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Cytograft in human trial breakthrough with tissue engineered blood vessel

The first ever human trial of tissue-engineered blood vessels grown from a person's own cells has produced positive early results.

In the two patients to have been implanted with the vessels to date, the devices are still functioning well at the six-and-a-half-month follow-up mark, reported Todd McAllister, president and CEO of Cytograft Tissue Engineering, the Novato, California firm developing the technology.

"We plan to begin commercial sales of our engineered vessel in Europe in 2007"

The creation of a blood vessel substitute has long been a "Holy Grail" in the cardiovascular research community. Man-made vessels would have many important uses – for example, they would provide an option for patients who require coronary bypass surgery but who do not have a healthy autologous vein that can be harvested from another part of the body for "re-plumbing" into the heart. However, the development of a device able to meet the biomechanical and functional demands of a native blood vessel has proved challenging.

Partnering opportunities

"We plan to begin commercial sales of our engineered vessel – called Lifeline

– in Europe in 2007," Dr McAllister told *Clinica*. "There are literally hundreds of laboratories working in this field, which highlights the importance of this work. However, none of the other laboratories have, so far, been able to produce a vessel suitable for clinical use as an arterial bypass." Cytograft is currently looking to link up with venture capitalists or corporate partners in Europe to help commercialise its product.

Regarding artificial bypass grafts made of synthetic materials, only two firms have managed to make inroads in this field. CardioTech International is currently seeking European market approval for its CardioPass graft and CABG Medical is persisting with development efforts for its Holly Graft system, after the device recently failed to meet satisfactory standards in human trials (see this issue, p 16). Commenting on the advantages of a tissue-engineered vessel over a synthetic one, Dr McAllister claimed: "Biomaterials used in synthetic grafts have fundamental challenges associated with chronic inflammation [that can lead to the device becoming blocked and failing]." The CEO admitted, though, that a "completely biological and completely autologous" approach would be more expensive than a synthetic graft. "It remains to be seen whether the scientific advantages of a natural graft will be borne out in the clinic with an **p18** ▶

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Cytograft in human trial breakthrough, cont'd from p1

increase in efficacy that justifies the price premium associated with a tissue-engineered approach."

Cytograft's sheet-based tissue engineering technology involves extracting from a small skin and vein biopsy harvested from the back of the patient's hand fibroblasts and endothelial cells. The fibroblasts build the vessel's mechanical backbone, while the endothelial cells provide its lining; the lining prevents the vessel from clotting. The cells are fed in a culture dish with a proprietary media that over six to eight weeks encourages the growth of high volumes of extracellular matrix proteins, such as collagen.

"At the end of that period, you end up with a robust sheet that's comprised of cells and the proteins that those cells have produced," Dr McAllister said. The sheet can then be detached from the cell culture substrate and rolled, stacked or moulded into more complex three-dimensional organs, such as a blood vessel. "This process is unique in that it is the first technology to use fibroblast-based tissues to provide mechanical strength; historically, tissue engineers have focused on the role of smooth muscle cells," said Dr McAllister. "This is also a novel approach in that it is the first demonstration of an engineered vessel that provides adequate mechanical strength without relying upon synthetic scaffolds or exogenous biomaterials."

"The possibilities are far-reaching – from building vessels to heart valves to flat tissue for other vascular repair"

The human trial of the technology, presented at last month's American Heart Association (AHA) meeting in Dallas, Texas, involved using the engineered vessels in haemodialysis patients. The device was used as an A-V shunt between the humeral artery and axillary vein in two dialysis patients; a total of nine participants are scheduled to be enrolled in the study. "We have time-points out to six and a half months now with no failures."

Lower limb and coronary trials

Cytograft also plans to test its vessel in other indications – including lower limb and coronary – and to enrol more trial patients to achieve a statistically powered study.

"We have an approval to do a clinical study at Papworth Hospital in Cambridge, in the UK, where we will replace the radial artery in heart bypass patients who have had their radial artery harvested for use in the coronary – this study will help transition us into coronary use." Cytograft also intends to expand the Papworth trial protocol to include lower limb bypass and A-V shunts; Papworth will be the second centre in the world to perform this surgery.

"Sheet-based tissue engineering is an opportunity for patients to have an endless supply of vessels made from their own cells for bypass or revascularisation surgeries." However, Dr McAllister noted that there were patient management issues that needed to be addressed, such as trying to identify patients several months in advance to allow time to harvest tissue and grow new vessels.

"The possibilities are far-reaching – from building vessels to heart valves to flat tissue for other vascular repair," Dr McAllister said. "There is also an exciting potential application for paediatric coronary repair, because this is a living product and can grow with the patient."

Cytograft was founded in 2000 and currently employs 12 people. The firm said that the Lifeline engineered blood vessel would be its first product to reach the market.

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Vulnerable plaque imager shows early promise

An experimental spectroscopic/imaging method for assessing plaque in arteries could help pinpoint those lesions most likely to rupture and block blood flow to the heart or brain.

The time-resolved laser-induced fluorescence spectroscopy (TR-LIFS) technique, which could help guide treatment, successfully identified markers of plaque vulnerability including inflammatory cells and a large core area of lipids covered by a thin fibrous cap, according to the results of a feasibility trial.

A catheter-based TR-LIFS device could reach the market in three to four years

There are currently no commercial tests available for identifying vulnerable plaque, believes TR-LIFS investigator Laura Marcu, who, with her research group, is currently moving from Cedars-Sinai Medical Center and the University of Southern California in Los Angeles to the University of California at Davis. Pending further development, a catheter-based TR-LIFS device that can assess plaque composition in coronary vessels and help dictate the most appropriate therapeutic intervention could reach the market in three to four years, Dr Marcu told *Clinica*.

The TR-LIFS apparatus used in the feasibility trial was configured for ex vivo investigations. It consisted of a laser, a fibre-optic probe through which the laser light is delivered to the tissue and the fluorescence collected, a spectrometer, a digital oscilloscope and a computer workstation that provides user interface, co-ordination of components and interpretation software.

The laser pulse heats up or "excites" molecules in the plaque while the researchers measure the "time" that molecules stay in the excited state. This time is specific to different types of molecules, which helps researchers determine the exact composition of the plaque.

Feasibility trial findings

During the feasibility trial, TR-LIFS was used to measure 353 plaque areas in the carotid arteries of 50 patients who had been scheduled to undergo carotid endarterectomy, a procedure in which the carotid arteries are opened and plaque is surgically removed. Following endarterectomy, pathologic examination was used to categorise the plaques as early (minimal thickening), fibrotic (collagen-rich lesions), or high-risk (necrotic core with a thin cap).

These results were then compared with those produced by the fluorescence spectroscopy method to categorise the same plaques as early, fibrotic and high-risk. TR-LIFS was 97% effective in identifying high-risk lesions, according to the study's results, presented at last month's American Heart Association meeting in Dallas, Texas.

Regarding Dr Marcu's plans to test the technology in the in vivo setting, her team is currently developing an intravascular catheter-based system that would permit minimally-invasive evaluation of arteries. "Clinical trials will require collaboration with companies willing to modify their existing intravascular catheters to accommodate fibre-optic probes for fluorescence studies," Dr Marcu said, adding that some companies have already expressed interest in the TR-LIFS technology.

Dr Marcu's group is one of a number of teams working to develop a method of detecting vulnerable plaque (see *Clinica* No 1173, p 22).