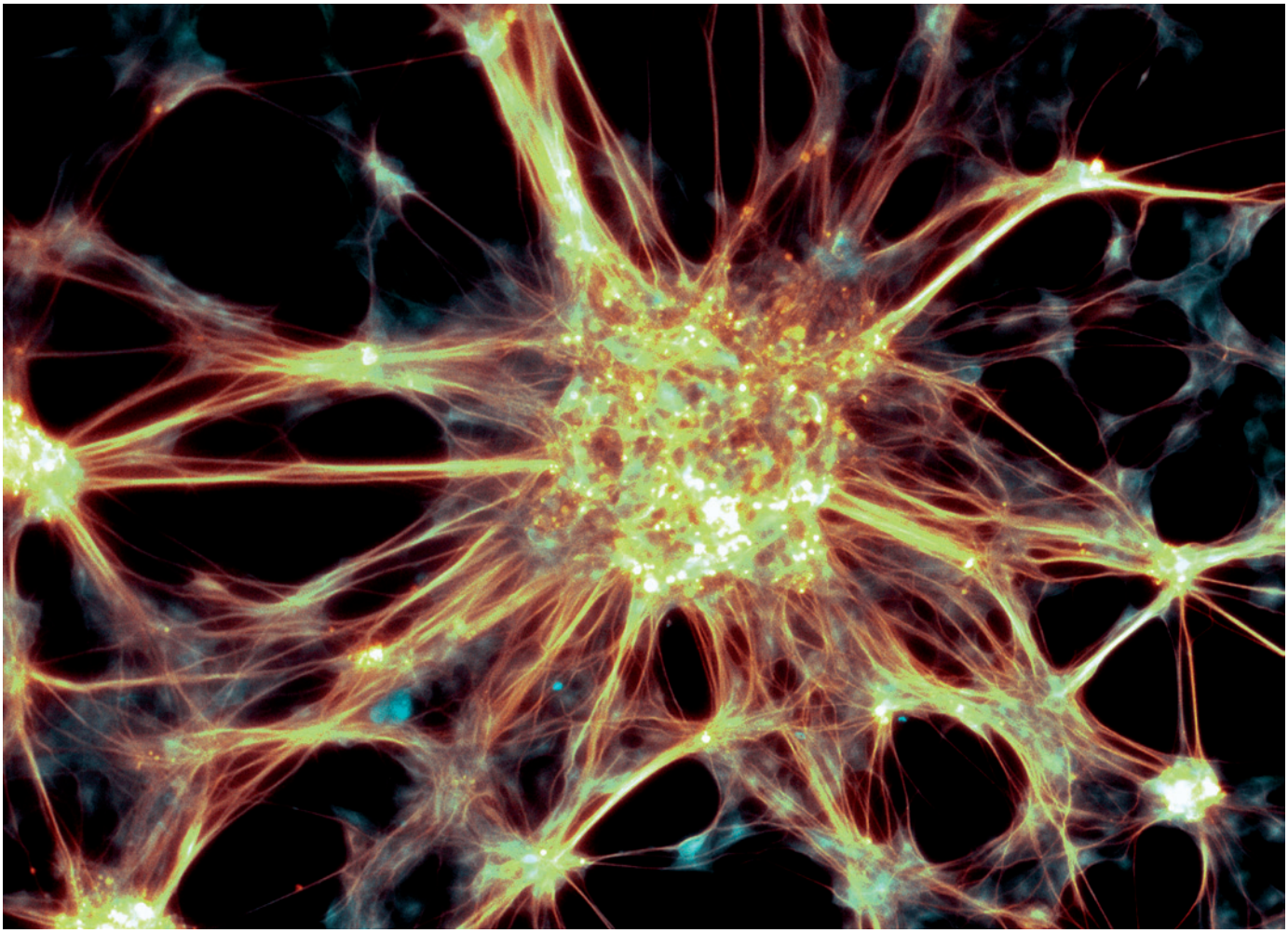

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Neural stem cells can spread out, hopefully revealing ways to repair damaged control circuits in the spine.

STEM CELLS

A time to heal

The first stem-cell therapies for spinal cord injuries are already being tested in clinical studies, but scientific and political uncertainty remain.

CASSANDRA WILLYARD

Just before sunrise on 2 November 2011, Katie Sharify got in her car and headed out on Interstate 5. The 23-year-old had been living with her parents in Pleasanton, California, while taking a break from her studies at the University of Southern California. On this day she needed to meet her academic advisor in Los Angeles to discuss her return.

After about an hour driving, Sharify unbuckled her seatbelt and reached across to the passenger's side to steady some energy drinks rolling around on the floor. She took her eyes off the road just long enough for the car to drift off the road. When the tires hit gravel, Sharify panicked and wrenched the steering wheel, sending the car careening off the opposite side of the highway and into a hill. "I remember everything up to the point where the air bag opened in my face," she says. The crash left her covered in cuts and bruises, with broken ribs and a head injury. It also bruised Sharify's spinal cord, paralysing her from the chest down.

Just weeks after her accident, Sharify agreed to participate in one of the first clinical trials of a therapy using embryonic stem (ES) cells. Stem cells can become neurons and other nervous-system cells, and thus hold promise for repairing a damaged spinal cord. Soon after Sharify signed up, however, the company backing the trial — the drugmaker Geron in Menlo Park, California — pulled the plug for financial reasons. Sharify, who was grandfathered in, still received the injection of 2 million stem cells, but she was the last of five patients ever enrolled. "There was a huge disappointment among patient advocates, patients and scientists," says Christopher Scott, a bioethicist at Stanford University.

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For many, the cessation of the trial was worse than disappointing. An estimated 180,000 individuals around the world experience a traumatic spinal cord injury each year[1]. It can be a life-altering injury, and doctors have little to offer in the way of treatments.

Today, however, the field seems to be

again making headway. In October, Asterias Biotherapeutics, a subsidiary of the biotechnology firm BioTime, acquired the rights to Geron's stem-cell division. The company, which occupies the same stem-cell research building Geron once occupied in Menlo Park and employs many of the same people, hopes to launch more trials to test therapies using ES cells in the coming years. Meanwhile, other companies are studying the safety of stem cells derived from fetal tissue. And scientists at the RIKEN Center for Developmental Biology in Kobe, Japan, are recruiting patients to a trial to test induced pluripotent stem (iPS) cells in treatments for an eye disease called age-related macular degeneration. These iPS cells are adult cells that have been coaxed into an embryonic-like state.

Keith Tansey, a neurologist at Emory University and the Shepherd Center in Atlanta, Georgia, where the first two participants in the Geron trial were enrolled, is glad to see the field moving forward. However, he and other researchers caution against unbridled optimism. A cure for spinal cord injuries might still be decades away, and US federal government support for stem-cell research is not a guarantee. When it comes to spinal cord injuries, "We just have to have reasonable expectations," Tansey says.

NEURONAL NURSEMAIDS

The millions of nerve cells that compose the spinal cord form bundles that convey electrical signals between the brain and the rest of the body. A sudden blow can damage the vertebrae and bruise the spinal cord, killing neurons and the glial cells that support them and severing connections between nerves. Once the dead cells are cleared away by the immune system, a cavity remains. No signals can bridge this gap and the scar tissue that forms around it impedes the growth of new neurons. Inflammation can also spark further damage to the cord. "The highest hope for a stem-cell therapy would be that [it] could actually replace neurons that were lost," Tansey says.

But there may be other ways to repair the spine. Although some neurons die upon injury, others may merely be damaged. The myelin sheath, a protective layer that encases the long segments of nerve cells and helps to direct the electrical impulses, can be lost. "It's like pulling insulation off an electric wire," says Thomas Okarma, Geron's former chief executive and now chief executive at Asterias Biotherapeutics. Without myelin, the impulses travel slowly or not at all, and the nerves can short-circuit.

Embryonic stem cells — first isolated in 1998 — have the potential to mature into any type of cell in the body. Before the cells are injected into the spinal cord, scientists have to coax them to develop in a certain way. Geron prompted its ES cells to form precursors destined to become oligodendrocytes, a type of glial cell that forms myelin. The hope was that these cells would re-insulate the axons that had been spared, improving their function. But Geron's research suggested that these cells can do more than just form myelin. They also promote the formation of new blood vessels and secrete growth factors called neurotrophins that help nerve cells recuperate[2]. "Injecting these cells is like injecting hundreds of drugs at the same time," Okarma says. "It's a new level of healing that goes far beyond what a scalpel or a pill could ever do."

But ES-cell therapy is not without risk. These cells can form a type of benign tumour known as a teratoma, one of the reasons researchers force them to differentiate before injecting them into the spine. They also secrete factors that may affect the activity of any remaining neurons. To gain approval for its ES-cell trial, Geron submitted an application to the US Food and Drug Administration (FDA) that was 21,000 pages long, one of the longest ever submitted to the agency.

So far Geron's treatment has not caused any adverse reactions related to the injection or the cell therapy. Okarma plans to request FDA approval to conduct a new trial using a higher dose of the cells in individuals with neck injuries. These patients have typically been excluded from trials because a loss of function could be life threatening — neck injuries can paralyse muscles that support breathing. But Okarma says that any gain in function would be easier to see and measure. "We're trying to up the likelihood of success," he says.

MULTIPOTENT SOLUTIONS

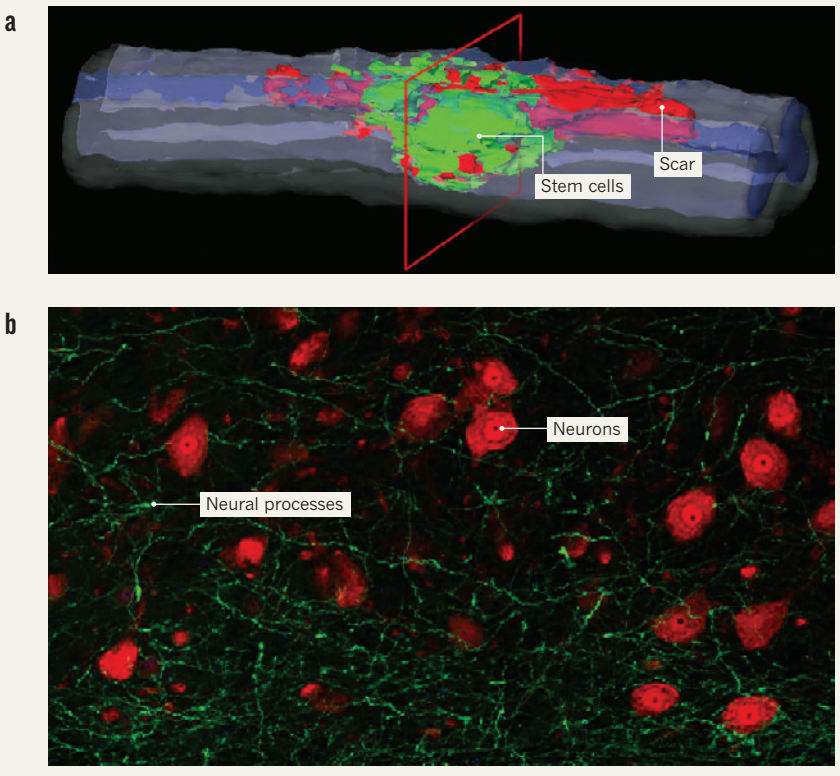
Other companies are banking on neural stem cells derived from donated fetal tissue. These cells can self-renew, but their potential is more limited than ES cells; they can only form neurons, astrocytes and oligodendrocytes. Some researchers argue that this limitation makes the fetal cells safer. "They're necessarily more restricted," says Aileen Anderson, a neurobiologist at the University of California, Irvine, who studies the cells. What's more, they have already been tested in clinical trials for other diseases.

In 2011, StemCells, a company based in Newark, California, began a clinical trial in Zurich, Switzerland, to test the safety and efficacy of neural stem cells in individuals with a spinal injury at chest level. A few patients with the most severe injuries have already received the treatment, a shot of 20 million cells. Mouse data suggest that the cells differentiate to form neurons and glia, and that the therapy can restore some function[3]. In February 2013, StemCells announced that two out of three subjects showed improved function a year after treatment. For example, one went from having no sensation or movement below the site of the

MARTIN MARSALA

REGENERATED REPAIR

This three-dimensional magnetic resonance imaging (MRI) (**a**) shows neural stem cells (green) packed into a rat's spinal cord (purple) injury between scars (red). These cells (**b**) can form new neural processes (green) with exiting neurons (red) to improve function.



BY LEGAL ORDER

Stem cells subject to political consent

Ethical and legal concerns surrounding the use of embryonic stem cells persist. In the late 1990s, research using embryonic stem cells (ES) cells sparked a tense political debate. As a result, in 2001, US President George W. Bush banned federal funding for research on newly created ES cells. In 2009, President Barack Obama reversed Bush's ban, but political uncertainty remains, hampering research efforts. As Debra Mathews, a bioethicist at the Johns Hopkins Berman Institute for Bioethics in Baltimore, Maryland, says, "There was a point [in 2010] where all embryonic stem cell research at the National Institutes of Health stopped. Everyone had to put down their pipettes, put their cells in the freezers, and not touch anything." Even now, Congress has not passed a law saying that ES cell research is legal, and the rules could change. "The next president could come in and say, 'It's illegal now'," says Mathews.

The concerns extend beyond the United States. Guidelines published by Japan's Ministry of Health, Labor and Welfare in 2006 prohibited the use of embryonic stem cells in clinical research. That restriction was lifted in 2010, but by then many Japanese researchers had already shifted to iPS cells.

Recent activities suggest that the pharmaceutical industry expects to be able to keep using iPS cells in clinical research. As an example, the StemBANCC — a public–private partnership that includes Eli Lilly in Basingstoke, UK, F. Hoffmann-La Roche in Basel, Switzerland, and the University of Oxford, UK — is creating and characterizing iPS cells from 500 people to use in drug research.

So far, iPS cells have not attracted the negative attention that continues to slow down research on ES cells and fetal stem cells. — ***C. W.***

injury to having some movement. In October, the company received approval from the FDA to enrol patients in the United States.

Neuralstem, based in Rockville, Maryland, received FDA approval to launch a phase I study in January 2013. As many as eight participants with spinal injury at chest level will receive six injections of either 100,000 or 200,000 spinal cord stem cells per injection. Neuralstem's cells have already been tested in 18 patients with amyotrophic lateral sclerosis, a motor neuron disease better known as Lou Gehrig's disease, with no reported serious side effects. And a study published in May 2013 reports that these cells repopulate the cavity that forms in the wake of spinal injury in rats and restore some of the lost function, including sensory responses and movement[4].

When the animals move, "the placement of the paw is much better controlled," says Martin Marsala, a stem-cell researcher at the University of California, San Diego, who led the study. But the rats were not cured. "You always have some degree of deficit," he says.

When to administer the cells remains uncertain. In the Geron trial, participants received the cells one or two weeks after injury. That comes with certain drawbacks. Patients who have been seriously injured are often too ill to make decisions about joining a clinical trial. And conditions at the injury site are not ideal. "The environment is unfriendly to regeneration," says Mani Vessal, a neuroscientist and scientific officer at the California Institute for Regenerative Medicine in San Francisco. "You have all these inflammatory factors that are rushing in."

StemCells and Neuralstem are waiting longer to treat. "There's a little bit of a dogma that one would have to transplant within the first couple of weeks in order to see a functional effect," Anderson says. But Anderson's research on rodents suggests that it might be possible to have an impact on chronic injuries as well[3]. StemCells is enrolling patients who are 3 months to 12 months post-injury. Neuralstem's trial will enrol individuals who are between one and two years past their injury. At this stage the patient will be easier to recruit, Tansey says. The downside is that they may not respond as well to the therapy. After the injury occurs, axons "start degenerating and sort of shrivel away," Vessal says.

One drawback of embryonic and fetal-derived cell lines is their immunogenicity. Because these cells come from unrelated donors, they are not genetically matched to the patients receiving them. So patients are required to take immunosuppression drugs for a few months up to a year, "just to get past the initial transplant period and let everything heal," Anderson says.

INDUCING OPTIONS

Induced pluripotent stem cells could bypass the problem of immune rejection, at least in theory. Cells could be removed from an injured patient, reprogrammed to become pluripotent and then turned into neural stem cells. In practice, however, the process becomes stickier. Developing iPS cells takes months. Hideyuki Okano, a stem-cell researcher at Keio University School of Medicine in Tokyo, has been studying the use of iPS cells to mend spinal injuries, and his unpublished research suggests that the best time to transplant stem cells is between two to four weeks post-injury. But according to Okano, "it's impossible to prepare the iPS neural stem cell in two, three, four weeks."

Although iPS cells might solve some problems, they might cause others. Reprogrammed cells can also form teratomas, and some reports suggest that they may be even more tumorigenic than ES cells. However, many researchers are striving to make them safer. For example, Okano's group studied the impact of immature neural cells — derived from a human iPS clone known not to form tumours — on a primate model of spinal cord injury; the results showed maturing neural cells of several types and no evidence of tumours[5]. In July, the Japanese Ministry of Health, Labour and Welfare approved the first clinical trial using iPS cells. The study will assess the cells' safety in individuals with age-related macular degeneration, and Okano hopes a clinical trial for patients with spinal cord injury will not be far behind. Shinya Yamanaka of Kyoto University in Japan is now developing clinical-grade iPS cells that Okano and other researchers could use for such a trial.

What makes iPS cells attractive to many scientists is that their use might avoid the political problem of using embryos (see 'By legal order').

Scientists are also investigating the potential of adult stem cells harvested from bone marrow or other tissues. These cells have been shown to secrete neurotrophic factors, but they do not seem to be able to replace lost neurons. A recent study found that three of ten patients with cervical spinal injury who received their own mesenchymal stem cells — progenitor cells that differentiate to form bone and cartilage — had more power in their upper limbs and less trouble performing daily activities than they did before receiving the stem cells[6].

Which cells will work best remains unclear. But Sharify hopes that researchers will eventually be able to answer that question. She says she envisages turning on the television one day, perhaps when she is "old and grey", to find that researchers have discovered a cure for spinal cord injury. "I believe that science and technology can find a cure," she says. "That's pretty much what keeps me going." ■

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