

# Mesoblast Limited



## Overview

**Mesoblast Limited** is an Australian biotechnology company committed to the commercialization of novel treatments for orthopedic conditions by using its unique adult stem cell technology for the regeneration and repair of bone and cartilage. A Phase 2a trial for spinal fusion using allogeneic (unrelated) mesenchymal precursor cells is underway in the United States to validate the business model for the development of off the shelf therapies. The technology has already achieved excellent results in a clinical trial for the repair of large bone fractures, and preclinical trials for the regeneration of vertebral discs and large joints such as the knee.

Mesoblast has acquired a substantial interest in Angioblast Systems Inc, an American company developing the platform MPC technology for the treatment of cardiovascular diseases, including repair and regeneration of blood vessels and heart muscle. Mesoblast and Angioblast are jointly funding and progressing their core technologies. Mesoblast's strategy is to maximize shareholder value through both corporate partnerships and the rapid and successful completion of clinical milestones.

## Regenerative Medicine

The exciting new field of regenerative medicine offers the promise of halting or reversing major diseases for which conventional drug therapies have either failed or been found severely wanting. In particular, orthopedic and cardiovascular diseases represent areas of major unmet clinical needs throughout the world where regenerative therapies, and specifically stem cells, may make dramatic inroads.

Adult stem cell technology is attracting enormous interest worldwide for its potential to cure many degenerative diseases that include arthritis, vertebral and intra-vertebral disc degeneration and cardiovascular disease. These diseases are very likely to affect us all at some stage our lives. They severely impact our quality of life, add enormous ongoing costs to the healthcare system and are currently treated predominantly through palliative means.

We believe that the mesenchymal precursor cell holds the key to developing novel regenerative treatments for orthopedic and cardiovascular diseases. Moreover, we believe that the patented MPCs being developed by Mesoblast and our sister company in the US, Angioblast Systems Inc, have the greatest near-term potential to generate a whole range of new treatment modalities capable of repairing bones, cartilage, blood vessels, heart muscle, and other tissues which have deteriorated because of age, disease, or lifestyle.

We are very encouraged by a whole series of trial results generated by both Mesoblast and Angioblast which have shown that the patented MPC technology has now advanced into a mature stage of clinical development.



## Mesoblast's Patented Technology

The basis to Mesoblast's technology is a patented ability to accurately characterize, select and greatly expand or multiply a population of adult stem cells known as mesenchymal precursor cells or MPCs. These cells are known to exist in all people and appear to be a mature and stable progenitor for the repair of damaged and diseased cells. Mesoblast's adult stem cells have unique characteristics that enable them to differentiate into a host of different cell types including bone, heart tissue and cartilage and to propagate significant blood supply. Importantly, Mesoblast's MPCs do not elicit an immune reaction in a recipient who is unrelated to the donor.

So what does all this mean? Mesoblast is commercializing a technology that can isolate adult stem cells from a simple donation of bone marrow in much the same way as blood is donated. Cells are isolated in one to two hours using monoclonal antibodies and are expanded over a four to six week period in a fully Good Manufacturing Practice (GMP) compliant facility. The expansion, or cell division process, enables the production of sufficient numbers of new adult stem cells to produce hundreds or thousands of doses for the treatment of disease in an extremely safe and proven environment. The new cells may be frozen indefinitely and made available immediately to many unrelated patients at the time and place of need. The end result is a

highly viable business model in a safe environment to treat patients.

The results of preclinical trials have been positively reviewed by the United States Food & Drug Administration (US FDA). Obtaining FDA clearance within 30 days of filing each of two investigational new drug (IND) submissions to begin Phase 2 trials using allogeneic MPCs attests to the robustness of the preclinical and manufacturing results, and underscores the rationale of our allogeneic business model. Both Mesoblast and Angioblast are confident that the preclinical success of the shared allogeneic MPC platform technology will be translated into commercial success by developing “off the shelf” products that will be highly effective in large, pivotal clinical trials. As Mesoblast and Angioblast are targeting huge clinical populations with unmet clinical needs, we are confident that there will be strong market acceptance worldwide of our adult stem cell products once the necessary regulatory, safety and efficacy goals are met.

### **Position in the Growing Global Stem Cell Market**

Both Mesoblast and Angioblast are confident that the preclinical success of the shared allogeneic MPC platform technology will be translated into commercial success by developing “off the shelf” products that will be highly effective in large, pivotal clinical trials. Both companies are also making significant progress in commercializing the technology and are well positioned to capitalize on the leading edge, shared platform technology, and are supported by robust patent protection, good management and corporate governance, sufficient funds, and solid communication

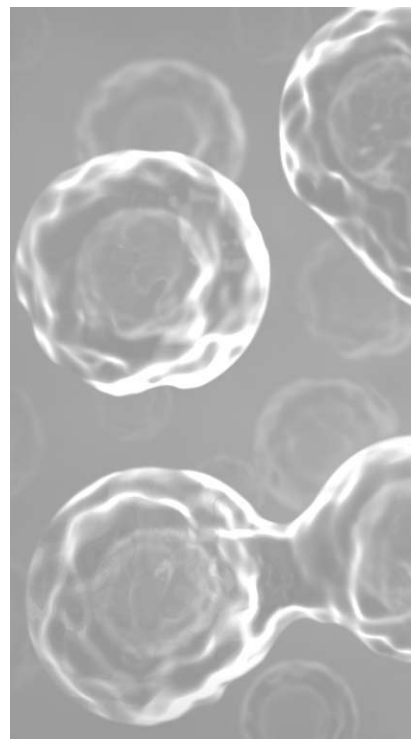
capabilities. Both companies have now progressed to the stage of mature clinical stage commercial development.

By the middle of 2008, it is anticipated that a total of five Phase 2 clinical trial IND submissions for orthopedic and cardiovascular indications will have been filed, and that at least two Phase 2 trials will be significantly advanced with a further three commencing. These characteristics underpin the emergence of Mesoblast and Angioblast as global leaders in the exciting field of regenerative medicine.

### **Mesoblast’s Therapeutic Applications**

Mesoblast is commercializing a unique population of adult stem cells for orthopedic applications, a franchise of regenerative products for spine disease, long bone fractures and disorders of cartilage, such as osteoarthritis. Mesoblast’s core patented technology enables isolation of a unique and highly potent type of adult stem cells, termed mesenchymal precursor cells, which can be derived from a single donor, expanded in culture into very large numbers, and used in many patients without the risk of rejection.

Mesoblast is conducting a Phase 1B Clinical Trial at The Royal Melbourne Hospital in patients suffering from non-healing, long bone fractures. Interim results indicated strong bone regeneration and fracture union in every one of the first five patients implanted with Mesoblast’s proprietary cells. The success of the stem cell therapy in these patients eliminated the need for a second operation to harvest bone from their hips. There have been no reported cell-related adverse events. The success of this trial will lead to



Mesoblast developing a proprietary stem cell product for repair of long bone fractures. By having an “off-the-shelf” stem cell therapy for fracture repair, Mesoblast will be able to provide a regenerative product that surgeons can use as soon as a patient is first brought to a trauma facility with a fracture needing intervention. The immediate availability of a stem cell therapy for bone repair has great implications for accelerating the healing of sporting injuries as well as preventing deformities and long term complications following trauma.

A second major application is for induction of spinal fusion in end-stage intervertebral disc disease, a major orthopedic market. Over 300,000 spinal fusion procedures are performed in the United States alone each year, with the number expected to grow to over 500,000 by 2009. Current fusion therapies use bone harvested from a patient’s own hip (termed autograft), that requires a second surgical procedure



which frequently results in long-term complications such as chronic pain and infection. Mesoblast's preclinical trials conducted at Colorado State University showed that the company's allogeneic, or "off-the-shelf", cells were as, or even more, robust in creating bony spinal fusion around the disc site than autograft hip bone. On the basis of these and other exceptional preclinical, manufacturing and safety studies, Mesoblast received rapid clearance from the United States Food and Drug Administration (US FDA) for its Investigational New Drug (IND) submission to commence a Phase 2 clinical trial of its NeoFuse™ allogeneic or off-the-shelf adult stem cell product for spinal fusion. The Phase 2 trial investigating the treatment of degenerative

intervertebral disc disease is being conducted at New York's Hospital for Special Surgery, a leading global orthopedic, rheumatologic and rehabilitation specialty hospital.

A third major targeted application for Mesoblast is low back pain which is present in 15–25% of the general population, and affects 70–90% of people at some stage in their lifetime, most often due to a degenerating intervertebral disc. While spinal fusion remains the therapeutic goal for end-stage disc degeneration, a less invasive approach is needed to address the needs of the much larger population with early-stage disc disease. To address this major market opportunity, Mesoblast is developing an allogeneic, or universal donor, adult stem cell product which can be injected by a minimally

invasive approach into degenerating discs of unrelated recipients in order to repair and regenerate disc cartilage, increase disc space height, and improve the biomechanics of the native disc. Mesoblast has commenced preclinical trials of its patented adult stem cell technology for the repair and regeneration of vertebral disc cartilage. These trials signal Mesoblast's expansion of its line of products for spinal diseases and its strategic aim to build a robust franchise for the massive global spinal disease market.

Regeneration and protection of cartilage in large joints of patients with osteoarthritis also represents a major disease indication targeted by Mesoblast. Osteoarthritis is a condition where irreversible loss of joint cartilage occurs through age-related degeneration or through injury. Current treatments attempt to alleviate painful symptoms but are unable to restore the cartilage lining the joint. Joint replacement is often the only option for restoring function. Inflammatory disease of the joints, such as osteoarthritis, affect more than 43 million people annually in the United States alone, with more than 10 million suffering from osteoarthritis of the knee, making it the most common joint disease. Mesoblast recently reported highly successful interim results of its first large joint cartilage repair program in osteoarthritis which showed that injection of our allogeneic, or "off-the-shelf", stem cells into damaged knee joints resulted in significant protection of the knee cartilage against destruction and improvement in osteoarthritis. After just three months, stem cell treated knee joints had significantly thicker and stronger cartilage compared with control joints. These results now support progression to osteoarthritis cartilage repair clinical trials, and the full outcomes will be used in

an IND submission to the US FDA for multiple Phase 2 clinical trials for the treatment of patients with degenerative osteoarthritis of the knee.

### **Mesoblast's Investor Base and Capital Raisings**

Mesoblast, listed on the Australian Stock Exchange in December 2004, is primarily owned by institutional shareholders. There is also increasing number of retail shareholders.

In December 2007, Mesoblast completed a capital rising of A\$13.44 million from Australian institutional and sophisticated investors in order to expand its clinical focus to new areas where our technology has shown great promise. The capital will be used to commence additional Phase 2 Clinical Trials in the United States and Australia in the areas of bone and cartilage repair and regeneration using Mesoblast's proprietary allogeneic, or "off-the-shelf", adult stem cells. The company intends to file additional Investigational New Drug (IND) submissions to the United States Food and Drug Administration (FDA) by early-mid 2008 for clearance to commence the trials.

Mesoblast continues to monitor its cash position and will raise funding at appropriate times using methods that will preferentially minimize impact on shareholders. Non-dilutive sources of funding through partnership arrangements and government grants will also be considered.

Angioblast will increasingly seek new means of funding its own goals. Sources for these funds will necessarily be through transactions with third parties or through an Initial public Offering on a US Exchange. In this transition, Mesoblast will

ensure that its substantial investment in Angioblast is protected and that shareholder returns are maximized.

### **Partnerships**

Mesoblast and Angioblast work closely with a large number of multinational organizations, including Johnson & Johnson, in progressing our technology through preclinical and clinical trials. We see these partnerships as providing a solid working foundation that is potentially mutually beneficial, and at the same time providing a platform for longer term commercial

relationships. We will continue to build on these relationships both in terms of numbers and applications.

### **Staffing**

Mesoblast has deliberately restricted its overheads and staffing commitments by proactively using best of breed contractors. Our key permanent staff number only eight, although as we take increasingly more complex steps towards commercializing our platform stem cell technology, there will be a growing requirement to increase our staff numbers and internal core skills. ■



### **Professor Silviu Itescu Founder of Mesoblast Limited**

Professor Itescu MBBS (Hons), FRACP, FACP, FACR founded Mesoblast in 2004. He is a Professor of Medicine at the Columbia University Medical Center in New York and Professor of Medicine at the University of Melbourne. While working as a clinician in the United States to prevent the rejection of transplanted organs, he began a global search to find

a more effective therapy which led him to South Australia's Hanson Institute where scientists had identified rare, extremely potent adult stem cells with the properties needed to regenerate heart tissue and to form new blood vessels to improve the heart's blood supply. The same cells were also able to replace bone at the site of fractures and form new blood vessels to deliver nutrients and oxygen to new bone. Professor Itescu established Mesoblast to commercialize these patented cells for bone fractures, spinal disease and for regeneration of damaged joint cartilage and intervertebral discs; and Angioblast Systems Inc for cardiovascular and other applications.



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