

## Stem Cell Approaches for Treatment of Neurodegenerative Diseases

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### Abstract

Neurodegenerative diseases are devastating age-related disorders severely affecting the patient, caregivers, and enormously increasing the financial burden of the nation. Despite decades of hard work both in laboratory and clinic, the effective treatment specifically designed for a patient is still far from reach. Stem cell therapy, though with several challenges including limited differentiation potential of adult stem cells, ethical issues with using embryonic and fetal stem cells, tumor formation upon transplantation of cells, etc., offers enormous potential for treatment of several neurodegenerative diseases. Pharmacological drugs currently available in the market on the other hand are mainly for alleviating the symptoms and not for treating the disease per se. The efficiency of drug delivery across the blood-brain barrier, stability, efficacy, and side effects these drugs show on patients are some of the hurdles pharmacological approach has to overcome. A detailed understanding of these complicated diseases at molecular level followed by the right combination of specifically tailored stem cell therapy and/or effective drugs e.g. MS-818 used to increase the endogenous stem cell population might be the best course of action in coming years for patients with little time left after their diagnosis.

**Keywords:** Pyrrolopyrimidine; Stem cell proliferator; Neurodegenerative diseases; Neural stem cells

**Abbreviations:** A $\beta$ : Amyloid- $\beta$  peptide; AD: Alzheimer Disease; ALS: Amyloid Lateral Sclerosis; APP: Amyloid Precursor Protein; (BBB): Blood-Brain Barrier; DA: Dopaminergic neurons; FGF: Fibroblasts Growth Factor; HD: Huntington Disease; L-DOPA: Laevo-3,4-dihydroxyphenylalanine; MAPK: Mitogen Activated Protein Kinase; MS-818: 2-piperadino-6-methyl-5-oxo-5, 6-dihydro (7H) pyrrolo [2,3-d] pyrimidine maleate; NGF: Nerve Growth Factor; NMDA: N-methyl-D-aspartate receptors; NPC: Neuronal Precursor Cells; PD: Parkinson Disease; ZFX: Zinc Finger and X-linked transcription factor

### Introduction

The nervous system and brain via a well-orchestrated network of electrical signals control the basic activities e.g. muscle movement, senses, speech, memories, thoughts, and emotions in humans. There are many forms of nerve diseases that in humans limit these functions in different ways. Neurodegenerative diseases are the result of the phenomenon of neurodegeneration which is an umbrella term used for the progressive structural and functional impairment of neurons eventually resulting in their death [1]. Acute neurodegeneration could result from stroke or trauma leading to damage and death of neurons at the site of injury, whereas chronic form develops over age and might result in loss of specific neuron subtype (e.g. in Parkinson Disease) or generalized population (e.g. in Alzheimer's Disease and Huntington's Disease) [2-5]. The different neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS) etc. reveal similarities including accumulation of insoluble protein aggregates, apoptosis, compromised communication system etc. at the cellular level [6-10]. With high morbidity and mortality rates, these diseases have a huge social and economical impact [11]. According to Alzheimer's association the number of people affected with Alzheimer's disease in US alone is expected to triple in 2050 to a figure of ~16 million, costing \$1.2 trillion in health care, long-term care and hospice care [12]. Not to mention that the emotional impact all of the aforementioned age-related disorders have on patients and their caregivers is hard to estimate and express in words. Unraveling the molecular mechanism underlying these complex diseases through scientific investigation would lay foundation for therapeutic intervention towards long-term

goal to ameliorate and cure them [13]. We understand that these areas of research are vast and fast growing; the purpose of this review is to evaluate some of the currently available stem cell transplantation and pharmacological approaches and suggest a new class of compounds increasing stem cell populations as a safer and noninvasive approach for treatment of a few selected neurodegenerative diseases.

### Conventional Pharmacological Approach

Alzheimer's disease (AD) considered to be a protein misfolding disorder damages and kills neurons and is believed to result from a combination of genetic, lifestyle, and environmental factors [14]. The two hallmarks of Alzheimer's: 1) accumulation of plaques made up of small peptides of beta-amyloid which is a fragment resulting from aberrant cleavage of amyloid precursor protein (APP) damages neurons by interfering with the communication system (8) 2) Neurofibrillary tangles which are made up of abnormally twisted hyperphosphorylated tau proteins causing damage and death of neurons by interfering with their transport system [3,14]. The common conventional therapeutic approaches include use of cholinesterase inhibitors by delaying the degradation of acetylcholine released from the synapse [15]. The N-methyl D-aspartate (NMDA) receptor antagonist named memantine or Namenda (generic) work on the glutamatergic system by blocking NMDA receptors and is another commonly used drug to alleviate the symptoms of AD [16]. Other conventional drugs are based on reducing A $\beta$  production by modulating secretase activity, reducing A $\beta$  aggregation, promoting A $\beta$  clearance, targeting tau phosphorylation and assembly, immunotherapy against A $\beta$ , altering

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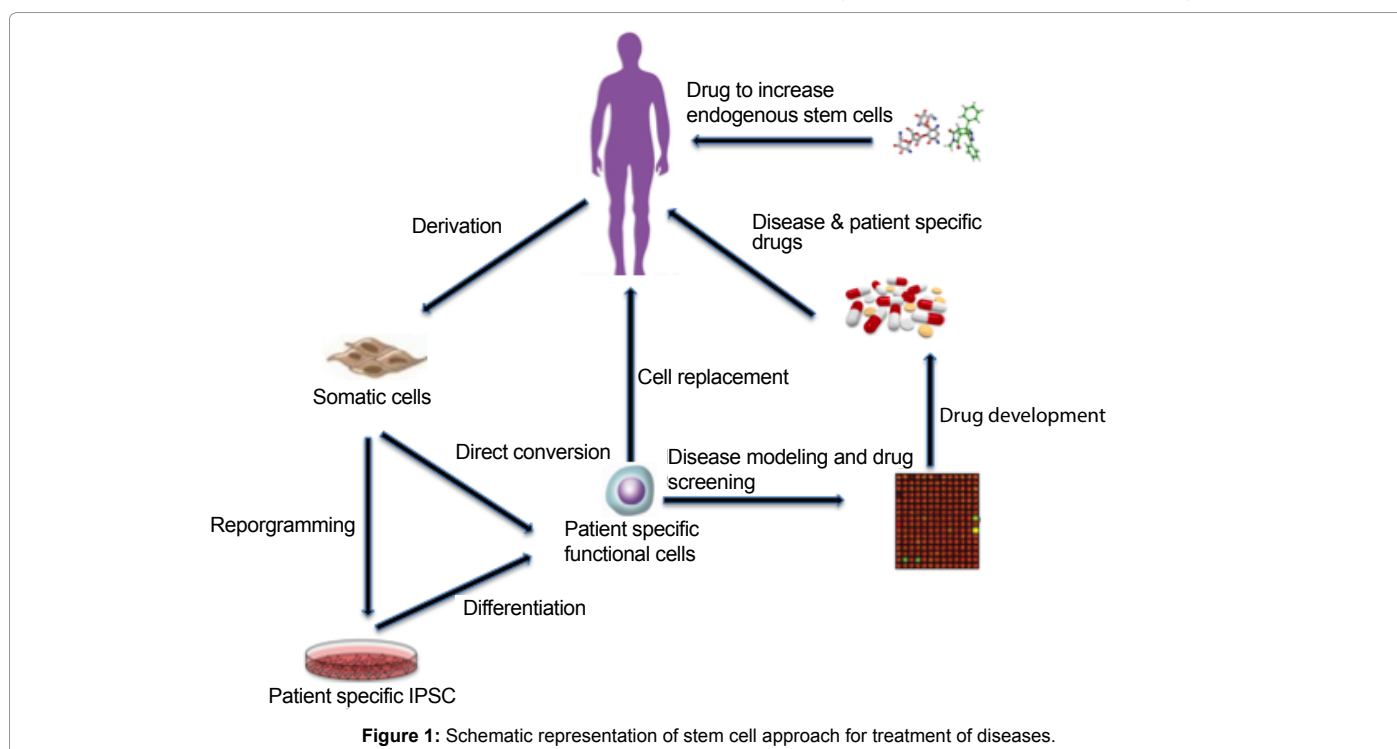
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metal ion's interaction with beta-amyloid, oxidative stress etc. [17-27]. Cholinesterase inhibitors and NMDA receptor antagonists provide symptomatic relief to patients but fail in curing the underlying disease [28]. The conventional drugs targeting A $\beta$  and tau failed in phase III clinical trials [23]. Parkinson's disease (PD) results from the death of dopamine producing cells in *substantia nigra* region of the midbrain [29]. The damaged neurons have been found to abnormally accumulate alpha-synuclein bound to ubiquitin not allowing the complex to be directed to proteasome for degradation, eventually accumulating proteinaceous cytoplasmic Lewy bodies [30]. Carbidopa/Levodopa or L-Dopa (Sinemet) is the most potent and effective conventional medication for PD [31]. However, the use of L-DOPA was discontinued due to movement problems (motor fluctuations) including dyskinesias, wearing-off effect, dystonias, etc. Many other dopamine agonists stimulating parts of the brain influenced by dopamine have also been used on patients [32,33]. Other anticholinergics decreasing the activity of acetylcholine regulating movement are helpful for tremors [34]. MAO-B inhibitors used for the treatment block enzymes in the brain that are responsible for breaking down dopamine [35]. They are used to make levodopa last longer or reduce the amount required. When selegiline (Eldepryl, Zelapar) is taken with levodopa, it results in dyskinesias, hallucinations etc. [36]. Rasagiline (Azilect) when taken without levodopa may result in headache, joint pain, indigestion, depression etc. [37]. COMT inhibitors on the other hand representing the newer class of drugs for PD inhibit the action of catechol-O-methyl transferase, an enzyme involved in degrading neurotransmitters. They have no direct effect on PD symptoms but have been found to prolong the effect of L-Dopa by blocking its metabolism [38]. Two of the pharmaceutical examples tolcapone and nictapone were found to be toxic to the liver [39]. All of these drugs help alleviate the symptoms of PD but none of them have yet been able to cure or reverse the effects of the disease. Huntington's disease (HD) is an inherited disease caused by a mutated form of the huntingtin gene where excessive CAG repeats result in formation of an unstable and aggregation-sensitive protein causing the progressive degeneration of GABAergic medium

spiny neurons (MSNs) in the brain [5,40]. It affects patient's abilities to perform basic functions usually resulting in movement, cognitive, and psychiatric disorders. The current drugs help manage the symptoms but cannot prevent the degeneration or cure the disease. Several drugs to treat movement disorders e.g. Tetrabenazine (Xenazine), antipsychotic drugs, antidepressants, and mood-stabilizing drugs are currently being used in patients with HD [41]. Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease specifically affects motor neurons eventually resulting in their death. As a result, the brain's ability to initiate and control muscle movement is lost [42]. Riluzole (Rilutek) is the only FDA approved drug for ALS. It slows down the disease's progression possibility by decreasing high levels of glutamate seen in ALS patients. This too causes side effects including dizziness, gastrointestinal complications, and abnormalities in liver function [43]. Another drug named Retigabine, an anticonvulsant, originally recommended for epilepsy, is a potassium channel opener, has recently been shown promising for ALS. Several adverse effects including drowsiness, dizziness, slurred speech etc. were noticed in phase II clinical trial for epilepsy; the side effects of this drug in ALS patients are currently under investigation [44].

### Stem Cell Transplantation Approach

Stem cell therapy has been proven to be promising for treatment of several human diseases [45,46]. The use of embryonic stem cells (ESC) and fetal stem cells (fetal proper stem cells and extra-embryonic fetal stem cells) for stem cell research faced several ethical issues in the past [47]. Induced pluripotent stem cells (iPSC) on the other hand are adult cells that have undergone reprogramming to an embryonic stem cell-like state by expression of genes responsible for maintaining the characteristics of ESCs [48]. IPS technology has broad scope of application possibilities as the adult cells can be isolated, differentiated into cells of interest in the plate, and injected back to the same patient, thus avoiding the complications of rejection post transplantation (Figure 1) [49]. Though adult stem cells are found in all the organs and theoretically can differentiate into different cell types, the differentiation



potential exhibited by them is limited. Since patients suffering from neurodegenerative diseases exhibit different neuronal pathologies and complications, deciding on the course of treatment using stem cell therapy involve many considerations [46,50]. The treatment objectives in these cases have been centered on replacing damaged or dead neurons with new ones and/or augmenting the brain environment by using engineered stem cells expressing brain-derived growth factors [51]. Neural stem cells (NSCs) are a population of adult cells with self-renewal and differentiation capacities. A major focus has been to use NSCs to combat age-related neurological disorders [52]. When NSCs were injected into the hippocampal area of the brain of transgenic AD mouse model, the cognitive function improved with no change in the A $\beta$  plaques or neurofibrillary tangles [53]. Interestingly, in 3xTg-AD mice, which develop both amyloid and tangle pathology, the clearance of intraneuronal A $\beta$  plaques by immunotherapy rescues the cognitive impairment. However, the reemergence A $\beta$  pathology in antibody-treated mice again results in cognitive deficits [54].

It was also seen in the study that the improved cognition was a result of increased brain-derived neurotrophic factor (BDNF) [53]. The high levels of APP in the brain not only reduce NSCs, but also increase glial differentiation of transplanted stem cells, hence negatively affecting the outcome of therapy [55]. We previously showed significantly high levels of neurogenesis from transplanted NSCs in APP transgenic mice when APP level was reduced upon phenserine treatment [56]. Several research studies on expression of growth factors like vascular endothelial growth factors (VEGF), brain-derived neurotrophic factors (BDNF), nerve growth factor (NGF) etc. have shown these to have neuroprotective effects [57-60]. Since PD results from progressive death of dopaminergic neurons (DA) neurons, stem cell therapy is focused on replacing the same in *substantia nigra* of the brain. Studies show functional recovery upon grafting both embryonic stem (ES)- and mesenchymal stem cells (MSC)-derived DA neurons into rat PD model [61,62]. Transplantation of stem cells engineered to produce growth factors like BDNF, VEGF, GDNF etc. have been shown to protect DA neurons and functional recovery in transgenic PD models [62,63]. As HD results from loss of GABAergic neurons, cellular therapies used are based on replacing dead neurons and also supplementing nerve growth factors in some cases. Transplantation of neural tissue and striatal grafts showed for the first time that MSNs could integrate and form circuitry in transgenic HD models [64]. NPCs engineered to overexpress GDNF protected neurons and promoted functional recovery in rodent models of HD [65]. In ALS that is currently considered incurable, the degradation of motor neurons that connect spinal cord to the muscles makes the life expectancy two to five years after diagnosis [66]. It has been shown that mouse embryonic stem cells can be differentiated into motor neurons and when transplanted into spinal cord of embryonic chick, motor neurons forms connections with skeletal muscles [61]. Thus in chick model replacement of dying motor neurons with healthy ones is a possibility but since body holds hundreds of different motor neurons, time will tell whether it will be practically feasible to convert stem cells into specific motor neuron and transplant to ALS patient in need [67].

There are many published studies on efforts made using approaches of stem cell therapy and pharmacology to treat neurodegenerative diseases (Figure 1). However, both approaches have met with several challenges in the past [68,69]. Although stem cell therapy has met with some significant success when utilized for treatment of neurodegenerative disease, as mentioned above there are several

important considerations and risk factors associated with this approach. The limited number of donors, intrinsic properties of the cell type used, difficulties in controlling the differentiation potential of iPSCs, immunorejection in case of allogeneic transplantation and subsequent use of immunosuppressants, growth of tumor resulting from injection of mixed populations of differentiated and undifferentiated cells etc. are some of the complications posed by this approach and ultimately putting patients at risk [70]. Recently, zinc finger and X-linked transcription factor (ZFX) was shown to play role in maintaining self-renewal and tumorigenic potential of glioma stem cells (GSCs) through upregulation of c-Myc expression. Thus, targeting ZFX could represent one of the promising strategies to overcome the risk of tumor formation posed by injecting mixed population of stem cells through inducing apoptosis or differentiation of brain tumor [71]. The pharmacological treatments on the other hand are mostly limited by the low permeability of compounds to cross the blood brain barrier (BBB) along with the side effects these compounds have shown in patients undergoing clinical trials [72].

### Pharmacological Approach to Increase Stem Cell Number

Blood-brain barrier (BBB) which acquired selectivity during the course of evolution for the very purpose of protecting the brain against potentially harmful materials floating around in the blood supply actually makes pharmacological means of administering small molecular compounds to central nervous system more challenging [73,74]. Efforts are being made to increase the lipophilicity of these compounds to increase their chances of getting internalized in the brain. The use of nanotechnology to attach immunoglobulins, liposomes, and nanoparticles to these compounds for more efficient delivery across the blood-brain barrier has attracted many researchers in recent years [75]. Thus synthetic biology and precision nanomedicine aid in making drug delivery more effective which is one of the important criteria towards developing a safe and efficacious drug [76].

Small molecules have also been routinely used as a tool in stem cell research laboratories for different purposes including but not limited to maintenance of stem cells in undifferentiated state in culture to increase proliferative potential of pluripotent cells, reprogramming, differentiation, and manipulation of different signaling cascades within the cells [77]. They offer several advantages such as high permeability, being chemically defined, high purity and stability, more economic in comparison to peptides and growth factors, and flexibility of playing around with concentration to alter the effect [78]. Many such useful compounds affecting Wnt signaling pathway by inhibiting glycogen synthase kinase-3 (GSK3-beta) are known to promote the self-renewal of embryonic stem cells [79]. Inhibitors of TGF- $\beta$  family type I receptor-like kinase (ALK5) preventing Smad2 phosphorylation and TGF- $\beta$  pathway can increase the self-renewal of induced pluripotent stem cells [80]. Similar to other stem cell types, the addition of small molecules to culture media can enhance neuronal proliferation and differentiation [81]. Some of the other commercially available compounds can selectively inhibit p38 mitogen-activated protein kinase (MAPK), which may be an intrinsic negative regulator of NSC proliferation during early brain development resulting in neural stem cell proliferation [82]. Additionally, 1-Oleoyl lysophosphatidic acid (LPA) sodium salt, an agonist of LPA receptors, inhibits human ESC-derived NSC differentiation [83]. Some of the P2Y receptor agonists maintaining neural stem cells in undifferentiated; proliferating, self-

renewing state can be utilized for treatment of neurodegenerative diseases [84]. The list of such molecules utilized for maintaining pluripotency in laboratory is increasing, thus holding a lot of promise for these to be used in treatment of human diseases.

### MS-818 as an Endogenous Stem Cell Proliferator

The currently available medications for neurodegenerative diseases only improve the symptoms and not treat the underlying disease. The fact that they show side effects in patients undergoing treatment calls for further refinement in the process of drug development. Different compounds including neurotransmission enhancers, anti-inflammation molecules, antioxidants, neurotropic factors, hormones have been utilized for developing promising therapies for neurodegenerative diseases [85]. Interestingly, different disease conditions, stressors, and the process of aging itself are known to negatively affect neurogenesis from endogenous NSCs highlighting the important roles played by endogenous factors [86]. So it is logical to target compounds resembling these factors for developing effective therapies. Several growth factors, peptides, and neurotransmitters including bFGF, TGF- $\alpha$ , insulin-like growth factor-1, monoamine neurotransmitters, collagen peptides etc. have been shown to enhance neurogenesis [87-91]. However, their use as a pharmacological compound has always been limited by the stability and their ability to cross the BBB. This makes a case for developing compounds that are highly permeable to the BBB, stable, safe, and efficacious. Several small molecules including purine analogs, AMPA receptor potentiators, neuroleptins, P7C3 class of neuroprotective compounds, and lithium etc. have been reported to enhance neurogenesis in different animal models [92-96].

We claimed in our patent (US 20110237574 A1), the application of MS-818's (2-piperadino-6-methyl-5-oxo-5, 6-dihydro (7H) pyrrolo [2,3-d] pyrimidine maleate) ability to increase the stem cell number to be utilized for treatment of several human diseases. MS-818, a bicyclic pyrrolopyrimidine compound was originally synthesized in the late 1990's by Awaya et al. [97] as an antimicrobial agent and later on shown to have neurotropic effects upon cultured human and mouse neuroblastoma cells, and upon nerve growth factor (NGF)-induced PC12 cell differentiation. Although initially thought to regulate neurite outgrowth, MS-818, since then has been shown to perform many important neural and non-neural functions in different animal models.

In our hands, MS-818 showed 7-fold increase in NSC population in the aged rats, which is much higher when compared with other aforementioned compounds [98]. To investigate the effect of MS-818 on proliferation of endogenous stem cells, MS-818 (3 mg/kg/day) was injected for 5 consecutive days into 27-month old rats, whereas control animals received the same amount of saline. Bromodeoxyuridine (BrdU) (100 mg/kg/day) was then injected for 3 days. The brains were removed after 24 hours of the last injection and fixed for immunohistochemical detection of the proliferating cells through BrdU staining. The number of BrdU positive cells increased more than seven folds in the cerebral cortices of MS-818-treated animals compared to controls, indicating an increased neural stem cell population in the brain. In the area of the subventricular zone, a significant increase not only in the proliferation but also in the migration of stem cells was found.

MS-818 plays a role in reduction of infarct size and amelioration of sensorimotor dysfunction as indicated by the results of forelimb and hindlimb placing tests following permanent focal cerebral ischemia in rats, thus making this small molecular compound a candidate for the treatment of focal cerebral ischemia [99]. It has been shown to enhance functional recovery of damaged sciatic nerves resulting from crush

injury by promoting axonal sprouting through indirect activation of Schwann cells and possibly by activation of local production of nerve growth factors (NGFs) [100]. It promotes axonal survival by inhibiting cell death in a dose dependent manner and enhances the neurotrophic actions of bFGF through stimulation of signaling cascades that may increase MAPK levels within neurons [101]. MS-818 activates Schwann cells, which migrated from proximal stump inducing axonal elongation *in vivo* [102].

Shimoda et al. [103] demonstrated dose-dependent suppression of UVB-induced increase in tumor necrosis factor alpha (TNF- $\alpha$ ) that is one of the cytokines inducing apoptosis by MS-818. MS-818 protects epidermal cells from UVB-induced damage and also suppresses melanogenesis in B16 melanoma cells through downregulation of tyrosinase expression mediated by microphthalmia-associated transcription factor (MITF) and extracellular signal-regulated kinase (ERK) making it a strong contender for protective and whitening agent towards applications in cosmetics [103]. It has been shown to possess neurotrophic activity and to enhance basic fibroblast growth factor (bFGF)-induced angiogenesis *in vivo* [104]. MS-818 affects endothelial cells directly and induces migration of tubes and their formation by endothelial cells *in vitro* [105]. MS-818 also mobilizes endothelial progenitor cells from the bone marrow and potentiates their differentiation to endothelial cells. Thus, MS-818 promotes both angiogenesis and vasculogenesis [105]. Sugiyama et al. [106] explored MS-818's effect on muscle regeneration and showed that the proliferation and differentiation of activated satellite cells and the fusion of myotubes to form immature myofibers were accelerated upon treatment with this compound [106]. MS-818 administered at a dose of 5 mg/kg intraperitoneally for 14 consecutive days promotes the fracture healing process in rat fracture model through enhancement of the effect of bFGF on endochondral ossification [107]. Its effect on *in vivo* gastric mucosal repair using a wound repair model with primary cultured gastric epithelial cells from rabbit was demonstrated by Watanabe et al. [108] MS-818 when administered alone had no effect but enhanced EGF-induced acceleration of gastric epithelial cell proliferation and migration at a dose of 10-100  $\mu$ M [108].

We demonstrated in our patent (US 20110237574 A1) MS-818's role in increasing corneal and retinal stem cell number. Ophthalmic formulations when applied upon removal of lachrymal gland resulted in increased stem cell population in cornea in rat model. When 10  $\mu$ g as one time injection of MS-818 was injected directly into the vitreous cavity of rat followed by BrdU administration, a dramatic increase in the number of BrdU-positive cells was seen in the retinal ciliary marginal zone after three days. Thus, MS-818 might find application in treatment of eye diseases, which affects millions in US and cost a fortune. The formulations we used for exploring MS-818's role in endogenous stem cell proliferation in eye were found to be slightly acidic. We are currently investigating whether increasing the pH of formulation to physiological range by changing the salt would improve its permeability across BBB, eventually resulting in higher stem cell proliferation potential. Different biochemical and biophysical assays will be used to screen these formulations for their permeability, solubility, and stability over time. The exact mechanism of action is not yet known for MS-818; however, there are some reports on it acting through MAPK [105]. Table 1 summarizes its functions, model systems used, and possible mechanisms of action. The quick biological response shown by MS-818, and its IC<sub>50</sub> being in nanomolar range possibly suggests some other mechanism of action. It could possibly be working through purinergic receptors, which play roles in proliferation and migration of neural stem cells, vascular reactivity, cytokine release, and

Function	Model	Possible mechanism	Reference
Regeneration of peripheral nerve fibers	Crush injury in mice	Not known	[109]
Promotion of angiogenesis induced by basic FGF (bFGF)	Chorioallantoic membrane (CAM) assay	Through bFGF	[104]
Regeneration of peripheral nerve	Rat transected peripheral nerve in a silicone tube	Not known	[110]
Activation of migratory schwann cells in peripheral nerve regeneration	Transected peripheral nerve in mice	Not known	[102]
Promotion of neuronal survival and enhancement of the neurotrophic actions of bFGF	Cultured neurons isolated from mouse cortices	Through enhancing MAPK levels	[101]
EGF-induced restoration of gastric epithelial wounds <i>in vitro</i>	Wound repair model with primary cultured gastric epithelial cells from rabbit	Not known	[108]
Enhancement of functional recovery of damaged sciatic nerves	Crush-injured sciatic nerves of rats	Through indirect activation of Schwann cells and possible activation of local NGF	[100]
Promotion of fracture healing process	Rat fracture model	Through enhancement of the effect of bFGF on endochondral ossification	[107]
Acceleration of early muscle regeneration and enhancement of muscle recovery after surgical transection	Wounded area (damaged and gap areas) of cut muscle in adult rat	Not known	[106]
Reduction of infarct size and amelioration of sensorimotor dysfunction following permanent focal cerebral ischemia	Rat model of focal ischemia	Not known	[99]
Regeneration of injured peripheral nerves	Cut-and-suture model of the right sciatic nerve of Wistar rats	Not known	[111]
Promotion of angiogenesis and vasculogenesis	Endothelial & mouse embryonic stem cells	Through activation of MAPK	[105]
Protection of epidermal cells from UVB-induced damage and suppression of melanogenesis in melanoma cells	Human keratinocyte HaCaT cells	Downregulation of tyrosinase expression mediated by microphthalmia-associated transcription factor (MITF) and extracellular signal-regulated kinase (ERK)	[103]

**Table 1:** Biological functions and possible mechanisms of action of MS-818 in different model systems.

apoptosis etc. It is also possible that MS-818 works through cytokine receptors, or through altering the gene expression.

Not only MS-818 but also any molecule that acts through any of the above mentioned mechanisms to proliferate the endogenous stem cell population could be a good candidate for a generalized stem cell proliferator to be utilized for treatment of neurodegenerative diseases. The studies performed in our laboratory show that MS-818 is highly permeable to the BBB and nontoxic even at very high dose. Our long-term goal is to develop oral pills of MS-818 as a stem cell proliferator. However, towards that goal its stability in highly acidic environment and adsorption in stomach have to be nailed down first.

## Conclusions

The absence of effective treatment for neurodegenerative diseases put enormous monetary and emotional burden on the nation. A lot of progress has been made in the last few decades utilizing stem cell therapy and pharmacology towards that goal. Although these endeavors have been successful in improving the symptoms of these diseases; designing an effective stem cell therapy or medication specifically tailored for each patient taking in consideration his age, hereditary, stage of illness, and other complications will certainly keep scientists and physicians busy for quite some time. As the patients suffering from neurodegenerative diseases have not much time left after their diagnosis, finding the right cure for them would certainly require collaboration among people from different walks of life e.g. scientists, physicians, clinicians, medicinal chemists, pharmacologists etc. As a means to increase stem cell number, treatment with MS-818 would serve as a powerful tool of regenerative medicine. Increasing endogenous stem cell population through drug treatment can become the future treatment of choice. As different disease conditions affect the differentiation pattern of newly formed stem cells, this demands for a more in-depth monitoring of how the patient's brain environment is affecting their neurogenesis.

## Competing Interests

The authors declare that they have no competing interests.

## Authors' Contributions

SA contributed to the framework, composition, and writing of the review. KS contributed to the conception, composition and editing of the review.

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