were found in the other groups. The tumor imaging results imply some transient retention of the toxin-secreting stem cells. Unfortunately, the investigators were unable to detect viable stem cells in the resection cavity after 72 hours by bioluminescence.

Many potential agents against glioblastoma will be challenged by drug stability and poor blood-brain barrier permeability. Using neural stem cells to secrete tailored tumor-specific toxins or other biological agents within the resection cavity in direct contact with residual tumor may help overcome these obstacles. Although there are significant barriers to the clinical use of either autologous or nonautologous neural stem cells for the treatment of glioblastoma, Stuckey and colleagues present important in vivo evidence of the feasibility of engineering neural stem cells to secrete targeted cytotoxins that affect tumor progression.

Alexander J. Gamble, DO*
John A. Boockvar, MD*‡
**Feinstein Institute for Medical Research*
Manhasset, New York
‡Lenox Hill Hospital
New York, New York

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Timing Is Everything in Corticospinal Tract Recovery After Stroke

Motor paralysis is a significant cause of disability in patients after cortical stroke. Although rehabilitative training remains the most successful therapy for restoring motor function, a broad range of outcomes exist, and we do not fully understand how such rehabilitation improves motor function. In addition to rehabilitation, there is a push to develop other therapeutic options such as pharmacotherapy to help with this difficult clinical problem. One promising therapy involves immune-mediated blockade of Nogo-A, an axonal growth inhibitory protein shown to be an important player in neuronal plasticity.

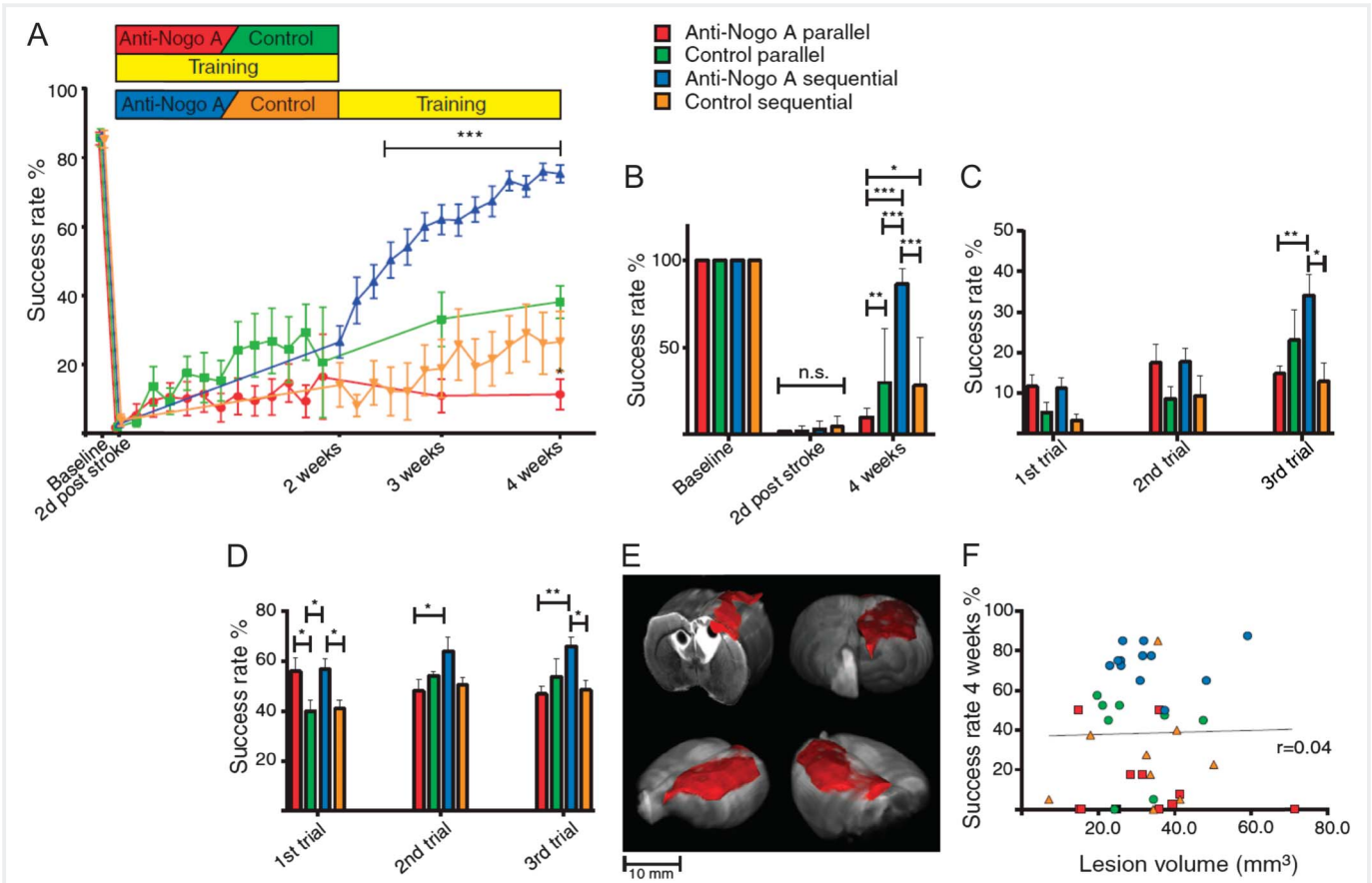

Figure. **A**, *success rates (%) in the single-pellet grasping task 2 days after large hemispheric stroke. The anti–Nogo A/sequential group showed the most significant recovery after injury.* **B**, *success rates (%) of the last testing session compared with normalized baseline levels.* **C**, *animals in the anti–Nogo A/sequential group also demonstrated improved success rates (%) in the Montoya staircase test and the (***D***) horizontal ladder–crossing task, both of which were introduced after completion of the single-pellet grasping task training schedule.* **E**, *ex vivo magnetic resonance image representing the results of a typical experimental stroke.* **F**, *final success rates (%) did not correlate with stroke lesion volume. From Wahl AS, Omlor W, Rubio JC, et al. Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke. Science. 2014;344(6189):1250-1255. doi: 10.1126/science.1253050. Reprinted with permission from AAAS.*

Antibodies targeting this protein have been investigated in animal models of stroke and spinal cord injury with encouraging results. However, no consensus exists on the timing of drug administration after injury and its use in combination with rehabilitative physical therapy.

In a recent research article published in *Science*, Wahl and colleagues[1] investigated whether the timing of anti–Nogo-A treatment and physical therapy influenced motor recovery in a rat model of stroke. Greater than 90% of the sensorimotor cortex was destroyed using blood vessel blockade with microthrombi after training animals on a single-pellet grasping task (baseline), resulting in significant loss of fine motor skills of the contralateral forelimb. The investigators then tested 4 different combinations of drug and physical therapy schedules (Figure). In the group receiving anti–Nogo-A treatment for 2 weeks followed by a sequential skilled physical therapy regiment (anti–Nogo-A/sequential), recovery of forelimb function reached almost 90% of pre-stroke function, significantly outperforming schedules with concurrent drug treatment and physical therapy or control drugs, which only reached levels close to 40%.

To better understand why sequential administration of drug followed by physical therapy outperformed concurrent administration, the investigators performed histological analyses of cervical spine cross sections and measured corticospinal tract fibers that crossed the midline to innervate the hemicord opposite the stroke. The anti–Nogo-A/sequential treatment group had the highest number of midline-crossing fibers. In addition, using computer vision algorithms, the investigators were able to characterize this group as having a more organized radial pattern with fewer branches and a preference for the premotor/motor spinal cord rather than the sensory cord. In contrast, the anti–Nogo-A/parallel treatment group had double the number of branches, a higher bouton density, and an aberrant growth pattern preferring a different laminar distribution.

The investigators performed a final pair of experiments using short-term and long-term reversible nerve blockade to convincingly show that neurons from the intact motor cortex were the ones responsible for regeneration of the midline-crossing fibers in the anti–Nogo-A/sequential treatment group. This was done by delivering a highly efficient lentivirus containing a doxycycline-inducible tetanus toxin to the stroke-denervated hemicord at C5-6. In addition, another virus carrying a reverse tetracycline transactivator was injected into the intact motor cortex; thus, only neurons infected with both viruses were susceptible to doxycycline-inducible neuronal blockade. Indeed, after exposure to doxycycline, animals in the anti–Nogo-A/sequential group lost their new forelimb function and regained it after doxycycline cessation. A comparable design of infecting the stroke-denervated hemicord and ipsilateral intact motor cortex was taken using different viruses, and genetic elements activated by a designer drug showed similar short-term effects, confirming the location of the neurons responsible for the corticospinal tract regeneration.

Taken together, these results help describe a critical period in stroke recovery in which animals are sensitive to plasticity-inducing drugs such as anti–Nogo-A and better define how physical therapy after a period of drug exposure may contribute to optimal functional recovery. The absence of a correlation between stroke lesion size and the ability to regain function after injury is particularly encouraging for patients with large territory injuries. As providers of care for patients afflicted with motor paralysis after stroke or spinal cord injury, understanding the interplay between physical therapy timing and administration of these drugs will be critical as we design clinical trials to capture the potential of these therapies.

Ziev B. Moses, MD
Muhammad M. Abd-El-Barr, MD, PhD
John H. Chi, MD, MPH
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

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A Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke Caused by Proximal Arterial Occlusion in the Anterior Circulation

Significant time and expenditure have been devoted to therapies for acute ischemic stroke, a worldwide leading cause of morbidity and mortality.[1,2] Currently, there are limited therapies approved for ischemic stroke, including care at a stroke center, initiation of aspirin, and revascularization with recombinant tissue-type plasminogen activator.

Tissue-type plasminogen activator use has a number of drawbacks, including a narrow time window, contraindications because of the risk of bleeding, and limited efficacy in recanalization of proximal major cerebral arteries.[3,4] Approximately one-third of anterior-circulation strokes are attributed to proximal major intracranial vessels, and these patients have a dismal prognosis when recanalization is not achieved.[5,6] Thus, therapies are limited in a significant number of patients with acute stroke.

Endovascular therapies have also been approved in the treatment of acute ischemic stroke, but the optimal patient selection has been unclear.[7] In the Prolyse in Acute Cerebral Thromboembolism II randomized clinical trials, patients with acute stroke had significantly better recanalization rates and outcomes when treated within 6 hours with intra-arterial prourokinase vs intravenous heparin.[8] Recently, 3 randomized clinical trials failed to demonstrate a benefit of endovascular therapy for acute ischemic stroke but helped solidify the use of recombinant tissue-type plasminogen activator in the treatment of these patients.[9-11] These trials were limited in that patients were not required to have vascular imaging to demonstrate a large vessel occlusion as the source of the stroke; thus, a number of patients were assigned to endovascular therapy that would not be beneficial. Subgroup analysis has demonstrated that analysis of only patients with large vessel occlusions revealed that patients treated with endovascular therapies had improved functional outcomes.[12]

Further limitations of these trials included the extensive number of years that it took for completion and the small number of potential patients who were included. Thus, patients receiving endovascular therapy were treated predominantly with first-generation stent retrievers. Newer generations of endovascular clot retrievers have demonstrated significantly higher recanalization rates and improved efficacy.[13,14]

To address these limitations, a number of further randomized trials were initiated. Most recently, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) was published.[15] Patients were randomized to either intra-arterial endovascular treatment (intra-arterial thrombolysis, mechanical treatment, or both) plus usual care or usual care alone (intravenous alteplase when possible). Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation confirmed on vessel imaging and that could be treated intra-arterially within 6 hours of symptom onset. The primary outcome was functional