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In this edition...
We cover two companies with alternative approaches to treating congestive heart failure. Mesoblast is confident its adult stem cell therapy is a viable approach and is beginning proof-of-concept trials in the next quarter. Sunshine Heart is using a more physical approach, a balloon cuff that wraps around the aorta and its clinical trials started this week. Mesoblast is applying its technology for cartilage and bone regeneration also and should be a company of interest to follow over the next 12 months. It is the feature of this week's edition.
We also update readers on developments at Optiscan Imaging, Arrow Pharmaceuticals and try to establish whether the waters have calmed around Australian Cancer Technology after some corporate instability earlier this year.
The editors
Companies covered: **ACU, AWP, OIL, MSB, SHC**

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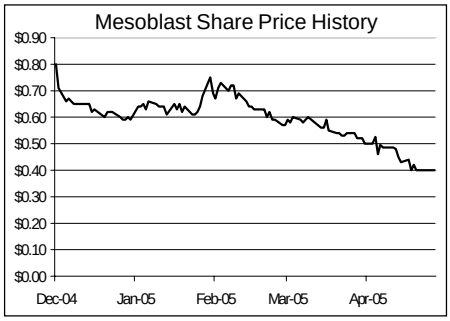
Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies.

Mesoblast – Adult Stem Cell Technology Set to Move into the Clinic

Mesoblast (MSB: 40 cents) listed on the ASX in December last year at 50 cents a share. The company's business objective is to commercial the use of selected adult stem cells in therapeutic applications, in particular in the field of orthopaedic tissue and bone regeneration, and tissue regeneration in the cardiovascular area through its investee company, Angioblast. Information regarding the advances the company has made with its technology has previously been obscure, however following detailed discussions with Mesoblast's scientists in Adelaide, there is good reason the company is confident of generating positive data from forthcoming clinical trials later this year.



The emergence of a new therapeutic class – Stem cell therapy
Traditional therapeutic modalities as we know them include behaviour modification, surgical intrusion and administration of small molecule pharmaceutical substances to modify cellular processes of pathogenic organisms or endogenous cells. Prophylactic vaccines, while not a therapy per se, have also been a significant medical technology. Over the last fifty or sixty years new technologies that have emerged and matured include organ and bone marrow transplants, artificial and supplemental mechanical device technologies (such as stents and pacemakers), and recombinant protein technologies, including monoclonal antibodies. Other technologies that have emerged but have encountered difficulties and set-backs include immuno-therapy, gene therapy and cell therapy, also known as regenerative medicine.

New technologies have emerged because of limitations with other technologies. Regenerative medicine takes its lead from the failure of pharmaceutical products and device technologies to provide orders of magnitude benefit in the treatment of many diseases, where bones, tissues and organs have deteriorated as a function of ageing, infection and lifestyle. Older technologies are not able to repair or regenerate tissue, whereas stem cell therapies have the potential to do so.

– continued over

There are two classes of stem cells, embryonic stem (ES) cells and adult stem cells, which have attracted scientists' interested in the regenerative medicine approach. Embryonic stem cells are the most basic stem cells that have the potential for growing into complete organisms, and several sub-sets of ES cells have the ability to self-renew. The goal of ES cell therapy has been to develop techniques to grow cells into tissues of choice. However, this has proved elusive technically, and met resistance at the ethics level. In contrast, adult stem cells offer different possibilities.

Adult Stem Cells

The study of adult stem cells is about forty years old. Like embryonic stem cells, adult stem cells are capable of self-renewal, in other words, they can make identical copies of themselves over long periods of time. They also give rise to a type of cell called a precursor cell, or committed cell, that generates mature cells with known functions and distinctly recognisable shapes. One major feature, and limitation, of adult stem cells is that they are rare. For example, between 1 in 10,000 to 1 in 15,000 bone marrow cells are hematopoietic stem cells, or blood forming cells. Mesoblast has developed a technology that meets this challenge of scarcity.

Bone marrow transplants have been around for many years, and it is bone marrow transplant studies, as well as the studies of both blood and bone cancers, that have advanced considerably the understanding of stem cell populations found in bone marrow. Currently, haematopoietic precursor adult stem cells are harvested and used to rebuild the immune system after high dose chemotherapy has been used. This is done using a patient's own cells (autologous), with the cells being extracted and cultured prior to chemotherapy treatment.

Another type of precursor cell found in bone marrow is the mesenchymal precursor cell (MPC). This cell gives rise to muscle, fat, bone and cartilage. This cell is the focus of Mesoblast's technology and commercial and investment proposition.

The Mesoblast technology

The core of the mesoblast technology is a proprietary MPC isolation method. Mesoblast scientists have identified a number of unique markers on the surface of MPCs. They have developed monoclonal antibodies (mab) that bind to these markers. Mesoblast's isolation process involves the introduction of the unique mab into a bone marrow extract, which is left for a period of time for the mab to 'find' and then bind to MPCs. Several other extraction steps follow that easily allow the extraction of a pure population of MPCs followed by expansion of the cells *ex-vivo.*

Technology applications

Mesoblast will be applying its technology in tissue and bone regeneration in orthopaedic applications and in tissue regeneration in the cardiovascular area via its investee company Angioblast in the US. The orthopaedic applications include:

- Regeneration of new bone and blood vessels in pronounced bone fractures
- Regeneration of damaged cartilage in the knee
- Regeneration of spinal cartilage (invertebral discs which cushion the stresses on the spine)

The cardiovascular applications involve:

- Regeneration of heart muscle following heart attack
- Rebuild damaged heart muscles in patients with congestive heart failure
- Rebuilding peripheral arteries throughout the body in conjunction with angioplasty procedures

Advantages and disadvantages of the technology

Carcinogenicity

One disadvantage of stem cells, both adult and embryonic, is that they both become cancer-causing cells as they pass a number of cell divisions. Recent studies have suggested that with adult stem cells, this occurs after about 90 replications. However, Mesoblast does not expect this to be an issue as it claims it needs between 20 and 40 divisions to produce sufficient numbers of cells for its treatments. The carcinogenicity of embryonic stem cells remains an unresolved issue.

Increased potency

Another advantage of the Mesoblast MPC technology is that they are able to generate very pure populations of cells. The company states that its approach yields a 1000-fold greater population compared to other existing methods. When injected into tissues or on bone targeted for re-generation, higher levels of purity in cultured cells increases the likelihood of correct tissue or bone formation. There is an increased potency effect.

One clear advantage is that MPC-based therapies bypass the ethical dilemmas and religious debates that has constrained the development of ES cell therapies. This is especially relevant in terms of optimising the time it takes to get Mesoblast's products to market.

Mesenchymal stem cells, or mesenchymal lineage cells, are attractive as basic building blocks because they have been found to not possess immuno-stimulatory molecules on their surface. In other words, they should not switch on the immune system and cause the destruction of the cells if they are cells that originate from a foreign source. This means that unrelated donors might be used as a source of cells. It is a potentially major benefit for Mesoblast as it aims to build a suite of less expensive products in a safe but off-the-shelf manner. But these properties need to be confirmed in clinical studies.

Existing market in orthopaedics

Mesoblast (and Angioblast) is seeking to address areas where there is a very large unmet clinical need. In the orthopaedic area, there is already an existing market for bone and invertebral disc regeneration that stem cell therapy could compete in and significantly improve upon. Stryker Corporation and Wyeth currently manufacture and sell bone growth factors called OP-1 and BMP-2 respectively. These are used in conjunction with a collagen matrix to repair large bone fractions where a bone autograft is not feasible and also in spinal fusion procedures. In 2004, Wyeth sales of BMP-2 totalled US$165 million, a 180%

increase over the previous year. There is now a defined clinical path for such products and also a growing market.

A new recruit to Mesoblast, Robyn Kildey, spend 11 years working a Stryker and seven of those years working on OP-1, including the launch onto the market in 2001. Her market and regulatory expertise will be particularly useful to Mesoblast in developing its stem cell product for bone and cartilage regeneration. Mesoblast's product will be incorporated with commercially available scaffolds and a collaboration with a scaffold manufacturer may help streamline the development of Mesoblast's technology.

Results to date

The preclinical results from bone regeneration studies look very impressive. Data has been generated from six sheep studies, where in some cases, full bone regeneration of 5cm bone defect (void) was achieved. In rat studies, Mesoblast's human MPCs were shown to regenerate the heart muscle following an induced heart attack and achieve a long-term improvement in heart function. Although the preclinical data is limited, there is mounting evidence that suggests these MPCs can regenerate bone and tissue cells in the body. Other groups have also previously shown that use of stem cells can improve cardiac output.

Clinical trials

Mesoblast has sufficient confidence in its technology to start patient trials in cardiovascular and orthopaedic areas in the third quarter of this year. The results achieved in the sheep study should be representative of what can be achieved in humans. Ethics approval for a cardiovascular trial at the John Hunter Hospital in Newcastle, in approximately 10 patients with severe coronary heart disease, has been received. Orthopaedic trials are also expected to begin in the third quarter in treating segmental bone defects and vertebral disc regeneration.

These clinical trials will involve autologous (patient's own) stem cell therapy and results should be available within 12 months. There should be no immune system rejection issues and regulatory approval is more straightforward because the patient's own cells are being used.

The plan for Mesoblast is to complete the autologous clinical trials to establish proof-of-principal evidence in humans. This will be followed by allogeneic (other person's cells) clinical trials that are expected to begin within two years. For this to occur, a GMP approved facility and process needs to be established and this should be ready by early 2007. The business plan for Mesoblast is to sell allogenic MPCs to promote tissue and bone regeneration.

Competition

Mesoblast has one main competitor at this stage in its field, Osiris Therapeutics in Baltimore, USA. Osiris has just started two clinical trials, one in March using allogeneic adult MPCs and in April this year it started a 48 patient trial using allogeneic adult MPCs to regenerate cartilage-like meniscus tissue in the knee. Whilst Osiris has granted US patents over its technology and has started its clinical program, Mesoblast believes its MPC separation technology achieves MPC concentrations 1000 times greater than its competitor.

Company structure

Mesoblast is an Australian listed operation that is focused in orthopedic applications of the MPC technology. It has set aside $10 million to invest in stages in a private US company, Angioblast, and eventually acquire a 33% stake. Angioblast is focussed on cardiovascular applications of the technology. Angioblast was founded by Silvui Itescu in 2001.

Management

Mesoblast is seeking to fill the position of CEO. Operational tasks are managed by Chief Operating Officer, Paul Rennie, who previously held positions with Merck (Australia), Bonlac and with FH Faulding subsidiary, Soltec. A key recent appointment was that of Robyn Kildey, who previously was the OP1 product manager in Boston for seven years, with orthopaedic products firm Stryker Corporation. Board members include chairman Michael Spooner, Donal O'Dwyer, Byron McAllister and founder Silviu Itescu.

Risks

Mesoblast is a speculative investment although it is targeting markets with very large unmet clinical needs. Risks for the company include its IP position – with no US granted patents at this stage although three have been filed – and the risk the tissue and bone regeneration will not be consistently achieved, that cell proliferation will not be contained, or an immune response will be evoked by patients. That the company at this stage does not have an appointed CEO is a negative although this situation may change in coming months. The $10 million proposed investment in Angioblast in the US lacks transparency and the company could benefit from fully communicating the use of those funds.

Summary

Mesoblast has a number of attractive features as an investment. Investors should get a good idea over the next 12 months of the capacity of the technology to deliver clinical results in both cardiovascular and orthopaedic applications. The company is well funded, with $16 million in cash. It is seeking to treat very large unmet clinical needs and the company has few competitors at this time. Adult stem cell therapy has been used for many years in the form of bone marrow transplants. The advance to using adult stem cell derived MPCs in regenerative medicine does not appear unachievable and preclinical results to date suggests it is possible. Mesoblast is capitalised at $37 million and *Bioshares* recommends the stock as a **Speculative Buy Class B investment**.

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, *Bioshares* divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, *Bioshares* grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell