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Cell Therapy and Functional Recovery of Stroke

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Abstract—Stroke is the most common cause of disability. Brain repair mechanisms are often insufficient to allow a full recovery. Stroke damage involve all brain cell type and extracellular matrix which represent the crucial ''glio-neurovascular niche" useful for brain plasticity. Regenerative medicine including cell therapies hold great promise to decrease post-stroke disability of many patients, by promoting both neuroprotection and neural repair through direct effects on brain lesion and/or systemic effects such as immunomodulation. Mechanisms of action vary according to each grafted cell type: ''peripheral" stem cells, such as mesenchymal stem cells (MSC), can provide paracrine trophic support, and neural stem/progenitor cells (NSC) or neurons can act as direct cells' replacements. Optimal time window, route, and doses are still debated, and may depend on the chosen medicinal product and its expected mechanism such as neuroprotection, delayed brain repair, systemic effects, or graft survival and integration in host network. MSC, mononuclear cells (MNC), umbilical cord stem cells and NSC are the most investigated. Innovative approaches are implemented concerning combinatorial approaches with growth factors and biomaterials such as injectable hydrogels which could protect a cell graft and/or deliver drugs into the post-stroke cavity at chronic stages. Through main publications of the last two decades, we provide in this review concepts and suggestions to improve future translational researches and larger clinical trials of cell therapy in stroke.

Key words: stem cell, cell therapy, stroke recovery, Neural repair, regenerative medicine.

INTRODUCTION

Stroke remains the second leading cause of death worldwide. From 1990 to 2019, the number of incident strokes increases by 70% (Global Burden Disease 1990–2019 (Feigin, 2021)). Moreover, it is the leading cause of severe disability affecting 60–70% of survivors. Ischemic strokes represent around 80% of all cases. Excepting early intravenous (IV) thrombolysis, endovascular thrombectomy, craniectomy for large strokes, and neurorehabilitation, no treatment currently exists to enhance recovery. Therefore, the development of treatment that can enhance brain remodeling processes is necessary but requires a global pathophysiological knowledge. It is well-known that stroke effects are not limited to neurons but involve both brain cells and extracellular matrix in a ''glio-neurovascular niche" that interacts with the peripheral immune system (Dirnagl, 2012; Dirnagl and Endres, 2014; George and Steinberg, 2015). Most of the acute damages have been specifically targeted by neuroprotective drugs without clinical success despite thousands of positive results in animal studies (O'Collins et al., 2006). For these reasons, therapeutic strategies must target all these systems rather than narrowly targeting an individual damage process. Regenerative cell-based therapies could achieve this goal with broad physiological action by simultaneously promoting both endogenous neuroprotection and neural repair (Detante et al., 2014; Toman et al., 2019). These approaches also have the advantage of action over an extended therapeutic

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Abbreviations: Ang1, angiopoietin 1; BDNF, brain derived neurotrophic factor; GABA, γ-aminobutyric acid; GCSF, granulocyte colony-stimulating factor; HIF1, hypoxia inducible factor; IAP, inhibitors of apoptosis proteins; IV, intravenous; MNC, mononuclear cells; MSC, mesenchymal stem cells; NSC, neural stem cells; NSC, neural stem/progenitor cells; SDF1, stromal-derived factor; SVZ, subventricular zone; TGFβ1, transforming growth factor β1; VEGF, vascular endothelial growth factor.

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time-window after stroke and thereby might be effective in many patients from acute to chronic stages.

Endogenous neural protection after stroke

Early after stroke, in addition to possible reperfusion *via* collateral arteries or fibrinolysis, several endogenous protective mechanisms are spontaneously engaged (Fig. 1). There is activation of "anti-excitotoxic" channels, receptors or regulators such as γ-aminobutyric acid (GABA) or K^+ receptors. These phenomena are followed by a transduction phase with amplification of kinases, transcription factors and growth factors (neurotrophin 3, granulocyte colony-stimulating factor (GCSF), vascular endothelial growth factor (VEGF), brain derived neurotrophic factor (BDNF)...). Finally, anti-apoptotic (heat shock protein (HSP 70), BCL2, inhibitors of apoptosis proteins (IAP), hypoxia inducible factor (HIF1)...), anti-inflammatory (IL10, transforming growth factor β1 (TGFβ1)...) and anti-oxidative (α-tocopherol, vitamin C) molecules stimulate neural repair processes (Lo, 2008).

Post-stroke plasticity and neural repair

The adult brain has a capacity for self-repair (Jurkowski et al., 2020) (Fig. 1). During stroke recovery, beyond to adaptive functional compensation, there is "structural" brain plasticity (Carmichael, 2006; Murphy and Corbett, 2009) based on the surviving tissue participating in reorganization of damaged networks (Favre et al., 2014), and exhibiting neuro-synaptogenesis with axonal sprouting. Stroke also increases neurogenesis from neural stem cells (NSC) of the subventricular zone (SVZ) and hippocampal dentate gyrus, generating neuroblasts that migrate to the lesion and differentiate into mature neurons (Ceanga et al., 2021). This post-stroke neurogenesis is closely linked to angio-vasculogenesis and glial function leading to the concept of a "glio-neurovascular niche" as a favorable "stem cell niche" (Zhang et al., 2012). For several months following stroke, neuroblasts from the SVZ migrate close to microvessels through an area exhibiting early vascular remodeling (Thored et al., 2007) stimulated by the release of neurotrophic factors such as angiopoietin 1 (Ang1), stromal-derived factor (SDF1), BDNF, VEGF or metalloproteases. Neuroblasts also enhance angiogenesis with the release of VEGF (Teng et al., 2008), underlining the bidirectional link between microvascular and neuronal remodeling. Additionally, glial cells play a key role with astrocytes removing excitatory neurotransmitters (glutamate) and K^+ and thereby limiting excitotoxic damage. These cells also modulate synaptogenesis by enhancing the formation of functional synapses (Pannasch et al., 2011). Otherwise, oligodendrocyte progenitors, that are resident in white matter or derived from SVZ NSCs, differentiate after stroke into mature oligodendrocytes, thereby enabling axonal remyelination (Arai and Lo, 2009). Microglia also contribute to this repair process, both acting as an inflam-

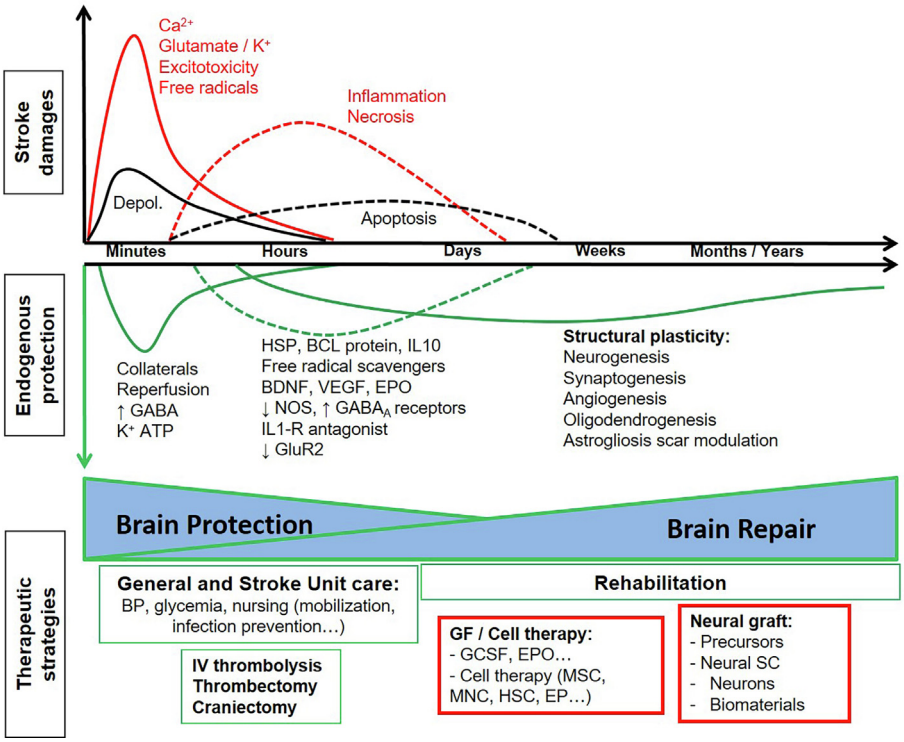

Fig. 1. Pathophysiology of stroke damage, post-stroke endogenous protection and brain repair. Red boxes indicate current experimental therapeutics of regenerative medicine. BCL: B-cell lymphoma protein; BDNF: brain derived neurotrophic factor; BP: blood pressure; Depol.: peri-infarct depolarisation; EP: endothelial progenitors (CD34 +); EPO: erythropoietin; GCSF: granulocyte-colony stimulating factor; GF: growth factors; GluR2: glutamate receptor (subunit 2); HSC: hematopoietic stem cells (CD34 +); HSP: heat-shock protein; IL: interleukin; IV: intravenous; MNC: mononuclear cells; MSC: mesenchymal stromal/stem cells; NOS: NO synthase; VEGF: vascular endothelial growth factor.

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mation modulator and releasing trophic factors such as BDNF (Madinier et al., 2009). Although the effects of these complex processes comprising post-stroke plasticity are reinforced by exercise and rehabilitation, post-stroke neurogenesis from endogenous NSCs is relatively weak and many new neurons die (Arvidsson et al., 2002), often resulting in incomplete functional recovery notably after large stroke. Thus, a deeper understanding of how post-stroke brain remodeling is affected by the integration of neurons into their "glio-vascular" microenvironment is crucial to develop effective regenerative therapies.

CELL THERAPY AFTER STROKE

Cell therapies are particularly relevant as regenerative treatment for stroke. With a wide therapeutic time-window, they could be used to treat many stroke patients, potentially generating significant increments in societal value (Svensson et al., 2012). Transplanted cells can act on endogenous neuroprotective and neural repair processes (Detante et al., 2014; Toman et al., 2019). Traditionally, we distinguish two main strategies: 1) Paracrine trophic support using "peripheral" stem or stromal cells mostly by systemic delivery; 2) Direct neural replacement using neural stem/progenitor cells or neurons mostly by intracerebral injection.

Cell sources and therapeutic cells

Today, the great variety of available cell types form a rich therapeutic arsenal which requires, prior to clinical use, careful consideration regarding the quality of cell manufacturing process, the cell product characterization and functionality, the safety / efficacy preclinical profile, and the *in vivo* biodistribution properties according to the delivery route. Labeling by competent authorities require strict quality control to obtain a clinical grade of advanced therapy medicinal product (ATMP). Currently, bone marrow-derived cell populations, such as mesenchymal stromal/stem cells (MSC) and mononuclear cells (MNC), umbilical cord stem cells, and NSCs are the most commonly investigated in clinical trials.

Cell sources (starting material) can be sorted by their adult, fetal (extra-embryonic), or *in vitro* cell-culture origin. While adult sources such as bone marrow or adipose tissue are widely used in clinical trials, peripheral blood, olfactory mucosa, menstrual blood, brain tissue, breast milk, hair follicles, or dental pulp (Nito et al., 2022) are interesting alternatives. "Fetal" sources, such as umbilical cord, are relatively easy to collect for banking and can provide cell products from the cord itself (Wharton's jelly) (Kim et al., 2013) or cord blood samples (Lee et al., 2021; Ercelen et al., 2023). Placenta (Barlow et al., 2008; Chen et al., 2013), amniotic fluid (Tajiri et al., 2012), or fetal brain samples, including striatum or 1st trimester cerebral cortex (Darsalia et al., 2007; Stroemer et al., 2009) are already used as cell sources in clinical trials (Boncoraglio et al., 2019). Finally, *in vitro* sources such as NSCs or neural cell cultures (Kondziolka et al., 2005; Stroemer et al., 2009) have been also used in clinics. From *in vitro* cultures, pluripotent cells such as embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC) from adult tissue cannot be directly used due to their associated high tumorgenicity risk (Koch et al., 2009). However, as sources, ESCs and iPSCs (Takahashi et al., 2007; Polentes et al., 2012) can be expanded over many passages, thereby providing an unlimited supply of multipotent or mature derived cells usable for cell therapy (Llorente et al., 2021).

Cell therapy products (advanced therapy medicinal products, ATMP) harvested from these different sources can be used for xenogenic, allogenic or autologous treatments. Firstly, stromal/stem cells isolated from bone marrow, adipose tissue, umbilical cord, or blood are widely used. MSCs and multipotent adult progenitor cells (MAPC) can be used under autologous or allogenic conditions without concomitant immunosuppressive drugs owing to their immunomodulatory properties (Chamberlain et al., 2007; Jiang et al., 2007; Honmou et al., 2012; Eckert et al., 2013; Chen et al., 2023). Secondly, NSCs can be harvested from brain tissue or from immortalized neural cell lines, or derived from ESCs or iPSCs (Polentes et al., 2012; Gronning Hansen et al., 2020). NSC grafts seem to provide functional benefit but usually require immunosuppressant treatments. We also include in this heterogeneous "NSC group" the olfactory ensheathing cells (Shyu et al., 2008), oligodendrocyte progenitors (Bulte et al., 1999), and immature neurons (Kondziolka et al., 2000; Kondziolka et al., 2005). Finally, the third type of therapeutic cells includes the hematopoietic stem cells (HSC CD34 +), and endothelial progenitors (EP CD34 +). They are easily harvested from cord blood, bone marrow or peripheral blood after mobilization and represent a type of MNC usable, without amplification, to enhance microvascular repair (Brenneman et al., 2010; Yang et al., 2011). Despite unclear cell characterization, MNCs have been used in several clinical trials with encouraging results particularly as a treatment applied a few days after stroke onset (Moniche et al., 2023).

Mechanisms of action

The functional benefits of cell therapy on stroke recovery are well established in animal models using the above-mentioned cell types coupled with different delivery routes. However, their respective mechanisms of action are complex and vary according to the transplanted cell type. A common characteristic of these cell products is that they simultaneously target many different host brain cell types, including NSCs, neurons, endothelial and glial cells, leading to improvements *via* endogenous repair processes, such as neuro-glio-angiogenesis, axonal sprouting, synaptogenesis. Direct replacement of injured neurons has been suggested after intracerebral (IC) injection (Darsalia et al., 2011; Smith et al., 2012) or intra-arterial (IA) injection of NSCs (Rosenblum et al., 2012), after injection of iPSC-derived neurons (Tornero et al., 2013), or of ESC-derived MSCs (Liu et al., 2009). However, long-term graft survival is relatively poor (Chen et al., 2001; Lu et al., 2002; Shen et al., 2007a; Shen et al., 2007b; Ramos-Cabrer et al., 2010). Moreover, despite possible integration of grafted NSCs

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(Englund et al., 2002; Ishibashi et al., 2004; Daadi et al., 2009) into the host circuitry, functional recovery occurs too early to be caused by newly formed neurons and synapses. Additionally, cell entry or integration into the host brain would not be required to obtain neural repair enhancement (Borlongan et al., 2004a; Boltze et al., 2012). Direct replacement of all damaged brain cells, including cells from ectoderm such as neurons or glia, and from mesoderm such as microglia or endothelium, would require transplantation of "native" pluripotent cells (ESC or iPSC) which might result in tumor formation (Seminatore et al., 2010). Thus, it seems more realistic to expect that cell therapy, notably employing "non-neural" cells, such as MSCs or MNCs, works through paracrine trophic support ("by stander") effects on the injured brain by secreting various growth factors (Teixeira et al., 2013). The improvement in host brain plasticity and associated recruitment of endogenous progenitors has been identified after injection of MSCs (Ding et al., 2013), NSCs by enhancing dendritic plasticity (Minnerup et al., 2011; Minassian et al., 2020). Moreover, the effects of cell therapies on post-stroke vasculogenesis and angiogenesis seem to be crucial in explaining early post-graft benefits. IC injection of endothelial cells can improve vasculogenesis linked to neurogenesis *via* VEGF release (Ishikawa et al., 2013). Proangiogenic effects were also observed early after IV injection of MSCs (Moisan et al., 2016; Kikuchi-Taura et al., 2021) that can contribute to VEGF-induced angiogenesis by supplying metalloprotease MMP-9 (Hao et al., 2011), after injection of NSCs (Roitbak et al., 2008; Horie et al., 2011), EPs (Rosell et al., 2013), or cord-blood MNCs CD34 + (Taguchi et al., 2004). These MNCs contain EPs and smooth muscle progenitors which may collaborate to form a mature vascular network supporting and enhancing neuroblast survival and migration after stroke (Nih et al., 2012). Moreover, EPs, MSCs or NSCs could also facilitate protection or restoration of the blood–brain barrier after stroke (Borlongan et al., 2004b; Horie et al., 2011; Shinozuka et al., 2013; Saft et al., 2020). Another important effect of cell therapy is enhanced glial remodeling and limitations in anterograde degeneration (Gao et al., 2005; Chopp et al., 2009; Li et al., 2014). For example, IV injection of MSCs has beneficial effects on both post-stroke glial remodeling and axonal remyelination (Li et al., 2006). It also increases GDNF levels, creating a hospitable environment for neural repair and neuroblast migration from the SVZ (Shen et al., 2010).

Finally, cell therapies can also limit host cell death through anti-apoptotic (Zhang et al., 2019a) and systemic immunomodulation (Boshuizen and Steinberg, 2018; Malone et al., 2019; Anthony et al., 2022). Although MSCs are well known to attenuate inflammation in both stroke brain and periphery (Bonsack et al., 2020), some immunomodulation properties were also observed for cord blood cells (Vendrame et al., 2005) or NSCs (Martino and Pluchino, 2006; Ben-Hur, 2007) which can both influence splenic inflammatory responses after stroke (Lee et al., 2008). All these mechanisms of action currently lead to the global "bioreactor" hypothesis in which transplanted cells migrate to peripheral organs, and modulate host cells to generate a regenerative environment (Savitz and Cox, 2023).

Optimal route for cell delivery?

The best combination of delivery route and dose for cell therapy after stroke strongly depends on the chosen cell products and expected therapeutic effects. We can expect that IC delivery would be preferred for cell replacement while IV or IA injection for systemic and trophic support. Intravascular injections are less invasive and easier to implement than neurosurgical implantation. The systemic infusion allows cell distribution into vascularized and viable areas of the lesion, not only into localized graft sites. Because cytokine, chemokine and inflammatory signals are released by compromised brain tissue, IV-injected MSCs can preferentially migrate to the damaged brain regions despite initial and transient lung trapping (Detante et al., 2009). As only 1 to 4 / 10,000 IV-injected cells reach the damaged brain, the acute pulmonary passage after IV injection is a major obstacle for IV delivery of NSCs, MAPCs or larger cells such as MSCs (Fischer et al., 2009). This pulmonary passage can be increased by inhibition of MSC CD49d, infusion *via* two boluses (Fischer et al., 2009), or vasodilator sodium nitroprusside preadministration (Schrepfer et al., 2007). Moreover, Mannitol should be used to increase blood brain barrier permeability in order to increase delivery into the brain (Choi et al., 2018).

Other graft routes, such as IA (Bhatia et al., 2018; Savitz et al., 2019; Moniche et al., 2023) or IC (Muir et al., 2020; Zhang et al., 2020; Palma-Tortosa et al., 2021), could avoid the lung entrapment and thereby increase the number of grafted cells in the target tissue. ^{111}In-labeled NSCs can be detected in the ischemic hemisphere after IA but not IV injection (Lappalainen et al., 2008). For NSC delivery, although the IA route seems to be efficient (Guzman et al., 2008), it could increase mortality (Li et al., 2010). For IC graft, most grafted cells die after graft into the damaged area. While a 6-week transplantation delay in NSC administration does not influence cell migration or neuronal differentiation, it could result in poorer graft survival compared to early transplantation (48 h) (Darsalia et al., 2011). Thus, whereas IA or IC grafts are feasible and currently developed, the IV cell injection has been selected for the majority of current clinical trials.

Optimal therapeutic time-window?

The optimal timing for cell therapy after stroke also depends on the cell type, a potential delay for *in vitro* amplification notably for autologous cultures (Jaillard et al., 2020), and their specific mechanism of action (acute neuroprotection *vs* delayed neural repair; trophic effects *vs* graft survival and integration). For example, early (6–24 h post-stroke) IA injection of NSCs leads to greater differentiation into astrocytes, whereas injection at later time points (7–14 days post-stroke) leads to greater differentiation into neurons (Rosenblum et al., 2012). MNCs, obtained from bone marrow aspirates or

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cord blood without amplification delay, could be good candidates for subacute delivery in the first days after stroke (Moniche et al., 2023), possibly serving as an adjunct to thrombolysis or mechanical thrombectomy (Misra et al., 2012). A great clinical advantage of cell therapies would be to delay stroke treatment until the rehabilitation phase in a majority of patients. Whereas some trials suggested that only early (< 48 h) IV injection could be effective (Hess et al., 2017), others have shown that treatment delays up to weeks or months after stroke could be promising by IV (Levy et al., 2019; Jaillard et al., 2020) or IC deliveries (Muir et al., 2020). Moreover, current researches also explore the effect of repeated IV injections (Takemura et al., 2021).

CLINICAL TRIALS OF CELL THERAPY IN STROKE

Many clinical trials have been published (He et al., 2020) (for systematic review, see the Cochrane Review (Boncoraglio et al., 2019)). Several cell products and routes were investigated in small sample trials: IC or intrathecal transplantation of NSCs or immortalized neurons (Muir et al., 2020; Zhang et al., 2020), IC or IV injection of autologous or allogeneic MSCs (Hess et al., 2017; Jaillard et al., 2020; Chung et al., 2021; Chiu et al., 2022; de Celis-Ruiz et al., 2022), IA injection of autologous bone marrow derived cells (ALD-401)(Savitz et al., 2019), IC, IA or IV injections of autologous MNCs (Bhatia et al., 2018; Hammadi and Alhimyari, 2019; Vahidy et al., 2019; Moniche et al., 2023), IC transplantation of HSCs/EPs CD34 + from autologous blood, and IV injection of allogenic cord blood (Laskowitz et al., 2018), IV injection of allogeneic amniotic epithelial cells (Phan et al., 2023), and IC injection of placenta-derived MSC exosomes (Dehghani et al., 2022) (Table 1).

These studies of cell therapy for stroke have reported a good feasibility and safety, and encouraging results about efficacy as suggest by meta-analysis of pioneer controlled trials (Detante et al., 2017) and randomized trials (Boncoraglio et al., 2019). However, direct comparisons are impossible due to the important differences in cell products, routes and post-stroke delays among the trials. Now, larger phase 2/3 trials are warranted, and future trials will also assessed alternatives strategies such as IV injection of allogenic dental pulp stem cells (Suda et al., 2022), or intranasal injection of NSC (Xie et al., 2022).

PERSPECTIVES OF REGENERATIVE MEDICINE IN STROKE

Progresses in cell cultures, combinatorial approaches and biomaterials

Enhancing the graft survival and cell therapy benefits is the common aim of numerous on-going experimental strategies, including combinations of neuroprotectants or growth factors with cell therapy, modification of therapeutic cells, co-transplantations of "synergic" cells (He et al., 2010; Nih et al., 2012), or protective biomaterials. With respect to combinations (Nishimura and Takata, 2021), erythropoietin (Esneault et al., 2008) or NO donor (Chen et al., 2004) can act in synergistic ways with MSC IV injection, as observed when VEGF is combined with IV injection of NSCs (Chu et al., 2005) resulting in a pro-angiogenic effect. Currently, cell manufacturing and bioengineering advances improve cell culture conditions (Roemeling-van Rhijn et al., 2013; Okinaka et al., 2019; Yuan et al., 2019) such as electrical stimulation of NSCs by conductive polymer scaffold (George et al., 2017), and provide genetic cell modifications to obtain products overexpressing interesting factors such as VEGF, BDNF, Ang1, or specific microRNAs (Onda et al., 2008; Steinberg et al., 2016; Yu et al., 2019; Deng et al., 2022; Wang et al., 2022). Moreover, the expected large-scale clinical trials require a greater production of therapeutic cells by using bioreactors and microcarriers, by implementing innovative banking such as iPSCs and derived cells (Pantazis et al., 2022), and by developing stem-cell derived extracellular vesicles (exosome) and microRNA as alternative treatment (Zhang et al., 2019b; Huang et al., 2020; Wang et al., 2020; Pincela Lins et al., 2023). The larger production must also carefully ensure the quality of final products using *in vitro* potency assays to predict the neurorestorative effect and their safety before clinical use (Thakor et al., 2018; Brown et al., 2020; Lyu et al., 2021).

Concerning biomaterials, the combination of drugs, growth factors and cells with biopolymer scaffolds (i.e. matrix) of extracellular matrix molecules (Ghuman et al., 2021; Yaguchi et al., 2021), including collagen and hyaluronic acid, may protect the graft and provide localized and controlled delivery of the therapeutic agent (Boisserand et al., 2016). The use of such "carrier" scaffolds or hydrogels are particularly relevant for injections into the stroke cavity at a chronic stages (Totten et al., 2022), as they might help to avoid a deleterious injection into the adjacent brain tissue where important recovery processes may be underway. Thus, close to the plastic brain regions, grafted scaffolds could provide a favorable environment for drug delivery or graft survival (George et al., 2018). To improve graft cells' proliferation, migration and differentiation, different hydrogels such as hyaluronic acid or collagen gels, or Matrigel have been assessed as cell-seeded scaffolds. The approaches include various combinations, for example, ESC-derived NSCs incorporated into Matrigel (Jin et al., 2010), MSCs into thermoreversible hydrogel (Osanai et al., 2010), into gelatin-laminin scaffold (Sarnowska et al., 2013), or into hyaluronic acid hydrogel optimized for imaging follow-up (Said et al., 2023). However, further optimization of biomaterials is warranted before clinical use to detail their biocompatibility with grafted cells and host brain, and their *in vivo* degradation.

Careful translation to study functional recovery

Lessons from past clinical trial failures should be carefully considered for future translational researches about stroke recovery (Cui et al., 2019; Lalu et al., 2020; Haupt et al., 2022). Although rodent models allow convenient exploration of a range of pathophysiological mechanisms and potential therapies, the anatomic and

Table 1. Selection of published pioneer and recent clinical trials of cell therapy in stroke

Reference	*Country*	*Cases (age)*	*Source*	*Cell type*	*Delay*	*Dose*	*Route*	*Results*
Kondziolka et al. 2005	Pittsburgh, StanfordUSA	6 IS 8 ICH (58 yo) 4 controls: 3 IS / 1 ICH (46 yo)	Human embryonic terato-carcinoma cell line (NT2/D1)	LBS-Neurons (Layton BioSc.)	3.5 years (1–5 years)	5 (n = 7) or 10 million (n = 7) (250 μL) + Cyclosporine	**IC**	FeasibleSafe (single post-operative seizure, n = 1; asymptomatic SDH, n = 1)
Savitz et al. 2005	BostonUSA	5 IS (25–52 yo)	Primordial porcine striatum + antiMHC1 pretreated	LGE cells (Genvec)	5 years (1.5–10 years)	1 million /cm^3 of infarct50 (n = 4) or 80 million (n = 1)	**IC**	Feasible Adverse events (cortical vein occlusion, n = 1; hyperglycemic seizures, n = 1; both with MRI transient abnormalities)FDA termination
Lee *et al.* STARTING 2010	SuwonS. Korea	16 IS (65 +/-14 yo) 36 controls (64 +/-12 yo) *including the previous trial*	Auto BMExpansion in fetal calf serum	MSCExpansion in fetal calf serum	2.5–5 and 5–9 weeks	50 million x 2	**IV**	Feasible Safe (3–5 year follow-up)Beneficial: recovery, increase of serum SDF1α
Savitz *et al.* SIVMAS 2011	HoustonUSA	10 IS (55 +/-15 yo) 79 historical controls (63 +/-12 yo)	Auto BM	MNC	1–3 days	7 (n = 1) or 8.5 (n = 1) or 10 million / kg	**IV**	FeasibleSafe (death from pulmonary embolism at 40 days, n = 1)
Honmou *et al.* 2011	SapporoJapan	12 IS (59 yo, 41–73)	Auto BM	MSCExpansion in autologous serum	10 weeks (5–19 weeks)	110 million (60–160 million)	**IV**	FeasibleSafe
Bhasin *et al.* 2013	New Delhi India	18 IS 2 ICH (45 +/-12 yo) 20 controls: 19 IS / 1 ICH (45 +/-10 yo) *including the previous trial*	Auto BM	MSC Expansion in animal serum-free mediaMNC	10 months 3 m-2y	MSC: 50–60 million (n = 6)MNC: 50–60 million (n = 14)	**IV**	Feasible SafeBeneficial: recovery (only for MNC), activation fMRI
Prasad *et al.* 2014	India	58 IS 62 controls (18–70 yo)	Auto BM	MNC	18 days (7–30)	281 million (30–500)	**IV**	Feasible Safe No benefit No change on ^{18}FDG PET
Taguchi *et al.* 2015	Osaka, KobeJapan	12 IS (20–75 yo)	Auto BM	MNC	7–10 days	250 or 340 million	**IV**	FeasibleSafe
Kalladka *et al.* PISCES 2016	Glasgow, UK	11 IS (64–82 yo)	Immortalised human NSC cell line	NSC CTX-DP (ReNeuron)	29 +/-14 months	2, 5, 10, or 20 million	**IC**	Feasible Safe Beneficial: recovery

Table 1 (*continued*)

Reference	*Country*	*Cases (age)*	*Source*	*Cell type*	*Delay*	*Dose*	*Route*	*Results*
Steinberg *et al.* 2016	Stanford, USA	18 IS (61 +/-10 yo)	Allo BM	Gene modified MSC (Notch1+, SanBio SB623)	6–60 months	2.5, 5 or 10 million	**IC**	Feasible Safe Beneficial: recovery
Hess *et al.* MASTERS 2017	USA / UK	8 IS + 65 IS 61 placebo (18–83 yo)	Allo BM	MAPC (Athersys)	1–2 days	400 or 1200 million	**IV**	Feasible Safe
Levy *et al.* 2019	California USA	15 IS + 21 IS (61 +/-11 yo)	Allo BM	Hypoxia cultured MSC	4 +/- 5 years	0.5, 1 or 1.5 million / kg	**IV**	Feasible Safe Beneficial: recovery
Vahidy *et al.* 2019	Houston USA	25 IS (61 +/-13 yo) 185 matched controls (64+/-12.5 yo)	Auto BM	MNC	1–3 days	10 million /kg	**IV**	Feasible Safe
Jaillard *et al.* ISIS 2020	Grenoble France	16 IS 15 controls (46–59 yo)	Auto BM	MSC	1 month	100 or 300 million	**IV**	Feasible SafeBeneficial: recovery, activation fMRI
de Ceilis-Ruiz *et al.* AMASCIS 2022	Madrid Spain	4 IS (70–82 yo) 9 placebo (69–80 yo)	Allo adipose tissue	ADSC	13 days	1 million /kg	**IV**	Feasible Safe
Moniche *et al.* IBIS 2023	Sevilla Spain	39 IS 38 controls (62 +/- 13 yo)	Auto BM	MNC	6 days	2 or 5 million /kg	**IA**	Feasible Safe

ADSC: adipose-derived stem cells; Auto: autologous; Allo: allogenic; BM: bone marrow; DTI: diffusion tensor imaging; ^{18}FDG PET: 18-fluorodeoxyglucose positon emission tomography; IA: intra-arterial; IC: intracerebral; ICH: intracerebral hemorrhage; IS: ischemic stroke; IV: intravenous; MNC: mononuclear cells; MSC: mesenchymal stromal/stem cells; NSC: neural stem cells.

pathophysiologic differences between rodent and human stroke arising from differences in cortical architecture, regional neuronal density, arterial network distribution, immunological mechanisms, pre-existing vascular risk factors, concomitant medical treatments, and recovery duration intervals that could easily impede the effective translation of animal study results to the clinic. The effect of these differences on clinical transfer potential might be anticipated by using computational modeling techniques. ‘‘In silico” mathematical stroke models can simulate cell therapy effects by implementing explicit models of neurogenesis (Aimone and Weick, 2013) and could facilitate the generation of mechanistic hypotheses. In addition, effort could profitably be exerted to improve experimental methods, relevant recovery scores, and statistical analysis by following common guidelines (Hommel et al., 2016; Boltze et al., 2019; Nagpal et al., 2021). Current studies must also include rehabilitation effects (Ghuman et al., 2022; Yabuno et al., 2023) and comorbidities in rodent models such as hypertension and diabetes (Gomez-de Frutos et al., 2019; Mangin et al., 2019; Diekhorst et al., 2020). Moreover, reliable biomarkers of stroke recovery should be added to corroborate behavioral effects: multimodal MRI (Bagdasarian et al., 2021; Dumot et al., 2022) and biological blood markers (Pala et al., 2020) such as, for example, SDF1, βNGF or circulating EPs or extracellular vesicles derived from injected MSCs (Bang et al., 2022).

In the future, the development of neurorestorative therapies should carefully take into consideration all these translational and safety concerns to allow an efficient transfer from bench to bedside, particularly for the emerging cell products such as genetically-modified cells.

Translation from bench to clinic is relatively slow and there is no clear evidence that cell therapy is effective in stroke patients. Beyond previous small proof-of-concept trials, larger multicentric clinical studies are warranted to clearly answer this question of efficacy. Main limitations to conduct large trials are the huge cost of clinical-grade cell products (ATMP) with complex and expansive cell manufacturing, and restrictive regulations by competent authorities about innovative biotherapies. In next decade, we can hope that large financial commitments, such as EU and French efforts through projects of industrialization and harmonization of stem cell manufactures, will provide sufficient cells’ stocks for these large trials. Moreover, if it is not clear that current cell products can be beneficial in humans, the fast development of new products by the very active field of cell and material engineering, as described above, should improve effects in patients in next years.

Today, although patients and proxies are requesting treatments to decrease stroke burden, the scientific approach must be encouraged to avoid the important ‘‘stem-cell medical tourism” (Barclay, 2009), and the patients’ need should be included during the conception of cell therapy trials (Nagpal et al., 2019).

Systemic or intracerebral neurorestorative therapies include both growth factors and cell based techniques that can be combined or used with biomaterials. They hold great promises for stroke treatment, as they both enhance several processes involved in post-stroke recovery and also can be used across a wide therapeutic time-window. However, preclinical studies must still be conducted in parallel with larger clinical trials. Indeed, related to the rapidly expanding therapeutic arsenal of these ‘‘advanced therapy medicinal products”, many interdependent questions remain to be answered about specific mechanisms of action and the details of the procedures themselves. Assuming these remaining questions, we can hope that regenerative biotherapies will decrease post-stroke disability for many patients.

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DECLARATION OF INTEREST

None.

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