INVESTOR BRIEFING

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With Silviu Itescu
Executive Director, Mesoblast Limited

The CEO Transcript
Keeping Investors Informed

Background
Mesoblast is a Melbourne-based biotechnology company commercialising a proprietary adult stem cell technology, called Mesenchymal Precursor Cells. It has established proof-of-concept with its technology and is now progressing Phase II clinical trials in the United States for a spine fusion application. Other orthopaedic indications being investigated include the treatment of non-healing long bone fractures, intervertebral disc repair and prevention and treatment of knee cartilage damage. It is also due to start a Phase II trial in bone marrow transplantation.

Mesoblast owns 39.2% of US-based Angioblast Systems Inc, which is applying the same adult stem cell technology for the treatment of cardiac, vascular and eye diseases with two Phase II trials underway in the US.

Topic: Market Update and Implications of Major Industry Stem Cell Deal between Osiris Therapeutics & Genzyme Corporation

The CEO Transcript: Osiris Therapeutics recently announced a US$130 million upfront deal with Genzyme Corporation to give it access to the Osiris adult stem cell technology platform (total potential deal value up to US$1.38 billion). What are the implications and relevance of that deal to Mesoblast?

SILVIU: That's the first major deal for the pharmaceutical industry in the stem cell space. What it says is that typical pharmaceutical companies, which are used to dealing with scaled up manufacturing and low cost of goods and high margins, are finally realising that there is a business model and a pipeline that stem cells can offer.

It's for the first time saying that a stem cell platform, in a similar way to monoclonal antibodies and RNAi, can be viewed by the pharma industry as a real pipeline for a future generation of products across multiple indications.

The CEO Transcript: What are the parallels between the Osiris technology and your own?

SILVIU: Up to now, most cell therapies have focused on developing products using patient specific autologous therapies or on device-like programs. These patient-specific therapies contain hematopoietic stem cells, which activate the immune system and result in rapid rejection. Such patient-specific therapies are very costly, limited to niche markets, difficult to get through regulatory authorities, and give inconsistent results because of differences in source material. Consequently, these therapies cannot meet the commercial and therapeutic needs of large unmet clinical indications.

The parallels between ourselves and Osiris is that both are developing allogeneic cell therapy products that are scaleable, will result in low cost of goods and high margin, and can be used broadly across major clinical needs. Both companies are developing products derived from cells of mesenchymal lineage, which have unique properties that result in no immune system activation and ability to be used allogeneically from one donor to treat many unrelated recipients.

It's no coincidence that the first major pharma deal in this space is with a company (Osiris) that's developing an off-the-shelf allogeneic stem cell product. In our view, that's really the only way that you're going to get a stem cell technology to mimic the characteristics of a pharmaceutical in terms of all of the manufacturing, the targets, the scale up, reimbursement etc.

The CEO Transcript: Can you explain what the differences are between your cells and the Osiris cells?

SILVIU: We isolate a very early progenitor cell, which we call the mesenchymal precursor cell. We use monoclonal antibodies to isolate these cells from all sorts of tissues. We start out with a very pure, very homogenous product that can be easily scaled up and can be very well controlled under manufacturing conditions that the regulators are looking for. That gives us a potent product that has very low cost of goods with broad functional capability.

Because our cells are early progenitor cells, they have very broad reparative characteristics with an ability to impact on a diverse range of tissue types. Our ability to keep them at an early stage of development during the manufacturing process enables us to scale up a very potent regenerative cell type.

The CEO Transcript: So does your therapy contain a concentrated level of cells?

SILVIU: Our products contain a high concentration of a very unique and potent cell type, which we call the mesenchymal precursor cell. Our cells are, in vivo, found around blood vessels, they create new vessels, they regulate blood vessels, and they can differentiate into a variety of other cell lineages. Once we extract them, we maintain them in that stage of distinctive early progenitor cell phenotype throughout the manufacturing and expansion process.

The CEO Transcript: The Company recently received approval from the FDA to proceed with a bone marrow transplantation trial in 30 patients using your adult stem cell technology. Can you explain how your stem cells might be used in that setting?

SILVIU: Sure. Today the majority of bone marrow transplants are using autologous human hematopoietic cells. And that's because even though many more patients could use an allogeneic transplant – an unrelated hematopoietic bone marrow transplant – when you get an unrelated bone marrow transplant, the risk of graft versus host disease is so high that it's just too dangerous to perform in many patients, unless they're really end stage with their particular cancer of the bone marrow, the primary condition for the transplant.

So people are looking at alternative sources of allogeneic bone marrow transplant and are using cord blood as a major alternative. It turns out that hematopoietic cells from the cord don't induce graft versus host (cell rejection) to anywhere near the frequency that adult bone marrow does. The problem with cord blood is that the amounts of hematopoietic cells in there are tiny. And that means that the likelihood that it's going to engraft – the likelihood that it's going to work – is significantly impaired.

So what we have found is that with our mesenchymal cells we are able to significantly expand the hematopoietic fraction from cord blood by something like 20-fold. And that we think is going to enable engraftment to occur much more effectively, much faster, and allow people to get transplanted with cord blood that gets them out of the intensive care unit and out of the hospital in up to half the time than conventional transplants, without the risk of graft versus host disease.

The CEO Transcript: And the bone marrow transplant procedure is used to rebuild the patient's immune system following chemotherapy?

SILVIU: That's right. Usually for leukaemia or cancers of the bone marrow.

Now, the advantage of this product for us is that it potentially goes down the road of orphan drug designation. In fact, we've been designated as an orphan drug for this exact application, using our cells to expand hematopoietic precursors. Not just from cord blood, but from any source where the transplant recipient needs more hematopoietic stem cells.

That means that the FDA will work very closely with us to assist us in fast tracking the product into the market. An orphan drug indicates that it is an area of need for which there are no alternative pharmaceutical drugs being developed.

The CEO Transcript: When is this trial due to begin?

SILVIU: It is commencing at the M.D. Anderson Cancer Center in Houston, and both the FDA, and the local Ethics Committee at the centre, has cleared the protocol. We believe the first patient will be recruited and will have the transplant within the next couple of weeks.

The CEO Transcript: Moving on to the spinal fusion application of your adult stem cell therapy, is that currently your leading program and can you provide an update on progress?

SILVIU: Spinal fusion and heart failure (through Angioblast) are the two leading applications, and both are progressing very nicely. The spinal fusion program to date has been more of a posterolateral fusion, meaning a larger procedure in the (lower) back where the cells have been implanted and in around the vertebrae in order to induce fusion on the outside of the vertebrae. The surgeons today in general are moving towards more minimally invasive procedures, with small surgical incisions and wanting to generate fusion in a very small space between the vertebrae. We're in the midst of developing a refinement to our product that would allow us to develop a spinal fusion product for minimally invasive surgery. The advantages are that we have surgeon buy-in, and it means that we can generate fusion with a dose of cells that may be one tenth lower than what we had previously anticipated using in the more traditional approach. That obviously has implications on cheaper cost of goods, which will impact ultimately on the type of product we launch into the market.

The CEO Transcript: You're going to be looking at the opportunity for cervical spine fusion. Can you explain what you mean by the term cervical spine and the market opportunities that might exist in this area?

SILVIU: Yes. The spine is divided into three areas - cervical, thoracic and lumbar. Most disc degeneration occurs in the lumbar, lower back and the cervical, which is in the neck, and the number of procedures is roughly distributed equally between those two areas. The FDA has recently put a warming letter against our major competitor in the cervical fusion space.

That product was associated with an unacceptable rate of allergic reaction and so that product has been given a warning not to be used in cervical fusion, which opens up that whole market for us without a competitor.

The objective of developing a product for cervical spine fusion is it has to be minimally invasive, it has to be fitted between the two vertebrae and that gives us an opportunity to then develop a uniform product, not just for the cervical spine but also for the lumbar spine, rather than having two very different products.

That's why we're trying to now harmonise so we move forward with one single product for both cervical and lumbar spine that is minimally invasive and that is a fraction of the cells needed to induce fusion.

The CEO Transcript: What were the consequences of those allergic reactions?

SILVIU: Thirty-eight cases of death were reported to have occurred as a result of swelling around the neck and an inability to breathe.

The CEO Transcript: So does cervical spine fusion provide a market entry opportunity for Mesoblast?

SILVIU: The cervical spine has a number of advantages. We're still refining our strategy in terms of whether the cervical spine would be the first port of entry into the market, whether it would be a parallel entry with lumbar (spine fusion) or whether it would be the second point of entry. There is no doubt that today cervical spine area does not have competition for us. It is a smaller market than the lumbar spine (fusion) even though the number of procedures is the same.

The CEO Transcript: When is the cervical spine fusion trial expected to start?

SILVIU: We're still having discussions with the FDA. That trial is likely to start early next year, although it depends on the FDA giving us the appropriate green light.

The CEO Transcript: And you've shown that your product is safe and effective in a preclinical model for cervical spine fusion?

SILVIU: In the appropriate preclinical model the FDA wants to see we've already shown, that it's safe and effective and superior to the standard of care, which is bone (grafted) from the hip, without any side effects. The sort of side effects that were reported to have been seen with our competitor's product has not been seen at all with our cells. So, that gives us great hope that we're going to be able to get clearance from the FDA to move into this trial.

The CEO Transcript: What's different about your cells to the existing product that potentially produces a safer product for this cervical spine fusion procedure?

SILVIU: The existing product is a bone morphogenetic protein. It's a genetically engineered protein that stimulates bone formation from stem cells that are present around the site where the protein is deposited. Because you can't turn it on and off once you've implanted it, it just continues to work until the protein is completely degraded. And you can't control any kind of immune reactions to the protein.

In contrast, a biological agent is stimulated by the local environment to either secrete factors or switch off the secretion of those factors, and that's very important because it eliminates the risk of excessive bone formation, which is one of the problems with the genetically engineered bone morphogenic protein.

Secondly, they don't activate the immune system. They're not seen as foreign in any way and they don't induce any kind of allergic reaction. So both of those abnormalities have not been seen at all with our cells. It's really the advantage of a biologic, just another example of why a biologic is safer than a chemical or a genetically engineered molecule.

The CEO Transcript: Presumably, your products are going to be commercialised by third parties. Can you give us an update on your licensing and partnering discussions and how they are progressing?

SILVIU: We've been approached by a number of parties involved in the orthopaedic and cardiovascular spaces. I think that really the strategy for us is to demonstrate the breadth of the technology across multiple clinical indications that have large market sizes. I think what we're looking for is really partners to complete Phase 3 trials and to take us through to market.

We're in the midst of Phase 2 trials in a number of indications and we're getting towards that time where you would want to be sitting down and discussing with appropriate partners what a Phase 3 trial might look like and what the primary endpoint should look like for the market we're targeting.

The CEO Transcript: Has the Osiris/Genzyme deal helped put this technology on the map for potential partners?

SILVIU: I think the Genzyme/Osiris deal has certainly ignited approaches by a number of organisations that probably for the first time are now seeing our stem cell platform as a competitive platform that they need to be looking at very closely.

The CEO Transcript: Would you be hopeful of securing a partnership or licensing agreement in 2009?

SILVIU: We're certainly working towards that, absolutely.

The CEO Transcript: How does the current financial crisis impact on Mesoblast's ability to commercialise its products in terms of its ability to raise funds and move forward?

SILVIU: The key in the biotechnology space is patents and commercialisation of those patents. The patents are all about time, so to the extent that we can increase the value of our company exponentially, it really depends on demonstrating multiple value lines linked to our patents in a parallel timeframe, which ultimately requires larger tranches of capital.

We have enough capital right now to get ourselves to the point where we said we would be when we raised the last tranche, which is really focussing on several lead applications through the Phase 2 stage. We have clearly demonstrated that we now have a platform with viable clinical applications across at least four major indications and there are probably going to be more. If we want to maximise the value of this company we're going to have to grow, increase our clinical programs and expand our product pipeline. If we hit milestones, we have a very strong group of investors who have demonstrated repeatedly that they have supported us and will continue to support us. But obviously we are looking at all strategies at this point in time for maximising funding over the next couple of years.

The CEO Transcript: Thank you for your time.

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
Hematopoietic stem cells – develop into all types of blood cells

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This is an edited record of interview conducted by The CEO Transcript with Silviu Itescu, Executive Director of Mesoblast Limited, conducted in November 2008.