The transplantation of exogenous stem cells and the activation of endogenous neural stem and progenitor cells (NSPCs) are promising treatments for stroke. These cells can modulate intrinsic responses to ischemic injury and may even integrate directly into damaged neural networks. However, the neuroprotective and neural regenerative effects that can be mediated by these cells are limited and may even be deleterious. Epigenetic reprogramming represents a novel strategy for enhancing the intrinsic potential of the brain to protect and repair itself by modulating pathologic neural gene expression and promoting the recapitulation of seminal neural developmental processes. In fact, recent evidence suggests that emerging epigenetic mechanisms are critical for orchestrating nearly every aspect of neural development and homeostasis, including brain patterning, neural stem cell maintenance, neurogenesis and gliogenesis, neural subtype specification, and synaptic and neural network connectivity and plasticity. In this review, we survey the therapeutic potential of exogenous stem cells and endogenous NSPCs and highlight innovative technological approaches for designing, developing, and delivering epigenetic therapies for targeted reprogramming of endogenous pools of NSPCs, neural cells at risk, and dysfunctional neural networks to rescue and restore neurologic function in the ischemic brain.

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Despite important advances in the prevention and treatment of various stroke syndromes, acute interventions offer only a limited range of utility and efficacy, and stroke remains a leading cause of serious long-term disability and death in the United States. Intensive research efforts have, therefore, focused on the development of therapies that can truly preserve and restore neurologic function. Many of these approaches have centered on the modulation of molecular and cellular cascades that follow ischemic injury in the brain, including excitotoxicity-, calcium-, and oxidative stress–mediated cell death in the infarct core and delayed events, such as neuroinflammation and apoptosis, in the ischemic penumbra. Additional strategies have attempted to use different populations of stem and progenitor cells to promote neuroprotection and regeneration of neural tissue and functional neural networks. There are 2 major paradigms for these stem cell–based therapies: (1) the transplantation of diverse populations of exogenous cells derived from embryonic tissue, fetal and adult brain, other organ systems (eg, bone marrow), and immortalized cell lines and, alternatively, (2) the stimulation of endogenous neural stem and progenitor cells (NSPCs) with various agents, such as cytokines and growth factors. In this review, we discuss the therapeutic potential of exogenous and endogenous cell-based strategies that focus on mechanisms such as modulation of intrinsic

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responses and direct integration into neural circuitry, through which they may differentially promote neuroprotection and neural regeneration.

We also highlight the critical roles that emerging epigenetic mechanisms play in mediating NSPC functions during development and adult life and suggest, therefore, that epigenetic reprogramming is a novel approach for targeted activation of endogenous NSPCs in the ischemic brain. In fact, DNA methylation, histone code modifications and chromatin remodeling, non–protein-coding RNAs (ncRNAs), and RNA editing are increasingly being implicated in orchestrating almost every aspect of NSPC self-renewal, proliferation, neurogenesis, gliogenesis, cell migration, and neural network integration and plasticity. Furthermore, these epigenetic mechanisms also represent the molecular interfaces for mediating gene-environmental interactions that dynamically sculpt neural cell identity, connectivity, and function throughout life. Thus, epigenetic mechanisms play an important role in generating the extraordinary diversity of cell types found in the nervous system, including the complete spectrum of distinct neuronal and glial cells that are distributed throughout the neuraxis and integrated into specialized regional neural networks. Together, these observations imply that the selective modulation of epigenetic processes in stroke represents a novel but complementary strategy for enhancing the intrinsic potential of the brain to protect and repair itself by reprogramming endogenous NSPCs. The development of targeted epigenetic therapies may help overcome inherent barriers that have previously limited the capacity for robust and appropriate endogenous stem cell activation, migration, differentiation, neural circuit integration, and survival. Moreover, the use of epigenetic cellular reprogramming strategies may circumvent recent arguments that question whether true neural stem cells even exist in the adult brain.

Finally, we survey the landscape for designing and developing highly specific and flexible next-generation epigenetic therapies using an array of emerging nanotechnologies, biomaterials, scaffolds, and additional tools for systemic and more localized delivery through endovascular and other approaches.

**EXOGENOUS STEM CELL TRANSPLANTATION**

Stem cells are undifferentiated cells that undergo self-renewal and proliferation and give rise to an array of different cell types and, thus, serve as attractive candidates for regenerative medicine strategies. In fact, the transplantation of bone marrow stem cells, which can differentiate into lymphoid and myeloid cells, has been performed for decades and can effectively reconstitute a healthy hematopoietic system after ablation. Correspondingly, the transplantation of diverse populations of exogenous stem and progenitor cells is being explored as a treatment for a range of neurologic diseases, with stroke as the vanguard. A variety of studies, including preclinical and phase 1 and 2 clinical trials, have generated much enthusiasm but have also raised important issues that must be addressed to advance the development of these approaches. For example, the most suitable cell type for therapy, the optimal route of its administration, and the molecular and cellular mechanisms through which it modulates the response to ischemic injury and mediates neural repair have not yet been defined.

The ideal stem cell–based strategies must provide the target cell type in sufficient quantities to meet clinical demand, be therapeutically effective, and have acceptable safety profiles. As such, experimental studies and clinical trials for stroke therapy have begun to characterize the efficacy of intracerebral, intravascular, and intraventricular delivery of a range of cell types derived from a variety of human and animal sources, including pluripotent embryonic stem cells (ESCs) differentiated into neural progenitor cells (NPCs) in vitro; multipotent NSPCs isolated from fetal and adult brains that can give rise to the 3 primary neural cell types present in the mature brain (neurons, oligodendrocytes, and astrocytes); and stem and progenitor cells from other tissues, such as bone marrow, umbilical cord, peripheral blood, and adipose tissue; and immortalized neural cell lines, such as those transformed with the myc oncogene, conditionally immortalized using temperature-sensitive alleles of the large T antigen or created from teratocarcinoma tissue, which can differentiate into neuronlike cells. The results of these studies have been discussed in an excellent series of review articles, and the cumulative evidence suggests that all these approaches generally have the potential to enhance functional recovery after stroke. Significant differences do, however, exist in the capacities of different cell types to proliferate, to become lineage-committed NPCs, and to undergo cellular transformation, and these differential characteristics may, ultimately, determine their usefulness for clinical applications. For example, ESCs are readily propagated in culture and may provide a limitless supply of NPCs. However, the use of ESCs raises political and ethical issues; derivation of NPCs from ESCs may lead to heterogeneous cell populations, and ESCs and NPCs derived from ESCs harbor the potential to form tumors, including gliomas and teratocarcinomas. Similarly, immortalized cell lines also have the capacity for unrestricted proliferation but carry the risk of undergoing malignant transformation. In contrast, fetal and adult brain–derived NSPCs can be expanded in culture to a more limited extent, although these cell types are less likely to form tumors. Stem and progenitor cells from other tissues may circumvent issues associated with obtaining embryonic and fetal cells, are already in clinical use, can be converted into cell types with features of NSPCs, and may obviate the need for immunosuppression because of the potential for autologous transplantation. Moreover, additional cell types with relatively uncharacterized risk profiles, such as induced pluripotent stem cells derived from fibroblasts or other sources, are yet to be evaluated for their potential to treat stroke.

Stem cell therapies are believed to promote neuroprotection and to participate in functional recovery by direct integration into neural circuitry and also by modulation of a spectrum of endogenous homeostatic and reparative responses, although the relative contributions of these different modes of action may vary depending on the specific treatment strategy (Table). For example, fetal and adult NSPCs, ESC-derived NPCs, and immor-
Table. Cell-Based Approaches for Treatment of Stroke

<table>
<thead>
<tr>
<th>Description</th>
<th>Exogenous Stem Cell Transplantation</th>
<th>Endogenous NSPC Activation</th>
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<tbody>
<tr>
<td>Strategy</td>
<td>Intracerebral, intravascular, and intraventricular delivery of a range of cell types derived from human or animal sources, including pluripotent embryonic stem cells differentiated into neural progenitor cells in vitro; multipotent NSPCs isolated from fetal and adult brains; stem and progenitor cells from other tissues, such as bone marrow, umbilical cord, peripheral blood, and adipose; immortalized neural cell lines; and induced pluripotent stem cells derived from fibroblasts or other sources.</td>
<td>Stimulation of regional endogenous NSPCs with various agents. Recapitulation of neural developmental events.</td>
</tr>
<tr>
<td>Potential advantages</td>
<td>Significant clinical experience exists with bone marrow stem cell transplantation. Preliminary clinical trials are currently under way. Seems to promote neuroprotection and neural regeneration to some degree.</td>
<td>NSPCs are present in the adult brain and participate in neurogenesis and gliogenesis and in neural network maintenance and remodeling. No need for external sources of cells. No risk of introducing exogenous pathogens. Minimal possibility for enhancing immune surveillance, inflammatory reactions, and tissue rejection. Does not raise political and ethical concerns. NSPCs normally participate in neural repair to a limited extent only. Complexity of nervous system structure and function requires sophisticated temporal, spatial, and cell type–specific manipulation of regenerative signals to successfully enhance neural tissue remodeling and repair.</td>
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<tr>
<td>Potential disadvantages</td>
<td>May carry significant risk of malignant transformation. Molecular and cellular mechanisms of action have not yet been defined. Role in mediating functional recovery is poorly defined. Many unknowns for further clinical development of therapies include the following: most suitable cell type, timing, dosing, optimal route of administration, supportive pharmacotherapy, and patient selection criteria.</td>
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Abbreviation: NSPC, neural stem and progenitor cell.

These analyses will help not only to optimize the cell type and source for therapies but also to inform efforts designed to maximize their potential for success. For example, exogenous cells can be manipulated before their transplantation (ex vivo) and imbued with the potential to deliver neurotrophic factors that may augment their ability to integrate into damaged neural tissue. Furthermore, elucidation of mechanisms that underlie the benefits of stem cell–based therapies will also enhance endeavors aimed at defining the appropriate timing, dosing, delivery method, supportive pharmacotherapy, and patient selection criteria required to optimize these approaches. Efforts aimed at advancing translational research for stroke, such as the Stem Cell Therapies as an Emerging Paradigm in Stroke meeting, have brought together representatives from academia, industry, and regulatory agencies to define these important issues, create common research standards, and accelerate the clinical development of stem cell therapies.

ENDOGENOUS NSPC ACTIVATION

Activation of endogenous NSPCs for remodeling neural tissue after ischemic injury has some obvious advantages over transplantation of exogenous cells. This strategy obviates the need for an external source of cells; the risk of introducing exogenous pathogens; the possibility of enhanced central nervous system (CNS) immune surveillance, inflammatory reactions, and tissue rejection; and the potential for raising political and ethical concerns. However, regional NSPCs participate in neural repair after injury only to a limited extent. Thus, studies that seek to enhance this intrinsic neural regenerative potential have focused on better characterizing specific popu-
lutions of endogenous NSPCs, their responses to injury, and their integration into existing regional neural networks, a requirement for the reestablishment of higher-order cognitive and behavioral functions.

Regional NSPCs are distributed in specialized niches throughout the neuraxis during development and adult life. In the adult brain, these cells are responsible for constitutive neurogenesis that is primarily restricted to the anterior subventricular zone (SVZa) of the lateral ventricles, rostral migratory stream, and olfactory bulb and to the subgranular zone (SGZ) of the dentate gyrus of the hippocampus. Neurons produced in the SGZ of the dentate gyrus of the hippocampus integrate into the adjacent granule cell layer, where they may have roles in promoting learning and memory, and those generated in the SVZa migrate through the rostral migratory stream to the olfactory bulb, where they become interneurons that may have roles in mediating complex olfactory (sensory) discrimination. These processes are dynamically regulated by a variety of extracellular, cell-cell, and interoceptive signals.

A variety of studies have demonstrated that pools of NSPCs expand after cerebral ischemia and that these cells can migrate to injured regions, where they differentiate into multiple mature cell types, including neurons. Interactions with blood vessels seem to play a role in guiding these cells to ischemic areas. For example, animals that overexpress vascular endothelial growth factor exhibit increased neurogenesis in the SVZ and at the site of ischemic injury with greater functional recovery. These observations and related findings strongly suggest that endogenous NSPCs participate in dynamic tissue remodeling after injury. However, neural regenerative responses are limited due to the presence of an inhibitory milieu within stem cell generative zones in the adult CNS and also because of complex and sequential neuroinflammatory and neuromodulatory responses present at injury sites. The manipulation of diverse factors in vitro and in vivo has revealed the potential for augmenting the responses of endogenous NSPCs to injury. For example, treatment with growth factors such as epidermal growth factor and fibroblast growth factor promotes recruitment of endogenous NSPCs and regeneration of hippocampal circuitry with restoration of synaptic function after ischemia. However, the complexity of CNS structure and function requires sophisticated temporal and spatial manipulations of regenerative signals to successfully enhance neural tissue remodeling and repair.

The behavior of NSPCs, including their potential to respond to injury and to repair neural tissue, is regulated in stem cell niches via cues derived from local and long-distance sources, including blood-borne and cerebrospinal fluid–borne factors, endothelial cells, microglia, astrocytes, and local or distal axons that terminate in the niche. These complex microenvironments are responsible for modulating NSPC self-renewal, maintenance, and differentiation, and different niches have common and unique features that affect their ability to perform these functions. For example, NSPCs in the SVZ and the SGZ are closely associated with a vascular plexus, a spectrum of cell types, and components of the basal lamina. However, the architecture of each of these niches is different, and the intrinsic features of each niche, such as extracellular matrix structure, elasticity, and composition, play roles in modulating the differentiation of cells by sequestering growth factors and by exerting mechanical effects that promote development along a specific lineage. These dynamic organizational features are spatially and temporally regulated, and they affect the functional properties of stem cells in the niche. For example, pools of NSPCs in the SVZa are intercalated with the ependymal cell layer and are closely associated with blood vessels, particularly at sites that lack astrocyte end feet and pericytes, which are important components of the blood-brain barrier. Small molecules from the peripheral circulation, therefore, have the ability to enter the SVZa and affect NSPCs in this niche.

The NSPCs have been the focus of numerous studies aimed at characterizing the molecular mechanisms that orchestrate their self-renewal, proliferation, lineage restriction, neuronal and glial lineage specification, progressive maturation, and terminal differentiation. These studies have begun to elucidate the temporal and spatial profiles of gradient morphogens, growth factors, additional cell signaling cues, and combinatorial transcription factor codes that establish neural cell identity and control the elaboration of neuronal and glial lineages from distinct regional subpopulations of NSPCs in the neuraxis. Gradient morphogens, such as sonic hedgehog and bone morphogenetic proteins, induce 3-dimensional patterning effects and complex profiles of gene expression in target NSPC species in specific areas of the developing neural tube. In ventral domains, sonic hedgehog establishes a characteristic profile of homeodomain and basic helix-loop-helix transcription factor expression, whereas bone morphogenetic proteins mediate a complementary developmental program in the dorsal aspect of the neural tube. These patterning and lineage-specific gene expression profiles establish discrete progenitor domains through cross-modulatory interactions that define the identities of individual neural progenitor species and promote the subsequent elaboration of specific neuronal and glial subtypes. The self-renewal, proliferation, lineage commitment, and progressive maturation of NSPCs are more finely regulated by complex patterns of local and long-distance cell intrinsic and extrinsic environmental signals that encompass fibroblast growth factor, Wnt, Notch, and mitogen-activated protein kinase signaling pathways. Most recently, epigenetic mechanisms have emerged as the molecular interface for integrating cues from these diverse cell autonomous and cell extrinsic signaling pathways and for regulating the deployment of genes and gene networks that are critical for determining neural cell identity and function.

**EPIGENETIC MECHANISMS MEDIATE NSPC FUNCTIONS**

The field of epigenetics is revolutionizing our understanding of NSPC functions by offering insights into the molecular processes responsible for executing genomic programs that promote self-renewal, proliferation, neuronal and glial lineage specification, progressive maturation, migration, and synaptic connectivity and plastic-
ity. A recent study reveals that these seminal processes are orchestrated by highly interrelated and exquisitely environmentally sensitive epigenetic mechanisms, including DNA methylation, histone code modifications and chromatin remodeling, ncRNAs, and RNA editing. Acting in concert with combinatorial transcription factor codes, gradient morphogens, growth factors, cytokines, and signal transduction cascades, complementary epigenetic processes regulate the transition from the global transcriptional hyperactivity that is a key feature of NSPCs to large-scale gene silencing and the specific deployment of genes and functional gene networks, which is characteristic of more differentiated neural cells. Indeed, NSPC lineage restriction and cell fate decisions are mediated by epigenetic regulatory factors that modify the ground states of NSPCs, and activity-dependent changes in CNS gene expression and function, in turn, are mediated by dynamic reorganization of the epigenome in postmitotic neurons and associated neural networks. DNA methylation is an epigenetic process responsible for repressing global and gene-specific transcription, and it has critical functions in neuronal and glial development. Factors that mediate DNA methylation events, such as DNA methyltransferase enzymes and methyl-CpG-binding proteins, and DNA methylation profiles are dynamically regulated during neuronal and glial cell differentiation. For example, DNA methylation status and DNA methyltransferase enzyme levels correlate inversely with NSPC differentiation, consistent with the view that higher levels of methylation and associated gene silencing are characteristics of more differentiated neural cells. In addition, the differential expression of certain DNA methylation factors is associated with the differentiation of NSPCs into specific neural lineages. In fact, the level of methyl-CpG-binding protein 1 expression increases with neuronal lineage maturation, consistent with previous studies suggesting that methyl-CpG-binding proteins are present in neurons, where they repress the expression of glial genes. Also, in NPCs destined to become astrocytes, astroglial gene promoter regions are selectively demethylated, implying that demethylation of these gene promoters is, in part, responsible for promoting astroglial gene expression and the elaboration of astrocytes.

In addition to roles in mediating neuronal cell fates, DNA methylation status in neurons also has a spectrum of effects, including the ability to modulate survival and migration and to promote the neural network plasticity associated with memory. For example, constitutive neurogenesis in the dentate gyrus of the adult hippocampus is implicated in activity-dependent neural plasticity, and Gadd45b is a factor involved in DNA methylation that links neuronal activation with subsequent neurogenesis. It is an immediate early gene expressed in mature hippocampal neurons that is implicated in selective activity-induced DNA demethylation and also in promoting the expression of genes critical for neurogenesis, including brain-derived neurotrophic factor and fibroblast growth factor. Thus, the functions of Gadd45b connect DNA methylation with neural network activity and neurogenesis in the hippocampus. Together, these examples suggest that DNA methylation is essential for NSPC maintenance, neural differentiation, and adult homeostatic functions.

Histone code modifications and higher-order chromatin remodeling also have key roles in mediating NSPC developmental functions by modulating neural gene expression. In fact, specific histone and chromatin code signatures are responsible for keeping neural differentiation genes in a repressed but “poised” state in ESCs. For example, the proneural Mash1 gene locus is preferentially positioned at the ESC nuclear periphery, which is associated with transcriptional suppression. During neural lineage commitment, Mash1 gene expression increases significantly as higher-order chromatin remodeling takes place and the Mash1 gene locus relocates toward the interior of the nucleus. Chromatin remodeling factors, such as trithorax group and polycomb group proteins, are also critical for regulating NSPC gene expression programs. For example, the polycomb group factor Bmi1 is required for NSPC self-renewal, and the trithorax group factor Mll1 is required for neurogenesis.

Various studies have investigated the roles of histone modifications in NSPC differentiation using the histone deacetylase enzyme inhibitor trichostatin A (TSA). Treatment of differentiating NSPCs with TSA increases the relative number of neuronal lineage cells and decreases the relative number of astroglial lineage cells. Furthermore, differentiation of NSPCs in the presence of TSA results in a relative reduction in the percentage of oligodendroglial species compared with astrocytes and neurons. Treatment of immature oligodendroglial lineage cells with TSA reprograms them into a multipotent state receptive to neurogenic and astrogligenic differentiation signals. These cumulative observations demonstrate that histone code modifications are important mediators of neuronal and glial lineage elaboration.

Moreover, ncRNAs (eg, microRNAs [miRNAs]) are also implicated in mediating neuronal development and homeostatic functions, including brain patterning, neuronal cell type specification, and synaptic connectivity and plasticity. For example, an increasing number of miRNAs, such as miR-9, miR-124a, and let-7, regulate neural gene expression during the acquisition of neural cell identity. These and other miRNAs are also responsible for modulating synaptic plasticity. For example, mir-134 is a dendritic miRNA that controls dendritic spine size and neurogenesis in an activity-dependent manner. Along with these miRNAs, other ncRNA transcripts (eg, long ncRNAs) exhibit specific temporal and spatial expression patterns in developing and adult brains. Along with protein-coding messenger RNAs, these ncRNAs are dynamically modulated through posttranscriptional RNA processing (eg, RNA modification, quality control, and intracellular and intercellular transport), and the structure and function of these complex and highly flexible RNA-based networks in the CNS are still emerging.

The repressor element-1 silencing transcription factor (REST)/neuron-restrictive silencing factor is an important epigenetic regulator that highlights the integrated nature of epigenic mechanisms regulating neural gene expression and function and their effect on NSPC functions. REST and its cofactor, CoREST, are implicated in NSPC maintenance, regional neuronal and glial...
subtype specification, and progressive stages of oligodendrocyte lineage maturation, including myelination.28,29 REST and CoREST bind to genomic regulatory sequences associated with neural genes, where they act as platforms for recruiting diverse factors that mediate DNA methylation and chromatin remodeling.30 REST and CoREST, thereby, regulate neural cell type- and developmental stage–specific gene repression, gene activation, and long-term gene silencing for protein-coding genes and for several classes of ncRNAs (eg, miRNAs and long ncRNAs). REST deregulation plays a role in mediating cerebral ischemia–induced neuronal cell death, suggesting that REST is important in the pathogenesis of stroke.46,47 This observation directly links the epigenetic processes that underlie NSPC functions with the molecular mechanisms that underlie ischemia and highlights the promise of efforts aimed at identifying and designing small molecules that can modulate the activity of REST and other epigenetic factors for treating neurologic diseases.48 The appropriate temporal, spatial, and cell type–specific delivery of these agents could potentially be used to halt cell death and neural network dysfunction in ischemic neural cells and to promote robust neural regenerative responses from endogenous NSPCs (Figure 1).

THE ERA OF EPIGENOMIC MEDICINE

The development of cell-based therapies for stroke is still in its infancy. Nevertheless, targeted epigenetic reprogramming represents a robust strategy that has the potential for promoting neuroprotection by mitigating pathophysiologic events and enhancing neural regeneration with high fidelity by recapitulating NSPC-mediated developmental processes. We previously reviewed emerging classes of epigenetic agents (eg, DNA methyltrans-

![Figure 1. Epigenetic mechanisms that underlie neural stem cell maintenance and maturation. Specific epigenetic codes define neural cell identity and function. Modulation of these codes using epigenetic therapeutic agents represents a novel strategy for neural cell reprogramming and treatment of stroke.]
Nanospheres and nanocapsules consist of synthetic or natural polymers coupled to cargo through covalent linkage, adsorption, encapsulation, or entrapment. Alternative nanocarriers (e.g., micelles and dendrimers) encompass other configurations of biomaterials and payloads. These technologies are highly flexible in terms of sizes, surface properties, and cargo-carrying abilities, imbuing them with the multifunctionality necessary to enable the selective targeting, internalization, and release of therapeutic oligonucleotides, small molecules, and proteins into specific pools of cells in the brain. For example, the surface characteristics of these vehicles can be modified with macromolecules or small molecules that recognize certain cell surface receptors for cell type–specific targeting. Therefore, a spectrum of epigenetic regulatory agents can potentially be delivered to NSPCs using these technologies. In fact, RNA interference agents are already being developed via these strategies.

These technologies may also allow controlled time release and manipulation of pharmacodynamic and pharmacokinetic properties of epigenetic agents. In addition, nanotechnologies can be functionalized further for specific imaging and active targeting applications. For example, iron oxide and “quantum dot” nanoparticles have unique optical and electrical properties that can be combined with conventional imaging techniques, such as magnetic resonance imaging, and be used to track pathophysiologic processes important in stroke (e.g., inflammation and apoptosis) and also to monitor NSPC activation and migration to sites of ischemic brain injury. Furthermore, these nanotechnologies can be guided by and programmed to release payloads in response to pH, near-infrared lasers, ultrasound, and externally applied magnetic fields. The ultimate goal for the development of these technologies is to create highly sensitive, specific, efficacious, and adaptable diagnostic and therapeutic “nanomachines” that can simultaneously participate in the prevention, early detection, and treatment of stroke.

Emerging biomaterials are also making it possible to enhance endogenous NSPC-mediated repair mechanisms by serving as platforms for controlling NSPC pool expansion, migration, lineage restriction, fate specification, maturation, and neural network integration. By attaching specific extracellular matrix components, epigenetic regulatory molecules, other cues, and even exogenous cells to these structures, they can be tailored to provide the molecular and cellular environment and substrates needed for restoring neural tissue architecture and rebuilding damaged circuits. In fact, this strategy for neural regeneration is now aiming to use biomaterials as artificial stem cell niches. These synthetic microenvironments can be engineered to attract NSPCs through cell-cell or cell-matrix interactions, control NSPC maintenance and maturation with intrinsic biophysical and biochemical cues, and promote signaling between vascular cells and neural cells that allows cells to escape from the niche in response to ischemic injury and participate in protective mechanisms.
and regenerative responses. Moreover, a spectrum of self-assembling nanofibers and nanotubes can concurrently be used to promote the orderly growth of neurites and axons, forming functional neuronal circuitry. Furthermore, the electrical properties of hybrid structures consisting of arrays of nanowires can be integrated with individual axons and dendrites to form artificial synapses.

Thus, these advanced technologies allow exquisite spatial and temporal control over molecular and cell interactions that can be used to deliver diverse systemic and more localized endovascular instructive cues and associated epigenetic signals to reprogram endogenous NSPCs, promote specific neural regenerative processes, and, ultimately, orchestrate the repair of damaged neuronal circuitry after stroke (Figure 2).

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