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Review

Mining human clinical waste as a rich source of stem cells for neural regeneration

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SUMMARY

Neural diseases are challenging to treat and are regarded as one of the major causes of disability and morbidity in the world. Stem cells can provide a solution, by offering a mechanism to replace damaged circuitry. However, obtaining sufficient cell sources for neural regeneration remains a significant challenge. In recent years, waste-derived stem(-like) cells (WDS-lCs) extracted from both prenatal and adult clinical waste tissues/products, have gained increasing attention for application in neural tissue repair and remodeling. This often-overlooked pool of cells possesses favorable characteristics; including self-renewal, neural differentiation, secretion of neurogenic factors, cost-effectiveness, and low ethical concerns. Here, we offer a perspective regarding the biological properties, extraction protocols, and pre-clinical and clinical treatments where prenatal and adult WDS-lCs have been utilized for cell replacement therapy in neural applications, and the challenges involved in optimizing these approaches toward patient led therapies.

INTRODUCTION

The adult nervous system has limited regenerative capacity, which is why loss or dysfunction of neurons is permanent post-injury or disease.[1,2] Cell replacement therapy (CRT) has the potential to replace damaged cells and tissues.[3] However, the limited number of stem cells (SCs) in neural tissues and the complications associated with their isolation and expansion[4] make it essential to explore other autologous stem cell sources. Recent studies have demonstrated the presence of SCs in human waste-derived products, which have many advantages over other sources of SCs. In this review, we provide an overview of the properties of the SCs extracted from human biological waste sources and their potential in neural cell regeneration.

Cellular sources in stem cell therapy for neural regeneration

SCs can be found in different tissues in which they rejuvenate or repair the aged/injured cells.[5] Based on the SCs' capability to differentiate into different cell lineages, they are categorized as totipotent, pluripotent, multipotent, and unipotent SCs. Some SC types applicable to neural CRT can be seen in Table 1 with their different differentiation capacities, advantages, and disadvantages. For more discussion on this please refer to the supplemental information section. Here, we will focus on neural stem cells or those that have been previously explored for neural applications.

As a new source of cells for the treatment of neural diseases, cells with regenerative potential can be extracted from otherwise discarded human waste tissues. For instance, cells that express the markers of MSCs and display high plasticity may be beneficial to CNS repair and can be obtained from prenatal tissues (which include the amniotic membrane, amniotic fluid, placenta, and umbilical cord [UC][15]), as well as postnatal tissues (including urine, waste adipose tissue from liposuction surgery,[16] and dental pulps) that are normal discarded as clinical waste. Traditionally these have not been considered a valid source, due to differences in self-renewal capacity, differentiation ability, growth kinetics, and immunomodulatory ability,[17,18] and the debate about defining cells extracted from parts of the body other than "traditional" bone marrow as mesenchymal stem cells (MSCs) or stromal cells[19] continues. Here, cells derived from waste tissues that demonstrate high plasticity

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Table 1. Applicable SCs with various differentiation capacities in neural CRT

Differentiation capacity	Applicable SCs source in neural CRT	Advantages	Disadvantages	Reference
Totipotent	Blastomere	• Perfect potential in differentiation to all cell types	• Probability of tumorigenesis and impaired behavior of cells • The risk of immunogenic issues • Ethical issues	Ruff et al.[6]; Adami et al.[7]
Pluripotent	Embryonic SCs (EmSCs)	• Good potential in differentiation to various cell types	• Probability of tumorigenesis and impaired behavior of cells • Risk of immunogenic issues • Ethical issues	Klimanskaya et al.[8]; Taupin[9]; Guha et al.[10]
	Induced pluripotent SCs (iPSCs)	• Good potential in differentiation to various cell types • Providing the exact genome of the patient	• Difficult culturing, differentiation, and maintenance process • High batch to batch heterogenicity • High cost	Bonaventura et al.[11]; Barral and Kurian[12]
Multipotent	Mesenchymal SCs (MSCs)	• Good potential in differentiation to cell types of a specific germ layer • Various available sources • No risk of immunogenic issues	• Invasion of the isolation process for the patients • Risk of infection for patients after isolation	Chao-Han et al.[6]; Biehl and Russell[13]; Alessandrini et al.[14]
Unipotent	Somatic cells (neural cells)	• No risk of immunogenic issues • Proper match as the prototype cells for replacing lost neural cells after injury	• Limited self-renewal as well as migration capacity • Invasion of the isolation process accompanied by damage to the intact brain	Taupin et al.[9]; Alessandrini et al.[14]

(either prenatal or postnatal tissues) are defined as waste-derived stem-like cells (WDS-IC). These WDS-ICs have many advantages over other sources of SCs, including a facilitated cellular extraction procedure with minor invasion, low cost, high cell content, and autologous isolation, which reduces the risk of eliciting an immune response, making them ideal candidates for a CRT in the nervous system. The CRT with these WDS-ICs can be done through direct administration of the cells to the nervous tissues, which suffer from spreading the cells to the non-target tissue, or via a biomaterial that both provides a good environment for the cells to either differentiate before administration or after that in the body and high cell retention[20] (Figure 1). While these WDS-ICs have the potential to be used for regeneration of different tissues, this review will focus on the cells with the ability to express MSC markers for neural applications.

HUMAN WDS-ICs IN NEURAL REGENERATIVE MEDICINE

Prenatal WDS-ICs

Prenatal WDS-ICs includes cells isolated from cord blood and discarded tissues at the time of birth, such as the fetal membrane (amnion and chorion), placenta, or UC.[21] Although the plasticity of prenatal WDS-ICs is between that of adult SCs and embryonic SC (EmSCs) (Figure 2)[22] this is balanced against the benefits of prenatal WDS-ICs, including lower ethical issues, low immunogenicity, easy-to-scale production,[23] high differential potency, and faster expansion compared to adult SCs. They are safe, collected in an non-invasive fashion, and therefore their potential in clinical applications attracts huge attention.[21] Hematopoietic SCs (HSCs), endothelial progenitor cells, and mesenchymal stem-like cells (MS-ICs) can be isolated from umbilical cord blood (UCB) as well as from Wharton's jelly of the UC, amniotic fluid, and the placenta. While all of these kinds of cells can be used for neural regeneration through direct or indirect differentiation, because of the challenges regarding the process of cell reprogramming, MS-ICs are the most common type of SCs that are used in neural regeneration. Therefore, the focus of this review is the ability of MSCs from clinical waste tissues where they can be extracted in sufficient numbers to be suitable for neural regeneration. However, there may be some confusion about MSCs' mesodermal origin and their ability to regenerate ectodermal-derived neural cells. Accordingly, it should be noted that some MSCs originate from the neural crest in mesoderm that has a wide range of abilities to differentiate into different cell types. However, the information about the origin of these cells after maturation and also the mechanism behind the differentiation of these cells into neural cells are insufficient and not completely clarified in the literature.[24]

Prenatal WD-ISCs can be distinguished based on their origin into three groups, which are discussed in the following subsections.

Amnion-derived stem-like cells

Interestingly, multipotent stem-like cells (S-ICs) can be derived from the amniotic fluid or membrane and express markers associated with the pluripotent EmSC phenotype (NANOG, OCT-4, and SOX-2),[25] immunosuppression (CD73),[26] cell-cell and cell-matrix interaction (CD90),[27] and angiogenic activity (CD105).[28] Also, amnion-derived stem-like cells (AmS-ICs) are inexpensive, readily available, and have high expandability, neuroprotective function, low teratogenic ability, immunomodulatory, and anti-inflammatory properties.[29–31]

Several types of SCs can be isolated from the amniotic membrane, including amniotic epithelial stem-like cells (AmES-ICs) from the amniotic epithelium and amniotic mesenchymal stem-like cells (AmMS-ICs) from the amniotic mesoderm. Also, in the case of amniotic

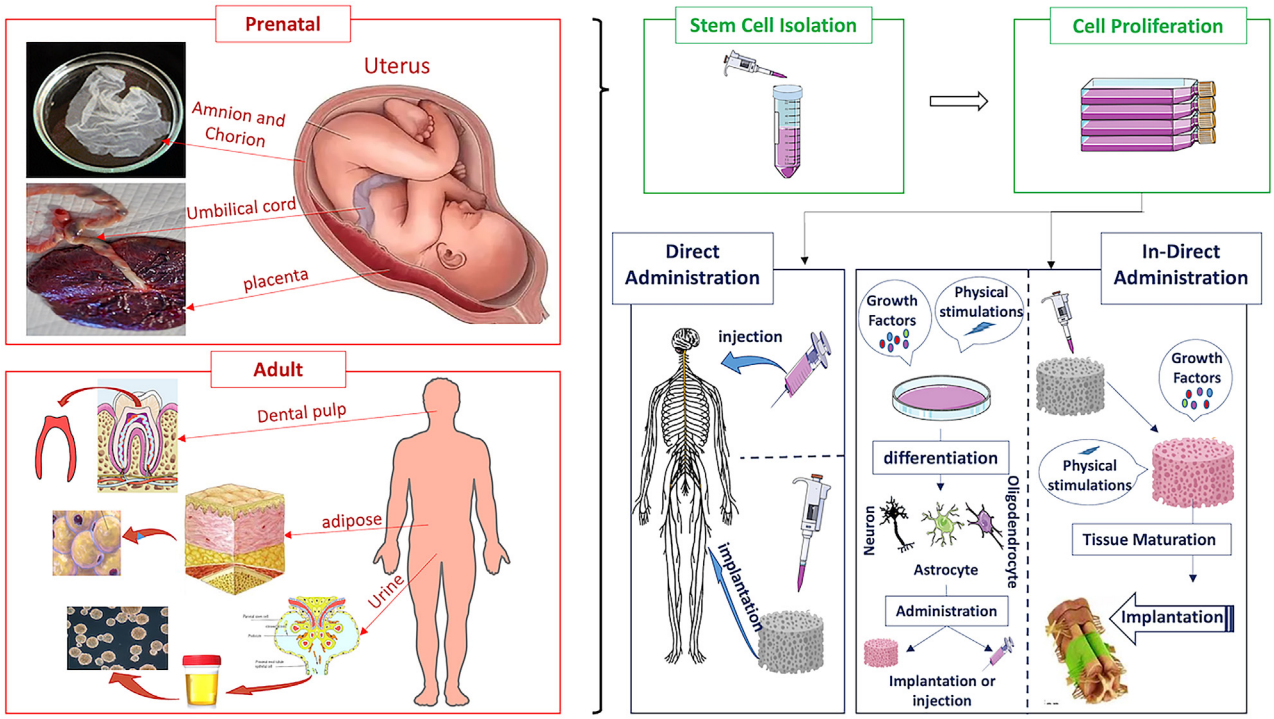

Figure 1. Isolation of WDS-ICs from either clinical prenatal or adult waste and the way of their administration in the CRT of nervous system
This figure contains modified elements from Servier Medical Art (http://smart.servier.com).

fluid-derived SCs (AmFS-ICs) along with heterogeneous cellular populations that are present, the major cells are amniotic fluid mesenchymal stem-like cells (AmFMS-ICs), which show MSC features.[31–33]

AmS-ICs can be easily isolated during prenatal checkups from the amniotic fluid using an amniocentesis procedure or upon removal of the amniotic membrane after birth. The extraction methods are carried out without destroying human embryos and therefore have fewer ethical concerns.[34] Moreover, enough SCs for therapeutic applications can be obtained from a small biopsy of either amniotic fluid or membrane.[35–37] Similarly, it is indicated that the broad multipotency of AmFS-ICs makes them ideal for differentiation into osteogenic, adipogenic, myogenic, neurogenic, and endothelial lineages.[38]

Due to the regenerative ability and lack of immune rejection associated with suppression of T and B cell responses, AmS-ICs have undergone several pre-clinical trials in the contexts of wound healing,[39] infertility,[40] lung diseases,[41] non-union fractures,[42] and neural disorders such as spinal cord disease and cerebral palsy.[43] For example, the world's first clinical trial aiming to investigate the efficacy and safety of using allogenic AmES-ICs in ischemic stroke patients was completed in Australia on Australian New Zealand Clinical Trials Registry (ANZCTR).[44,45] In these applications, the isolated and expanded AmSCs can be cryopreserved in cell banks as potential future treatments for the patients. Further details about the cryopreservation process were mentioned in the studies by Moon et al. and Yong et al.[46,47] which is out of the scope of the current review paper.

Neural application of AmS-ICs. AmS-ICs have outstanding characteristics that make them ideal to use in neural tissue engineering and cell therapy. In addition to their availability, studies show that AmS-ICs can synthesize and secrete neural growth factors and neurotransmitters, promoting neural tissue regeneration.[48] For instance, ischemic and hemorrhagic brain injuries are one of the targets of using human AmS-ICs. Most studies use intracerebral (IC) or intravenous (IV) injection to administer the cells for treatment.[31] It was demonstrated that after IC injection of AmES-ICs in a rat cerebral artery occlusion model, the infarcted regions and neuronal apoptosis were reduced along with improved cognitive function caused by an increased number of differentiated AmES-ICs into neuronal-like cells.[49] In addition, the intraventricular transplantation of AmES-ICs in cerebral hemorrhagic rats resulted in activation of microglia, a decrease in brain edema, and regeneration of surrounding tissue.[50] Similarly, a recent study investigated the efficacy of IV grafting of AmFS-ICs in ameliorating behavioral disorders in the ischemic stroke brain rat model.[51] It was shown that after injection of AmFS-ICs labeled with multimodal iron oxide nanoparticles into the tail vein, the implanted cells were able to readily migrate toward ischemic regions, decrease the infarct volume, and improve motor functions. The transplanted cells increased the expression and secretion of neuroprotective factors as well as angiogenic factors such as vascular endothelial growth factors (VEGFs).[51] Preclinical studies suggested that the application of AmS-ICs therapy in these brain injuries exhibited promising outcomes due to the replacement of damaged neural cells with newly differentiated cells, suppression of immune/inflammatory response, and secretion of cytokines, growth factors, and neuroprotective factors, which mimic the native cellular microenvironment and facilitate neural regeneration.[31]

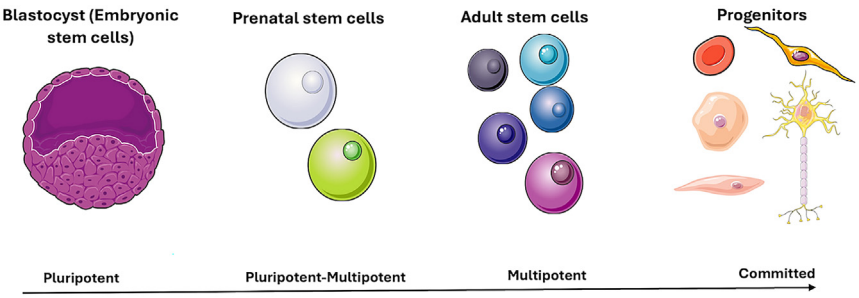

Figure 2. Plasticity of different types of cells
This figure is created with Servier Medical Art (http://smart.servier.com).

However, it is worth mentioning that the time of cellular administration after stroke is critical, especially during early treatment. Accordingly, the effects of IV human AmES-ICs therapy within the first three days of ischemic stroke in animal models were evaluated.[52] Acutely post-stroke administration of AmES-ICs led to the migration of cells to the infarct area as well as the spleen, which, respectively, restored neural function partially and attenuated systemic immunosuppression. The injection in 1–3 days post-stroke resulted in significantly fewer apoptotic cells, exhibited greater grip strength, long-term neural function recovery, attenuation of behavioral deficits, and greater survival rate than other groups.[52] This study showed that functional recovery in 1–3 days post-stroke injection particularly is carried out via modulation of post-stroke inflammatory responses. Human AmES-ICs reduced inflammation, polarized macrophages to M2 or pro-healing, and induced regulatory T cells to the site of injury, which caused accelerated repair. Also, IV injections of cells are considered more clinically feasible than IC injections to some extent, since IC injection requires expensive imaging technologies and expert knowledge to trace the cells within the target tissues, which may not be readily available at some stroke centers. Moreover, there is a chance of iatrogenic injury caused during cell administration.[53]

AmS-ICs were also shown to have significant effects on the treatment of spinal cord injuries (SCIs) and their associated disorders by promoting axonal sprouting, neuronal differentiation, and prevention of glial scar formation at the lesion site.[33,54,55] Studies have used either direct administration of cells using local injection to the injury site or by transplantation of cell-laden scaffolds. For example, a study evaluated the efficacy of transplantation of human AmFS-ICs into the site of injury for treatment of the bladder dysfunction in spinal cord-injured rats and regeneration of the bladder wall. They revealed that compared to human embryonic kidney 293 cells (HEK293) that could only heal a fraction of bladder wall, injection of AmFS-ICs led to higher secretion of insulin-like growth factor-1 (IGF-1) and transforming growth factor β1 (TGF-β1), and subsequently, the synthesis of elastin and collagen and bladder wall remodeling (Figure 3A). Additionally, increased level of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) resulted in tissue reinnervation and therefore restoration of bladder functionality.[56]

While these cell-based therapies appear promising in the treatment of neurological disorders, their long-term effectiveness and success in clinical applications require careful verification, as well as an understanding of their mechanisms of action. An overview of the mentioned studies in the application of AmS-ICs is illustrated in Table 2 after the discussion of other prenatal stem-like cell sources.

Placental-derived stem-like cells

Having fewer ethical issues (as opposed to EmSCs) in addition to the abundance of discarded placental tissue makes this tissue a promising source for stem-like cell extraction. Almost 350,000 births happen every day around the world, in which prenatal tissues are discarded.[93,94] While placental-derived stem-like cells (PS-ICs) are as pluripotent as EmSCs, with a lower ethical barrier.[64]

Placental tissue is enriched with embryonic progenitor cells, trophoblastic cells, HSCs, and MSCs. Still, cells with MSC characteristics are the most extracted cell line from the placenta and play essential roles during placental development. They contribute to the vascularization and stability of the cytotrophoblast column through paracrine signals.[95] Similar to AmS-ICs the PS-ICs also express OCT-4, SOX2, CD29, CD37, and CD166, which helps for neural differentiation.[64]

In terms of the superiority of PS-ICs, it can be said that the absence of aging prevents deterioration of proliferation, differentiation, and therapeutic and immunomodulatory properties.[96] Additionally, the therapeutic effects of paracrine secretome of PS-ICs, and their capacity to be a delivery agent and migration ability of PS-ICs to be attracted to an injury site put these cells in the spotlight for tissue engineering applications. However, the clinical usage of these cells is still in its infancy, and as such their safety has not been confirmed, especially for allogeneic applications. The time-consuming procedure of expanding these cells before clinical use is one obstacle that should be tackled by addition of different signals *in vitro* to speed up this procedure.[97] Overall, optimizing extraction, culturing, expansion as well as cryopreservation and storage is the main key to pave the path for these cells' clinical applications.

Neural application of PS-ICs. PS-IC-based therapy has been widely investigated for neurological diseases in different animal models. The PS-ICs can be used directly, or they can be differentiated beforehand, and their neural lineage can be used. Moreover, the growth factor secreted by PS-ICs or their differentiated lineage growth factor secretion can be used for the treatment of different neurological diseases.[98–100]

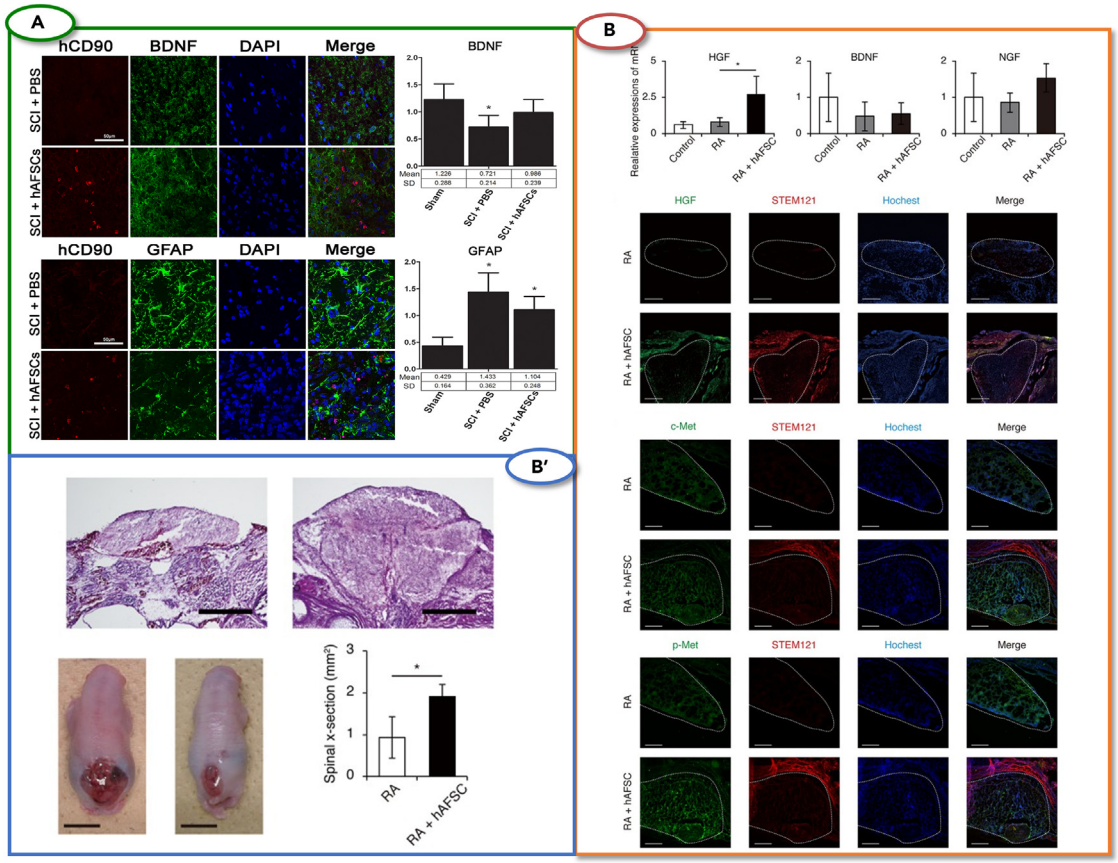

Figure 3. The neurogenic potential of transplanted human AmS-ICs in treatment of spinal cord injuries and nerve hernia

(A) Representative Immunoconfocal microscopy images of neural marker expression in sections of spinal cords in controls and AFS-ICs implanted group (n = 6).[56] HGF: hepatocyte growth factor, BDNF: brain-derived neurotrophic factor, NGF: nerve growth factor, STEM121: human stem cell cytoplasm antibody, c-Met: tyrosine-protein kinase Met, and phosphorylated c-Met, hCD90: human CD90, GFAP: glial fibrillary acidic protein, and DAPI: 4′,6-diamidino-2- phenylindole.

(B) The graph of produced neurogenic factors and representative immunostained images of spinal cross-sections in myelomeningocele rat model injected with retinoic acid (RA) and human AmS-ICs derived from amniotic fluid (hAFSCs).

(B′) H&E stained and macroscopic images of isolated rat spinal samples before (left) and after (right) treatment showed reduction in cross-section area (×40; scale bars: 500 μm, n = 5).[57]

For instance, direct IV injection of PS-ICs resulted in upregulation of VEGF, HGF, and BDNF in a rat with stroke and it decreased the anti-inflammatory response, in a mouse with Alzheimer's disease (AD).[64] In addition to stroke and AD, other neurological conditions such as myelomeningocele, ballistic-like brain injury, and Parkinson's disease (PD) have also been considered for PS-ICs-based cell therapy.[98–100]

The addition of growth factors can be used to adjust differentiation conditions, such as retinoic acid and glial-derived neurotrophic factor (GDNF) to facilitate neural differentiation of PS-ICs and extract neural progenitors. It has been demonstrated that inhibiting histone deacetylase expression through valproic acid led to an increase in the expression of neurites and neural lineage markers.[101] Valproic acid helps with S-IC maintenance and differentiation and affects BDNF and GDNF expression in astrocytes, which protects dopaminergic (DA) neurons and leads to a full commitment to neural linage differentiation. Hence, the proposed protocol can be used to differentiate PS-ICs for nerve tissue engineering applications.[101] Overall, providing desirable growth conditions and addition of neural stimulant signals for PS-ICs *in vitro* can lead to optimizing expansion of these cells before clinical application to not only have fully committed cells but also to increase their population to achieve the highest success.

Another way to make use of PS-ICs for neural tissue engineering is with their secreted vesicles. These secreted vesicles are a communication path for intracellular communication. Furthermore, they can act as therapeutic agents or differentiation signals. Recently, the potential of the secreted extracellular vesicle in treating MS in a murine model was demonstrated by reducing oligodendroglia's DNA damage. Moreover, they led to an increase in myelination of spinal cord cells by affecting endogenous oligodendrocyte precursor cells.[66] The advantage of utilizing exosomes and growth factors of PS-ICs over cells is reduced donor rejection rate, otherwise both groups led to the same result regarding neuron regeneration.[66] Different applications of PS-ICs for the treatment of neurological diseases are present in Table 2.

Overall, placental-derived cells, have great potency for neural regeneration applications thanks to their similarity to MSCs.

Table 2. Overview of prenatal WDS-IC studies

Source	Disorder	Model	Final achievement	Reference
AmES-ICs	Stroke	Rat	• Reduction of infarcted regions caused by cerebral artery occlusion and neuronal apoptosis • Improvement of cognitive functions • Increase of differentiation into neuronal-like cells	Liu et al.[49]
AmES-ICs	Stroke	Rat	• Activation of microglia • Decrease in brain edema • Tissue regeneration	Dong et al.[50]
AmES-ICs	Stroke	Rat	• Migration of cells toward the infarct area • Neural function recovery • Attenuation of behavioral deficits	Evans et al.[52]
AmES-ICs	SCI	Rat	• Regrowth of damaged axons and paracrine factors secretion	Xue et al.[58]
AmES-ICs	SCI	Rat	• Neural sprouting • Microglial inactivation	Wang et al.[59]
AmES-ICs	MS	Rat	• Immunomodulation • Remyelination • Neuroprotection	Liu et al.[60]
AmES-ICs	Autism spectrum disorder	Mouse	• Mitigation of social deficits • Improvement of neurogenesis in the hippocampus	Zhang et al.[61]
AmFS-ICs	Stroke	Rat	• Reduction of the infarct volume • Improvement of motor functions, • Increase of neuroprotective and angiogenic factors secretion	Sibov et al.[51]
AmES-ICs	SCI	Rat	• Improvement of migration of SCs to the site of injury in the myelomeningocele model • Increase of neurogenesis and neuroprotection caused by HGF secretion	Abe et al.[57]
AmMS-ICs	Sciatic nerve injury	Rat	• Differentiation of AmMS-ICs into Schwann cell-like cells • Peripheral nerve regeneration • Functional recovery	Chen et al.[62]
AmMS-ICs	MS	Mouse	• Promotion of angiogenesis • Neural tissue survival • Regulation of MMPs activity • Increase of neural differentiation	Abbasi-Kangevari et al.[63]
PS-ICs	Stroke	Rat	• Upregulation of VEGF, HGF, and BDNF • Neuroprotectivity	Oliveira and Barreto-Filho[64]
PS-ICs	AD	Mouse	• Lower anti-inflammatory responses	Oliveira and Barreto-Filho[64]
PS-ICs	Spinal Cord Injury	Rat	• Enhancement of motor function • Improvement of sensory and motor dysfunctions	Yang et al.[65]
PS-ICs and secretes	MS	Mouse	• Boost in the motor function • Reduction the DNA damage of oligodendroglia. • Increase in myelination of spinal cord cells	Clark et al.[66]
UCMS-ICs	stroke	Rat	• Reduction of the infarct size • Improvement of neurobehavioral function	Koh et al.[67]
UCMS-ICs	stroke	Rat	• Reduction of the infarct size • Improvement of neurobehavioral function • Promotion of the angiogenesis process of the injured part	Liao et al.[68]
UCMS-ICs	stroke	Rat	• Increase of synaptophysin and vascular density • The proliferation of endogenous neural progenitor cells	Zhang et al.[69]
UCMS-ICs	stroke	Rat	• Secretion of biological potent cytokines from UCMS-ICs is more effective than the route and time of administration in IV infusion	Shehadah et al.[70]
UCMS-ICs	stroke	Rat	• Increase of remyelination and gliosis	Oppliger et al.[71]

(*Continued on next page*)

Table 2. *Continued*

Source	Disorder	Model	Final achievement	Reference
UCMS-ICs	stroke	Human	• Improvement of muscle strength in two patients of ischemic and no significant change was observed in the patient with hemorrhage stroke	Jiang et al.[72]
UCMS-ICs	SCI	Rat	• Improvement of motor function	Li et al.[73]
UCMS-ICs	SCI	Rat	• Suppression of mechanical allodynia	Roh et al.[55]
UCMS-ICs	SCI	Rat	• Higher survival rate than bone marrow MSCs • Improvement of functional recovery • Reduction of allodynia • Improvement of hyperalgesia	Yousefifard et al.[74]
UCMS-ICs	SCI	Human	• Effective treatment in ~60% of patients • Improvement of their motor and sensory function, bowel and bladder ability	Liu et al.[75]
UCMS-ICs	SCI	Human	• Improvement of neurological functional recovery	Cheng et al.[76]
UCMS-ICs	PD	Monkey	• Amelioration of the functional deficits	Yan et al.[77]
UCMS-ICs	PD	Rat	• Progressive enhancement of motor behavior	Han et al.[78]
UCMS-ICs	AD	Mouse	• Enhancement of cognitive and sensorimotor task	Boutajangout et al.[79]
UCMS-ICs	AD	Mouse	• Improvement of memory and reduction of Abeta deposition	Yang et al.[80]
UCMS-ICs	MS	Rat	• Prevention of EAE onset • Amelioration of outcome of established EAE	Donders et al.[81]
UCMS-ICs	MS	Rat	• Reduction perivascular immune cell infiltrations, demyelination, and axonal injury in the spinal cord • Enhancement of survival of the EAE model	Liu et al.[82]
UCMS-ICs	MS	Human	• Improvement of symptoms • Decrease the relapse occurrence of MS	Li et al.[83]
UCMS-ICs	MS	Human	• Enhancement of EDSS scores, bladder, bowel, and sexual function • Enhancement of non-dominant hand average scores, walk time, and generally their quality of life after one month of treatment and appearance of the inactive lesion in the MRI image of 83.3% of patients after one year	Riordan et al.[84]
UCBMS-ICs	Stroke	Dog	• Differentiation into neurons and astrocytes • Reduction of the lesion volume • Increase in secretion of von Willebrand factor and neuroprotective factors, such as BDNF and VEGF	Chung et al.[85]
UCBMS-ICs	Stroke	Rat	• Improvement of motor function by both intrathecal and IV administration	Lim et al.[86]
UCBMS-ICs	Stroke	Rat	• Lack of connection between the donor of the cells and their therapeutic effect	Park et al.[87]
UCBMS-ICs	Stroke	Rat	• Improvement of histologic abnormalities of penumbra only after 6 h of UBCMS-ICs administration	Kim et al.[88]
UCBMS-ICs	SCI	Dog	• More nerve regeneration and anti-inflammatory effect in comparison with fat, bone marrow, Wharton's jelly derived MSCs	Ryu et al.[89]
UCBMS-ICs	SCI	Dog	• Enhancement of nerve conduction velocity • Consistency of the nerve cell bodies structurally	Lim et al.[90]
UCBMS-ICs	SCI	Rat	• Promotion of the recovery of damaged spinal cord	Cui et al.[91]
UCBMS-ICs	AD	Mouse	• Reduction of markers of glial activation, oxidative stress, and apoptosis levels	Lee et al.[92]

In order to boost their performance even further, different techniques can be used, such as pre-differentiating these cells before treatment, injecting them with differentiating factors, and utilizing their secretomes. Although the application of PS-ICs in a clinical trial has not been evaluated broadly, this waste-based stem-like cell holds great promise for treating neural-based disorders.

Umbilical cord-derived stem-like cells

The importance of UCB as a source of HSCs and endothelial progenitor cells was first announced in 1974 by Knudtzon.[102] The first successful transplant of UCB-derived HSCs (UCHSCs) was done in 1988 for a boy with Fanconi's anemia from his younger sister's UCB.[103] Since then, because of the therapeutic application of these cells, cryopreservation of UCB for future use was developed.[104] In 1991, researchers found that UCB is not the only source of stem-like cells (S-ICs), but that a broad range of cells can be obtained by isolating fibroblast-like cells from Wharton's jelly.[105] This declaration was completed in 2004 by investigating the markers of isolated cells, which are the same as what is expressed by MSCs such as CD29, CD44, CD51, CD73, and CD105, and not CD34 and CD45 that are the markers of HSCs.[106,107]

Neural application of UCS-ICs. Umbilical cord-derived stem-like cells (UCS-ICs) are the most studied prenatal S-ICs in the field of stroke treatment.[108] For instance, IC implantation of UCMS-ICs in the brain of immunosuppressed ischemic stroke rats showed that they homed in on the injured part, decreased the infarct size as can be seen in Figure 4A, and enhanced neurobehavioral function, but they could not become functional active neuronal cells. These results were explained by the neuroprotective effect of UCMS-ICs and their disability in constructing a new network between implanted cells and host tissue.[67] It is also indicated that transplantation of UCMSCs in a stroke model not only reduced the infarct volume and improved neurobehavioral function (Figure 4B) but also increased the amount of VEGF and basic fibroblast growth factor (bFGF) in the brain and substantially encouraged the angiogenesis process of the injured part (Figure 4B').[68] Similarly, transplantation of UCMSCs in the injured part of the brain of three patients improved muscle strength in two patients with ischemic stroke, and no significant change was observed in the patients with hemorrhagic stroke.[72]

UCMS-IC transplantation can also be delivered intravenously, which improved neurobehavioral function by increasing synaptophysin and vascular density and promoting endogenous neural progenitor cell proliferation, but it did not result in a reduction in injury size.[69] During the administration of UCMS-ICs via IV infusion, the biodistribution of the injected UCMS-ICs labeled by indium-111 (In-111) oxine was analyzed by single-photon emission computed tomography. The results demonstrated that about 1% of administrated UCMS-ICs reached the injured part of the brain. The low homing ability of cells in this study, shows that the success of this transplantation came from other factors like the secreted potent cytokine that results in the enhancement of angiogenesis (Figure 4C).[70,110] Some of the beneficial secreted biological compounds from UCMS-ICs, namely IL-8 and VEGF-A, are related to their angiogenic impact.[111] The intranasal transplantation of UCMS-ICs as an alternative to IV or IC, also caused an increase in remyelination and gliosis in Wistar rat pups with a hypoxic-ischemic insult.[71] All of these results have strengthened this view that although these kinds of cells express MSCs markers, they are stromal cells and cannot proliferate and differentiate like SCs.[18]

Although all administration methods showed promising results, they can still affect therapeutic outcomes. As an illustration, in comparison between intrathecally or intravenously administered UCBMS-ICs to a rat stroke model, migration of cells to the ischemic area through intrathecal was higher than that through IV. However, both groups showed significant improvement in motor function.[86] On the other hand, different donors of UCB cannot contribute to the therapeutic effect of UCBMS-ICs as revealed that different types of donor-derived UCBMS-ICs administrated intracerebrally caused the same tissue regeneration.[87] It was also reported that both UCBMS-ICs with the low and high number of passages revealed the same effect on the treatment of the middle cerebral artery occlusion rat model.[112]

UCMS-ICs have been shown to be more effective in treating PD than bone marrow MSCs in previous studies, since dopaminergic cells differentiated from UCMS-ICs expressed higher levels of tyrosine hydroxylase and Nurr1 compared to those differentiated from bone marrow MSCs.[113]

In addition, differentiated cells can be more beneficial in clinical use if they reach and stay in the target site sufficiently compared with undifferentiated cells.[108,113] Therefore, some genetic modifications on UCMS-ICs[77] or the use of growth factors during cell administration[78] can enhance the efficacy of the treatment. For example, the transplantation of genetically modified UCMS-ICs by two important genes in PD (Lmx1α and NTN) into PD monkey models showed recuperation of the functional deficits.[77] In another *in vivo* test on 6-hydroxydopamine-induced PD rat models, UCMS-ICs were transplanted with a growth factor cocktail into the lesion part of the brain, and the results indicated that DA neurons conversion in the midbrain and progressive improvement of motor behavior.[78] UCMS-ICs can also secrete soluble factors with immunomodulatory and anti-inflammatory functions, such as soluble intracellular adhesion molecule-1 108, which increases neurogenesis and decreases neuroinflammation.[114] Accordingly, the transplantation of UCBMS-ICs to an AD mouse model reduced glial activation, oxidative stress, and apoptosis levels.[92]

The modulation of immune cell function in UCMS-ICs can prevent the onset of experimental autoimmune encephalomyelitis (EAE) and improve the results of established EAE in MS.[81] Moreover, transplantation of UCMS-ICs could reduce perivascular immune cell infiltrations, demyelination, and axonal injury in the spinal cord and subsequently enhance survival of the EAE model through secretion of an anti-inflammatory protein, such as tumor necrosis factor alpha (TNF-α)-stimulated gene/protein 6 (TSG-6).[82]

Finally, in a large clinical study on the effect of intrathecally administrated UCMS-ICs on a vast range of neurological disorders, 100 patients enrolled and followed up for more than one year after treatment. The results of this study showed that 47% of patients (contained 12% with SCI, 11% with cerebral palsy, 9% with post-traumatic brain syndromes, 9% with post-brain infarction, 3% with spinocerebellar ataxias, and 3%

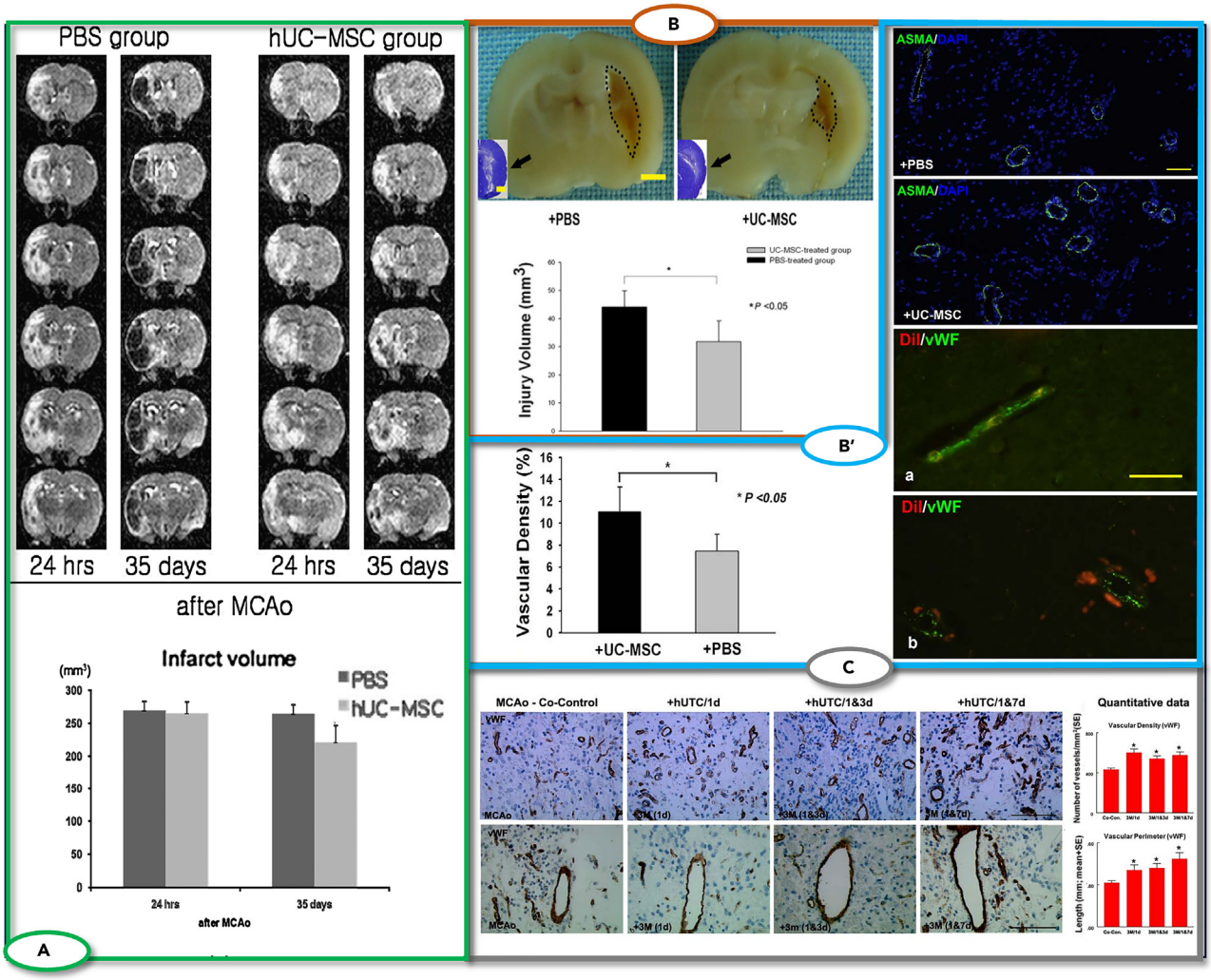

Figure 4. The effect of UCMSC administration on infarct size reduction and vascular density

(A) significant reduction of infarct volume in the human UCMS-IC treated group compared to the PBS-treated group.[67]

(B) Representative macroscopic appearance of brain slices at 28 days after transplantation and quantitative data of infarct volume in PBS and UCMS-ICs treated group, (B′) Representative DAPI staining image of PBS and UCMS-ICs treated intracerebral hemorrhage 14 days post-transplantation, and vWF immunostaining images to display incorporation of UCMS-ICs into endothelium and their maintenance in the blood vessel wall.[109]

(C) significant increase of vascular density and perimeter in human UCS-ICs treated tissue over time in comparison with control tissue.[70]

with motor neuron disease) responded to the treatment and their functional indices were improved and only 22% of patients, had mild or moderate side effects.[115]

Although there is a large number of *in vitro*, *in vivo*, and clinical trials on the application of UCMS-ICs, and in most of the studies they were considered as MSCs, they usually did not differentiate into the neural cells completely or proliferate like SCs and behaved more like the stromal cells to support the tissues by their secretions. Therefore, the outcomes of these studies can be enhanced by using some cell reprogramming approaches[77] or introducing biomaterials to induce neural differentiation of UCMS-ICs[116,117] or materials that can control the delivery of the secretion of these cells in the target tissues and continue such supportive behavior.[118]

Adult WDS-ICs

Because of the great importance of SCs in the treatment of a vast range of diseases, some parameters such as the harvesting method from the donor and the number of collected cells are taken into account. The current method of adult SC harvesting needs needle insertion, biopsy, or physical dislodgement by scraping. However, adult WDS-ICs can be considered as a suitable choice with advantages such as the non-invasive method of cell collection, lack of bioethical concerns, and their higher proliferation potential. Adult WDS-ICs can be obtained from urine, waste adipose after liposuction, dental pulp, and peripheral blood.

Urine-derived stem-like cells

A promising and readily available type of S-ICs derived from adult waste materials is urine-derived stem-like cells (US-ICs).[119] Despite heterogeneous cell populations in human urine, there are generally two types of cellular colony morphologies presented in urine samples; firstly, flat and smooth surface with high cell-cell contact categorized as renal squamous epithelium-like cells and secondly, single, dense, adherent, and disperse cells known as US-ICs. The main origins of these cells are kidney tubules or papilla (i.e., kidney glomerulus epithelial cells) and the upper urinary tract. Although the first cell colony showed limited application in kidney regeneration, US-ICs provide high expandability *in vitro* with approximately 100–140 cellular colonies grown from each urine sample during 24 h culture time and better plasticity to differentiate into different cell types (e.g., osteogenic, chondrogenic, adipogenic, myogenic, and neurogenic lineages) compared to renal stem/progenitor cells.[120–123] US-ICs can be regarded as multipotent MS-ICs residing in the urinary tract system that present cobblestone to spindle-like phenotypes and express various surface markers associated with self-renewal, immunomodulation, endothelialization, and the ability of differentiation to hematopoietic SCs and neurons, including CD44, CD73, CD29, CD105, CD166, CD90, CD224, CD146, and CD13.[122–124] In addition to controlled telomerase activity, which would not cause teratoma formation, US-ICs have high efficacy for reprogramming into iPSCs, can secrete regenerative growth factors, and exhibit immunomodulatory properties.[120]

It has been suggested that US-ICs can be introduced as an alternative cell source for the generation of mature cells after *in vivo* transplantation in the treatment of neurological disorders and brain regeneration.[125–127] Therefore, as a benefit of using such potent and patient-specific cells, the number of clinical trials would increase noticeably compared to previous clinical studies using iPSC-derived dopamine neurons, which took nearly 2 months for the generation of functional and matured neurons.[128,129]

Neural application of US-ICs. Regarding the use of US-ICs in neural tissue regeneration, studies employed various approaches from growing in biomaterial-based hydrogels to exposure to small molecule/growth factor cocktails for efficient generation of neural progenitor cells.[130,131] For instance, a protocol was developed to generate large quantities of neural progenitor cells from US-ICs by treating them with a small molecule formulation. The results showed that these treated cells serve neuronal properties and functions (including electrophysiological activity and survival after transplantation) both *in vitro* and *in vivo*.[132] These results notwithstanding, there is still room for the development of a standardized protocol for US-IC differentiation that shows reliable outcomes and feasibility.

After isolation, US-ICs can undergo either direct reprogramming to neuronal cells or first be reprogrammed to iPSCs and then differentiated to neural SCs and finally converted into astrocytes, oligodendrocytes, and neurons.[119,133] The process of cellular reprogramming is carried out using an inductive medium containing specific growth factors, small molecules, drugs, and physical stimulants or by genetic manipulation of cells through transfection with viral/non-viral vectors to increase the differentiation efficacy.[133]

As mentioned previously, neural cell transplantation is one of the effective methods of treating neurodegenerative diseases such as stroke, AD, PD, etc.[133] Due to the safety concerns associated with using transcriptional factors and viral vectors for cellular transfection, a combination of small molecules as a safe and cost-effective approach can be applied to improve the reprogramming efficacy of US-ICs.[131] Accordingly, centrifuged US-ICs were cultured into the gelatin-coated plate and subjected to the neuron induction medium containing special small molecules. Based on the results, using a medium supplemented with a chemical cocktail including ISX9, I-BET, and RA (the metabolite of vitamin A) resulted in increased neuronal differentiation, inhibited non-neuronal genes, and promoted neurogenesis, respectively. This work established a protocol for converting both renal cells and US-ICs into neuronal cells not only for cell therapy but also for disease modeling and drug screening applications.[131]

MSC-generated exosomes have been proven to have a direct effect on promoting neurogenesis. However, their application is limited due to the lack of cell sources and invasive extraction procedures.[134–136] Alternatively, the use of US-ICs is restricted not only to the cells themselves but also to their paracrine secretions. To illustrate, exosomes derived from US-ICs showed positive outcomes for post-ischemic stroke treatment in rats. The research findings demonstrated that promoting neurogenesis and functional recovery increased proliferation and neuronal differentiation using IV injection of US-ICs exosomes in rat models.[137]

It is worth mentioning that considering several challenges in successful and functional differentiation of SCs to neural lineages and despite some studies examining US-ICs direct differentiation to neuronal cells, most research has used iPSC-derived USCs (UiPSCs) for this application.[119,123] Moreover, due to high reprogramming efficacy and the omission of the mesenchymal-to-epithelial transitional step leading to short induction time, US-ICs seem more advantageous rather than other somatic cells for the generation of iPSCs.[123,133,138]

As an example, a rapid and efficient method for the differentiation of UiPSCs into motor neurons was investigated. With the benefit of using small molecules supplemented in neural differentiation medium, mature motor neurons were generated after 26 days of culture, and they expressed neural markers. Moreover, the co-culture of these differentiated cells with C2C12 cells, mouse muscle cells, led to the formation of neuromuscular junctions. These results revealed the functional capacity of using UiPSCs as a promising treatment for motor neuron diseases.[129]

Application of US-ICs/UiPSCs for the development of a platform for investigation of disease underlying reactions and investigation of appropriate therapeutic strategies has noticeably attracted both research and clinical focus.[139] To generate simple and cost-effective approaches for understanding the molecular mechanisms of disease, testing potential drug reactions, and developing an efficient treatment for diabetic brain disorders, diabetic patients' urine samples were used and the isolated US-ICs were reprogrammed into UiPSCs and then differentiated to neurons, astrocytes, and microvascular endothelial cells. A co-culture of these three resultant cells in a 3D system was used to produce a disease model *in vitro*, which significantly mimicked the cerebral microenvironment of diabetic patients.[140]

Similarly, functional cerebral organoids were created from UiPSC embryoid bodies with robust capacity for neurogenesis and astrogliogenesis, which represented practical biospecimens for studying neurodevelopment and pharmacological responses. It was reported that despite some variations associated with different urine samples and cell reprogramming procedures, all the UiPSC aggregates differentiated in a neural induction medium and developed into cerebral organoids, which also induced tissue vascularization in the brains of adult mice.[141] Despite showing promising results in various studies, US-ICs are less likely to be frequently used in neural regeneration applications due to the challenges in their differentiation into neural lineages compared to their differentiation into urinary and kidney cells. However, with further work such as genetic manipulation and reprogramming of these cells, as well as the application of UiPSCs, this opinion may prove to be incorrect. An overview of the mentioned studies in the application of US-ICs is illustrated in Table 3 (section Peripheral blood stem cells).

Adipose-derived MS-ICs

Adipose tissue is a connective tissue in bidirectional interactions with other organs. It is more than just a passive source of energy. It is an endocrine tissue that plays a critical role in metabolism, immunity, and hematopoietic systems.[163] Adipose-derived MS-ICs (ADMS-ICs) are rich sources of MS-ICs with the ability to differentiate into nerve-like cells.[164] The specific antigens of ADMS-ICs include CD34, CD73, and CD90. ADMS-ICs do not express the blood cell markers like CD45 and CD31. Moreover, CD13, CD29, CD44, CD58, and CD166 are MSC markers expressed by ADMS-ICs. It should be noted that the isolation method and culture protocol affect the expression of these markers.[165,166] Various methods are used to separate adipose tissue, including Coleman's technique, liposuction, and direct excision. Based on the location of excision and the age of the person, the function of the SCs may be affected.[164] Rodbell first carried out progenitor cell extraction from adipose tissue in 1964,[167] which was altered by Zuk et al. in the year 2001 using liposuction wastes.[168] These methods can be used to provide autologous cell sources and consequently the lack of undesired host versus graft disease.[164,167]

Differentiation of ADMS-ICs into desired cell lineages such as neurons depends on various parameters such as culturing conditions.[169] The induction medium for neuronal cells consists of butylated hydroxyanisole (an antioxidant that enhances neural SC survival), valproic acid (a branch-chained fatty acid that participates in the blockade of voltage-dependent sodium channels and the potentiation of gamma-aminobutyric acid [GABA; GABA is a chemical messenger widely distributed in the brain that reduces neuron activity in the neurons to which it binds]), and forskolin (a neural stimulus that regulates the neurotransmitter transporters and ion channels[169,170]). It is also possible to differentiate ADM-ICs into Schwann cells using a cell growth medium supplemented with PDGF, bFGF, forskolin, and glial growth factor (GGF)-2.[171,160] A genetics-based protocol contained a sequential treatment of ADMS-ICs with FGF 2 (for 10 days) and miR-218, which led to differentiated neural cells from ADMS-ICs.[172]

Neural application of ADMS-ICs. ADMS-ICs secrete numerous growth factors, namely VEGF, bFGF, NGF, BDNF, and neurotrophins, which play a critical role in remyelination, reducing neural cell apoptosis, and maintaining the CNS functions.[150] Transplantation of ADMS-ICs into the hippocampi of transgenic AD model mice was accompanied by reduced oxidative stress and alleviated cognitive impairment. Immunofluorescence staining revealed that the number of newly generated cells in the hippocampus in AD mice was significantly higher after adipose-derived MSC transplantation. Adipose-derived MSC transplantation enhanced neurogenic activity as well.[144] IC transplantation of ADMS-ICs also demonstrated improved omission of amyloid beta (Aβ) from the hippocampus because of the alteration of the microglial activation after ADMS-IC transplantation, which was also accompanied by a reduction in expression of toxic inflammatory cytokines. Overall, these results reduced disease symptoms.[145] The potential of IV injection of ADMS-ICs in the treatment of AD was also evaluated on the transgenic mice model of Tg2576, which confirmed the migration of intravenously injected ADMS-ICs through the blood-brain barrier into the brain.[91,146] A comparison between the efficacy of two IV and IC injection methods, which are related to the prevention of AD inception and the therapeutic potential of the transplanted ADMS-ICs, respectively, demonstrated the acceptable potential of both methods. They both resulted in a reduction of Aβ peptides by regulating neurotrophic factors like VEGF, which led to enhanced learning and memory abilities.[146]

It is suggested that the deficiency of the mitochondria can be involved in the degeneration process of dopaminergic cells by the production of reactive oxygen species, which leads to PD.[148] ADMS-ICs have been shown to have neuroprotective effects on animal models of PD.[148] IV transplantation of ADMS-ICs caused a reduction of dopaminergic cell death as well as the functional recovery of mitochondria by increasing the activity of mitochondrial complex I, which led to the recovery of dopaminergic cells.[148] PD animal models have been created using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a PD-inducing agent that causes motor deficiency by killing dopaminergic cells, and n-butylidenephthalide (BP), a herbal anti-inflammatory and anti-cancer agent that reduces Aβ.[149] The transplantation of ADMS-ICs in the striatum of the mouse resulted in balance improvement as well as an increased number of dopaminergic cells. The pretreatment of ADMS-ICs with BP led to the expression of neurogenic genes *in vitro* and better behavioral improvement in the disease model.[149]

When ADMS-ICs and neurotrophic factor secreting cells were co-transplanted into rat MS spinal cords that were locally demyelinated, motor responses were enhanced, possibly due to reduced apoptosis and improved differentiation of ADMS-ICs into oligodendrocytes in the presence of neurotrophic factors.[150] When used in combination with ADMS-IC transplantation on remyelination in cuprizone-induced MS rat models, injection of pregnenolone (steroid hormones produced locally by the nervous system) showed improved regeneration with increased thickness of myelinated axons. The results also demonstrated increased expression of oligodendrocyte differentiation-related genes, which showed the positive potential of ADMS-ICs and pregnenolone in the treatment of MS.[151]

ADMS-IC transplantation prevented further pathologic changes, like secretion of inflammatory cytokines or apoptotic responses of neural cells, after ischemic stroke and led to neural regeneration. Also, the effectiveness of ADMS-ICs was found to be independent of the

Table 3. Overview of adult WDS-ICs studies

Source	Disorder	Model	Final achievement	Reference
US-ICs	Neurological diseases	Rat	• Neuronal differentiation and neurogenesis	Liu et al.[131]
US-ICs	Cerebral diseases	Mouse	• Formation of functional cerebral organoids from UiPSCs with high capacity of neurogenesis, astrogliogenesis, and vascularization	Lin et al.[141]
US-ICs	PD	Rat	• Increase of neural differentiation and proliferation • Expression of neural markers using PDGF and laminin	Kim et al.[122]
US-ICs	SCI	Rat	• Regeneration of nerve structure and erectile function • Improvement of vascular cell function around damaged tissue after injection of modified USCs	Yang et al.[142]
US-ICs	SCI	Rat	• Improvement of cellular migration • Differentiation in damaged nerve with neuroprotective effect inhibiting tissue loss	Liu et al.[143]
US-ICs	Stroke	Rat	• Promotion of neurogenesis • Functional recovery	Ling et al.[137]
AS-ICs	AD	Mouse, Rat	• Reduction of Aβ • Reduction of inflammatory cytokines expression • Improvement of learning and memory ability	Yan et al.[144]; Ma et al.[145]; Kim et al.[146]; Nasiri et al.[147]
AS-ICs	PD	Mouse	• Increase of dopaminergic cells • Reduction of Aβ • Balance improvement	Choi et al.[148]; Chi et al.[149]
AS-ICs	MS	Rat	• Improvement of axonal regeneration • Increase in the myelin sheet thickness • Increase of differentiation to oligodendrocytes • Enhancement of motor responses	Razavi et al.[150]; Ganji et al.[151]
AS-ICs	Stroke	Rat	• Reduction of the lesion area, • Inhibition to further pathologic changes • Enhancement of motor function	Yousefifard et al.[152]; Zhao et al.[153]
AS-ICs	SCI	Mouse, Rat, Dog	• Improvement of cell survival, • Reduction of scar formation • Axonal regeneration • Improvement of functional recovery	Ohta et al.[154]; Razavi et al.[155]; Gao et al.[156]; Tang et al.[157]; Bach et al.[158]
AS-ICs	SCI	Human	• 71% showed sensory recovery, while the limited motor recovery was observed	Hur et al.[159]
AS-ICs	Sciatic nerve injury	Rat	• Improvement of axonal regeneration	Summa e al.[160]; Nakada et al.[161]
DPS-ICs	SCI	Rat	• High rate of neural differentiation • Increase in neurotrophic factor expression and significant locomotor regeneration	Zhang et al.[162]

administration route.[152] The potential of the cell-free protein extracts of ADMS-ICs as alternatives for complete ADMS-ICs in the treatment of stroke has also been evaluated. The IV injection of ADMS-ICs and extracts of ADMS-ICs in transient middle cerebral artery occlusion rat models reduced lesion area in the long-term for both groups. However, their molecular mechanism of action was reported to be different. ADMS-ICs provided higher expression of neurotrophic factors, which resulted in a prolonged reduction of symptoms. While injection of extracts of ADMS-ICs led to fast neurological improvements, which might be a result of more efficient downregulation of proinflammatory cytokines' expression.[153]

The potential of ADMS-ICs in the treatment of SCI has been investigated in numerous studies, and interestingly, the cells promoted functional recovery without achieving long-term survival of the transplanted cells. Instead, the secretion of various growth factors and immunomodulatory cytokines like VEGF, bFGF, IL-3, IL-6, neural growth factor, and HGF by ADMS-ICs led to SCI recovery.[154,155,173] The successful differentiation of human-derived ADMS-ICs to motor neurons in the presence of sonic hedgehog, retinoic acid, and neurotrophic factors has also been reported. The differentiated cells transplanted in the SCI mice model showed the expression of anti-inflammatory cytokines in addition to providing an optimized microenvironment. Moreover, behavioral recovery was demonstrated after cell transplantation in the animal model.[156] The positive potential of IV transplantation of ADMS-ICs in the functional recovery of SCI rat models is also reported. There was a high likelihood of ADMS-IC differentiation, as well as a slow accumulation at the injury site of injected cells. The secretion of factors that participate in cell survival was also reported, which all together enhanced the functional recovery in rats.[154] Neurotrophic secreting cells

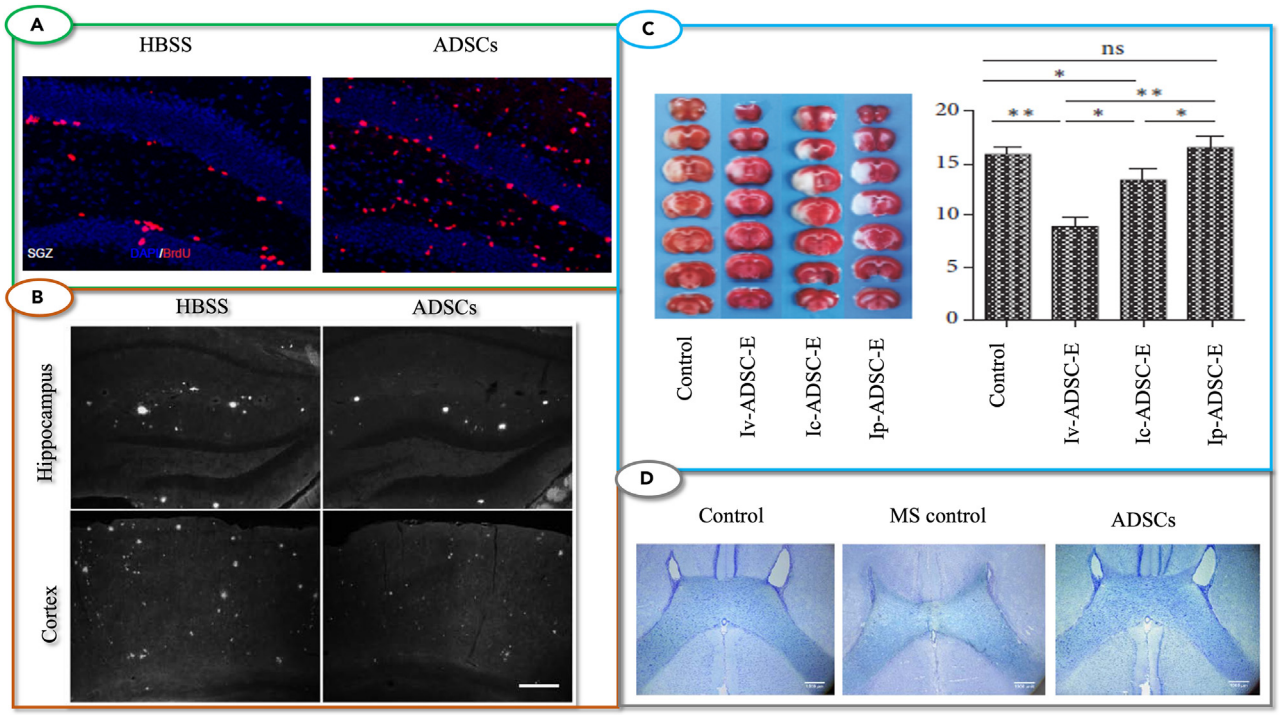

Figure 5. The neurogenic potential of adipose-derived mesenchymal stem-like cells (ADMS-lCs) in the treatment of neural disorders

(A) shows an increased number of newly born neural-potent cells in the presence of ADMS-lCs, dispersed throughout the dentate gyrus of Alzheimer's disease mice model in comparison with the group that received Hank's balanced salt solution (HSBB).[144]

(B) decreased number of Aβ plaques in the presence of ADSCs in both cortex and hippocampus of Alzheimer's disease mice model, scale bar:100 μm.[145]

(C) The picture demonstrates the remyelination of demyelinated corpus callosum in multiple sclerosis rat model due to transplantation of ADMS-lCs.[153]

(D) Shows the effect of the administration route of ADMS-lCs extracts on the lesion area during stroke in rat models. The IV administration resulted in the least lesion area compared with intraperitoneal (Ip) and intracerebral (Ic) administration.[151]

differentiated from ADMS-lCs were also confirmed to have a higher potential in remyelination and increase of myelin sheath thickness compared with undifferentiated ADMS-lCs because of their secretion of growth and neurotrophic factors.[155]

Genetically modified Ngn2-ADMS-lCs in an SCI rat model led to improved functional recovery, showing more neural differentiation, decreased scar formation, as well as secretion of BDNF and VEGF. Ngn2 is a proneural gene responsible for neural differentiation while preventing astrocytes from differentiating and, as a result, inhibiting scar formation, which is an obstacle for axon regeneration.[157] Autologous ADMS-lC intrathecal transplantation in patients who suffered from SCI showed limited motor behavior recovery in five out of 14 patients, which might be low due to measurements were recorded only for 8 months. However, 71% of patients showed improved sensory recovery. In conclusion, despite the safe behavior of ADMS-lCs after transplantation and no sign of tumor formation, the clinical efficacy of ADMS-lC-based cell therapies needs more evaluation.[159]

Chronic pain after SCI is another issue that SCI patients confront. The use of low-level laser therapy is one physiotherapy approach to controlling such pain.[174] The administration of low-level laser in combination with human-derived ADMS-lC transplantation in SCI rat models revealed decreased neuropathic pain after SCI by increased expression of GDNF and GABA receptors, which are responsible for neurogenesis as well as myelination and control of the pain, respectively[174] Figure 5.

Dental pulp-derived stem-like cells

Dental pulp-derived stem-like cells (DPS-lCs) include dental pulp stem cells (DPSCs) from the pulp of extracted permanent and wisdom teeth, as well as SCs from human exfoliated deciduous teeth (SHED). DPS-lCs distinctly originate from the embryonic neural crest and exhibit unique neurotrophic properties that set them apart from other MSCs sources[175]; however, DPS-lCs are cells like other MSCs in terms of multipotency and self-renewal ability.[176] These features underscore DPSCs and SHED's potential utility for regenerative medicine, leveraging what is otherwise considered medical waste. In addition to the high plasticity of DPS-lCs, they can secrete different factors (secretome) and affect injured tissue regeneration through the paracrine mechanism.[177]

The advantage of DPS-lCs in comparison to bone marrow-derived SCs is related to their high regenerative ability, which makes them suitable for regenerative applications. Additionally, their high proliferation capacity and noninvasive isolation techniques without strict ethics requirements have placed these cells in the spotlight for cell therapy and tissue engineering applications.[176,177]

Neural application of DPS-ICs. DPS-ICs can be directly used for neural disease or they can be differentiated into the neural lineage beforehand. The differentiated cells can be used for cell therapy or their secretome can be used for neuron regeneration or treatment of neural diseases. An appropriate differentiation medium and signals through adding growth factors or loading cells into a scaffold make neural differentiation possible from DPS-ICs. Different growth factors such as PDGF, TGF-β, bFGF, BMPs, and especially NGF can affect DPS-IC proliferation and differentiation.[178] Differentiated neural cells from DPS-ICs can generate action potentials due to developing a voltage-dependent sodium channel, which is essential for the treatment of neurodegenerative diseases.[179] DPS-ICs can differentiate into specific neural cells, such as dopaminergic neurons, as long as a suitable differentiation medium is provided.[180] The secretome of DPS-ICs includes neurotrophic factors, such as VEGF, neurotrophin-3 (NT-3), GDNF, BDNF, etc.[181–183] The role of DPS-ICs for neuro-related diseases can be classified as protective or therapeutic. In the protective role, the DPS-ICs attenuate the death of neuron cells in a toxic microenvironment[184]; moreover secreted neurotrophic factors from DPS-ICs affect substantia nigra dopaminergic neuron apoptosis and lead to an increase in dopamine uptake.[185] In the therapeutic role, DPS-ICs reduce the apoptosis rate, but also they change the morphology of diseased cells to healthy cells by re-elongating dendrites AD.[186]

While DPS-ICs cannot be classified as MSCs, their neurotrophic factors make them promising for neurodegenerative disease therapies. This type of cell can be used directly for neural diseases by injection, protecting neural cells, and stimulating their healthy environment, or they can be expanded *ex vivo*, and their secretion and exosome can be collected for the treatment of neural diseases. The neurotrophic factors in their secretome can directly affect neuron cells' behavior and help their regeneration, yet a clinical trial has not been conducted, and all investigations are in the *in vivo* and *in vitro* stages.

Peripheral blood SCs

Peripheral blood stem cells (PBSCs) are the same as blood-forming cells in the bone marrow, which includes HSCs, MSCs, endothelial progenitor cells, $CD34^+$ SCs, $CD14^-$ SCs, and very small embryonic-like (VSEL) SCs.[187] Extraction of SCs from the peripheral blood enjoys some benefits rather than the bone marrow-originated cells, like a minimal invasive collection method, lower limitation in the number of autologous SCs and a lower risk of malignant cells' existence.[187] However, the lower number of MSCs in this source of SCs, makes the isolation process of MSCs challenging and unreasonable. Consequently, this source of SCs may not be a good option for neural regeneration. However, some studies reported the differentiation of peripheral blood-derived MSCs into the Schwann cells for the regeneration of injured peripheral nerves.[188,189]

ADVANTAGES AND LIMITATIONS

As with every therapeutic approach, using WDS-LCs for neural tissue regeneration has its challenges as well as advantages. WDS-LCs are most notable for their non-invasive harvesting process, as mentioned previously. Moreover, as they are harvested from waste tissues, there is almost no concern about their supply or ethical issues. Using WDS-ICs also paves the way for autologous SCs implantation in some cases, which decreases the risk of immunogenicity significantly. However, adult SCs properties are greatly dependent on the age of the donor.[190] Moreover, the health condition of the donor affects derived-cell behavior and harvesting procedures, which affect the outcome. For example, diabetic patients would not be great candidates for US-IC-based therapy due to the high concentration of glucose and the presence of proteases in their urine caused by diabetic nephropathy, the derived SCs show poor expandability and regeneration potential. Table 4 displays more details of the advantages and limitations of each type of WDS-ICs.

CLINICAL TRIALS

About 60 clinical trials on the application of WDS-ICs in neural disorders have been listed on the NIH clinical trial webpage at the time of writing. Most of the studies are related to the application of UCS-ICs (42 cases in total with 20 trials in phase 1 and 20 trials in phase 2), followed by ADS-ICs (34 cases in total with 15 cases in phase 1 and 14 cases in phase 2 of clinical trials). However, there are seldom reports regarding the clinical applications of PSCs and DPSs. These trials are mainly carried out to evaluate the safety and efficacy of different insertion routes used for the delivery of WDS-ICs to the neural system. Clinical trials on neurological disorders, particularly stroke and SCIs, have increased over time (Figure S2). The details of reported clinical trials on different kinds of neurological disorders are presented in Table S1.

According to the literature reviewed in this paper, each type of WDS-ICs has experienced different levels of progress. For instance, UCS-ICs showed the highest level of progress, with phase 2 and 3 level trials for the treatment of neural diseases. The reason behind the interest in selecting UCS-ICs is mainly related to their ability to suppress mitogen-induced lymphocyte proliferation as well as multilineage differentiation capabilities.[198,199] Furthermore, AmES-ICs have completed the clinical safety and efficacy tests in Australia and New Zealand for ischemic stroke, which achieved improvement in cognitive functions and modulating neuropathology.[45] Figure 6 displays the progress level of the different WDS-ICs in the treatment of five common neural disorders, namely, stroke, SCI, PD, AD, and MS. Based on the progression of the use of WDS-ICs in the treatment of neural diseases and high numbers of trials reaching the phase 2, there is a hope for further development of a cell-based therapy with low/lacking risk of immunogenicity.

Considering the ethical and tumorgenicity concerns related to some of the WDS-ICs (particularly from the prenatal origins), multiple animal studies and some clinical studies currently focus instead on using the secretion of these cells in the form of extracellular vehicles (EVs). Preliminary results have proved their efficacy in AD treatment. EVs derived from UCMS-ICs and PS-ICs improved neural recovery more than other mesenchymal stem cell (MSC)-derived EVs as the small vesicles can penetrate the blood-brain barrier and exhibit potency similar to their parental cells.[45,200]

Table 4. Advantages and limitations of using different types of waste-derived SCs

Source	Advantages	Limitations	Reference
AmS-ICs and AmFS-ICs	• Low immunogenicity • Inexpensive and high availability • Neuroprotective function • Low teratogenic ability • Broad multipotency • Immunomodulatory and anti-inflammatory properties • Self-renewal and multi-lineage differentiation	• The harvesting procedure through amniocentesis can be challenging.	Deus et al.[31]; Kubiak et al.[33]; Cananzi et al.[35]; Joo et al.[36]; Kim et al.[37]; Nawaz et al.[38]; Veneruso et al.[48]
PS-ICs	• Abundancy of discarded placental tissue • Non-invasive isolation • High differentiation capacity • Immunomodulatory properties • Ability to differentiate to all three layers • High expression of neurogenic markers • Enriched with embryonic progenitor cells and MSCs • Low chance of tumorigenicity	• Chance of infection, • Chance of rejection • Lack of clinical trial	Farmer[93]; Maltepe and Fisher[94]; Oliveira and Barreto-Filho[64]; Fauza[95]; Matikainen and Laine[191]
UCMS-ICs and UCBMS-ICs	• Low cost • Convenient isolation • Large cell content • High proliferation potential • Fast self-renewal • High differentiation capability • Low immunogenicity • Noninvasive harvesting • Low risk of infections • Low possibility of teratomas production • Constant doubling time (DT) up to 10 passages • Higher frequency of colonogenic cells compared with other SCs	• The low survival rate after injection • Disability of homing to the lesion site that decreases their differentiation potential	Zhang et al.[23]; Li et al.[192]; Dalous et al.[193]; Yin et al.[194]; Azzopardi and Blundell[195]
US-ICs	• Cost-effectiveness • High availability • Simple and non-invasive isolation • High expandability • High differentiation capability • Self-renewal • Immunomodulatory properties • Obtainable regardless of age, gender, health condition, and the genetic origin • Low teratogenesis • Being patient-specific	• Require fast and fresh sample collection • Low adherence to non-coated culture plates • Heterogeneous cell population	Bento et al.[119]; Huang et al.[120]; Sato et al.[123]; Pavathuparambil Abdul Manaph[124]; Denham and Dottori[126]; Frega et al.[127]; Gunhanlar et al.[128]
ADS-ICs	• Autologous transplantation • Free of immunogenicity • Ability to secret neurotrophic factors and cytokines • High availability • Self-renewal ability • Pluripotency • Safety • Low-invasive harvesting	• Heterogeneous cell population • Lack of standard isolation and culture protocols • Controversial carcinogenicity	Dai et al.[164]; Choi et al.[148]; Gao et al.[156]; Câmara et al.[196]
DPS-ICs	• Multipotency and self-renewal ability • High plasticity • Patient-specific • Non-invasive isolation	• Low cell density after extraction	Yamada et al.[176]; Kichenbrand et al.[177]; Liu et al.[197]

However, there is a need for more investigation regarding the influence of WDS-ICs transplantation on injured neural systems and their therapeutic efficacy. Moreover, standardization of the isolation, culture, and characterization of stem cells derived from human waste is necessary to ensure consistency and reproducibility of results across different studies and clinical trials. Moreover, long-term follow-up data from clinical trials particularly for WDS-ICs with prenatal origin are needed to monitor for any potential long-term complications or adverse effects.

CONCLUSION AND FUTURE TREND

Considering the low capacity of cellular renewal in neural tissues, cell delivery to the injury site is one of the most effective approaches in treating neural diseases. Accordingly, WDS-ICs show great promise in neural regeneration among various cell sources because of their

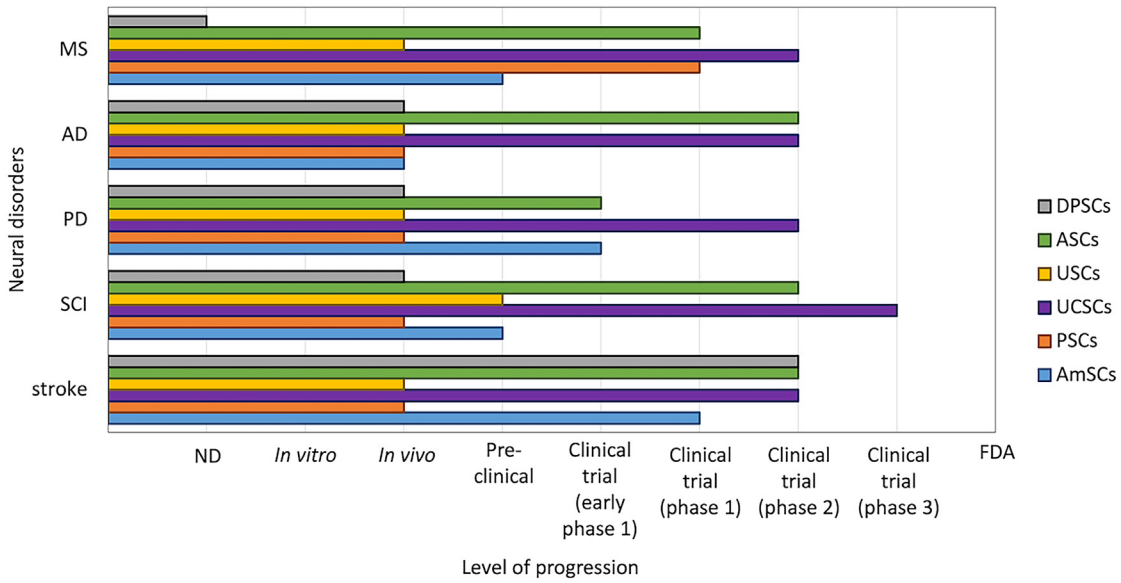

Figure 6. Progress level of different types of WDS-ICs in the treatment of the most common neural disorders, including stroke, SCI, PD, AD, and MS

multipotency and high expandability. These characteristics, along with their cost-effectiveness and low ethical concerns, have increased their application in neural regenerative medicine, either in cell therapy or cell-encapsulated biomaterials. In addition, it's worth noting that certain WDS-ICs, like USCs, possess abundant resources that allow for the utilization of autologous cell sources. This approach reduces immune response risk compared to allogeneic cell sources. These autologous cell sources can pave the way to the development of personalized neural medicine, which has attracted the world's attention.

Extraction techniques are paramount to utilizing the full potential of WDS-ICs fully. This review paper has introduced various non-invasive extraction methods, including utilizing modified cell culture protocols such as culturing cells in growth factor-supplemented media. These innovative techniques have shown promising results in enhancing cellular potency, as well as improving the survival and proliferation rates of WDS-ICs. It is crucial to note that differentiating stem cells always carries inherent safety risks. Therefore, it is imperative to conduct a comprehensive evaluation of the genetic profile of WDS-ICs, both before and after differentiation. This evaluation can help mitigate teratogenesis, the formation of unwanted cell lineages, and the emergence of undesirable cellular responses. By implementing a concise and thorough genetic assessment, the risks associated with these cellular therapies can be effectively minimized, ensuring the safe and optimal utilization of WDS-ICs in regenerative medicine.

Apart from the impact of extraction methods on the ultimate therapeutic outcomes, additional factors related to cell transplantation, such as the method and timing of transplantation, also play a role in obtaining a better outcome. Most studies have consistently demonstrated that early-stage transplantation yields more favorable treatment outcomes, particularly within the initial three days post-injury. In terms of transplantation methods, each approach possesses distinct advantages and disadvantages, necessitating careful consideration of the specific type and location of the neural disorders when making a selection. By considering these factors, healthcare professionals and researchers can make informed decisions regarding the most appropriate transplantation method, thereby optimizing the potential benefits of WDS-IC therapy in neural regenerative medicine.

Regarding the therapeutic effects of WDS-ICs in neural diseases, this research underscores not only the therapeutic potential of transplanted WDS-ICs in addressing neural disorders but also sheds light on the significant alterations in the secretion of cytokines and growth factors, particularly prompting the neuroprotective factors production in the presence of these cells that could improve treatment outcomes. However, the mechanism behind these changes and whether the transplanted cells or their secretion caused the regeneration is still unclear and necessitates further investigation.

Furthermore, this review paper assesses the impact of different delivery techniques on the ultimate therapeutic outcomes. Despite the considerable number of studies investigating the utilization of WDS-ICs for treating neurological diseases, there remains an imperative demand to enhance the efficacy of stem cell delivery for tissue repair or regeneration. In the case of direct delivery of stem cells into the injured site, the selection of an appropriate method for cell administration is of utmost importance to ensure treatment success. In the context of encapsulation or engraftment of stem cells within a carrier, choosing suitable biomaterials possessing suitable physicochemical properties, with or without releasing exogenous bioactive factors, plays a critical role in creating a protective niche. This niche facilitates enhanced cell retention, attachment, viability, and ultimately contributes to long-term neural healing.

In conclusion, given that WDS-ICs represent novel sources of SCs, it is essential to conduct further investigations to advance cellular engineering techniques, gain a comprehensive understanding of potential adverse effects, and achieve successful clinical outcomes. These

endeavors will contribute to refining and optimizing WDS-IC-based therapies, paving the way for their widespread application in neural regenerative medicine.

LIMITATIONS OF THE STUDY

As discussed previously, apart from the type of WDSCs used in CRT for neural diseases, some other parameters, such as the extraction method, time and the pathway of administration, the stage of the diseases, etc. significantly influence the success of the CRT. Because of the lack of a universal guideline for these types of CRT, the general limitations and advantages of WDSCs were reviewed in the context of neural diseases in this study.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110307.

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AUTHOR CONTRIBUTIONS

Conceptualization, Z.E.Z., S.N., S.K., and F.J.S.; investigation, Z.E.Z., S.N., S.K., and F.J.S.; writing – original draft, Z.E.Z., S.N., S.K., and F.J.S.; visualization, Z.E.Z. and K.F.B.; writing – review and editing, R.J.W., D.R.N., and K.F.B.; project administration, Z.E.Z.; supervision, D.R.N. and K.F.B.

DECLARATION OF INTERESTS

The authors declare no financial interest.

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