

Review

Cell-Based Therapies and Drug Repurposing in Stroke

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Ischemic stroke is a leading cause of death and disability worldwide, and contributes substantially to the global burden of disease. Although reperfusion therapies such as intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) and mechanical thrombectomy have transformed acute management, the stringent eligibility criteria, narrow treatment windows, and limited accessibility restrict their use to <20% of patients. Many treated individuals have significant neurological deficits, and this underscores the urgent need for therapies that extend beyond revascularization. Two promising approaches have emerged: cell-based therapy and drug repurposing. Stem cell-based interventions, including mesenchymal stem cells, neural stem cells, and induced pluripotent stem cell-derived products, primarily act via paracrine mechanisms to modulate inflammation, attenuate oxidative stress, promote angiogenesis, and enhance neuroplasticity. Simultaneously, drug repurposing leverages the established safety and pharmacology of existing agents to accelerate clinical translation. Valproic acid, a histone deacetylase inhibitor, and perampanel, a selective AMPA receptor antagonist, target key mechanisms, such as excitotoxicity, oxidative injury, and epigenetic regulation. This review synthesizes the current evidence on both strategies and emphasizes mechanistic overlaps, clinical trial findings, translational barriers, and future directions. Unlike previous reviews that have addressed cell-based therapies or drug repurposing separately, we propose a unique phase-specific integrative framework that rationally combines these complementary strategies with reperfusion therapy and rehabilitation to achieve durable neuroprotection and meaningful recovery in ischemic stroke.

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Introduction

Stroke is the second-leading cause of death, with more than 12 million strokes occurring worldwide¹ and 300,000 occurring in Japan annually. Stroke remains a leading cause of long-term institutionalization and socioeconomic burden² that, beyond its devastating effects on individuals and families, imposes a global cost, including direct medical expenses and loss of productivity, of hundreds of billions of US dollars annually^{3,4}.

Over the past two decades, reperfusion therapies have revolutionized acute ischemic stroke care. Intravenous

thrombolysis with recombinant tissue plasminogen activator (rt-PA) and mechanical thrombectomy improved outcomes in selected patients⁵. Thrombolysis is limited to a narrow 4.5-h window and thrombectomy is indicated in only large-vessel occlusion and at advanced-care facilities; thus, fewer than one in five patients worldwide receive these treatments, and efficacy is limited by complications, such as hemorrhagic transformation, incomplete reperfusion, and microvascular injury. Up to half of stroke survivors have significant residual disabilities, including hemiparesis, aphasia, or cognitive impairment,

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that compromise their independence and quality of life.

Adjunctive strategies that extend beyond acute revascularization are urgently needed. Neuroprotection preserves the ischemic penumbra in the hyperacute phase whereas restorative approaches enhance repair, neurogenesis, and plasticity during subacute and chronic stroke. However, decades of preclinical research with more than 100 candidates that showed efficacy in animal models have not translated into effective human therapies^{4,6,7}. Notable examples include N-methyl-D-aspartate (NMDA) receptor antagonists and free radical scavengers that, despite robust neuroprotection in rodents, proved ineffective or unsafe in clinical trials owing to toxicity, poor target engagement, or inadequate trial design^{6,8}.

Two complementary strategies demonstrated particular promise. Cell-based therapies exploit the immunomodulatory and trophic properties of stem cells and progenitor cells that, instead of direct neuron replacement, act through paracrine signaling to suppress inflammation, promote angiogenesis, and enhance neuroplasticity. Advances in cell culture, cryopreservation, and transplantation have facilitated clinical translation into multiple cell types, including mesenchymal stem cells (MSCs), neural stem cells (NSCs), endothelial progenitor cells (EPCs), and induced pluripotent stem cell (iPSC)-derived derivatives, that remain under active investigation^{9–14}.

Drug repurposing constitutes a practical approach that leverages existing pharmacological and safety data, reduces the time and cost required for drug development, and accelerates clinical evaluation; leading examples include valproic acid (VPA), a histone deacetylase inhibitor with pleiotropic effects^{11,15–17}, and perampanel (PER), a selective AMPA-receptor antagonist that targets excitotoxicity^{17–21}.

Although several previous reviews have discussed cell-based therapies or drug repurposing for stroke in isolation, no prior review has systematically integrated both strategies within a single, phase-specific therapeutic framework. The present review addresses this gap by synthesizing the current evidence for cell-based interventions and repurposed drugs, highlighting their mechanistic convergence on shared pathophysiological targets, and proposing an integrative treatment paradigm that aligns each modality with the optimal therapeutic window—from the hyperacute phase through chronic recovery. This approach provides a clinically actionable framework for designing future combination trials and translational strategies.

Mechanistic Overlaps in Cell Therapy and Drug Repurposing

Ischemic stroke is driven by a complex, dynamic cascade of pathophysiological events, including excitotoxicity, oxidative stress, neuroinflammation, endothelial dysfunction, and impaired neuroplasticity, that interact in a vicious cycle that amplifies tissue damage and hinders recovery²². Cell-based therapies and repurposed drugs target multiple nodes within this cascade, and frequently converge on shared molecular pathways. This mechanistic overlap strongly supports combination therapy for additive or synergistic effects across acute, subacute, and chronic stroke.

Inflammation

Neuroinflammation is among the earliest, most persistent contributors to stroke-associated secondary injury. Within hours, microglia are activated and peripheral leukocytes infiltrate the ischemic brain, releasing proinflammatory cytokines and matrix metalloproteinases that disrupt the blood–brain barrier (BBB) and promote neuronal death. Prolonged inflammation impedes tissue repair and plasticity.

Cell therapies: MSCs secrete anti-inflammatory cytokines, such as IL-10 and TGF- β , and suppress proinflammatory mediators, including IL-1 β , TNF- α , and IL-6^{10,12,23,24}. NSCs regulate microglial activation by promoting a shift from the M1 proinflammatory to the reparative M2 phenotype. MSC-derived exosomes carry microRNAs, such as miR-21 and miR-124, which regulate NF- κ B and STAT 3 signaling to attenuate inflammatory cascades^{25,26}.

Valproic acid: VPA suppresses NF- κ B signaling and downregulates adhesion molecules, such as ICAM-1, to limit immune cell infiltration. An HDAC inhibitor, VPA reprograms the transcriptional landscape of immune cells toward a reparative phenotype^{27,28}.

Perampanel: PER reduces glutamate-driven activation of microglia and astrocytes and, in preclinical studies, reduced IL-1 β and TNF- α levels and increased IL-10 expression, to foster a neuroprotective environment^{29,30}.

Oxidative Stress

Reperfusion of ischemic tissue generates reactive oxygen species (ROS) that induces lipid peroxidation, protein nitration, and DNA fragmentation, and further destabilizes mitochondria, amplifies excitotoxicity, and compromises vascular integrity³¹. Oxidative stress links acute and delayed neurodegeneration.

Cell therapies: MSCs enhance endogenous antioxidant

defenses by upregulating superoxide dismutase, catalase, and glutathione peroxidase. Exosomes deliver antioxidant enzymes and miRNAs that stabilize mitochondrial function and prevent apoptosis^{32,33}.

VPA: In rodent models of stroke, VPA reduces malondialdehyde (a marker of lipid peroxidation) and boosts antioxidant enzyme activity³⁴. VPA corrects ischemia-induced trace-metal imbalances and mitigates oxidative stress-induced neuronal injury³⁵.

PER: PER preserves mitochondrial membrane potential and reduces oxidative DNA fragmentation. The attenuation of excitotoxicity indirectly decreases ROS generation and sustains neuronal viability²⁹.

Excitotoxicity

Excessive glutamate release during ischemia overstimulates NMDA and AMPA receptors, causing calcium overload, mitochondrial collapse, and apoptotic cell death³⁶. Excitotoxicity is one of the earliest, most destructive injury mechanisms, and peaks within hours of stroke onset.

Cell therapies: Although transplanted cells do not directly block glutamate receptors, they secrete neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), which improve synaptic resilience and enhance neuronal survival³⁷.

VPA: VPA indirectly mitigates excitotoxicity by modulating glutamatergic gene expression via HDAC inhibition, enhancing protective gene expression, and reducing neuronal vulnerability³⁸.

PER: A potent, selective, noncompetitive AMPA antagonist, PER directly blocks excitotoxic signaling and reduces calcium influx and neuronal death. In preclinical models, PER decreased infarct volume and preserved hippocampal integrity, which makes it an attractive acute-phase candidate²¹.

Vascular Protection and Angiogenesis

The cerebral endothelium plays a pivotal role in stroke progression. Endothelial dysfunction and BBB breakdown contribute to edema, hemorrhagic transformation, and impaired recovery³⁹. Promoting vascular stability and angiogenesis is critical for long-term improvement.

Cell therapies: EPCs and MSCs secrete angiogenic factors, such as VEGF, angiopoietins, and SDF-1, to support vessel formation and stabilization, and reinforce BBB integrity by restoring tight-junction proteins (claudin-5 and occludin) and protecting endothelial cells^{10,40}. Transplanted cells enhance perfusion in the peri-infarct tissue

and stimulate collateral vessel growth, creating a repair-permissive environment^{41,42}.

VPA: VPA, an HDAC inhibitor, protects endothelial function by enhancing endothelial nitric oxide synthase (eNOS) activity and nitric oxide bioavailability whereas attenuating oxidative stress and inflammation⁴³. This mitigates hyperglycemia-induced vascular injury and may suppress von Willebrand factor release, to collectively promote vasodilation and improve cerebral blood flow^{15,17}.

PER: Although not primarily a vascular agent, PER indirectly protects the vasculature by limiting oxidative and inflammatory stress, and thereby reducing secondary BBB disruption⁴⁴.

Neuroplasticity and Cognitive Recovery

Post-stroke functional recovery depends on neuronal plasticity, including axonal sprouting, dendritic remodeling, synaptogenesis, and remyelination. Enhancing plasticity is essential for effective rehabilitation and long-term cognitive preservation⁴⁵.

Cell therapies: Stem cells secrete trophic factors (e.g., BDNF, NGF, IGF-1) that support axonal growth, synaptic connectivity, and white matter repair. These stimulate endogenous neurogenesis in the subventricular zone and hippocampus and promote remyelination via oligodendrocyte precursor cells^{46,47}. Some transplanted cells integrate into host circuits, further facilitating recovery.

VPA: VPA enhances chromatin accessibility and upregulates neuroplasticity-associated genes by inhibiting HDACs. In animal studies, increased BDNF expression consistently improved motor recovery and rehabilitation responsiveness⁴⁸.

PER: Beyond acute neuroprotection, PER preserves synaptic integrity and hippocampal function and, in preclinical studies, demonstrated improved learning and memory that indicate benefits extending into the chronic-recovery phase^{21,44}.

Clinical Trials Landscape

Translating promising preclinical findings into effective clinical therapies for ischemic stroke remains challenging. Nevertheless, both cell-based interventions and drug repurposing have advanced to early- and mid-phase clinical trials that offer important insights into their feasibility, safety, and preliminary signals of efficacy, although definitive evidence of clinical effectiveness remains to be established.

Table 1 Summary of major cell-based therapy trials in ischemic stroke

Trial	Cell type (Product)	Route/Timing	Primary endpoint result	Key findings/Safety
MASTERS (USA/EU)	Allogeneic MAPC (MultiStem)	IV within 24–48 h	No difference at 90 d (global recovery)	Safe; 1-yr analysis suggested better outcomes in < 36 h group
TREASURE (Japan)	Allogeneic MAPC (HLCM051)	IV 18–36 h	No difference (11.5% vs 9.8%)	Safe but higher AE rate in MultiStem group; favorable signals in ≤ 64 y or large core patients
J-REPAIR (Japan)	Allogeneic Dental pulp stem cell (JTR-161)	IV ≤ 48 h	Excellent outcome (mRS ≤1, NIHSS ≤1, BI ≥95) used for evaluation	Detailed results not yet published
CL2020 (Japan)	Allogeneic Muse cells (CL2020)	IV 14–28 d	Safety at 12 wk achieved	1 serious AE (status epilepticus); Fugl-Meyer scores improved to 52 wk
PISCES (UK)	Conditionally immortalized human NSC (CTX0E03)	Intracerebral implant (putamen), 2–13 mo	Safety confirmed; Phase IIa primary endpoint not met	Well tolerated; modest motor improvement in patients with residual movement

Cell-based Therapies

Acute-to-subacute Stroke Trials

Several randomized and early-phase studies have evaluated the safety and feasibility of cell therapies administered within days of ischemic stroke onset (**Table 1**):

MASTERS (MultiStem, Athersys): A multicenter, randomized, double-blind, placebo-controlled phase II trial (NCT01436487) evaluated the intravenous administration of allogeneic multipotent adult progenitor cells (MAPCs; MultiStem) in 129 patients with moderate-to-moderately severe acute ischemic stroke, randomized to receive 1.2×10^9 cells or placebo within 24–48 hours (initially 24–36 h, later extended for feasibility) of stroke onset. The treatment was safe and well-tolerated, without infusion reactions, immune complications, or dose-limiting toxicities. However, the trial did not meet its primary endpoint: at 90 days, there was no significant between-group difference in global stroke recovery (odds ratio 1.08, 95% CI 0.55–2.09, $p = 0.83$). Subsequent exploratory (hypothesis-generating) analyses at 1 year suggested higher rates of excellent outcome (23% vs. 8%, $p = 0.02$) and mRS ≤ 1 (28% vs. 13%, $p = 0.04$) in the MultiStem group; however, these findings require prospective validation. Post-hoc analysis indicated that earlier treatment (< 36 h) conferred greater functional improvement and fewer secondary infections, supporting the concept of time-dependent immunomodulatory efficacy⁴⁹.

TREASURE (MultiStem, Japan): The phase II/III multicenter, randomized, double-blind, placebo-controlled TREASURE trial (NCT02961504) evaluated intravenous administration of MultiStem (HLCM051) allogeneic multipotent adult progenitor cells within 18–36 h after acute ischemic stroke. A total of 206 patients were enrolled from 44 centers in Japan. The trial did not meet its pri-

mary endpoint: the proportion of patients achieving excellent outcome at day 90 (mRS ≤ 1, NIHSS ≤ 1, Barthel Index ≥ 95) showed no significant between-group difference (11.5% vs 9.8%; $p = 0.90$). Notably, adverse events occurred more frequently in the MultiStem group than in the placebo group, an observation that warrants careful consideration in future trial design. Exploratory analyses suggested better outcomes with MultiStem in patients ≤ 64 years old or with large ischemic cores (≥ 50 mL), and post hoc 1-year analyses showed higher rates of global stroke recovery and Barthel Index ≥ 95; however, these subgroup findings are hypothesis-generating and require confirmation in adequately powered prospective studies. Although TREASURE did not meet its primary endpoint, it confirmed the feasibility and safety of early-window intravenous MultiStem therapy⁵⁰.

J-REPAIR (Dental pulp stem cell, Japan): Post-reperfusion systemic delivery of human dental pulp stem cells (DPSCs) reduced ischemic damage and improved functional recovery in a rodent ischemia model, with a clinically relevant therapeutic window in a rat stroke model^{9,13}. A multicenter, randomized, double-blind, placebo-controlled phase I/II trial (JapicCTI-194570, NCT 04608838) evaluated JTR-161, an allogeneic human DPSC-based product, in patients with acute ischemic stroke. The participants (NIHSS, 5–20; anterior-circulation infarction) received a single intravenous infusion within 48 h of onset. The study comprised three sequential cohorts (1×10^8 , 3×10^8 , and a higher tolerated dose), with 76 patients from multiple centers in Japan. The primary endpoint—excellent outcome at day 91 (mRS ≤ 1, NIHSS ≤ 1, Barthel Index ≥ 95)—was used to evaluate efficacy and safety at the optimal dose⁵¹.

CL2020 (Muse cells, Japan): A single-center, random-

ized, double-blind, placebo-controlled phase II trial (JapicCTI-184103) tested intravenous CL2020, an allogeneic Muse cell product, administered 14–28 days after ischemic stroke. Thirty-five patients (25 CL2020, 10 placebo) were followed-up for 52 weeks. The primary endpoint (safety at 12 weeks) was met; no major safety issues occurred, although one serious adverse reaction and several mild events (e.g., hair darkening) were reported. The key secondary endpoint, mRS ≤ 2 at 12 weeks, was 40.0% vs. 10.0%, which exceeded the predefined efficacy threshold (8.7%). Motor recovery, including Fugl-Meyer upper limb and total scores, remained significantly improved beyond 52 weeks. CL2020 showed acceptable safety and preliminary exploratory efficacy signals, supporting its ongoing phase III development⁵².

Chronic Stroke Trials

Cell therapy is being investigated in patients with persistent deficits, months to years after stroke, to enhance repair and plasticity.

PISCES (CTX0E03 neural stem cells, UK): The Pilot Investigation of Stem Cells in Stroke (PISCES) program evaluated CTX0E03, a conditionally immortalized human NSC line derived from the fetal cortical neuroepithelium, for chronic ischemic stroke. In phase I (PISCES-1), intracerebral implantation of up to 20 million cells into the putamen was well tolerated, without serious cell-related adverse events, and induced modest motor improvements in some patients⁵³. In phase IIa (PISCES-2), 23 patients received a single stereotactic injection 2–13 months after the stroke. The treatment was safe and feasible, although the primary efficacy endpoint (≥ 2 -point ARAT improvement at 3 months) was not met⁵⁴.

Emerging Mechanistic Concept: The Bioreactor Hypothesis

Recent findings indicate that intravenously infused stem cells exert therapeutic effects mainly through peripheral immunomodulation, rather than direct engraftment in the brain. After infusion, most cells are transiently trapped in the lung and spleen, where they reprogram host immune responses—enhancing IL-10 and regulatory T cells whereas suppressing TNF- α and IL-1 β . This systemic shift reduces neuroinflammation, stabilizes the BBB, and promotes microglial transition toward a reparative M2 phenotype. This “bioreactor hypothesis” views transplanted cells as temporary catalysts that transform peripheral organs into sources of neuroprotective signals. This concept explains why early administration (within

24–36 h, as seen in MASTERS and TREASURE) yields stronger benefits and provides a rationale for next-generation cell-free approaches, such as extracellular vesicles. Cell therapy is best understood as an immune reprogramming strategy that indirectly promotes brain repair⁵⁵. It should be noted, however, that the bioreactor hypothesis is primarily supported by preclinical evidence and indirect clinical observations. Definitive clinical validation through prospective trials specifically designed to test this mechanistic model has not yet been achieved, and the concept should be considered a working hypothesis that requires further investigation.

Drug Repurposing

Valproic Acid

In preclinical studies, VPA reduced edema/BBB disruption and improved outcomes in rodent stroke models. Small clinical/observational signals suggest potential benefits; however, the evidence remains preliminary, and randomized trials are ongoing (NCT06020898). It is important to emphasize that, to date, no stroke-specific randomized controlled trial has demonstrated the efficacy of VPA for neuroprotection in ischemic stroke. The current clinical evidence is limited to small observational studies and extrapolation from preclinical data. The ongoing trial (NCT06020898) will provide the first rigorous evaluation of VPA in this context. Accordingly, the proposed therapeutic positioning of VPA in ischemic stroke should be regarded as conceptual and at the research stage, rather than ready for clinical application.

Perampanel

No large randomized controlled trials (RCTs) have evaluated PER in stroke; however, the preclinical evidence is strong. In rodent models, PER reduced infarct size and preserved hippocampal networks^{19,21,56}. Clinical experience in cardiac arrest survivors suggests improved neurological recovery⁵⁷. However, it is critical to acknowledge the fundamental pathophysiological differences between global hypoxic-ischemic encephalopathy, which involves diffuse brain injury from prolonged global hypoperfusion, and focal cerebral ischemia, which is territory-specific with penumbral dynamics and collateral-dependent perfusion. Although both conditions share excitotoxic and inflammatory cascades that may respond to AMPA receptor antagonism, the therapeutic response may differ substantially, and direct extrapolation from cardiac arrest to ischemic stroke should be avoided. As with VPA, the proposed clinical positioning of PER in

ischemic stroke remains conceptual and at the research stage. Stroke-specific RCTs are warranted to establish its efficacy and safety in this population⁴⁴.

Comparative Insights

Cell-based therapies and drug repurposing are complementary paradigms for post-stroke neurorestoration.

Cell therapies exert broad pleiotropic effects, including immunomodulation, angiogenesis, and neuroplasticity, which are particularly relevant during the subacute and chronic phases of recovery.

Drug repurposing has advantages in terms of speed, scalability, and cost-effectiveness, making it appealing for acute-phase interventions and early neuroprotection.

Both strategies face similar challenges, including patient heterogeneity, uncertainty in therapeutic timing, non-standardized outcome measures, and insufficiently powered multicenter trials.

Collectively, these insights highlight the need for multimodal, combination-based approaches rather than relying on any single-target therapy to achieve meaningful recovery after stroke. However, it must be emphasized that both cell-based therapies and repurposed drugs are still at relatively early stages of clinical development, and no definitive evidence of efficacy has been established for either approach in ischemic stroke to date.

Translational Challenges

Despite encouraging results from preclinical and early clinical studies, the translation of cell-based therapies and repurposed drugs for routine clinical use in patients with ischemic stroke remains highly challenging. These barriers span biological, methodological, ethical, and regulatory domains.

Preclinical–Clinical Gap

One of the major hurdles is the limited translatability of preclinical findings to human patients.

Animal models: Most studies have used young, healthy rodents whereas stroke predominantly affects older individuals with comorbidities, such as hypertension, diabetes, and atrial fibrillation. Incorporating age and comorbid models would enhance predictive validity⁵⁸.

Stroke models: The middle cerebral artery occlusion (MCAO) model remains standard but fails to capture the heterogeneity of human stroke (e.g., cortical vs. subcortical, large vs. small-vessel)⁵⁹. Therefore, refined or large animal models may provide more clinically relevant in-

sights.

Outcome measures: Preclinical studies often focus on infarct volume, whereas long-term functional recovery (motor, cognitive, and behavioral) remains underexplored. Emphasizing durable functional outcomes is essential for successful translation⁶⁰.

Timing and Therapeutic Windows

The optimal therapeutic window differs markedly between the strategies.

Cell therapies: Early (24–48 h) administration primarily targets post-ischemic inflammation, whereas delayed or chronic delivery may promote angiogenesis, neurogenesis, and white-matter repair⁶¹.

Repurposed drugs: Perampanel is the most effective drug in the hyperacute phase, which coincides with peak excitotoxicity, and potentially synergizes with reperfusion therapies. Valproic acid may act across a broader subacute window to enhance neuroplasticity and network remodeling.

Safety Considerations

Safety remains central to translation efforts.

Cell therapies: Potential risks include tumorigenesis (especially with iPSC/ESC derivatives), immune rejection of allogeneic products, and procedural complications, such as microembolism or hemorrhage⁶¹. Therefore, rigorous long-term surveillance is essential.

Valproic acid: Although widely used, VPA carries risks of hepatotoxicity, thrombocytopenia, sedation, and teratogenicity⁶².

Perampanel: Although generally well tolerated in epilepsy, dizziness or agitation can complicate its management in acute stroke settings⁶³.

Delivery and Dosing Challenges

Cell therapies: Intravenous infusion is technically simple and well tolerated, but yields low brain engraftment because most cells are trapped in the pulmonary and splenic circulation⁵⁵. Intra-arterial delivery enhances targeted delivery to ischemic tissue but carries the risk of microvascular occlusion and procedural complications. Intracerebral transplantation facilitates direct local administration and may be appropriate for chronic stroke; however, it is invasive and impractical in acute settings. The optimal cell dose and delivery schedule remain undefined, with substantial variability across trials (10^6 – 10^9 cells reported).

Repurposed drugs: Stroke alters pharmacokinetics, as

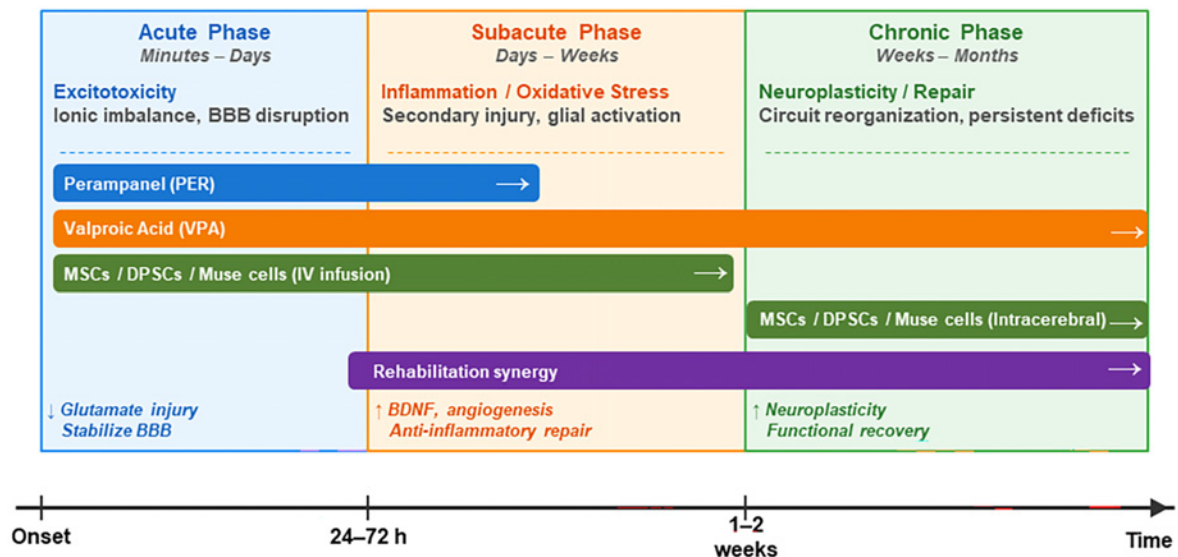


Figure 1 Phase-specific integration of cell-based and repurposed drug therapies in ischemic stroke

The figure illustrates the temporal progression of ischemic stroke through three overlapping phases—acute (minutes–days), subacute (days–weeks), and chronic (weeks–months)—with a continuous timeline depicting the dynamic pathophysiological transitions. Pharmacological (VPA and PER) and cell-based interventions (MSCs, DPSCs, and Muse cells) are positioned at their optimal therapeutic windows within each phase. The acute, subacute, and chronic phases target excitotoxicity, inflammation–oxidative stress, and neuroplasticity–long-term recovery, respectively.

BBB disruption, hepatic congestion, and metabolic stress modify absorption and clearance. Polypharmacy is common among stroke survivors, which increases concerns about drug–drug interactions and additive toxicity. Genetic polymorphisms, including CYP450 variants that affect metabolism and HDAC gene variations that influence the response to valproate, may modulate therapeutic efficacy⁶⁴.

Future Directions

The paradigm of ischemic stroke therapy is shifting from single-target interventions to multimodal, phase-specific, and patient-tailored strategies⁶⁵. Cell-based therapies and drug repurposing occupy central positions in this evolving landscape. Future studies should focus on integrating these modalities into cohesive regimens that reflect the complex, time-dependent pathophysiology of stroke.

Phase-Specific Interventions

Stroke progresses through distinct yet overlapping phases, with each requiring tailored therapeutic priorities (Figure 1):

Acute phase (minutes–days): Excitotoxicity and ionic imbalance dominate. Rapid interventions, such as PER (AMPA receptor blockade), combined with reperfusion therapy or early intravenous MSC infusion to mitigate inflammatory injury may confer benefit^{29,66}.

Subacute phase (days–weeks): Characterized by inflammation, oxidative stress, and glial scarring. VPA, through HDAC inhibition, can modulate epigenetic and neurotrophic pathways (e.g., BDNF upregulation) and enhance synaptic plasticity, particularly when paired with structured rehabilitation. Cell-based therapies may promote angiogenesis, neurogenesis, and remyelination⁶⁶.

Chronic phase (weeks–months): Persistent neurological deficits require therapies that foster long-term plasticity, cognitive resilience, and network remodeling. Sustained or low-dose VPA, metformin, or next-generation engineered stem cell platforms can complement intensive rehabilitation and enhance functional recovery.

Conclusion

Emerging strategies extend beyond revascularization. Cell-based therapies exert pleiotropic reparative actions, such as immunomodulation, angiogenesis, and neuroplasticity enhancement, and early trials have confirmed their safety and feasibility, although no cell-based therapy trial has yet demonstrated definitive efficacy in achieving primary endpoints. Drug repurposing of VPA and PER leverages their established safety profiles to target excitotoxicity, inflammation, and epigenetic regulation; however, clinical evidence supporting their use in ischemic stroke remains at a preliminary stage, and their proposed therapeutic positioning should be considered

conceptual. Integrating these approaches into multimodal phase-specific regimens that combine cell therapy, repurposed drugs, reperfusion, and rehabilitation may bridge the gap between acute protection and long-term recovery. Future progress will depend on biomarker-guided timing, optimized delivery, innovative trials, and global access. The convergence of these strategies offers a promising path toward durable neuroprotection and functional restoration in stroke survivors worldwide, pending validation through rigorously designed randomized controlled trials.

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