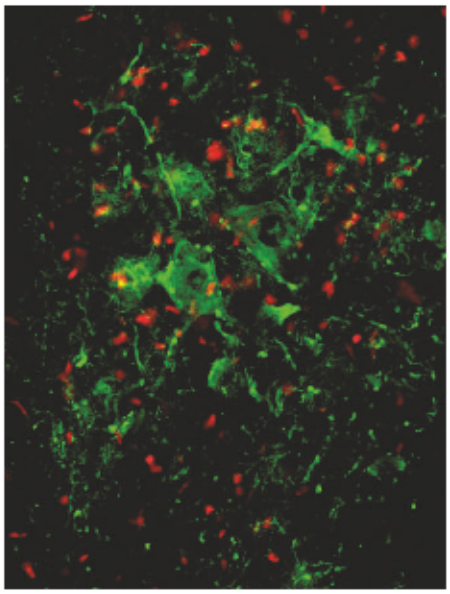


KLEIN ET AL. HUM. GENE THER. 2005 (LEFT); ZEPHYR/SPL (CENTRE); A. & H.-F. MICHLER/SPL

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Ready to use? Stem cells may be able to protect depleted nerve cells (green, left), kill brain tumours (centre, green) or help heal damaged heart muscle.

THE FIRST WAVE

Treatments that use stem cells to replace damaged or diseased tissues are thought to lie many years away. But the cells might find other clinical applications in the near future, says Catherine Zandonella.

When patients with the paralysing illness amyotrophic lateral sclerosis (ALS) call Jennifer Brand to ask when stem-cell therapies will be available, she has a stock answer. Brand, who is director of patient services for the California-based ALS Association, says that stem-cell research is still in its infancy. It's just too soon to tell when it might move into clinical trials, she tells her callers.

Indeed, most experts predict that many years of laboratory work will be needed before stem cells can be used reliably to replace damaged cells and tissues. But some enthusiasts argue that this timeline overlooks more immediate clinical opportunities. These researchers want to exploit stem cells' abilities to home in on sites of injury and to deliver biochemicals that protect other cells[1]. And, controversially, they hope to move quickly into the clinic. "Disease targets thought to be far in the future are closer to our grasp," claims Evan Snyder, who works at the Burnham Institute in La Jolla, California.

Stem cells have been widely touted as eventual cures for neurodegenerative diseases such as ALS and Parkinson's. The conventional wisdom is that they would be grown to produce the particular nerve cells that are lost in each disease, which would then be grafted into the nervous system to repair it. But researchers currently understand little about the signals that make stem cells differentiate into particular cell types, nor are they sure how to get grafted cells to integrate effectively into tissues and organs.

Snyder agrees that cell replacement is an exciting future prospect. But apart from replacing lost cells, he notes that stem cells have other, more subtle roles that could be exploited therapeutically. Snyder has evidence that, in the nervous system, stem cells can act as 'chaperones' that nurse sick and injured neurons back to health.

Neural stem cells secrete biochemicals that make the neurons function better, promote survival, decrease inflammation and encourage the growth of blood vessels. One of these factors is glial cell line-derived neurotrophic factor, or GDNF — which seems to protect both the cells that secrete the neurotransmitter dopamine[2], lost in Parkinson's disease, and the motor neurons that are destroyed in ALS (ref. 3).

Snyder has shown that neural stem cells taken from mouse fetuses secrete GDNF and promote recovery in mouse models of Parkinson's disease[4]. More recently, his team has found that human neural stem cells, from lines originally derived from the brains of aborted fetuses, can migrate from one side of a mouse's brain to the other in response to distress signals issued by injured tissue[5]. The potential to exploit these twin effects therapeutically is clear, Snyder argues. "You are not trying to replace the lost cells," he says. "Instead, you are trying to protect what is there."

Other researchers are working along similar lines — but are tweaking their cells genetically to make them into better nursemaids. At the University of Wisconsin, Madison, Clive Svendsen's team has engineered fetal neural stem cells so that they pump out greater quantities of GDNF. When the researchers injected these cells into the spinal cords of rats suffering from an ALS-like disease, they survived well and continued to secrete GDNF (ref. 6).

Taking the chance

Svendsen plans to approach the US Food and Drug Administration within the next few months to discuss testing the cells in ALS patients. He believes that the ideal time to give the treatment will be shortly after diagnosis, when a patient begins to lose limb function but before paralysis sets in. "You have a window of about a year-and-a-half to get in and do something," Svendsen argues. Although he hasn't yet published firm evidence from animal experiments that shows his engineered cells are protecting motor neurons, Svendsen has few doubts about pressing ahead into the clinic with a novel experimental therapy — given the severity of the disease and the lack of any effective treatment.

Similar risk–benefit arguments apply for patients with inoperable brain tumours. Here,

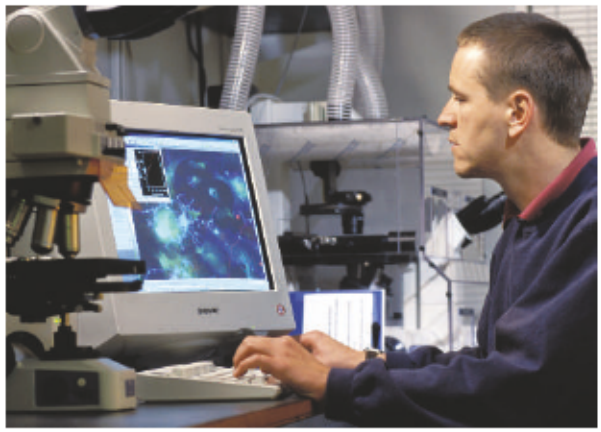
too, some researchers are thinking about using genetically engineered stem cells. "The advantage is that these cells can track down and migrate through the tumour," says Frederick Lang, a brain surgeon at the University of Texas M. D. Anderson Cancer Center in Houston. His team has taken cells from bone marrow known as mesenchymal stem cells and inserted a gene for interferon-β — a protein that can kill tumour cells. When the researchers injected the cells into the carotid artery of mice suffering from brain cancer, the cells migrated to the tumour. Encouragingly, these animals lived significantly longer than those who received injections of normal cells[7].

Heart of the matter

Lang's approach may offer hope for patients who have no other treatment options, but many stem-cell researchers are alarmed about trials for patients with heart disease that are already under way. Based on contested results from animal experiments[8], clinicians in the United States and Europe are now injecting stem cells into patients' damaged hearts in the hope that they will help repair the damaged tissue.

The problem is that nobody knows for sure whether these cells are differentiating into heart muscle cells, fusing with cells that are already there, or exerting a protective effect by secreting growth factors. It could be a combination of all three, says Emerson Perin, who is heading a study of bone-marrow stem cells injected directly into patients' diseased hearts at the Texas Heart Institute of St Luke's Episcopal Hospital in Houston.

Given the limited understanding of how stem cells behave when injected into the body, some researchers argue that it is too soon to be entering the clinic. For instance, Roger Barker, a neurologist at the Centre for Brain Repair at the University of Cambridge, UK, worries that neural stem cells might give rise to neurons that could integrate incorrectly into the nervous system, causing adverse effects such as a heightened sensitivity to pain. If so, he fears that the resulting publicity could damage the entire field. "A negative trial doesn't do any good," says Barker.



T. MILLER/UNIV. WISCONSIN, MADISON

"You don't want bone or teeth or hair growing inside the spinal cord. It just wouldn't look good for the stem-cell field." — Clive Svendsen

Snyder agrees that caution is necessary, but he argues that early trials using stem cells as nursemaids to protect sick and dying tissues will do the field a service, by giving the regulators and institutional review boards that must approve clinical trials some experience of handling stem-cell protocols. This will blaze a trail for later trials with the loftier goal of replacing damaged tissues, Snyder claims.

In any case, Snyder believes that the risks are relatively constrained for stem cells derived from fetal or adult tissues, provided they are used only in the places where they would normally be found. If cells aren't being put in alien tissues, he argues, they are likely to behave normally.

Growing pains

But embryonic stem cells, which can develop into any of the body's tissues, are another matter. In particular, they can form tumours called teratomas that contain all sorts of tissue types. "You don't want bone or teeth or hair growing inside the spinal cord," says Svendsen. "It just wouldn't look good for the stem-cell field." Nevertheless, some researchers are exploring the idea of using embryonic stem cells to exert nursemaid effects. They note that the cells could be engineered to include a 'suicide' gene that could be activated to kill them, if any problems arise.

E. SNYDER

"You are not trying to replace the lost cells. Instead, you are trying to protect what is there." — Evan Snyder

Robert Benezra of the Memorial Sloan-Kettering Cancer Center in New York and his colleagues are studying a genetic condition that normally causes female mice to lose their young before birth because of heart defects. When Benezra's team injected pregnant females with mouse embryonic stem cells, they gave birth to live young[9]. The stem cells didn't cross the placenta, but they secreted a heart-repairing substance called insulin-like growth factor 1, which seemed to protect the fetuses.

Benezra has no plans to move ahead into clinical trials. But cells grown directly from embryonic stem cells could start being injected into patients with paralysing spinal injuries as early as next year. Hans Keirstead, a stem-cell researcher at the University of California, Irvine, has derived cells that seem to restore some mobility to rats with spinal injuries[10]. These cells make the myelin protein coat that serves as electrical insulation for neurons — although Keirstead suspects that other protective mechanisms are also involved. "I believe that they are playing some mysterious 'nurse' role," he says. "They are doing a lot more than just producing myelin."

Keirstead's plan to move rapidly into the clinic has already caused some alarm[11]. But with other trials of stem cells as nursemaids for sick and dying cells also in the works, patient advocates such as Brand may soon have to revise their message. With luck, these trials will bring fresh hopes for the sufferers of ALS and other debilitating conditions — and not scare stories about adverse reactions. ■

Catherine Zandonella is a freelance writer in Princeton, New Jersey.

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