Stem cell therapy or snake oil?

Desperate patients are traveling abroad for dubious stem cell therapies. Monya Baker investigates the potential damage not only to human lives but also to reputable stem cell research.

This October, the US Food and Drug Administration (FDA) gave the green light to the Palo Alto, California-based company, Stem Cells, to inject fetal neural stem cells into the brains of children suffering from Battan disease, a devastating neurodegenerative disorder. Although this is an important first step, it will likely be years before this therapy, or any one like it, is approved. Many patients with untreatable, debilitating diseases aren’t willing to wait and are making their way to far-flung places, where clinics are administering unproven cell therapies to patients who can pay for them. Some go after learning of the procedure from researchers based at prestigious medical schools who claim they are getting treatments to patients faster and gathering evidence for cures. Critics say these researchers are unnecessarily blurring the lines between quackery, science and treatment, risking grave harm to both research and patients.

If you build it, they will come

“Whether you agree with it or not, it’s happening,” says Stephen Hinderer, a physiatrist at Detroit Medical Center. “To not learn from that doesn’t make sense.” For him, the solution is not to learn from that failure, but he already has plans to return to Thailand to try new techniques. Though both Hinderer and Patel frankly acknowledge that their collections of individual case studies cannot demonstrate efficacy, they maintain that patient-funded procedures abroad can be the most feasible way to gather evidence necessary to convince US authorities that a procedure is safe. “When you’re doing innovative work with a new procedure, there is no ready funding source to collect initial data,” says Hinderer. Patel could have filed for an Investigational New Drug (IND) application through animal studies alone, he says, but that would have delayed studies with human patients and supplied less relevant data.

Even so, Patel is very careful about whom he treats; he turns away four out of five people who come to him for cell therapy. But even if patients and their physicians are convinced a procedure is safe, it may not be the best option. Choosing a procedure means patients must make a commitment to that technology, explains Hinderer. “If a clinical trial comes along six months later, they’ll be excluded.”

Not ready for prime time

Like other experimental medicines, cell therapies cannot be given to people in the US without the FDA’s permission. Minimally manipulated autologous cells are not regulated when used for their natural function (such as using hematopoietic stem cells to replace a blood system). However, if researchers want to inject a patient’s blood cells to repair heart tissue or transplant olfactory ensheathing cells to spur spinal cord growth, they must file an IND and convince the FDA that the procedures are likely to be safe. Unlike small molecules, where the process is relatively straightforward, evaluating cell therapies is more complex; it’s hard to know which populations of cells are being administered and hard to predict what the cells will do in patients’ bodies.

These complications imply that the field is too young for widespread human research, says David Beck, a stem-cell advocate and head of the Coriell Institute for Medical Research in Camden, New Jersey, which is developing the first public bank of donated umbilical cord blood for patients needing stem cell transplants. “I’d like to see a lot more basic science done before we start willy-nilly plugging stem cells into people.” Work in animals is yielding far more useful data about what approaches will ultimately be therapeutic, he says, such as what different cell types exist and what environments make them most effective. Without this information, he says, it is hype, not science, that is being used to justify human trials, and overly high expectations could breed cynicism that would set the field back. Both patients and researchers need to “push for the science rather than push for the premature translation of the science,” he says, even if the science is unlikely to yield clinical solutions anytime soon.

That attitude will delay therapies, worries Joshua Hare, a cardiologist at Johns Hopkins Medical School in Baltimore. Work in animals can only take therapies so far. Clinical research, he believes, is essential to move the field forward. In the US, clinical researchers have had to fight an uphill battle. Now, the environment is friendlier. In September, the National Heart, Lung, and Blood Institute of the National Institutes of Health pledged $6.5 million to help move stem cell therapies into the clinic.
Box 1 Desperate measures

Over a thousand people are estimated to be on waiting lists to go abroad to receive stem cell therapies that are illegal in the US. This February, twenty-six-year-old Jason Feasel of Battle Creek, Michigan, took his trip. In July 2003, Feasel, an aspiring professional American football player, crashed his motorcycle when a Jeep Cherokee pulled out in front of him. The accident left him paralyzed from the chest down and brought him to the Detroit Medical Center. There, he learned about experimental treatments for spinal cord injury in Portugal and China.

After investigating other patients’ experiences, passing a psychiatric evaluation for reasonable expectations and promising to spend two more years in physical therapy, Feasel was scheduled for surgery at Hospital Egas Moniz in Lisbon. To raise the $50,000 to pay for the surgery and 12-day trip to Portugal, Feasel and his friends organized a comedy show and raffled off a Corvette. In Portugal, a surgeon gathered tissue from Feasel’s nasal mucosa just under the olfactory bulb, where neuron-like cells known to regenerate are found. Then, the material was transplanted to Feasel’s injured spinal cord.

In the months of therapy before his surgery, Feasel regained some control over his trunk, but nothing else. Now, he says, he can crawl under his own power and feel when therapists move his legs. He knows it’s unlikely, but he is striving to walk again. Feasel won’t advise other patients whether to try the surgery or not, but he’s glad he made his own pilgrimage. “I’d do it again,” he says. “I’ve already done things that they told me I’d never do”.

Hare received one of those grants and is also one of a select few who has received FDA approval to study stem-cell therapies in heart disease. Hare is conducting a double-blind clinical trial to examine whether mesenchymal stem cells derived from blood donors can be used to reverse muscle damage caused by heart attacks. Hare credits work at Goethe-University and Hanover Medical School in Germany for stimulating cell-therapy research in the US1,2. These groups moved from animal studies to an early clinical trial within a year, and immediately followed up on that work with larger clinical trials showing that treated patients had stronger hearts by measuring ejection fraction (a standard measure of heart function). But Hare sees a huge difference between the German trials, which were designed to answer clinical questions and approved by regulatory authorities, and simply recording what happens when patients go abroad for experimental therapies.

Without a rigorously controlled trial, Hare believes, clinicians are conducting potentially dangerous experiments without being able to show their effects. To file an IND, he explains, his team identified a candidate stem cell—the bone marrow derived mesenchymal stem cell—and evaluated it in rats, pigs and chimpanzees3. When the FDA requested more safety data, the trial sponsor, Baltimore’s Osiris Therapeutics conducted an additional, six-month study in pigs. So little information can be gleaned from individual human treatments, claims Hare, that he can’t condone them. “If a patient of mine asked me, I would say ‘you’re better off waiting or participating in a randomized study’.”

Full steam ahead

Besides Stem Cells, other companies are moving toward the clinic with stem cell therapies for nonhomologous functions. Geron of Menlo Park, California plans to file an IND next year to use cells derived from embryonic stem cells to treat spinal cord injury. The company has spent years learning how to grow and characterize reasonably homogenous populations of oligodendrocyte progenitor cells and is conducting 12-month studies in rats to check for tumor formation. Osiris Therapeutics is running three trials for different cell therapies, all backed by animal data.

But many of the barriers to beginning clinical work are not regulatory. “Getting FDA approval is not all that difficult,” according to Wise Young, director of the W.M. Keck Center for Collaborative Neuroscience at Rutgers University in Piscataway, New Jersey. What can be harder is finding reliable sources of funding. “One of the major problems with clinical trials in the United States is that they are driven by commercial motivation,” he says. Revenue models for cell therapies are difficult, especially when therapies rely on cells that are collected from patients5. Researchers interviewed for this article said they did not want to deal with the political and ethical issues of obtaining fetal stem cells, and that many of their colleagues feared lawsuits if any stem-cell treated patients subsequently developed tumors.

Unfortunately, that means that the value of patient-funded experimentation cannot be disregarded. “Almost all new types of surgeries arise via this route,” says Young. Clinicians who try to review experimental therapies generally complain that the techniques are insufficiently described, the cells used are poorly characterized and patients’ conditions before and after surgery are not thoroughly documented. The trick then is to make this work as useful as possible by standardizing procedures and evaluations, implementing rigorous follow-up and helping patients get all the information they can. Young runs a website, http://www.care-cure.org, where patients can describe their experiences with experimental therapies. “We can’t squeeze information out where there is none. I am very concerned that many of the clinical trial centers around the world are simply not being very rigorous about the way they document the recovery of their patients,” he writes. “I urge people to be skeptical. Over the years, I have heard many claims that have turned out to be wrong.”

Young spent much of October in China, meeting with directors of 17 spinal cord injury centers to form the first clinical trial network in that country, where treatments that transplant fetal olfactory cells into patients’ injured spinal cords have received much publicity but have also been widely criticized for their lack of documentation6.

Another criticism of patient-funded research is that it blurs the lines between well-intentioned researchers and profiteers. Desperate patients and their families grasp at straws. Patel recalls one woman who contacted him after her mother suffered a stroke. “Your patients have heart ischemia; my mother has brain ischemia,” she told him. Would he inject cells into her mother’s brain? Patel had to tell her he would not; there was no evidence that such a procedure would work.

But she could probably find someone else. Even cursory internet research on stem cells brings up ads for Medra, a company with a mailing address in Malibu, California, which, according to its website, provides infusions of fetal stem cells that can successfully treat stroke, cancer, autism, lupus, impotence, even aging. The website boasts that the procedure is painless, takes about an hour and has no negative side effects. Patients just have to make their way to the Dominican Republic, “a one-hour-and-forty-five-minute flight from Miami.”

According to Stephan Barrett of Quackwatch, a nonprofit watchdog organization (http://www.quackwatch.org/), Medra is just the latest incarnation of a company that has existed under a variety of names including Mediquest Ltd., Czech Foundation and Dulcinea. The company is run by a former medical expert
for a Los Angeles television station, William Rader MD, who, according to the Los Angeles Times, was asked to leave the Bahamas, where he had set up a clinic. He also is on record as refusing to publish information about his therapy because he believes that a “conspiracy” of scientists, drug companies, abortion opponents and government authorities would attack his work. (Medra did not respond to requests for an interview.)

The Institute of Regenerative Medicine (IRM), headquartered in Barbados, is taking a different approach. Like some other clinics (Table 1), it traces its roots to the Institute of Cryobiology in the Ukraine. (One of its scientists, Yuliy Baltaytis, told the LA Times that he also collaborated on the founding of Medra.)

Located in a building that formerly housed Vita Nova, an apparently defunct stem cell clinic with ties to Baltaytis, IRM will infuse patients with human fetal stem cells at its Barbados clinic for around $25,000 (ref. 7). IRM CEO Barnett Suskind would not give the exact number of patients treated, but said it was between 12 and 100 patients. Some of them, he says, “come again and again.” The treatment is offered for AIDS, Alzheimer disease, arthritis and other afflictions, including aging.

However, IRM is sponsoring clinical researchers, including Federico Benetti, for example, a published surgeon who pioneered beating-heart surgery and treats patients with autologous stem cells. Benetti received a grant from IRM to use fetal cells in an open label study at Luis Vernaza Hospital in Guayaquil, Ecuador, for ten patients with advanced heart failure. The study, approved by the hospital’s institutional review board, was presented in June at the annual meeting for the International Society of Minimally Invasive Cardiothoracic Surgery in San Francisco, and, according to Suskind, is being submitted for publication.

Benetti, a native Argentinian heart surgeon describes the circuitous path the cells take in order to be used in therapy. They are obtained and processed at the Institute for Cryobiology in the Ukraine, frozen at –196 °C, shipped to Nottingham, England, where the cells are screened for infectious agents, then shipped to IRM headquarters in Barbados where they receive a certificate of viability, and finally shipped to Ecuador, where they are injected into patients with failing hearts. The cells come typically from neural, liver and hematopoietic tissues from different-aged fetuses, says Suskind, who explains that the clinicians have found that using mixed cell types is more effective than using a single cell type and that they can be tailored to different treatments. Suskind says that these human cells are inappropriate for animal studies and won’t be shared with other researchers.

Patients in the IRM study showed no cell rejection, according to Benetti. They could walk farther than before and had improved ejection fractions, gains that were sustained for 90 days after the surgeries. Of the ten patients receiving treatment, one could not complete follow-up because of a stroke, and another was lost to follow-up, and died five months later, apparently from starvation. According to Benetti, an examination of his heart showed that the cells underwent more mitosis than expected in heart failure patients. The company is eager for scientific acceptance. “What we’re doing is trying to find the most effective way of building peer support in the scientific community,” says Suskind. At least one other clinic is following suit. Emcell, a Ukrainian stem cell clinic, described outcomes for several dozen patients treated since 1995 on for amyotrophic lateral sclerosis and Duchenne muscular dystrophy at the 4th International Meeting on the European Tissue Engineering Society this September.

However, patients may not appreciate the difference between meeting presentations, which have a low bar to entry, and scientific publications that are rigorously peer reviewed, warns Christopher Scott, head of the Program on Stem Cells and Society at Stanford University’s Center for Biomedical Ethics. Many stem cell clinics claim that their therapies are based on decades of research and yet have hardly any presence in the peer-reviewed literature. Patel and Hinderer say that most of the patients who arrive in their clinics have done extensive research on therapies offered abroad, but they know some patients head off for futile and potentially dangerous treatments. “There is a lot of quackery, and that is a problem and that does weaken the field,” says Patel.

Arlene Chiu, head of scientific activity at the California Institute of Regenerative Medicine in San Francisco, worries about the effects on patients and those working to bring them effective therapies. “It doesn’t take a lot of bad work to tar the whole field, and there are serious people who are attempting serious trials who are careful and reasoned.”

Monya Baker, San Francisco

Table 1 Selected stem cell tourist hot spots

<table>
<thead>
<tr>
<th>Company (chief scientist)</th>
<th>Source of cells/route of delivery</th>
<th>Indication</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangkok Heart Hospital, Bangkok, Thailand (Kit Arnon, working with Amit Patel)</td>
<td>Autologous blood-derived stem cells injected into hearts</td>
<td>Cardiac myopathy</td>
<td>$25,000</td>
</tr>
<tr>
<td>Chaoyang Hospital, Beijing (Hongyun Huang)</td>
<td>Fetal olfactory ensheathing cells</td>
<td>Neurodegenerative diseases, spinal cord injury</td>
<td>$20,000</td>
</tr>
<tr>
<td>EmCell, Kiev, Ukraine (Alexandr Smikodub)</td>
<td>Suspensions of cells from 4- to 12-week-old fetuses, usually injected intravenously</td>
<td>Aging, AIDS, cancer, diabetes, multiple sclerosis</td>
<td>$10,000–15,000 per treatment</td>
</tr>
<tr>
<td>Hospital Egas Moniz, Lisbon, Portugal (Carlos Lima)</td>
<td>Autologous olfactory ensheathing cells transplanted into spine</td>
<td>Spinal cord injury</td>
<td>$50,000</td>
</tr>
<tr>
<td>Institute of Regenerative Medicine, St. John, Barbados (Yuliy V. Baltaytis)</td>
<td>Fetal cells injected intravenously</td>
<td>Over 20 diseases listed</td>
<td>$25,000 per treatment</td>
</tr>
<tr>
<td>Medra, Malibu, California (clinic in the Dominican Republic) (William Rader)</td>
<td>Fetal cells injected subcutaneously or intravenously</td>
<td>Over 20 diseases listed</td>
<td>$25,000 per treatment</td>
</tr>
<tr>
<td>NeuroVita Clinic, Moscow (Andrey S. Bryukhovetsky)</td>
<td>Autologous neural and hematopoietic stem cells, often transplanted intrathecally</td>
<td>Neurological disorders and spinal cord injury</td>
<td>$9,000–50,000</td>
</tr>
</tbody>
</table>

© 2005 Nature Publishing Group http://www.nature.com/naturebiotechnology