

# **OZEQUITIES NEWSLETTER**

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## ***FEATURE***

### **Week's Special:**

### **MSB: PROPRIETARY ADULT STEM CELLS TECHNOLOGY WITH IMMENSE POTENTIAL**

**By Jenny Prabhu and Gerald Stanley**

Mesoblast Ltd, whose share price has roughly trebled over the year as positive news flow from clinical trials accelerates, is testimony to investor interest in the possibilities for healing bones, arthritis, ailing hearts, and in treating a variety of diseases and injuries that affect the vast majority of people at some stage during their lives through the use of adult stem cells - a therapeutic that works, is safe, has no side effects nor does it raise any ethical questions and is likely to replace many of the treatments and devices in use today - not in the distant future but within the next 5 years or so.

Stem cell research is not new. Adult blood forming stem cells from bone marrow have been used in transplants for 30 years. Almost exclusively until recently, "autologous" stem cells - stem cells obtained from the patient's own body - were the only stem cells to be used.

Adult stem cells (that do not give rise to any of the ethical issues that embryonic stem cells raise) can be obtained from various tissues in adults including bone marrow, fat, skeletal muscle, skin, dental pulp and liver.

There are two broad types, haematopoietic precursors that give rise to new blood cells and mesenchymal precursors that give rise to cells and tissues that make up solid organs in the body such as bone, heart muscle and cartilage.

There are a very small number of stem cells in each tissue. They are thought to reside in a specific area of each tissue where they may remain quiescent for many years until activated by disease or tissue injury. Scientists in many laboratories worldwide - a report on Google offers details on 82 companies involved in stem cell research - are trying to find ways to grow adult stem cells in cell culture and to manipulate them to generate specific cell types so they can be used to treat injury and disease. Some examples of potential treatments include replacing the dopamine producing cells in the brains of Parkinson's patients, developing insulin-producing cells for type 1 diabetes and repairing damaged heart muscles following a heart attack with cardiac muscle cells.

A single adult stem cell can give rise to a clone of cells in cell culture or a purified population of candidate stem cells can repopulate the injured tissues in a living animal.

### **Published case studies**

\*In the US, National Review Online in April 2002 reported on the success in treating a patient with stem cells harvested from his own brain. A man in his mid 50s had been diagnosed with Parkinson's at age 49. The disease led to tremors and rigidity in the patient's right arm. Traditional drug therapy did not help. Stem cells were harvested from the patient's brain using a routine brain biopsy procedure. They were cultured and expanded to several million cells. About 20 percent of these matured into dopamine secreting neurons. In March 1999 the cells were injected into the patient's brain. Three months after the procedure, the man's motor skills had improved by 37 pct and there was an increase in dopamine production of 55.6 pct. One year after the procedure the patient's overall Unified Parkinson's Disease Rating Scale had improved 83 pct.

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\*Time magazine on April 16 2001 reported immune systems destroyed by cancer were said to have been restored in children using stem cells from umbilical cord blood.

\*A study conducted by the Washington Medical Center in Seattle involved 26 rapidly deteriorating MS patients. Physicians stimulated stem cells from the patients' bone marrow to enter the bloodstream. They then harvested the stem cells and gave the patients strong chemotherapy to destroy their immune systems (MS is an autoimmune disorder in which the patient's body attacks the protective sheaths that surround bundles of nerves). Finally the researchers reintroduced the stem cells into the patients, hoping they would rebuild healthy immune systems and ameliorate the MS symptoms. Of the 26 patients, 20 stabilised and six improved.

Younger MS patients in Canada whose diseases were not as far advanced showed even greater benefit from the same procedure.

\*The Globe and Mail, June 15 2001 reported Israeli doctors inserted a paraplegic patient's own white blood cells into her severed spinal cord after which she regained bladder control and the ability to wiggle her toes and move her legs.

\*Harvard University Gazette reported mice with Type 1 diabetes were completely cured of their disease when treated with adult stem cells. They achieved full insulin production and all lived.

#### **Mesoblast's break through technology**

The purification technology developed by Adelaide scientists in the Institute of Medical and Veterinary Science and the Hanson Institute Adelaide, now being commercialized by Mesoblast who has refined the technology further, enables efficient extraction, isolation and scale up of the most potent of adult stem cells, called mesenchymal precursor cells or MPC. MPC from one donor has not elicited an immune response when exposed to immune cells from unrelated recipients.

Generating universal MPC in large numbers means also that instead of having to wait several weeks to culture a patient's own stem cells for treatment of the patient, universal MPC products will immediately be available for use in treating a patient's condition as soon as diagnosed, whether bone fracture or heart attack.

The other important point is that many patients treated with donor adult stem cells may require ongoing repeat doses when the underlying disease process is ongoing such as coronary arterial disease or osteoporotic disease.

#### **A lucrative opportunity almost beyond compare**

A treatment that is safe, that works, that is comparatively inexpensive both to produce and to purchase due to its ability to be frozen for virtual "off the shelf" instant treatment, that can potentially deliver 90 pct plus profit margins to the company on a comparable basis to a pharmaceutical - a treatment that also eliminates the expenses involved in cultivating a patient's own stem cells - and that in many cases will need repeat doses on a six monthly, yearly or 5 year basis - offers Mesoblast an immense opportunity.

The size of the markets, which cover so wide an array of diseases and injuries, runs into several hundred billions of dollars annually.

#### ***What the brokers say***

Two brokers, Lodge Partners, who floated Mesoblast and Ord Minnett have issued comprehensive reports on the company in March and April respectively. Lodge Partners is believed to have a "buy" recommendation on the stock while Ord Minnett has refrained at this early stage from making a valuation or recommendation.

BioShares publisher David Blake said while autologous adult stem cells extracted from the patient have been proven to be efficacious in several technologies, it as yet remains to be proven whether mesenchymal precursor cells from a universal donor don't have the features or attributes that will be picked up by the surveillance components of the immune system of a human patient. The concept works from a pilot stage

point of view. If Mesoblast can use MPC's from a single donor with no special side effects this would be a major advance. David said even if the universal donor concept did not work, medical technologies are not always a binary play. The autologous approach may still have meaning. The difference is that that may be a more expensive product with a lower return on margin, but nevertheless a valuable product. The universal donor product would have much greater revenue potential.

David described the current market capitalisation of Mesoblast as fairly generous, adding that share price is indicative of market perception of what a technology is worth.

### MESOBLAST LTD - A SNAPSHOT

Mesoblast's technology was developed over ten years prior to 2001 by the Institute of Medical and Veterinary Science (Medvet) and the Hanson Institute Adelaide, enabling the efficient extraction, isolation and scale up of adult mesenchymal precursor cells which are the building blocks for cells and tissues that make up support structures and solid organs in the body such as arteries, heart muscle, bone and cartilage. Scientists at the IMVS using their proprietary Adult Stem Cell Technology were most advanced in the fields of bone and cartilage and had already achieved outstanding results in *in vivo* studies.

Mesoblast was established in July 2004 and listed on the ASX on December 16 2004, closing at 80c after an issue of 42 million shares at 50c.

With the listing monies Mesoblast acquired a 33.3 pct interest in Angioblast Systems Inc, headquartered in the US - both companies founded by Prof Silviu Itescu.

Mesoblast was granted a proprietary, worldwide licence to develop and commercialise the proprietary Adult Stem Cell Technology for Orthopaedic Applications by Medvet and will make milestone payments to Medvet of \$US250,000 on completion of Phase III clinical trials and \$US350,000 on FDA marketing approval, also a commercial arms length royalty based on net sales with similar milestone payments to be paid by Angioblast including royalties at 2.5 pct of net sales.

While Mesoblast has a proprietary world wide licence to develop and commercialise the Adult Stem Cell Technology for orthopaedic applications, Angioblast is commercialising the Technology for cardiovascular and other applications including repair and regeneration of heart muscle and growth of new blood vessels for peripheral arterial disease and skin ulcers

MSB and Angioblast have a Mutual Licence Agreement to use the technology for their different applications.

[MSB](#) ADRS trade on the NYSE under the code MBLTY.

### THE MESOBLAST TECHNOLOGY

Mesoblast uses a universal donor system to produce an off the shelf product.

So far in stem cells transplanted into many hundreds of sheep no immunological response to these cells has been seen.

A bone marrow culture is taken from a donor and within 30 to 60 minutes the adult stem cells are isolated using monoclonal antibodies. Over a 4 to 6 week period the purified adult stem cells are expanded or cultured to potentially billions of cells. Each batch of cells is frozen and made available in lots of 200/250 million cells. Frozen cells are then dispatched to hospitals for immediate use at the time and place of need. Importantly, the physician delivering the cells uses exactly the same procedures and tools to deliver cells to a patient that he or she currently uses. This enhances the physicians ability to deliver a curative procedure. Patients receiving the cells don't have to be type matched.

The company is first focusing on diseases such as arthritis, bone fractures and heart disease that impact the vast majority of people at some stage during their lives in an aging population that can afford and is demanding better treatment. These indications generally tend to be the source of greatest cost to the community in ongoing care and severely impact the quality of life for those sufferers. providing an ethical and efficacious medical solution.

Further down the track the company looks to expand its indications to diseases and disorders including neurological, macular and so forth.

Costs associated with the cells are expected to be small whilst dramatically reducing the overall cost and hospital time for procedures.

#### **THE PATENTS**

The earliest of Medvet's US and worldwide patents were filed in 1999 and run to 2016 with subsequent patent families running through to 2021 and beyond. An Australian patent was granted in January 2006 covering the composition of matter relating to a unique population of adult stem cells known as Mesenchymal Precursor Cells or MPCs as well as methods associated with purifying and enriching these cells. The granted patent is fundamental to Mesoblast's commercial model of creating a world leading, adult stem cell platform technology.

#### **MANUFACTURING**

Mesoblast and Angioblast have contracted Cambrex Corp to manufacture their MPCs. Cambrex has cell therapy manufacturing services focusing on bone marrow mesenchymal stem cells. It has cGMP compliance with manufacturing sites worldwide, also providing regulatory services. Cambrex is preparing Mesoblast's manufacturing dossier for the FDA IND applications.

#### **THE REGULATORY PATH**

As a biologic, adult stem cells are not dissimilar to the (much easier vs pharmaceuticals) regulatory protocols for a device. Stem cells are not new chemical entities that require extensive preclinical and clinical build up. In this respect the FDA has already indicated that for its chosen medical indications, Mesoblast can proceed directly to Phase II Clinical Trials in the US and in doing so has avoided substantial cost and time to market.

#### **REIMBURSEMENT**

Reimbursement for adult stem cell treatment is likely to be similar to reimbursement for treatment of bone breakages using Bone Morphogenic Proteins. Reimbursement levels for these proteins in bone regeneration are currently around \$US5000 per BMP treatment, excluding surgical fees and hospital stay. For treatment of heart disease, no comparable therapies currently exist and reimbursement is expected to be significantly higher than \$US5000 per treatment.

#### **COLLABORATIONS**

Key to Mesoblast technology is an ability to work with existing technologies including catheter manufacturers for the delivery of cells, similarly the cells can be mixed with bone fillers that are commonly used in operations today. Each of these technologies command billion dollar markets. The opportunity for Mesoblast and for international device manufacturers and pharmaceutical companies is to work together to produce a blockbuster combination product to take massive market share.

Mesoblast has already proven an ability to enter into collaborative agreements and it is expected that these agreement will be an important part of the company's future strategy. Some of these agreements include:

\*On August 24 2005 Mesoblast announced it had entered into an agreement with one of the world's largest medical device companies. Under this agreement the medical device company which has a major international presence in the orthopaedic field provides its US FDA approved carrier materials for use in combination with Mesoblast's proprietary adult stem cells in pre clinical trials supporting Mesoblast's Investigational New Drug submissions to the FDA.

\*Cordis Corporation, a Johnson & Johnson company is a collaborator in the adult stem cell Pilot Cardiac Clinical Trial through an agreement with Mesoblast's American affiliated company, Angioblast Systems Inc. The Principal Investigator of the Pilot Clinical Trial at Newcastle's John Hunter hospital, Dr Suku Thambar is using the Biosense Webster NOGA XP catheter technology to deliver the proprietary adult stem cells directly into the damaged heart muscle of up to ten patients suffering from severe multi-vessel coronary artery disease.

This should maximise the potential benefit of adult stem cells for patients with ischemic heart disease while providing clinicians with a user friendly method to deliver the cells.

Mesoblast Executive Chairman Michael Spooner said there was substantial international interest in Mesoblast's imminent clinical trials and platform technology.

#### **THE STORY SO FAR ..**

**May 22 2006** : Mesoblast Ltd announced positive initial results in preclinical trials of its proprietary adult stem cells for prevention of heart failure progression following a heart attack. Mesoblast's founder and Chief Scientific Adviser Prof Silviu Itescu said the initial positive results using adult stem cells from one universal donor to treat unrelated recipients demonstrated the safety of the company's product and validated its plan to develop an "off the shelf" cell based therapy for heart failure.

**Apr 27 2006** : Mesoblast Ltd announced results from a pre-clinical trial of its proprietary adult stem cells for spinal fusion, one of several being conducted at Colorado State University in the US, which revealed MSB's adult stem cells were highly effective for induction of spinal fusion with efficacy proportional to stem cell dose. Results are equal to or better than current gold standard treatment for degenerative intervertebral disc disease (autograft) indicating that Mesoblast's therapy can eliminate need for second operation to harvest bone. [MSB](#) has decided to proceed with FDA Phase II clinical trial submission for spinal fusion, expected by the 4<sup>th</sup> quarter 2006 and over six months ahead of Mesoblast's original schedule. Mesoblast said spinal fusion is used to treat patients with degenerative intervertebral disc disease. Over 300,000 spinal fusion procedures are currently performed annually in the US alone. Current fusion therapies use bone harvested from a patient's own hip (termed autograft) and require a second surgical procedure that frequently results in long term complications such as chronic pain and infection.

**Apr 3 2006**: Mesoblast Ltd announced a first orthopaedic patient has been safely implanted with the company's specialist adult stem cells developed using its patented technology. The director of Orthopaedics at The Royal Melbourne Hospital Mr Richard de Steiger said in the report the patient was in a stable condition after the procedure and was expected to be released from hospital shortly. The patient had sustained a major fracture of his femur some nine months ago which had not healed and resulted in a 5 cm defect. In the case of a non healing defect, a bone graft would typically be considered, using a large amount of bone taken from the patient's own hip. However this often results in long term complications including pain and possible infection.

If the adult stem cell process is successful this procedure may significantly reduce or eliminate long term patient complications whilst decreasing hospital time and costs associated with the treatment of long bone fractures.

The pilot trial will involve up to 10 patients suffering from non union long bone fractures.

**Feb 28 2006** : Mesoblast announced it is well ahead of schedule for FDA submissions for its proprietary adult stem cell technology which has been safely implanted into the first two patients taking part in a world first cardiovascular clinical trial, bringing new hope to patients in Class [III](#) congestive heart failure with severe coronary artery disease. The implant procedure under local anaesthetic went well for both patients and the company is looking forward to completing the trial of up to 10 patients as quickly as possible.

**Feb 13 2006**: Mesoblast Ltd announced positive initial results from two pre-clinical trials in the US for bone regeneration. Mesoblast founder and Chief Scientific Adviser Prof Silviu Itescu said the initial results clearly indicated that Mesoblast's adult stem cells obtained from a universal donor and produced using its proprietary technology were highly successful in generating new bone growth in multiple unrelated recipients. The extent of bone regeneration seen was in direct proportion to stem cell dose escalation.

#### **THE COMPETITION**

There were in 2005 some 82 companies worldwide conducting stem cell research.

Some of these include MultiCell Technologies Inc, Aastrom Biosciences Inc, StemCell, Osiris Therapeutics Inc, Endovasc Inc, Geron Corporation, PharmaGap Inc, Moraga Biotechnology Corporation, Ortec International Inc and Transition Therapeutics Inc.

Near competitors are seen as including **Osiris Therapeutic Inc**, a private company with three products in clinical trials, Prochymal, in Phase II clinical trials a formulation of adult stem cells to treat Graft vs Host Disease, Provacel, a formulation of stem cells to repair damaged heart tissue which is in a Phase I clinical trial and Chondrogen, where patients are being enrolled in Phase I/II study involving an injection of stem cells to repair damaged tissue in the knee joint and prevent the progression of arthritis.

Osiris also has a product line, Osteocel, a stem cell product for bone repair derived from cadaveric donors and distributed by Blackstone Medical under the Trinity brand.

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**Aastrom Biosciences** is engaged in research and development of adult stem cells for autologous therapies, using its ex vivo cell production technology to generate the company's proprietary Tissue Repair Cells for bone marrow derived adult stem cell tissue repair and regeneration.

#### **EFFECT ON OTHER COMPANIES WITH TECHNOLOGIES ADDRESSING THE SAME DISABILITIES**

\*While, if all goes to plan, Mesoblast is likely to supersede to some extent technologies such as the mechanical heart assist devices - including those developed by Australian companies Ventracor, Heartware and Sunshine Heart as well as superseding the orthopaedic knee, hip and other prosthetics along with success in the treatment of diseases including arthritis and other ailments in many cases it is likely that adult stem cells will be used in conjunction with devices including pins and plates for large bone fractures used to keep broken limbs in place whilst the bone repairs.

(Mesoblast is not a competitor to companies such as pSivida, in fact pSivida has some evaluation agreements with stem cell development companies to grow their stem cells on a biosilicon scaffold).

#### **THE DANGER OF CANCER**

While embryonic stem cells (almost universally regarded as unethical) are seen as far more likely to cause cancer, there is a danger of cancer if cells are grown outside the body for a long time.

Researchers at the Autonomous University of Madrid grew adult stem cells extracted from fat tissue for up to eight months. In that time the cells divided between 90 and 140 times. When they were transplanted into animals, the oldest cells formed cancers. Antonio Bernad, who is leading the research team, told the New Scientist magazine that pioneering treatments which already test bone marrow stem cells in humans should be safe because the cells are grown outside the body for a short time.

"In normal conditions in clinical applications we think the cells are pretty safe, but we must be careful, he said. "The key is not to grow them for too long."

Mesoblast's GMP manufacturing process eliminates these risks by working with a pure population of stem cells that are divided by 20 to 30 times only. Furthermore, batch manufacturing is adopted by the company so as to provide absolute quality assurance of the end product.

To date Mesoblast's cells have been implanted into hundreds of small and large animals, with no evidence of any cancer formation.

#### **MESOBLAST FINANCIALS**

Last Traded price           \$1.41  
Shares Issued               93.51 mln (in escrow 46.79 mln)  
Unlisted options issued:  5.66 mln at 55 and 60 cents  
Market Cap                 \$136.7 mln  
Year ended June 30, Values in \$000s

<b>INCOME</b>	<b>2006 Int</b>	<b>2005</b>
Op Revenue	883	503
Op (loss)	(2883)	(1517)
Net (loss)	(2883)	(1517)
(loss)PS (Cents)	(3.08)	(2.12)

BALANCE SHEET	2006	2005
Current Assets	12864	15326
Non Current Assets..	5373	6027
Current Liabilities	1707	2203
Non Current Liabilities	-	-
Net Assets & Shareholders' Funds	16530	19150
Intangibles	750	705
Net Tangible Assets	15780	18445
Gearing (Net of Cash) %	Nil	Nil
NTA per share (cents)	16.9	19.7
Shares Issued (Millions)	93.51	93.51
Options Issued (millions)	5.66	5.66

Cash Flows:	2006 3rd Qtr	2006 Int	2005
Cash on hand (at open)	11980	15094	-
Operating Activities	(796)	(1982)	(605)
Investing	(1968)	(1132)	(4969)
Financing Activates	-	-	20668
<b>Cash on hand at Year end</b>	<b>9216</b>	<b>11980</b>	<b>15094</b>

1/The company expects to have sufficient funding to take it to approval for Phase II trials estimated early 2007. It is on budget and well ahead of schedule.

2/In 2005 Silviu Itescu received a \$1.5 million grant from the National Health & Medical Research Council for use in preclinical and clinical studies into the use of MSB's MPCs.

3/This was followed by \$2.7 million Commercial Ready Grant given directly to MSB by the Australian Government to develop the MPC technology for the treatment of arthritic and other cartilage diseases in large joints in December 2005. The full \$2.7 million is expected by end 2006.

**Directors:**

**Michael Spooner**, Executive Chairman. Was Managing Director and CEO of Ventracor Ltd, before that a Principal Partner and Director of Consulting Services with PriceWaterhouse Coopers in Hong Kong for 7 years.

**Prof Silviu Itescu**, MBBS (Hons), FRACP, FACP, FACR Founder of both Mesoblast and Angioblast and a director and Chief Scientific Adviser to each company. He is based at New York's Columbia University and is also on the faculty of Melbourne University. Prof Itescu has established an outstanding international reputation in the fields of stem cell biology, autoimmune diseases, organ transplantation and heart failure. He is a non exec director of Amrad Corporation and Ambri Ltd.

**Donal O'Dwyer**, non exec. Almost 20 years experience as a senior executive in the global cardiovascular and medical devices industries. From 1996 to 2003 Mr O'Dwyer worked for Cordis Cardiology, the cardiology division of Johnson & Johnson. Prior to joining Cordis Mr O'Dwyer worked for 12 years with Baxter Healthcare. He is also on the board of Cochlear Limited, AtCor Medical Holdings Limited and Sunshine Heart Inc.

**Bryon McAllister**, non exec. Mr McAllister has extensive expertise in product development, quality assurance and obtaining FDA regulatory approval within the healthcare industry. Most recently, Mr McAllister served as Vice President, Worldwide Quality Assurance for the Ares-Serono Group based in Geneva and Boston.

**Chief Operating Officer:** Paul Rennie, over 25 years experience in marketing and business development. Formerly with Soltec (FH Faulding), Bonlac and Merck.

**Secretary and CFO:** Kevin Hollingsworth, was a director and company secretary for Alpha Technologies Corp.

**Joint Scientific Advisory Board:**

**Prof Silviu Itescu**, MBBS (Hons), FRACP, FACP, FACR, chair

**Prof Steven Graves**, MBBS, D. Phil FRACS, FA, Orth A. inaugural Professor of Orthopaedics at the University of Melbourne and director of Orthopaedics at the Royal Melbourne Hospital where he remains director of Orthopaedic Research

**Prof Robert M Graham**, FAA, MBBS (Hons), MD, FRACP, FACP, FAHA. The Des Renford Prof of Medicine, University of NSW, executive director, Victor Chang Cardiac Research Institute Sydney. Has been a consultant to pharmaceutical and biotechnology companies such as Bristol-Myers Squibb, Glaxo, the CSIRO (Pharmaceutical Division).

**Prof Henry Krum**, MBBS, Ph D, FRACP. Chair of Medical Therapeutics at Monash Uni Melbourne and an Adjunct Faculty member of Columbia University New York. Prof Krum is currently a member of the Pfizer Global Heart Failure Advisory Board.

**Prof Richard E Gilbert**, MBBS, Ph D, FRACP. Prof of Medicine at the University of Melbourne where he directs a large research program exploring new therapeutic strategies for the treatment of cardiovascular and kidney disease.

**Prof Joseph Lane** based in the US.

**Prof Peter Ghosh**

**Major shareholders:**

Prof Silviu Itescu with 46.11 pct.

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