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What Matters in Cellular Transplantation for Spinal Cord Injury: The Cells, the Rehabilitation, or the Best Mix?

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Lima and colleagues recently reported the results on 20 patients with chronic sensorimotor or motor complete spinal cord injury (SCI) after they performed partial scar removal and implantation of a mix of neural stem and olfactory ensheathing cells (OECs) derived from mucosal autografts¹. In this uncontrolled but well-planned phase 2 study^{2,3}, the subjects also received, immediately prior to the cellular intervention, a median of 400 hours of lower extremity step training either over ground or with a Lokomat electromechanical device. These therapies were restarted and continued for at least a year after surgery. Thus, an intensive, task-related rehabilitation program for walking was built into the trial to try to produce further recovery⁴. Preoperatively, they sought a stable baseline, reducing the likelihood that latent function might improve from physical therapies alone. Then, they hoped the therapies would maximize contributions from the cells. Remarkably, new signs of motor control were found from 1 to 3 years later. For example, 75% of subjects developed electromyographic activity below their lesions, and the American Spinal Injury Association Impairment Scale of motor strength improved by 4 to 8 points in 5 subjects and by 14 to 20 in another 4. The Walking Index for SCI scores of assisted walking improved in relation to greater motor control^{5,6}. The increase in voluntary movement was found, however, only in the patients at the 2 sites that provided assisted overground stance and step training but not at the site that offered only the robotic stepper. The implication, then, is that the cells had a biological effect that depended on the type of practice. In this case, the 2 rehabilitation strategies differed in that overground training may enable greater incorporation of feedback and more trial and error to successfully approximate components of movements, compared with the rather inflexible kinematics with training on the robotic device. This potential confounder for the utility of electromechanical assists has been noted in randomized clinical trials of upper and lower extremity devices, in which the robotics were no better, or worse than, hands-on therapy of the same intensity and duration⁷⁻¹¹.

Many aspects of this study and other safety trials of cellular interventions for SCI are of interest to rehabilitation clinicians¹²⁻¹⁴, especially in light of the planned Geron Corp safety trial of their patented OECs that will be injected to possibly remyelinate surviving axons. This procedure is based on the autopsy finding of intact axons at the periphery of large human SCI lesions, which may also have partially demyelinated fibers, and on published¹⁵ and unpublished rodent studies that employed these cells. The issue of the type, timing,

intensity, and duration of a parallel rehabilitation intervention that aims at the most likely potential benefit of a biological intervention is one that those involved in neurorehabilitation and neural repair must address. These parameters may be as important as better recognized barriers in transplantation, such as cell type, timing of implantation, need for immunosuppression, cell survival, migration and differentiation, production of trophic or other regenerative molecules, and incorporation into a network or modulation of nearby cells and synapses¹⁶. Does the type and intensity of the rehabilitation intervention hold one of the keys to increasing the likelihood of successful effects of cellular interventions? Do mechanisms of activity-dependent plasticity provide cell signals that make the implants more functional? Can a randomized clinical trial be considered a scientifically sound comparison, unless a design like that of Lima and colleagues is employed, including a phase-in of task-related physical therapy for all subjects, followed by task-related therapy after the sham and experimental interventions? Soon to come noncellular procedures to regenerate or sprout axons past the lesion to motor pools or locomotor central pattern generators will also have to address these issues¹⁷⁻²⁰.

Gains in motor function can be made within the context of what is practiced at almost any time after SCI, as well as after stroke and other neurological diseases, by a variety of specific rehabilitation interventions²¹⁻²⁶. The amount of improvement, however, may be modest in highly impaired patients who have the least residual motor control and corticospinal tract input to the motor pools of the extremities^{27,28}. In patients as impaired as those operated on by Lima and colleagues, the intensity, duration, focus, and rehabilitation strategy of practice may be especially critical to enable improvements in taking steps, to recover motor control of the upper extremity at least 2 levels below the lesion, and to increase balance, bladder, and autonomic function.

OECs and other types of autologous and embryonic or fetal-derived cell interventions are being offered as blood and organ injectables at several dozen clinics in China (eg, www.Beikebiotech.com, www.nrrfr.com/), Thailand, the Caribbean, Brazil, Mexico, Russia, Bulgaria, Ukraine, India, and other sites for stem cell tourism²⁹. Westerners continue to travel to these cell spas in the hope of a cure at a cost of \$10 000 to \$25 000 a shot. What is fascinating about the anecdotal Web site reports from the higher profile clinics is that people who believe they are better seem to have engaged in considerable rehabilitation postoperatively but not in the months immediately prior to the intervention. Indeed, although we do not have published reports about the more than 1000 patients injected with Dr Hongyun Huang's fetal-derived OECs for the treatment of SCI (and other diseases), he has stated in his oral presentations that the patients who tell him that they have improved are the ones who get much more physical therapy than the others^{29,30}. These uncontrolled uses of cellular interventions offer little if any formal pretesting and posttesting and never employ standard measures at specific intervals to try to detect changes in impairment and disability, however. One is left to wonder whether it is the effects of postoperative rehabilitation that make some patients better from their perspective.

Experimental models of injury and repair suggest that training may be an important component to complement cellular therapies^{31,32}. Clinical trials of neurotransplantation, however, have at most encouraged postoperative rehabilitation but have not stipulated how

much and what type³³. Several recent trials of interventions other than cellular implants have incorporated preintervention training³⁴. Rehabilitation practices offer insight into training paradigms, but few rules can be drawn about the optimal intensity of retraining to maximize the potential effects of cellular interventions on walking or upper extremity function³⁵⁻³⁷. Simply controlling for the dose of 2 different active rehabilitation interventions has been a relatively new aspect of trials^{11,23,38-40}.

The best course for a clinical trial of a biological intervention, then, may be to aim for a stable baseline of selected impairments and disabilities in chronically disabled patients by employing at least 20 hours⁴¹ of presurgical rehabilitation that is focused on the primary motor outcome, then continue with movement and task-oriented therapies that are progressive in difficulty and target critically needed strength, timing, multijoint coordination, and motor control for the upper or lower extremity goals of the trial, until subjects reach a persistent plateau in gains. With collaboration^{42,43} between the scientists who develop preclinical models of repair, the physicians who consider their applications, and neurorehabilitation clinicians who understand how to train motor skills, we can design phase 2 and 3 trials in the most ethical and conceptually sound way to determine whether cellular interventions will augment rehabilitation-driven outcomes.

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