Southern Cross Equities

3 March 2011

Mesoblast (MSB)

The stem cell opportunity in 2011

Analyst
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Authorisation
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Recommendation
Buy
Price
$5.80
Target (12 months)
$11.00

Mesoblast (MSB) is developing adult stem cell technology for various applications including heart failure. MSB's clinical data to date has been favourable. There is potential for multiple licensing opportunities beyond the recent Cephalon deal. Time to market is fairly short. And management is capable. Recommendation switches to Buy (was Spec. Buy) with a new target price of $11.00 (was $7.00).

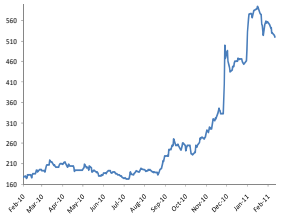
Expected Return

Capital growth	**90%**
Dividend yield	**0%**
Total expected return	**90%**

Company Data & Ratios

Enterprise value	**$1,341m**
Market cap	**$1,619m**
Issued capital	**279.1m**
Free float	**56%**
12 month price range	**$1.71-$5.98**
GICS sector	**Healthcare Equipment and Services**

Absolute Price



SOURCE: IRESS

NOTE: In May 2010 Southern Cross Equities managed a $37m capital raising for Mesoblast, while in December 2010 Southern Cross Equities placed, to institutional investors, 14.4 million of the MSB shares issued to acquire Angioblast. In each case Southern Cross earned fees.

This note updates our 10 January 2010 initiation piece on Mesoblast as well as subsequent research in 2010.

Stem cells are the wave of the future in medicine

Stem cells, which are cells with the ability to develop into many different cell types, have demonstrated over the last ten years that they can potentially cure a wide variety of diseases. This makes stem cell technologies increasingly powerful in terms of the upcoming commercial payoff from new drugs, particular with Big and Specialty Pharma now interested in the area.

MSB has stem cell technology that works

Mesoblast (MSB) is commercialising Mesenchymal Precursor Cell technology that allows adult stem cells to be extracted from the bone marrow of donors, grown into therapeutic quantities and administered to non-related patients. The technology is non-controversial, and clinical data is starting to emerge showing it to be effective compared to existing therapies. MSB is primarily targeting the orthopaedic and cardiovascular space with its stem cells. In both areas there are a large number of high-value applications where MSB's technology can make a difference. With the FDA only requiring one Phase II and one pivotal trial before approving a successful stem cell therapy, MSB has potential to be yielding commercial revenues by 2012/13.

Commercial management, and a quality partner

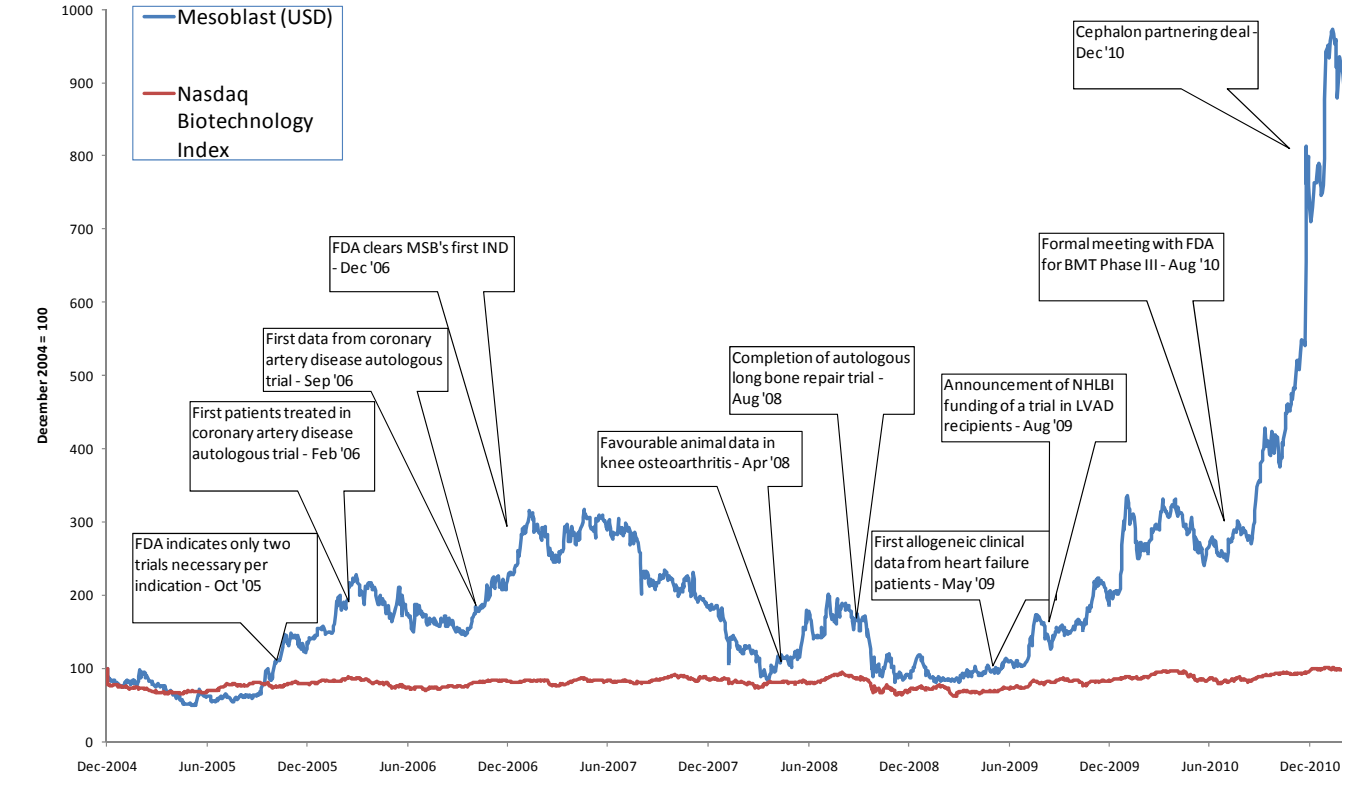
Management led by Executive Director Professor Silviu Itescu has taken a commercial approach to creating shareholder value from MSB's technology. This has helped attract the US specialty pharma company Cephalon as a partner in various MSB programmes, as well as a 19.99% shareholder.

Target price $11.00 attainable with the help of clinical data

We value the MSB pipeline using a probability-weighted DCF approach with a base case $7.34 and optimistic case $14.56. Our $11.00 target price sits at the midpoint of our DCF range. There is potential for the market to rerate MSB stock as further clinical data on the therapeutic power of MPCs emerges during 2011.

Mesoblast – the stem cell opportunity

Figure 1 – Major developments for MSB since its December 2004 IPO



SOURCE: NASDAQ, ASX, MSB, SOUTHERN CROSS EQUITIES

The best way to predict the future is to create it – Peter Drucker (1909-2005), American theorist of management.

Fifteen reasons to own MSB

Introducing Mesoblast, ASX Code MSB. A Melbourne-based biotechnology company, Mesoblast is creating clinical therapies from a class of adult stem cell called Mesenchymal Precursor Cells (MPCs). The company is currently conducting six Phase II trials of the technology, mainly in orthopaedic and cardiovascular applications, and is getting ready for its first pivotal trial, in bone marrow transplantation. Three Phase II trials are pending. In many cases there are multi-billion dollar markets to enter in the event of clinical success. Until 2010 Mesoblast focused on the orthopaedic applications of the technology while a 39%-owned associated American company called Angioblast Systems focused on the cardiovascular applications. Mesoblast acquired the Angioblast shares it did not previously hold late in 2010.

We see fifteen reasons why investors should own MSB at current prices:

1. **MSB is part of a wave of the future that is capitalised at only US$3.3bn globally.** Stem cells, which are cells with the ability to develop into many different cell types, have demonstrated over the last ten years that they can potentially cure a wide variety of diseases. This makes stem cell technologies such as those owned by MSB increasingly powerful in terms of the upcoming commercial payoff from new drugs. Currently the entire listed stem cell sector of 15 companies is capitalised at just over US$3.3bn, reflecting the early stages of what we think will be one of the most commercially significant areas of healthcare in the 21st Century.
2. **There is solid science behind Mesoblast's technology.** Since 2001 Mesoblast has perfected methods for obtaining and expanding its stem cells from donors so they can be stored and then used in unrelated patients as an 'off the shelf' therapy.
3. **Favourable clinical data is starting to emerge.** Between 2005 and 2007 the company trialled its technology first in 'autologous' applications – ie the patient was given his own stem cells - in the orthopaedics and cardiovascular space. From 2007 it has been successfully trialling them in 'allogeneic' settings where stem cells from a donor are transplanted in an unrelated recipient. The first favourable allogeneic clinical data was obtained from Phase II trials in 2009, markedly boosting the credibility of the MSB story.

Cephalon has bought 19.99% of MSB

4. **A major partnering deal with Cephalon has derisked the company.** In one of the largest biotechnology transactions of 2010 globally, MSB announced, in December, a partnering deal with the American specialty pharma company Cephalon (Nasdaq: CEPH) that saw Cephalon 1) take a 19.99% stake in the company 2) partner with MSB on the heart failure, heart attack and bone marrow transplant applications of the MPC technology and 3) agree to help fund new programmes in Alzheimer's and Parkinson's disease. We see this deal as a transforming one for the stem cell space, in that it sees an established pharma company commit substantial resources to stem cell development as a significant part of its pipeline for the first time. It is also transforming for Mesoblast in that it substantially derisks the company by providing adequate funding for all programmes, an established distribution platform for products as they gain regulatory approval, and strong financial upside. Cephalon's due diligence prior to the deal will also serve as a comfort factor for investors.
5. **MSB now has A$281m in cash.** The upfront payment and equity placement associated with the Cepahlon deal has left MSB amply funded for further

clinical development and negated the possibility of further capital raisings.

6. **Multiple trials are now underway with a pivotal coming soon**. As we noted above, MSB is currently conducting or working towards Phase II trials in nine different applications, mostly cardiovascular and orthopaedic. In each case the MPC technology has been demonstrated to be able to make a difference in what have to date been underserved patient populations. With MSB collaborating on furthering the science of MPCs, we see the potential for other indications to emerge. Significantly, the embryonic stem cell company Geron, which currently has a market capitalisation of US$577m[1], is only entering Phase I now for its stem cell products (although it has made it to Phase II with a cancer vaccine based on the enzyme telomerase).

Figure 2 - Clinical trials being undertaken by MSB

Application	Current Phase	SCE estimate of completion - optimistic case	SCE estimate of completion - base case	Patients
Posterior interbudy lumbar fusion	II	Mar-11	Aug-11	24
Cervical spinal fusion	II	Mar-11	Aug-11	24
Intervertebral disc repair	II pending			48
Heart failure	II	Jul-11	Aug-11	60
Heart failure with LVADS	II	Nov-11	May-12	80
Acute myocardial infarction	II pending			25
Knee osteoarthritis	II	Mar-11	Jul-11	24
AMD / diabetic retinopathy	II pending			25
Bone marrow transplant	III[2]	Jul-12	Oct-12	100

SOURCE: MSB, SOUTHERN CROSS EQUITIES. NOTE - ACUTE MYOCARDIAL INFARCTION AND AMD / DIABETIC RETINOPATHY PATIENT NUMBERS ARE SOUTHERN CROSS EQUITIES ASSUMPTIONS

7. **MSB is now a Phase III company with its bone marrow transplant application.** After a successful Phase II trial, MSB's Phase III trial of MPC technology in bone marrow transplantation (BMT) is being readied for commencement, with a Special Protocol Assessment to be sought from the FDA. We think the market is now in a good position to start rating MSB as a Phase III opportunity. We see the BMT indication as indicative of substantial upside for MSB. The indication will serve a patient population about as large as that currently served by Cochlear, which has a market capitalisation of A$4.5bn. Also, we see the success of the Phase II trial as pointing towards a significant derisking of the technology.

MSB's heart failure trial has generated solid interim data

8. **MSB's heart failure trial is on track for successful completion mid-2011.** With a 60-patient Phase II trial in Class II and III heart failure patients having generated solid interim Phase II data in January 2011, we expect a favourable outcome from this trial in mid-2011, opening up multi-billion dollar opportunities in heart failure.

9. **MSB has started to build a valuable spinal 'franchise'.** With the MPC technology being successfully applied across a spectrum of spine-related procedures in a Phase II setting, we see substantial value accruing to MSB for this franchise, since it allows a potential acquirer to comprehensively access a large and growing segment of the orthopaedics market.

[1] 2 March close on Nasdaq.

[2] Initiating early 2011.

The FDA only requires two clinical trials per MSB application

10. **Other applications are growing in importance**. We like MSB's potential in applications such as knee osteoarthritis, long bone repair, AMD/diabetic retinopathy and Type I and II diabetes, where the animal data looks good.
11. **The path to market is fast.** With the FDA only requiring one Phase II and one pivotal trial before approving a stem cell therapy, we see MSB as requiring a relatively short time before the MPC technology begins to yield commercial revenues.
12. **The management is commercial.** We have a high regard for MSB's leadership team led by Executive Director Professor Silviu Itescu, who owns 24.5% of the company and is its largest shareholder. We like the commercial approach the company has taken to create shareholder value, as typified by the decision to make orthopaedic applications a key focus in the early days of the company.
13. **We expect substantial news flow in 2011.** The next 6-9 months will feature some strong news flow from MSB, with potential announcements including:
    - Initiation of clinical work on diabetes and AMD/diabetic retinopathy;
    - Potential completion of the spinal fusion trials;
    - Completion of the heart failure trial;
    - Potential completion of the knee osteoarthritis trial;
    - Formal completion of the Phase II BMT trial, and clearing of the pivotal trial and Special Protocol Assessment by the FDA;
    - IND filings for intervertebral disc repair and acute myocardial infarction (the latter a refined version of an earlier IND); and
    - Animal data on new MPC indications including Alzheimer's and Parkinson's.
14. **There is potential for M&A activity.** We see a number of reasons why Mesoblast may attract further M&A interest from Big and Specialty Pharma:
    - *Mesoblast has long-dated patent protection*, with its earliest patent having a 1999 priority date and the most meaningful priority date having been established in 2006, allowing patent protection out to at least 2026;
    - *Mesoblast is being set up to enjoy 'pharma-style' economics from its off-the-shelf business model*. The ability to obtain MPCs from one donor and then administer them to an unrelated donor allows Mesoblast's products to be sold like they were small molecules or monoclonal antibodies;
    - *Mesoblast would give its partners 'first mover advantage'*. When Roche first acquired a majority stake in Genentech in 1990 (the minorities were taken out in 2009) it effectively acquired first mover advantage in the Next Big Thing in pharmaceuticals – monoclonal antibodies - from which it benefited in a major way from the mid- 1990s on. We think Mesoblast can yield a similar advantage today in stem cells.
15. **The stock is trading significantly below our target price.** We assume the MSB pipeline has value for the both the older as well as newer programmes. Our $11.00 target price for MSB is at the midpoint of our base case $7.34 / optimistic case $14.56 per share probability-weighted DCF valuation.

Valuing MSB and realising that value

We value MSB at $7.34 base case and $14.56 optimistic case

Our valuation of MSB

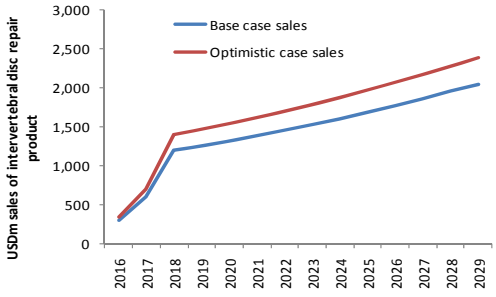
We value MSB on a per-product basis. To value MSB we took seven programmes on which MSB is currently working, and valued each using a probability-weighted DCF methodology where we assumed dates in which products enter the clinic and gain regulatory approval. We modelled each product using certain notional sales levels reached at the point of maximum sales growth in year 3, after which sales only rise 5% pa (see our intervertebral disc repair example in the figure below). We estimated in each case the milestone and royalty payments that could be realised. We applied various probability assumptions, which give the products a roughly 1-in-3 chance of clinical success. We then calculated the NPV of the resulting cash flow at a 25% discount rate, adjusted for a 30% tax rate, and subtracted a 3% royalty for the main technology providers, the Hanson Institute in Adelaide and Columbia University in New York. We converted the resulting valuations back to AUD at a long run AUDUSD exchange rate of 0.80. The various valuation parameters used are laid out below.

We assume an effective 17-20% royalty. As we note below, under the company's partnering deal with Cephalon, MSB will retain manufacturing rights for MPCs and will manufacture products either through its own facilities or in contracted facilities, selling them to Cephalon for a set transfer price out to patent expiry. The transfer pricing arrangements have not been disclosed, however we assume a transfer pricing arrangement of 32-35% of average selling price[3], offset by an MSB cost of manufacture worth 15% of average selling price. This translates to an effective royalty on sales of 17-20%. We think this may prove conservative in the long run, since MSB and its contractors will likely learn over time how to lower their cost of goods and take advantage of increasing economies of scale.

We assume no further capital needs to be raised. With around A$281m in the bank after the Cephalon deal we assume that MSB is fully funded for any clinical programmes it undertakes going forward.

Target price $11.00. The result of our valuation work for MSB was base case $7.34 per share and optimistic case $14.56. We used the midpoint of our DCF as our 12-month target price for the stock.

Figure 3 - Assumed sales profile for intervertebral disc repair product



SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

[3] We understand that Wyeth's arrangement with Medtronic for BMP, where Wyeth makes the product and sells it to Medtronic, works at a transfer price of 50% of average selling price.

Figure 4 – Key parameters for valuing MSB's products

Product	Sales at maximum growth rate base (USD)	Sales at maximum growth rate optimistic (USD)	MSB remaining investment base (USD)	MSB remaining investment optimistic (USD)	Effective royalty base	Effective royalty optimistic	Year of launch	Upfronts and milestones base (USDm)	Upfronts and milestones optimistic (USDm)
Spinal fusion (100%)	500	600	20	10	17%	20%	2016	100	200
Invertebral disc repair (100%)	1200	1400	10	5	17%	20%	2016	100	200
Knee ostoarthritis (100%)	800	900	20	10	17%	20%	2016	100	200
Congestive heart failure (100%)	1400	1600	0	0	17%	20%	2015	200	300
Acute myocardial infarction (100%)	900	1000	0	0	17%	20%	2017	200	300
AMD/Diabetic retinopathy (100%)	300	500	20	10	17%	20%	2017	100	200
Bone marrow transplantation (100%)	200	400	0	0	17%	20%	2017	200	300

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

Figure 5 - Our valuation of MSB

	Base case	Optimistic case
Cephalon-partnered applications (AUDm)	947.7	1,856.9
Unpartnered applications (AUDm)	874.5	2,050.1
Cash (AUDm)	281.1	281.1
Cash from options (AUDm)	14.8	14.8
Total value (AUDm)	2,118.2	4,203.0
Total diluted shares on issue (million)	288.7	288.7
Value per share	$7.34	$14.56
Valuation midpoint	$10.95	
Share price now	$5.80	
Upside	88.7%	

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

The path to $11.00 per share

We see a number of catalysts helping to re-rate MSB over the next twelve months.

We see clinical data in 2011 as helping re-rate MSB to our $11.00 per share target

1) **Continued interest in stem cell therapies.** We see public interest across the Western world in stem cells as helping to increase sentiment towards MSB, particularly since there are no ethical issues surrounding adult stem cells.
2) **Continuing clinical success from the Phase II trials**, with data being progressively released from most of these.
3) **Continued favourable animal data**. MSB's findings from animal data have been a common theme in announcements from the company over the last six years and we see this pattern continuing.
4) **US and European patent grants**. At present MSB's intellectual property is largely in the form of published and unpublished patent applications. We see US and European patent grants as helping boost the company's commercial and scientific credibility and, by extension, sentiment towards the stock.

Cephalon has begun to unlock MSB's upside

A transforming deal from MSB's first commercial partner. In one of the largest biotechnology transactions of the past twelve months, MSB announced, in December 2010, a partnering deal with the American specialty pharma company Cephalon[4] which saw that company 1) take a 19.99% stake in MSB at A$4.35 per share[5], 2) partner with MSB on the heart failure, heart attack and bone marrow transplant applications of the MPC technology and 3) agree to help fund new programmes in Alzheimer's and Parkinson's disease. We see this deal as a transforming one for MSB and the stem cell space, in that it:

- sees an established pharma company commit substantial resources to stem cell development as a significant part of its pipeline for the first time;
- provides adequate funding for all MSB's programmes;
- brings an established distribution platform for MSB products as they gain regulatory approval;
- has strong financial upside for MSB.

The Cephalon deal bought US$1.7bn in potential milestone payments

The numbers reflect the potential of stem cells. In partnering with MSB, Cephalon paid US$130m upfront payments (helping to raise MSB's cash resources to A$281m as at 31 December) and another US$1.7bn in potential milestone payments contingent on clinical success in the relevant programmes. Mesoblast will also share in new product sales through its retention of all manufacturing rights, which we think is equivalent to a double digit royalty. We see this deal as capitalising on the tremendous potential of stem cell therapies in modern medicine.

Cephalon needs pipeline from Mesoblast, to create its own 'Next Big Thing'. Cephalon is a specialty pharma company now capitalised at US$4.3bn[6] that has been built on the back of two products:

- Provigil, an anti-sleep drug[7] which in 2009 became a blockbuster, and
- Actiq, a fentanyl lozenge product[8], which continues to deliver shareholder value post patent expiry.

The company is currently growing the top-line strongly on the back of these franchises and others. Cephalon's revenue in 2010 was US$2.8bn, up from US$2.2bn in 2009, and the company is guiding to $3.015-$3.095bn for calendar 2011. Cephalon has a problem, however – generic competition is eroding the Actiq franchise while the modafinil[9] franchise is nearing the end of its patent life. The company is therefore incentivised to invest heavily in its pipeline, which it is doing in the fields of CNS, inflammation, oncology and pain[10]. We see the willingness to invest in and partner with Mesoblast as indicative of this continued hunger. Also, a higher level of biological products in its pipeline will enable Cephalon to be

[4] Frazer, Pa, Nasdaq: CEPH, www.cephalon.com.

[5] Significantly above the $3.33 prior to announcement of the deal.

[6] 2/3/2011 close on Nasdaq.

[7] Indicated among other things for narcolepsy, a sleep disorder characterised by sudden and uncontrollable episodes of deep sleep. This rare neurological problem affects around 0.05% of the general population.

[8] Fentanyl is an opioid analgesic. Actiq is, in effect, a fentanyl 'lollypop'.

[9] Provigil's generic name.

[10] To that end it paid A$318m to acquire the Sydney-based antibody company Arana in 2009.

compared more favourably with American specialty biopharmas like Genzyme[11] (market cap US$19.56bn) and Celgene[12] (market cap US$25.3bn) that naturally attract a premium because of the strong pricing and demand for their products.

Cephalon is renowned for the quality of its field force

Cephalon has a strong distribution platform for Mesoblast's products. A key part of Cephalon's success over the last ten years has been the quality of its sales force. This is typified by the Actiq story. Actiq, which was launched in the US market in 2001, grew from US$15m in sales that year to US$580m in global sales in 2006 prior to US patent expiry in part because of a sales effort that could detail the entire American market for pain specialists with only 90 people. Obviously other areas of medicine require higher levels of investment in sales teams than does pain, but the example shows that Cephalon has the smarts to be able to build market reach for Mesoblast's products. We think a sales force of only 30 people would likely be required for Mesoblast's lead product, which is MPCs used in improving bone marrow transplant outcomes. As things stand Cephalon already has a sales force for oncology, detailing products like the leukaemia drugs Treanda and Trisenox.

This deal leaves Mesoblast amply funded for future commercial development. As we noted above, Mesoblast has around ~A$281m cash after the current transaction, from:

- The US$130m (A$127.9m) upfront payment from Cephalon to access the clinical programmes;
- A$107.5m from new stock being issued to Cephalon so that it can take its 19.99% stake[13];
- ~A$45.7m cash after settlement of the May 2010 share placement at $1.70 per share.

The deal takes forward the valuable cardiovascular and BMT programmes. Under the partnership arrangement Mesoblast will fund products through to Phase IIa and Cephalon from Phase IIb. Mesoblast's guidance from the FDA so far has been that only one Phase II and one Phase III trial is required. What the Cephalon deal means is that:

- Cephalon will fund the US bone marrow transplant pivotal, expected to launch in early 2011, and
- Cephalon will be funding the US pivotal for heart failure that should follow from Phase II data, which is expected to be available in mid-2011.

The heart failure upside in particular is significant because around 5.8 million Americans or 2.6% of the adult population suffers from heart failure. Should Mesoblast garner twelve month efficacy data on hospitalisations and level of survival using MPCs, doctors treating Class II and III patients, worth around 60% of the heart failure market, are likely to be highly receptive[14].

The deal also adds a couple of new programmes. Cephalon's willingness to 50% fund pre-clinical and Phase I and IIa work in Alzheimer's and Parkinson's suggest that Mesoblast has some interesting *in vitro* and possibly *in vivo* data in this area. Various groups have been looking into the possibility that neural stem cells can

[11] Nasdaq: GENZ; Cambridge, Ma; www.genzyme.com.

[12] Nasdaq: CELG; Summit, NJ; www.celgene.com.

[13] Cephalon bought 31.08 million MSB shares from vendors of Angioblast who had recently received MSB stock, and then bought 24.7 million new shares from MSB, both at A$4.35 each.

[14] It's worthwhile noting that HeartWare (ASX: HIN), whose LVAD is indicated for Class IV patients (see our note of 11/11/2010, headlined *The quest for the world's smallest LVAD*), serves only 5% of the heart failure market but is now a billion dollar company in terms of market capitalisation.

treat these conditions[15], and given the versatility MPCs have shown, we would not be surprised to see favourable data from Mesoblast in 2011[16].

The deal allows Mesoblast to push harder on its other programmes. The cash on hand from the deal will allow Mesoblast to fund late stage trials of its spinal fusion, intervertebral disc repair, knee osteoarthritis and AMD/diabetic retinopathy, all of which have potential to enjoy sales in the hundreds of millions or billions of dollars on regulatory approval.

The milestone upside for Mesoblast is strong. Cephalon will pay US$1.7bn in milestone payments in the event of clinical success, which we think the market will value more highly as the passage into Phase III of the BMT and heart failure lessen the clinical risks of MPCs. We think there is potential to receive ~US$100m each time a product gets through Phase III under this deal.

MSB have retained manufacturing rights to its MPCs

The manufacturing upside is possibly stronger. While the milestones are solid we see the real upside as being in the fact that Mesoblast will '*retain all manufacturing rights and will share significantly in the net product sales*'. This means that upon regulatory approval Mesoblast will manufacture products either through its own facilities or in contracted facilities (it prefers contracted, at this stage), and sell them to Cephalon for a set transfer price out to patent expiry (around 2026). This is similar to Pfizer/Wyeth's arrangement with Medtronic for BMP, where Wyeth makes the product and sells it to Medtronic at a predefined transfer price. We assume (and we think this is conservative) that the arrangement allows the equivalent of a 17-20% royalty to Mesoblast, with Mesoblast having further upside depending on how much it can drive down production costs of stem cells[17].

[15] See *Neural stem cell may rescue memory in advanced Alzheimer's, mouse study suggests*, Science Daily, 22/7/2009, and *Adult stem cell research reverses effects of Parkinson's disease in human trial* by Steven Ertelt, LifeNews.com, 16/2/2009.

[16] Consider that in December 2009 Mesoblast generated favourable pre-clinical data in diabetes which is still being followed up, we understand with favourable results.

[17] The company now plans to do some work on scale up of culture processes as well as technologies for efficient use of culture media, among other things.

MSB is a stem cell success story

MSB has been working on technology for both obtaining adult stem cells and making enough of those cells to bring about a therapeutic difference in patients. The main commercial focus for the MPC technology is the billion dollar markets for cardiovascular and orthopaedic treatments. A key attraction of MSB is the quality of the technology, which has enabled the company to access the therapeutic power of stem cells without the scientific and ethical drawbacks that have hindered other stem cell approaches in the past. To understand the commercial potential of the technology, it's first necessary to understand some of the science behind it.

MSB benefits from rising public awareness of stem cells

Stem cells are 'the next big thing' in modern medicine.

What are stem cells? Stem cells are cells with the ability to develop into many different cell types, making them important as potential therapies requiring the replacement of cells that have been lost or damaged, such as Parkinson's disease or diabetes. Public awareness of stem cells has been growing strongly over the last ten years, mainly due to a multiplicity of stem cell breakthroughs in the lab and clinic, many in hard-to-treat conditions such as:

- *Heart disease* – MSB's MPC technology originated with animal work showing that adult blood vessel stem cell injections could repair damaged heart muscle (see Appendix I).
- *Spinal cord injury* – In work funded by the stem cell company Geron[18], nerve cells derived from human embryonic stem cells, when transplanted into paralysed rats, enabled the animals to walk again.
- *Diabetes* - Researchers at the University of Sao Paulo in Brazil have used injections of a patient's own stem cells to reverse type 1 diabetes – those treated no longer need insulin to control their blood sugar levels.
- *Parkinson's disease* – Primate models of Parkinson's administered human neural stem cells by Yale researchers saw their condition stabilise for about four months.
- *Tissue repair* - Researchers and doctors in the UK, Italy and Spain were able to rebuild a trachea that had been destroyed by the tuberculosis bacterium, through use of her own stem cells plus donated tracheal tissue.

Stem cells are the wave of the future in medicine. As well as the scientific evidence there are three other reasons why stem cells will loom large in 21st Century medicine:

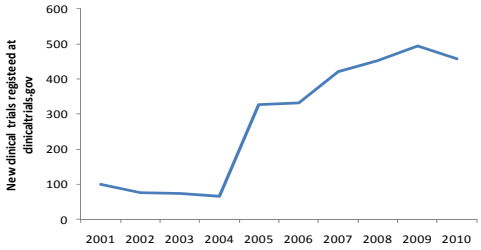
1) *Big Pharma is starting to get involved in the area*, with Pfizer having led the way, first by starting a Regenerative Medicine unit in late 2008, and then in late 2009 by announcing a partnering deal with the adult stem cell company Athersys (see Appendix II). Attracting Big Pharma is the fact that many of its blockbuster small molecule drugs are going off-patent over the next five years, and stem cells represent a patentable area that can potentially result in 'off-the-shelf' therapies similar to existing drugs and vaccines.
2) *Increased public funding is flowing towards stem cell research*, reflecting growing interest by voters in the success of this field.

[18] Nasdaq: GERN; Menlo Park, Ca; www.geron.com.

3) *Science is starting to work towards an 'end-run' around the various ethical issues* concerning embryonic stem cells, as evidenced by the development of a new kind of cell called the induced Pluripotent Stem cell.

For more on the background to the emergence of the stem cell field see Appendix III of this note. We think the widespread successes being registered in the stem cell space is helping investor reception for the MSB story, with MSB a great play on the future commerciality of the field.

Figure 6 - The volume of new stem-cell related trials is also increasing as the science translates to the clinic



SOURCE: CLINICALTRIALS.GOV

There is strong science behind MSB's technology

The key to stem cell therapy is mesenchymal stem cells. Speaking very broadly, an adult's bone marrow contains two kinds of stem cells - *haemopoietic stem cells* (also known as CD34+ cells) that help build the body's blood supply, and *mesenchymal stem cells* that can differentiate themselves into a number of different cell types including bone, cartilage, fat and heart. Mesenchymal stem cells, once obtained, are easy to work with because:

- they are relatively easy to 'expand', where expansion is the process of taking a small initial batch and creating from it sizeable quantities of cells. Unlike haemopoietic stem cells, mesenchymal stem cells seem to respond quite well to expansion reagents and stay relatively undifferentiated in the process.
- cell biologists have found that the transfer of such cells from one individual to another presents little in the way of immune system rejection problems[19].

As a consequence of this ease of use, and the fact that adult stem cells don't attract the ethical controversy surrounding embryonic stem cells, academic interest in mesenchymal stem cells, as measured by published papers in scientific journals, has been rising markedly in recent years.

MSB's technology avoids the ethical issues surrounding embryonic stem cells

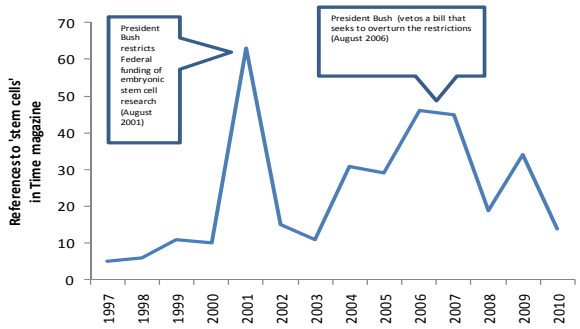
MSB knows how to get and expand mesenchymal stem cells. MSB's intellectual property, which we collectively call the MPC technology and which has primarily been obtained from the Hanson Institute in Adelaide[20] (see Appendix I), covers key methods for obtaining and then expanding 'mesenchymal precursor cells' (MPCs) from bone marrow, precursor cells being cells that can eventually turn into mesenchymal stem cells proper. Traditionally scientists seeking to obtain mesenchymal cells had a hard time separating those cells from the other kinds of cells in the marrow, since only around one in 100,000 cells in bone marrow is a mesenchymal precursor. Basically MSB makes the needle-in-a-

[19] This is because the cells lack so-called co-stimulatory molecules such as CD40, CD80 and CD46, which attract the attention of T-cells, on their surface.

[20] A medical research facility primarily focused on cancer as well as neurological and bone disorders. See www.hansoninstitute.sa.gov.au.

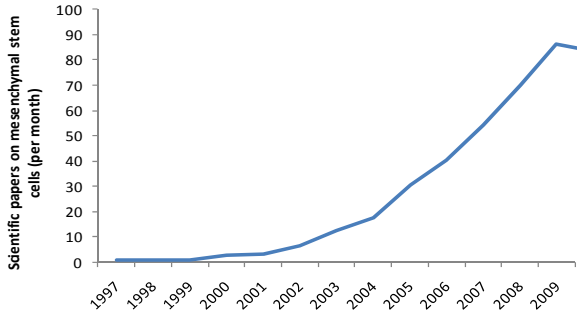
haystack job easy by using antibodies highly specific for mesenchymal precursors, after which conventional cell expansion methods can grow therapeutic batches of the cells, with 10 billion stem cells able to be produced from a starting batch of only one million cell over a six-week period[21].

Figure 7 – There has been heightened public awareness of stem cells for over ten years now



SOURCE: TIME, SOUTHERN CROSS EQUITIES

Figure 8 – Scientific publication on mesenchymal stem cells has been growing exponentially



SOURCE: PUBMED

Mesenchymal stem cells can prompt new bone and tissue growth. Mesenchymal stem cells are 'multipotent', meaning that they can turn into various, albeit limited, cell types. A large body of work has built up over the last six years demonstrating that MPCs, injected or otherwise delivered to the site where new bone and tissue is required, are able to prompt the needed cells to proliferate. For more on this see Appendix I.

The technology has competitive advantage

We see seven key advantages of the MPC technology over others in the stem cell space:

MPCs do not get rejected by the immune system of the recipient

1 **No immune system issues.** Mesenchymal precursor cells stand out from the stem cells crowd in part because it doesn't matter whether or not the cell donor and recipient are related. Ordinarily stem cell transfers from one person to another, where the two are unrelated, generate an immune response in the recipient. This is not the case with mesenchymal precursors. This means they can be used allogeneically – ie from donor to patient - whereas most adult stem cell approaches are only good for autologous therapy, where the patient's own cells are used.

2 **No ethical issues.** Whereas the laboratory and clinical use of embryonic stem cells is tied up in ethical controversy right across the Western world, there are no such issues with adult stem cells.

3 **No carcinogenicity.** There is a body of scientific opinion which suggests the potential for embryonic stem cells to be tumorigenic[22]. This can cause regulators to be cautious. Mesenchymal stem cells do not have this issue.

4 **An easier regulatory pathway.** The MPC technology is likely to enjoy a speedier journey to market than would be the case with, say, small molecule drugs, because mesenchymal precursors are 100%-natural. That is, cells cultured for use inside a patient will be no different in kind from those

[21] Put another way, one batch of cells from a single donor can be used to treat up to 500-1,000 patients depending on the treatment concerned. We understand that mesenchymal stem cells can theoretically double around 60 times (the upper end of the so-called 'Hayflick limit') before chromosomal damage starts to show up (see *Experimental Cell Research* 295 (2004) 395– 406). MSB's cell expansion processes only involve around 20 doublings.

[22] See *PLoS Med.* 2009 Feb 17;6(2):e1000029.

circulating in any healthy person's bone marrow. As a consequence, regulators may have less safety concerns and therefore require less subjects to be tested before allowing mesenchymal precursors onto the market. In pre-IND meetings with the FDA in 2005, that regulator indicated to MSB that only one Phase II and one pivotal trial would be required before an MPC product would be ready for FDA approval.

5 **A purer starting batch.** The antibodies involved in the MPC technology can pick up a starting batch of precursor cells from bone marrow 1,000 times purer than can the only significant competitor, the Baltimore-based Osiris Therapeutics[23], which relies on a less-efficient density separation technique to get its starting batches. As a result, MSB's technology can allow one bone marrow donor to provide many stem cell doses, making for easy access to source material.

6 **Superior economics.** Over the last four years MSB has demonstrated that it can scale up this technology so it can be used commercially[24].This is likely to allow the cost of production to come down over time.

7 **Easy access by clinicians to the product.** The ability to use the product 'off-the shelf' means that it can be stockpiled and used later. This is likely to be attractive to Big Pharma partners who are accustomed to such an approach.

Proof that the MPC technology works in patients

Since MSB's late 2004 IPO the MPC technology has overcome a number of clinical hurdles on its way to commercialisation:

MSB's stem cells worked well in autologous trials

AUTOLOGOUS TRIALS

In 2006 MSB performed two pilot trials in Australia involving autologous transfers of MPCs in order to develop proof of concept for the MPC technology before allogeneic trials proceeded. The thinking here was that the cell expansion process would be optimised and the best dosing methods delineated before the clinical development team moved to allogeneic work. Both the autologous trials were successful.

MPCs successfully treated severe multi-vessel coronary artery disease. A small study of MPCs in coronary artery disease commenced in early 2006 at John Hunter Hospital in Newcastle, NSW with Dr Suku Thambar as principal investigator[25]. This trial had generated efficacy data by September 2006, with MSB reporting that the patients' average global heart function had improved of 20-60% relative to baseline as a result of the therapy. Final results in August 2007 revealed that:

- all six patients in the trial experienced strengthened heart muscle within three months;
- four out of six saw a reduction in heart failure;
- five out of six saw a reduction in angina symptoms.

MPCs healed multiple non-union bone fractures. A second pilot trial in patients with bone fractures was conducted at the Royal Melbourne Hospital from April 2006. This was similarly a 'good news story', in that:

[23] Nasdaq: OSIR; Columbia, Md; www.osiristx.com.

[24] A key issue for MSB after the IPO was demonstrating that MPC expansion could happen on a commercial scale rather than merely at the benchtop level. $6m was set aside from the IPO funds to prove this, and two firms were brought in to make and ship the cells used in the initial autologous pilot trials - Cell Therapies, a specialist arm of Melbourne's Peter MacCallum Cancer Centre whose specialty is cell collection, manipulation and storage, and Cambrex, a US contract manufacturer of pharmaceutical products. With MSB having successfully dosed dozens of animals and humans with MPCs since 2005 we can now assume that there were no issues in the scale-up process.

[25] In 2002 Thambar became one of the first physicians in the world to use marrow-derived stem cells in the repair of damaged heart muscle.

- the trial generated its first data point in August 2006 when a femur fracture that had failed to heal nine months prior to MPC therapy closed only three months after receipt of MPCs;
- interim data in June 2007 showed strong bone regeneration and fracture union in the first five patients, and elimination in those patients of the need for a second operation to harvest more bone;
- six month follow-up data for all ten patients in February 2008 showed 7 out of 10 patients achieving bone union with a median time of 4.9 months, with the other three showing signs of bone formation, whereas before the trial none had shown any bone growth for some months prior to entering the trial. Higher doses led to faster bone growth, suggesting a dose response.

Long bone repair is potentially a significant market opportunity. In America there are estimated to be in excess of half a million fractures where union of the bone is delayed or where there is no union[26]. In 2006 MSB reported good evidence that MPCs will work allogeneically in this area[27]. However since 2006 the company has focused on higher-value-added orthopaedic procedures, in particular in spinal fusion. While MSB has not announced any further clinical work in long bone repair, the company is likely to use the data it has generated in treating sports injuries in Australia under 'Special Access Scheme' arrangements[28].

MSB has started to gain Phase II clinical data in allogeneic applications

ALLOGENEIC TRIALS

Success in heart failure and bone marrow transplantation. MSB took its technology into its first allogeneic clinical trials in 2007. Favourable data has now started to emerge from these trials as well:

- In 2009 MSB reported that a Phase II trial of MPCs in heart failure patients had produced a statistically significant improvement in a measure of heart function called 'Ejection Fraction'[29] for the first 20 treated patients at both the three and six month mark. In January 2011 the company announced that adverse cardiac events in the treatment group across all dosage levels at the six month mark were around half that of the control group, with statistical significance.
- In 2009 the company announced that its MPCs had helped speed the recovery of cancer patients undergoing bone marrow transplant in a Phase I/II trial. This was followed by favourable survival data in July 2010.

A 'one dose' policy raises credibility. MSB's policy going forward is that the MPCs will be tested as 'one dose therapies', meaning that only a single infusion or injection of MPCs will be administered to patients at baseline in order to determine clinical efficacy. We think this conservatism will help boost MSB's credibility with key prospective partners of the technology.

[26] A common assumption in orthopaedics is that around 5-10% of fractures will be delayed union or non-union - see Praemer, Furner and Rice, *Musculoskeletal Conditions in the United States* (Rosemont, Illinois: American Academy of Orthopaedic Surgeons, 1999). In 2006 there were around 5.6 million fractures in the US, 1.6 million resulting in hospital admissions from the Emergency Department, the other 4 million being treated in the ED and then discharged (source: HCUP Statistics on Emergency Department Use).

[27] In a sheep model of bone fracture where the tibia (the inner bone between knee and thigh) is broken, MSB cells plus the bone graft Hydroxyapatite/Tri-calcium phosphate (HA/TPC) and collagen were able to bring about bone union within three months in 80% of cases versus only 40-50% of cases for HA/TPC/collagen. MSB announced these results in February 2006.

[28] Australia's Special Access Scheme allows patients to receive drugs where there are no other alternatives but where the drug has yet to receive formal marketing approval. Many fractures suffered by sportsmen fit within the definition of 'no other alternatives'.

[29] The percentage of blood pumped out of the heart with each beat – this drops markedly in patients experiencing heart failure.

How MSB's stem cells will make money

We see MSB increasing shareholder value through:

- Targeting large markets;
- Going for high margins on its products; and
- Doing multiple partnering deals for various applications.

Large markets

In each application MSB has targeted there is a large market to address. The exception to this, possibly, is acute myocardial infarction, which we have estimated as a smaller market in its own right but which really fits the larger market of heart failure due to the tendency of many heart attack victims to go on to develop heart failure.

Figure 9 - Applications being pursued by MSB

Area	Indication	US market
Orthopaedic applications	Spinal fusion	$1.5-2.0bn
	Invertebral disc repair	$2.0bn
	Knee osteoarthritis	$3.0-3.50bn
Cardiovascular applications	Heart failure	$2.5bn
	Acute myocardial infarction	$350m
	AMD / Diabetic retinopathy	$1bn
	Bone marrow translant	$2.0-$3.0bn

SOURCE: MSB, SOUTHERN CROSS EQUITIES

MPCs have a chance to be high margin

MSB is going after biological-style costs and pricing. While we don't have any hard data on MSB's production costs, we think that the MPC technology has the potential to create products with profitability of the kind normally experienced by biological drugs – ie gross margins in the order of 85-90%. There are two reasons for this:

MSB's 'off the shelf' products potentially have good economics

1) The MPCs can be made in one central location under Good Manufacturing Practice and then transported where they are needed, as opposed to having to set up cell manufacturing facilities in individual hospitals. In effect, the product is sold 'off the shelf', allowing economies of scale and progressively lower cost of goods.

2) The rapid working of the MPCs means that the products have the potential to deliver better healthcare outcomes as measured in dollars per quality-adjusted life year than existing treatments. As a consequence they can still sell for high prices and be cost effective to healthcare systems:
   - A$20,000 per dose in bone marrow transplantation patients;
   - A$15,000-20,000 per dose in heart failure patients (which is below the US$25,000-30,000 for CRT-D devices);
   - A$8,000 in disc regeneration (which is below the typical US$11,000 cost of an artificial disc).

MSB has options in term of manufacturing. The high margins MSB expects for

its product potentially gives it options in terms of manufacturing – it can own this itself and bring in 'distribution partners'[30], or contract it out to a company such as the Swiss contract pharmaceutical manufacturer Lonza, depending on its assessment of the capital involved. We think for most applications MSB will choose to outsource manufacturing.

The manufacturing process has been approved in Australia. In July 2010 the Therapeutic Goods Administration, which is Australia's answer to the FDA, granted Mesoblast approval of the MPC manufacturing process. In the short term manufacturing approval is noteworthy because it allows MSB to earn some revenue from 'Special Access Scheme' patients in the high-priced sports injuries market. However the real importance of TGA approval is that it has allowed MSB to validated the know-how and protocols to manufacture MPCs in quantity, which will be important as the company nears FDA approval for the the leading MPC indications.

Partnering potential remains strong

We're optimistic about MSB's partnering potential beyond Cephalon

As we noted above, MSB has already done one significant partnering deal, with Cephalon. However we see multiple partnering opportunities beyond Cephalon:

1) Clinical data so far is likely to attract partnering interest in unpartnered programmes;
2) MPCs can work to improve the quality of existing medical devices made by Medtronic, Stryker etc, as well as approved drugs (ie Roche/Genentech's Lucentis drug for the treatment of AMD). Consequently large companies will be motivate to license so as to build or defend their existing product franchises;
3) MPCs can help Big Pharma move into the stem cell field without abandoning their traditional approach of making products that can be sold off the shelf;
4) The fewer clinical trials required by MPCs prior to regulatory approval is likely to appeal to partners concerned over prospective development costs;
5) The MPC technology has already been associated with two large drug/device companies - J&J and Abbott catheters have been used in clinical work, and Abbott took an equity stake in Angioblast in early 2008. The Abbott investment will have suggested to other companies that a certain amount of due diligence has already been expended on MPCs by sophisticated players in the field[31];
6) The willingness of the US government's National Heart, Lung and Blood Institute to fund a Phase II trial of MPCs in LVAD recipients from 2009 suggests that the technology has undergone further due diligence;
7) The intellectual property covering MPCs is fairly straightforward and relatively fresh, with an earliest priority date on patent applications of 1999 and the most relevant priority date being registered in 2005[32] (see Appendix I).

[30] This could be similar to Wyeth's arrangement with Medtronic for BMP, where we understand Wyeth makes the product and sells it to Medtronic at 50% of the retail price.

[31] Also boosting Abbott's interest was the fact that it is a player in the spinal implant area while its Humira antibody drug is used in treating ankylosing spondylitis, an inflammatory disorder that affects the spine.

[32] For WO 2006/108229, which covers the STRO-3 antibody MSB uses to obtain MPCs.

A strong lead application in bone marrow transplantation

Bone marrow transplants are expensive, but MSB can make them cheaper

Bone marrow transplantation (BMT) is a procedure for the treatment of blood cancers such as leukaemia or myeloma where the patient's own bone marrow, the source of the cancerous cells, is blasted away by chemotherapy and/or radiotherapy, and then rebuilt through infusions of either

- donated haemopoietic stem cells; or
- the patient's own stem cells where these have been removed prior to the treatment.

BMTs are generally effective treatments for blood cancers but they come with four problems:

1. *They're expensive* - in the United States around 11,000 transplants are performed annually at a cost of around US$200,000 each, for a US$2.2bn market[33].
2. *Marrow-derived stem cells for allogeneic transplant are difficult to source* - Donated cells need to be a good genetic match to the recipient in the HLA complex or the result is 'Graft versus Host Disease' (GvHD), where the patient's own immune system rejects the transplanted cells[34]. Generally only around 30% of patients will be able to source marrow from a family member. For those whose search is facilitated by a marrow registry such as America's National Marrow Donor Program, there can often be a long wait[35].
3. *Autologous transplants are problematic*. This issue of sourcing well-match donor cells means that many BMTs for blood cancers are autologous transplants of previously harvested cells. However the problem here is that the transplant still seems to retain some cancerous cells even after procedures to 'purge' such cells, limiting the clinical utility[36].
4. *Cord blood, the best source of stem cells for allogeneic use, comes in small doses* – Umbilical cord blood, which is increasingly collected and stored after a child is born, is rich in haemopoietic stem cells[37], with those cells allowing a less rigorous genetic match in transplant situations than marrow-derived stem cells[38]. This makes finding a donor match much easier, helped by the fact that cord blood storage is growing in popularity. However the number of cells required in a typical transplant is generally more than are contained in a single cord

[33] Source: HCUP, *Procedures in U.S. Hospitals, 2003*.

[34] Resulting amongst other things in skin inflammation, diarrhoea and jaundice.

[35] At least 55% of white people searching that registry do not find a genetic match within six months. For black people the figure is 83%. Source: National Marrow Donor Program *Report to the Community 2007*.

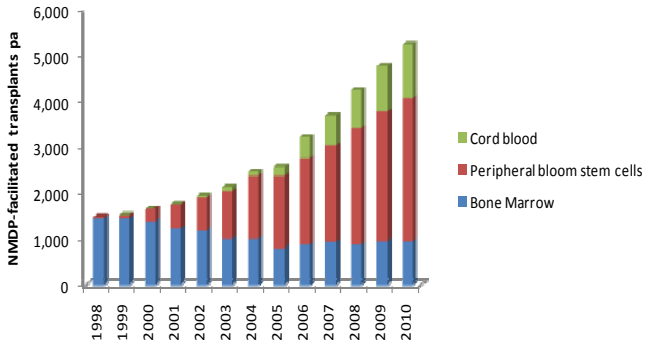
[36] See, for example, *J Clin Oncol.* 1996 Sep;14(9):2454-64, where Williams et. al., analysing purging in non-Hodgkin's lymphoma patients, found there is no significant difference in progression-free survival for purged patients.

[37] A 100-ml unit of cord blood contains one-tenth the nucleated cells and haemopoietic progenitor cells (CD34+ cells) present in 1000 ml of marrow. See editorial in *NEJM*, Volume 344:1860-1861.

[38] Bone marrow usually requires a 6/6 HLA match (see glossary) between the donor and recipient. Cord blood has been transplanted successfully with as few as 3/6 matches, although patients do best when their cord blood graft is at least a 5/6 match.

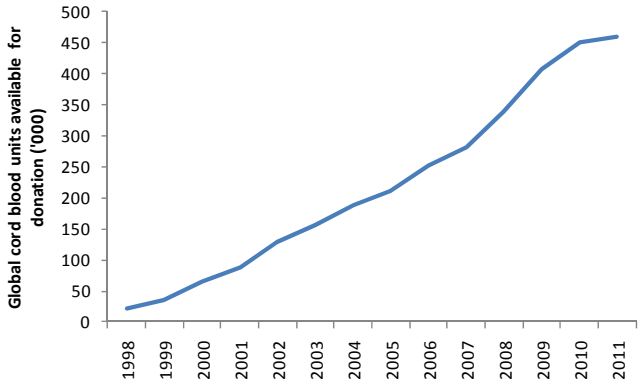
blood unit[39], meaning that the search is on for effective ways to expand the number of cells available.

Figure 10 – Stem cell transplants from cord blood have been rising



SOURCE: C.W. BILL YOUNG CELL TRANSPLANTATION PROGRAM

Figure 11 – Cord blood banks are growing around the world



SOURCE: BONE MARROW DONORS WORLDWIDE

The data from MSB's BMT trial was outstanding

MSB has gathered good clinical data on MPC-driven cord blood stem cell expansion for bone marrow transplant patients. MSB announced in November 2008 the clearing of an IND related to a 30-patient Phase I/II clinical trial of MPCs in bone marrow transplant patients where MPCs would be used to expand cord blood cells prior to infusion[40]. This trial, which is being funded by a National Institutes of Health grant, generated some solid data in 2009 and 2010:

- *Significant expansion of cells.* The company indicated in November 2009 that MPCs were expanding haemopoietic stem cells available for delivery by a factor of 40;
- *Rapid engraftment time.* Data from the first five patients available in June 2009 indicated a median engraftment time of only 15 days, around two weeks less than expected[41]. This kind of accelerated engraftment, if widely practiced, would contribute to a significant cut in the cost of a BMT by reducing Intensive Care Unit costs;
- *Fast neutrophil recovery.* MSB reported in November 2009 a median time to neutrophil recovery of 16 days for the first 18 patients, indicating that the patients' own immune systems were booting up much faster than the usual three-to-five weeks[42]. This suggests a potentially lower mortality risk from BMT;
- *Fast platelet recovery.* The 18-patient data also showed a reduction in platelet recovery to only 38 days, as against the usual eight weeks or more[43], thereby markedly reducing the risk of blood loss in these patients;

[39] A cord blood unit is the amount obtained from a single umbilical cord, and is generally around 80 ml. As an example of the shortage of stem cells in a cord blood unit, consider the case of the Red Cross Blood Service in East Flanders, Belgium, which stores cord blood units containing an average 5.2 million CD34+ cells (see *Blood*, ASH Annual Meeting Abstracts, 2004 104: Abstract 4999). A 4/6 match of cord blood should contain at least 170,000 CD34+ cells per kilogram of body weight for the graft to survive (see *Blood.* 2002;100:1611-1618). Consequently a 75 kg patient would need 12.75 million CD34+ cells or 2.45 of the East Flanders units.

[40] See NCT00498316 at www.clinicaltrials.gov.

[41] Laughlin et. al. found a median 27 days to neutrophil engraftment in 68 patients receiving cord blood transfusions. See *N Engl J Med.* 2001 Jun 14;344(24):1815-22.

[42] Rocha et. al found a median 26 days to neutrophil recovery in around 100 leukaemia patients that had received unrelated cord blood transfusions. See *N Engl J Med* 2004;351:2276-85.

[43] Michel et. al. found a median 52 days for platelet recovery in 58% of 100-or-so leukaemia patients studied who were infused with unrelated cord blood and then enjoyed platelet recovery within six months. See *Blood.* 2003;102:4290-4297.

- *Potentially less GvHD.* Only two of the first 18 patients experienced Grade III/IV GvHD (the most serious kinds), for 11% of the total. If the GvHD in question was acute rather than chronic - ie in the first 100 days post transplant - 11% is only slightly less than other studies have suggested[44]. That said, 11% GvHD suggests a good safety profile given the potentially higher doses available with cord blood expansion.
- *Survival advantage.* In July 2010 MSB reported that of the first 25 patients in the BMT trial, 20 had survived 100 days with both neutrophils and platelets successfully engrafting. This was significant because ordinarily the survival rate is only half that. The level of severe GvHD was 16%, which was in line with the company's November 2009 data. The July 2010 news is positive because it is the first indication that MPC-driven cord blood cell expansion can play a significant role in patient survival. We think this data substantially derisks the MPC technology as it applies to BMT moving into Phase III.

Bone marrow transplant could be MSB's first pivotal trial

Phase III from 2011. While this favourable data may have been driven in part by the extent of the genetic match between patient and donor[45], it nonetheless points to the potential for a strong overall clinical outcome. Consequently we expect a pivotal trial of around 100 patients from early 2011. A formal meeting with the FDA was held in August 2010. We understand the Agency indicated that it would happy to see 100-day outcomes such as cell engraftment, neutrophil recovery, platelet recovery and GvHD as endpoints in the proposed trial, but will not be requiring survival data since the other factors already indicate clinical benefit[46]. We think the data to date supports a successful Phase III outcome, which can be completed in around 18 months and be ready for FDA approval by 2013.

MSB is seeking Special Protocol Assessment. A Special Protocol Assessment (SPA) is a declaration by the FDA that a pivotal trial's clinical endpoints are acceptable for FDA approval of the drug. It effectively ensures that the FDA can't change its mind with regard to approval and ask for further data when the final results of the trial come in. An SPA may ensure that only one trial is required before MSB is seeking regulatory approval[47].

The BMT indication has Orphan Drug status. Prior to the commencement of the Phase I/II trial, MSB obtained Orphan Drug designation for the use of MPCs in stem cell expansion, where the indication is the treatment of blood cancers. In the US an Orphan Drug is one treating a disease affecting less than 200,000 patients, which would ordinarily limit the attractiveness of the market for drug developers. Designation as an Orphan Drug brings with it, among other goodies:

- seven years of marketing exclusivity after approval;
- 50% tax credits for clinical trial expenses.

[44] MacMillan et. al. found an 18% incidence of acute Grade III/IV GvHD in 80 patients receiving a single unexpanded cord blood graft where 56% of recipients had 4/6 HLA matches, 35% had 5/6 and 9% 6/6 (see *Blood.* 2009;113: 2410-2415). MSB in its 6/11/2009 announcement compared the 11% Grade III/IV incidences in its trial to *'approximately 40% in published reports of patients transplanted with unexpanded cord blood',* which equates with the historical experience of acute Grade III/IV GvHD in bone marrow transplants rather than cord blood transplants or transplants of peripheral-blood-derived HSCs (see *Bone Marrow Transplantation* (2008) 41, 215–221).

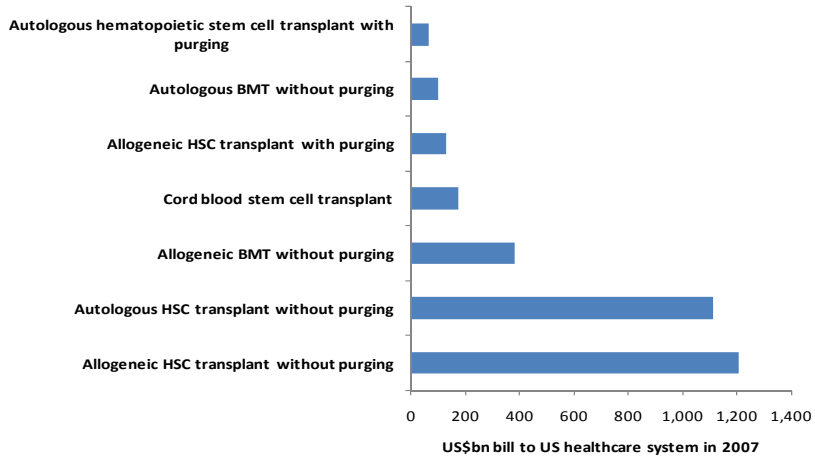
[45] Which is to say, a 5/6 HLA match in the trial would notionally yield better data than a 4/6 match, which is the minimum match level required by the trial protocol.

[46] 100 days is the generally-accepted point at which the outcome of a bone marrow transplant can be ascertained with certainty.

[47] Thereby avoiding the kind of problem which Chemgenex (ASX: CXS, www chemgenex.com) ran into on 23 March 2010. That was the day when the company announced an adverse decision from an FDA committee, which decided that a diagnostic related to OMAPRO, a cancer drug CXS had developed, should be reviewed by the FDA prior to approval of the drug. OMAPRO had completed pivotal trials but now can't be approved before the T315I diagnostic is ready for the FDA tick. OMAPRO is for the treatment of patients with chronic myeloid leukaemia who have failed on Novartis' Gleevec drug and who have developed the Bcr-Abl T315I mutation. CXS stock dropped 37% to 44 cents on this news.

We think Orphan Drug designation overcomes a potential downside of the use of MPCs in stem cell expansion, which is that there are a number of competing expansion technologies in development[48].

Figure 12 – Around the same is spent in the US on autologous HSC transplants as on allogeneic



SOURCE: HCUP SEARCH USING ICD-9-CM CODES 41.05, 41.04, 41.03, 41.06, 41.08, 41.01 AND 41.07

The bone marrow transplant application has gained Orphan Drug status

There is potential to significantly grow the bone marrow transplant market. We think a demonstrated cord blood stem cell expansion technology has the potential to at least double the number of people undergoing BMTs, for two reasons:

- at present around the same amount is spent in the US on autologous HSC transplants as on allogeneic because of the donor-matching issues. MPCs can allow physicians to dispense with autologous transplants if they and their patients prefer;
- MSB reported evidence, in October 2010, that its technology allows better purging of cancer cells from bone marrow after expansion, which would make autologous transplant approaches more viable if validated by further work. This suggests the potential to use MPCs in treating multiple myeloma, where autologous transplants have more successful outcomes than allogeneic transplants[49].

Bone marrow transplant alone represents 'another Cochlear'. For an idea of the potential value of MSB's stem cell indications as a whole, consider that an estimated 10,000 or 11,000 cochlear implants are installed in the US each year. This is around the same as the number of BMTs that MSB will seek to target with its lead MPC indication. Cochlear Ltd[50], which enjoys around 70% of the cochlear implant market globally, is currently capitalised at A$4.5bn.

[48] For example, Dr Colleen Delaney at the Fred Hutchison Cancer Research Center in Seattle has developed a cord blood expansion method that yields a 160-fold increase in CD34+ cells and that had an average 14 day engraftment time in a 2008 clinical trial (source: FHCRC).

[49] See Bone Marrow Transplant. 2005 Jun;35(12):1133-40. Autologous transplants are preferred in multiple myeloma because allogeneic transplants have traditionally been regarded as too toxic due to high GvHD. See *Bone Marrow Transplantation* (2003) 32, 1145–1151.

[50] ASX: COH, Sydney, Australia, www.cochlear.com.

A powerful cardiovascular franchise

Mesoblast is working on two major opportunities in the cardiovascular space, in partnership with Cepahalon:

- *Heart failure (*also known as congestive heart failure or CHF[51]) which is the progressive inability of the heart to pump properly due to weakened heart muscle[52].
- *Acute myocardial infarction* (AMI – what the rest of us know as a 'heart attack'), where a blockage in one or more of the blood vessels leading to the heart results in the death of heart muscle tissue.

The science is good and so is the clinical evidence to date. The experimental evidence that MPCs can make a difference in both these conditions is well established in both rat models[53] and sheep models and is based on recovery in heart function after a heart attack ('early CHF')[54], as well as recovery in heart function in established heart failure situations[55]. We noted earlier that a Phase II trial of MPCs in heart failure has already registered success at the six-month mark.

MPCs may be the next big thing in heart failure

Heart failure is a large scale opportunity for MSB not only because of the size of the market but because of the current standard of care:

2.6% of US adults have heart failure

- *Prevalence of heart failure is high*. Heart failure affects around 5.8 million Americans adults or 2.6% of the adult population, which is a knock-on effect of the high prevalence of cardiovascular disease generally. Multiplying the US number by four may give a sense of the global patient size[56]. In Europe heart failure prevalence has been estimated at more like 3.5% of the adult population[57].
- *The costs are high and rising*. Heart failure costs the US healthcare system in the order of US$35bn pa in direct medical expenses[58].
- *Incidence outruns deaths*. Heart failure incidence probably runs between 400,000 and 500,000 new cases a year in the US[59], and in our view is likely to rise in the years ahead given the aging population and the

[51] Heart failure is sometimes called congestive heart failure or CHF due to congestion in the lungs being one of its symptoms.

[52] Heart failure can start from a myocardial infarction, from coronary artery disease, from high blood pressure or from a number of other cardiovascular problems. It manifests itself in progressively more tiredness, pain and shortness of breath on the part of the patient whenever he or she engages in physical activity.

[53] See Example 4 in the WO 2004/084921 patent application.

[54] In a sheep model of heart attack MSB was able, with only low doses of MPCs, to both increase blood flow into the infarct area (the damaged heart muscle) by ~60% more than the controls as well as reduce left ventricular end-diastolic volume (DVOL), a measure of how hard the heart has to pump in the wake of the heart attack, by around 50% compared to the controls. What this suggested was that MSB's cells could reduce the risk of the sheep moving to heart failure after the heart attack. A second experiment in sheep models of heart attack measured improvement in heart function when the MPCs were delivered with a new generation cardiac catheter from J&J. Here there was an improvement in Ejection Fraction for the treated sheep, versus a decline for the controls (p=0.039), suggesting better heart function *and* no progression to heart failure (see MSB's AGM presentation, November 2006).

[55] In a sheep model of heart attack where MPCs were administered four weeks after infarction rather than shortly afterwards, DVOL for the treated sheep was stable whereas for the controls it rose 20%. For Ejection Fraction treated sheep improved 13% but the controls declined 13% out to week 12 (see MSB's AGM presentation, November 2007).

[56] In its 21/10/2010 investor presentation HeartWare suggests that heart failure 'affects over 20 million people globally'.

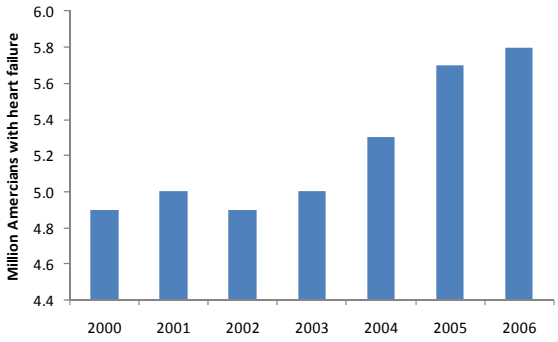
[57] An estimated 14 million adults in the EU have heart failure – source: SHAPE, the Study group on Heart failure Awareness and Perception in Europe (www.heartfailure-europe.com).

[58] Source: American Heart Association Heart Disease & Stroke Statistics 2010. These costs have risen around 7% pa for the last seven years. Heart failure-related hospital visits increased 1.7% pa between 2000 and 2006, which was 45% faster than the growth of the US adult population. Around 37% of US Medicare's spending is on patients with heart failure (see Circulation. 2008;118:S_1030).

[59] The American Heart Association estimated 550,000 cases in the early 2000s (source: Heart Disease & Stroke Statistics 2005).

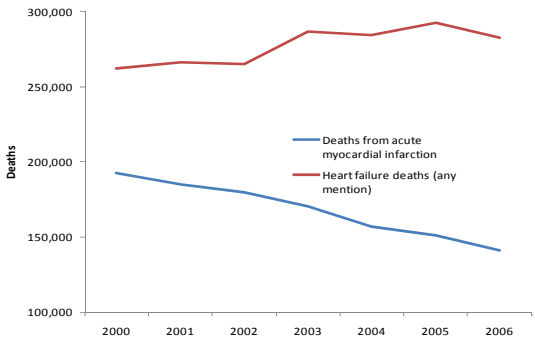
decreasing risk of dying from acute myocardial infarction[60]. In 2006 283,000 deaths were registered in the US where heart failure was an issue at the time of death[61].

Figure 13 – Estimated prevalence of heart failure is rising



SOURCE: AMERICAN HEART ASSOCIATION HEART DISEASE & STROKE STATISTICS

Figure 14 – Less Americans are dying from heart attacks, but more are dying from heart failure



SOURCE: CDC NATIONAL VITAL STATISTICS REPORTS

MPCs can be used in Class II and Class III heart failure patients

- *Existing drug therapies have only modest efficacy and only provide symptomatic relief.* While the average life expectancy of a well-treated heart failure patient today can be as high as 9 or 10 years[62], there are no drug or device therapies at present that can reverse the muscle damage which causes and progresses heart failure, whereas there's evidence that MPCs can achieve this[63].
- *LVADs are generally only used in Class IV heart failure patients, and they're costly.* The emergence of the LVAD, or left-ventricular assist device, has been one of the more promising developments in heart failure over the last decade. LVADs are implanted electromechanical pumps that assist the heart in its normal pumping action. They work very well in terms of reversing the symptoms of heart failure. However at present they are largely the preserve of Class IV heart failure patients, which represent the sickest patient group in the heart failure spectrum[64] and only constitute around 5% of the heart failure population[65]. They're also costly, with the pump along costing around US$130,000. MPCs would represent a new, and lower cost, treatment alternative for Class II and Class III patients, which at present represents perhaps 3.5 million patients in the US alone.
- *The drug market is large.* Around US$2.5bn is spent in the US on drugs indicated for heart failure such as Novartis' Diovan, GSK's Coreg CR and AstraZeneca's Atacand.

[60] There was a 22% reduction in death from acute myocardial infarction between 2001 and 2007 (Source: CDC National Vital Statistics reports) thanks primarily to devices such as stents, pacemakers and implanted defibrillators.

[61] Source: American Heart Association's *Heart Disease and Stroke Statistics* 2010 update.

[62] See University of Washington press release headlined *Seattle Heart Failure Model is able to accurately predict survival and the impact of medications and devices for patients with heart failure*, 16/3/2006.

[63] See, for example, Psaltis et. al. (*Stem Cells* 2008 Sep;26(9):2201-10. Epub 2008 Jul 3), which notes that '*following MSC transplantation, myocardial injection sites have been shown to contain Ki67-positive cardiomyocytes'.* Ki67 is a cellular marker of proliferation while cardiomyocytes are heart muscle cells.

[64] There are four classes of heart failure as denoted by the New York Heart Association: 'Class I' (you barely notice it), then Class II (occasionally you find it hard to do things), then Class III (you can't do much at all) and finally Class IV (Death's Door).

[65] The vast majority of heart failure patients are in the first three classes, with an estimated 35% in Class I, 35% in Class II and 25% in Class III. While these figures are anecdotal, they correspond well with recent Portuguese data on the diagnosis of heart failure in primary care (see Fonseca et. al., Eur J Heart Fail. 2004 Oct;6(6):795-800, 821-2).

MSB is involved in two Phase II trials in heart failure patients

MPCs have performed well in heart failure

A 'CONVENTIONAL' HEART FAILURE TRIAL, WHICH IS PERFORMING WELL

This 60-patient trial (IND cleared June 2008[66]) measures three progressively higher MPCs doses[67] against standard of care where Ejection Fraction has dropped below 40%[68]. In the trial, 45 patients randomised to the three MPCs doses and 15 to placebo. With each dose, patients received a single injection and are being evaluated for heart function recovery at three, six and twelve months. In January 2011 MSB reported favourable six month data from the trial[69]:

- the single injection of MPCs reduced the number of patients who developed any severe adverse cardiac events over the follow-up period from 93.3% in the control group to 44.4% in the treated patients (p=0.001).
- the number of patients suffering MACE (major adverse cardiac events, that is, death, heart attack, or coronary revascularisation procedures) dropped from 40% to 6.7% (p=0.005).
- the overall MACE monthly event rate went down by 84% compared with controls (p=0.01).

Twelve month data available mid-2011. This data suggests that MPCs are potentially the Next Big Thing in mid-to-late heart failure, something we expect that twelve month trial data, due mid-2011, will confirm. We expect that if the Phase II trial works out as expected, MSB and Cephalon will proceed to a >300-patient Phase III trial in 2011, with completion around mid-2013 based on 12-month follow-up from a single injection.

A 'HEART ASSIST DEVICE' TRIAL LINKS MPCS WITH THE OTHER 'NEXT BIG THING' IN HEART FAILURE.

This 80-patient trial (IND filed June 2009 and cleared in August[70]) measures two MPC doses against placebo where the patient has an LVAD implanted. It recruited over the period to June 2010 in 17 sites.

LVADs represent the team to beat. There are two main companies in the LVAD field who are pioneering its growth:

- Thoratec[71] whose Heartmate II LVAD became FDA-approved in April 2008 as a 'Bridge to Transplant'[72]. The data from the pivotal trial related to this approval was encouraging - all completing patients in the trial were 'NYHA Class IV' at baseline, but 85% of them improved to Class I or II while the other 15% at least improved to Class III. Subsequently Heartmate II became approved as a 'Destination Therapy' in January 2010[73].
- Heartware[74], whose HVAD device, which is considerably lighter and smaller than HeartMate II and which, unlike HeartWare II, is implantable within the pericardial space next to the heart. HVAD gained European

[66] See NCT00721045 at www.clinicaltrials.gov

[67] The animal work has suggested that the effects of MPC in heart failure are dose-related.

[68] A normal heart has a 55-70% EF. Around 40% of heart failure patients have EFs below 40%.

[69] Previously MSB had only reported two data points from this trial – the three months EF for the lowest dose at the three month mark (May 2009) and six month data from this same cohort. At three months there was a 9-point improvement in EF for treated patients and a 4 point decline for the controls, which was statistically significant. At six months (November 2009) mean EF was up 22% in the treated patients and down 18% in the controls.

[70] See NCT00927784 at www.clinicaltrials.gov.

[71] Nasdaq: THOR; Pleasonton, Ca; www.thoratec.com.

[72] Meaning that the device could only be implanted into people awaiting a heart transplant.

[73] Where the LVAD is implanted into the patient permanently.

[74] Nasdaq: HTWR; Framingham, Ma; www.heartware.com. HeartWare is also traded on the ASX (code HIN) , where it originally did its IPO in 2005. We initiated coverage on HeartWare on 11/11/2010 in a note headlined *The quest for the world's smallest LVAD.*

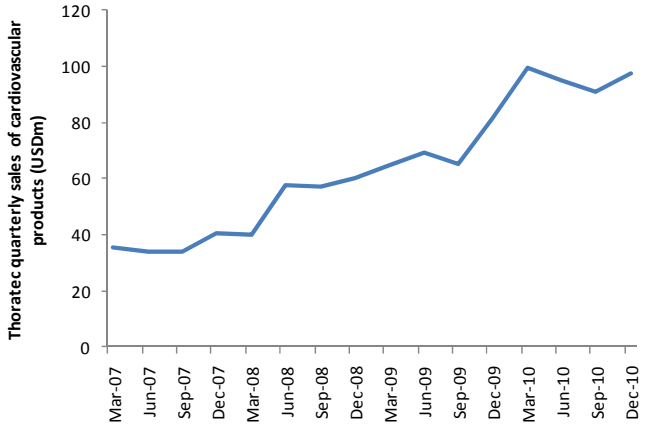
approval in 2009 and has performed well in a Bridge to Transplant trial in the US, for which data was released in November 2010.

In our view the success of LVADs in reversing the symptoms of heart failure effectively began the push of LVADs into the cardiology mainstream, which has accelerated with HeartMate II's Destination Therapy indication and the emergence of HVAD as a viable competitor. Some have suggested that LVADs, by effectively resting the heart, can help rebuild heart muscle and may be a 'bridge to recovery' where ultimately the device can be removed. However some clinical work[75] has cast some doubt on this prospect, encouraging a continued search for agents that can reverse heart failure.

The US government is funding the LVAD trial after serious peer review of the technology

NHLBI involvement is a key credibility boost for MPCs. Enter the US government's National Heart, Lung, and Blood Institute (NHLBI)[76], which will fund the Phase II LVAD study of MPCs at its expense, with the LVAD to be used being Heartmate II. The involvement of the NHLBI suggests that MPCs have been able to pass a rigorous peer review process. As for the trial itself, if it records an improvement in heart function in the treated patients above and beyond LVADs, the likely outcome is a strong boost to the credibility of MPCs in the cardiology community given the general optimism that remains around LVADs as effective therapies for heart failure symptoms[77]. We think this trial can yield data by mid-2011, possibly leading to 300-patient pivotal that could yield an LVAD indication by 2014.

Figure 15 - Thoratec is growing a solid business in LVADs



SOURCE: THORATEC

[75] Maybaum et. al. studied 67 patients who received a Thoratec LVAD and found only 6 that had recovered sufficiently to explants the device by 120 days (see *Circulation.* 2007 May 15;115(19):2497-505. Epub 2007 May 7.) Birks et. al. at Harefield Hospital in the UK, a noted heart transplant centre, found by contrast with 15 Thoratec LVAD patients that 11 had recovered to explants after an average of 320 days (see N Engl J Med. 2006 Nov 2;355(18):1873-84.). Some HVAD patients in HeartWare's clinical trials have experienced recovery, such as the patient who recovered after 268 days in 2006/07 (see the 24/7/2007 HeartWare announcement).

[76] Part of the National Institutes of Health, the primary agency of the US government for biomedical and health-related research.

[77] Since LVAD therapy is expensive any data on improved therapeutic effect helps bolster the health economics of the product, making it potentially attractive for Thoratec, HeartWare or another LVAD developer to license MSB's technology.

MPCs may prevent heart failure after AMI

AMI is another large market. Around 900,000 million heart attacks happen every year in the US[78], generating drug costs around the time of the event we estimate to be at least US$350m pa[79]. It is estimated that around half of all heart attack patients move on to heart failure over the next six years due to loss of heart muscle that started with the initial attack[80]. Consequently early treatment with MPCs after an AMI has the potential to significantly cut into the heart failure treatment costs we noted above.

Safety but no efficacy data at this stage. MSB filed an IND for a 25-patient AMI trial in April 2007[81], with the trial testing various doses of MPCs against standard of care to measure recovery in heart function post an AMI where the EF at entry is below 45%. At this stage, this trial has yet to yield efficacy data due to slow recruitment, even though the safety data has been favourable:

- *The EF<45 requirement has limited the patient pool*, since less than 20% of heart attack patients survive a first attack but develop heart failure shortly after[82] - most enter heart failure more gradually.
- *The use of the catheter has also limited recruitment.* In this trial the MPCs are delivered via a new-generation J&J catheter into the myocardium 10 to 14 days after the initial angioplasty procedure to open the blocked artery. We postulate that the additional new technology (ie the J&J catheter) tended to deter patient willingness to sign up.

MPCs can help in recovery after a heart attack

A new AMI trial is being designed. We understand that MSB is working on a new trial with better recruitment prospects. This trial will replace the catheterisation of stem cells with a simple infusion into the coronary artery at the time of the angioplasty and then measure the rate of heart failure incidence post infusion over the next twelve months. This figure, if lower than the historical average, will indicate that MPCs are useful in preventing heart failure post-AMI. Recent pre-clinical data looks encouraging[83].

Osiris data bodes well. In December 2009 investigators working with Osiris Therapeutics, which as we noted above is also developing the therapeutic potential of mesenchymal stem cells, published data from a 53 patient trial showing that allogeneic stem cell perfusions can improve cardiac function at the six month point after a heart attack[84]. This suggests the potential for MSB's trial to yield good data once the recruitment issues can be overcome, particularly since the dosing of Osiris' product was via intravenous injection rather than via infusion at the coronary artery. MSB thinks the latter approach can potentially boost the therapeutic effect through more localised delivery.

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[78] There are some 610,000 new attacks and 325,000 recurrent attacks annually. This is one of the knock-on effects of smoking and poor diet. Source: American Heart Association Heart Disease & Stroke Statistics 2009.

[79] Around 4-5% of all people in the US experiencing 'heart conditions' are people who had a heart attack over the last twelve months, while the cost of drugs for all heart conditions in the US is around US$8bn. Sources: American Heart Association, Heart Disease & Stroke Statistics 2006 and AHRQ Medical Expenditure Panel Survey, 2006 data.

[80] 22% of males and 46% of females have historically progressed to heart failure within six years. Source: American Heart Association, quoting follow-up data from the NHLBI's Framingham Heart Study.

[81] See NCT00555828 at www.clinicaltrials.gov.

[82] In a study of 199 AMI admissions in a UK hospital group Torabi et al. found 110 patients were discharged from hospital with heart failure from a group of 661 where the AMI was the patient's first, being 16.6% of the total (see *Eur Heart J.* 2008 Apr;29(7):859-70. Epub 2008 Mar 19).

[83] Data generated by interventional cardiologists at Erasmus University Medical Center in Rotterdam, and presented at the American Heart Association's annual meeting in November 2010, showed allogeneic MPCs outperform saline in 30 sheep undergoing myocardial infarction in terms of the progression to heart failure, with average Ejection Fraction of 54.4 versus 42.5 ($p < 0.01$), average mean end systolic volumes 66 mL versus 98.6 ($p < 0.001$), 50% less scar formation and fibrosis in heart muscle ($p < 0.005$), and significantly increased blood vessel formation ($p < 0.001$).

[84] There was lower ventricular tachycardia episodes ($p = 0.025$), and improved 'forced expiratory volume in 1 second' ($p = 0.003$). See *J Am Coll Cardiol*, 2009; 54:2277-2286.

Realising value from the cardiovascular space

MPCs will be bigger than CRT-D

Cardiac Resynchronisation Therapy provides a good insight into the upside. We see the experience of Cardiac Resynchronisation Therapy (CRT) devices over the last decade as an indication of the market opportunity in heart failure. CRT involves the use of specialised pacemakers or defibrillators to re-coordinate the action of the right and left ventricles of the heart where an abnormality in the heart's electrical conducting system has caused the two ventricles to beat in an asynchronous fashion. It's been found to be useful in treating late stage heart failure, and this fuelled US sales growth of CRT defibrillators (CRT-Ds) from the first FDA approval in 2001 to around US$1.5bn four or five years later[85] even though:

- the products are only useful in the 30% or so of patients with conduction defects[86]; and
- Ejection Fraction in CRT-D treated patients has risen much more modestly than what we noted above with MPCs[87].

We think the heart failure market is so large that MPCs can follow a similar growth path to CRT-D's should the clinical data come in favourably. It is worth noting as well that in mid-2009 the MADIT-CRT study found that CRT-Ds cut deaths and heart failure events in early stage patients as well[88], thereby significantly enlarging the market. There is potential for MPCs to similarly be found useful in treating early stage heart failure over time, even though mid-to-late stage heart failure is currently the focus.

[85] We estimate US$1.75bn pa in US sales now. The European market for CRT devices more than doubled between 2004 and 2008. See *Eur J Heart Fail.* 2009 Dec;11(12):1143-51. Epub 2009 Nov 1.

[86] See *Indian Pacing Electrophysiol J.* 2003 Jul–Sep; 3(3): 129–142.

[87] Results of some of the trials of CRT devices have suggested that a mere 4 point improvement in EF at the six month mark has a significant effect on mortality compared to the controls.

[88] See *N Engl J Med.* 2009 Oct 1;361(14):1329-38. Epub 2009 Sep 1.

MSB's emerging spinal franchise

There is corporate appeal in the spinal programmes of MSB

A key part of the value of MSB lies in the various applications of MPCs that are emerging for the treatment of spinal disorders. MSB has created products for spinal fusion and for disc repair that could potentially be 'game changing'. We believe that this facet of MSB has significant corporate appeal.

A potentially game-changing technology in spinal fusion

What is spinal fusion? Spinal fusion is a surgical procedure to reduce back pain arising from degeneration or damage to the discs between vertebrae. The idea is to fuse the vertebrae on either side of the faulty discs so that they do not move around and thereby cause pain. This fusion is effected by placing either the patient's own bone (called an 'autograft'[89]) or an 'osteoconductive'[90] bone substitute such as HA/TCP at the fusion site, and allowing Mother Nature to gradually join the bones together.

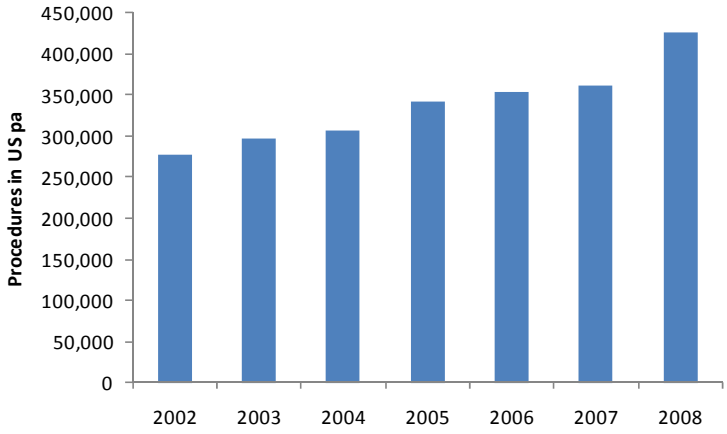
There are two basic kinds of spinal fusion...

- *Posterolateral spinal fusion*, where the bone or bone graft is places on the so-called 'transverse processes' of the vertebrae[91] to be joined.
- *Interbody spinal fusion*, where the bone graft is placed directly in the intervertebral disc area[92].

...and two main places in the spine where it is performed:

- *The lumbar spine*, which is the lower back, and
- *The cervical spine*, which is the upper back supporting the neck.

Figure 16 - Spinal fusion is growing in popularity in US orthopaedic circles



SOURCE: HCUP SEARCH USING ICD-9-CM CODES 81.00-81.09, 81.30-81.39, AND 81.60-81.65

[89] The graft is generally taken from a bone at the side of the pelvis called the 'iliac crest'.

[90] That is, able to move new bone cells into the area.

[91] The transverse processes are small bones that connect the vertebrae to the back muscles.

[92] Actual bone is rarely used in interbody spinal fusion.

Spinal fusion has been booming. Currently around 450,000-500,000 spinal fusion procedures are performed annually in the United States alone, up from under 300,000 in 2002. While there was some evidence in 2010 that the spinal fusion market was cooling[93], we think the rapid growth up to then reflects three important trends:

- an aging population with increased incidence of back pain – for example, it is estimated that around 14% of the Australian population over age 15 has a back or disc disorder of some kind[94];
- growing use of Bone Morphogenetic Protein as a bone graft material;
- the rise of minimally invasive spinal fusion surgery.

MSB has targeted its clinical programme for spinal fusion to tap into the second and third of these three trends.

MSB aims to displace BMP's use in spinal fusion

MSB aims to displace Bone Morphogenetic Protein as a key spinal fusion bone graft material. The Bone Morphogenetic Proteins or BMPs are a group of naturally occurring growth factors that are 'osteoinductive', that is, able to induce the formation of bone and cartilage. They have been important in spinal fusion since 2002 when the FDA approved a BMP-based spinal fusion product called INFUSE, from the Minneapolis-based medical device major Medtronic[95]. BMP has since proved popular with orthopaedic surgeons doing spinal fusions because it can effect fusion without any of the patient's own bone[96], eliminating the need for a second, bone-harvesting operation.

- At least 25% of spinal fusions by 2006 were performed using BMP, only four years after FDA approval, with an average dose selling for US$4,000[97];
- As a consequence of this rapid growth Medtronic's INFUSE is estimated to have done US$800m in sales in 2008[98];
- This has helped grow the US market for bone graft and bone graft substitutes to an estimated US$1.5-2.0bn pa in 2008[99].

There are two key issues for BMP, however, which provides MSB with an opportunity to displace the product:

Most BMP usage is off-label. The FDA has only approved BMP for use in lumbar spinal fusions where the method of implantation is 'anterior' (ie from the patient's front), whereas most usage of the product – an estimated four-fifths - has been for 'posterior' lumbar spinal fusions (ie from the back) as well as cervical spinal fusions. This lack of a formal FDA indication has raised the notional risk level related to most usage of the product, particularly since Medtronic's trial of INFUSE in posterior lumbar fusion was halted in 1999 due to a 75% incidence of excessive bone growth in the spinal canal.

There has been a health warning from the FDA related to BMP. In July 2008 the FDA issued a Public Health Notification related to a number of cases where

[93] For example, Medtronic's spine product sales rose only 2% on a constant-currency basis in the year to April 2010.

[94] See the ABS's National Health Survey for 2007/08. MSB has estimated that '*low back pain is present in 15-25% of the general population and affects 70-90% of people at some stage in their lifetime*'.

[95] This product carried BMP-2 inside a device called the LT-Cage, for placement in the intervertebral disc area in interbody fusion. BMP-2 had initially been developed by Wyeth, which picked up the product when it bought a biotech company called Genetics Institute in 1995. A Stryker product called OP-1 Putty carries another BMP called BMP-7.

[96] See, for example, *Spine* 2008 Sep 15;33(20):2153-9.

[97] See *JAMA*. 2009;302(1):58-66.

[98] See the complaint from the Minneapolis Firefighters' Relief Association in their class action lawsuit against Medtronic. The US$800m figure suggests that many spinal fusion surgeries require two doses of BMP rather than one.

[99] See the Biotech Ireland (www.biotechnologyireland.com) abstract headlined *A Novel Bone Graft Substitute*, profiling an Irish-developed technology on offer to potential licensees/acquirers.

use of BMP in cervical spinal fusion had resulted in swelling of the neck and breathing difficulties.

BMP's problems are MSB's opportunity. MSB has structured its clinical work in spinal fusion around demonstrating that its MPCs are safe and effective in those indications where BMP hasn't gained FDA approval[100]. Ultimately the company hopes to be able to displace BMP in spinal fusion, while still enjoying a similar sell price for the product – around US$5,000 for a 10cc vial[101].The company is conducting two Phase II trials in lumbar spinal fusion and one in cervical spinal fusion. Each trial will compare various doses of MPC with autograft, which effectively represents 'standard of care' as far as the FDA is concerned outside of anterior lumbar spinal fusions.

MSB'S THREE CLINICAL TRIALS IN FUSION

The posterolateral lumbar fusion trial. MSB filed an IND for a 60-patient trial in November 2006 and the first patient was treated in July 2007[102]. The animal data looked good going into the trial[103], and for those patients that have been treated MSB has reported '*safe and robust fusion over a twelve month period*'[104]. Moreover in late April 2010, after completion of enrolment for the trial, MSB indicated that the fusion rate[105] at six months was 60% versus only 14% for autograft. However in the years since MSB started work on spinal fusion, the trend in lumbar fusion has been for less posterolateral work due to the large, 5cm incisions required, in favour of a minimally invasive posterior interbody fusion, where the incision is more like 1cm. Consequently the company moved in 2009 to initiate a new lumbar fusion trial, this one in posterior interbody lumbar fusion[106].

MSB's animal data in posterior interbody lumbar fusion was exciting

The posterior interbody lumbar fusion trial, announced in August 2009[107], is smaller than the previous trial at only 24 patients. MSB hasn't disclosed any animal data related to the effectiveness of MPCs in posterior interbody lumbar fusion except to observe that in sheep '*a lower dose than has previously been used in the lumbar spine resulted in significantly earlier bony fusion over three to six months, compared with autograft, without any safety issues'*. However the significance of this trial will be that BMP never gained FDA approval for a posterior lumbar interbody fusion indication. Consequently if the trial works – and in October 2010 MSB announced interim results showing 90% of treated patients achieving bony bridging at three months, with pain reduction scores down 20%[108] - MPCs will be on track for the first approval in this area. We argue that this would yield MPCs significant competitive advantage, so long as the rate and speed of fusion was comparable with BMP.

The cervical spinal fusion trial. This 36-patient trial was unveiled by MSB in April 2009 with the relevant INDs clearing in May 2010[109]. MSB unveiled favourable

[100] So far MSB has found no evidence of 'cell trafficking' for MPCs, meaning that they more-or-less stay in the place where they are injected. For posterior lumbar spinal fusion the company has tested MPCs in animal models and found no ectopic (ie out of place) bone growth like that registered by BMP in this application.

[101] We understand that two vials of BMP are generally needed to do a bone graft.

[102] See NCT00810212 at www.clinicaltrials.gov.

[103] In April 2006 MSB announced that experiments with sheep had shown MPCs effecting spinal fusion superior to the controls. A subsequent presentation (at the November 2006 AGM) revealed that, against controls treated with HA/TPC, MPCs outperformed by 75% in terms of 'fusion mass' over five months ($p = 0.023$). This outperformance continued for the entire nine months of the experiment.

[104] MSB market release, 17/8/2009.

[105] Where 'fusion' is bony bridging between two vertebrae.

[106] We expect that posterolateral lumbar fusion will not be a major part of MSB's future clinical development.

[107] See NCT00996073 at www.clinicaltrials.gov. This trial is being conducted at six sites in California, Colorado, Indiana and Texas.

[108] This was with the first 17 patients.

[109] See NCT01106417 and NCT01097486 at clinicaltrials.gov. The trial will see 24 patients recruited in the US and 12 in Australia. The trial currently recruits at only one site in Australia, Monash Medical Centre in Melbourne, while five sites are open in the US.

animal data for the use of MPCs in cervical spinal fusion in August 2008[110]. Around 40% of all spinal fusion procedures in the US are for the cervical spine.

A PAYOFF IN SPINAL FUSION IS COMING BY 2014

Clinical data in 2011. We expect that the trials described above can yield results in 2011, after which 300-350 patient pivotal trials could be run over the period to 2014. The aim would be to show spinal fusion being achieved over a 12-month period with follow up to show that the fusion is sustained over the succeeding six months.

Nuvasive is doing the 'commercial pioneering' of MPCs in spinal fusion. While MSB completes the clinical work to validate the utility of MPCs in spinal fusion, the commercial opportunity is already growing thanks to an emerging American orthopaedics device player called Nuvasive[111]. That company currently markets a bone graft for spinal fusion called Osteocel Plus, which is essentially the same MPCs as MSB's product, having been developed by the aforementioned Osiris Therapeutics and launched by it in 2005 as its first commercial application of MPCs. Nuvasive bought Osteocel Plus from Osiris in May 2008[112]. The reason why MSB doesn't regard Osteocel Plus as a threat is that the product is being marketed without validating clinical data - Osiris was able to get Osteocel on the market without obtaining pre-market approval due to new rules from the FDA regarding human tissue.[113] MSB believes that once its trials provide the data on clinical efficacy its product will be more competitive than Osteocel but will benefit from the commercial use which Nuvasive has fostered. The only risk here is that Nuvasive is also conducting trials in various spinal fusion indications, so MSB needs to win the 'data race'.

MSB's disc repair trial could open up a US$2bn market

Intervertebral disc repair provides the blue sky

The intervertebral disc repair market is wide open. Currently spinal fusion has most of the running in terms of treating back pain related to faulty discs. However a potential alternative approach is to actually deal with the discs themselves through replacing them with artificial discs made out of various metals and polymers. Medical device companies have started introducing artificial discs for total disc replacement in recent years[114], however the market has yet to take off, with current US sales understood to be under US$40m[115] due to poor reimbursement[116] and concerns over method of surgical placement.

A US$2bn market which is MSB's for the taking. The failure of artificial discs leaves the disc repair/replacement field open for other therapies, which MSB believes can include MPCs. The market for an MSB product would be a large one – after analysing the relevant data the company estimates that there would be 4 million potential patients in the US worth US$2bn pa[117].

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[110] 9 out of 12 cell-treated sheep achieved 'continuous interbody bony bridging' within 3 months versus only 1 out of 6 for autograft and 3 out of 6 for Mastergraft, an HA/TPC product from Medtronic. The p values for these comparisons were 0.019 and 0.043 respectively. We understand the 5-10 million MPCs used for treatment were considerably below what the investigators had previously considered necessary to achieve fusion.

[111] Nasdaq: NUVA; San Diego, Ca; www.nuvasive.com.

[112] For $30m cash and $50m in milestone payments (which have since been paid), based on product revenue.

[113] Under the FDA's Human Cell, Tissue, and Cellular and Tissue-based Products regulations, effective May 2005 (21 CFR 1271), tissues that are 'minimally manipulated', which includes stem cells, can be marketed without pre-market approval.

[114] J&J's Charité disc gained FDA approval in 2004 while Synthes gained approval for the Prodisc-L device in 2006.

[115] See *Tennessee judge's ruling on artificial discs causes Medtronic pain* by Arundhati Parmar, Dolan Media Newswire, 15/9/2009.

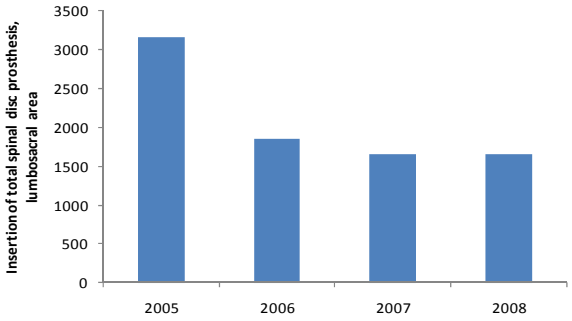
[116] For lumbar disc replacement, the Centers for Medicare & Medicaid Services, which runs Medicare and Medicaid in the US, issued a 'non-coverage decision' for beneficiaries over 60 in August 2007, due to what it considered to be a paucity of data on effectiveness.

[117] See Slide 2 of the company's presentation to the World Congress on Osteoarthritis in Montreal in September 2009, which was filed with the ASX on 15/9/2009.

MPCs can repair damaged intervertebral discs. In September 2009 MSB presented encouraging animal data on the utility of low dose MPCs plus hyaluronic acid - which is commonly used in joint therapy - into degenerating vertebral discs[118]. This was encouraging because it showed that mere percutaneous injections into the disc area could potentially achieve a similar outcome to total disc replacement.

MSB's disc repair trial shows promise. The pre-clinical work has encouraged MSB to prepare to file an IND for a 48-patient Phase II trial in disc repair. The trial will compare two MPC doses against placebo, with a six month endpoint. We expect that it will commence in 2011, after which a move into a pivotal trials would follow with a likely completion date of 2014. We regard regulatory approval of MPCs for disc repair as relatively straightforward, since the primary endpoint would be reduced pain over a 12-18 month period. Also, we expect that MPCs can overcome the reimbursement issues if animal data translates into human data on disc recovery, since reimbursement agencies are generally happy to 'pay up' when there is clear therapeutic benefit.

Figure 17 – Artificial discs haven't really caught on



SOURCE: HCUP SEARCH USING ICD-9-CM CODE 84.65

MSB's partners in spinal may be large companies

Realising value from the spinal franchise

Partnering interest is likely to be strong. Spinal orthopaedics is dominated by only a few large companies but competition between these companies tends to be stiff. Given the US$4-5bn already spent on spinal implants in the US market alone, we see strong potential for MSB to be partnered or acquired by a spinal player aiming to defend its existing spine business as well as gain competitive advantage.

MSB may be able to help some big companies get a return of some expensive investments. For an idea of the partnering upside for MSB consider that from 2002 to 2004 four major orthopaedic device players made notable acquisitions in the artificial disc area in order to position themselves for what they expected was 'the next big thing' in back pain. With artificial discs so far not delivering as planned, we think their attention may turn to products like MSB's, positioning the company for a deal potentially worth ~US$300m in upfronts and milestones.

[118] MPC plus hyaluronic acid injections into sheep models of degenerative disc disease boosted disc height by around 46% versus 33% from hyaluronic acid alone over six months ($p < 0.05$). With MPCs disc height was virtually restored to normal. Disc structure and histopathology were also equivalent to normal sheep after six months. This study is documented in Example 4 of MSB's WO 2009/018613 patent application.

Figure 18 - Major players in spinal fusion and artificial discs

Name	Code	Location	USDm 2008 orthopaedics revenue
J&J Depuy[119]	NYSE: JNJ	Raynham, Ma, www.depuyspine.com	4,989
Medtronic	NYSE: MDT	Minneapolis, Mn, www.medtronic.com	3,400
Synthes	SIX: SYST	Solothurn, Switzerland, www.synthes.com	3,193
Smith & Nephew	LSE: SN	London, UK, www.smith-nephew.com	2,158
Stryker	NYSE: SYK	Kalamazoo, MI, www.stryker.com	1,017
Nuvasive	Nasdaq: NUVA	San Diego, Ca, www.nuvasive.com	250

SOURCE: SOUTHERN CROSS EQUITIES

Figure 19 - Acquisitions in the artificial disc space

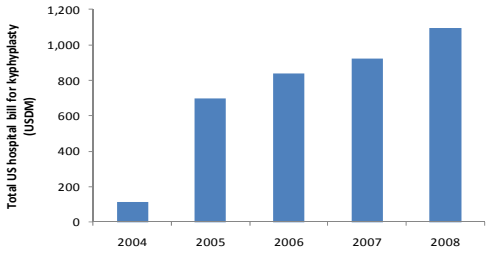
Company	Acquired	Price (USDm)	Date	Note
Medtronic	Spinal Dynamics	269.5	Jun-02	Maverick device effectively locked out by Synthes success in patent infringement case decided September 2009
Synthes	Spine Solutions	350	Feb-03	Prodisc-L FDA approved 2006
J&J Depuy	Link Spine	325	Jun-03	Charité FDA approved 2004
Stryker	Spinecore	360	Jul-04	Flexicore device in development

SOURCE: COMPANY DATA

An acquisition of MSB could take place at a high premium

Kyphon demonstrates the potential upside value from an acquisition. We see Medtronic's acquisition of the California-based medical device company Kyphon in 2007 as a good example of the possible upside from a well-structured spinal franchise. Kyphon was built on the Kyphon balloon, a kind of 'bellows' device to correct spinal fractures by propping up compressed vertebrae. The appeal of the device was the fact that kyphoplasty was minimally invasive, so that after the FDA approved the first bone cement for use in the indication in 2004 sales started to grow at around 20% pa. This boom ultimately resulted in a huge takeout premium for Kyphon. The company's last twelve months of sales prior to integration into Medtronic were around US$530m, but Medtronic paid US$4.2bn or around 8 times sales, which to some commentators in 2009 seemed excessive given that Kyphon's growth slowed markedly following the transaction[120]. We argue that Medtronic paid a premium in order to control an entire field that had the potential to be a 'next big thing' in the spinal area.

Figure 20 – Kyphoplasty boomed in the US after 2004



SOURCE: HCUP SEARCH USING ICD-9-CM CODES 81.66

[119] Depuy is the orthopaedics arm of J&J.

[120] Sales growth in the three months to late April 2009, the last quarter for which Medtronic published Kyphon-specific figures, was only 2.7%.

Other big MPC opportunities

MSB has done work in various other areas to demonstrate that their MPC technology holds promise. The markets in each case are significant.

Knee osteoarthritis

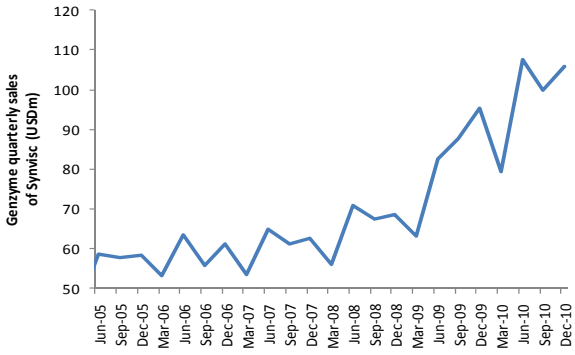
Around 4-5% of the population has knee osteoarthritis

Knee osteoarthritis is the progressive wearing down of the cartilage in the knee joint as a result of inflammation. Whether it occurs simply because of age, or because of inflammation related to injuries such as the anterior cruciate ligament ruptures commonly suffered by sportspeople[121], knee osteoarthritis is common, affecting an estimated 14 million Americans or 4-5% of the population[122]. In recent years this large patient group has driven three major markets in the US:

- A market for knee arthroscopies[123] worth at least US$5bn. Close to one million of these were performed in the US in 2006[124] in spite of dubious therapeutic utility[125].
- A US$400-500m market for hyaluronic acid injections such the Synvisc and Synvisc One products[126] from the biotech major Genzyme[127]. Hyaluronic acid can't rebuild cartilage but can reduce pain by replacing some of the lost fluid in the joint area.
- US$3bn market for the implants used in total knee replacement surgery covering around 600,000 operations pa[128].

We estimate that the hyaluronic acid and total knee replacement markets are currently growing around 9% pa.

Figure 21 - Knee osteoarthritis has helped Genzyme grow its Synvisc franchise



SOURCE: GENZYME

[121] Around 50% of people suffering anterior cruciate ligament tearing have osteoarthritis within ten years. See *Am J Sports Med.* 2007 Oct;35(10):1756-69. Epub 2007 Aug 29.

[122] Source: Genzyme 2008 10-K SEC filing.

[123] A knee arthroscopy is a minimally invasive surgical procedure involving insertion of an arthroscope and other instruments into the joint through small incisions in order to remove cartilage fragments and smooth the joint surfaces.

[124] See CDC, *Ambulatory Surgery in the United States*, 2006.

[125] See *N Engl J Med.* 2008 Sep 11;359(11):1097-107. This study found no additional benefit from knee arthroscopy for osteoarthritis sufferers above anti-inflammatories and physical therapy.

[126] See www.synviscone.com. Synvisc is the leading player in this market with an estimated 60% share.

[127] Nasdaq: GENZ; Cambridge, Ma; www.genzyme.com.

[128] See *Cartilage Repair - Replacing Joint Arthroplasty?* by Scott Ellison, a 12/9/2008 article posted at www.pearldiver.inc.

Knee osteoarthritis could be an early licensing candidate for MSB

MSB has initiated a Phase II trial for knee osteoarthritis related to acute knee injury. After generating animal data showing that MPCs are more effective than hyaluronic acid in treating osteoarthritis for around six months post injection[129], MSB announced, in January 2009, a 24-patient Phase II clinical trial in patients to test the ability of MPCs to prevent knee osteoarthritis after an anterior cruciate ligament rupture over the succeeding twelve months. This trial will be conducted in Australia[130]. It is possible that the study could yield data in 2011.

It makes sense to partner early in knee osteoarthritis. MSB sees two potential markets for MPCs in knee osteoarthritis, one relatively easy to access and one more difficult:

- *Prevention of osteoarthritis post a traumatic knee injury*, as per the abovementioned clinical trial. This indication is likely to need relatively few patients in a pivotal trial to demonstrate effectiveness given that at present standard of care – hyaluronic acid injections - is more or less ineffective. MSB estimates around 120 patients would be required. Consequently this represents a faster path to market.
- *General knee osteoarthritis*. Given the widespread availability of orthopaedic specialists to manage knee osteoarthritis with anti-inflammatories and physical therapy, a much larger trial would be required for this indication – MSB estimates around a thousand patients.

The expense involved in clinical trials of the second of these two indications suggests the wisdom of MSB seeking a partner in knee osteoarthritis at an early stage, probably with Phase II prophylactic data in hand.

The Belgians have paved the way for market acceptance of MPCs. What's encouraging to us about MSB's position in knee osteoarthritis is the fact that stem cells are about to make their first serious commercial appearance in cartilage repair. In October 2009 the Belgian biotech company Tigenix[131] gained European approval for its Chrondocelect product, an autologous stem cell therapy with an initial application in repair of defective knee cartilage[132]. Tigenix's technology involves taking chondrocytes, that is, cartilage-forming cells, from a healthy region of the patient's cartilage, expanding these cells in a lab setting and then re-implanting them at the site of the defective cartilage. Notionally MPCs have an advantage over Chrondocelect in that, being allogeneic, an initial, cell-harvesting surgical procedure will not be required with MPCs. As data on the clinical effectiveness and reimbursement of Tigenix's product builds over the next couple of years[133], MSB will be well-placed to license its product as a potential Tigenix competitor.

AMD/Diabetic retinopathy

Age-related macular degeneration (AMD[134]) and diabetic retinopathy are similar eye conditions, in that both can be caused by neovascularisation - the formation

[129] MSB announced a favourable sheep experiment in August 2007 showing that injecting MPCs into damaged knee joints reduced cartilage damage to a greater extent than hyaluronic acid, as measured by both quality and thickness of cartilage (ie, MPCs could be prophylactic against knee oesteoarthritis). In April 2008 the company indicated that the effect of the improvement ran to between six and twelve months, while in August 2008 it indicated that sheep data from post-menopausal knee arthritis is also favourable at the six month mark (ie MPCs can be therapeutic in established knee osteoarthritis). These studies are documented in Examples 2 and 3 of MSB's WO 2009/018613 patent application. The most noteworthy aspect of this data was cartilage thickness, which was 20-25% better than the controls in the post-menopausal model (p = 0.01-0.03), indicating that MPCs were capable of cartilage repair.

[130] See NCT01088191 at clinicaltrials.gov.

[131] Euronext Brussels: TIG; Leuven, Belgium; www.tigenix.com.

[132] Specifically, for the repair of defects in the cartilage of the 'femoral condyle', which is at the thighbone.

[133] The product recently gained reimbursement in Belgium.

[134] The macula is the area of the retina responsible for detailed central vision.

of new blood vessels - in the eye, leading to damage of the retina and resulting impaired vision and blindness. Markets for both conditions are large, costing the US healthcare system alone around US$1bn for direct medical expenses[135]. This is driven largely by the substantial patient communities involved:

- **Around 1.4 million Americans have late stage 'wet' AMD**, which is AMD that results from abnormal blood vessel formation[136], as opposed to 'dry' AMD, where the light-sensitive cells in the macula slowly break down.[137]
- **There are around 4.5 million American diabetics with diabetic retinopathy,** with around 40%-45% of the total diabetic population affected.[138] These numbers are rising fast. Around 7.7% of the US population now has diabetes[139] but another quarter of the population (77 million people) are estimated to be pre-diabetic or at increased risk for developing diabetes in the future[140]. Moreover in 2007 around 1.6 million Americans were newly diagnosed with diabetes[141]. All this adds up to a strong future patient pool for eye doctors.

Treatment is expensive, so new drugs are being sought. Until the 2006 FDA approval of the antibody drug Lucentis[142], from Genentech/Roche, there were no adequate treatments for neovascularisation in the eye beyond steroids. Lucentis is now a blockbuster and still growing around ~20% pa. However the drug is expensive, costing just under US$2,000 per month. Many ophthalmologists are now looking to a related and approved Genentech product called Avastin as a preferred option, since the cost is more like US$50 per month[143]. However, while six month data from a blinded comparison trial in wet AMD has recently shown that Avastin and Lucentis are equally effective[144], it's likely that Genentech will simply increase the price of Avastin to accommodate the extra demand from what would be a new 'off label' indication. Consequently the search for new AMD/diabetic retinopathy drugs is set to continue, with MSB well-placed to participate.

The blockbuster eye drug Lucentis works even better with MPCs

Evidence that MPCs can make a difference in diabetic retinopathy. In September 2007 and July 2008 announced favourable animal data[145] related to both diabetic retinopathy and AMD, showing MPCs working well in conjunction with Lucentis to treat these disorders. What the data appears to show is that MPCs not only improve vision but reduce the frequency of Lucentis injections required to keep AMD / diabetic retinopathy in remission.

A Phase II trial is pending. MSB intends to file an IND for a Phase II trial with a pre-IND meeting having been held in 2009. The trial would test MPCs as an adjunct in those that have failed Lucentis treatment. We think this study can be completed in 2012.

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[135] See Prevent Blindess America's report entitled *The Economic Impact of Vision Problems*.

[136] Dry AMD is around 90% of total AMD incidence.

[137] Wet AMD typically makes up around two thirds of the people suffering late AMD. For late AMD prevalence, see Prevent Blindess America's *Vision Problems in the US, 2008 update*. For the distribution of late AMD into wet and dry forms, see *Risk factors for wet AMD revisited, Ophthalmology Times* meeting e-news, 20/2/2006.

[138] See Prevent Blindess America's *Vision Problems in the US, 2008 update*.

[139] Source: CDC.

[140] Source: Roper Global Diabetes Group.

[141] Source: NIDDK.

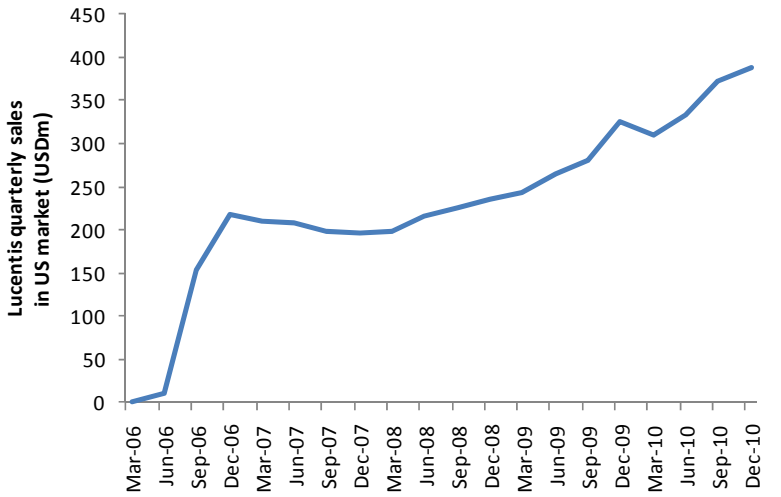
[142] Lucentis is a humanized anti-VEGF antibody fragment. VEGF is Vascular Endothelial Growth Factor, which stimulates the growth of new blood vessels.

[143] Specifically, Lucentis is the 'Fab fragment' of Avastin, which gained FDA approval in 2004 for colorectal cancer. Drug costs are from *Avastin versus Lucentis: Why It Matters*, Medical Research Modernization, Cleveland, Oh.

[144] See *Am J Ophthalmol.* 2009 Oct 2. [Epub ahead of print].

[145] In primates. We understand this particular work was costly but warranted given the market opportunity.

Figure 22 - Lucentis sales have been growing strongly



SOURCE: GENENTECH / ROCHE

Diabetes

In December 2009 MPC announced the results of early-stage laboratory work indicating that its MPCs may have utility in treating diabetes. This represented a potentially significant breakthrough for MSB given the massive market for diabetes therapies and the fact that existing treatments do not seem to be able to stem the decline of pancreatic insulin production in the medium term.

MPCs may be able to regenerate insulin-producing pancreatic islet cells

MSB's data is interesting. In a 35-subject experiment, single-dose injections of MPCs boosted pancreatic islet cells two-fold in mouse models of diabetes compared to the controls ($p = 0.0012$), with the ratio of beta-to-alpha islet cells 29% higher ($p = 0.005$)[146] , blood glucose levels down 35% ($p = 0.012$) and blood insulin levels up 35% ($p=0.04$). This indicated that MPCs could potentially regenerate pancreatic islet beta cells in Type II diabetics, a finding which, if it translates into the clinic, would doubtless create widespread excitement in the diabetes community and intense licensing interest from Big Pharma.

An interesting mechanism of action. MSB has disclosed[147] that MPCs appear to be able to treat diabetes through PDX-1[148], a transcription factor that helps in beta cell maturation. This is interesting because in the body PDX-1 expression is induced by GLP-1, a peptide that is part of the mechanism of action for new generation drugs such as Byetta, from the biotech company Amylin Pharmaceuticals[149], and Januvia, from Merck & Co[150]. Januvia and Byetta are significant new generation diabetes drugs, with Januvia enjoying US$2.4bn in 2010 sales worldwide, and Amylin US$710m. We think there is potential for MPCs to enjoy a sales profile similar to Januvia given:

- the ability, albeit demonstrated only in animal models to date, to induce beta cell regeneration even when there are few beta cells left.
- the known drawbacks of Januvia and Byetta, which is their short half life and lack of potency when beta cell loss is far gone.

[146] Islet cells in the pancreas are so-called because when looking at the cells through a microscope, they look like islands floating in the pancreas. Beta cells are the islet cells that actually produce the insulin which lowers blood glucose. Alpha cells produce glucagon, which increases blood glucose. A higher ratio of beta cells to alpha cells means less blood glucose.

[147] In WO/2010/057260.

[148] Short for Pancreatic and duodenal homeobox 1.

[149] Nasdaq: AMLN, San Diego, Ca., www.amylin.com.

[150] Byetta is a GLP-1 analogue while Januvia is a DPPIV antagonist, meaning that it can extends the life of natural GLP-1, which is degraded by DPPIV.

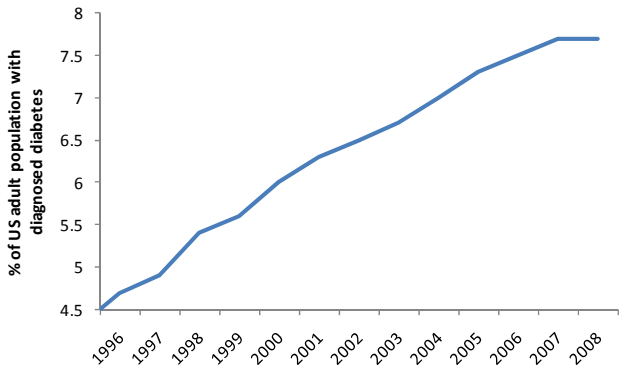
We understand that MSB has done pre-clinical work on MPCs as a diabetes treatment in non-human primates, for which results will be available later in 2011.

Around 8% of the US population is diabetic

The opportunity for MSB is huge. Diabetes is a significant market opportunity, particularly in America.

- Between 1995 and 2010 it is estimated that the age-adjusted prevalence of diagnosed diabetes in the US rose 80%, from 4.5% to 7.7% of the adult population.
- There are currently around 280 million adult diabetics worldwide (4% of the planet's population), with their numbers currently rising 6-7% pa and strong growth expected for the next 20 years[151].
- Around half of all diabetics become insulin-dependent within six years of diagnosis[152], indicating lack of long-term effectiveness for existing diabetes pills.

Figure 23 – The number of Type II diabetics in America is rising fast



SOURCE: CDC

Alzheimer's and Parkinson's

We noted above Cephalon's willingness to fund 50% of pre-clinical and Phase I and IIa work in Alzheimer's and Parkinson's under its collaboration with MSB. While MSB hasn't released any data generated by the company or its collaborators in these areas, the upside is strong in each case:

- Around one in eight people over the age of 65 in the United States have Alzheimer's disease, making for 5 million patients in that country alone[153]. Globally the patient population may be 36 million once other forms of dementia are included[154]. Existing drugs to treat Alzheimer's do not appear to prevent declines in cognition beyond about 9-12 months, but in 2008/09 they enjoyed in excess of US$6bn in sales globally.

Around one million Americans have Parkinson's disease

- Around 1-2% of people over the age of 55 may have Parkinson's disease, a degenerative movement disorder[155]. That would translate to around one million patients in the US alone, where total health care costs are estimated to be US$5-6bn and where the disease is the 15th largest cause of death[156]. What makes Parkinson's a particularly lucrative target for drug

[151] Source: International Diabetes Federation.

[152] This was a finding of the United Kingdom Prospective Diabetes Study.

[153] US figures come from The Alzheimer's Association, *2009 Alzheimer's Disease Facts and Figures*.

[154] Source: Alzheimer's Disease International, *World Alzheimer's Report 2009*.

[155] See a Dutch study, done in the city of Rotterdam, which suggested prevalence in over 55s of 1.4% (Neurology. 1995 Dec;45(12):2143-6).

[156] Source: CDC, Deaths, Preliminary data for 2008.

developers is the relatively long time a patient will be on medication – in many instances longer than ten years[157].

Inflammatory diseases

In recent months MSB has started to contemplate a move into inflammatory diseases, which has some merit given what we know about the interaction between MPCs and elements of the immune system[158]. For all applications MSB is seeking robust animal data before proceeding so as to minimise the risk of clinical failure. If MSB finds something here there is potentially a strong payoff:

- Around 13 million U.S. adults have COPD, a disease driven by inflammation, as a knock-on effect of smoking
- There are 1.3 million Americans with rheumatoid arthritis (source: Arthritis Foundation)
- Around a million have Crohn's disease and ulcerative colitis (Source: NIDDK)

Realising value from other big MPC opportunities

We see multiple partnering opportunities arising in MSB's unpartnered non-orthopaedic applications:

Knee osteoarthritis. We take the $100m in development milestones and $400m in sales milestones in the Genzyme/Osiris partnering deal of 2008 (see Appendix II) as potentially indicative of the kind of deal MSB can realise in knee osteoarthritis, although in Genzyme's case there was a defensive element to the numbers due to the need to maintain the Synvisc franchise. Also noteworthy in the space is a partnership between GSK and the Belgian drug discovery company Galapagos[159] seeking disease-modifying osteoarthritis drugs. Under that collaboration, started in 2006, Galapagos will earn up to €186m from the development of two marketable products. So far it has earned €30m.

AMD/Diabetic retinopathy. We see a potential partnering of MPCs to Roche/Genentech as making sense, since it would help defend both the Avastin and Lucentis franchises. A June 2009 licensing by Genentech/Roche of biodegradable microparticle drug delivery technology from Surmodics[160], for use with Lucentis and other products, gives an indication of the potential payoff - this deal featured $200m in milestones. However probably the benchmark deal in the space in recent years has been the 2006 partnership between Bayer and the American biotech Regeneron[161] related to wet AMD and other eye diseases. For Regeneron this arrangement is worth US$75m upfront and around US$245m in milestones.

[157] One UK study estimated an anticipated age at the time of death for Parkinsonians who were diagnosed over the age of 65 at only three years less than non-Parkinsonians of the same age. See J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1304-9. Epub 2007 Mar 30.

[158] There is some evidence that MPCs can down-regulate the pro-inflammatory cytokine TNA-α while up-regulating IL-4 and IL-10, known to have anti-inflammatory properties.

[159] Euronext Brussels: GPLG; Mechelen, Belgium; www.gplg.com.

[160] Nasdaq: SRDX; Eden Prairie, Minnesota.; www.surmodix.com.

[161] Nasdaq: REGN; Tarrytown, NY; www.regeneron.com.

Strong leadership

We regard favourably the leadership of Executive Director Professor Silviu Itescu, who founded Mesoblast in 2001 and who has since displayed considerable commerciality along the road to perfecting the MPC technology. Itescu, a clinician with a medical research background, initially trained in Melbourne before moving to New York. By the early 2000s he was Director of Transplantation Immunology at Columbia University Medical Center. In spite of never having been in business before, we think Itescu, who retains 24.5% of MSB, has done a good job of building shareholder value for the company:

Itescu has focused MSB on the big-value payoffs for MPCs

- **Focusing on the biggest 'bang for buck' and a portfolio approach**. The decision to target MSB initially on orthopaedics, where patient numbers are potentially smaller but competitors less apparent, showed a focus on shareholder return. Moreover as the case of long bone repair has shown, Itescu has not persisted in pursuing lower-value MPC applications where there are higher-value opportunities emerging from the animal data.
- **Practicing 'evidence-based biotech'.** The MSB scientific work has been focused on gathering solid evidence of potential efficacy – in both small and, importantly, large animal models - before human trials start, so as to avoid the difficulties that Osiris Therapeutics fell into in 2009[162].
- **Building redundancy into the company and managing the technical risks.** Itescu and his colleagues have built a solid pipeline out of the MPC concept, so that MSB cannot be regarded as a 'one trick pony'. Itescu's 'mistakes' – if they could be called that - have been limited to clinical trial designs which have been modified as market conditions for the product have changed or become better understood. The cost to shareholder value here has been, in our view, negligible[163].
- **Getting the right people.** Itescu has worked to bring around him a team of capable people who understand the biotech commercialisation process. At the board level these have included Donal O'Dwyer (formerly President of the J&J unit Cordis, whose big achievement was bringing to market Cypher, the world's first drug-eluting stent). In terms of operational people, Itescu continues to strengthen his team. A 2009 addition was Graeme Kaufman, formerly of CSL[164] and later Executive Director of the life sciences incubator Circadian Technologies. Kaufman has served within MSB as a kind of 'Minister Without Portfolio' and we think he will enable Itescu to better evaluate commercial opportunities as they emerge.
- **Getting the right regulatory expertise.** Many biotech companies run into the problem of not understanding the rules of the game as it is understood by the people who have to approve the end-product. That Itescu does not have this problem is suggested by the fact that under Dr Donna Skerrett, MSB's head of Clinical and Regulatory Affairs, the various IND applications have been cleared in the minimum 30 days allowed by the FDA.

[162] See Apppendix III for more on this.

[163] *'When the facts change, I change my mind. What do you do, sir?* - Lord Keynes (1883-1946), British economist.

[164] Where he was Manufacturing Manager (1984-87), Finance Director (1987-94) and General Manager, Biosciences Division (1994-99).

The risks

Biotechnology is risky

The stocks of biotechnology companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology companies in Australia fit this description, the speculative moniker also applies to the entire sector. The fact that biotechnology's intellectual property base lies in science not generally regarded as accessible to the layman adds further to the riskiness with which biotechnology ought to be regarded. Investors are advised to be cognisant of this risk before buying any Australian biotech stock including MSB.

MSB is not without risk

We see seven major risks specifically related to MSB as a company and a stock:

1 **Clinical risk** – There is the risk that any of MSB's clinical trials could fail to reach their endpoints.

2 **Regulatory risk.** There is the risk that the EMEA may prove less liberal in terms of its guidance for stem cell clinical studies than the FDA has been to date.

3 **Sentiment risk** – Biotech tends to go in and out of favour, especially where there are no commercial revenues.

4 **Timing risk** – There is the risk that MSB could take much longer to organise pivotal trials and then recruit and treat patients than the timing we have postulated in this note.

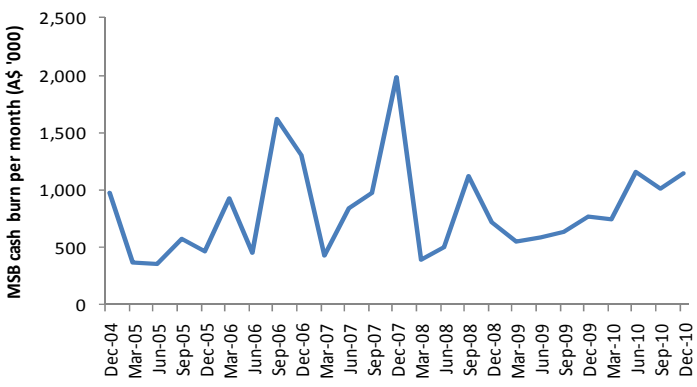
5 **Partnering risk** – There is the risk that MSB's prospective partners after Cephalon may strike too hard a bargain for MSB shareholders to enjoy a strong return outside.

6 **IP risk** – There is the risk that MSB could find itself locked in dispute over patent infringement should its science be found to lean too heavily on unrelated or unlicensed predecessor science.

MSB's current burn rate is A$1.1m per month

7 **Burn rate** – With $281m in cash resources MSB no longer needs to raise more capital in the near term. Any substantial increase in burn rate, however, may reduce this reserve. MSB currently burns around A$1.1m per month.

Figure 24 – MSB's burn rate since 2004



SOURCE: MSB

Appendix I - The MPC technology

The origins of the Mesoblast / Angioblast technology

Angioblast injections can repair heart muscle. In 2001 Professor Silviu Itescu's laboratory at Columbia University's New York-Presbyterian Hospital was the first to demonstrate (in rat models) that damaged heart muscles could be repaired by way of injections of angioblasts, that is, adult blood vessel stem cells, with the angioblasts working some noticeable neovascularisation at the site of the damage[165]. Itescu filed for patent protection over this treatment approach[166] and published the work in *Nature Medicine*[167], but wondered if there wasn't a better stem cell to use in heart muscle repair.

Itescu preferred mesenchymal cells to angioblasts. What Itescu was looking for was cells that would be more easily cultured than angioblasts, and that didn't have issues with potential rejection by the cell recipient's immune system - Itescu's angioblasts had worked in the treated rats only after their immune systems had been shut down. A worldwide search brought Itescu and a company he founded – Angioblast Systems - back to Australia and to Adelaide, where researchers at the Hanson Institute led by Dr Stan Gronthos had during the 1990s developed methods for extracting, purifying and culturing mesenchymal precursor cells from adult bone marrow.

A key part of the MPC technology relates to methods of obtaining the cells

The Hanson Institute had the best way of getting mesenchymal cells. The Hanson scientists had figured out, beginning around 1994, that one could use certain well-characterised monoclonal antibodies to pull mesenchymal precursor cells out of bone marrow. These cells could then be prompted to turn into brand new bone cells. The discovery was no mean feat because sometimes only one in 100,000 cells in bone marrow is a mesenchymal precursor cell, and fewer still are specifically osteogenic, that is, capable of bone formation. It must be said that part of the needle-in-the-marrow-haystack job had already been done by Dr Paul Simmons of Melbourne's Peter MacCallum Cancer Institute, who in 1991 helped raise and characterise an antibody for STRO-1, a molecule to be found only on non-haemopoetic stem cells. What the Hanson team did was add to STRO-1 another antibody, this one specific to a molecule called VCAM-1, and together the two antibodies proved highly capable of zeroing in on good osteogenic mesenchymal precursors[168].

Proving that mesenchymal cells were as good as angioblasts. This technology started to look particularly interesting after the 2002 Hanson discovery that the STRO-1 antibodies could be combined with other antibodies[169] to pull out of the bone marrow mix mesenchymal precursors potentially capable of neovascularisation[170]. We say 'potentially' because what they were getting were merely 'pericytes', cells that help give the walls of blood vessels their structure. But they were vascular in nature, so to Itescu it looked like the Hanson know-how could enable him to get the blood-vessel-forming stem cells he needed, and thereby do an end-run around the expansion and immunogenicity problems of angioblasts. First, however, he had to be convinced that neovascularisation could

[165] See *Mending broken hearts* by Philip Cohen, *New Scientist*, 2/4/2001.

[166] See WO 01/94420, priority date 5 June 2000, which is not a MSB patent application but was filed on behalf of Columbia University by Itescu. We understand this intellectual property has been licensed by MSB, with Columbia holding a small equity position in MSB as a result.

[167] See *Nat Med.* 2001 Apr;7(4):430-6.

[168] This work was covered in MSB's first published patent application, which is WO/2001/004268.

[169] Specific to other cell surface markers with names like 3G5 and MUC18.

[170] See *J Bone Miner Res.* 2003 Apr;18(4):696-704.

be prompted to take place in animal models using the Hanson pericytes, and a series of experiments in which Angioblast Systems worked with the Gronthos team proved in 2003 that this was possible. Patent applications over this use of MPCs in neovascularisation, as well as an appropriate expansion methodology for the cells, were published in late 2004[171].

Two companies originated from the technology. It then occurred to Itescu and his colleagues that there were in fact two companies that could be built around the Hanson technology. Angioblast Systems could further tease out the cardiovascular implications, while a new company, Mesoblast, could pursue the technology's original implications in the orthopaedic space, under an exclusive license from Angioblast. A licensing agreement was negotiated with the Hanson Institute in which the institute took equity in Mesoblast in returns for the rights to the technology[172]. As we noted above, until the merger of the two companies in 2010 Mesoblast owned 39% fully diluted of Angioblast[173], which had remained privately held.

Various methods of obtaining MPCs have been developed. The Hanson scientists continued to refine their method of obtaining MPCs after the formation of Mesoblast. They have made two significant breakthroughs since then:

- In 2005 they found that undifferentiated STRO-1-positive MPCs had an enzyme molecule on their surface called TNAP, short for tissue non-specific alkaline phosphatase. A monoclonal antibody called STRO-3 was raised against TNAP which made separation of MPCs a fairly straightforward process. The STRO-3 patent application was published in late 2006[174].
- In 2008 they found that a heat shock protein called HSP-90beta also expressed on the surface of MPCs, and raised an antibody called STRO-4 against it. The STRO-4 patent application was published in early 2010[175].

Mesoblast patent applications

At present the MSB intellectual property is covered by 14 published patent applications, all filed in the name of Angioblast Systems[176], as well as various unpublished applications[177]. Probably the most important patent applications to date are Numbers 1, 2, 3 and 6 below, which establish MSB's ownership of MPCs through antibodies to STRO-1, VCAM-1 and STRO-3. This makes enforcement of intellectual property a relatively straightforward proposition, since non-infringing antibodies would be difficult to raise. Importantly, the first US patent over the STRO-1/VCAM approach to isolating MPCs from bone marrow was granted in late 2006, strengthening MSB's overall IP position.

MSB has started to receive US patent coverage for its technology

1 **A Mesenchymal Precursor cell**, WO/2001/004268[178] (Invented by Paul Simmons, Andrew Zenettino and Stan Gronthos. Priority date 7/7/1999). This patent application covers the basic method of obtaining MPCs using the STRO-1 and VCAM-1 antibodies.

2 **Perivascular Mesenchymal Precursor Cells**, WO/2004/085630. Invented by Songtao Shi, Andrew Zenettino and Stan Gronthos with priority date 28/3/2003. This patent application

[171] This work was covered in MSB's second and third patent applications, which were WO/2001/085630 and WO 2004/084921.

[172] We understand Medvet Sciences, a Hanson Institute company, currently holds around 2% of MSB's ordinary shares.

[173] Mesoblast acquired the equity in Angioblast it did not own for 90.8 million of its shares in December 2010.

[174] This work was covered in MSB's sixth patent application, which was WO 2006/108229.

[175] This work was covered in MSB's 11th patent application, which was WO 2010/019997.

[176] There are obviously other unpublished applications still to come as MSB continues to protect its intellectual property.

[177] Generally patent applications are published around 18 months after the first provisional patent application.

[178] This patent was granted in the US as Patent Numbers 7,122,178 (October 2006), 7,399,632 (July 2008) and 7,670,628 (March 2010).

covers the basic method of obtaining perivascular MPCs capable of forming vascular tissue, using the antibodies for the relevant cell surface markers such as the aforementioned VCAM-1 and STRO-1.

3 **Perivascular Mesenchymal Precursor Cell Induced Blood Vessel**, WO/2004/084921, Invented by Andrew Zenettino and Stan Gronthos with priority date 28/3/2003. This patent application covers the use of the perivascular MPCs in neovascularisation and improvement in cardiac function.

4 **Method of enhancing proliferation and/or survival of mesenchymal precursor cells (MPC)**, WO 2006/032075, Invented by Andrew Zenettino and Stan Gronthos with priority date 29/4/2004. This patent application covers the use of a chemokine called SDF-1, already known to promote the growth of osteoclast cells[179], in promoting growth of an MPC population as well as committing the MPCs to downstream differentiation into bone cells.

5 **Multipotential expanded mesenchymal precursor cell progeny (MEMP) and uses thereof**, WO 2006/032092. Invented by Andrew Zenettino and Stan Gronthos with priority date 29/4/2004. This patent application covers a sub-class of MPCs called STRO-1^{bri} cells, which have high levels of STRO-1 on their surface but do not express an enzyme called alkaline phosphatise. The Hanson scientists found that such cells, so long as they comprised around 5-20% of an MPC batch, could produce an optimal level of multipotent 'tissue specific stem cells' once administered to a test subject.

MSB's key patent application has a 2005 priority date

6 **Isolation of adult multipotential cells by tissue non-specific alkaline phosphatase,** WO 2006/108229. Invented by Andrew Zenettino, Stan Gronthos and Paul Simmons with priority date 12/4/2005. This patent application covers a different method of obtaining MPCs than the earlier applications. Here the scientists simply use an enzyme molecule called TNAP, or tissue non-specific alkaline phosphatise, as the sole surface marker to identify undifferentiated MPCs. This method was found to be more efficient than earlier methods in obtaining undifferentiated MPCs (as indicated by STRO-1 on the surface of the cells). The patent application covers a monoclonal antibody called STRO-3 specific to TNAP which was raised and characterised by the Hanson scientists.

7 **Treatment of excessive neovascularisation**, WO 2008/006168. Invented by Piroska Rakoczyof the Lions Eye Institute with priority date 12/7/2006. This patent application covers the use of MPCs in treating AMD and diabetic retinopathy, with evidence from animal experiments conducted in 2006 and 2007 at the Lions Eye Institute in Perth.

8 **Methods of generating, repairing and/or maintaining connective tissue *in vivo***, WO 2009/018613. Invented by Peter Ghosh with priority date 6/8/2007. Peter Ghosh is Mesoblast's Vice President for Cartilage Regenerative Programs. This patent application covers the use of MPCs in treating cartilage-based diseases, with examples from treating knee osteoarthritis and degenerative disc disease.

9 **Repair and/or reconstitution of invertebral discs**, WO/2009/155656 Invented by Peter Ghosh with priority date 25/6/2008. This patent application covers the use of MPCs in intervertebral disc repair, with examples from sheep models of degenerative disc disease.

10 **Treatment of eye diseases and excessive neovascularization using a combined therapy**, WO/2010/005527 Invented by Shelly Fehr with priority date 30/6/2008. This patent application covers the use of MPCs in treating AMD and diabetic retinopathy in combination with anti-VEGF drugs such as Lucentis, with examples from work done in non-human primates.

[179] Osteoclasts are cells that help in the breakdown and resorption of bone tissue.

11 **Monoclonal antibody STRO-4**, WO/2010/019997 Invented by Stan Gronthos and Andrew Zenettino with priority date 18/8/2008. This patent application covers the STRO-4 antibody that helps select MPCs from bone marrow.

12 **Expansion of haemopoietic precursors**, WO/2010/025506. Invented by Silviu Itescu and Michael Schuster with priority date 3/9/2008. This patent application covers the use of MPCs in expanding cord blood for use in bone marrow transplantation.

13 **Method for treating or preventing a pancreatic dysfunction**, WO/2010/057260. Invented by Silviu Itescu and Ravi Krishnan with priority date 20/11/2008. This patent application covers the use of MPCs in treating diabetes.

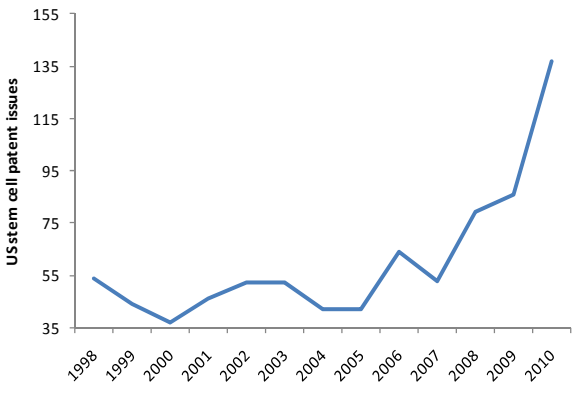
14 **Production of reprogrammed pluripotent cells**,WO/2010/105311. Invented by Silviu Itescu with priority date 20/3/2009. This patent application covers the use of the standard reprogramming techniques used in the induced Pluripotent Stem cell field to reprogram STRO-1-positive MPCs so that they could be transformed into other kinds of cells.

US health reform has helped clarify the commercial life of MSB's products

MSB now has more clarity on US market exclusivity for its products

Mesoblast will now get a minimum 12-years market exclusivity in the US. One of the many healthcare reforms which the US Congress passed and President Obama signed into law in March 2010[180] was a provision that biological drug products would have twelve years market exclusivity in the US before 'biosimilars' – generic versions of those products – could enter the market. This provision of the new law was designed to encourage a clear regulatory pathway for allowing low-cost biological drugs onto the market. Such a pathway had until last year been lacking in the US healthcare system. What the 12-year provision allows us is certainty with regard to the market life of MSB's products. In our modelling of MSB we have assumed around 13 years of market exclusivity per product, based on the assumption that existing patent life, patent extensions, paediatric extensions and (perhaps) some litigation could provide this kind of commercial life. The new law simplifies our basic assumption on product life, while also providing the possibility of further market exclusivity should MSB develop newer versions of its products – say, more patient-friendly delivery vehicles or stem cells with better tissue targeting.

Figure 25 - US stem cell patent issuance has risen markedly in recent years



SOURCE: US PATENT AND TRADEMARK OFFICE – ALL PATENTS ISSUED WITH THE PHRASE 'STEM CELLS' IN THE ABSTRACT

[180] The United States Patient Protection and Affordable Care Act of 2010.

Appendix II– The stem cell corporate landscape

MSB is one of around 15 listed companies around the world that have stem cells as their primary technology development and commercialisation focus.

We think MSB has the world's leading stem cell technology

Why MSB is in the lead, in our view

In surveying the landscape we feel that MSB has considerable competitive advantages that warrant a premium to the competitor companies:

- **The MPC technology does not involve embryonic stem cells**. This puts MSB ahead of Geron, StemCells and NeuralStem;
- **The technology can be used allogeneically**. This puts MSB ahead of Tigenix, Cytori, Advanced Cell Technology, Aastrom, International Stem Cell and Bioheart;
- **MPCs are easy to obtain**. This puts MSB ahead of many of the companies on the list below;
- **MPCs have generated clinical data.** We think that only Osiris Therapeutics can compete with MSB on this score, and the credibility of that company has been impacted by some 2009 clinical issues.

Figure 26 – MSB comparable companies

Company	Location	Code	Cap (USDm)	Website
Geron	Menlo Park, Ca	Nasdaq: GERN	512.9	www.geron.com
Cytori Therapeutics	San Diego, Ca	Nasdaq: CYTX	273.8	www.cytoritx.com
Osiris Therapeutics	Columbia, Md	Nasdaq: OSIR	237.4	www.osiristx.com
Advanced Cell Technology	Santa Monica, Ca	OTCBB: ACTC	173.0	www.advancedcell.com
StemCells	Palo Alto, Ca	Nasdaq: STEM	146.1	www.stemcellsinc.com
International Stem Cell	Oceanside, Ca	OTCBB: ISCO	112.3	www.internationalstemcell.com
NeuralStem	Rockville, Md	Amex: CUR	92.5	www.neuralstem.com
Aastrom Biosciences	Ann Arbor, Mi	Nasdaq: ASTM	85.6	www.aastrom.com
Tigenix	Leuven, Belgium	Euronext Brussels: TIG	58.2	www.tigenix.com
ReNeuron	Guildford, UK	LSE: RENE	51.2	www.reneuron.com
Athersys	Cleveland, Oh	Nasdaq: ATHX	48.3	www.athersys.com
Pluristem Therapeutics	Haifa, Israel	Nasdaq: PSTI	39.2	www.pluristem.com
BrainStorm Cell Therapeutics	Petah Tikva, Israel	OTCBB: BCLI	16.9	www.brainstorm-cell.com
Bioheart	Sunrise, Fl	OTCBB: BHRT	11.2	www.bioheartinc.com

SOURCE: SOUTHERN CROSS EQUITIES – MARKET CAPITALISATION DATA AS AT 28 FEBRUARY 2011

What Osiris Therapeutics means for Mesoblast

Osiris is the most relevant comparable. As we've noted in this report, Osiris Therapeutics is the player in mesenchymal stem cells that is most directly comparable to MSB. The main technological difference between the two companies is that Osiris's method of obtaining its mesenchymal stem cell products is around 1,000 times less efficient than MSB's. Osiris has two products in development, Prochymal for various indications and Chrondogen for meniscal tears and osteoarthritis.

A big issue for Osiris in 2009 was clinical issues, with four pieces of bad news through the course of the year:

- In March 2009 a Phase III trial of Prochymal in Crohn's disease was ended due to 'significantly higher than expected placebo response rates'[181];
- In June 2009 Prochymal failed in a Phase II trial in chronic obstructive pulmonary disease (COPD);
- In September there were apparent failures in two Phase III trials in GvHD[182].

The Genzyme/Osiris deal shows the potential for a commercial payoff. In November 2008 Osiris partnered Prochymal and Chrondogen to Genzyme in a deal worth US $130m upfront and potentially US$1.25bn more in milestones and an indeterminate amount in escalating royalties, which we think are high single digit percentage of sales:

- Osiris agreed to fund clinical development through to the end of Phase II with Genzyme sharing the cost of Phases III and IV on a 60% Osiris / 40% Genzyme split;
- Osiris will commercialise the products in the US and Canada while Genzyme will take the rest-of-world;
- Osiris may receive up to $500 million in development milestone payments for Prochymal and $100m for Chrondogen;
- Based on sales in Genzyme territories, Osiris is eligible to receive up to $250 million in sales milestones for Prochymal and $400m for Chrondogen.

Genzyme/Osiris and Mesoblast/Cephalon have established benchmarks for stem cell deals

This deal is significant for MSB in three ways

1) It represents the partnering interest of a large, established company that didn't have loss of patents on key products. Genzyme had US$4.6bn in revenue in 2008 and NPAT of US$1.1bn;
2) It was done on the basis of Phase II data, although products had arrived in Phase III;
3) The dollar values involved suggested the potential for a significant commercial payoff for MSB in the event of clinical success.

We think that the Genzyme/Osiris and now the Mesoblast /Cephalon deals have established strong benchmarks for future deals in the stem cell space.

MSB's other listed competitors

1) **Geron** (Menlo Park, Ca, Nasdaq: GERN, market cap US$513m as at 28/2/2011). This company has been a major player in human embryonic stem cells for a decade now due to its work in commercialising the early methods of growing stem cells in culture that had been discovered at the University of Wisconsin in the late 1990s[183]. We noted above that a drawback to dealing with embryonic stem cells is the issue of potential tumours. This impacted Geron in August 2009 when the FDA halted a clinical trial of Geron stem cells in spinal cord injury due to the development of cysts at the injection sites of

[181] In May 2010 the company restarted this trial after an interim analysis showed that disease remission is 'approaching statistical significance in the intent to treat population'. The analysis showed that one doze size in the trial was performing 'consistent with the original statistical assumptions of the protocol and is significantly outperforming placebo'.

[182] Osiris thinks there is still value in its GvHD work. For example, in February 2010 it unveiled data suggesting effectiveness as a rescue therapy for children with severe GvHD.

[183] It also holds important intellectual property on the use of therapeutic uses of telomerase, which is interesting because 2009's Nobel laureates in medicine were related in part to this field.

animals on which the cells had been tested. Subsequent discussions with the FDA appears to have resolved these issues, and the clinical hold was removed in July 2010, allowing the trial to start in October.

2) **Cytori Therapeutics** (San Diego, Ca, Nasdaq: CYTX, market cap US$274m). This company's technology centres on adipose-derived regenerative cells (ADRCs), which are effectively autologous stem cell transplants where the cells are derived from a patient's own fat tissue. The company is conducting Phase II trials of this approach in acute myocardial infarction and coronary artery disease as well as breast reconstruction after lumpectomy for breast cancer. We see this company as being a good comparable for MSB due to the progress the company has made in the clinic, with the market excited about the prospects for near term approval of the devices which comprise Cytori's cell harvest and processing system. We see the principal drawback of the ADRC approach as being the liposuction surgery required prior to cell selection, which may limit the cardiovascular applications, although favourable data was reported in 2010[184]. It's also worth noting that much of its clinical work is currently conducted in Europe with no US trials at this stage.

Advanced Cell has attracted a lot of attention in the US because of pioneering work in stem cells

3) **Advanced Cell Technology** (Santa Monica, Ca, OTCBB: ACTC, market cap US$173m). This company has a reputation for pioneering research in stem cells[185], with recent technical achievements including the 2006 derivation of embryonic stem cells without embryo destruction[186] and the 2009 creation of induced Pluripotent Stem cells via direct delivery of reprogramming proteins[187]. Commercially, however, the company is not very advanced, with its most developed programme being treatment of heart failure via autologous transplants of adult stem cells derived from skeletal muscle. In December 2009 the company filed an IND over a potential treatment for Stargardt's macular dystrophy, a rare cause of blindness. The IND was cleared in November 2010. A second IND, for dry AMD, was cleared in January 2011.

4) **StemCells Inc.** (Palo Alto, Ca, Nasdaq: STEM, market cap US$146m). This company is another embryonic stem cell player, with its HuCNS-SC, a neural stem cell, having been trialled in a Phase I setting as a potential treatment for a rare CNS disorder called Batten's disease[188]. In this trial StemCells gained some evidence of cell engraftment and long-term survival. Another Phase I, this one in Pelizaeus-Merzbacher disease, a myelination disorder that mainly affects children, commenced in February 2010. A trial in spinal cord injury is planned.

5) **International Stem Cell** (Oceanside, Ca, OTCBB: ISCO, market cap US$112m). This company is based on technology to produce functional pluripotent stem cells through parthenogenesis[189]. This would notionally make cells even more powerful than multipotent cells like MPCs, in that pluripotent cells are capable of differentiating into all of the various cell types that make up the body. The technology, if credible, could sidestep the potential ethical issues of embryonic stem cell use. However development is

[184] Since liposuction happens under general anaesthesia, this kind of treatment would not be an option for advanced heart failure, for example. Also, while the technology appears to be able to obtain therapeutic quantities of cells in around one hour, the liposuction raises the amount of time and trouble a patient would have to expend before receiving stem cell therapy post the angioplasty. This may limit the commercial use in AMI, where the technology is being trialled.

[185] For more on the pioneering early achievements of this somewhat controversial company see *Merchants of Immortality: Chasing the Dream of Human Life Extension* by Stephen S. Hall (New York: Houghton Mifflin Harcourt, 2003).

[186] *Nature*. 2006 Nov 23;444(7118):481-5. Epub 2006 Aug 23..

[187] *Cell Stem Cell*. 2009 Jun 5;4(6):472-6. Epub 2009 May 28.

[188] Also called neuronal ceroid lipofuscinosis.

[189] See *Cloning Stem Cells*. 2007 Fall;9(3):432-49.

at an early stage. Animal experiments have been done on corneal repair to improve photorefractive keratectomy (PRK), a form of corrective laser eye surgery.

6) **NeuralStem** (Rockville, Md, Amex: CUR, market cap US$93m). This company is based on technology to isolate and expand embryonic neural stem cells. In 2010 the company commenced a Phase I trial in ALS ('Lou Gehring's disease') while other intended applications include spinal cord injury.

7) **Aastrom Biosciences** (Ann Arbor, Mi, Nasdaq: ASTM, market cap US$86m). This company has been built around Tissue Repair Cell technology, involving a machine which, by replicating the internal environment of bone marrow, enables rapid expansion of stem cells derived from marrow and autologous transplant of those cells, but doesn't attempt to enrich the resulting cell batches for MPCs. The technology is currently in Phase II trials in two cardiovascular conditions - dilated cardiomyopathy[190] and critical limb ischemia[191] –while a Phase III trial is being conducted in patients suffering osteonecrosis (ie 'bone death').

Tigenix's autologous stem cell therapy in knee osteoarthritis paves the way for an allogeneic approach from MSB

8) **Tigenix** (Leuven, Belgium, Euronext Brussels: TIG, market cap US$58m). As we noted above, this company has gained European approval for its Chrondocelect autologous stem cell therapy, with an initial application in repair of defective knee cartilage. Tigenix's technology involves taking chondrocytes, that is, cartilage-forming cells, from a healthy region of the patient's cartilage, expanding these cells in a lab setting and then re-implanting them at the site of the defective cartilage. We think MSB's technology has strong advantages over Chrondocelect in knee osteoarthritis in that, being allogeneic, an initial, cell-harvesting surgical procedure will not be required with MPCs. Tigenix is working on a second-generation Chrondocelect that uses a biocompatible and biodegradable three-dimensional cell culture matrix, as well as an application of its approach in meniscal tears.

9) **ReNeuron** (Guildford, UK, LSE: RENE, market cap US$51m). This company is another adult stem cell player, with stem cell lines that have been immortalised using the c-MycER fusion protein, and that can proliferate after a chemical constituent of the growth media is removed. The company encapsulates the cells so as to protect them from an immunological response in the recipient, the claim being that this allows them to be used allogeneically. ReNeuron is focused in particular on neural cells, and initiated a clinical trial in disabled stroke patients in November 2010. We regard this initial application as a difficult proposition given the number of failed drug candidates in the stroke arena historically.

Athersys has done a small partnering deal with Pfizer, indicating Big Pharma interest in the stem cell area

10) **Athersys** (Cleveland, Oh, Nasdaq: ATHX, market cap US$48m). This company is seeking to commercialise a class of mesenchymal stem cells called 'multipotent adult progenitor cells' or MAPCs, which appear to have many of the advantages of MSB's MPCs including the ability to be used allogeneically. In July 2010 Athersys reported favourable Phase I data from a trial of MAPCs in acute myocardial infarction. There is also a Phase I trial ongoing in bone marrow transplants[192] while INDs for ischemic stroke and inflammatory bowel disease have been cleared by the FDA. There have been concerns raised in scientific circles regarding the reproducibility of the science behind MAPCs[193]. However that didn't deter Pfizer Regenerative Medicine

[190] A severe form of chronic heart failure.

[191] A severe blockage in the arteries of the lower extremities.

[192] Specifically, the company wants to see if MAPCs can treat the complications, including GvHD, associated with bone marrow transplants.

[193] See *Fresh questions on stem cell findings* by Peter Aldhous and Eugenie Samuel Reich, *New Scientist*, 21/3/2007.

from partnering with Athersys in December 2009 over a potential inflammatory bowel disease treatment in a deal worth US$6m upfront and US$105m in milestones.

11) **Pluristem Therapeutics** (Haifa, Israel, Nasdaq: PSTI, market cap US$39m). This company is based on technology to extract and expand 'mesenchymal-like' stromal cells from the human placenta. Like MPCs there are apparently no immunity issues with these cells so they can be used allogeneically. The company has trialled the technology first in peripheral artery disease (PAD), where in a Phase I setting it has shown some effectiveness in critical limb ischemia, the end-stage of PAD. Other targets include inflammatory bowel disease, Multiple Sclerosis, HSC engraftment in bone marrow transplant and ischemic stroke.

12) **BrainStorm Cell Therapeutics** (Petah Tikva, Israel, OTCBB: BCLI, market cap US$17m). This company, whose focus in treatment of CNS disorders such as Parkinson's disease and Lou Gehrig's disease, is based on technology to differentiate marrow-derived mesenchymal stem cells into Neurotrophic Factor Stem Cells helpful in replacing the dopamine-producing cells that are lost in Parkinson's. The company is also working on a neuroprotective agent called glial-derived neurotrophic factor (GDNF)[194]. Clinical trials are planned.

13) **Bioheart** (Sunrise, Fl, Nasdaq: BHRT, market cap US$11m). This company is another autologous stem cell player focused on the cardiac space, with its main product involving transplant of myoblast cells taken from the patient's thigh muscle. In September 2009 the company announced six-month data from 330-patient a Phase II/III trial in heart failure, with treated patients improving their six-minute walk distance by 91m versus 4m for placebo.

[194] Using, among other things, docosahexaenoic acid, an omega-3 fatty acid known to be good for nerve cells.

Appendix III – Stem cells are the future in medicine

What are stem cells?

Stem cells are cells in the body with the capacity to 'differentiate' themselves into other, more specialised kinds of cells. This makes them potentially useful as factories where fresh cells can be manufactured to treat diseases that are the result of out-of-control cell death, such as Parkinson's disease or osteoporosis. Here, if one can deliver, into the right part of the body, the right kind of stem cell, the result may be a 'cell therapy' that puts back the cells that have been lost and thereby restores to the patient at least some of the body function which the disease had impaired.

There are basically two kinds of stem cells…

- Embryonic stem cells, derived from embryos and generally pluripotent, meaning they can turn into almost all of the body's 200-or-so cell types, and
- Adult stem cells, derived from various human tissues and generally multipotent, meaning that meaning that they can turn into various, albeit limited, cell types.

…and each comes with its issues…

- Embryonic stem cells are controversial because obtaining them has traditionally required embryos to be destroyed in the harvesting process. Among other things this factor led US President George W. Bush to limit Federal funding for human embryonic stem cell research from 2001, a ban overturned by President Obama in 2009.
- Some adult stem cells have issues with immunogenicity, with allogeneic transfers of cells – is, between unrelated parties – having the potential to provoking an immune response in the recipient. This has tended to limit most adult stem cell use to autologous applications, meaning the patient's own stem cells are used in his or her treatment. MSB's stem cells, however, don't have this immunogenicity problem.

Stem cells are getting easier to isolate and expand

…however scientific and lay interest is rising. Stem cells came to widespread lay public attention in November 1998 when researchers at the University of Wisconsin and Johns Hopkins University reported the first isolation of human embryonic stem cells[195]. Since then scientific knowledge and public interest concerning stem cells has expanded considerably. We see three reasons for this

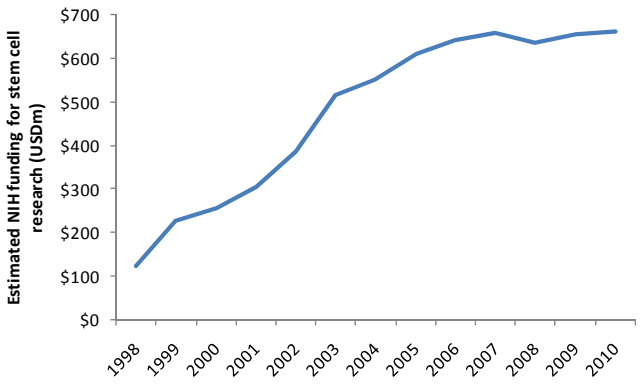
1) Stem cells are getting easier to obtain thanks to isolation and expansion techniques developed since 1998;
2) The cells have been used to demonstrate potential treatments across a range of hitherto untreatable disease conditions;
3) There have been high profile advocates of embryonic stem cell research such as the American actors Michael J. Fox, who has Parkinson's disease, and Christopher Reeve, who died in 2004 after nine years as a quadriplegic.

…and this has resulted in increased government funding. The US government upped its research budget considerably in 2001 to compensate for President Bush's limits on Federal funding for embryonic stem cell research, while various

[195] See *Science*. 1998 Nov 6;282(5391):1145-7.

American states have also done some embryonic funding. The UK announced a strong increase in government funding in 2005 from around £25m pa in 2005 to more like £50m in 2007[196]. And in 2009 Korea announced a planned tripling of its spending on embryonic stem cell research by 2015, to around US$100m[197].

Figure 27 – US federal funding for stem cells has been rising



SOURCE: NIH – NOTE, FIGURES FOR 2009 AND 2010 BASED ON NIH ESTIMATES RATHER THAN ACTUALS. FOR 2008 TO 2010 NIH NUMBERS ARE ADJUSTED DOWNWARDS TO REFLECT THE 2007 CHANGE TO 'REVISED' REPORTING AS OPPOSEDTO 'HISTORICAL' REPORTING.

Figure 28 –Various US states are funding stem cell research

State	Year programme announced	Funding (USDm)	Term
New Jersey	2004	35	10 years
California	2004	3,000	10 years
Wisconsin	2004	750	
Connecticut	2005	100	10 years
Illinois	2005	15	10 years
Maryland	2006	38	
New York	2007	600	11 years
Massachusetts	2008	1,000	10 years

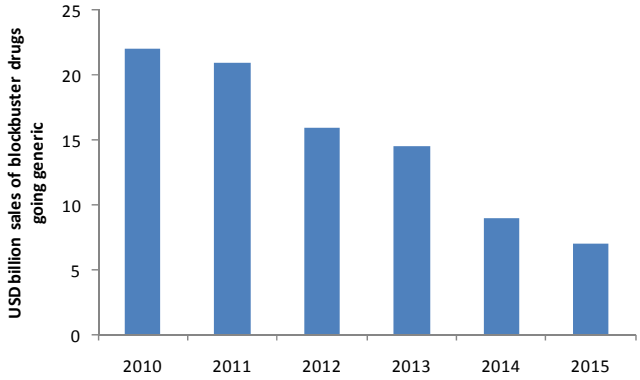
SOURCE: SOUTHERN CROSS EQUITIES

Figure 29 – Many governments are funding stem cell research

Country	Est. 2006 central government funding, USDm	Country	Est. 2006 central government funding, USDm
USA	570	Israel	15
UK	100	China	10
Korea	45	Japan	10
Canada	30	Sweden	10
Singapore	25	Switzerland	5
Australia	20	India	2

SOURCE: JULY 2006 PRESENTATION ENTITLED STEM CELLS AND THE NEW "AGE OF DISCOVERY" BY WILLIAM HOFFMAN OF THE UNIVERSTY OF MINNESOTA.

Figure 30 – Many blockbuster drugs are going generic right now



SOURCE: PHARMA FUTUROLOGY - JOINED-UP HEALTHCARE 2016 AND BEYOND, BRITISH TELECOMMUNICATIONS TOUCH BRIEFING, 2007

Blockbuster drugs going off-patent are an inducement to Big Pharma to look at stem cells

…as well as Big Pharma starting to play. The ability to scale up embryonic, induced Pluripotent or adult mesenchymal stem cell production[198] means that these kinds of cells have the potential to replace the billions of dollars in sales of blockbuster drugs that will be impacted by generic competition over the next five years. Pfizer is already starting to get involved, driven, we believe, by the end of US patent protection for Lipitor in 2011, and we expect its competitors will follow suit over the next few years.

[196] See *Pledge to make Britain 'leading location for research into drugs and treatments'* by Roger Highfield, *The Telegraph*, 6/12/2005

[197] See *State funding for stem cell research to triple* by Kim Tong-hyung, *Korea Times*, 30/7/2009

[198] Where there are no immunogenicity issues.

Widespread evidence of potential efficacy

Many incurable diseases may be treatable using stem cells

There is hardly an area of modern medicine that has not been touched by at least the hint of a stem cell breakthrough over the last decade:

Spinal cord injury – In work funded by Geron, nerve cells derived from human embryonic stem cells, when transplanted into paralysed rats, enabled the animals to walk again[199] (story reported November 2003). Spinal cord injury costs the US around US$10bn a year, with 11,000 new cases annually (source: CDC).

Chronic liver disease – Researchers at Yamaguchi University in western Japan were able to reverse liver fibrosis, a precursor to cirrhosis of the liver, in mice with injections of donated murine bone marrow cells (December 2004). A subsequent small clinical trial in humans resulted in a report of improved liver function [200]. There are over 100,000 US hospitalisations a year for chronic liver disease (source: CDC).

Muscular dystrophy – Researchers at Milan's San Raffaele Scientific Institute were able to restore muscle function in a dog model of muscular dystrophy through injections of a kind of stem cell called a mesoangioblast. This enabled production of the protein dystrophin, which muscular dystrophy patients lack [201] (November 2006). Muscular dystrophy is rare – only 500 infants are born each year in the US with the main forms of the disease – but hitherto incurable.

Dental implants – Researchers at Tokyo University of Science have used murine embryonic stem cells to engineer new teeth in mice[202] (March 2007). Around 70% of adults over the age of 35 have lost at least one permanent tooth (Source: AAOMS).

Breast implants – In a mouse experiment, researchers at the University of Illinois at Chicago used fat-cell-derived mesenchymal stem cells to engineer breast implants which retained their size and shape after implantation[203] (March 2005). There were over 300,000 breast augmentation surgeries in the US in 2008 (Source: American Society of Plastic Surgeons).

Sandhoffs and Tay-Sachs diseases – Researchers at San Diego's Burnham Institute used adult and embryonic stem cells to prolong the lives of mice with a genetic defect similar to that which causes Sandhoffs and a related disease called Tay-Sachs [204]. As with muscular dystrophy, incidence of these diseases - characterised by progressive deterioration of the central nervous system - is rare, but there are no treatments at present (April 2007).

Parkinson's disease– Primate models of Parkinson's administered human neural stem cells by Yale researchers saw their condition stabilise for about four months[205] (July 2007). Parkinson's is an attractive market for drug developers because there are around one million patients in the US (source: Parkinson's Disease Foundation) with life expectancy in many cases longer than ten years.

Alzheimer's disease – Researches at the University of California, Irvine have demonstrated that mice in which memory cells had been destroyed can experience improved memory after receiving injections of murine neural stem

[199] See Geron press release of 11/11/2003 headlined *Geron announces presentation of pre-clinical studies on human embryonic stem cell-based treatment of acute spinal cord injury.*

[200] See *Hepatology.* 2004 Dec;40(6):1304-11 and *Stem Cells.* 2006 Oct;24(10):2292-8. Epub 2006 Jun 15.

[201] See *Nature.* 2006 Nov 30;444(7119):574-9. Epub 2006 Nov 15.

[202] See *Nat Methods.* 2007 Mar;4(3):227-30. Epub 2007 Feb 18.

[203] See *Tissue Eng.* 2005 Mar-Apr;11(3-4):556-66.

[204] See *Nat Med.* 2007 Apr;13(4):439-47. Epub 2007 Mar 11.

[205] See *Proc Natl Acad Sci U S A.* 2007 Jul 17;104(29):12175-80. Epub 2007 Jun 22.

cells [206] (November 2007). There are around 5 million Alzheimer's patients in the US (source: Alzheimer's Association) with existing treatments only serve to stem the cognitive decline for around one year.

Blindness – There have been some key breakthroughs in this area in recent years, most notably:

- Advanced Cell Technology scientists rescued visual function in rat models of macular degeneration through implantation of retinal pigment epithelial cells derived from human embryonic stem cells[207] (September 2006).
- A small clinical trial in Newcastle-upon-Tyne in the UK demonstrated restoration of sight in patients suffering an eye condition called limbal stem cell deficiency, where the stem cells that can help rebuild a damaged cornea have themselves been damaged [208]. The treatment involved autologous transplant of limbal cells from a remaining healthy eye (December 2009).

As we noted above, around six million Americans suffer from wet AMD and diabetic retinopathy, with the numbers rising fast.

Type 1 diabetes – This form of diabetes - where the patient's pancreatic islet cells have been destroyed by an autoimmune disorder - has seen two key experimental stem cell breakthroughs over the last two years:

- The privately held San Diego biotech company Novocell has demonstrated that human embryonic stem (hES) cells can be turned into pancreatic cells capable of producing insulin in mice[209] (February 2008);
- Researchers at the University of Sao Paulo in Brazil have used reversed type 1 diabetes in humans using autologous stem cell injections, with those treated no longer needing insulin to control their blood sugar levels[210] (April 2009).

Around 5-10% of the diabetic population has the Type 1 variety (source: NIDDK).

Osteogenesis imperfecta – This genetic disorder, characterised by bones that break easily, only affects 25,000-50,000 Americans (source: Osteogenesis Imperfecta Foundation) but has no viable treatment options. Researchers at Imperial College London found that injections of human foetal mesenchymal stem cells into unborn mouse models of osteogenesis imperfecta could cut the incidence of long bone fractures compared to the controls by two-thirds[211].

Stem cells may provide a new treatment path for cancer

Cancer – Researchers at Northwestern University in Illinois have found that tumour cells exposed to an environment of human embryonic stem cells lose their former aggressiveness, and even start to die, with the stem cells apparently secreting proteins which switch off aberrant signalling pathways in the tumour cells[212] (March 2008). There were around 1.5 million new cancer cases in the US in 2009 (source: American Cancer Society).

Stroke – Researchers at Tulane University in New Orleans induced strokes in mice and then injected human adult stem cells into the resulting oxygen-deprived areas of the brain. The result was 60% less cell death in the treated mice, who seemed to experience no noticeable behaviour changes compared to the more

[206] See J *Neurosci.* 2007 Oct 31;27(44):11925-33.

[207] See *Cloning Stem Cells.* 2006 Fall;8(3):189-99..

[208] This work was published online in the journal *Stem Cells* on 10 Dec 2009.

[209] See www.novocell.com. The paper covering the work was *Nat Biotechnol.* 2008 Apr;26(4):443-52. Epub 2008 Feb 20.

[210] See *JAMA.* 2009;301(15):1573-1579.

[211] See *Blood.* 2008 Feb 1;111(3):1717-25. Epub 2007 Oct 29.

[212] See *Proc Natl Acad Sci U S A.* 2008 Mar 18;105(11):4329-34. Epub 2008 Mar 11.

lethargic control mice[213] (September 2008). There are around 800,000 strokes a year in the US (source: American Heart Association).

Tissue repair - Researchers and doctors in the UK, Italy and Spain were able to rebuild a trachea that had been destroyed by the tuberculosis bacteria through autologous stem cells plus donated tracheal tissue[214] (November 2008).

Blood transfusions – In work funded by Advanced Cell Technology, researchers were able to turn human embryonic stem cells into a blood cell precursor called haemangioblasts, and from there into mature red blood cells. This work opens up the possibility of eliminating blood donations[215] (December 2008). In the US around 5 million blood transfusions take place each year (source: American Red Cross). Only around 5% of the US adult population regularly donates blood, leading to periodic shortages.

Reproduction – There is now laboratory evidence that stem cells can play a role in reproduction. Scientists at China's Shanghai Jiao Tong University have identified mouse ovarian stem cells, with female mice rendered sterile by chemotherapy able to produce offspring after receiving the cells[216] (May 2009). Meanwhile at England's Newcastle University, researchers claim to have created human sperm cells from embryonic stem cells[217] (July 2009). Around 60,000 babies are born in the US each year through assisted reproductive technologies (source: CDC).

Stem cells could one day displace the cochlear implant

Deafness – Researchers at the University of Sheffield in the UK have demonstrated that human foetal-derived cochlear stem cells can be expanded and then differentiate into auditory neurons, suggesting a potential stem-cell therapy for deafness[218] (May 2009). At least one in 500 children in the US is born deaf or hard-of-hearing (source: NIDCD).

Motor neurone disease – In mouse experiments researchers at the University of Milan have used stem cells to repair the damage involved in a form of motor neurone disease called spinal muscular atrophy[219] (September 2009). MND is rare – only around 30,000 Americans have the MND known as Lou Gehrig's disease (source: ALS Association) - but hitherto incurable.

Heart disease – Subsequent to the 2001 breakthrough by Silviu Itescu's team on repairing damaged rat hearts numerous other labs have pursued the heart disease implications of stem cell therapy. Probably the most notable development so far has been the engineering of heart valves from marrow-derived stem cells by researchers associated with the British heart transplant surgeon Sir Magdi Yacoub[220] (April 2007). There are around 100,000 heart valve surgeries performed annually in the US.

Racehorse injuries – Stem cell treatment for injured racehorses is starting to become commonplace. In Britain, for example, Dream Alliance was treated for a severed front leg tendon with stem cells in 2008 and went on to win the Welsh National in December 2009[221].

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[213] See *Proc Natl Acad Sci* U S A. 2008 Sep 23;105(38):14638-43. Epub 2008 Sep 15.

[214] See *The Lancet* (DOI: 10.1016/S0140-6736(08)61598-6).

[215] See *Blood.* 2008 Dec 1;112(12):4475-84. Epub 2008 Aug 19.

[216] See *Nat Cell Biol.* 2009 May;11(5):631-6. Epub 2009 Apr 12.

[217] A paper in the journal *Stem Cells and Development* was retracted by the journal when it was found that two paragraphs in its introduction had been plagiarised.

[218] See *Stem Cells.* 2009 May;27(5):1196-204.

[219] See *J Neurosci.* 2009 Sep 23;29(38):11761-71.

[220] See *British team grows human heart valve from stem cells* by Alok Jha, *The Guardian*, 2/4/2007.

[221] See *Nag that won the National* by Jane Fryer, *Daily Mail*, 31/12/2009

Gut repair – Human intestinal tissue has been engineered using pluripotent stem cells by a team at Cincinnati Children's Hospital[222]. This suggests the possibility of replacing tissue damaged by diseases such as Crohn's (December 2010).

Baldness – Researchers at the University of Pennsylvania have established that stem cells are capable of regenerating hair follicles[223] (January 2011). Around 85% of men over age 50 have some degree of hair loss (Source: American Hair Loss Association)

Urological tissue repair – Scientists at Wake Forest University in Winston-Salem, NC engineered urethra-like tissue by growing stem cells extracted from urine on scaffolds made from pig gut tissue[224] (January 2011).

Working around the ethical issues

The ethical problems concerning embryonic stem cells have resulted in two basic efforts to 'work around' the issue:

- A focus on adult stem cells as the non-controversial alternative
- A move to develop so-called 'induced Pluripotent Stem cells' (iPS cells).

The most commercially straightforward type of stem cell is the kind owned by MSB

Why adult stem cells like MSB's are in the lead. Adult stem cells have tended to move forward fastest because of the relative ease with which they can be obtained and the higher level of government funding. Mesoblast's MPC technology is therefore well placed to benefit from the rise in stem cell therapies because it is an adult stem cell and can be administered allogeneically.

There is potential for adult stem cells to be displaced as the leading technology paradigm in the long run. While we think adult stem cells will stay in the lead for a long while, particularly if the science translates into high-revenue approved therapies, embryonic stem cells and iPS cells remain a potential long-term threat to adult stem cells because:

- Technologies are emerging that allow embryonic stem cells to be created without damaging an embryo. An example of this approach was first announced by Advanced Cell Technology in 2006 (see Appendix II);
- iPS cells, where adult stem cells are transformed into cells having the pluripotency of embryonic stem cells, have the potential for sidestepping the ethical issues of embryonic stem cells entirely. The science of iPS cells is exciting, with, for example, *Time* magazine naming the creation of mice from iPS cells as No 5 in its Top 10 Medical Breakthroughs list for 2009. However the iPS field is still very new, with the first discoveries in the field having been made only in late 2007[225]. Moreover iPS cells are created by transfecting certain stem cell-associated genes into non-pluripotent adult cells, and this process is likely to attract strong regulatory interest due to traditional safety concerns related to the field of gene therapy[226].

MSB has taken steps towards showing that its MPCs are compatible with iPS cells in work which demonstrates that MPCs can be 'reprogrammed' using techniques standard to the iPS field[227].

[222] See *Nature*. 2011 Feb 3;470(7332):105-9. Epub 2010 Dec 12.

[223] See *J Clin Invest*. 2011 Feb 1;121(2):613-22. doi: 10.1172/JCI44478. Epub 2011 Jan 4.

[224] See Biomaterials. 2011 Feb;32(5):1317-26. Epub 2010 Nov 4.

[225] See *Science*. 2007 Dec 21;318(5858):1917-20. Epub 2007 Nov 20.

[226] It ought to be noted that in 2009 Advanced Cell Technology developed a less controversial method in which the reprogramming proteins are delivered directly rather than via transfection. What this illustrates to us is the ingenuity which is being brought to the technical and ethical issues concerning stem cells.

[227] See the company's WO/2010/105311 patent application.

Appendix IV – MSB's capital structure

MSB has raised $206m since its late 2004 IPO

Figure 31 - MSB's current capital structure

Shares (ASX Code MSB)	279,068,562	Price (c)	517.0
Shares that may result from the conversion of options *	9,652,993	Undiluted cap ($m)	1,442.8
Total diluted shares	288,721,555	F.D. Cap ($m)	1,492.7

* Estimated option exercise price $1.54 by July 2013

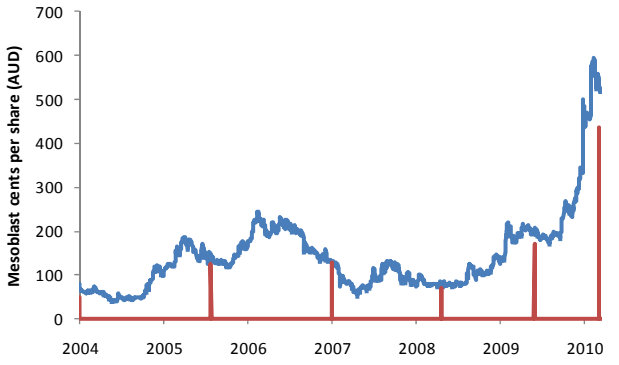
SOURCE: MSB, SOUTHERN CROSS EQUITIES.

Figure 32 - MSB's capital raising history

Date	Shares (million)	% of current shares on issue	Price	Amount raised ($m)	Discount to market
Dec-04	42.0	29.9%	$0.50	21.0	IPO
Jul-06	13.9	9.9%	$1.25	17.4	10.7%
Dec-07	10.5	7.5%	$1.28	13.4	4.5%
Apr-09	15.0	10.7%	$0.72	10.8	10.0%
May-10	21.1	7.6%	$1.70	35.8	12.1%
Feb-11[228]	24.7	8.9%	$4.35	107.5	21.5%
Total	127.2	45.6%	$1.62	205.9	

SOURCE: MSB

Figure 33 – MSB has made five placements since its 2004 IPO



SOURCE: MSB, IRESS

[228] To Cephalon as part of major partnering deal.

Appendix V – An MSB glossary

Acute myocardial infarction - The medical term for a heart attack, that is, a blockage of blood supply to the heart muscle (the myocardium).

Agonist – A drug that stimulates or enhances activity of cell receptors.

Allogeneic – A type of bone marrow or stem cell transplant in which the donor and recipient are genetically dissimilar. MSB's stem cells products can be used in allogeneic transplants, enabling them to be used as 'off the shelf' products.

AMD – Short for Age-related Macular Degeneration, an eye disease in which the central area of the retina (the macula) loses function and leaves the patient with only peripheral vision. MSB has done preclinical work indicating that its stem cells can be useful in the treatment of AMD.

AMI – see Acute myocardial infarction.

Angioblasts - Adult blood vessel stem cells.

Angioblast Systems- A privately-held US company which has licensed the rights to MSB's stem cells for cardiovascular conditions. MSB owned 39% of Angioblast Systems fully diluted until it acquired the other 61% in 2010.

Angioplasty - A procedure to open clogged arteries, performed after a heart attack.

Antibodies – Immune system proteins that can bind to an antigen and help to neutralise the potentially harmful effects of the cells carrying the antigen. Antibodies are commonly used in drug therapy for this reason. A monoclonal antibody is an antibody specific to a single target. STRO-3 is a monoclonal antibody.

Autograft – Use of a patient's own bone in orthopaedics work.

Autologous - A type of bone marrow or stem cell transplant in which the recipient receives his own cells. MSB's stem cells were initially trialled in autologous transplants before work began on allogeneic applications of the cells.

Baseline – The beginning point of a clinical study.

Big Pharma – A collective term referring to the world's largest pharmaceutical companies, including J&J, Abbott Laboratories, and Pfizer.

BMP – Short for Bone Morphogenetic Protein, a growth factor than can help create new bone. MSB is seeking to displace BMP's use in spinal fusion.

Bone graft – Material which helps an orthopaedics patient grow new bone.

Bone marrow transplantation – A treatment for leukaemia in which a patient's bone marrow is destroyed by chemotherapy and/or radiation therapy and then replaced by previously harvested bone marrow from a donor or the patient himself. MSB is working on using its stem cells to enhance the effectiveness of bone marrow transplantation through expansion of cord blood.

Blockbuster – A drug that enjoys more than US$1bn in annual sales.

Bony bridging – The fusion of two bones.

Cartilage – The connective tissue that covers the ends of bones in a joint. MSB's stem cells are being applied to the treatment of cartilage damage in osteoarthritis.

Catheter - A tube inserted into a body cavity, duct or vessel to allow drainage, injection of fluids, or access by surgical instruments.

CD34+ cells – Another term for haemopoietic stem cells.

Cervical spine – The upper back which supports the neck area.

CHF – Short for congestive heart failure.

Chemokine – A protein that activates immune cells, stimulates their migration, and helps direct immune cell traffic throughout the body.

Cleared – A clinical trial for which approval has been gained from the FDA.

Congestive heart failure – See heart failure.

Cord blood – Blood from the umbilical cord of a newborn child. Cord blood is rich in haemopoietic stem cells.

Coronary artery disease - A narrowing or hardening of the heart's arteries, leading to other cardiovascular problems such as heart attack. MSB's stem cells have been used in patients suffering coronary artery disease.

Diabetes - A disease condition in which a person's pancreas fails to produce enough of the hormone insulin, which the body needs in order to be able to regulate levels of glucose in the blood. There are two types of diabetes, Type I, which generally shows up in childhood and where the pancreas produce no insulin at all, and Type II, representing 95% of total diabetes incidence, where insulin production gradually declines, generally after the age of 40.

Diabetic retinopathy - A disease of the small blood vessels of the retina in the eye that originates from the diabetic condition of the patient. Diabetic retinopathy results in blurred vision and ultimately blindness. MSB is seeking to apply its stem cells to the treatment of diabetic retinopathy.

Differentiation - The process by which a less specialised cell becomes a more specialised cell type.

Dose response – A situation in which increased doses of a drug results in a higher level of biochemical effect in the patient, which often is more therapeutic for the patient.

Down-regulating - Suppressing the expression of a particular molecule.

DVOL – Short for Left ventricular end-diastolic volume.

Ejection Fraction (EF) – A measure of the capacity at which the heart is pumping, calculated by percentage of blood ejected with each contraction of the ventricles. A normal left ventricular EF is 55% to 70%. MSB is testing MPCs in patients with EFs below 40%.

Embryonic stem cells – Stem cells derived from human embryos. Embryonic stem cells are controversial in the Western world due to ethical issues and the potential of such cells to be carcinogenic.

Endpoint - The outcome that a clinical trial is designed to evaluate, such as disease progression or death.

Enzyme - A protein that helps speed up biochemical reactions in the body.

Expansion – The creation of more cells from a starting batch.

Femur – The thigh bone.

Good Manufacturing Practice (GMP) - The set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals.

GvHD – Short for Graft-versus-host-disease, a condition where the patient's own immune system rejects transplanted tissues or cells. This results in skin inflammation, diarrhoea and jaundice.

Haemopoietic stem cells – Stem cells that help build the body's blood supply. Also known as CD34+ cells.

HA/TPC – Short for hydroxyapatite / tricalcium phosphate, materials used as bone substitutes in orthopaedic surgery. MSB's MPC cells have performed well in orthopaedic applications against HA/TPC.

Heart failure – A condition where the heart is unable to pump adequate amounts of blood around the body. There are four classes of heart failure (see NYHA class). Heart failure is sometimes called congestive heart failure or CHF due to congestion in the lungs being one of its symptoms.

Heat shock proteins – Proteins expressed by cells when they are exposed to elevated temperatures.

HLA match – HLA is short for Human Leukocyte Antigen complex, a group of genes on chromosome 6 that play a role in the body's immune response to foreign substances. Six genes in particular are used to determine the level of match (eg 3/6 or 6/6) between donor and recipient in bone marrow transplants.

Hyaluronic acid - A naturally occurring polysaccharide that is found particularly in the joints and is often injected into the joints as a therapy.

ICD-9-CM – A universally-accepted classification system for medical diagnoses and procedures, with each diagnosis or procedure being given a numeric code, such as 84.65 for 'insertion of total spinal disc prosthesis, lumbosacral area'.

IND – Short for Investigation New Drug, an FDA designation of a drug that has been approved for clinical trials in the US.

Indication - A reason to prescribe a drug or perform a procedure.

induced Pluripotent Stem cells – Stem cells derived from adult cells that have been transformed, through the transfection of various genes, into cells having the pluripotency of embryonic stem cells.

Intervertebral discs – The cartilage-based discs that make up the spine. MSB is seeking to apply its stem cells to repair of this cartilage.

In vitro – In the test tube.

In vivo – In animal models.

iPS cells – See induced Pluripotent Stem cells

Left ventricle – The chamber of the heart principally responsible for pumping blood out of the heart and on to the rest of the body.

Left ventricular end-diastolic volume (DVOL) – The volume of blood in the left ventricle at the end of filling. DVOL is a measure of how hard the heart has to pump, with rising DVOL an indication of worsening heart failure.

Long bone fracture – A break in bones such as those between the hip and the knee. MSB's stem cells have been used to repair long bone fractures.

Lumbar spine – The lower back.

LVAD – Short for Left Ventricular Assist Device, a mechanical device that can assist in the pumping of blood through the left ventricle of the heart.

Meniscal tears – Tears in the meniscus, a cartilage which provides shock absorbent properties to the knee. There is potential for MPCs to be applied to the treatment of such tears.

Mesenchymal stem cells – Stem cells that give rise to a variety of cell types in the body such as fat, blood vessel and bone cells.

Minimally invasive – Surgery that involves only a small incision, allowing more

rapid recovery for the patient.

MPCs – Short for Mesenchymal Precursor Cells, cells capable of differentiating into Mensechymal Stem Cells.

MSCs – Short for Mensechymal Stem Cells.

Multipotent – A stem cell capable of turning into various, albeit limited, cell types. MPCs are multipotent.

National Institutes of Health – The various medical research centres maintained by the US government. The National Heart, Lung and Blood Institute (NHLBI) is one of the National Institutes of Health.

Neofuse – MSB's trademark for the orthopaedic applications of its stem cells.

Neutrophil – A white blood cell vital for immune system function. Neutrophils work by ingesting foreign cells. Neutrophil recovery is a key measure of the effectiveness of a bone marrow transplant.

NHLBI – See National Institutes of Health.

NYHA Class – One of four classes of heart failure patients as determined by the New York Heart Association, ranging from Class I (least affected) to Class IV (death's door).

Off-label – Usage of a drug or device in a way which that a regulator has not specifically approved even though the product is approved for use. Off-label use is permitted so long as a doctor is doing the prescribing.

Orphan Drug – A drug that benefits less than 200,000 potential patients in the US. Orphan drug designation by the FDA makes a drug eligible for various benefits such as seven years of US market exclusivity.

Osteoarthritis – Progressive degeneration of bone tissue such as cartilage resulting from inflammation.

Osteogenic - Capable of bone formation.

Percutaneous – Passed through the skin.

Peripheral blood - Blood circulating in the body as opposed to bone marrow.

Phase I – A clinical trial in humans to test safety in a small sample.

Phase I/II – An early-stage safety study (a Phase I study) but one conducted in patients rather than in healthy volunteers.

Phase II – A clinical trial in humans to test efficacy in a small sample.

Phase III – A clinical trial in humans to test efficacy in a large sample.

Phase IV – A study of a drug in patients after it has gained regulatory approval.

Pilot trial – A clinical trial in humans designed to provide proof-of-concept.

Pivotal trial – A Phase III trial.

Pluripotent – A stem cell capable of turning into almost all cell types. Embryonic stem cells are pluripotent.

Posterior lateral interbody fusion – A kind of spinal fusion in which the bone graft is placed between the vertebrae in the area usually occupied by the intervertebral disc, with the incision being made from the back. This kind of spinal fusion is considered 'minimally invasive'.

Posterolateral spinal fusion – Spinal fusion where the bone graft is placed between the transverse processes.

Preclinical – Work such as animal testing that prepares a drug for clinical trials in

humans.

Precursor cells – A cell that turns into another kind of cell. Precursor denotes a relatively immature cell. With stem cells, the less mature the cell is, the more desirable from a potential therapy point of view.

Pre-market approval – Regulatory clearance for a drug or medical device to be marketed.

Priority date – The date on which an invention is considered to have 'occurred' for patent protection purposes.

p-value – A measure of statistical significance. Generally a p-value below 0.05 is considered 'statistically significant'.

Revascor – The MSB trademark for the cardiovascular applications of MPCs.

Specialty pharma – A drug company with approved products that specialises in a particular kind of drug. For example, Cephalon is a specialty pharma company traditionally focused on CNS drugs.

Spinal fusion – Surgery to fuse the vertebrae in the spine, generally through use of a bone graft or bone substitute. MSB is seeking to commercialise a stem cell alternative.

Standard of care – The current 'best practice' therapy for a disease, which MSB generally uses as 'placebo' in its clinical trials.

Statistical significance - The probability that an observed outcome of an experiment or trial is due to chance alone. Generally p-values below 0.05 are taken as markers of statistical significance.

Stem cells – Cells that can differentiate into many different cell types when subjected to the right biochemical signals. MSB's MPCs are a kind of stem cell.

STRO-1 – The primary cell surface marker on bone marrow cells that characterises undifferentiated mesenchymal precursor cells. STRO is short for 'stromal cell'.

STRO-3 – An antibody specific to TNAP that MSB uses to identify MPCs.

Stromal cells - The connective tissue cells that form the supportive structure in which the functional cells of the tissue reside. Mensechymal stem cells come primarily from marrow stromal cells.

TNAP – Short for tissue non-specific alkaline phosphatase, a marker which MSB uses to identify undifferentiated MPCs.

Transverse processes - Small bones that connect the vertebrae to the back muscles.

Transcription factor - A protein that binds to specific DNA sequences and thereby controls the transfer of genetic information to messenger RNA and ultimately into protein.

Transfection - The transfer of DNA into a cell, often with the help of a virus.

Traumatic bone fractures – Bone fractures that are the result of wound or injury.

Up-regulating - Promoting the expression of a particular molecule.

Ventricle – One of the heart's two pumping chambers.

Mesoblast

COMPANY DESCRIPTION

The Melbourne-based Mesoblast (MSB) is a biotechnology company commercialising the therapeutic use of mesenchymal precursor cells or MPCs – a kind of adult stem cell. MSB's MPC technology allows these cells to be extracted from the bone marrow of donors, grown into therapeutic quantities and administered 'allogeneically' – ie, to patients that are not related to the donor - to treat disorders where new bone or tissue growth is required. We like the effectiveness of the technology as against existing therapies, as well as its non-controversial nature. The technology is being applied to a wide variety of orthopaedic and cardiovascular applications with the first commercial products set to emerge from the clinic around 2012/13. Mesoblast now has A$281m in cash on hand and therefore no further need to raise capital from the equity markets.

INVESTMENT STRATEGY

We see a major partnering deal with Cephalon (MSB's 19.99% shareholder) inked in late 2010 as providing significant upside since it funds the company's leading programmes in bone marrow transplantation and heart failure. We also see a payoff to shareholders arising from further partnering deals for individual applications as the stem cells prove themselves in clinical trials. We expect a typical licensing deal will yield upfront and milestone payments as well as royalties.

VALUATION

We assume the MSB pipeline has value across a range of clinical development programmes. Our $11.00 target price for MSB is at the lower level of our base case $7.34 / optimistic case $14.56 per share probability-weighted DCF valuation. We assume that MSB can be re-rated by the market as the near-term nature of the stem cell opportunity become apparent, and further clinical data emerges.

RISKS

We see the main risk in MSB as being clinical risk – ie that products fail to perform in human trials. Another major risk facing the company is that prospective licensing partners may drive too hard a bargain for MSB shareholders to enjoy a strong return.

Recommendation structure

Spec Buy: Expect >30% total return on a 12 month view but carries significantly higher risk than its sector

Buy: Expect >15% total return on a 12 month view

Accumulate: Expect total return between 0% and +15% on a 12 month view

Reduce: Expect -15% and 0% total return on a 12 month view

Sell: Expect <-15% total return on a 12 month view

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