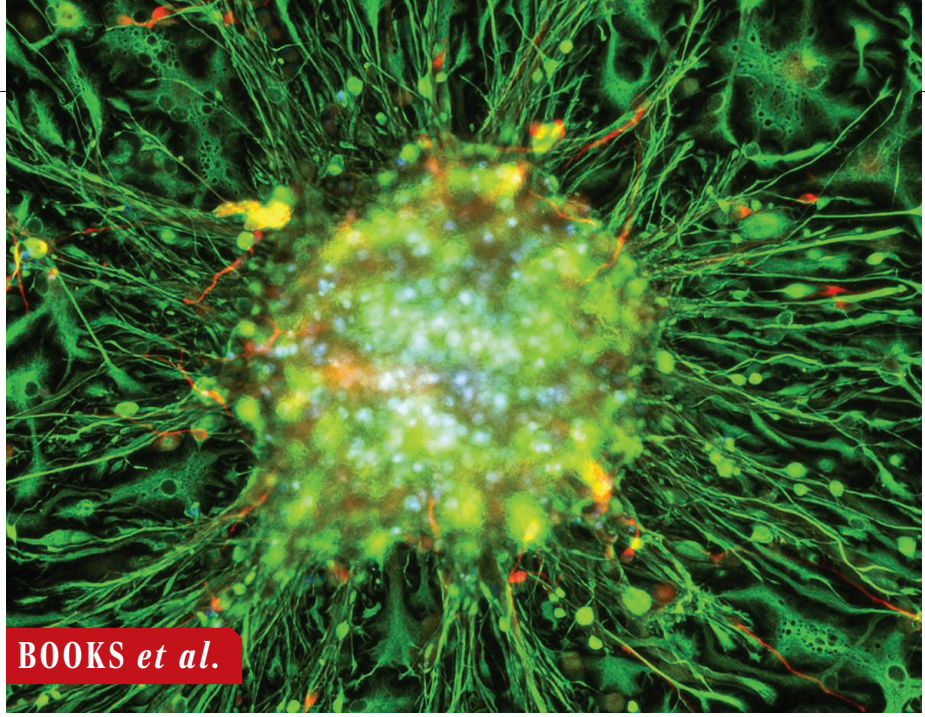


The therapeutic promise of neurosphere stem cells (shown here) has not yet been realized.

IMAGE: RICCARDO CASSIANI-INGONI/SCIENCE SOURCE

BOOKS *et al.*

NEUROSCIENCE

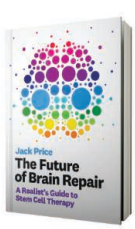
# Repairing damaged brains

## Stem cell therapies slowly gain traction as viable treatments for brain disorders

*By* **Adrian Woolfson**

In the late 19th century, the Spanish neuroanatomist Santiago Ramón y Cajal documented, in exquisite detail, the fantastical, uncharted landscapes of the human brain. The ornate cellular structures he drew were, according to Cajal, fragile and irreplaceable. Brain cells, he stated, "may die" and cannot "be regenerated." Cajal then threw down the gauntlet, asserting that it was the job of the "science of the future to change, if possible, this harsh decree."

Jack Price's engaging book *The Future of Brain Repair* details past, present, and future attempts to address Cajal's formidable challenge. In so doing, it provides a vibrant and compelling guide to the important and rapidly evolving fields of stem cell–based therapies and brain repair, which together, he believes, are poised to deliver unprecedented changes to the management of brain diseases.




**The Future of Brain Repair**
*Jack Price*
MIT Press, 2020. 288 pp.

Unlike the diverse blood cells generated throughout life by specialized stem cells in bone marrow, the two known brain stem cell types—"tucked into the underside of the dentate gyrus" of the hippocampus and surrounding the ventricles of the forebrain in the subependymal zone—differentiate into a much more restricted set of cells. This intrinsic lack of versatility, coupled with the fact that brain cells are postmitotic and consequently unable to divide, underlies the brain's inability to efficiently repair itself.

Two broad strategies for repair are suggested. The first would be to bypass endogenous neural stem cells by introducing nonnative brain cells. The second would be to coax native cells into a different set of behaviors.

Parkinson's disease, a progressive movement disorder caused by the incremental destruction of dopaminergic neurons, has provided a fertile testing ground for the first strategy. The first human neural transplantation experiments conducted during the 1980s, which used dopamine-producing cells from human fetal brain cells or from patients' own adrenal medullas, failed to meet expectations. It appeared as if not any old cells would do. Although a proof of concept for the feasibility of such approaches was provided, a more precisely defined and renewable source of donor cells was lacking, as was an accompanying robust and affordable commercial-scale manufacturing process.

In the 1990s, researchers showed that neural progenitor cells could be cultured as "neurospheres"—balls of cells that maintain self-replication and multipotency over protracted durations. This discovery led, in 2006, to the first human neural stem cell transplant in a group of children with Batten disease, a rare neurodegenerative disorder. The results, again, were disappointing: The overall survival of treated patients showed no discernible improvement over that of untreated patients. Similar studies in patients with ischemic stroke have proved more promising, but researchers suspect improvements in these cases resulted from the graft's secretion of neuroprotective proteins rather than from cell replacement.

Two other innovations, however, have the potential to address Cajal's regenerative vision. The first is our ability to culture embryonic stem cells (ES cells) to produce billions of pluripotent stem cells, which are, in turn, capable of producing every cell type in the human body. Therapies derived from ES cells have been shown to be highly effective in animal models of Parkinson's disease, with evidence suggesting that the transplanted neurons exert their effect by synthesizing dopamine.

The second innovation issues from the work of Shinya Yamanaka, who demonstrated in 2006 that terminally differentiated cells of any type can be reprogrammed into induced pluripotent stem cells (iPSCs) through the administration of just four transcription factors. iPSCs may then be converted into select cell types using different transcription factor cocktails.

Although not without complications—extended culture of iPSCs has been shown, for example, to result in mutations in P53 and other oncogenes—ES cells and iPSCs have the potential to transform the science of brain repair and regenerative medicine by enabling the generation and therapeutic deployment of relevant neuronal subtypes in a scalable and low-cost manner. These cells have the additional advantage of retaining the capacity to build new tissues from scratch.

Perhaps most interesting, however, is the recent convergence of pluripotent stem cells with gene editing. Together, these technologies offer the possibility of augmenting natural neural stem cell behavior. ■

**ACKNOWLEDGMENTS**

The reviewer is a shareholder of Sangamo Therapeutics.

10.1126/science.abb1642

The reviewer is the executive vice president of research and development at Sangamo Therapeutics, Brisbane, CA, USA. Email: adrianwoolfson@yahoo.com

# Repairing damaged brains

Adrian Woolfson

*Science* **368** (6488), 249.
DOI: 10.1126/science.abb1642