still in their early phase. Therefore, although the findings are encouraging, more experiments are needed before the efficacy and efficiency of these treatment approaches can be fully evaluated, including a detailed asessment of their potential side effects.

6.3. Parkinson's disease

In spite of some metabolic treatments like levodopa (L-DOPA) and dopamine (DA) agonists, or neurosurgical intervention in the form of DBS, a full-restorative treatment for PD is not available at this time (55). As a result, since SCs secrete neurotrophic factors that prevent dopaminergic neurons from dying and stimulate them to regenerate, researchers are increasingly looking into stem cell-based treatments (55). To replace the damaged neurons, one of these treatment methods is autologous transplantation of patient-specific iPSC-derived dopaminergic neurons (21). This could potentially halt the neurodegenerative process and provide a sustainable, long-lasting dopamine supply. However, the transplantation of iPSC-derived dopaminergic neurons is not a compherensive treatment due to the potential deterimental effects caused by alpha-synuclein clustering (21). This protein is associated with death of dopaminergic cells and neural dysfunction. Therefore, additional methods are essential for the therapy to be effective. Here, research suggests that nanobodies produced by camels could potentially treat PD by reducing alpha-synuclein clumps in the neuropil and abnormal alpha-synuclein groups in the temporal cortex and striatum (21). The Lymphocyte Activation Gene 3 (LAG3) receptor facilitates the passage of harmful alpha-synuclein and tau, which inhibits inflammation and damage. Genetic

reduction and anti-LAG3 treatments can assist PD patients and address damage specific to certain brain regions (21).

Similarly, existing preclinical studies in animal models of PD suggest that DA cell replacement therapies could be an attractive alternative to oral DA medications (56). In experimental models of PD, DA cell replacement products manufactured from pluripotent stem cells can fully reverse motor impairments. In order to test the efficacy of this approach, a clinical trial on people with moderate PD is currently being conducted in Europe (56). In the STEM-PD trial, hESC-derived DA progenitor cells will be implanted into the putamen of patients with moderate Parkinson's disease as part of a phase 1/2 dose escalation trial. Participants with moderately advanced PD will participate in an open label trial using fetal ventral striatum tissue (56). In the next few years, patients with moderate disease may be eligible for some form of invasive interventional therapy. During the trial, the goal is to avoid treating early-stage patients who could be managed quite well with the current standard of care.

In addition to the transplantation of dopaminergic neurons derived from iPSCs, studies are also exploring the potential impacts of SC infusion. For example, in a case report by Vij et al., a 77 year old woman with Parkinson's disease received multiple infusions of bone marrow-derived MSCs (HB-adMSCs) in order to improve her symptoms and overall quality of life (57). She suffered from PD for 17 years, after being diagnosed in 2004. Even with the treatments, she experienced frequent falls, severe dyskinesia, and repeated freezing episodes. From the patient's adipose tissue, the isolated autologous adMSCs were extracted via liposuction. Over a period of 2.5 years, 26 infusions of MSCs were administered intravenously to the patient, 20 monthly and 6 bimonthly (57). She showed noticeable improvements in her posture after receiving 10 infusions of HB-adMSCs, and was no longer suffering from severe dyskinesia, exhibited no sign of tremors, and demonstrated an improvement in her ability to carry out daily living activities independently.

6.4. Stroke

Stroke is one of the most common types of neurological diseases associated with high mortality and disability (58). Stroke can be either ischemic, caused by blood vessel blockage, or hemorrhagic, due to vessel rupture. Ischemic stroke is treated by restoring blood flow, while hemorrhagic stroke is managed by removing blood clots and reducing pressure in the brain. (58). Even though they are commonly employed, both of these treatment methods have a short

window of effectiveness. Therefore, much of current research in the field is dealing with finding alternative treatment methods, poised to make more of an impact. One of these is the use of exosomes.

Exosomes, identified by markers such as tetraspanins (CD9, CD63, CD81), MVB-related proteins (Alix and TSG101), and heat shock proteins (HSPs), facilitate cell-to-cell communication by transferring proteins and genetic information (58). They carry miRNAs that mirror the state of the host cell and can influence gene expression and cellular pathways in recipient cells. Particularly, exosomal miRNAs may regulate biological processes post-ischemic stroke and contribute to brain remodeling (58). Thus, exosomes present a promising avenue as potential biomarkers and therapeutic agents in stroke management.

On top of exosome delivery, other research is looking into cell-based therapies, including MSC infusion, which has been shown to improve outcome after stroke (59). This is done following manufacturing of allogenic MSCs. These enable broad clinical application without concomitant immunosuppression. As reported by Levy et al., chronic ischemic stroke patients with chronic ischemia received allogeneic ischemia-tolerant MSCs as a single intravenous infusion (59). Under low oxygen (5%) conditions, MSCs were grown from a single human donor's bone marrow and cryopreserved in liquid nitrogen. Infusion of MSCs was followed up by constant monitoring until discharge from the telemetry unit for one year with tests of behavior, serology, blood chemistry, and cell counts, electrocardiogram, urine, and CT of chest, abdomen, and pelvis. A total of 36 subjects were enrolled and treated from March to December 2016. 26 out of 36 subjects received the planned dose within 2mL of the target, while 10 subjects did not receive 7.6ml as planned. 15 serious adverse events were reported, of which 2 were possibly related to the investigation product (59). All subjects improved in several outcome measures at 6-month and 12-month follow-ups. 36 patients with chronic stroke and substantial functional deficits were found to benefit from intravenous infusions of allogeneic MSCs: the 12 months of continued functional improvement, the proportion of patients with an excellent functional outcome increased from 11.4% to 27.3% at baseline and 35.5% at 12 months (59). MSC administered intravenously early after stroke localized to the lungs, spleen, and peri-infarct region, and patients' Mini-Mental Status Exam (MMSE) and Geriatric Depression Scale (GDS) improved significantly. Hence, the administration of allogeneic MSCs intravenously can potentially enhance functional recovery in stroke patients.

Besides mesenchymal stem cells in clinical trials, preclinical research is also being done on neural stem which demonstrates high potential improving neuroregeneration (60). As shown by Kalladka et al., human NSCs were studied in rats with induced middle cerebral arterial occlusion (MCAO), through implantation of CTX0E03 cells. These cells are clonally derived from human fetal cortical neuroepithelial cells and immortalized with c-mycER TAM conditional immortalization and c-mycER TAM transgenes (60). An early expansion of a single isolation of fetal cortical neuroepithelium results in improved behaviors after four weeks and increased striatal angiogenesis and neurogenesis (60).

6.5. Multiple sclerosis (MS)

Treatments for MS focus on the immune system, although many patients relapse or develop MS. No treatment has yet produced a significant and long-term neurological improvement (61). Nevertheless, many clinical trials and preclinical studies are underway, exploring the potential of stem cell-based therapies. One of these was the 2-stage, single-arm phase 2 clinical trial by Atkins et al., conducted throughout three hospitals in Canada (61). The trial consisted of MS patients ranging from 18 to 50 years of age with a poor prognosis, advanced disease activity, and Expanded Disability Status Scale (EDSS) score of 3.0 to 6.0. Autologous CD34-selected hematopoietic stem cell transplantation was perfomed after mobilization with cyclophophmid and filgrastim, busulfan and rabbit anti-thymocyte globuline (61). These were utilized to deplete the immune system prior to autologus hematopoietic stem cell transplantation (aHSCT). Following SCT, patients were evaluated every 2 months through clinical, laboratory, and MRI tests (61). Within 2 years, the test were carried out every 3 months, and then every 6 months. Throughout the extended follow-up period, all clinical and radiological hallmarks of disease-related CNS inflammation were eradicated without the use of disease-modifying drugs (61). Moreover, and after SCT, none of the 179 patients experinced clinical relapses. In the five months following aHSCT, none of the 237 scans showed Gd-enhancing lesions, and only one scan showed four new T2 lesions (61). If progressive loss of functional abilities before transplantation was observed, this was reflected in higher EDSS scores. In 6 cases, patients were able to come off disability insurance, while two had childeren via gametes donated or stored previously. Ultimately, and following the trial, 70% of patients demonstrated a decrease in symptom occurrence and severity following aHSCT, with better outcomes observed in younger patients who underwent the transplantation earlier (61).

Besides hematopoetic stem cells, other clinical trials employed neural stem-precursor cells (NPSc) (62). Since NPCs are known to differentiate into astrocytes and oligodendrocytes, they can relocate to specific biological niches or damaged areas to facilitate functional and structural repair by re-establishing functional interactions between neural and glial cells or activating endogenous neural cells (62). NPC-based therapies are a good choice in PMS due to their substantial pre-clinical evaluation of multiple therpeutic benefits. As shown by Genchi et al. NPCs provide long-term neuroprotection through a bimodal strategy that included differentiation into mature brain cells with reduced demyelination, astrogliosis, and axonal loss, as well as trophic support and anti-inflammatory actions, all while maintaining undifferentiated features (62). Because of their replicative ability in standardised and quality-controlled circumstances, NPCs produced from human foetal NPC (hfNPCs) can generate cell lines which can be exploited to develop new therapeutic approaches.

STEMS was the first phase 1 clinical trial to evaluate the safety of intrathecally implanted hfNPC in PMS patients (62). hfNPCs were generated form non-immortalized human fetal brain corpuscles obtained from human fetuses after a single 10/12 weeks gestation following selective termination of pregnancy. Subsequently, STEMS demontrated that hfNPCs may play a neuroprotective role by acting as a source of trophic factors and immunological modulators. The study comprised of hfNPCs injected into patients through a lumbar pucture, following removal of about 10 ml of CSF (62). After this, the patients received immune suppression in the form of tacrolimus 13 and prednisone 50 mg. Administration of these started the day before the procedure and tapered over 35 days. Overall, 12 patients received the drug product, 2 left the trial due to immunosuppressive therapy contraindication and 1 decided to spontaneouly leave the trial before transplantation (62). Interestingly, the study exhibited significant results. The survival of the patients treated with hfNPCs was 100% at least 3 years after the last treated patients. There were no noticeable side effects seen related to the procedure. During the 2 year follow-up period, patients were observed via MRI assessment and standard laboratory CSF analysis (62). The test have shown an upregulation of trophic factors and immune-related molecules and a downregulation of inflammatory chemokines in patients who underwent hfNPC transplantation, demonstrating neuroprotective function of hfNPCs (62). Additionally, as shown in CSF samples from patients who received low and high doses of hfNPC, hfNPCs also have the ability to increase the production of growth factors and cytokines (62).

7. Conclusion

In recent years, significant advancements have been made in the development of treatments for neurological disorders such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke, and amyotrophic lateral sclerosis. One of these includes stem cell transplantation. Stem cells, with their ability to differentiate into various cell types, play a pivotal role in tissue regeneration and growth promotion. They have demonstrated potential in improving patient quality of life and reducing future treatment costs.

Thus, for example, BM-MSCs that have been engineered to produce elevated levels of NTFs can have a beneficial impact in patients with mild to moderate ALS, with neuroprotective and anti-inflammatory effects observed in phase 3 clinical trials. Similar results were found by Petrou et al., where improvements in motor and respiratory function was observed in phase 2 clinical trials following intrathecal injection of autologous MSCs. Apart from in ALS, MSCs are also being used in clinical trials on patients with Alzheimer's disease. The best example of these are clinical trials by Xie et al. and Kim et al. who tested the effects of intranasal delivery of Aha-MSCS-Exos and intracerebroventricular injections of hUCB-MSCs, respectively. Both of these trials showed promising results, reporting improvements in patient's spatial memory and increase in neurogenesis.

Besides transplantation of SCs or SC-derived exosomes, clinical trials employing stem cells for treatment of brain disorders also utilize SC-derived neurons, specifically iPSC-derived dopaminergic neurons or precursors as reported by Shasty et al. and Kirkeby et al., respectively. The goal of these approaches is to replace the damaged dopaminergic neurons in patients with PD and, thereby, improve the patient's condition. Even though replacement of damaged neurons appears to be a promising approach, intravenous infusion of HB-adMSCs in patients with PD is also being evaluated.

Furthermore, and when it comes to treatment of stroke, a multitude of methods are being reported in the literature – ranging from SC-derived exosome delivery to SC transplantation. One of these is the transplantation of allogeneic ischemia-tolerant MSCs in a phase 1 clinical trial conducted by Levy et al. In the 12 months following intravenous delivery of MSCs, enhanced functional recovery in stroke patients has been observed.

Finally, since MS is characterized by increased inflammation resulting in demyelination of neurons in the CNS, clinical trials employing SCT are increasingly moving away from MSCs and

towards other stem cell types, including heamopoietic stem cells (aHSCs) and neural stem-precursor cells (NSPCs), with a goal of replacing damaged cells. For example, a phase 2 clincal trial by Atkins et al., which used aHSCs, has shown 70% decrease in simptom severity following treatment. Similarly, a phase 1 clinical trial by Genchi et al., employing delivery of hfNSPCs through lumbar pucture, demonstrated a downregulation of inflammatory chemokines 2 years following SCT, showing evidence of neuroprotective effects of NSPCs.

Even though SCT holds significant potential in neurology, some ethical and practical challenges exist. These mainly pertain to ensuring informed consent is obtained from donors, establishing of appropriate biobanking models and addressing the issues sorrounding the isolation, application and commercialisation of stem-cell based treatments, in particular those using ESCs. However, the remarkable versatility and differentiation capacities of SCs cannot be overlooked. Therefore, they present a promising treatment approach for patients suffering from disorders of the nervous system, including Parkinson's, Alzheimer's, MS, ALS and stroke.

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Biography

Eun Joo Park was born in Cheorwon Gangwon–Do, Republic of Korea. She grew up and was educated in Seoul. When she was young, she discovered a musical talent and began singing as a piano accompanist. She was accepted to the College of Arts and Music at Dongduk Women's University in Seoul. She had a strong interest in medicine and took a leave of absence to major in biology at the University of Hawaii in the United States. She received her Bachelor of Biology and was inducted into the Phi Beta Kappa society. After graduating, she completed multiple voluntary internships at hospitals in Israel, Ghana, and Oman. In addition, Eun Joo volunteered for a medical mission to assist with acute respiratory issues after a volcanic eruption in Guatemala. Before entering medical school, she completed a major course in vocal opera and performed her debut at a concert in Southern Italy. While in medical school, she arranged and performed in two significant concerts at the International Conference on Neurological Disorders and Neurorestoration between 2019 and 2024. In 2024, Eun Joo also did clinical rotations at the Cleveland Clinic in Abu Dhabi in the United Arab Emirates at the Department of Plastic Surgery and the Department of Cardiology. Eun Joo is in her final year of medicine at the University of Zagreb School of Medicine.