Adult stem cell therapies walk the line

Tension between practitioners who believe autologous stem cells should be considered a service and the FDA, which considers some of them biologics, has come to a head in recent months. Laura DeFrancesco investigates.

Almost a year after Texas governor Rick Perry received injections of his own stem cells for a back ailment, a US Food and Drug Administration (FDA) inspection of the company that prepared the cells—Sugar Land, Texas–based Celltex—has raised red flags. The FDA's inspection report, a so-called form 483, details myriad problems with facilities and sample preparation. As *Nature Biotechnology* went to press, Celltex is still operating and claims to be cooperating with the FDA. But Celltex's problems are indicative of those at other adult stem cell companies that have fallen afoul of FDA oversight. For example, a legal battle that dragged on for four years between the FDA and Broomfield, Colorado–based Regenerative Sciences, which offers mesenchymal stem cell treatments for orthopedic indications. The company claims that it has altered the procedures that originally infringed FDA rules and that it is now compliant. Meanwhile, it has filed suit against the agency for interfering with what its management (and others) consider a legitimate use of autologous stem cells[1]. As *Nature Biotechnology* was going to press, the US District Court for the District of Columbia ruled in favor of the FDA's position.

Celltex and other such outfits that prepare autologous stem cells for medical uses claim that they provide a medical product, not a drug, and hence lie outside the FDA's jurisdiction. The FDA begs to differ (**Box 1**). It has designated Celltex a biological drug manufacturer, which must, as such, follow good manufacturing practices. But groups of stem cell practitioners in both the US and Europe continue to push back against regulators. The issues involved are varied and complex—from states' and patients' rights to the mechanism of stem cell action. The field is waiting to see whether the resulting wrangle will mean regulators will clamp down or give it more freedom.

The proven pathway

Numerous autologous cell therapies are being taken down the established regulatory pathway for cellular products, with a small number having received approval. According to data compiled by Lee Buckler of the Cell Therapy Group, a consultancy group located in Bellingham, Washington, 47 industry-sponsored clinical trials of autologous cells are in pivotal or late stages involving 37 companies. (http://celltherapyblog.blogspot.ca/2011/12/active-phase-iii-or-iiiii-cel-therapy.html). The majority of these trials, however, originate not in companies but in academia or hospital settings, many of which are being conducted outside of the US. Commercial entities, although active in the space, face considerable hurdles with autologous stem cells, due to the difficulty and expense of creating individualized drugs. Seattle-based Dendreon's epic problems with both the manufacture and the uptake of its autologous prostate cancer vaccine (Provenge, sipuleucel-T) typify the difficulty with this approach.

Tyler Rudick/CultureMap, Houston

Coming to a state near you. Celltex Therapeutics celebrates its new 15,000-square-foot facility in Sugar Land, Texas, and its new partner, the Korean stem cell outfit RNL BIO, in this picture from last December.

However, a few autologous cell therapies have passed regulatory muster in various locales. In the US, in addition to Provenge, an autologous fibroblast product for filling in wrinkles was approved this year (laViv, manufactured by Fibrocell; Exton, PA, USA) and autologous chondrocytes were approved in the mid-nineties for cartilage repair (Carticel, Genzyme/Sanofi, Paris). In South Korea, two autologous programs have received approval in the past few years—an autologous bone marrow–derived cell therapy for myocardial infarction (Hearticellgram, manufactured by Pharmacell of Seoul.) and an adipose tissue–derived cell therapy for anal fistulas (Cupistem, manufactured by Anterogen of Seoul). Clinical trials results have never been published for the products approved in Korea nor have the claims been replicated in laboratories outside of the companies.

Elsewhere, a small cadre of companies is trying to make a go of it with autologous stem cells (**Table 1**). Aastrom Biosciences, based in Ann Arbor, Michigan, may be the farthest along; the company reported positive phase 2 results with its autologous bone marrow–derived product (ixmyelocel-T) for critical limb ischemia last November[2] and has initiated phase 3 studies, which are expected to be completed in 2014, according to Aastrom CEO Tim Mayleben.

Going rogue

Other groups, both within the US and outside of it, are treating patients and collecting payments—rather substantial ones, in the tens of thousands of dollars—for procedures that have not been thoroughly vetted, from breast augmentation and other cosmetic procedures to orthopedic conditions and a host of hard-to-treat disorders, such as Alzheimer's disease and amyotrophic lateral sclerosis. In the past, these clinics operated largely outside the US, but increasingly they are popping up within US borders.

Whereas certain autologous cell-based therapies are regulated by the FDA's Center for Biological Evaluation and Research (CBER), those posing minimal risk and fulfilling other requirements, are not (**Box 2**), enabling companies to go straight to the market if they feel they do not qualify for oversight. This ostensibly puts the onus on the FDA to find firms that have flouted rules and stop them if they continue to do business outside the law. The ability to operate under the FDA's radar provides some unscrupulous companies with a window of opportunity to profit from products that are of dubious efficacy at best or, at worst, unsafe for patients.

Another strategy for commercializing cell-based therapies that companies like Celltex are using is to position themselves as producers of cells, which they then provide to physicians who can decide, based on their medical expertise, how best use to use the preparation. Celltex believes this puts the therapy in the realm of medical practice, which the FDA does not regulate.

Box 1 Troubled waters

Several companies offering autologous stem cell therapies have run into problems outlined below.

- Regenerative Sciences. This company isolates mesenchymal stem cells from patient bone marrow and delivers them to various sites to treat joint, tendon, ligament or bone pain. The company website claims to have treated 1,300 patients with bone marrow–derived stem cells. In 2008, they received a form 483, later enjoined by FDA to stop treating patients with unapproved treatments. The company sought injunctive relief from the FDA claiming that their therapies are not drugs or biologics, and questioning FDA's ability to regulate such products.
- Young Medical Spa (Lansdale, PA, USA). The enterprise removes adipose tissue from patients, isolates stem cells and returns them to fat to produce a stem cell–enriched sample, which is then injected into breasts and joints. The FDA issued a warning letter in April 2012, after two inspections. Infraction: procedure alters the relevant characteristics of adipose tissue and does not meet homologous-use requirement.
- Intellicell BioSciences (New York). Company prepares adipose-derived stem cells and injects them intravenously into lips, cheeks, knees, scalp, osteoarthritic joints, receding gums. FDA issued a warning letter in March 2012 for not meeting requirements of minimally manipulated or homologous use and for deviations from good manufacturing practice.
- Celltex. Company supplies adult stem cells to physicians in Texas. The FDA issued a form 483 in April 2012 for numerous infractions of good manufacturing practices.
- Six patients in California filed suit against the Korean stem cell company RNL BIO (partner of Celltex), for misrepresentation of fact and elder abuse, among other things. Patient cells were harvested in Korea, sent to China, then Los Angeles, and reimplanted in the patients in Mexico. The case is before the US District Court in Los Angeles.

As regulatory agencies struggle to come up with guidelines and attempt to reign in some practices, scientists are lining up on both sides of the argument. One argument put forth by those who favor unrestricted use of autologous stem cells is that such therapies are no different from bone marrow transplantation or *in vitro* fertilization (IVF), both of which fall under the rubric of medical practice and hence are subject to oversight by state medical boards in the US. In fact, as if to promulgate this line of thinking, last April, the Texas Medical Board, at the urging of Governor Perry, instituted a set of state regulations to oversee the use of stem cells as investigational drugs, essentially doing an end run around the FDA and putting local institutional review boards (IRBs) in charge[3].

Dave Audley, executive director of the International Cell Medicines Society (ICMS) of Salem, Oregon applauds this move, viewing it as a way of bringing more of these treatments on shore and under better control. "We're happy to see that if this could happen in Texas that we might be able to provide treatments in the [US], under the US medical system. From a patient perspective, this would be great, as opposed to having patients travel abroad to access these treatments, where there's very little oversight and transparency," he says.

Another argument is that patients have a right to their cells and they should be able to receive them so long as they have been fully informed that the procedure they are undergoing has not been proven to have any clinical benefit. Patients' own tissues are used routinely in medical and hospital practice for wound healing and heart bypass surgery. Christopher Centeno, the director of Regenerative Sciences, described to US business magazine *Forbes* earlier this year how his company's case with the FDA could help to establish this principle. "We see this lawsuit as a twenty-first century civil rights issue that will define what control you have about the use of your own cells and tissue. If a loved one is dying in intensive care and a well-done study shows that the patient's own cells can be used to help, does the patient get to decide to use those cells or is that a decision for the FDA? Will the patient still be alive while we wait on Washington to issue this decision"[4]?

Table 1 Autologous cell–based therapies in late stage clinical trials

Cell therapy name	Company	Autologous cells product	Clinical status
Ixmyelocel-T	Aastrom	Bone marrow stem and progenitor cells	Phase 3 trials for peripheral arterial disease (PAD) and congestive heart failure (CHF)
Autologous CD34$^+$ cells	Baxter (Deerfield, IL, USA)	CD34$^+$ cells	Phase 3 trials for angina and PAD
Myocell	Bioheart (Sunrise, FL, USA)	Myoblasts	Phase 3 trial for CHF
Chondrosphere	Co.Don	Chondrocytes	Phase 3 trial for cartilage repair
C-Cure	Cardio3 Sciences (Belgium)	Bone marrow–derived and treated with cardiopoietic cocktail	Phase 3 trial for CHF
CD 133$^+$ stem cells	Miltenyi Biotech	CD-133$^+$ cells	Phase 3 trial for ischemia (with bypass surgery)
Autologous muscle derived cells	The Cook Group (Bloomington,IN, USA)	Muscle-derived cells	Phase 3 trial for urinary incontinence
MACI	Sanofi	Cartilage-derived cells	Phase 3 trial for cartilage repair

The devil in the details

The argument that any particular preparation of autologous stem cells is exempt from regulatory review can fail on several grounds. To be exempt (to be 21 CFR 1271 compliant in the eyes of the FDA), cells must be minimally manipulated, a requirement intended to protect the cells against contamination and adulteration, and to protect the patient from the possibility of infection. Some practices, particularly in the orthopedic and cosmetic sectors, avoid culturing or expanding cells—culturing only to identify appropriate cells—to stay out of the FDA's purview.

But others not only expand cells, but also claim to direct the differentiation pathway of stem cells along particular lines depending on the intended use (http://www.regenocyte.com/the-regenocyte-process.html). Celltex's procedures are not publicly available, but information gleaned from blog posts of Celltex customers suggests that cells are cultured for some time. Regenerative Science, which had been offering a cultured product (Regenexx-C) until the FDA stepped in, now offers only same-day service (Regenexx-SD). Speaking of Celltex, Buckler says, "I wouldn't try to understand their strategy. It boggles my mind why you would consciously invite this

fight with the FDA. It also boggles my mind how you would set this up and not think you were inviting [them]."

However, a counterargument has been made that with IVF procedures, cells are likewise cultured and stored before being reimplanted in patients. Marlene Angel, director of an IVF laboratory, who also inspects IVF sites for the College of American Pathologists, in an affidavit submitted in behalf of Regenerative Sciences in the FDA's case against the company, said that the laboratory conditions she observed at their site were superior to those she has observed in IVF laboratories. Furthermore, she attests that were IVF laboratories or stem cell clinics held to the same standards as manufacturers of drugs or devices, the cost would be prohibitive. In a recent paper in response to the European Medicines Agency's (EMA; London) publication of a guidance on the use of bone marrow–derived stem cells, Natividad Cuende, executive director of the Andalusian Initiative for Advanced Therapies in Seville, Spain, made a similar argument. "Depending on the patient, hospitals will be able to process the bone marrow (for bone marrow transplantation in immunocompromised patients receiving an allogeneic product) or will be obliged to send it to a company for processing with the attendant costs (for immunocompetent patients receiving their own cells)[5].

A second requirement for exemption from oversight is that the cells be put to homologous use, as when bone marrow–derived stem cells are used to replenish the blood-forming system of cancer patients. Whereas adipose-derived stem cells have been reported to have a multitude of properties *in vitro* (adipogenic, osteogenic, chondrogenic, myogenic, neurogenic, pancreatic, as well as immunomodulatory and anti-inflammatory[6]), and are accordingly being applied to various conditions (including diabetes, arthritis and cardiac conditions), no evidence has been gathered to show the cells perform these functions *in vivo*. Paul Simmons, Executive Vice President, Corporate Research and Product Development of Mesoblast, a Melbourne, Australia, stem cell company says, "I'm not aware of anything in the literature that speaks of any cells derived from fat tissue to generate functional load-bearing bone tissue. It's all based on *in vitro* assays, which in fact we and others have shown …do not predict *in vivo* biological properties."

Is 'first do no harm' enough?

People on both sides of the argument would agree that patient safety has to be the overriding principle in deciding whether to offer treatments. And the fact that autologous stem cell preparations isolated from bone and adipose tissue, about which the most is known, are not immunogenic—and in fact have immunomodulatory properties—might provide safe harbor for those wishing to provide this service. Even so, for many researchers, this is not ample justification. Melissa Carpenter, a former cell therapy researcher both in academia and industry and now director of the consultancy Carpenter Group in San Diego, says, "Just because it's not overtly unsafe, it doesn't mean that it's okay. In my view, it needs to be tied to some reasonable expectation that it will benefit the patient." Stanford University's Irv Weissman agrees and worries about the long-term effects of programs offering unproven treatments. "[Even if there are] no safety signals, the danger is that the field will be polluted and that real advances won't be believed," he says.

But Buckler points out that not everything requires approval. "We've set up this framework where you can treat patients with stem cells or cells that are not officially approved, we've facilitated that. It's okay, you just can't step over certain lines," says Buckler. The attitude among some practitioners and companies is that they can "hit the market with something that they [can legitimately] claim is minimally manipulated and [is for] homologous use, get a few key opinion leaders using it, then sell the product, make a good margin and if the FDA comes and slaps them, then they'll just pull out," he says.

Whereas at one time, Americans had to travel to exotic places like Thailand or Russia to receive such treatments, there are places now in the US and its territories that provide these services; indeed, if Governor Perry has his way, such facilities will make Texas the Mecca of stem cell therapy. In a letter to his medical board, sent as they were working on the adult stem cell guidelines, Perry wrote, "It is my hope that Texas will become the world's leader in the research and use of stem cells….With the right policies in place, we can lead the nation in advancing adult stem cell research that will treat diseases, cure cancers and ultimately save lives."

For some stem cell proponents, this represents their worst fears come to pass. As David Bales, chairman of Texans for Stem Cell Research puts it, "One thing that we've always been afraid of is stem cell tourism. And I now feel like it's taking place in our backyard."

Laura DeFrancesco, Pasadena, California

Box 2 FDA guidelines

Autologous cells are regulated by Center for Biologics Evaluation and Research as human cells, tissues, and cellular and tissue-based products (HCT/Ps) under the authority of Section 361 of the Public Health Service Act, as well as Title 21 of the Code of Federal Regulations (CFR) Part 1271, following a tiered regulatory approach that is based on the degree of risk posed by the products. For lower risk products (so-called 361 products), the regulatory framework focuses on minimizing the risk of transmission of infectious diseases. Higher risk HCT/P products (351 products), those presenting greater risks in their processing or use, are subject to licensure and must be shown to be safe and effective. To receive a 361 designation, a product must: be minimally manipulated, perform the same basic function in the donor as the recipient (homologous use), not be combined with other agents and not have a systemic affect.

Whether there is a need to alter the guidelines is debatable. Joyce Frey-Vasconcells, former deputy director of the FDA's Office of Cellular Tissue and Gene Therapies Division (now a consultant with PharmaNet of Princeton, New Jersey), thinks the FDA has done its job in terms of creating the guidelines, but perhaps not in the dissemination. "I don't think the rules are that onerous, [they] are serving the public very well…. Quite frankly, people are just not aware [of the rules]," she says.

But for those straining under the current regulations, ignoring them may not be the best course of action. Irv Weissman, director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, says, "If the FDA is overcautious, then our job is to educate the FDA, not do away with it. Doing away with FDA oversight is walking right into the hands of the people who are the most unscrupulous."

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