



Boning up on mesenchymal stem cells

As it begins Phase IIa clinical trials, Mesoblast is riding high: its share price is climbing, its market capitalisation is booming and all that promise seems to be coming good. Kate McDonald profiles the Melbourne-based adult stem cell company and talks to its founder. Silviu Itescu.

WHILE RESEARCHERS, ethicists and policy makers are consumed by the philosophical debate around embryonic stem cell research and its potential, Mesoblast sidestepped the whole minefield by going straight for the older guys and setting out to develop a range of adult stem cell-based therapies. It wasn't a hard decision for Mesoblast's founder and chief scientific officer, Professor Silviu Itescu, to make, however. While embryonic stem cells have undoubted potential, clinical therapies are years, if not decades, away. If you want to get a product to market, he says, adult stem cells are the way to go.

The sharemarket certainly seems to like his plan. Since listing on the stock exchange in December 2004, Mesoblast has made sure and steady progress in its plan to produce a range of stem-cell therapies, primarily in orthopaedic applications and through its older, US-based sister company Angioblast, in the cardiovascular arena. The stock price has risen gradually, market capitalisation is a very impressive \$230 million, and the company is now showing the safety and efficacy of its products in clinical trials.

Itescu has long had an interest in cardiovascular stem cell therapies, having served as director of transplantation immunology at New York's Columbia University Medical Center, where he and his colleagues have been researching stem cells for use in the treatment of heart disease for many years and where he still holds a faculty appointment. Through his research he came across the work of a group based at the Hanson Institute and the Institute for Medical and Veterinary Sciences (IMVS) in South Australia, which was studying the potential of mesenchymal stem cells.

"I was involved in cardiovascular stem cell therapies and I was open to working with any kind of stem cells that were going to work," Itescu says. "I started to collaborate with those guys [at the Hanson] and evaluated those cells and they clearly were superior to any cells we were working with. At which point I made the transition from academic

to entrepreneur. So I set up a company and took a licence on the technology."

That company was Angioblast, still a privately held company based in the US which originally acquired the entire platform technology for all applications from the inventors. Angioblast was and is focused on cardiovascular disease but the inventors had been primarily working in the orthopaedic area. To further develop these applications, Itescu set up Mesoblast in Australia.

The inventors – Dr Andrew Zannettino and Dr Stan Gronthos, who are still based in Adelaide, and Professor Paul Simmons, who now leads a stem cell lab at the University of Texas Health Science Center in Houston – are still heavily involved in both Mesoblast and Angioblast, acting as consultants and contract researchers and filing further patents. Last year, Mesoblast and Angioblast were granted a valuable patent in the US that gives them ownership of their particular stem cells, correctly called mesenchymal precursor cells.

The company is now moving into Phase IIa trials, one in spinal fusion at the Hospital for Special Surgery in New York and one in cardiovascular disease at the Texas Heart Institute.

"Adult stem cells are the way to go to get something to market," Itescu says. "Embryonic stem cells have the ability to turn into every cell that's known, but that doesn't mean it translates into a clinical product. An adult stem cell product will get into the clinic in a relatively short period of time for various applications, and research will continue with embryonic stem cells. But if you want to put your money into a stem cell based product you've got to do it with adult stem cells in the short term."

Mesenchymal precursor cells

Mesoblast's core technology is based on the identification, extraction and enrichment of mesenchymal precursor cells (MPCs), very rare non-haematopoietic progenitor cells that are found in many types of tissue and that give rise to

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Silviu Itescu





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multipotential cell colonies when isolated and purified. The Hanson Institute inventors discovered that MPCs could be identified by selecting for cells that express the 3G5 and Stro-I cell surface markers and that these cells are capable of giving rise to colony forming unit fibroblast (CFU-F). It is now known that

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bone marrow, dental pulp, adipose tissue, skin, spleen, pancreas, brain, kidney, liver and heart tissue.

The company's patent covers the identification of MPCs via a novel monoclonal antibody and a method of enrichment, including the step of enriching cells based on the two surface markers. Mesoblast has also developed and patented the identifying monoclonal antibody.

"We can pull out the cells to pretty much 100 per cent homogeneity within half an hour and purify the cells completely," Itescu says. "These cells, when they are initially isolated, are quiescent and they can be very precisely controlled in terms of their ability to divide and replicate and give rise to daughter cells. Over a period of about six weeks, from about a million such cells, we can end up with about 10-15 billion cells, precisely regulated and we know how many cells divisions they have gone under and the safety of the manufacturing process can be guaranteed. These cells can differentiate into a variety of tissues such as bone, cartilage, heart muscle and arterial wall and that's where the business opportunities arise."

Crucially, MPCs do not express cell surface antigens responsible for triggering an immune response, which is of enormous value considering the company's big advantage – it can harvest and enrich cells for implantation from non-related donors, not just from the patient him or herself. Autologous stem cell transplantation is one thing – a range of allogeneic products is a whole new ballgame.

"We've now got patents that are not just around how to enrich cells but cells that are enriched," Itescu says. "That's a very strong patent position. Cells that have those markers that are enriched in any way you want mean that you've now got a patent over the cells. If you don't want a pure population of stem cells then we can't stop you – so you can use whole bone marrow and that's okay. But if you want to use a purer product which ought to be more effective, then you'd be infringing our patents."

Probably the only competitor that Mesoblast has in the world in this area is the US biotech Osiris, which already has products on the market. This is a good thing for Mesoblast, Itescu says, as the ground has already been broken with the FDA and Mesoblast can continue in Osiris' slipstream.

Osiris has a range of products in development and on the market, including one called Osteocel, an unexpanded preparation

of mesenchymal stem cells extracted from bone marrow aspirate. It also has products for graft-versus-bone disease, cartilage applications and cardiac applications. For Osiris, however, the enrichment process relies on the adhesion of mesenchymal stem cells to plastic surfaces, meaning that other cells can get caught in the mix.

"When you use plastic adherence you don't grow more than one in a thousand mesenchymal precursor cells so it's a very impure population," Itescu says. "They can't get it any purer than that because then they infringe on our patent. We don't infringe on them and they don't infringe on us and we have two separate populations of cells."



“Osiris is a good company which has proven that an allogeneic stem cell product is safe and they’ve gone to the FDA ahead of us, so they have cleared that path for us. We think that’s great. The market is big enough that there is room for two companies. In my opinion they are the only company besides ourselves that have the right business model. Their market cap in the US is around US\$400 million, so that tells you something in itself.”

Spinal franchise

So the science is proven, the business model is in place, and now for clinical trials. Preclinical trials have been ongoing for a number of years but now the company is moving into the big time. It has two Phase IIa trials starting in the US in spinal fusion and cardiovascular disease, has completed some pilot studies in humans in long bone fractures and early stage intervertebral disc cartilage, and is completing large animal studies in knee cartilage and osteoarthritis.

The New York trial is of an allogeneic product for patients with severe intervertebral disc disease requiring spinal fusion. It is taking place at the specialist orthopaedic Hospital for Special Surgery in New York, led by an orthopaedic surgeon, Dr Joseph Lane. “Once we get started properly in that trial we’ll spread it out to get multiple centres involved,” Itescu says. “That trial is to show that we are as good as autograft, which requires a second operation. And 30 to 40 per cent of people who have that procedure have worse pain for the rest of their lives than they ever had in their back, so if you have a drug that you can put in there that can create as good a fusion, then you have a product.”

Allied to this trial is a preclinical trial for repair and regeneration of vertebral disc

cartilage, which is taking place at the IMVS in Adelaide, led by Associate Professor Robert Moore, who is head of the Adelaide Centre for Spinal Research.

“The idea is to build a whole spinal franchise,” Itescu says. “With early disc disease, all they can do is take anti-inflammatory drugs, which cause ulcers and don’t work very well. So if you have the ability to actually repair the disc ...

“We have embarked on a study in sheep where you actually replace the cells in the existing disc, and we are looking at a three-month study to see if you can increase the disc height.

Of great interest are Mesoblast’s early trials in repairing and regenerating meniscus cartilage in the knee. This is not just aimed at the odd football player who tears his knee cartilage, however: it is the osteoarthritis arena that is most exciting. Preclinical trials in sheep, led by Professor Rick Read at Murdoch University, of allogeneic cells to treat osteoarthritis of the knee have shown very promising results indeed.

“We did [this trial] primarily for osteoarthritis, although we didn’t want to emphasise that because we thought it would be a harder ask,” Itescu says. “If we had a result with osteoarthritis, we’d have a blockbuster, and we have good data now that I’m very happy about.”

The results showed that joint cartilage in osteoarthritic knees had significantly greater thickness, reduced breakdown and greater biomechanical strength three months after injection into the knee than did control joints receiving injections of hyaluronic acid.

Mesoblast is currently designing further trials for this application and

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is extremely hopeful of its potential, as osteoarthritis is at least as great a commercial opportunity as bone repair. The company has also completed a pilot clinical trial of autologous stem cells at the Royal Melbourne Hospital for non-healing, long bone fractures, led by Dr Richard De Steiger. This showed that each of the first five patients followed up have demonstrated complete bony union.

Hearts and deals

While it is Angioblast rather than Mesoblast that runs the cardiovascular sphere, Mesoblast recently completed a pilot clinical trial at the John Hunter Hospital in Newcastle, under the supervision of interventional cardiologist and Hunter Medical Research Institute researcher Dr Suku Thambar. This was also a trial of an autologous product, although Angioblast's bigger Phase IIa in Texas will be with allogeneic cells.

The Hunter pilot trial, which recorded no adverse events from the cells after six months and showed significant improvement in either symptoms of heart failure or in heart function in six patients with severe coronary artery disease and heart muscle damaged, used the platform technology that will be used in Texas to deliver the cultured cells via a new generation of cardiac catheters produced by Johnson & Johnson companies Cordis Corporation and Biosense Webster.

Both Mesoblast and Angioblast work closely with manufacturers such as Cordis and Biosense, as well as the likes of Medtronic, which makes the biomedical support matrix used for delivery of the cells in orthopaedic applications, Itescu is not yet committing himself or the company to exclusive deals with medical device com-

panies, or big pharma for that matter. He is holding his horses for the next 12 months or so as the trials move through the Phase I and II processes and then he'll have a bit more to show the big boys.

"The question is, when do you do the right deal?" he says. "Historically, Australian companies, because they have been low in cash, have done licensing deals far too early. The earlier you do a deal, the worse the terms are going to be. The more results you get, the better the deal.

"You may never want to do a deal but in fact optimally, we don't want to be in the business of funding Phase III trials. Each Phase III is going to cost \$50 million plus. The ideal time to do a deal is at the end of Phase II, when you have results to show the thing works, and then you bring in a partner and they pay for it and become your distributor.

"We are only starting Phase II now so really we have a window to execute those kinds of transactions. To see us as a good company you wouldn't want to see us doing a deal now – you'd want us to get some data and then look over the next 12 to 18 months to do the right deals.

"Another question is, can we do some type of earlier, collaborative deals that allow us to get our feet in the water with one or more potential partners but that don't lock us up. That is what we are intending to do in the short term.

"In 18 months, I think we will have had one or more serious co-development deals with one or more pharma or device companies, or one or more applications that we may hold because we see the value in that, or we may have undertaken one or more M&A transactions. There's no preference for me – they are all very possible. Things are looking very good, however. Our progress has certainly exceeded our expectations from two and a half years ago." **ALS**