Stem Cell Showdown

Jennifer Ziegler
200 million stem cells
$15,000

Tracy Thompson
700 million stem cells
$58,000

Carla Hickman
75 million stem cells
$30,000

Preston Walker
20 million stem cells
$20,000

The FDA has put the brakes on a Texas company looking to profit from controversial new therapies

By Susan Berfield
Photographs by Thomas Prior

Bill DeVore
100 million stem cells
$33,000

SammyJo Wilkinson
600 million stem cells
$28,000

Cecelia Johnson
800 million stem cells
$45,000

Debbie Bertrand
2 billion stem cells
$41,000

Cecelia Johnson was an artist, cellist, tap dancer, and 22-year-old college student when she was diagnosed with multiple sclerosis in 2001. The disease, in which the body's immune system attacks the tissue protecting nerves, proceeds at its own pace: Sometimes the deterioration is halting, sometimes it can be delayed, but there is no cure. Johnson's decline was swift.

Six years after her diagnosis, undone by fatigue and pain and often unable to walk, Johnson gave up on conventional medicine. In the spring of 2007 she traveled from her home in Houston to Mexico, where an American doctor gave her an infusion of adult stem cells that were supposed to regenerate her damaged tissue. "I thought this guy might be peddling snake oil," says Johnson. "But I would have taken snake oil." The procedure cost her $14,000.

Within a few months, she began to feel better. The effects weren't lasting, though, and she returned to Mexico every year until the Federal Bureau of Investigation arrested her doctor in December 2011. Francisco Morales was accused of conspiracy and fraud: He wasn't a licensed doctor, and he was using umbilical-cord stem cells he bought in the U.S. for treatments that the Food and Drug Administration had not approved. He pleaded guilty in September 2012 and awaits sentencing.

By then, Johnson had learned she could receive infusions of her own stem cells in Houston. An orthopedic surgeon there, Stanley Jones, had recently co-founded Celltex Therapeutics, a company that multiplied and stored adult stem cells. It took Johnson and her mother much of the spring and summer of 2012 to raise the $30,000 fee for the treatment, which was part of a clinical study. "A study I have to pay $30,000 for? Sure, I'm skeptical," says Johnson. "The point is that stem cells are available, I desperately need them, and I will pay for them." In August, Johnson had several hundred thousand stem cells harvested from her abdominal fat.

Jones was not just a doctor, he was also a satisfied customer. He had been treated for autoimmune arthritis with his own adult stem cells through a South Korean company, RNL Bio. In March 2011, he and Houston businessman David Eller founded Celltex, one of the first commercial stem cell laboratories in the country. They had RNL's technology and eventually some 200 paying patients desperate for relief. One of them was Texas Governor Rick Perry, who suffered from back problems. Together they encouraged the state medical authority to let doctors provide stem cell treatments under its supervision.

Then the FDA got involved: The agency inspected Celltex's lab, found 14 major manufacturing problems, and later warned the company it was illegally marketing an unlicensed drug. Celltex shut down the lab in early October 2012, four days before Johnson was to receive her first batch of cells. It hasn't yet resumed processing stem cells for Johnson or anyone else. In a December letter to patients the company stated: "Celltex remains fully committed to advance the most promising new field in human health in decades–regenerative medicine."

Celltex's venture raises some of the most vexing, emotional issues in the business of medicine. Stem cells hold enormous promise, but promise isn't proof, and anecdotal evidence isn't science. Small companies often can't do the research required by the FDA and make money at the same time. Some patients will pay to be part of an experiment, but many doctors and regulators don't think they should. In Texas the science of stem cells has collided with a governor's ambitions, a businessman's optimism, a doctor's faith, and patients' hopes. "It seemed too good to be true," Johnson says, "and it was."

Stem cells, often thought of as the body's master cells, help form and repair tissue, organs, and blood. There are different types of stem cells, each with their own capabilities. Embryonic stem cells, potentially the most powerful, are the most controversial; George W. Bush restricted federal funding for embryonic stem cell research when he was in office. Induced pluripotent stem cells are adult cells that have been genetically reprogrammed to have some attributes of embryonic stem cells. Adult stem cells are believed to exist in tissue throughout the body. The main function of mesenchymal adult stem cells, the type Celltex works with, is to repair tissue damaged by daily use. They also have anti-inflammatory properties. The cells can be found in special niches in bone marrow, umbilical-cord blood, muscle, and fat. When the body is injured, the cells leave their niche and become more specialized, but they are not, like embryonic stem cells, able to transform into any kind of cell. A blood-forming cell can become a red blood cell; it can't become a brain cell.

Hundreds of clinical studies are under way in the U.S. to test the safety and efficacy of stem cells for all sorts of disorders: Alzheimer's, Crohn's, Epstein-Barr, lymphoma, diabetes, multiple sclerosis, infertility. Scientists say stem cells could help repair the heart or spine, regenerate cartilage, and improve brain function after a stroke. "We're formed from stem cells, everything about our body is a stem cell product," says James Willerson, president of the Texas Heart Institute, where about half of the research conducted involves stem cells. "I believe the right cells in the right place in the right person will do amazing things." Arnold Caplan, a professor of biology at Case Western Reserve University and founder of two stem cell companies, says: "It sounds like stem cells could be the magic elixir for every malady. The answer is that, on a scientific basis, they could be."

So far the FDA has approved only one stem cell product, Hemacord, derived from the umbilical cord, which could help those with certain blood cancers as well as metabolic and immune system disorders. (Bone marrow transplants such as those used to treat leukemia patients are considered medical procedures, not products.) In a note to consumers on its website, the agency warns about the potential for stem cells to grow excessively once back in the body and develop into tumors. "Stem cells seem so seductive," says George Daley, a founder of the Harvard Stem Cell Institute, an organization that supports research and its clinical applications. "It's easy to be told how they work and think they can help you. But we know from centuries of experience with medicine that anecdote is a very unreliable way of making medical advances. Medicine has been misled since the time of the leeches."

Jones used to think stem cells were hokum. That began to change in September 2009, when he experienced his first stab of pain. His right wrist swelled, then his left knee. The pain became excruciating. Jones, who was 66, had a thriving surgical practice in Houston. He also owned a medical day spa with his wife that offered skin rejuvenating treatments and other services. Yet he could barely work.

He was diagnosed with a form of arthritis that occurs when the immune system turns on a person, attacking the joints. The symptoms come and go, and no one really knows why. Jones took medicine to reduce the inflammation, but he was nauseated, lost 30 pounds, and was often bedridden. Then he heard from a friend who had also suffered severe arthritis. She had been successfully treated with her own adult stem cells through RNL Bio. "It was a call from heaven," says Jones.

When he contacted RNL in December 2009, Jones learned that the company was trying to break into the U.S. market and planned to open a clinic in Koreatown in Los Angeles. An executive from its American subsidiary, Human Biostar, quickly met with Jones. Soon after, the doctor signed on as a customer. His wife, Kathi, who had Reynaud's, a disorder that affected the blood flow to her fingers, decided to be treated, too.

"People ... critical of what we're trying to accomplish will wake up one day with a debilitating disease, and they'll be begging for stem cells"

Eller and Jones founded Celltex in 2011

In March 2010 they each had about two teaspoons of fat extracted from their abdomens at their medical spa: a mini-liposuction. The fat was sent to RNL's lab in Seoul, where technicians removed about 250,000 stem cells from each fatty lump, then multiplied the cells in a medium that included ascorbic acid, calcium, insulin, hydrocortisone, an antibiotic, a bit of bovine pituitary extract, and a protein that acts as a growth factor. By May there were 600 million cells waiting in vials for Jones and 600 million for his wife. The couple stopped in Seoul to see the lab before going to Kyoto, Japan, where once a week for three weeks they each received 200 million cells intravenously.

RNL's stem cell technology is patented, and clinical trials are under way in South Korea, but the therapy has not been approved there as a treatment for any disease. Patients must get their infusions and injections from doctors in China and Japan. Jeong Chan Ra, the veterinary doctor who founded RNL in 2000, has received 46 infusions of adult stem cells in the past four years. "In the grand tradition of many scientists like Sir Isaac Newton and Jonas Salk, I experimented upon myself first to confirm that adult stem cells cultured and expanded by RNL Bio are safe," he says via e-mail.

While in Seoul, Jones called a patient of his: Governor Perry, who had declared his intention to make Texas the adult stem cell capital of the world. (Perry opposes embryonic stem cell research on the grounds that it destroys life.) Jones told Perry about the miraculous recoveries he had witnessed and said he felt called to bring the technology to Texas–although he had not yet undergone the treatments. After he returned to Houston, five months passed–he felt no improvements. "Then I woke up one morning and I felt fantastic," he says. "It was a new beginning." Kathi's symptoms disappeared, too.

Jones found he needed another stem cell infusion four months later (he has had them every four months since) to keep his symptoms under control. "I'm afraid to be without stem cells," he says. So far he's received 3 billion stem cells by infusion and injection and spent more than $100,000. Plenty of people, including medical colleagues, have suggested he's experiencing a placebo effect. Jones is convinced he's not. "My therapy was real, it was effective, and it made me better." The most rigorous trials–double-blind, randomized, placebo-controlled–are designed to prove any benefits are due solely to the treatment. "There's no question that with therapies like this there is a very high placebo effect," says Caplan of Case Western. "The FDA will shudder, but I say, if you want to pay $25,000 and get pain relief for four months as a placebo, go do it."

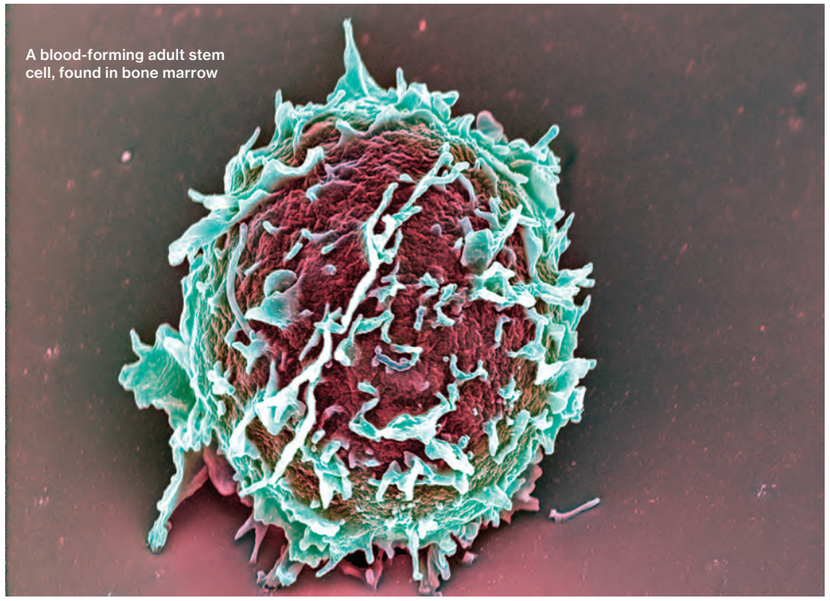
In December 2010, a few months after Jones's initial recovery, RNL was the subject of an investigation by the International Cellular Medicine Society, a group trying to establish stem cell standards, which counted RNL among its members. Two patients had died after receiving stem cells expanded by RNL's lab in Seoul. The report concluded that the death of one patient was likely to have been caused or triggered by the administration of the stem cells by a doctor in Japan. RNL says the report relieved it of responsibility. The South Korean government did not look into the deaths.

Back in Texas, Governor Perry told David Eller about Jones's improved health. Eller, 74, is a longtime campaign contributor and occasional adviser to Perry who has known Jones for more than three decades. He's served as chairman of the Board of Regents at Texas A&M University, Perry's alma mater, and president of DuPont Pharmaceuticals' European operations. He also founded Granada, a company that specialized in the genetic engineering of farm animals. In 1992 it settled an investor lawsuit alleging securities fraud and denied any wrongdoing.

Governor Perry and Eller saw in Jones's recovery a promising business opportunity. "Stem cells are my passion," Perry says. "I have two interests. The first is finding cures for diseases that are complicating people's lives. The second is economic, the companies that come out of the work with adult stem cells." Others were optimistic about stem cells, too: A 2011 report from Rice University's Baker Institute cited figures predicting U.S. revenue from stem cell products could reach $16 billion by 2020. (They were $12.6 million in 2007.)

Eller looked into RNL's record and came away satisfied. "I felt that RNL had as good a therapy and technology as anyone else I knew of," he says. "Because of that, and the state of Texas was behind it and I knew the poster child, Stan, I decided I would try."

Eller says RNL's stem cell science was ahead of the FDA's regulations. At issue was a fundamental question: Are stem cell infusions and injections biologic drugs like vaccines, which require FDA oversight, or are they part of the practice of medicine, which falls under the exclusive jurisdiction of the Texas Medical Board? The answer turns on the notion of "minimal manipulation." If the cells are more than minimally manipulated in the lab, they're considered a drug. RNL says the new cells are always identical copies of those it harvests from a patient, which makes them a treatment, not a drug. The FDA and many in the scientific community have not come to the same conclusion. "The reason we started in Texas this way is that adult stem cells are not considered a drug in Texas," says RNL's Ra. "We had the expectation that treatment in Texas was possible without FDA approval."



A blood-forming adult stem cell, found in bone marrow

"I was excited to be first," says Texas Governor Rick Perry

Eller and Ra signed a licensing agreement in mid-March 2011 that laid out an ambitious business plan. Celltex paid $30 million to RNL, money Eller raised from at least 10 investors, including Jones and himself. Eller became the chairman and chief executive officer of Celltex, Jones the chief medical officer. RNL would set up a lab in nearby Sugar Land, Tex., and run it until Celltex was ready to take over. The lab would process the cells of 250 patients a month; doctors would administer the treatments in their own offices. RNL would receive 20 percent of any revenue Celltex earned from licensing the technology to others in North America; the terms suggest RNL believed Celltex could bring in some $1.5 billion this way. RNL also purchased a 10 percent share of Celltex, and Ra took a seat on the board of directors. Celltex says an independent assessment later valued the company at $250 million.

Governor Perry was the first patient. "I was excited to be first," he says. In June 2011, Jones took two teaspoons of fat from Perry's hip, then sent it to Celltex's new lab. On July 1, Jones performed a previously scheduled back operation on Perry, during which he injected adult stem cells into Perry's spine and blood system to help speed his recovery. In early August the *Texas Tribune* revealed that Perry had undergone the treatment. Daley, of the Harvard Stem Cell Institute, said Perry had exercised poor judgment. Perry said he felt great. On Aug. 13 he declared his candidacy for president.

Rick Hardcastle, a Texas legislator who'd been living with multiple sclerosis for a decade, became patient No. 5. "The infusions were completely uneventful. I was eating Popeyes chicken and getting an IV," he says. After the first one, Hardcastle says his balance was restored. (MS can damage the cerebellum, which maintains balance in the body.) "Celltex tells you that half the time the treatment might not do what you want. But it won't hurt you. I'll take 50-50 odds, and I'll pay for it." It cost $30,000.

Jones received lots of phone calls at his private practice during the fall of 2011 from people interested in the treatments Perry and Hardcastle had undergone. "Word spreads quickly when you're miserable, desperate for help," he says. Celltex didn't advertise its services. The Texas Medical Board had not yet come up with a regulatory framework for doctors to offer stem cell therapies. It did hold monthly informational seminars at a luxury hotel in Houston. Debbie Bertrand attended one in September and became patient No. 13 a few weeks later. Bertrand, 60, who was diagnosed with MS in 2001, had tried to get into FDA-approved drug trials but never qualified. Instead she gave herself daily injections of a standard MS drug that ate away tissue at the site of the shot and left her feeling like she had the flu. In the fall of 2010 she traveled to Tijuana, Mexico, for a stem cell treatment that improved her double vision and left her less fatigued. She was hoping the more potent dose of stem cells she could receive through Celltex would allow her to get out of her wheelchair.

Last April, 10 months after Celltex's lab opened, two FDA inspectors arrived in Sugar Land and stayed for 10 days. They found the lab couldn't guarantee the viability and sterility of the cells or their type. Its manufacturing records were sloppy or incomplete; tabletop equipment was operated on the floor; and it was using supplies labeled "FOR RESEARCH USE ONLY. CAUTION: Not intended for human or animal diagnostic or therapeutic uses."

"To read it as they wrote it sounds just horrible," says Eller. He and Celltex's executive vice president, Andrea Ferrenz, say the inspection was complicated by the fact that the records were in Korean. "We're confident that the lab's procedures were sterile, the cells were viable, they were given back to the right person," says Ferrenz. As for the supplies labeled for research only, she says it's commonly understood that facilities determine how they will use such material. Says Ricardo Rodriguez, president of the board of the International Cellular Medicine Society: "It's one thing for Celltex to take an ideological position [with regard to the FDA] and still do everything possible to guarantee patient safety. They were not doing everything possible."

Bertrand read the report, too. "Whatever they were doing wrong wasn't hurting me," she says. "I was feeling better." Bertrand has had eight infusions through Celltex, about 1.6 billion stem cells altogether, at a cost of $27,000. She uses a walker instead of a wheelchair and says she's strong enough to exercise, can straighten her fingers, and has improved bladder control.

Nor did the report dissuade other MS patients from signing on with Celltex. The FDA-approved drugs for MS don't work for everyone and can have terrible side effects. "The FDA has created a group of risk takers," says Jennifer Ziegler, who was diagnosed with MS in 2004. A former Kansas City Chiefs cheerleader, she has become the unofficial leader of a band of MS patients agitating to receive stem cell treatments in the U.S. "When we heard the FDA had been down to Sugar Land, all it made me do was want to hurry up faster," she says.

Lester Smith, a prominent Houston oilman, cancer survivor, and philanthropist, had the same thought: better get as many stem cells as possible. He had osteoarthritis, brought on by his years as a competitive ballroom dancer. From January 2012 through September, he received 2.5 billion stem cells, hoping for relief. His wife, and dance partner, received 1.4 billion—her arthritis wasn't as bad. The couple paid $165,000 in all. Smith, who also uses testosterone gel, says his pain is gone; his cholesterol level, blood pressure, pulse, and body fat percentage have all dropped. "Ninety-nine percent of the doctors I talked to said I shouldn't do this," he says. "After a while I quit asking."

Just as the FDA inspection of Celltex's lab was getting under way, the Texas Medical Board made the announcement Eller and Jones had been anticipating: Doctors could charge patients for experimental therapies as long as the experiments had been approved by a local institutional review board. Those boards could be for-profit operations themselves. "We effectively said these federal rules protecting patients no longer apply," says W. Roy Smythe, a surgeon and member of the medical board who voted against the changes.

The ruling was criticized by many in the scientific community who would have preferred that Texas work with the FDA. "But people who want to make money don't want to wait to make money," says Paul Knoepfler, an associate professor at the University of California at Davis School of Medicine who conducts research with induced pluripotent and cancer stem cells. "And there's a lot of patients who don't want to wait, either."

In May, six Korean-American patients living near Los Angeles sued RNL's U.S. subsidiary, Human Biostar, for fraud, alleging that the treatments they received did not improve their diabetes, arthritis, high blood pressure, or insomnia. Eller says the suit has nothing to do with Celltex. Says Ra in an e-mail: "I am well aware that many people are worried about the reputation of RNL Bio. These are not good events. However, since I have confidence in the scientific verification of the safety and efficacy of RNL technology, I do not worry about this." RNL has filed a counterclaim.

There were soon other matters to worry about. In September the FDA issued a warning letter stating that Celltex was illegally promoting an unlicensed product (the cultured and expanded cells) it considers a biologic drug. And the agency reiterated its concerns about the lab, despite attempts by Celltex and RNL over the summer to comply with the requirements. "We're going to do whatever the FDA tells us to do," says Eller. "It doesn't mean we agree. We respectfully disagree. The FDA thinks everyone who's walking around is a biologic drug. We want to explain why we think what we're doing is correct." Governor Perry says he disagrees with the regulators, too. "Hopefully, the FDA will realize that what's going on in Texas is good medicine and good economics."

"Medicine has been misled since the time of the leeches"

"The FDA shares the same goal as patients with serious and life-threatening diseases of getting novel products to the individuals who so desperately need them," Rita Chappelle, a spokeswoman for the agency, says via e-mail. "The regulations for cellular and tissue products are risk-based: If the risk is low, the level of regulatory oversight is correspondingly low. This unique regulatory approach ensures that the regulations are not too burdensome."

In the meantime, Eller says Celltex has collected data from 230 patients, all of whom paid to be treated for different maladies, mostly related to the immune system. "We wanted to help people like me," says Jones. The studies were approved by a company called Texas Applied Biomedical Services in January 2012. It, too, received a warning letter from the FDA in September stating that its members didn't have the expertise to review specific research, had conflicts of interest, and kept inadequate records. The president, Joyce Heinrich, says the company has made the changes the FDA sought and is waiting to hear back. It continues to oversee Celltex's studies.

Eller expects the results to be published sometime next year. "It will be the largest and possibly most important study on adult stem cells that's been produced anywhere," he says. Adds Jones: "I can tell you it looks good."

Following the FDA's rules for approval for a new drug is usually an expensive and lengthy process and not an easy way to run a profitable business. Celltex won't be able to charge patients tens of thousands of dollars to participate in its trials. And some patients will receive placebos instead of stem cells. "I don't want to treat people with placebos," says Jones. "You wouldn't want to be in a trial where you were next to someone who might get well and you might die." Jones has given up his role as the company's chief medical officer, though he remains a board member. "All the people who are critical of what we're trying to accomplish will wake up one day with a debilitating disease, and they'll be begging for stem cells."

By late November, Celltex's situation became more complicated. The company sought an injunction against RNL, alleging it was holding hostage the stem cells of its customers. The cells are stored at -400F in vials suspended in a stainless steel tank filled with liquid nitrogen. According to Celltex's court filings, RNL had barred Celltex from entering the lab and refused to release the cells to anyone. RNL also told Celltex that its subsidiary, Human Biostar, was independent and wanted $1 million in fees as well as $6,000 a day for storing the cells. Human Biostar filed its own lawsuit against Celltex, claiming the unpaid processing and storage fees. In mid-December a judge issued a temporary restraining order that reads like a child custody arrangement. Celltex can set up supervised visits to the lab and tank. It can also remove a customer's cells with a doctor's order and a check for $5,000. The company says it's now building its own lab.

Among the cells being fought over are those of Jennifer Ziegler and Cecelia Johnson. Ziegler, one of the last to receive stem cells processed at the Sugar Land lab, is pleading with the FDA to rethink how it regulates stem cell therapies. "We want the right to be treated with our own stem cells," she says. As for Johnson, she says: "Our hopes were built up by Celltex, and then we were dropped low." In November she paid $12,000 for a stem cell injection into her spine and an intravenous infusion at a clinic in Frankfurt. She had been in severe pain for the past two years, rarely leaving home, and then only in a wheelchair. A few weeks after her treatment, she started to feel lighter, clearer. The pain diminished. "I walked around a tree outside my apartment. I lay on the grass," she says. "I don't want to sound like an infomercial or someone at a church revival. This is a cruel disease. I'm not waiting for a miracle. But if I could have stem cells every six months, I could live." B

DR. GARY D. GAUGLER/PHOTOTAKE