

In Vascular Disease, a Sustainable Model for Cell Therapy

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Summary: If there's one word that ought to sum up the goal of cell therapy today, it's sustainability. Certainly that's the hope of using living cells to restore health and function to diseased tissues so that they perform as the body intended them to. But more to the point, in today's tough financing environment for venture-capital-backed start-ups, sustainability is the watchword for companies facing 15- to 20-year development curves. Tissue-engineered three-dimensional organs are complex, decades-long projects. Embryonic stem cells are much simpler in concept but are far from a commercial reality. Between those two extremes of tissue-engineering, however, there exist some well-defined opportunities, notably in the treatment of blood vessel disease. Start-ups Pervasis and Cytograft are gaining clinical validation in those areas.

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In Vascular Disease, a Sustainable Model for Cell Therapy

Therapy

Two start-ups using living cells to restore diseased blood vessels believe they have the right technology, business model, and clinical applications to create a sustainable business around cell therapy.

by Mary Stuart

In the 30-year history of using living cells to regenerate tissue, there have been notable scientific and clinical successes but no business successes--at least not from the standpoint of investors.

The development cycle and the clinical model for cell therapies are unlike those of either pharmaceuticals or devices and as a result, the field must develop its own investment and business models.

Between the two extremes of tissue-engineered three-dimensional organs and embryonic stem cells are some well-defined opportunities, notably in the treatment of blood vessel disease.

Start-ups Pervasis Therapeutics and Cytograft are gaining clinical validation in those areas.

The firms share attributes that take some of the risk out of the equation: they re using simple sets of cells characterized before implantation, gaining proof-of-concept in an application that validates and advances the technology platform, targeting clinical indications with clear end points and measures of cost-effectiveness, and operating on lower budgets than the tissue engineering companies of the past.

If there s one word that ought to sum up the goal of cell therapy today, it s sustainability. Certainly that s the hope of using living cells to restore health and function to diseased tissues so that they perform as the body intended them to. But more to the point, in today s tough financing environment for venture-capital-backed start-ups, sustainability is the watchword for companies that have already faced, or will face in the future, 15- to 20-year development curves. First-generation tissue engineering companies Advanced Tissue Sciences and **Organogenesis Inc.** spent hundreds of millions of dollars on diverse research programs before filing for bankruptcy in 2002. Their products tissue-engineered skin substitutes are back on the market today, but neither market-leading *Apligraf* from Organogenesis nor *Dermagraft* (now sold by **Advanced BioHealing Inc.**) have yet recouped the hundreds of millions of dollars invested in them. Next-generation organ replacement company **Tengion Inc.** has already raised more than \$170 million (most of it before the recent economic downturn) for its platform for using autologous cells and scaffolds to recreate the bladder and other tissues. [W#200530320] [W#200630369] [W#200730727] The company is only in Phase II on its first program, an autologous tissue-engineered bladder, where it will serve, at best, a few thousand patients per year, and it will need to raise more funds in the future. Tengion appears to have successfully recreated an entire organ from cells and biomaterials one that can grow with the patient--a breakthrough. But while there ought to be a model that sustains companies with outstanding science that serve dire medical needs particularly in children (one of Tengion s target populations)--this is not the kind of scenario venture capitalists like these days.

One venture capitalist recently pointed out to *START-UP* that if several private companies have recently closed their doors it s because they had already raised more than \$150 million in a device market where most acquisitions last year didn t exceed \$175 million, and they were facing the prospect of investing in expensive clinical trials. There probably can t be too many more Tengions in this type of environment.

Granted, the aforementioned cell therapy companies took some of the most difficult pathways through tissue engineering, in terms of creating complicated products made up of multiple cell types and biomaterials, and attempting to understand how they all work together, which translate into more time, more money. Those types of complex products also face the challenge of scaling up with a reasonable cost of goods, calling into question the ultimate return for investors.

Risks still abound. Failed clinical trials have put a damper on some sectors of the industry, in some cases underscoring just how much we don't know about how, when, and where to deliver which kinds of cells. In cardiac cell therapy for the regeneration of damaged heart tissue for example, large and expensive clinical trials have disappointed, notably the MAGIC study, the largest cardiac cell therapy trial (at the time), sponsored by **Genzyme Corp.** and **Medtronic Inc.**, abandoned in Phase II. (*See "Cardiac Cell Therapy: Are There Easier Ways to Restore Function? Probably," IN VIVO, November 2006 [A#2006800195].*)

Recently, the lay press has rallied around stem cell science, especially as the Obama administration has begun to relax restrictions on the development of embryonic stem cell lines. Research is set to bound ahead, although the noise level is deceptive; there are no embryonic stem cell treatments in the clinic.

Despite all these disclaimers, there are potential cell therapies where the technology, the applications, and the markets appear to be lining up to provide real and defined product opportunities. Blood vessel disease is one of them, offering for its developers the ability to apply a single platform technology to a variety of markets with great revenue and reimbursement potential. (*See Exhibit 1.*) These include improving vascular access for hemodialysis, peripheral artery disease, abdominal aortic aneurysms, and, to a lesser extent because it is already well served by other kinds of technologies, coronary artery disease.

In blood vessel repair, two start-ups are seeing opportunities with important clinical needs, substantial patient populations, hard clinical end points by which to demonstrate clinical and cost-effectiveness, and the ability to leverage a single core technology over multiple markets. **Pervasis Therapeutics Inc.** is delivering endothelial cells on a matrix as an adjunctive treatment that improves the outcomes of vascular interventions in patients with end-stage renal disease who need arteriovenous access (AV) for hemodialysis, as well as peripheral artery and other vascular diseases; **Cytograft Tissue Engineering Inc.** is advancing a tissue-engineered vascular graft. Both these firms point out that the ability to create multiple applications from a single technology platform has made mesenchymal stem cell therapy company **Osiris Therapeutics Inc.** successful in dealmaking with its model of keeping certain applications for itself, and out-licensing others by indication and geographic market, for a source of licensing fees and manufacturing revenues.

In November 2008, Osiris sold to Genzyme commercial rights outside the US and Canada, territories which it keeps for itself--on its Phase III anti-inflammatory treatments *Prochymal* and *Chondrogen*. The potential value of the deal is almost \$1.4 billion--\$75 million up front, \$55 million in July 2009, \$600 million in regulatory milestones (if Genzyme goes forward with both products), and \$650 million in sales milestones (for both products). [W#200820619]. *Prochymal* is in Phase III for graft-versus-host disease and Crohn's disease, and *Chondrogen* is in Phase II/III for osteoarthritis of the knee. Earlier in the year, Osiris had divested its *Osteocel* bone matrix business, including a processing facility, to **NuVasive Inc.** for \$35 million up front and up to \$50 million in milestones, and the cell therapy company has an opportunity for ongoing manufacturing revenues. [W#200810078]

Pervasis and Cytograft are already making plans to follow the lead of Osiris, in staying focused on a single, lucrative application, for the time being, and partnering out the rest.

Exhibit 1

US Vascular Market Opportunities

Application	Open	Minimally Invasive	US Market
AV Access			
AV Graft	60K	100K	\$180M-\$480M
AV Fistula	87K	75K	\$260M-\$485M
PAD/LLI	300K	800K	\$900M-\$3.3B
Peripheral Sub-Total	447K	975K	\$1.3B-\$4.3B
Coronary Stent	-	1M	\$3B

SOURCE: Pervasis and MDA Consulting

Pervasis Cells Restore Function, Not Structure

Pervasis approach to delivering living cells is about as simple as it gets. The company's product is tissue-engineered endothelium, the single layer of cells that lines all blood vessels, and its initial applications include hemodialysis access grafts and peripheral artery disease. Rather than reconstructing tissue, the company says it is regenerating the function of healthy blood vessels with a cell therapy formulation that uses only a single cell type allogeneic endothelial cells derived from the aorta in a matrix.

Pervasis is relatively young, but its technological roots go back to Reprogenesis, which was founded in 1993. One of Reprogenesis's technologies was an endothelial cell therapy licensed from the **Massachusetts Institute of Technology** (MIT) where it originated in the laboratory of Elazer Edelman, MD, PhD, a cardiologist as well as director of the Harvard-MIT Biomedical Engineering Center. Helen Nugent, PhD, VP of research and development and a co-founder of Pervasis, became involved with the endothelial cell platform as a post-doc at MIT and followed the program to Reprogenesis. After Reprogenesis merged with Ontogeny and Creative BioMolecules to form regenerative medicine company **Curis Inc.** in 2000, the rights to tissue-engineered endothelium reverted back to MIT in 2002. [W#200010037] (*See "Ontogeny Grows the Family Tree," IN VIVO, March 2000 [A#2000800044].*)

In 2004, the endothelial cell platform found a new home in Pervasis, launched with seed funding from MIT's Deshpande Center, (which provides commercial opportunities for technologies emerging from the MIT School of Engineering), Polaris Ventures, and Flagship Ventures. To date, the company has raised \$29 million, with additional venture capital from Highland Capital Partners and Musket Research Associates. [W#200430212] [W#200730028] [W3200830037]

Pervasis unique approach to healing vessel disease (a category that includes the damage to vessels caused by balloon angioplasty or stenting, the injury from cutting and joining two vessels in an anastomosis to create an AV access, coronary bypass or peripheral bypass graft) involves delivering endothelial cells attached to matrices to the adventitia of a blood vessel.

It might seem counterintuitive that Pervasis delivers its therapy to the outside covering of the vessel rather than the inside where the damage occurs. Nugent says that in the early days, when Edelman would describe this method, people would say, "That's crazy. How do you expect cells in the adventitia to control what's happening on the luminal side?" But disbelievers weren't counting on the fact that the endothelium is more than a barrier that facilitates smooth blood flow; it's also a regulatory organ that influences inflammation, thrombosis, restenosis, negative remodeling, and every phase of an injury response, Nugent says. Besides, endothelial cells aren't found only inside major vessels, they are also contained within the vasa vasorum, the tiny network of vessels that supplies blood to the larger vessels. By boosting the presence of endothelial cells on the outside of vessels, Pervasis is simply enhancing the sort of regulation that healthy endothelial cells provide.

While others are working on vessel health from the inside of the vessel stent companies like **OrbusNeich**, for example, which has a coated stent designed to capture endothelial progenitor cells, Pervasis has shown in early clinical trials that it can elicit a desired therapeutic effect by working from the outside in. That's because the company is relying on the paracrine function of the endothelial cells it implants—the factors that the living cells secrete, which diffuse into blood vessels. (The compounds pervade the blood vessels, hence the name Pervasis.) "We are putting the cells in a different place than they would normally be, but we are providing functional control. That separates us from other companies in the space," Nugent says.

Letting Endothelial Cells Do the Work

Pervasis's IP involves several aspects of working with endothelial cells: the delivery of the cells to the outside of the vessel, the incorporation of the cells in matrices that help promote their functionality during a key window of healing before the entire product is resorbed, and a process for selecting cells at a particular phase of development and adhering them to a delivery matrix.

The advantages of the Pervasis cell therapy are in part due to the way endothelial cells are embedded in the company's bioabsorbable collagen matrix, Nugent explains. Endothelial cells are anchorage dependent, so merely injecting them as free-standing cells wouldn't be effective. "The endothelium doesn't float around in the body, it is attached to the blood vessel. Endothelial cells are contact inhibited. They like to have neighbors, and when they sense that they are touching other cells on all sides, they perform their regulatory functions. Sparse endothelial cells see themselves as injured, which results in a different phenotype and function," she says.

To test out its hypothesis, Pervasis studied the delivery of freely circulating endothelial cells as compared with cells embedded in its matrix, and found that compounds important to immune regulation are down-regulated when the cells are on the matrices. According to Nugent, adhered onto the matrices, the host doesn't see the cells as foreign. "The endothelial cell has a bottom and a top," she says. "In the body, only one side would be exposed, and we are replicating that by having the top side exposed and the bottom side attached to the matrix."

In fact, the Pervasis cell-plus-matrix combination, called *Vascugel*, accomplishes several things. The matrix helps keep cells healthy in the storage vial such that the product has a shelf life of three weeks at room temperature, which is unheard of in the cell therapy field, says president and CEO Frederic Chereau; many cell therapy products on the market generally have shelf lives of only hours to days. The matrix also helps the cells behave as though they are in a healthy environment when they are delivered to the adventitia, where they're also protected from blood flow and the inflammation response that's going on inside the vessel.

Pervasis has at least one other trade secret; a method for characterizing and formulating cells so that they are implanted on the matrix at a specific point in their life cycle. "One difference between us and other cell therapies is that our cells are already differentiated. We know what their function is. We are not implanting them and asking them to differentiate into something else or to figure out where to go. They are functioning the moment we place them in the body, because we have formulated and characterized them that way. That is

part of our IP," Nugent says.

For both clinical and commercial reasons, the company has chosen to work with allogeneic rather than autologous cells. Nugent points out that autologous cells from diseased patients may not make the best therapeutic products and allogeneic cells offer logistic and economic benefits in scale-up. The company is creating master banks of allogeneic endothelial cells and one donor can create 200,000 doses of product, according to Chereau. The company is not discussing pricing, but Chereau says it will enjoy a reasonable cost of goods.

Focusing on the Right Applications

With a single platform, Pervasis has before it potential applications in vascular injury and other types of inflammatory settings including general wound healing, bone and joint injuries. But Pervasis knows that it has to gain proof-of-concept in an indication that will both encourage funding for future large market indications and advance its platform for those future markets. The company thus began developing *Vascugel*, its first cell therapy product, as an adjunctive therapy to improve arteriovenous access for hemodialysis. That market, although relatively small, has several attractive aspects. It addresses a serious unmet clinical need; the device is delivered via an open surgery, allowing validation of the implant before minimally invasive versions are developed; safety can be monitored closely because clinicians follow patients every other day in the course of hemodialysis treatments; and there are clear-cut outcomes measures that support clinical proof-of-concept and economic benefits. Finally, it is a very difficult indication; a large number of end-stage renal disease (ESRD) patients have diabetes, and they are prone to higher degrees of endothelial dysfunction. A win in that indication really does pave the way for other difficult diseases such as peripheral artery disease.

Chereau started his career in nephrology (before he joined Genzyme where he was most recently VP and general manager of Genzyme Cardiovascular as well as COO of Genzyme's cell therapy joint venture with Medtronic). He says, "Nephrologists see hemodialysis patients every other day. There are no other diseases where you have such regularly recurring contact between the doctors and patients. When I would talk to doctors, they would tell me there were three major issues. The first two, anemia and phosphorous management, have been resolved. The third one was AV access."

Between 300,000 and 350,000 patients in the US with end-stage renal disease undergo hemodialysis and all require a vascular access site from which to draw out and return blood. There are two principal options for vascular access. Clinicians prefer to use native tissue to create an arteriovenous (AV) fistula by a surgical procedure that connects a vein near the surface of the arm to an artery. The second option is an AV graft, which replaces the vein with a synthetic tube, usually made of ePTFE (expanded polytetrafluoroethylene).

Synthetic grafts are immediately accessible, but have higher failure rates than AV fistulas, as well as higher rates of intervention for such problems as thrombosis, vessel stenosis, and infection. Sources vary, but on average, 80% of AV fistulas are patent at two years compared with only 40% of grafts. (This difference however, is somewhat overstated, as a relatively large proportion of AV fistulas perhaps 20%--fail to mature for hemodialysis, and these initial failures aren't included in patency statistics). At one year, the primary unassisted (without additional intervention) patency of grafts is only 23%. For that reason, the Centers for Medicare and Medicaid Services (CMS) is pushing for a majority of patients to have the AV fistula option. However, the split between fistulas and grafts is only approximately 50-50 today, because many hemodialysis patients have diabetes and other co-morbidities that impact the quality of their veins. As noted, many fistulas, which can take up to six months to mature enough so that they can withstand high blood flow and repeated needle sticks, don't ever mature sufficiently. This is a problem waiting to be solved; and in addition to Pervasis, and Cytograft, device companies like **Bioconnect Systems Inc.** and **Hemosphere Inc.** hope to improve upon the grafts, and drug companies like **Proteon Therapeutics Inc.**, which closed a \$50 million Series B round in May 2009 [W#200930070]--want to play their part in keeping blood flowing smoothly. In short, there is a great deal of interest in this space, both because it represents an unmet clinical need and because it opens the door to other vascular disease markets.

In December 2008, Pervasis completed its Phase I/II safety trial called V-HEALTH which, in addition to safety, was also designed to give early hints of efficacy to help the company determine its first market indication. In that trial, investigators used an implantable version of *Vascugel*, a tacky patch that surgeons applied with forceps to the vessel without sutures. The trial was a double blind, 2-to-1 randomized placebo-controlled study of 65 patients in which the company looked for primary end points at four weeks including local infection, the need for interventions to treat access complications, and acute thrombosis. Secondary end points reviewed at six months included incidence and duration of patency, measurements of luminal diameter, signs of vein remodeling, and immunological sensitization.

The placebo-controlled group experienced more than twice the rate of local wound infection and thrombosis and an increase in the need for access intervention at four weeks. Efficacy trends were more dramatic for the group that received an AV graft (as opposed to a fistula). At 24 weeks, the *Vascugel* population had a primary patency rate of 49% compared with 25% in the placebo-controlled group. It was a small trial, but, says Chereau, it achieved the company's primary safety end points and revealed some strong trends to help the company formulate its strategy.

Cell Therapy versus Capital Efficiency

In April 2009, the FDA granted Pervasis an Orphan Drug Designation for *Vascugel* for the prevention of AV fistula or graft failure. The company is now set to begin Phase III in the AV graft indication, for which it is seeking a partner. Chereau's next near-term challenge is to raise approximately \$15 million to conduct a Phase II clinical trial for the minimally invasive treatment of interventions related to peripheral artery disease. For this indication, Pervasis is developing an injectable formulation of cells plus matrix particulate, which it plans to deliver via a needle adjacent to the adventitia of peripheral arteries under ultrasound guidance.

The peripheral vascular market is enormous and open, because drug-eluting stents aren't approved for use in peripheral vessels nor do they show any benefit there. At the recent EuroPCR (European Association of Percutaneous Cardiovascular Revascularization) meeting in Barcelona, Pervasis presented promising preclinical results on the ultrasound-guided delivery of its injectable therapy (PVS-10200) to the outside of porcine arteries following angioplasty and stent treatment. After 90 days, the treated arteries demonstrated a 50% decrease in percent occlusion compared with a sham control, Nugent says. Having already demonstrated safety in the AV graft application, the company is ready to file an IND and quickly move on to Phase II. Meanwhile, Pervasis is also working on developing a catheter that will deliver therapy with a needle inserted through to the outside of the vessel from within the lumen for broader cardiovascular applications.

Cytograft Redefines Success in Cell Therapy

For its part, Cytograft aims to operate in many of the same markets as Pervasis, but in a different segment. It is developing a tissue-engineered blood vessel designed to serve as an implantable graft for AV access in the hemodialysis patient, for coronary or peripheral artery bypass procedures, as a replacement graft for abdominal aortic aneurysms, and as a patch for endarterectomy procedures. Cytograft cultures autologous endothelial cells and fibroblasts from biopsies taken from patients into sheets of living tissue fused into multi-layer vessels; no synthetic scaffolds are used in the process.

CEO Todd McAllister, PhD, doesn't want to see any more failures in the field of tissue engineering, he says, and he wants to make it clear to investors that the business models for cell therapy can't replicate those of the first-generation companies such as Advanced Tissue Sciences, Organogenesis, and Systemix Inc. (acquired by **Novartis AG**)--which, he points out, cumulatively had research budgets that exceeded \$3 billion between 1990 and 2001. He holds up Cytograft as a model of a company that has the right pace, burn rate, and scientific approach for a field that is distinct from either medical devices or pharmaceuticals.

With 15- to 20-year development time lines and therapies that cost in the double-digit thousands of dollars, he says, it makes little sense to talk about getting to market as fast as possible with the easiest niche application,

the value of IP protection, or, on Day One, margins and manufacturing scale-up--the types of questions venture capitalists might ask about traditional medical device and biotech start-ups.

McAllister might adopt this stance, since, founded in 2000, Cytograft has only one 10-person clinical trial to report upon, and at its present stage, the company appears to have one of the most difficult product models yet proposed. Its first product requires a six- to nine-month lead time to engineer autologous tissue into a blood vessel. From a patient biopsy and a 2- to 3-cm segment of the superficial vein from the back of the patient's hand, the company extracts the appropriate cells and grows a new blood vessel. Depending upon the patient, that process takes between six and nine months. McAllister acknowledges that this time lag doesn't lend itself to the most clinically or commercially feasible product, but he says that the technology will improve, and even under the current autologous cell sourcing scenario, Cytograft has a model that is both clinically and commercially viable. "We can make the product for less than what we are likely to receive for reimbursement, and we can identify the vast majority of patients who can tolerate the wait time well in advance." But, McAllister adds, "Obviously our hope is that we are able to replicate the positive results we have had in the autologous setting with an allogeneic model."

Again, according to the standards of a typical VC-backed device company, that rate of progress might not be a cause for jubilation on the part of investors. But McAllister believes his company is on the right track. "Our philosophy is that this is a very new field. So rather than making clinical mistakes, killing patients, or risking adverse reactions that turn the regulatory agencies against us, we took an extremely conservative pace through our clinical trials. We have had a big stagger between patients, and long periods of observation, so we can sit back and see the results, then make appropriate changes to the process." McAllister also points out that there is no competition yet, which affords the company its cautious pace.

"While we had a generally positive clinical trial, and we have made good progress, obviously we have not solved all the problems yet, and we are still evolving through the manufacturing changes and the science to make this work," he says. But McAllister wants to emphasize one point: his company has spent, to date, less than \$10 million in private equity.

The First All-Human Tissue-Engineered Blood Vessel

Cytograft is working entirely without synthetic materials no ePTFE or *Dacron* to help shore up vessels against burst pressure or the ravages of needle punctures, and that requires making a multi-layer vessel in several steps.

The cornerstone of its technology is the ability to turn fibroblasts taken from skin and the extracellular matrix proteins they make into a sheet. That takes as little as three weeks, McAllister says; the time-consuming part of the product generation process involves detaching the sheet from the cell culture substrate, rolling it around a temporary mandrel, and going through a secondary maturation phase, where the individual plies of rolled sheet fuse together to form homogenous tissue, which generally takes about 12 weeks and is repeated twice.

"We started with arguably the most complex and difficult model from a commercial standpoint," McAllister says, "but the one that is most likely to work from a scientific and clinical perspective. Our philosophy is that if it works in this relatively complicated autologous environment, transitioning to allogeneic is probably a lot easier from that point." He adds that the company is beginning to prepare protocols for allogeneic applications. "We have spent our money on those problems that were the most difficult to solve. But the ways of speeding up fusion are engineering and bioreactor or media design processes, which in general are more defined and easier to solve than the biological challenges."

An Ideal Proof-of-Principle Market

Later this year, Cytograft plans to spin out development of certain of its potential applications in sheet-based tissue engineering a graft for AAA repair, a percutaneous bypass approach, and an endarterectomy patch to

entities with separate management, separate funding, and separate facilities, but in which Cytograft will hold a large stake. Meanwhile, it will focus on its proof-of-principle market, the AV access application in ESRD, where the treatment infrastructure and the economics support a tissue-engineered blood vessel. Patients with ESRD have a life expectancy of six to eight years, and each year, hundreds of thousands of patients are evolving through the disease. "Identifying the risk factors to determine which patients are most likely to suffer a graft failure is easy, based on co-morbidities, or the best correlate, which is previous graft failure," says McAllister.

An ESRD patient who is just beginning dialysis is not a target for the Cytograft product, because that patient will probably start with an AV fistula made from his or her own tissue. But the average life span for tissue fistulas or synthetic grafts is between 12 and 24 months.

With ePTFE grafts, one of primary failure modes is distal intimal hyperplasia. "You have turbulent flow coming through this plastic graft because it is non-compliant, and the turbulent flow downstream triggers cellular changes that result in intimal hyperplasia," says McAllister. That process happens relatively slowly, he adds; it is relatively predictable and a physician can see it happening just by looking at venous back pressure in the dialysis machine. "So here you can identify patients well in advance of the clinical need to revise the graft based on clinical presentations that you can see three times a week," he says, because the patient is undergoing a regimen of dialysis.

That kind of patient surveillance and relationship isn't available in the CABG and lower limb applications, for example, where physicians see patients only if there is a problem--another benefit of hemodialysis for helping the company go up the learning curve. Finally, in hemodialysis, there is a bailout mechanism for patients whose access sites fail the catheter, which can last from weeks to months. "Here we have the perfect clinical model to bridge that patient to longer-term solutions," McAllister says.

As for the economics of Cytograft's autologous product, McAllister believes his company will be able to sell the device for roughly \$25,000, a significant premium over the cost of the native vein fistula (an AV graft adds \$2,000 to \$3,000, for a synthetic tube). "Each intervention for thrombolysis, to treat infection, or balloon dilation to keep an AV access graft patent--costs, on average \$10,000," McAllister says. "You will frequently go through three to five of these different procedures before the graft finally fails and you have to replace it. In the subset of patients that the company has been looking at in its clinical trial, [patients with one previous access failure who are on course to fail again] that intervention rate is between one and three per year." If Cytograft decreases the intervention rate by one or one-and-a-half interventions per year, and its graft lasts as long as a ePTFE graft, or about 18 months, it will reduce treatment costs by \$20,000 over 18 months. Those are the kinds of cost savings Cytograft will need to investigate in large clinical trials.

Indeed, that's one final point that McAllister makes about the unique requirements of cell therapy. "It will take fewer patients to demonstrate safety and efficacy to the FDA than it will to demonstrate cost-effectiveness to CMS. Some of these cell-based therapies have to work significantly better than the standard of care because they are more expensive. We are budgeting long term for the CMS study," he says. Cytograft will thus be ready if, one day, comparative effectiveness begins to dictate which therapies will be reimbursed for which patients.