



Tomorrow's treatments today—that's the promise of a growing number of companies offering cell therapies untested in rigorous clinical trials. Some experts say the claims must be challenged

Selling the Stem Cell Dream

IF YOU SUFFER FROM AN INCURABLE neurological disease such as multiple sclerosis (MS), Parkinson's, amyotrophic lateral sclerosis (ALS), or Huntington's disease, a clinic in the Netherlands says it may be able to help you. In a procedure that takes just a few hours and costs \$23,000, the Preventive Medicine Center (PMC) in Rotterdam will inject stem cells obtained from umbilical cord blood into your bloodstream and under your skin.

The clinic has treated more than 200 patients so far; the results are "often spectacular," according to its Web site. Although PMC sees mostly neurological patients, it offers stem cell treatments for a wide variety of other diseases as well, including arthritis, lupus, Crohn's disease, heart disease, hernia, insomnia, sexual dysfunction, depression, and loss of memory, hair, or appetite.

PMC is one of a growing and diverse group of companies and institutes around the globe offering patients stem cell therapies or related treatments that are viewed by mainstream researchers as unproven. Some clinics use umbilical cord blood, whereas others inject fetal cells or cells derived from patients' own bone marrow. Some carry out operations themselves, whereas others act as middlemen, providing cells and linking patients with doctors willing to

inject them. Almost all have Web sites to advertise the promise of the new therapies, often with hopeful case reports. The sites help recruit patients with what regular medicine cannot provide: a hope of recovery.

Although these clinics have already treated thousands of patients, a dozen stem cell scientists and physicians familiar with one or more of the treatments told *Science* they oppose them, often vehemently. Not only is there little or no evidence for the procedures' efficacy, the experts say; in many cases, there's also no published animal work to suggest they might work in humans. Most clinics appear to have no interest in rigorously collecting data about benefits and risks, critics say, and some may harm patients' health. Some companies are "preying on desperate patients," says stem cell scientist Irving Weissman of Stanford University in Palo Alto, California. "It's a horrible disservice."

Most of the clinics have not revealed full details of their treatment protocols. A handful of researchers have attempted to get a foot in the door, however, hoping to glean information about risks and benefits of cell therapy by systematically studying patients before and after they embark on treatment. Patient organizations and research foundations are

trying to find out more, too, although they say it can be impossible to get even basic facts about the treatments.

The result, Weissman fears, may be that stem cell research—already under criticism for its use of embryos and suffering from the Korean cloning scandal—could see its reputation tarnished further. "I'm beginning to get pretty angry about this," says stem cell researcher Christine Mummery of the Hubrecht Laboratory in Utrecht, the Netherlands. "I think as a scientific community we have to speak up," adds Stephen Minger, director of King's College's Stem Cell Laboratory in London.

Indeed, some scientists have asked regulatory authorities to intervene. After Dutch neurologists complained, for instance, the Dutch Health Inspectorate began looking into PMC and a second company in the Netherlands, Cells4Health.

A quest for a cure

John Franken of Landgraaf, the Netherlands, was a gymnastics champion before he broke his neck during a trampoline accident 18 years ago. Since then, Franken, 44, who has an administrative job at the Open University in Heerlen, has been unable to move without a wheelchair and unable to sit up for more than 6 hours a day. He

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◀ **A wide net.** Many providers of cell therapy recruit patients through their Web sites.

follows spinal cord research closely on the Internet, and he started a foundation to promote the search for a cure in 1995. He got very interested in Huang Hongyun, a doctor in Beijing who injects patients suffering from spinal cord injuries or neurological diseases with cells from aborted fetuses. But when Franken contacted Huang for an appointment, he learned that he'd be on the waiting list for years.

Then in May 2005, Franken read a message posted on a patient forum by Cornelis Kleinbloesem, director of Cells4Health, who said his company had helped a paraplegic patient get a treatment with her own bone marrow cells in a Turkish hospital. Four weeks later, she was able to walk again, as a Turkish magazine called *Tempo* had documented, Kleinbloesem wrote. A second patient had seen functional improvement as well; "these results are very promising," Kleinbloesem's message concluded.

After a series of medical tests, Franken was approved to undergo the same therapy. Friends and colleagues helped raise the \$23,000 for medical fees and travel. In January, Franken flew to Baku, Azerbaijan; at a private clinic, neurosurgeon Elchin Jabrayilbayov made a 12-centimeter cut in his neck and upper back—the graphic pictures are on Franken's Web site—to inject the stem cells directly into the lesion.

When he returned home, Franken started describing his experiences on his Web site. "I know my body is working on something," he wrote after 3 weeks, "but I'm trying to be realistic." He was told it might take at least 6 weeks before the cells had any effect—and so he waited.

Franken's story is not unusual. Many patients hear about anecdotal evidence through the Internet, says John McCarty, a biologist hired last year by the ALS Treatment Development Foundation (ALSTDF) in Cambridge, Massachusetts, to investigate stem cell treatments and other new therapeutic options for ALS. Many spend upward of \$20,000; some borrow to the limit or sell their homes, McCarty says.

What they get differs from clinic to clinic (see table, p. 162). Whereas PMC uses cells derived from cord blood, Cells4Health arranges for patients' own bone marrow cells to be transplanted directly at the site of the lesion to treat spinal cord injuries, vascular diseases, and damage from heart attacks and strokes. Huang, who works at the Beijing Xishan Institute for Neuroregeneration and Functional Recovery in Shijingshan District, says he uses so-called olfactory ensheathing glial (OEG) cells to treat neurological patients. In Kiev, Ukraine, a clinic called EmCell also uses various types of cells derived from fetuses to treat more than 50 different diseases, including many aging-related problems and HIV.

Verifying the claims

Amid all the hype about stem cells, it's easy to forget that very few cell-based therapies have proven their mettle in rigorous clinical trials. For some leukemias, doctors can obliterate a patient's own bone marrow and transplant cells from a donor—a well-established stem cell therapy. In the past few years, several studies have also shown that bone marrow cells can help repair the heart after a myocardial infarction (*Science*, 9 April 2004, p. 192), and others have suggested benefit for patients with a damaged cornea. "That's it, in terms of stem cell therapy," says Minger.

For the moment, most stem cell scientists say they are working on basic questions: how to make stem cells morph into exactly the cell type

ALSTDF's Web site, the foundation's investigators talked to the doctor performing transplants and sent the company a detailed questionnaire. "EmCell didn't answer many of the questions, and in some areas refused to elaborate on important details such as their method for screening against the AIDS or hepatitis viruses," the ALSTDF report says.

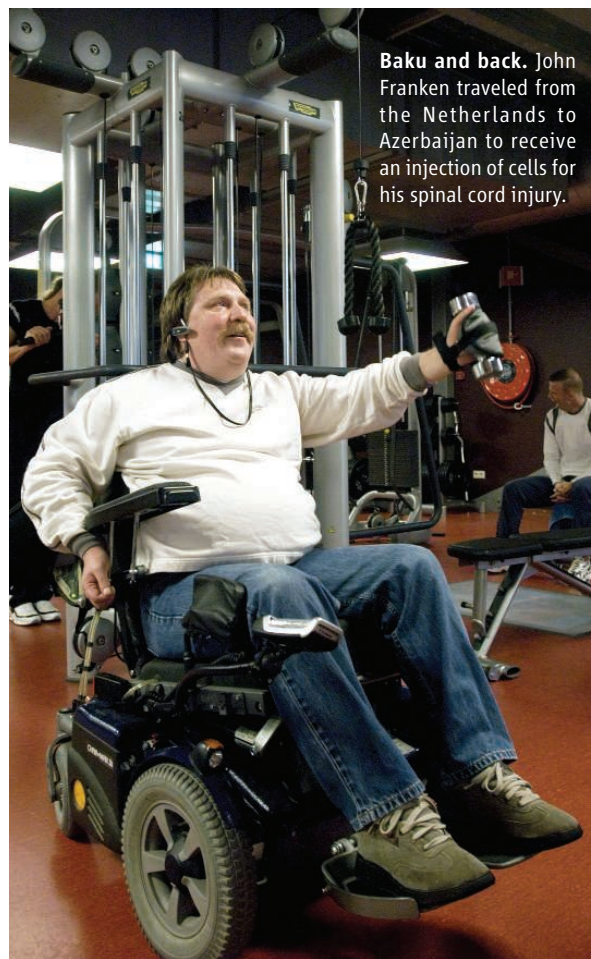
But some of EmCell's procedures "clearly raise red flags," the report goes on. For instance, the company injects cells into patients' abdomens; most doctors think it's "implausible" that they would travel to the brain and work against ALS, the ALSTDF investigators say. The inventor of EmCell's therapy, according to the company's Web site, is its president, Alexandr

Smikodub, who also heads the Cell Therapy Clinic at Ukraine's National Medical University. He has published seven PubMed-listed papers, six in Russian and one in Slovak, the last in 2001. In response to questions from *Science*, Smikodub sent a fax detailing his professional history and EmCell's procedures and giving examples of successfully treated patients. Although he has made presentations at many scientific meetings, Smikodub wrote, the international scientific community has largely ignored him. He did not respond to ALSTDF's allegations.

PMC Director Robert Trossel discussed his company's therapy but said details will be in a paper he plans to submit later this summer to *Nature*, *Science*, or *The Lancet*. "We're dying to let you know," Trossel says. (If accepted, the paper would be his first in a PubMed-listed journal.) PMC specializes in alternative treatments such as herbal medicine and ozone therapy. But recently, Trossel says, his team has learned how to make stem cells home in on the place where they are needed by coinjecting bits of messenger RNA and using each tissue's

"specific electromagnetic frequency." (To avoid having the injected cells seek the wrong target, he also recommends that patients replace mercury-containing fillings first.)

The unconventional cell therapy that's received the most scientific scrutiny so far has been Huang's. With his staff of about 70, Huang has treated more than 1000 patients. His therapy is based on a line of research pioneered by neurobiologist Geoffrey Raisman at University College London, who discovered 20 years ago that OEG cells, which reside in the nasal



Baku and back. John Franken traveled from the Netherlands to Azerbaijan to receive an injection of cells for his spinal cord injury.

needed to treat a condition and how to ensure that they survive after being injected, are not rejected by the host's immune system, and don't start multiplying unchecked.

The cell clinics are forging ahead with treatments anyway. Take EmCell, which says it has experience in multiple diseases from treating more than 2000 patients in 13 years. ALSTDF decided to take a close look in 2004, after a story in a Wyoming newspaper reported that an ALS patient could walk again thanks to treatment by EmCell. According to a review on

Selected Companies and Clinics Offering Stem Cell Therapies

Company	Location	Conditions	Patients treated	Cost (\$)	Remarks
PATIENTS' OWN CELLS					
Cells4Health	Leuvenheim, the Netherlands	Myocardial infarction, vascular disease, spinal cord injury, stroke	NA	+25,000	Treatment takes place at clinics in Turkey and Azerbaijan
NeuraVita	Moscow, Russia	Neurological diseases and injuries	NA	~20,000	
FETAL CELLS					
EmCell	Kiev, Ukraine	More than 50, including neurological disorders, aging, impotence, diabetes, cancer, HIV	Almost 2000 in 13 years	+15,000	
Medra	Malibu, U.S.A.	More than 20, including neurological disorders, depression, autism, sickle cell anemia	More than 1000	NA	Procedures performed in Dominican Republic
Beijing Xishan Institute for Neuroregeneration and Functional Recovery	Beijing, China	Spinal cord injury, ALS, and other neurological conditions	More than 1000 since 2001	20,000	Thousands more on waiting list
Institute for Regenerative Medicine	St. John, Barbados	More than 40	More than 50 since 2004	25,000	Treatment based on research in the former Soviet Union
UMBILICAL CORD BLOOD CELLS					
Biomark	Atlanta, U.S.A.	ALS, Parkinson's, muscular dystrophy, and others	At least 23 in 2003	10,000 to 32,000	No longer operative; founders wanted by FBI
Advanced Cell Therapeutics	Zurich, Switzerland	More than 80	More than 600 in 4 years	25,000	Treatments performed at 12 collaborating clinics worldwide
Preventive Medicine Center	Rotterdam, the Netherlands	More than 50, including neurological, digestive, and psychological disorders and aging	More than 200 in 2 years	23,000	Also treats patients referred by Advanced Cell Therapeutics

SOURCE: COMPANY AND CLINIC WEB SITES, INFORMATION PACKAGES, INTERVIEWS, ALSTDF, BIOMARK CRIMINAL INDICTMENT. NA=INFORMATION NOT AVAILABLE.

mucosa, guide olfactory nerve fibers into the brain during development. After culturing, Raisman and others have found, these cells can help repair rats' damaged spinal cords. (Patients often refer to them as "stem cells" on the Internet, but Huang says they're not; Raisman says "you could call them adult stem cells.")

Raisman and colleagues are planning a small clinical trial in which they will treat patients who have a specific nerve injury that paralyzes the arm with their own OEG cells. But he points out that Huang's treatment is different: It uses fetal cells, which have not been proven effective in published animal studies and which could cause rejection problems because they are not matched to the patients' tissue type. Raisman sees little scientific basis for Huang's treatment, which "saddens" him.

Still, some scientists are intrigued by Huang's claims of success. In 2004, with Huang's consent, a group from the Miami Project to Cure Paralysis at the University of Miami in Florida sent two scientists, James Guest and Tie Qian, to Chaoyang Hospital in Beijing, where Huang then worked. The U.S. duo followed 12 patients from just before treatment until a few days after and took home a sample of therapeutic cells. In a report on the Miami Project Web site, the scientists say that they observed some "modest improvements" in the patients but also noted side effects, including meningitis. Earlier this year, Guest and Qian published an extensive report in *Spinal Cord* about one patient, an 18-year-old Japanese boy with spinal cord injury. They reported that he experienced "rapid partial recovery" after the procedure—even though a lab analysis

cast doubt on the claim that the injected cells were OEG cells. The researchers suggested they might be another cell type and added that the injection may have contained other "neurotrophic" compounds.

Others became interested. Bruce Dobkin, a spinal cord-injury specialist at the University of California, Los Angeles, recalls how he and others quizzed Huang at a dinner party during a 2004 meeting in Vancouver, Canada. Several scientists offered to do a more extensive follow-up of his patients, Dobkin says. Huang appeared "delighted," and Dobkin, Guest, and Armin Curt of Balgrist University Hospital in Zürich, Switzerland, examined seven patients before they traveled to Huang's clinic and again up to 14 months after therapy.

Their paper in *Neurorehabilitation and Neural Repair* 2 months ago delivered a harsh verdict. Five patients came home with side effects, the U.S. group reported, including three with meningitis, and none showed improvement. What's more, the report says, Huang's team doesn't appear to follow up on patients, nor does it systematically collect data about the treatment's efficacy and risks. "It shocked even us," says Dobkin.

In an e-mail to *Science*, Huang called Dobkin's paper "rubbish" and a "vicious attack" that he would not discuss. The Miami team did not find OEG cells in his sample, he says, because they used the wrong staining techniques. And Huang accuses Guest of "misconduct" for publishing the paper in *Spinal Cord* without his permission and without consent from the Japanese patient. Huang has filed complaints with the University of Miami's

Institutional Review Board and the Office of Research Integrity (ORI) at the U.S. Department of Health and Human Services. ORI says it has no jurisdiction, but a university panel is investigating the allegations.

Meanwhile, neuroscientist Wise Young of Rutgers University in Piscataway, New Jersey, where Huang worked from 1999 to 2000, has defended Huang. On CareCure, an Internet forum that Young administers, he wrote that Dobkin "evaluated seven patients out of several hundreds operated on by Dr. Huang ... to make some far-reaching negative conclusions about the work."

Ideally, any unproven cell treatment that's tried on humans should be tested as part of a randomized, controlled clinical trial, most stem cell researchers say; patients should participate free of charge, be fully aware of the risks, and be carefully monitored. Few clinics or companies in the new cell-therapy market appear to have run trials on these lines.

But one of them has tried—only to be rebuffed. Cells4Health set up a clinical trial last year in collaboration with Massimo Mariani, a heart surgeon at Medisch Spectrum Twente, a regional hospital in the Netherlands. According to the protocol, approved by a hospital ethical panel, 10 myocardial infarction patients were to be injected with their own bone marrow cells. The trial was halted in March, however, after a second review by the Dutch Central Committee on Research Involving Human Subjects (CCMO), which criticized the poor trial design, the ill-defined role of Cells4Health, the risks to patients, and the poor information they received. Mariani, who strongly disagrees with the ver-

dict, says eight patients had already been treated before CCMO panned the study; he intends to publish the results.

In a regional hospital in Belgium, meanwhile, Cells4Health tried to set up a trial in stroke and spinal cord injury patients. Again, the trial design was poor, and there was “no scientific basis whatsoever,” says Catherine Verfaillie, a stem cell researcher of Belgian origin at the University of Minnesota, Twin Cities, who was asked to review the study by the hospital. The trial was canceled. Cells4Health Director Kleinbloesem, citing recent “bad experiences” with the press, declined to be interviewed.

Regulatory patchwork

It's no coincidence, critics say, that most stem cell treatments take place in less-developed countries, where regulatory systems are weaker. But even in Western countries, cell-based treatments often fall into a regulatory gap.

Recently, U.S. Food and Drug Administration (FDA) agents investigated Biomark International, a company in Atlanta, Georgia, that provided stem cell therapies for ALS and other diseases. A 51-count indictment returned by a grand jury on 28 March charged that among other things, Biomark's founders, Laura Brown and Stephen van Rooyen, lured patients with “false, misleading, and inaccurate statements on the Biomark Web site and in other advertisements.” A successful prosecution could put the duo in jail for many years. The pair is now wanted by federal authorities.

According to media reports, Van Rooyen returned to his native South Africa, and Brown is now involved in Advanced Cell Therapeutics (ACT), a company with a mailing address in Switzerland and a telephone number in London that the British MS Society says has treated well over 300 MS patients from the United Kingdom. (Its name resembles that of Advanced Cell Technology in Worcester, Massachusetts; the company was alerted to the existence of a second ACT only weeks ago, says Vice President of Research and Scientific Development Robert Lanza.)

According to a Web site maintained by Advanced Cell Therapeutics, its clinical procedures take place in 12 locations around the world, from Mexico and Argentina to Thailand and Pakistan. One of the clinics on the list is PMC in Rotterdam; ACT also provides PMC with its stem cells, says Trossel. Another one of ACT's collaborating clinics, in Cork, Ireland,

is now under investigation by the Irish Medicines Board. (ACT offered to respond to questions sent by e-mail but didn't respond to e-mails or follow-up calls from *Science*.)

In response to media stories about stem cell companies, both the British and Belgian governments recently announced new rules to limit their activities. In the Netherlands, neurologist Rogier Hintzen of Erasmus Medical Center in Rotterdam prodded authorities last year to look at therapies offered by Cells4Health and PMC. A Dutch Health Inspectorate spokesperson says an investigation will be finished this summer. Pending the outcome, however, the agency issued an unusual letter to

more than 1000 patients using fetus-derived stem cells, performs its procedures in the Dominican Republic.

Still waiting

Many stem cell companies quote recently published scientific studies on their Web sites. But at least one scientist has objected to being linked to what she considers a dubious company. Verfaillie says she was “horrified” when Biomark International cited her research on multipotent adult progenitor cells on its Web site. Her university alerted FDA multiple times, she says. Today, ACT uses the references to Verfaillie's work in its patient package.

Some say that scientists themselves may be partly to blame for the growing popularity of unproven therapies. The tremendous

Spreading hope. Personal stories have fueled interest in companies such as Advanced Cell Therapeutics, which is believed to have treated more than 300 British MS patients.

hype surrounding stem cells “has created very unrealistic expectations in patients,” says neurologist Neil Scolding of the University of Bristol, U.K.—adding that researchers, politicians, and the media all bear some responsibility. “It's like the dot-com bubble,” says Raisman. But others disagree. “The scientific community has been trying hard to educate the public,” says Lanza; the field shouldn't be judged by “one or two bad apples,” he adds.

Still, scientists are finding that they have to throw cold water on the high hopes. At the request of the Association of British Neurologists, Scolding is currently drawing up guidelines for doctors confronted with MS patients inquiring about cell treatments. The sad message, he says: They just have to wait. There is no treatment yet.

John Franken is still waiting, too. Almost 6 months after his operation in Azerbaijan, he has noted some changes: One toe has become hypersensitive, for instance, and he can feel temperature changes in his left leg and knee. He hasn't regained control of his paralyzed muscles, however.

After his telephone interview, he asked *Science* in an e-mail not to write a negative story about Cells4Health. Scientists should give Kleinbloesem, “a courageous pioneer,” a fair chance, says Franken, who says he may return to Baku: “I simply refuse to accept that I have to live like this the rest of my life.”

—MARTIN ENSERINK



patients warning that there “is no scientific proof” for the treatments and that “skepticism and caution are in order.” Elsewhere in Europe, stem cell treatments are governed by a patchwork of laws—or none at all. That could change; in order to facilitate Europe-wide market access for so-called advanced therapies, the European Commission recently proposed uniform new regulations, which include a new scientific panel at the European Medicines Agency in London to assess therapies. But its adoption could take years, and it's not clear it will cover work by clinics such as PMC.

And even if regulations are tightened up in Europe, it may be impossible to ban companies from flying patients to other countries for treatment, as Cells4Health does. The same is true in the United States: Medra, a company in Malibu, California, that says it has treated

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