Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic

Zheng Gang Zhang, Michael Chopp

Restorative cell-based and pharmacological therapies for experimental stroke substantially improve functional outcome. These therapies target several types of parenchymal cells (including neural stem cells, cerebral endothelial cells, astrocytes, oligodendrocytes, and neurons), leading to enhancement of endogenous neurogenesis, angiogenesis, axonal sprouting, and synaptogenesis in the ischaemic brain. Interaction between these restorative events probably underpins the improvement in functional outcome. This Review provides examples of cell-based and pharmacological restorative treatments for stroke that stimulate brain plasticity and functional recovery. The molecular pathways activated by these therapies, which induce remodelling of the injured brain via angiogenesis, neurogenesis, and axonal and dendritic plasticity, are discussed. The ease of treating intact brain tissue to stimulate functional benefit in restorative therapy compared with treating injured brain tissue in neuroprotective therapy might more readily help with translation of restorative therapy from the laboratory to the clinic.

Introduction
Stroke is a major cause of morbidity and mortality worldwide. Thrombolytic therapy with alteplase is effective when given within 4·5 h after stroke.1,2 However, fewer than 5% of patients with ischaemic stroke in the USA receive this treatment. Even with effective thrombolysis, most patients will have neurological deficits.3,4 Therefore, development of therapies for ischaemic stroke designed specifically to reduce neurological deficits is crucial.

Preclinical data indicate that cell-based and pharmacological therapies that enhance brain-repair processes substantially improve functional recovery when given 24 h or later after stroke or brain injury.5–11 Cell-based therapies under investigation include use of bone-marrow mesenchymal cells, cord blood cells, fetal cells, and embryonic cells.12–20 Pharmacological treatments include drugs that increase cGMP (eg, phosphodiesterase 5 inhibitors, such as sildenafil and tadalafil), statins, erythropoietin, granulocyte-colony stimulating factor, nicotinic acid, and minocycline.17,21–25 The common restorative characteristic of these therapies is that they target many types of parenchymal cells (including neural stem cells, cerebral endothelial cells, astrocytes, oligodendrocytes, and neurons), leading to enhancement of endogenous neurogenesis, angiogenesis, axonal sprouting, and synaptogenesis in ischaemic brain tissue. These events collectively improve neurological function after stroke. Furthermore, in addition to providing enhanced cerebral tissue perfusion, angiogenic vessels produce neurotrophic compounds, which create a suitable microenvironment within the injured brain that attracts endogenous stem cells and promotes integration of these cells within the parenchyma. Together with parenchymal astrocytes, angiogenic vessels contribute to enhancement of synaptogenesis and axonal sprouting.

In this Review, we describe the mechanisms by which cell-based and pharmacological treatments stimulate endogenous brain remodelling after stroke, particularly neurogenesis, angiogenesis, axonal plasticity, and white-matter change. We also briefly outline the potential of MRI to view these restorative events. Finally, we discuss the challenges of translating these therapies into the clinic and ongoing clinical trials.

Enhancement of neurogenesis
The subventricular zone (SVZ) of the lateral ventricle and the dentate gyrus of the hippocampus of adult rodent brains contain neural stem cells that produce neuroblasts.26,27 Under physiological conditions, neuroblasts in the SVZ travel via the rostral migratory stream to the olfactory bulb where they differentiate into granule and periglomerular neurons throughout adult life.28–30 In the SVZ of adult human brains, neural stem cells are present in a band of astrocytes separated from the ependyma.31–33 In experimental stroke, focal cerebral ischaemia increases neurogenesis in the ipsilateral SVZ (figure 1) and neuroblasts emigrate from the SVZ to the ischaemic boundary regions of the striatum and cortex where they have the phenotypes of mature neurons.34–37 Stroke-induced neurogenesis also takes place in the SVZ and ischaemic boundary of adult human brains, even in elderly patients aged 60–87 years.38–40

Neurogenesis induced by stroke involves proliferation of neural stem and progenitor cells, differentiation of neural progenitor cells, and migration of neuroblasts to the ischaemic boundary where neuroblasts mature into resident neurons and integrate into the parenchymal tissue. In adult mice, gene-profile analysis of neural progenitor cells from the SVZ that were isolated by laser-capture microdissection has shown that these cells share more than 70% of all expressed genes with embryonic cortical neural progenitor cells.41 In murine neural progenitor cells from the SVZ, stroke activates many genes involved in neurogenesis during embryonic development.42 The most upregulated genes after stroke are those in the transforming growth factor β superfamily, such as bone morphogenetic protein 8, bone morphogenetic protein type I receptors, and growth differentiation factor 2.43 After stroke, adult neural progenitor cells seem to recapture

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Department of Neurology, Henry Ford Hospital, Detroit, MI, USA (Z G Zhang MD, M Chopp PhD); and Department of Physics, Oakland University, Rochester, MI, USA (M Chopp)
Correspondence to: Michael Chopp, Neurology Department, Research Division, Education and Research Building, Room 3056, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA
chopp@neuro.hfh.edu
embryonic molecular signals, which probably mediate neuroblast migration and stroke-induced proliferation and differentiation of neural progenitor cells.

In vivo analysis of the cytokinetics of neural progenitor cells has suggested that stroke might trigger actively proliferating neural progenitor cells from the SVZ in adult rodents to repeat the cell-cycle kinetics of the embryonic form of these cells. During cortical neurogenesis, cell-cycle length is associated with progression of neural progenitor cells from proliferation to neurogenic division, and lengthening of the G phase of the neuroepithelial cell cycle activates neuronal differentiation. Decreasing the G phase of the cell cycle at 2 to 4 days after stroke was associated with an increase in dividing daughter cells that remained within the cell cycle to expand the SVZ progenitor pool rapidly. By contrast, lengthening the G phase at 4 to 14 days after stroke was accompanied by an increased number of daughter cells that left the cell cycle to differentiate into neurons. These data indicate that stroke triggers dynamic changes in the G phase of the actively dividing SVZ cell cycle, resulting in early expansion of a neural progenitor pool and subsequent neuronal differentiation, which leads to increased neurogenesis. Neuroblasts in the ischaemic boundary have the phenotypes of mature neurons by use of the patch-clamp technique, new neurons in the ischaemic boundary were shown to have the electrophysiological characteristics of mature neurons. These findings suggest that neuroblasts mature into resident neurons and integrate into local neuronal circuitry. However, neurogenesis is diminished after stroke and many newly formed neurons die.

Cell-based and pharmacological therapies increase neurogenesis in the ischaemic brain (figure 1). These therapies activate the phosphatidylinositol 3-kinase (PI3K)-Akt signalling pathway in neural progenitor cells. The PI3K-Akt pathway affects several cellular functions such as cell survival, proliferation, differentiation, and migration. Akt regulates proliferation of neural stem cells and neuronal differentiation in embryonic mice, and blockage of Akt activation with a selective PI3K inhibitor decreases proliferation of neural progenitor cells. Therefore, the PI3K-Akt signalling pathway seems to be important in the regulation of neurogenesis enhanced by restorative therapies. However, initiation of the PI3K-Akt signalling pathway could differ with individual therapies. Treatment with bone-marrow mesenchymal cells stimulates brain parenchymal cells to secrete an array of neurotrophic factors, including basic fibroblast growth factor and brain-derived neurotrophic factor, which are known to activate Akt. Erythropoietin activates the PI3K-Akt pathway by interaction with its receptor in neural progenitor cells, whereas phosphodiesterase 5 inhibitors and statins are thought to activate Akt via increased concentrations of cGMP.

Mammalian achaete-scute homolog 1 (Mash1) and neurogenin 1 (Neurog1; also known as Ngn1) are pro-neuronal basic helix-loop-helix (bHLH) transcription factors that mediate differentiation of neural progenitor cells into neurons. Akt regulates the assembly and activity of bHLH-coactivator complexes to promote this differentiation. Inhibition of the PI3K-Akt pathway in neural progenitor cells suppresses expression of Mash1 and Ngn1. As a result, neuronal differentiation induced by erythropoietin and statins is prevented. Small interfering RNA in neural progenitor cells also attenuates expression of endogenous Mash1 and Ngn1, which further minimises the rise in the neuronal population caused by erythropoietin and statins. These findings indicate that the PI3K-Akt signalling pathway activated by these restorative therapies can trigger pro-neuronal bHLH transcription factors in neural progenitor cells, leading to neuronal, but not astrocytic, differentiation.
Neurogenesis in the adult brain is associated with neurological function.79 Ionising radiation applied to the subgranular zone of the dentate gyrus where there are neural progenitor cells reduces neurogenesis and impairs functional recovery after global ischaemia.80 Neurogenesis enhanced by cell-based and pharmacological therapies might drive functional improvement during stroke recovery. A substantial improvement in neurological function and enhancement of neurogenesis has been observed even 1 year after stroke in animals treated with bone-marrow mesenchymal cells.90 However, currently, there are no data on the mechanisms of endogenous neurogenesis in functional recovery after stroke. In a recent genetic study in adult mice, conditional ablation of newly formed neurons in the olfactory bulb resulted in shrinkage of the olfactory bulb, and removal of new neurons in the dentate gyrus caused impairment of memory.51 This transgenic mouse line could provide insight into the direct effect of neurogenesis on functional outcome during stroke recovery.

**Enhancement of cerebral angiogenesis**

The cerebral vascular system mainly develops through angiogenesis.76 Although proliferation of cerebral endothelial cells ceases in the adult brain, angiogenesis in adult human and rodent brains can take place under pathophysiological conditions.71,72 In the rodent brain, capillary sprouting is initiated at the border of the infarct and new vessels develop in the ischaemic boundary between 2 and 28 days after the onset of stroke,72,74 whereas angiogenesis takes place in the penumbra of human ischaemic brains 3 to 4 days after stroke.72 Angiogenic vessels are permeable during the early stages of development and new vessels become less leaky as they mature.72,75 We have used this transient increase in vascular permeability as a signal to identify formation of new blood vessels.86 Vascular permeability can be quantified and detected with MRI T1 indices of brain-to-blood transfer constants of extrinsic-contrast agents, such as gadolinium DTPA (diethylene triamine pentaacetic acid), as well as intrinsic magnetisation-contrast techniques.91,92 Cerebral blood flow can be measured by perfusion-weighted MRI. With these MRI indices, we found that a transient increase in vascular permeability in the ischaemic boundary 2 to 3 weeks after stroke led to increased cerebral blood flow 6 weeks after stroke.93 Histological measurement of vascular density showed notable correlation between increased cerebral blood flow and rises in vascular density indicative of angiogenesis.86 These findings show that stroke induces new functional vessels in the ischaemic boundary and that angiogenesis can be monitored with MRI.

Angiogenesis is a multi-step process that involves endothelial-cell proliferation, migration, tube formation, branching, and anastomosis (figure 2).77–79 Vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR2) initiate angiogenesis, and angiopoietins 1 and 2 and their receptor, Tie2, are involved in maturation, stabilisation, and remodelling of vessels.79 In rodent ischaemic brain tissue, upregulation of VEGF and VEGFR2 and of angiopoietins and Tie2 lasts for at least 28 days.80,81 Patients with stroke have high serum concentrations of VEGF 7 days after acute stroke, and these concentrations remain high for 14 days after stroke.82 The VEGF and VEGFR2 and the angiopoietin and Tie2 pathways mediate angiogenesis in the ischaemic boundary.71,72,74 VEGF and VEGFR2 upregulated by stroke promote cerebral-vessel sprouting to form new permeable vessels, whereas upregulation of angiopoietin 1 and Tie2 leads to maturation of the vessels to functional cerebral vessels.71,72,74,75 Treatment with VEGF 24 h after stroke enhances angiogenesis.7,86 In rodents, cell-based and pharmacological therapies increase angiogenesis in the ischaemic boundary by regulating expression of VEGF and VEGFR2, as well as angiopoietins 1 and 2 and Tie2.87–90 In preclinical studies, drugs such as recombinant human erythropoietin, statins, and phosphodiesterase 5 inhibitors increase concentrations of VEGF in the ischaemic boundary. In a tube-formation assay, blockade of VEGFR2 in endothelial cells suppressed angiogenesis promoted by these drugs.3,8,93,94 In mice, endothelial nitric oxide synthase mediated statin-induced angiogenesis.95 Bone-marrow mesenchymal cells stimulated parenchymal cells in rats to express VEGF, angiopoietin 1, and Tie2,96 leading to increased angiogenesis.

**Figure 2:** Stroke induces angiogenesis within the ischaemic boundary

![Image](image-url)
and maturation of newly formed vessels by reducing vascular permeability and increasing the expression of tight-junction proteins.86

The effect of cell-based and pharmacological therapies on angiogenesis has been non-invasively monitored with MRI indices, including susceptibility-weighted imaging and T2*-weighted imaging. These techniques use susceptibility differences in cerebral tissues and are sensitive to blood in cerebral veins because of blood oxygenation level dependent (BOLD) effects.10,15,16 Treatment of stroke with sildenafil or erythropoietin in rats substantially increases angiogenesis detected by susceptibility-weighted and T2*-weighted imaging in the ischaemic boundary, and enhanced angiogenesis lasts for at least 6 weeks after stroke (figure 3).14–16

Angiogenesis is essential for ischaemic brain repair as this event stimulates blood flow and metabolism in the ischaemic boundary. In patients with stroke, there was a significant correlation between the number of cerebral blood vessels in the cortical rim and survival times.7,8,9 Patients who have a high density of blood vessels seem to survive longer than patients with low vascular density.7 In ischaemic brain tissue of animals treated with cell-based and pharmacological therapies, angiogenesis was increased, which was associated with improvements in functional outcome.3,10,19,81 These findings suggest that, in addition to neurogenesis, angiogenesis increased by these restorative therapies also improves functional recovery.

**Coupling of neurogenesis and angiogenesis**

Stroke induces angiogenesis and neurogenesis, two processes that are linked together.7,17,18,20,21,22,23 Cerebral blood vessels mainly provide nutritive blood flow. However, cerebral endothelial cells secrete factors that regulate the biological activity of neural progenitor cells. Under physiological conditions, neurogenesis in the subgranular zone of the dentate gyrus takes place within an angiogenic microenvironment.82 The laminin receptor α6β1 integrin expressed by neural stem and progenitor cells interacts with laminin-containing vessels in the SVZ of adult mice: blockage of this interaction increases the proliferation of neural stem cells and progenitor cells.104,105 After stroke, neuroblasts formed in the SVZ migrate to the ischaemic boundary where angiogenesis takes place and, during migration, these cells are closely associated with cerebral vessels.25–27 Suppression of angiogenesis either with endostatins or with a neutralising antibody against Tie2 substantially reduces migration of newly formed neuroblasts to the ischaemic region.88 Activated endothelial cells in angiogenic areas secrete many factors, among which are stromal-derived factor 1α and matrix metalloproteinases (MMPs).20,103,104 Stromal-derived factor 1α is a CXC chemokine that mediates neuroblast migration in the developing brain.107 In adult rodent brains, stromal-derived factor 1α released by activated endothelial cells in the ischaemic boundary attracts neuroblasts from the SVZ to the boundary by interacting with its receptor CXCR4 expressed in neuroblasts.27,30,108,109 Blocking CXCR4 inhibits stroke-induced neuroblast migration.105,110,111 Treatment with bone-marrow mesenchymal cells increases concentrations of stromal-derived factor 1α and promotes migration of neuroblasts to the ischaemic boundary.111–113

MMPs degrade the extracellular matrix, which enables cells to penetrate the extracellular matrix.104,110 MMP2 and MMP9 facilitate neuroblast migration to the ischaemic boundary.104,110 In vitro, erythropoietin stimulates cerebral endothelial cells to secrete active forms of MMP2 and MMP9.112 Co-culture of cerebral endothelial cells activated by erythropoietin with neural progenitor cells promotes neuroblast migration, and MMP2 and MMP9 mediate cell motility.112 These data indicate that MMPs regulate the relation between erythropoietin-enhanced angiogenesis and neurogenesis.10,111

In addition to guiding neuroblast migration, activated endothelial cells secrete VEGF to increase neurogenesis.103 Co-culture of cerebral endothelial cells from the ischaemic boundary with neural progenitor cells from the non-ischaemic SVZ substantially increases the number of neurons.105 Blockage of VEGFR2 with a VEGFR2 antagonist suppresses the effect of endothelial cells on neurogenesis.102 VEGF is an angiogenic and a neurogenic growth factor.108 Intraventricular infusion of VEGF increases neurogenesis in the SVZ and dentate gyrus of adult mice.104 Therefore, VEGF and VEGFR2 could be common factors involved in the promotion of angiogenesis and neurogenesis.

Neuronal progenitor cells also enhance angiogenesis.104,105 In a microarray analysis of neural progenitor cells isolated by laser-capture microdissection, ischaemic neural progenitor cells in the SVZ expressed several angiogenic factors, including angiopoietin 2, VEGF, and fibroblast growth factor.46 These neural progenitor cells promote...
angiogenesis in vitro, as measured by a capillary-like tube-formation assay. Transplantation of neural progenitor cells into ischaemic brains also promoted angiogenesis. Collectively, these data provide insight into the molecular mechanisms that underlie the coupling of angiogenesis and neurogenesis enhanced by cell-based and pharmacological therapies. These findings suggest that, in vivo, neurogenesis and angiogenesis are highly interdependent and work together to promote brain remodelling and subsequent improvement of neurological function after stroke.

**Effects on astrocytes, oligodendrocytes, and axons**

Axons in ischaemic brains have little capability to sprout. Astrocytes form glial scars along ischaemic lesions and produce proteoglycans that inhibit axonal growth and that act as physical and biochemical barriers to axonal regeneration. In experimental stroke, treatment with bone-marrow mesenchymal cells substantially increases axonal density around the ischaemic lesion, extends axonal fibres, and orients these fibres parallel to the boundary of a coronal section of an ischaemic lesion. The increased axonal density is maintained for at least 1 year after stroke. Bone-marrow mesenchymal cells substantially reduce expression of axonal-growth inhibitory proteins, such as reticulon (Rtn4; also known as Nogo), enabling axonal and neurite outgrowth. Real-time RT-PCR analysis of astrocytes isolated by laser-capture microdissection showed that transplantation of bone-marrow mesenchymal cells notably downregulated neurocan (Ncan), a proteoglycan that inhibits axonal growth. Co-culture of bone-marrow mesenchymal cells with astrocytes also substantially reduced expression of Ncan in astrocytes activated by deprivation of oxygen-glucose. These findings suggest that, in addition to induction of many growth factors within astrocytes, bone-marrow mesenchymal cells suppress inhibitory genes for axonal regeneration, which could contribute to facilitation of axonal remodelling. Suppression of inhibitory proteoglycans by cell-based therapies also leads to neurite outgrowth and axonal remodelling in the spinal cord and ipsilateral and contralateral hemispheres, which significantly correlate with improved functional outcome after stroke.

Mature oligodendrocytes form myelin sheaths for sprouting axons in ischaemic brain tissue. These oligodendrocytes are derived from non-myelinating oligodendrocyte progenitor cells that are present in the corpus callosum, striatum, and SVZ of adult rodent brains. Transplantation of bone-marrow mesenchymal cells substantially increased the number of oligodendrocyte progenitor cells in these areas of the ischaemic hemisphere and the number of mature oligodendrocytes in the ischaemic boundary adjacent to myelinated axons. Treatment of stroke with erythropoietin or sildenafil also notably enhanced myelinated axons adjacent to the ischaemic boundary. Therefore, cell-based and pharmacological therapies might promote generation of oligodendrocyte progenitor cells in the ischaemic brain, which migrate to target axons where they extend their processes and myelinate axons. In addition to erythropoietin, statins promote neurite outgrowth in vitro and increase synaptogenesis around the ischaemic boundary.

Diffusion-tensor imaging enables delineation of the anatomical connectivity of white-matter pathways. Water in white matter moves more easily in the direction parallel to the tract than perpendicular to it. This diffusional directionality is known as fractional anisotropy and can be used to detect changes in white-matter structure in the ischaemic brain. Fractional anisotropy is directly correlated with histological markers of myelination (figure 4). Diffusion-tensor imaging measurements have shown that treatment of stroke with sildenafil or erythropoietin substantially increases fractional anisotropy measurements around the ischaemic boundary starting 2 weeks after stroke; these increases lasted for at least 6 weeks after stroke. Histological analysis verified that axons in areas with high fractional anisotropy measurements were myelinated. Angiogenesis detected with T2*-weighted imaging was shown to take place 1 week earlier than increased fractional anisotropy measurements, suggesting that angiogenesis is closely associated with axonal remodelling.

![Figure 4: Diffusion tensor imaging measurements of FA and fibre tracking](image-url)
Translation to the clinic
Apart from treatment with alteplase, translation of therapies for stroke to the clinic from those in the laboratory has not been successful.125 These attempts all aimed to develop neuroprotective treatments of stroke with early intervention to reduce the volume of cerebral infarction. Reasons for failure include the short time window required to intervene to salvage cerebral tissue. Many of the drugs tested in the laboratory were given immediately after or within the first hours after onset of stroke. Translation to the clinic frequently involved extending the therapeutic window to 6 h or longer after stroke: times at which animals showed no evidence of adverse effects.134 Furthermore, without adequate tissue perfusion, neuroprotective drugs cannot target the compromised tissue.

The essential difference between neuroprotective and neurorestorative treatments is that the former treat the lesion and the latter, whether they are cell-based or pharmacological therapies, treat the intact tissue.135,136 The therapeutic window and treatment protocols will thus be very different. Restorative therapies are effective when initiated 1 month after stroke onset110 and cerebral perfusion is not problematic because the therapeutic target is cerebral tissue with normal perfusion. Restorative treatments are expected to reduce some of the impediments to the translation of laboratory-proven therapies to patients. However, restorative treatments have their own sets of complicating factors. The treatments must be clearly proven to be safe in patients; this is particularly challenging for cell-based therapies. A further complication is that patients who have had stroke are commonly not in a controlled environment. Moreover, patients often have various types and conditions of rehabilitation and home and social environments, which can affect functional response.135 The interactions between restorative interventions and different environments, comorbidities, and rehabilitation strategies must be taken into account. More extensive and specific neurological outcome measures, beyond the National Institutes of Health stroke scale, Barthel index, and European stroke scale, need to be developed and implemented for restorative treatments.125 Recommendations and guidelines for translation of laboratory stroke studies with stem cells to patients have been published after the Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS) conference.138 MRI could have an important role in the management of patients with stroke who receive neurorestorative treatment. The focus of MRI should not be on the ischaemic lesion volume and cerebral oedema, but on the restructuring of white matter, angiogenesis, and, possibly, neurogenesis and synaptic activity. These changes form the biological basis of functional improvement and can be non-invasively monitored with MRI and magnetic resonance spectroscopy, which could be used to monitor response to treatment and, possibly, to predict therapeutic response.

Clinical trials
Approaches to enhance recovery of function after stroke in the laboratory and in clinical trials extend beyond the use of drugs and cell-based treatments and include electromagnetic stimulation, device-based strategies, repetitive training, and task-oriented strategies.136 The recent Extremity Constraint Induced Therapy Evaluation (EXCITE) trial reported significantly positive results for distal and proximal arm motor function in response to constraint-induced therapy.139,140 Here, we focus on cell-based and pharmacological approaches and how these approaches change brain structure and neural plasticity to promote functional recovery; few such restorative therapies tested in the laboratory have moved to clinical trials (table).141–145 Patients with ischaemic stroke treated with autologous bone-marrow mesenchymal cells had no adverse effects and showed functional improvement.140 A dose-tiered phase I safety trial of sildenafil in patients with stroke is in progress,145 with patients receiving treatment 3–7 days after stroke. In a case of compassionate use, sildenafil caused notable recovery in a patient with locked-in syndrome.146 Plasticity of human and animal brains is increased after stroke, with clear induction of angiogenesis and neurogenesis. The available preclinical data show functional improvement through brain remodelling. Many of the therapies under consideration for restorative treatment of stroke are in clinical use for other indications; therefore, assuring the safety of these compounds for patients with stroke might not be difficult. Because most patients with stroke could be treated with restorative therapy, and the clinical need to promote recovery in patients with stroke is great, efforts to translate laboratory studies into the clinic safely and quickly are needed.

Conclusions
The cell-based and pharmacological therapies described in this Review target multiple types of parenchymal cells in ischaemic brain tissue to increase neurogenesis,
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Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "cell-based and pharmacological therapies", "experimental stroke", "restorative therapies", "neurogenesis", "angiogenesis", "MRI", from January, 1975, to January, 2009. Papers for cell-based and pharmacological therapies were only included if treatments were initiated 24 h or longer after stroke. Only papers published in English were reviewed.

angiogenesis, and axonal outgrowth during recovery. Potential mechanisms underlying these beneficial therapies are emerging. Future studies must investigate mechanisms that temporally and spatially coordinate these events.

Brain remodelling after stroke and subsequent improvement of functional outcome probably result from several restorative events that are enhanced by restorative therapies. Induction of angiogenesis couples with and promotes neurogenesis and neuroblast migration to the lesion. These interlinked remodelling events could create a microenvironment within the injured brain through their interaction with astrocytes and oligodendrocytes, which then promote neurite outgrowth and plasticity within the brain and spinal cord. These restorative events enhanced by restorative cell-based and pharmacological therapies lead to improved functional outcome.

One main difference between cell-based and pharmacological treatments is that transplanted cells actively interact with parenchymal cells depending on their microenvironment, whereas drugs interact with brain cells depending on their pharmacokinetic profiles. Understanding the mechanisms underlying the beneficial effects of these therapies will greatly enhance translation of these treatments to clinical use.

Contributors
Both authors contributed equally to this Review.

Conflicts of interest
We have no conflicts of interest.

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