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Stem cells: Don't believe the hype

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Researchers are still a long way from using stem cells to halt the decline caused by multiple sclerosis and to restore patients' health. But they are following some promising trails.

The remarkable potential of stem cells to develop into healthy adult tissue has led many people to view them as a biomedical 'Wizard of Oz', ready to grant them a healthy new heart or brain on demand. This perception has been fuelled by feverish media coverage extolling their vast therapeutic potential. But as with the great and powerful Oz, misconceptions abound. The capabilities of current therapies are sometimes overstated, and some patients with serious degenerative disorders such as multiple sclerosis (MS) are disappointed once they peer behind the curtain.

"Most of the patients that come to us ask me to give them stem cells because they want to walk again," says Antonio Uccelli, a neuroimmunologist who performs clinical stem-cell research at Italy's University of Genoa. "Patients are mesmerized by the hope that stem-cell treatment is a treatment for regenerating tissue, and it's difficult to convince them otherwise."

Anthony Ucce/li, U of Genoa

"Most of the patients that come to us ask me to give them stem cells because they want to walk again," says immunologist Antonio Uccelli, shown here working under the tissue culture hood at his University of Genoa laboratory. Early studies suggest that adult stem cells could potentially stop MS the progression.

Embryonic stem (ES) cells, which can transform into any cell in the body, might one day offer this potential. But ES cells are only slowly making their way into clinical trials, in part because research has been bogged down by strict regulations arising from the debate over the ethics of using material derived from human embryos. A more promising route for MS treatment involves various kinds of adult stem cells, which can develop into a much more limited range of cell types but nevertheless seem to exert far-reaching effects on both the immune system and the natural repair mechanisms in the central nervous system. Early studies suggest that adult stem cells might offer a way to halt the progression of therapy-resistant MS, even if the goal of reversing the existing damage remains over the horizon.

Resetting the system

In MS, the immune system attacks the central nervous system, stripping neurons of the protective myelin sheaths that insulate their axons and allow effective signal transmission. Stem cells offer the promise of essentially rebooting the immune system, thereby eradicating this autoimmune response. There is a precedent for this therapeutic approach. More than 25 years ago, Richard Burt, an immunotherapy researcher at Northwestern University in Chicago, Illinois, was inspired by outcomes he observed with leukaemia patients undergoing

myeloablative treatment - the use of radiation and chemicals to wipe out the body's capacity for blood-cell production - followed by a transplant of healthy bone marrow. These treatments were spectacularly effective at resetting the immune system. "Patients would come back after transplants and have to be reimmunized for childhood vaccines - measles, mumps, rubella and things like that," says Burt. "It occurred to me that this is exactly what you want to happen with an autoimmune disease."

Since then, Burt and others have demonstrated the therapeutic potential of haematopoietic stem-cell transplantation (HSCT) for MS and other conditions. In HSCT, blood-cell precursors (HSCs) are purified from a patient's own bone marrow. The patient then undergoes a 'conditioning' chemotherapy regimen that heavily suppresses or even wipes out their defective immune system. The stem cells are then transplanted intravenously back into the patient, restoring immunity. The results have been remarkable: in many studies at least 60-70% of transplant recipients achieved relief from MS progression, and it seemed to last far beyond the initial treatment[1]. "In 10 years, we have never seen a renewal of inflammatory disease activity in any of our successfully treated patients," says Mark Freedman, a neurologist at the University of Ottawa in Canada who has extensive experience of HSCT clinical trials.

Burt says his team has observed not only a halt in deterioration, but also, in several transplant recipients, quantifiable improvements in motor and cognitive function. Some studies suggest that implanted stem cells might facilitate repair by localizing to damaged nervous-system tissues, but other scientists believe that any recovery is simply the result of relief from the immune onslaught. "The signs are quite encouraging that once you stop the immune system in its tracks, the brain's own repair capacity is able to manifest itself," says neuroscientist Charles ffrench-Constant of the University of Edinburgh in the United Kingdom.

Practitioners see HSCT as a powerful way to help patients with aggressive forms of MS that have been resistant to standard drug regimens. But it is not a therapy to be taken lightly. Severe side effects include loss of hair and fingernails, as well as premature menopause for female patients. "The regimen that we use is completely myeloablative - it's a standard bone-marrow transplant, and it's no cakewalk," says Freedman, "but the trade-off is years and years of not needing therapy." Burt's group has instead opted for a more moderate conditioning regimen that does not completely eradicate the patient's bone marrow. Results suggest that this gentler approach can reduce the toxic effects of treatment without significantly undermining its efficacy[2].

Repairing the damage

Other types of stem cell might offer a more palatable option for patients with less aggressive or less advanced disease. Gianvito Martino of the San Raffaele Scientific Institute in Milan, Italy, began working in mouse models of MS using neural precursor cells (NPCs), the stem cells that give rise to brain tissue. Martino hoped that the NPCs might penetrate brain lesions and turn into cells called oligodendrocytes, which can apply new layers of myelin to damaged cells.

Success was limited. "We didn't find that those cells differentiate into myelin-forming cells, but they still had apparent curative potential," Martino explains. "It turned out that they were capable of remaining undifferentiated, and still produced a whole bunch of substances that are neuroprotective." His team termed this the 'bystander effect', whereby NPCs secrete signals that calm the immune system and promote natural processes of neuronal regeneration and remyelination. ffrench-Constant, who has studied myelination extensively, suggests that such strategies for reawakening the brain's resident stem cells might be the best way to achieve effective repair in many MS patients. His team has identified several molecules that might stimulate the differentiation of existing precursor cells into active oligodendrocytes.

One clear advantage of NPCs is that they are operating in their natural surroundings. "They're not only in the brain to replace the cells that you lose, they're also there to keep that microenvironment in a healthy state," says Martino. Although no clinical trials are currently underway for MS, researchers are closely watching a phase I trial being conducted by a company called StemCells in Palo Alto, California, to test the safety of transplanting fetal tissue-derived NPCs into young children with a congenital myelin deficiency disorder called Pelizaeus-Merzbacher disease. "The problem with MS cell therapy is that you're transplanting cells into an adult nervous system that's been damaged," says ifrench-Constant. "If these cells don't myelinate effectively in the developing brains of these children, it's going to be exceptionally hard to get them to myelinate in the MS-affected adult CNS, where the hurdles are so much higher."

Even if the NPCs are successful in remyelinating the damaged neurons, they will still face another problem. They are derived from donated fetal tissue and so carry a risk of host rejection, which means that recipients will need to be given immunosuppressant drugs. However, there is another, remarkably abundant reservoir of stem cells that might offer many of the same therapeutic benefits as fetal NPCs but with the safety and simplicity of transplanting someone's own cells.

Joining forces

Mesenchymal stem cells (MSC5), which normally develop into fat, bone and connective tissue, are typically found in the bone marrow. However, they might also exert long-range, beneficial bystander effects, and have been examined as a possible therapy for a variety of autoimmune and other conditions. Once injected into MS patients, MSCs appear to migrate far and wide within the body, focusing on sites of tissue damage and even penetrating the central nervous system. However, their residence there seems to be brief, with therapeutic efficacy arising largely from the same bystander effect observed with NPCs. "Engraftment in the central nervous system is very limited and probably extremely transient," says Uccelli. "It would be very difficult to believe that this 1-2% of cells [that reach the central nervous system] can justify the significant and clear evidence of improvement that we observe."

Although formal demonstrations of efficacy in humans are lacking, studies in mouse models have given cause for hope. "If you administer [MSCs] early on, the recovery of the animals tends to be fairly enhanced," says Freedman. A team led by neuroscientist Robert Miller of Case Western Reserve University in Cleveland, Ohio, has even demonstrated that administering human MSCs in the commonly used

experimental autoimmune encephalomyelitis (EAE) mouse model can actively promote the growth and activation of myelin-repairing oligodendrocyte precursors within the brain[3]. "MSCs are probably not as good at intense immunosuppression as the [HSC] treatment, but at least in animal studies, it's been demonstrated that the ability of MSCs to foster repair is certainly much stronger," says Uccelli. Although such stem-cell therapy is unlikely to displace front-line immunotherapeutics, it might offer a promising middle-ground therapy before committing to the rigours of HSCT. "There's no bone-marrow suppression or chemo poisons, you're simply putting in a cell product," says Freedman, "and since they don't get rejected, you don't need anti-rejection medicine."

There are roughly half a dozen phase I clinical trials underway to assess the safety of MSCs and perhaps glean some insight as to whether they might ameliorate symptoms. A recent study offers some early signs of hope, describing a small trial by scientists at the University of Cambridge in the United Kingdom, which showed no adverse effects in 10 patients treated with marrow-derived autologous MSCs[4]. The study also reports some signs of improvement in visual symptoms, although it is impossible to draw meaningful conclusions without a larger-scale, randomized, controlled trial. Indeed, issues of scale represent a broader problem for the handful of clinical trials on stem-cell MS therapy that have been completed to date. "What happens with stem-cell studies is that there are three patients here, three patients there, and at the end of the day it's too few to draw any conclusions," says Martino.

Even with HSCT, which has been successfully performed in several hundred patients worldwide, clinical trials have been limited to individual research centres assessing a few dozen patients. This has led to a confusing patchwork of studies that are virtually impossible to compare with one another. "It's a dog's breakfast," says Freedman. "Different conditioning regimens, different choice of patients, different types of follow-up - it really doesn't help us to have all these different approaches."

Many leading MS researchers working with MSCs have joined forces to launch the International Mesenchymal Stem Cell Transplantation Study Group, devising a consensus roadmap on how future trials should be conducted[5]. The resulting guidelines will be implemented in a large-scale, multi-institutional, randomized controlled trial with patients in North America and Europe, which consortium members hope will begin in 2012. "Each individual group might be doing 15-30 patients, but if we have 20 groups doing that and we're all using the same protocol and all analysing our data centrally, we'll have something that's not exactly equivalent but close to a multi-centre study," says Freedman.

He points out that bone marrow-transplantation researchers have also begun to consolidate their efforts, and a similar 'best practices' document is on its way. Researchers in the United States, Canada and Europe are formulating plans for a large-scale, multi-centre trial. Burt has already embarked on a phase III randomized controlled trial of HSCT in partnership with researchers in Sweden and Brazil, and has recruited one-third of his 110 study subjects. "The neurologist doing the evaluation of disability has no idea of the treatment the patient has received, and our magnetic resonance imaging (MRI) data are being analysed at an MRI reading centre in Houston that is also blinded," says Burt. "I'm very optimistic that a randomized trial will remove a lot of scepticism."

Hope not hype

Despite the best efforts of researchers, stem cells are often portrayed as a miracle cure, and many MS patients who learn about stem-cell therapy from breathless newspaper articles or television features face let-downs. Even the clinicians had to learn some hard lessons in early studies. "In our HSCT clinical trial, we started with patients who had fairly advanced disease, wheelchair-bound or even bed-ridden," says Richard Nash, a specialist in immunotherapy at the Colorado Blood Cancer Institute in Denver, Colorado "and we found that for many of these patients, even after transplantation they are going to continue to get worse."

The outcomes of subsequent trials have been markedly improved by the recognition that patients with advanced MS might have crossed a threshold of nervous-system degeneration beyond which anything short of neuronal regrowth or replacement is likely to fail. This can be a difficult message for individuals with severe MS to hear. "The only time that patients get mad at me is when we don't offer the transplant," says Burt. "It's hard to get patients to understand that this isn't going to help them."

In some cases, patients have pursued treatment at so-called 'stem-cell clinics' around the world, where they pay tens of thousands of dollars to be injected with cells of dubious provenance in an environment with minimal regulatory oversight. These clinics claim to treat any number of conditions with stem cells but offer little in the way of peer-reviewed efficacy data. At least one published report described a patient who developed tumours after a clinic transplanted fetal stem cells[6], and in May 2011 Germany shut down the XCeII Centre, where a young patient died from complications following autologous MSC transplantation. More recently, a case report from a team of neurologists in Arizona described how a teenage MS patient suffered a severe and debilitating inflammatory response during a course of stem-cell treatments at a clinic in Costa Rica[7]. The physicians were unable to determine the extent to which this strong immune response was attributable to the transplant, but they cite this example as justification for restricting experimental stem-cell treatments to clinical trial settings with proper oversight and safeguards. "We are really fighting those clinics," says Martino, who has collaborated with colleagues in a survey of clinical stem-cell research in MS[8]. "We prepared this leaflet that anybody can easily download from various MS society websites, where we explained exactly what stage we're at with the different types of stem cells."

Most stem-cell researchers see cause for optimism but point out that good science and good medicine require considerable amounts of both time and effort. "The stem cell you use and how you use it will depend on the disease you're treating as well as the stage, and it's just beginning," says Burt. "When I first started I thought I'd have all the answers in five years. But it doesn't work that way - it takes time."

References

1. Mancardi, G. & Saccardi, R. *Lancet Neurol. 7,* 626-636 (2008).

2. Burt, R. K. *et at. Lancet Neurot. 8,* 244-253 (2009).
3. Bai, L. *etal. Glia 57,* 1192-636 (2009).
4. Freedman, M. S. *etal. Mutt. Scter. 16,* 503-636 (2010).
5. Connick, P. *etal. LancetNeurot. 11,* 150-636 (2012).
6. Amariglio, N. *et at. PLoS Med. 6,* el 000029 (2009).
7. Alderazi, Y. J., Coons, S. W. & Chapman, K. J. *Child Neurot.* doi: 10.1177/0883073811422831 (7 December 2011).
8. Martino, G. *etal. Nature Rev. Neuro!. 6, 247-636 (2010).*

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