Another highly relevant factor may be the lack of care in patient selection, excellent surgical technique, meticulous intraoperative and perioperative management, and attentive patient follow-up. Moreover, although this study does not prove that a combined indirect and direct revascularization procedure is superior to other approaches, the low rate of recurrent stroke and hemorrhage is compelling. Moving forward, prospective cohort and randomized trials are needed to further define best evidence-based practice. Future studies should also assess cognitive function and quality of life in greater depth. Adult moyamoya disease is an important cause of stroke and cognitive decline and a critical area for continued research.

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Toxin-Secreting Implantable Therapeutic Stem Cells

Pseudomonas exotoxin (PE) exerts cellular toxicity by inactivating elongation factor-2 and blocking protein synthesis. Conjugation of PE to ligands directed at cancer cell-specific antigens has clinical success in the treatment of some leukemias and lymphomas and limited success in solid tumors. One of the more recent therapeutic targets to gain attention in glioblastoma research has been the interleukin-13 (IL13) receptor α2, a variant overexpressed in glioblastoma cells but not in normal brain. There has been strong preclinical evidence for targeting this receptor to selectively deliver PE to glioblastoma cells. This strategy has yet to yield positive clinical results, as evidenced by the phase III PRECISE trial, which compared convection-enhanced delivery of an IL13-PE conjugate to carmustine implants (Gliadel wafers) in patients with first recurrence of glioblastoma. The lack of improved outcomes with the IL13-PE–conjugated drug compared with Gliadel wafers was partly attributed to poor drug delivery from suboptimal catheter positioning in more than half of the subjects. Another highly relevant factor may be the short half-life of the drug and the short administration period of only 4 days.

Conceptually, Gliadel has the advantage of implantation directly at the margins of resection with carmustine diffusion into the surrounding parenchyma over time as the polymer degrades. What if this concept could be used to deliver a highly effective and stable biological agent? Snuckey and colleagues report engineering human neural stem cells to stably express IL13-PE. They first generated PE-resistant human neural stem cells by inducing specific mutations in the elongation factor-2 gene. They then selected and engineered the PE-resistant clones to stably express...

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IL13-PE. Multiple established glioblastoma cell lines and 5 patient-derived glioblastoma cell lines were cocultured with the toxin-secreting stem cells. The toxicity of the engineered cells was highly correlated with the IL13 receptor α2 expression level in the glioblastoma cell lines. Additionally, the researchers provide strong evidence that inhibition of protein synthesis is the molecular mechanism mediating the IL13-PE stem cell toxicity (Figure).

The IL13-PE–secreting neural stem cells were encapsulated in a synthetic extracellular matrix and tested in a mouse tumor resection model. One week after glioblastoma cell implantation, tumors were surgically debulked, and the resection cavity was filled with the IL13-PE–secreting stem cells encapsulated in a synthetic extracellular matrix from which they could diffuse freely. Tumor progression was tracked with bioluminescence imaging. This treatment was compared with injection of IL13-PE in conditioned media and with resection alone. A significant survival benefit was observed. Mice receiving the toxin-secreting stem cells embedded within the matrix demonstrated a median survival of 79 days vs 48 and 26 days in the IL13-PE injection and resection-only groups, respectively. Additionally, at 21 days after resection, no tumor masses developed in the encapsulated toxin-secreting stem cell group, whereas tumors of various sizes

**Figure.** Stem cell-delivered interleukin-13 (IL13)–pseudomonas exotoxin (PE) kills residual tumor and prolongs survival of mice in a glioblastoma multiforme (GBM) resection cavity. A, schematic showing how the resection experiment was performed. B, U87 GBM cells were transduced with LV-Fluc-eGFP and imaged 48 hours later for eGFP expression. C, a cranial window was established in mice, and 2 × 10⁵ U87-Fluc-eGFP cells per mouse were superficially implanted through the cranial window. Dashed circle demarcates the established tumor in the cranial window. D, fluorescence photomicrograph showing an established U87-Fluc-eGFP GBM (green) in the cranial window. E, light image of the cranial window after tumor resection. F, fluorescence photomicrograph showing hNSC-mCherry cells (red) encapsulated in sECM and placed in the tumor resection cavity. G, light image showing encapsulated hNSC in tumor resection cavity. H, light image and fluorescent photomicrograph of a coronal brain section after GBM resection. U87-Fluc-eGFP (green), DAPI-stained nuclei (blue). Mean Fluc signal intensity was quantified and plotted before and after surgical resection in both stem cell groups to determine the extent of resection. I, plot of Fluc signal intensity before and after tumor resection in treatment groups. J, representative visible light plus superimposed bioluminescence images (color scale units, photons per minute per centimeter) before and at various time points after tumor resection. The 4 treatment groups correspond to resection alone, resection plus hNSC-mCherry in sECM, resection plus hNSC-IL13PE in sECM, and resection plus infusion of IL13-PE conditioned medium (40 ng per mouse) into the resection cavity. Tumor recurrence was determined 21 days after tumor resection in the 4 treatment groups, assessed histologically and by correlative fluorescence imaging of serial coronal brain sections. U87-Fluc-eGFP (green), DAPI-stained nuclei (blue). Dashed white boxes indicate region of interest. K, Kaplan-Meier survival curves of mice bearing resected U87-Fluc-eGFP tumors in the 4 treatment groups. Significance of comparison groups assessed by Mantel-Cox log-rank test and tabulated. Scale bars, 100 μm [B, H (right), J (far right)] and 400 μm [B, H (left)]. Data are expressed as mean ± SEM. From Stuckey et al.
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.

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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.