Behavioral, Temporal, and Spatial Targets for Cellular Transplants as Adjuncts to Rehabilitation for Stroke

Bruce H. Dobkin, MD

Abstract—Stem cell and more differentiated neural cell transplantation strategies are an intriguing approach for neural repair to augment rehabilitation interventions after stroke. In the cortex, exogenous cells could create, augment, or extend in time endogenous peri-infarct and remote molecular signals, such as those for neurogenesis, cell differentiation, axonal and dendritic sprouting, network connectivity, and long-term potentiation, as well as deliver engineered genes and provide replacement cells in a network. If demyelinated axons exist in the periphery of an infarct, they could be targets for remyelination to reestablish conductivity. Much is unknown, however, about the mechanisms by which pluripotent embryonic and multipotent neural stem cells serve as agents of therapeutic plasticity. The robustness of their effects on neuromodulation, reorganization, regeneration, and behavioral recovery is a work in progress. Invasive interventions may have adverse effects not appreciated in preclinical testing. These should initially be offered only to patients with specific profound impairments after it is clinically certain that major disabilities will not improve. If a cellular strategy is very safe, it may be offered to subjects with moderate impairments when they are no longer likely to make further functional gains. Clinical trial designs are suggested that take into account the optimal timing after stroke and specific targets for cellular therapies to foster repair, remapping, and modulation of neural circuits. Cell-mediated rehabilitation would then use task-specific therapies in an optimal dose to maximize training-induced reorganization and learning and, most important, reduce unwanted disability. (Stroke. 2007;38[part 2]:832-839.)

Key Words: brain recovery ■ cell transplantation ■ clinical trials ■ ethics ■ functional recovery ■ neural stem cells ■ neuroregeneration ■ outcomes ■ rehabilitation ■ stroke recovery ■ transcranial magnetic stimulation ■ trophic factors

Rehabilitation is concerned with addressing impairments such as leg weakness, daily activities such as independence in walking and self-care, and participation in usual roles such as walking quickly and safely enough to enable socialization in the home and community.1 Measures of impairment, activities of daily living, and participation in home and community life must be incorporated into the design of assessments, targets for therapy, and outcomes for trials that inject or implant embryonic, hematopoietic, and adult stem cells and more differentiated neural precursors into patients disabled by stroke.2

Cell-mediated strategies seek to partially restore the neural controls for complex cognitive, sensory, or motor functions. The acquisition of skills ordinarily evolves through progressive practice that draws on declarative and procedural mechanisms of learning and memory. The fundamental neurobiology of learning underlies the essential components of strategies for neurorehabilitation as well.3 Indeed, animal models of normal learning and for recovery of function after stroke reveal that repetitive practice, exercise, or an enriched environment can evoke endogenous neurogenesis and the expression of signaling molecules such as brain-derived neurotrophic factor and modulate other molecular pathways for experience-induced learning.4 Functional neuroimaging studies in patients after stroke, combined with in situ microstimulation studies in animals, have revealed how activity-dependent plasticity induces greater synaptic efficacy.5,6 These adaptations evolve over the course of skills learning within, eg, sensorimotor representational maps for voluntary movements, as well as in other components of the networks that contribute to skills.7

Cellular therapies, then, and perhaps other types of biological and pharmacological interventions, could serve as adjuncts to the neurorehabilitation program of highly impaired subjects. Therapeutic cells may be capable of enhancing fundamental mechanisms for learning within circuits that they reconstruct or modulate, as well as by inducing, delivering, or extending in time peri-infarct and more distant molecular signals for neurogenesis, cell differentiation, axonal and dendritic sprouting, network connectivity, and long-term potentiation. These gene-induced, biochemical, physiological, and morphological modulations may be especially important for optimizing the function of spared pathways.

Each cellular strategy must be proven in preclinical models and phase 1 and 2 clinical trials to be safe from inducing hemorrhage, infection from a virus or other organism, inflammation, tumorigenesis, epilepsy, and aberrant plasticity that increases disability. The method of delivery of cells will also

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impact safety issues. Intravenous, intrathecal, intraventricular, and direct injection into brain parenchyma near a cystic cavity are all viable, each with possible side effects. The effectiveness of the route may be limited by the receptivity of the cerebral milieu over the time after stroke as to how well cells penetrate, migrate, survive, differentiate, and integrate to make connections or produce modulating substances in an optimal distribution. If safe, interventions for profoundly impaired subjects may also be applied to patients with fixed, moderate impairments to enhance defined functions, such as greater use of a paretic hand. Unfortunately, a tendency to overly interpret the robustness of the results of cellular strategies in animal models has led to questionably ethical practices by some clinicians who are already injecting cells into patients without following the standards of a clinical trial. Investigators in poststroke studies must shun the unscientific designs used, e.g., in patients with spinal cord injury and atrophy of lateral sclerosis in China and other countries, as well as false starts such as those that occurred in early treatments of Parkinson’s disease with implants of adrenal cells.

Temporal and Behavioral Targets
The timing for a biologic intervention for the neural repair of specific deficits ought to take into account both the state of the injury milieu and clinical criteria. The timing of transplantation of stem cells or neural precursors for repair, rather than for neuroprotection, after stroke will depend on the readiness of the peri-infarct milieu into which cells are exposed, including the effects of inflammation, reactive astrocyes, macrophages, local gene expression and signaling, architectural barriers to migration, and others. For example, during the first 2 to 3 weeks and probably longer after an experimental stroke, the peri-infarct cortex expresses a rise or fall in a range of neuronal growth-promoting and growth-inhibiting genes that affect the making of cytoskeletal proteins, direct axon growth cones, and produce angiogenesis and other molecular signals for the proliferation and migration of endogenous stem cells from the subventricular zone. Exogenous stem cell interventions, including bone marrow stromal cells, may be most useful within this time frame to extend and sculpt these mechanisms for axonal regeneration, cellular signaling, and synaptogenesis.

Timing must also account for the point at which clinicians can state with some confidence that further measurable recovery of an impairment is unlikely. An entry requirement for initial clinical trials may be that subjects have no ability to grasp or pinch objects and perform no more than a few degrees of voluntary flexion and extension at the elbow, wrist, and fingers. How soon after stroke can clinicians predict that the rate of gains has reached a plateau? The stroke outcomes literature suggests that the rate of increase in functional improvement in the majority of survivors peaks by 12 weeks for activities of daily living (ADL) with some gains that continue out to 24 weeks. On admission for inpatient rehabilitation at 2 weeks after a stroke, poor function by the Barthel Index (BI <45/100) and Functional Independence Measure motor score (<27/90) each anticipate dependence in ADL at discharge. Week-to-week improvements stop sooner for patients with the most severe impairments. These ADL scales, however, do not measure the degree of weakness or sensory loss of the affected extremities or require their use. The initial degree of impairment, according to the National Institutes of Health Stroke Scale (NIHSS), may be a useful marker for predicting very high and very low levels of subsequent function. An NIHSS at 1 week after stroke of <10 predicts a 20% chance of an excellent outcome (BI ≥95), whereas a score >17 to 19 is a predictor of poor outcomes with a BI <65 and Glasgow Outcome Score ≥3 or death. An Op рождения Prognostic score >5 is also associated with poor functional outcomes. The combination of severe sensorimotor impairment and hemianopia predicts that only approximately one third of patients will walk without physical help by 6 months. Thus, by 2 weeks after stroke, clinicians can anticipate which patients are least likely to recover the ability to care for themselves.

Kwikkel and colleagues and Kollen et al examined in greater detail at trying to predict when gains may slow in their longitudinal study of 100 patients who had a first stroke in the middle cerebral artery distribution. Subjects were tested weekly on 18 variables from weeks 1 to 10 after onset, biweekly from weeks 10 to 20, and at weeks 26, 38, and 52. The subjects had participated in a randomized trial for intensity of treatment of an arm or leg intervention. The investigators used random coefficient modeling of change scores to examine the impact of improvements on walking, upper extremity dexterity, and functional independence. At 6 months, some dexterity in the paretic arm was found in 38%, and complete functional recovery was seen in 12% of the patients. Infarcts of two thirds of the hemisphere, a right hemisphere stroke, a homonymous hemianopia, visual gaze deficit and visual inattention, and the severity of paresis were significantly associated with poor arm function. In other observational studies, these factors had also tended to predict poorer outcomes for ADL. Motricity Index scores of leg movement and strength of at least 25 points in the first week and Fugl-Meyer arm scores of 11 points in the second week that increased to 19 points in the fourth week raised the probability of developing some dexterity of the hand from 74% to 94% at 6 months, based on the Action Research Arm Test (dexterity was captured by a score ≥10 points). The investigators found no significant change in the probabilities for regaining hand dexterity based on measures taken after 4 weeks. Lack of voluntary motor control of the leg in the first week with no emergence of synergistic flexor or extensor arm movements by 4 weeks was also associated with poor outcome at 6 months for the upper extremity. This finding suggests profound loss of the descending corticospinal and corticoreticulospinal projections. Compatible with other studies, the absence of wrist and finger extension or a persistently flaccid arm at 2 to 4 weeks after stroke predicts no functional use of the arm and hand at 6 months. If some finger flexion and extension are present within 4 weeks of stroke onset, however, progress may continue toward the ability to grasp and release items held in the palm, possibly followed by development of a key pinch, 3-finger pinch, and finer individuation of finger and wrist movements. Initial cellular implant studies that focus on restoration of a functional hand will, therefore, want to include patients who have minimal or no wrist and finger extension that persists at least 2 and preferably 4 weeks after the stroke.
Time-dependent covariates for gains in the level of independence for walking (by the functional ambulation index, or FAC, with its 6 categories) were more difficult to determine in the studies by Kwakkel and colleagues. They found that postural control for standing balance (by the Timed Balance Test) was most important, followed by a higher change score on the Fugl-Meyer Motor Assessment for selective movements, fewer omissions on a letter cancellation task, and greater strength (measured by the Motricity Index). The explained variance, however, was only 18%, and the regression coefficients were rather low. Thus, recovery of walking is more difficult to predict than recovery of hand dexterity, probably because less readily measurable behavioral adaptations may enable walking despite marked loss of selective leg movements. Some general rules for inclusion of patients for cellular implant trials to aid the recovery of walking can be offered, however. Subjects should not have hip flexor or knee extensor strength against gravity or resistance, if the intervention is being offered within the first 2 to 3 months after onset. If a cell strategy is attempted for subjects who are able to walk, walking speed should probably be \(<0.3\, m/s\) for a 15-m walk and associated primarily with poor motor control,\(^{22}\) not due to comorbid conditions such as joint pain and deconditioning. Finer assessment of outcomes beyond strength, speed, and endurance for trials of repair can include temporal and spatial measures of the pattern of gait, such as the equality of single-limb support times for the legs and the stride length, which may better reflect fine neural changes in motor control.\(^{23}\)

Stroke may, of course, induce more than motor impairments. Aphasia occurs in up to 30% of patients after stroke, but only about half of these patients still have impaired language 1 month later. Global aphasia for 1 month has a poor prognosis for functional communication, but language gains in specifically trained aspects of aphasia can occur in patients even with chronic stroke. A temporal window for reaching a plateau in patients with mild to moderate impairments is wide. The types of linguistic impairment must be well defined before trying to intervene to attain measurable changes in outcome. Hemispatial neglect often improves by 4 months after stroke in all but the most impaired hemiplegic subjects, who initially have anosognosia. Aspects of spatial inattention may persist, however, so measures of change must be comprehensive. As many as 50% of patients with a homonymous hemianopia have improved within the first month after onset, and up to 20% may improve for 3 to 6 months. Gains are due to compensation, early restitution of conduction along the involved optic radiations, and perhaps neural plasticity. The timing for a cellular intervention for a specific impairment, then, ought to be as soon as a high threshold for further clinically meaningful gains has been reached.

Several potential confounders make temporal and behavioral data about recovery after stroke somewhat unreliable. The rehabilitation experience of patients in most observational studies was usually left open ended. Evidence-based therapy approaches and strategies best suited for an individual’s impairments and disabilities may not have been used. For example, task-specific practice to improve reaching and pinching or for walking may have led to better gains had it been tried (the Table). Indeed, the optimal intensity and duration of therapy to maximize gains are almost never determined even within clinical trials. Most studies of augmented practice have offered \(~16\) hours of additional treatment for a specified problem in patients with mild to moderate impairments or disabilities, and most of these trials have revealed less than a 10% improvement with that modest increment in treatment time. Thus, the maximal level of recovery over time for a specific impairment or disability with conventional rehabilitation techniques in patients with severe stroke, the type most likely to be considered for invasive cellular implantation, cannot be calculated with certainty.

A brief pulse of a task-oriented therapy (the Table) can lead to rapid changes in function in subacute and chronically disabled patients who retain some motor control. Much of the gain found for patients with chronic hemiparesis who have at least 20 degrees of residual voluntary wrist and finger extension, for example, has occurred within the first few days of a 2-week course of therapy that constrained the use of the unaffected hand and pushed 6 hours of daily therapy with the affected one. Improvements that are elicited by brief training, from 6 to 18 hours of focused therapy, could confound

### Stroke Rehabilitation Practices for Sensorimotor-Related Impairments and Disabilities to Drive the Functional Effects of Cellular Transplants

<table>
<thead>
<tr>
<th>Evidence-Based Practices</th>
<th>Evidence-Evolving Practices</th>
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<tbody>
<tr>
<td>● Bobath and neurodevelopmental therapy approaches</td>
<td>● Increase cortical excitation by transcranial magnetic, direct motor cortex, or peripheral nerve stimulation</td>
</tr>
<tr>
<td>● Correct qualitative deviations in kinematics, kinetics, and temporospatial components of functional movements, such as sitting balance, reach, grasp, pinch, or walk</td>
<td>● Repetitive practice with feedback in a virtual reality environs</td>
</tr>
<tr>
<td>● Shaping: practice with feedback to gradually incorporate simple, then more complex, multijoint components of task-specific movements</td>
<td>● Simultaneous bimanual practice of similar movements</td>
</tr>
<tr>
<td>● Task-oriented massed practice: treadmill training of gait with partial body weight support; constrain unaffected arm to encourage use of affected one; robotics-assistive arm and leg devices</td>
<td>● Combinational interventions: eg, robotics-assisted treadmill training of walking in a virtual environment</td>
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<tr>
<td>● Electromyographic or joint angle biofeedback to increase joint motion or induce electrical stimulation of a muscle</td>
<td>● Pharmacotherapy: replace depleted neurotransmitters and modulators, enhance neuronal excitability or long-term potentiation to enhance learning</td>
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<tr>
<td>● Functional electrical stimulation of single or sequential muscles for grasp or foot clearance</td>
<td>● Spinal cord electrical stimulation to drive flexor-extensor movements, such as stepping</td>
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<tr>
<td>● Increase strength (resistance exercises), endurance (treadmill walking or recumbent pedaling), speed (feedback about time to perform task), and accuracy (visual feedback)</td>
<td>● Biologic neural repair strategies</td>
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The table above outlines various strategies and approaches for rehabilitation practices that can potentially drive functional effects of cellular transplants in stroke rehabilitation. Each strategy is designed to target specific impairments and disabilities, with an emphasis on enhancing cortical excitation, increasing strength and endurance, and improving accuracy and speed in movements. The table includes both evidence-based practices and evolving practices, reflecting the dynamic nature of stroke rehabilitation techniques.
efforts to interpret the effects of an implant. To lessen the impact of early rapid improvement related to rehabilitation, a phase-in of therapy for the targeted behavioral outcomes, before a cellular implant, should be part of experimental protocols. Another concern in trials for cell-mediated repair is that the clinical science of cellular transplants may benefit from success in restoration of hand movement, even if this provides no gain in function, but patients would not benefit. Improvement in voluntary wrist extension of the hemiplegic arm without the ability to grasp and release for holding and manipulating objects will have little impact on the daily activities of the patient with stroke, because the subject will have to continue to use the unaffected hand for all gross and dexterous actions. An intervention that carries risk, such as invasive cell implantation, must aim to enable better function.

Spatial Targets

Anatomic and functional neuroimaging may help determine the site for an implant, the intactness of residual pathways, and the physiological incorporation and actions of the new cells. Insights into the physiological effects of cellular transplants may be revealed in vivo by functional magnetic resonance imaging (fMRI) during a passive or voluntary movement, by positron emission tomography (PET) with a glucose or oxygen radionucleotide during rest or with an activation paradigm, and by PET with a marker for a specific ligand or neurotransmitter function, such as [18F]fluorodopa and [11C]raclopride for dopamine activity. These techniques have revealed patterns of cerebral reorganization after stroke and during task-oriented rehabilitation suggesting that best clinical recovery occurs when the primary regions that represent a motor or language task are activated. Indeed, the anatomic volume of a cortical infarct may not predict recovery of the hand as well as the percentage of functionally intact tissue in M1, as determined by fMRI. Most of the imaging studies, however, were performed on patients who evolved good motor recovery, so past patterns of activation may not be relevant to studies of highly impaired subjects. Still, the observation in animal models and in human studies that peri-infarct tissue plays a critical role in clinical recovery makes this area, defined by anatomic and functional imaging, a region of interest for implantation.

Functional neuroimaging could be a tool to explore other locations for a cell implant, to determine whether the motor network is engaged by task-specific rehabilitation, and to monitor the dose of therapy needed to maximize cerebral reorganization after cell therapy. For example, if ipsilesional M1 or secondary motor areas were active during an fMRI task, the subject may be a better candidate for restoration of functional movements than the patient who exhibited no residual function in critical pathways. In a related strategy, if the fMRI activation pattern evolved in response to a brief trial of therapy, the investigators would have evidence to suspect that the sensorimotor network was accessible and intact enough to be a reservoir for motor learning. The network, then, might be responsive to cell implantation at a critical site as an adjunct to task-specific rehabilitation to help drive partial anatomic or physiological reconstruction of the network and enhance motor skill learning. Several small studies of rehabilitation interventions for the upper extremity and for walking monitored by repeated fMRI or transcranial magnetic stimulation at regular intervals during therapy suggest that this approach may give insight into gradually adapting brain-behavior and dose-response relationships. Although a strategy of serial clinical and neuroimaging probes to ascertain whether therapies produce ongoing cerebral reorganization may oversimplify the neurobiologic processes involved in neural connectivity and synaptic efficacy, it aims to find a clinical means to address whether the subject has any spared and responsive capacity before transplantation and whether the cells may be involved in augmenting recovery of function after transplantation. For example, a trial of implantation of a human teratoma (NT-2) cell line of neurons into the region of the basal ganglia in patients with deep infarcts found metabolic activity for labeled glucose at the graft site in some of the subjects, which may reflect functioning cells or local inflammation. Metabolic activity that increased transsynaptically beyond the implant would be a more convincing demonstration of functional inclusion of the graft.

Targets in Gray Matter

Specific anatomic sites for transplanted cells will depend, of course, on the functional properties of the cells and their ability to migrate and survive to contribute to the actions of the residual network. The tissue immediately surrounding an infarction, which includes the ischemic penumbra, has been characterized by the expression of cytotoxic and cytoprotective molecules that may trigger repair processes and serve as a milieu that supports learning by exciting long-term potentiation. These processes could be amplified or sustained beyond their usual temporal course with intravenous injection of exogenous cells that produce a neurotrophic factor. Cellular gene delivery to the intact cortex could amplify the production of neurotrophins, neurotransmitters, and other modulators involved in learning as well as genes to drive axonal regeneration and augment corticocortical dendritic and axonal sprouting. These new connections, however, may not contribute to clinically useful sensorimotor activity without rehabilitative training. New sprouts may also create aberrant connections that either have no effect or even lessen function in the newly modulated circuit and the patient. For example, the new axons that arose after a microinfarction of the primary motor cortex forelimb region of a monkey revealed the capacity for a regenerative axonal response from the ventral premotor region into the primary sensory cortex, but it is not clear how this input would affect recovery, because it is a unique pathway.

In the gray matter, cells could serve as a synaptic bridge that reunites dendrites within a disrupted intracortical pathway, a site that especially lends itself to monitoring by functional neuroimaging techniques. Given the complexities of the signaling cascades that lead to functional circuits during development, however, an attempt to recreate a circuit seems more formidable than to use repair techniques to increase the efficacy of a surviving circuit. For example, some experiments reveal that adult hippocampal neural stem cells can integrate into neuronal networks and make functional synapses. Most studies of adult bone marrow–derived stem cells reveal morphological and marker genes of neurons but not clearly functional neurons.
nally restricted precursors, however, may be more likely to survive to make synaptic connections, at least in rodent models.47

An increase in the descending motor command by a modest amount, even oligosynaptically via reticulospinal pathways to propriospinal projections and then to spinal motoneurons,48 could have a large functional benefit. In another potential approach, stem cells that reach into homologous M1 of the unaffected hemisphere may theoretically enhance or sustain endogenous growth programs triggered by the stroke.49,50 The corticospinal tract has projections that either remain uncrossed or recross under the central canal of the spinal cord51,52 and may sprout within the cord after injury.53 Cell modulation of unaffected M1 could, then, augment the local increase in dendritic spines that have been reported in animal models59 and augment input into subcortical and spinal targets.

**Targets in White Matter**

White matter lesions that cause paralysis may be confined to the centrum semiovale, internal capsule, or pons or extend from the periphery of a cortical infarction or intracerebral hemorrhage. White matter lesions may disrupt association, commissural, fascicular, and other projection fibers. Pathological studies of cavitated infarcts usually describe severed axons and Wallerian degeneration. If demyelination exists among spared axons, a remyelination strategy with stem cells or oligodendrocyte precursors to rescue axons becomes of interest.54 In addition to the goal of restoration of a small percentage of nonconducting motor and sensory projections, cortical language areas disrupted within the superior arcuate fasciculus and visual field impairments from lesions in the optic radiations could be improved modestly by remyelination that restores the transmission of action potentials, perhaps enough for patients to respond to rehabilitation training. Remyelination strategies for spinal cord injury have been proposed on the basis of autopsy findings of intact axons in the surroundings of cystic lesions.55 In animal models, short segments of axons appear to have been remyelinated by stem cells, olfactory ensheathing glia,56,57 and endogenous and exogenous oligodendrocyte progenitors.58 No reports, however, have described intact axons that have been stripped of myelin for short segments around a stroke in autopsy tissue. It will be important for pathology studies to determine whether axon markers in the absence of myelin markers near a cavitation can be found after stroke in patients. Recent MR sequences such as diffusion tensor imaging,59 perhaps combined with magnetic resonance spectroscopy,60 may also become useful for determining whether remyelination of spared axons is a potential target and whether the cellular strategy is successful.61

Cellular transplants could modulate the sprouting of spared axons and the regeneration of disrupted axons by providing neurotrophins or acting on axon growth cone inhibitors, such as Nogo-A.62 Cells with or without gene modifications for producing trophic or tropic substances could be placed into the perilesional or distal milieu to augment axon growth through white matter. The complexity of long distance (≥ 1 cm) axonal regeneration is formidable, however. The architectural barriers and the balance of progrowth and inhibitory molecules in the milieu must be managed to guide axons through white matter to their targets. Axon extension beyond the lesion site has been accomplished in select experimental conditions in animal models, however.63,64

**Rehabilitation Designs for Cell-Mediated Trials**

To successfully sow rewards from seeding the brain, specific neurorehabilitation strategies will be needed to propagate the functional effects of implants (the Table). Given what is known about the temporal course of endogenous peri-infarct gene expression in animal models and the course for recovery of hand function, the earliest time point for an intervention aimed at recovery of functional use of the hand, as noted, will be 2 to 4 weeks after hemiplegic stroke. Investigators who test cell-mediated interventions for other behavioral targets and at later times may want to take the following approach until more is understood about when and how each biologic intervention may best be deployed to enhance recovery.

Once subjects are entered into a trial for neural repair, they could be given 6 therapy sessions over 2 weeks with 12 hours of therapist contact for progressive task-oriented treatment aimed at impairments and functional outcomes designated for the trial (the Table). Where evidence-based practices exist, these rehabilitation interventions can be incorporated into the therapy regimen.15 Therapies with a strong conceptual basis that are applicable to the behavioral and network targets for the cellular intervention should also be incorporated into the rehabilitation component of the trial (the Table).65 The subjects would then be reassessed on the study’s motor and functional scales, if better use of the arm or walking were the goal. These scores become the new baseline. If change exceeds a predefined level on any of the primary outcome assessments, eg, ≥ 10% better, the rehabilitation intervention should continue for 6 additional sessions. If no further change occurs and the subject still meets the entry criteria for impairment and disability, the transplant (or placebo) proceeds and progressive practice is continued for at least 3 contact hours per week for 24 weeks, along with a daily home program. This approach minimizes the experimental “noise” of gains that are unlikely to be related to the cellular intervention. A stable behavioral baseline may also decrease the number of subjects needed to power a randomized clinical trial. Most important, this strategy aims to maximize the potential benefits of cell-based therapy as an adjunct to rehabilitation for stroke.

**Deployment of Cellular Strategies in Patients**

Preclinical studies that reveal positive results for an experimental intervention for neuroprotection or neural repair have an enormous impact on the expectations of clinicians, disabled patients, and the media. Animal experiments after stroke have led to several reasonably well-designed safety trials in patients, in that the cell types were characterized, an estimate of the optimal volume of cells and their survival were determined, cell placement procedures were standardized, the patient population was defined, valid measures of behavior were obtained, a prospective search for adverse effects was made, and standard statistical analyses were presented. The safety trials included intravenous injection of
autologous mesenchymal stem cells \( \approx 40 \) days after a hemispheric stroke\(^{66} \) and implantation of human neuronal cells derived from a teratocarcinoma cell line (NT-2 cells; LBS-Neurons, Layton Bioscience, Inc) into the edge of chronic deep infarcts near the basal ganglia.\(^{38} \) Any positive note of efficacy was imputed from secondary analyses of the small sample sizes. Safety studies in spinal cord injury have proceeded with injection of human fetal spinal cord tissue into a syrinx.\(^{67} \) autologous activated macrophage injections into the acute injury (Proneuron Biotechnologies, Israel), and porcine oligodendrocyte progenitors (www.diacrin.com) and autologous olfactory ensheathing glia into chronic injuries without any efficacy noted.\(^{68} \) A biased interpretation of the animal preclinical literature has also led to commercial infusions of cells, presumably of hematopoietic or neural origin, that are marketed for whatever neurological disease and deficit the recipient wishes to mollify (eg, see http://stemedia.com, www.stemcellschina.com). No knowledge of course can be gained from this misuse of a new technology. Do the cells survive, act in some way on neural tissue, or lessen specified and carefully assessed impairments and disabilities? Disabled patients are ready, but are cellular strategies ready for clinical efficacy trials?

Adult autologous neural stem cells, endogenous cells from the subventricular zone, hematopoietic and umbilical stem cells, embryonic stem cells, and lines developed from these types hold promise, but their characteristics and specific actions, the specific goals for deployment, and their effects on behavior in animal models need ongoing development. The scientific investigations behind manipulating cells to carry out recognizable functions that significantly augment behavioral recovery are hopeful, but they have not yet created a “road map” toward safely helping patients. The modulation of neuroprotection, neural reorganization, and regeneration is reasonably apparent in published experiments in animal models; eg, when intraparenchymal and intravenous transplants survive and migrate in modest numbers, stimulate or produce growth factors, alter proteins in the microenvironment, make regenerative substances, or possibly integrate with other neurons or with demyelinated axons. Behavioral gains, however, appear modest in animal models of stroke. Even when care has been taken to try to define the effects of cellular manipulations on a behavioral scale to assess outcomes, the gains seem less than robust.\(^{13,69} \) Often, the relation between an increase in behavioral function on a simple scale and the presumed biologic effects of the cell transplantation compared with placebo lacks a demonstrated neurophysiological or morphological correlation. In the modeling and treatment of any neurological disease, making brain-behavior correlations owing to injury or gains is challenging. Therapeutic trials in neurorehabilitation that have been built on a strong basic science foundation and animal modeling often prove no better than what is already available,\(^{70,71} \) in part because of the many biologic and behavioral differences between humans and rodents in health and disease. Indeed, the animal models of injury and repair for stroke and spinal cord injury have inherent limitations for their applicability to human interventions.\(^{72} \)

Preclinical experiments that best inform the design of human trials ideally include a lesion of etiology, volume, and location that parallels 1 of the varieties of stroke in patients; examine changes induced by injury and by repair procedures both near and remote from the lesion; distinguish between reactive molecular and histological changes versus changes critical to repair cascades; include explicit training paradigms for the reacquisition of testable skills; correlate morphological and physiological measures of repair with behavioral measures of task reacquisition; and reproduce key results in \( > 1 \) laboratory, in different strains or species of rodent, and in a larger mammal such as a nonhuman primate.\(^{73} \)

The capacity of stem cells to adapt their fate and function to a changing pathological environment after ischemia and anatomic disconnection is the basis for transplantation and for manipulating proliferating endogenous cells to achieve therapeutic plasticity.\(^{73} \) So far, the quest for human interventions has been built primarily on conjecture and modest demonstrations of cell activities and altered sensorimotor behaviors in rodents, rather than on a clear definition of cell capabilities and physiological and morphological objectives for repair by a specific cell line. More preclinical work is indicated. Guidelines for safety and efficacy in preclinical and clinical trials\(^{67,74} \) may help investigators learn as much as possible, in the inevitable absence of full understanding, about their experimental intervention. In promoting clinical trials, investigators must protect highly disabled persons from lightly interpreted preclinical results, as well as from physical and emotional harm. Patients weigh uncertain risks and benefits against the hope for extraordinary new therapies that easily capture the imagination.

Disclosures

None.

References


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