From women's health to cardiology: Cytori grows potential of cell technology

Chris Calhoun

In the past year, regenerative medicine specialist Cytori Therapeutics has been piecing together a puzzle that it hopes will lead to success for its lead product, the Celution system. Used to enrich fat grafts, it is already available for breast reconstruction, but could have myriad other uses, including cardiovascular therapies. However, clinical evidence and reimbursement are key for boosting uptake, the firm's CEO Chris Calhoun told Madeleine Armstrong

"It's been a very productive year," Chris Calhoun, CEO of Cytori Therapeutics, a specialist in medical technologies that provide access to the body's adipose-derived stem and regenerative cells (ADRCs), told *Clinica*. The company has been focusing on building the evidence base for its lead product, the Celution system, which is used to enrich fat grafts.

The product is already available in Europe, having first been CE marked in January 2006 as a generic tool for extracting ADRCs that can then be re-implanted into the patient for clinical benefit. Last July, Cytori expanded the CE mark to include new and more specific indications including using the extracted cells for breast reconstruction, repair of soft tissue defects, and to help the healing of certain wounds, such as fistulas resulting from Crohn's disease (www.clinica.co.uk, 29 July 2010). It also includes its use for aesthetic procedures such as breast and buttock augmentation.

One of the most common applications for the product is breast reconstruction, for example in breast cancer patients who have undergone lumpectomy or partial mastectomy. These patients cannot receive breast implants as they cannot be fitted to the exact size of the defect. Another option is conventional fat grafts, which are not supplemented with cells. However, these also have their drawbacks. "Fat grafting can work for small volumes, but if you're going to do larger volumes, say for breast reconstruction, you really want to supplement that fat graft with cells to get the graft to persist," Mr Calhoun said. Celution provides a more stable and predictable result than traditional fat grafting, and could also reduce the times it takes to get to a satisfactory result, Cytori claims.

Proving Celution's efficacy is integral to the San Diego, California firm's step-by-step approach to getting its products to market, Mr Calhoun explained. There are three pieces to the puzzle: approval, evidence and reimbursement. "First, we get the device approved in a very generic way," he said. "But it's not enough just to put the tool on the market – you need the discipline of doing clinical trials, which generate data that not only help us market the product but also to get specific label claims. These claims and the data will help us get reimbursement. Once we have that, we can really build a channel around the specific market."

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"Just getting something on the market does not necessarily mean you can sell it broadly," he added. "That's not our strategy. And it's not been what we've done."

Indeed, gathering evidence in support of Celution has already proven to be important. The expanded CE mark was based on results from the RESTORE 2 study in 71 partial mastectomy patients in Europe. The results found that at six and 12 months, patient satisfaction levels were 73% and 75%, respectively, while physician satisfaction levels were 82% and 98%.

A separate UK-based study followed up 23 patients who had received Celution between three months and two years previously for breast contour defects following cancer treatment or benign conditions including implant complications. Last month, the researchers reported that 82% of patients reported good-to-excellent results, with a mean satisfaction score of 5.1 (the scale ranged from 1 at worst to 6 at best). The mean investigator satisfaction score was 4.3, and there was a low rate of complications. The investigators concluded that the procedure is a viable option for breast reconstruction with no safety concerns. The results were presented at the Association of Breast Surgery Conference, held in Manchester, UK, on 16-17 May.

Reimbursement is key

The next step in Europe will be reimbursement. "We're working pretty closely with the UK's National Innovation Centre (NIC), and European reimbursement agencies," Mr Calhoun said.

But as for widespread adoption of Celution, the firm is not quite there yet. "We have seen an increase in utilisation [of Celution] in general, but nothing that shows we've reached an inflection point where something changed, leading to widespread penetration of the market," he conceded. "Being successful depends on all the ingredients coming together. We've got a number of the pieces in place and we're working hard to add the reimbursement piece. I think when we achieve reimbursement, then you'll really see [Celution] begin to get more broadly adopted."

There is already evidence that the product could save healthcare systems

money, which should improve its chances of gaining reimbursement and boost its uptake. An economic analysis carried out by the UK's National Innovation Centre reported in May that if Celution replaced conventional fat grafting for breast reconstruction, it could save the National Health Service £16m ($26.3m) per year. This is mainly because conventional fat grafting requires an average of three procedures to repair the defect, while Celution – where the fat graft is enriched with ADRCs – typically only needs one or two operations. Therefore Cytori's product could "reduce or eliminate the practice of repeat procedures, leading to significant cost savings for the NHS", according to Brian Winn, head of technology and product innovation at NIC.

The centre's recognition of Celution is important, "since it may support wider adoption of cell-enriched reconstruction within the UK", according to Eric Daniels, managing director for Cytori's European division.

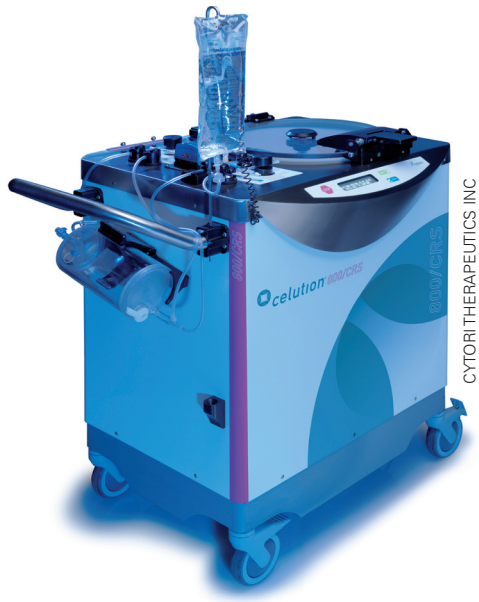
US next?

Cytori is pursuing a similar strategy in the US, where Celution is not currently approved. "We're working with the US FDA for a foundational device approval," Mr Calhoun said, adding this would come in the form of a 510(k) clearance. "The Celution system does have a number of 510(k) clearances, for example one for red blood cell processing, and our [processing] enzyme also has a 510(k) clearance. But we don't sell the Celution system in the US today, because we're going through this process of establishing the foundational device, and then we're going to carry out trials."

Mr Calhoun was reluctant to speculate on when the device might be approved: "It's tricky, because it's something that's really out of our control. As much as we can say is that we're applying for a number of [clearances], and that process takes anywhere from months to a year or two."

But even once 510(k) clearance is in place, it "doesn't all of a sudden open up this massive market for us", he added. "It just means the device part of the equation gets solved, so we can go back to the FDA and look towards therapeutic claims to build on that foundation."

If Cytori can prove Celution's value, it will open up a sizeable market, with around 180,000 new breast cancer patients diagnosed in the US each year, on top of 330,000 per year in Europe. Of these, 70-80% are currently eligible for breast-conserving surgery and, therefore, treatment with Celution. This will only increase with the growing trend towards breast conservation, Cytori believes.



Cytori's Celution 800CRS cell extraction device

In addition, Celution could also be used for breast reconstruction in women who had surgery up to 10 years ago, further increasing the size of the potential market. Mr Calhoun was reluctant to put a value on the overall segment, but Cytori has previously told *Clinica* that the cosmetic and reconstructive surgery market as a whole is worth over $3bn (www.clinica.co.uk, 24 March 2010).

The heart of the matter

Cytori is also developing Celution and its cell output for cardiovascular uses. "We're attacking heart disease on two different fronts, and completed two trials last year, one for acute heart attack and one for chronic heart failure," Mr Calhoun said. "The first looked at treating patients with cell therapy right after their heart attack: at the six-month timepoint we found our therapy had erased about half of the damage done by the heart attack." The study was not big enough to measure the clinical impact of this in the longer term, but existing data suggest that repairing this damage could dramatically reduce the risk of disease progression to heart failure and mortality.

To investigate this, Cytori has started enrolment in a larger 370-patient double-blind, randomised, placebo-controlled European trial in heart attack, called ADVANCE, and expects to report data "in two to three years".

"The second trial was in patients who previously had a heart attack and are now classed as "no-option" chronic myocardial ischaemia patients – they've basically exhausted all their treatment options and are now dying of heart failure," Mr Calhoun continued. "It showed that cell therapy could improve function even in these later-stage patients, and the benefit persisted for up to 18 months." Around a third of the control group, who were treated with the current standard of care, died within two years, compared with less than 5% of the cell-treated patients. However, this difference was not statistically significant due to the small number of patients (six in the control group and 21 in the treatment group).

Based on these results, Cytori hopes to get European approval for patients who have no other treatment options, who number around two hundred thousand new patients a year. Approval could come as early as this year, Mr Calhoun believes. The firm is also planning a trial in the US for this indication.

The cardiovascular product works in the same way as Celution for breast reconstruction, but uses different software and enzymes to increase the purity of the device's cell output, he explained: "When you put cells into tissue, as is the case with Celution for soft tissue applications such as breast reconstruction, there can be collagen fragments and other debris, and it's not a problem, because it improves adherence. But when you put them into the bloodstream, as with the cardiovascular product, you need a very clean, pure cell product, to make sure the cells aren't aggregating and to minimise the risk of blood clots. And that was non-trivial, it took us a couple of years and millions of dollars to figure out how to do that safely before we ever started a trial."

The cardiovascular market promises to be even more lucrative than the breast reconstruction segment. "It's an enormous market. In Europe each year, there are nearly two million heart attacks. Additionally, there are an estimated two million no-option heart failure patients," Mr Calhoun said. "The therapy price we're targeting is around £6,000-7,000 (roughly $10,000) per treatment. So that's a £14bn ($20bn) annual market just for this no-option category." He added that the acute heart attack market is around the same size.

Cytori's platform could eventually be expanded to treat other disorders, including liver and kidney problems, chronic wounds, stroke and peripheral vascular disease. "But as a small company, we have to focus, and we're currently focused on breast reconstruction, with the cardiovascular applications just behind," Mr Calhoun concluded. "It's an exciting time for this new field of cell therapy."