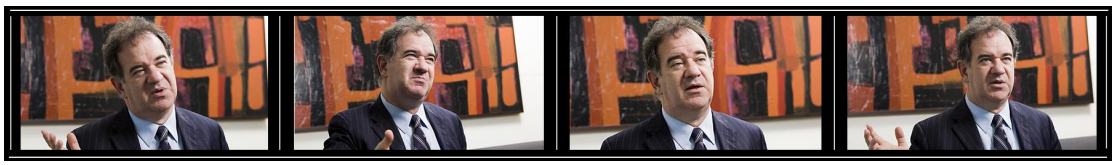

The CEO Transcript – Investor Briefing with Silviu Itescu, Founder and Executive Director, Mesoblast Limited

21 July 2008

This investor briefing is part of a regular communication process to keep investors fully informed of developments at Mesoblast.

Background

Mesoblast is a Melbourne-based biotech company commercialising a proprietary adult stem cell technology, called Mesenchymal Precursor Cells, for orthopaedic applications. It has established proof-of-concept with its technology and is now progressing Phase II clinical trials in the United States for a spinal fusion application. Other orthopaedic indications being developed include the treatment of non-healing long bone fractures, intervertebral disc repair and prevention and treatment of knee cartilage damage.

Mesoblast owns 39.2% of US-based Angioblast Systems Inc., which is applying the same adult stem cell technology for the treatment of cardiovascular and other diseases with two Phase II trials underway in the US in congestive heart failure and heart attack patients.

Topic: Product Development Briefing and Overview on Phase II Clinical Programs Underway

The CEO Transcript: **Mesoblast is developing therapies for a number of orthopaedic applications. The lead program, a treatment for spinal fusion, is in Phase II trials under an IND in the US using your allogeneic mesenchymal precursor adult stem cells which started in July last year. Firstly, can you explain the spinal fusion procedure and how your therapy is going to assist with that?**

SILVIU: Sure. Intervertebral disc disease is a very common degenerate condition that affects up to 20% of the population, and after many years of low back pain and damage to the intervertebral cartilage, really the only option left for a patient is to have a procedure called spinal fusion. This is where orthopaedic surgeons take a piece of bone from the hip called an autograft, which contains mixtures of small amounts of stem cells and growth factors. The autograft is then surgically implanted into the intervertebral space. The objective is to create bone where there used to be an intervertebral disc made of cartilage and that the bone bridges the vertebral body above to the vertebral body below. So you obliterate the intervertebral state. You no longer have pieces of cartilage that can break off and cause pain by compressing spinal nerve roots.

The CEO Transcript: **Does that decrease their mobility to some degree?**

SILVIU: It does, but as long as you're limiting it to one or two, or maximum three vertebral spaces, it doesn't (significantly) affect overall mobility.

The CEO Transcript: **What are the problems with this current procedure?**

SILVIU: The two problems with autografts are that firstly you end up with severe pain at the site of the bone graft donor material. Secondly, there's variability in how the autograft will take. The effectiveness of autograft is dependent on the numbers of stem cells that we have in our bones and bone marrow. And as is known, the older you get, the more diseased you are, and the less of these stem cells you have. So for that, amongst other reasons, the success rates of autografts are only in the order of about 60% or so.

What surgeons are looking for is an alternative to autograft, a procedure, drug or a process that eliminates the need for a second operation to harvest bone from a part of the hip and eradicates the secondary pain, an alternative that produces a uniform and reliable outcome.

With the mesenchymal precursor cell technology that we've developed using allogeneic cells – material from one donor to treat potentially thousands of unrelated recipients – we end up with a batched product that delivers reliability and uniform results from dose to dose.

The objective is to have a therapeutic dose of cells that are frozen and can be thawed in the operating theatre by the surgeon within five minutes of implanting into the vertebral body sites, mixing the cells with some type of carrier that allows the cells to localise and stay fixed in that area, and result in a fusion.

The CEO Transcript: **With the bone grafts that are being conducted at the moment, would there be some mesenchymal stem cells present there as well?**

SILVIU: Absolutely. And that's the reason why the bone graft actually works. Because bone is really a combination of mesenchymal stem cells, calcium, growth factors and structural proteins like collagen.

The structural proteins themselves don't create new bone. You need to lay down new bone, which contains stem cells and some growth factors. The only other alternative to our stem cells is a growth factor that has been developed by Medtronic called Infuse or BMP2. BMP2 is one of the growth factors that are present in native bone in the autograph procedure. It's one of the components that result in good fusion. A combination of mesenchymal stem cells and BMPs, or growth factors, is probably ideal to get the best outcome in a fusion procedure.

The CEO Transcript: **So will your treatment include both the stem cells and the BMP2 material?**

SILVIU: Not initially. The stem cells make BMP2 and a number of other BMPs. So we think that our stem cells on their own are likely to be as least as good, if not superior, to a single BMP treatment. But we certainly would potentially envision that surgeons down the track, once our product is FDA approved, might consider using our product in combination with the existing BMP product.

The CEO Transcript: **Is Infuse the only BMP2 product on the market at the moment?**

SILVIU: That's correct.

The CEO Transcript: **And what is the current market for that product?**

SILVIU: The reason we've targeted spinal fusion as our first potential market opportunity is because it's a world proven market, and it's really the only one in the orthopaedic space where a biological has actually demonstrated how it can make a major inroad and change the behaviour patterns and outcomes of surgeons.

There are between 400,000 - 500,000 spinal fusions performed in the US annually. It is expected to continue to grow at a rate of 10% to 20% annually for the next few years. Today the BMP product is currently reimbursed by Medicare in the US at about US$5000 per dose and often there might be two or three vials of BMP used by the surgeon.

The CEO Transcript: **Do you know what proportion of those procedures BMP is used in?**

SILVIU: Most recent public figures from Medtronic indicate it generates about $800m in sales in the US from BMP, of which 80% to 90% of those sales are specifically for spinal fusion procedures. We would anticipate that they're currently getting about 40 per cent penetration of the spinal fusion market.

The CEO Transcript: **At the moment you're conducting a Phase II study in the US in spinal fusion. Can you provide an update on that trial?**

SILVIU: We've commenced the Phase II trial using allogeneic cells in the first group of patients, where we randomised to autograft (bone graft). The objective of the initial trial was primarily safety in testing three different increasing doses of the cells. So we anticipate that we'll complete recruitment in this trial by early next year, and the result of this Phase IIA trial is likely to go towards a Phase IIb/III registration trial of a spinal fusion product that's likely to be an even lower dose than the current doses that we're testing.

The CEO Transcript: **Why is it you don't need a Phase I trial for this type of a product?**

SILVIU: The fact that we're using stem cells, which are defined as a biological product, means that preclinical results that we've generated, both in terms of safety and efficacy, are much more reliable in terms of predictability of outcome in humans than would be the case with a new chemical entity, that is a typical drug that one would be taking on a daily basis. The trials have been extensive and they've been generated in at least two animal species for every indication we've gone into.

For those reasons, the FDA seems comfortable that the lack of toxicity at any given dose in preclinical studies is a high predictor of (expected) lack of toxicity in human trials. Across the board in multiple applications that we've tested ourselves in dose ranges of up to 20-fold from lowest to highest, we have yet to see a maximum tolerated toxic dose. In other words, we just have not had any cell-related adverse events.

The CEO Transcript: **So how is the regulatory path different to that for a pharmaceutical product?**

SILVIU: For cell therapy specifically, a new division has been created at the FDA that really is a combination of both the biologicals and the device groups. We are being regulated by both, but quite distinctly from a pharmaceutical product. And the two main differences are firstly, no need for a structured Phase I, II and III kind of program.

Equally as important, since toxicity is less of an issue because we're injecting these cell-based products once without repeat dosing and certainly not on a regular basis as drugs are delivered; the toxicity profiling and the follow-ups are more closely related to the way devices are assessed. This means that the pivotal trials are likely to be in the order of ten times smaller than the pivotal trials for a pharmaceutical product.

The CEO Transcript: **How big would your pivotal trial be?**

SILVIU: I think we're looking at about a 300 to 350 patient trial.

The CEO Transcript: **Would you need more than one trial?**

SILVIU: At the moment we're being told no. You can never be certain until you get to the end, but we're being told we only need one pivotal trial. Our view would be that we would like to have pivotal trials that generate sufficient data simultaneously to get approval in both the US and Europe. To do that - and that's really more a strategic question - we might have to do two trials where there's overlapping populations across multiple jurisdictions. But that's really to assist us in getting simultaneous approval; it's not that the US FDA is looking for two trials.

The CEO Transcript: **So you start the pivotal trial next year.**

SILVIU: That is what we are targeting, assuming completion of Phase II and that we receive FDA clearance to commence the pivotal trial.

The CEO Transcript: **And how long do you think it would take before you would file this product for approval?**

SILVIU: We think that the follow up period is likely to be about 18 - 24 months. We're targeting 2012 completion and product registration. By the end of 2012, we think we will have gained product approval. And really we're as good as the ability to recruit those 300 odd patients across 20 or 30 sites, predominantly in the US, and there would probably be some sites in Australia and in Europe.

The CEO Transcript: **Will you be selling your products through a major distributor?**

SILVIU: Yes. I think it's pretty clear that the orthopaedic space is a very specialised industry, where there are a large number of major players who sell generic orthopaedic devices directly to the surgeons and to the clinical centres. These relationships are well entrenched. The ability to distribute widely new products in this industry is dependent on our cells being bundled up as part of a whole range of instruments and devices.

It may be that various indications will require different partners. It's clear that for instance the type of surgical companies that have relationships and technology facilitating spinal disease might be quite different from the type of companies that work with trauma surgeons, or the type of companies that work with arthritis surgeons, or with hip replacement surgeons.

The CEO Transcript: **And with manufacturing, are you going to keep that in-house?**

SILVIU: I think it's important for us to maintain control of productisation. We're likely to have several spine products - one for spinal fusion, one for disc repair and regeneration. There is likely to be several products for bone repair and trauma, one for intra-operative use for large traumatic fractures, and one that may be for a minimally invasive injection into small fractures. There will be different products for osteoarthritis of the knee, injectable directly into knee joints, into soft tissues, tendons and for cartilage repair.

The way to separate these products, apart from having different partners and distributors, is by controlling manufacture and ensuring that formulations are different, dosages are different, cells may be pre-packaged, through delivery devices, and perhaps their state of cellular differentiation. As long as we control manufacture across each of those product lines, we control product separation.

That has an important implication in terms of pricing strategy and reimbursement because the type of reimbursement - particularly in the US - that you get back is very dramatic. We certainly wouldn't want the same product to be used across multiple different indications because it would simply reduce our ability to appropriately price them. When you do all of that, each product has its own regulatory and approval process that makes it a distinct product.

The CEO Transcript: **Why is it that you started clinical trials with autologous (patient's own) stem cells rather than allogeneic cells?**

SILVIU: We commenced with autologous cells because whilst we were scaling up our whole manufacturing process, it was clear that if we wanted to go to the clinic and get some early clinical indicators of efficacy, we would want to eliminate any question around safety of the allogeneic process. So that's why we were able to start our clinical trials maybe two years early using patients' own or autologous cells.

The limitations to autologous therapy are clear. The costs involved on a per patient basis are very large, and make the business model very unwieldy. What we learned from those autologous trials is that we are absolutely right in going with an allogeneic business model given the cost of goods differential.

In addition to that, patient specific therapies are limited by the fact that we all have different numbers and qualities of stem cells. So it allows the ability of having a uniform product with batch-to-batch reliability.

With those caveats in mind, we're still very excited by the spectacular results of the autologous trials. And I think it says a lot about the underlying technology.

The CEO Transcript: **You have shown your treatment to be effective in improving the healing of non-union long bone fractures and also in treating congestive heart failure using your autologous MPC treatment. Can you describe the results from these trials?**

SILVIU: We've completed a 10-patient trial at The Royal Melbourne Hospital, in patients who had what are called non-union fractures of their long bones – the tibias and the femurs in their legs. Non-union is defined as a fracture that just doesn't heal, and will never heal spontaneously. These 10 patients had fractures, some as wide as five centimetres or more, that did not heal for a median duration of between 5 and 41 months.

These were bad fractures that caused these people to be in wheelchairs or on crutches and to be chronically disabled. Three of the ten patients previously had and failed either autograft or BMP (the Infuse product) treatment. So really we've taken patients at the very extreme of this condition. The objective of this first trial was primarily safety, but really with the hope that we would see some efficacy.

Whilst a final 12-month analysis of all patients is not complete – we anticipate The Royal Melbourne Hospital announcing the full results over the next month or so – we had a six- month interim analysis, at which point seven of the first ten patients had completely united. And the mean time to union was something of the order of four to five months.

So people, who otherwise were up to 41 months with no union, had complete union within four to five months after the cells were implanted and some earlier. The cells had been expanded for six weeks, and a range of numbers of cells was implanted, between 60 million to 200 million cells. The numbers of cells implanted were a function of the qualitative differences between the stem cells from any one given individual, which just goes to show you how hard it is to do an autologous trial.

The results were spectacular and the people who have united and had complete union confirmed by X-ray are all back to work, back to normal lives. None of them requires any longer a wheelchair or crutches, and the surgeries have been unqualified successes.

The CEO Transcript: **Out of interest, of those seven that did heal, had any of those patients received the BMP product?**

SILVIU: All three who had received these alternative approaches and failed (two received BMP and one an autograft), were part of the seven who united after being implanted with our cells.

The CEO Transcript: **And the results with treating heart failure by Angioblast?**

SILVIU: The cardiovascular side is very different from the orthopaedic side. Heart failure is a large market, where a variety of approaches has been tried, mainly pharmaceutical. And the vast majority that have been tried have failed. It's a very high-risk area, but clearly there's a major need.

In the US alone there are five million patients with heart failure, all of whom are on beta-blockers and inhibitors, but those drugs do very little to arrest the disease.

So you've got a large market, and the question is what is different technologically that can arrest this disease. Our stem cell technology has been primarily developed to increase blood flow to improve new blood vessel formation in the heart, and simultaneously to induce the endogenous heart muscle cells to start dividing again and regenerate.

In our trial in six patients in Newcastle, New South Wales, where the autologous trial was performed, patients' own cells were expanded and re-injected back into their hearts, using a later generation catheter-based technology from Johnson & Johnson. The results were very exciting. In these six patients, all of them were selected not just because they had heart failure, but because they also had severe angina due to blockages in their arteries that were not amenable to any kind of surgery.

So what we think is due to the creation of new blood vessels and improved blood vessel flow, all six patients demonstrated very significant reduction in their anginal symptoms and use of anti-anginal medications within three months of a single injection of our stem cells. Equally important is that by the three months they had also shown significant improvement in cardiac function as measured on echocardiograms. Additionally, four out of the six patients have improved by at least one heart failure class, by at least one grade, either Grade III to II, or Grade II to I.

That's very encouraging, and it's the basis now of a 60-patient randomised Phase IIA trial testing the allogeneic stem cell technology using three doses, randomised against controls, again by the same catheter-based delivery across up to 10 sites in the US.

The CEO Transcript: **All of these results have been generated with the autologous cells. What gives you confidence that you're going to replicate those results using allogeneic cells in the current Phase II trials?**

SILVIU: Whilst the autologous trials were ongoing, we embarked on a large number of preclinical studies in large animals, predominantly sheep, testing GMP manufactured allogeneic cells in exactly the diseases that we were going to be targeting with the allogeneic human cells in humans. Across the board, over 400 sheep have been implanted with allogeneic cells in tibial bony defects, in models of spinal fusion, in models of osteoarthritis of the knee, in heart failure and in heart attacks. These are precisely the diseases that we are now moving into human trials.

So as the autologous trials gave us confidence that the cells were safe and demonstrated some degree of efficacy, the allogeneic studies in preclinical models gave us the kind of reassurance that we wanted to see that the allogeneic cells behaved in a similar way. This is where we are today, currently in three Phase II trials, and we hope to have another two INDs submitted before the end of this year, commencing with a knee osteoarthritis trial.

The CEO Transcript: **So by the end of this year, Mesoblast and Angioblast will have five Phase II trials underway or in the planning?**

SILVIU: That's certainly the plan.

The CEO Transcript: **With the heart failure applications, what are the existing products that you're going up against?**

SILVIU: There are no products out there that we see as very competitive. Probably the only reasonable comparable in this industry is what's called Cardiac Resynchronisation Therapy (CRT), which is a recent advance in the treatment of heart failure. It is the placement of a permanent pacemaker/defibrillator into the atrium and the ventricle of a patient by an invasive cardiologist through a pacemaker lead.

That is a product that's currently sold by each of the major device players in the field. Certainly, Medtronic and Boston Scientific would be seen as the leaders in that area. The CRT therapy is a one off device and can only be used in a subset of patients with Class III/IV heart failure. They target at most about 14% of the total heart failure market. It's only potentially applicable in patients with severe heart failure that also have conduction abnormality. So the pacemaker/defibrillator corrects the conduction abnormality, which then allows the heart to pump a little bit more efficiently.
That 14% of the heart failure market is available to us as well, for our cells could be used in conjunction with this device. But we also have the entire heart failure market available to us. There's no rationale why you wouldn't be using our cells across the board in all classes of heart failure.

But the instructive point about CRT therapy is that you can see how this approach for heart failure has been rapidly adopted, and the type of revenue generated over the last few years. I think in the four to five years since the first one of these was approved by the FDA, the market sales for these products are at least $1.5 billion a year in the US alone and projected to grow for the next ten years at a rate of something like 10% to 15% per year.

The fact that there's a large backlog of heart failure patients - in addition to the existing five million, there's another 500,000 new heart failure patients per year - means that just like with CRT, our therapy is not likely to be limited by the numbers of patients, but really by the numbers of invasive cardiologists who have got time to take up our procedures.

The CEO Transcript: **What are your milestones for the next 12 to 15 months?**

SILVIU: I think the majority of the milestones are going to be clinical and commercial. Clinical in terms of interim data analysis and final analysis of our Phase II spinal fusion trial, and commencement of a Phase III spinal fusion trial. Similarly our (Phase II) heart failure trials, interim and final analyses, all in parallel time frames.

I would expect that we would not be beginning Phase III trials without having partners on board. The two would feed off each other. As we get clinical data, I think it will make the commercial arrangements fall into place a lot easier too. For whatever reason, we may decide to move forward prior to partners being locked in, but I think strategically it would make a lot more sense to have partners in first.

I think that what we're certainly hoping is to have a fair amount of activity on the commercial front in parallel to clinical results.

The CEO Transcript: **What type of deal will you be looking for?**

SILVIU: The type of partnership deal that we're likely to do obviously would be quite different the later we are in executing them. Therefore, we're looking at retaining significant components of the downstream sales, and we're looking at real partnerships where we can participate in both the designs and the funding of the pivotal trial.

The CEO Transcript: **Thank you for your time**.

SILVIU: A pleasure.

Terms
Autologous adult stem cells – Stem cells derived from patient's own bone marrow
Allogeneic adult stem cells – Stem cells derived from unrelated source
Mesoblast core technology – Mesenchymal precursor stem cells

This is an edited record of interview conducted by The CEO Transcript with Silviu Itescu, Founder and Executive Director of Mesoblast Limited (ASX:MSB;USOTC:MBLTY), in July 2008.