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Mesoblast (MSB)

The heart of the matter

Recommendation
Buy (Buy)
Price
$7.55
Target (12 months)
$16.00 (previously $11.00)

Expected Return	
Capital growth	**112%**
Dividend yield	**0**
Total expected return	**112%**

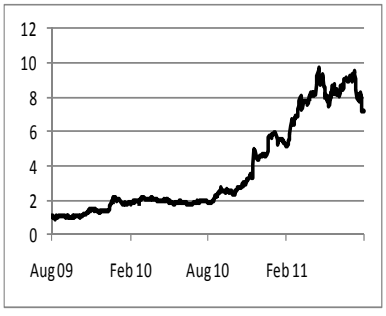
Company Data & Ratios	
Enterprise value	**$1,854m**
Market cap	**$2,117m**
Issued capital	**280.4m**
Free float	**100%**
Avg. daily vol. (52wk)	**0.62m**
12 month price range	**$1.80-$9.95.**
GICS sector	
Healthcare Equipment and Services	

Disclosure: Bell Potter Securities acted as lead manager in a capital raising in May 2010 and in a selldown of stock in December 2010 and received fees for that service.

Price Performance

	(1m)	(3m)	(12m)
Price (A$)	9.14	8.63	1.90
Absolute (%)	-21.55	-16.92	277.37
Rel market (%)	-13.61	-6.69	282.94

Absolute Price



SOURCE: IRESS

This report is an update of a previous Southern Cross Equities report which has been compiled for compliance and rebranding purposes. Our comprehensive coverage of Mesoblast, which was initiated on 10/1/2010, is updated in this document. Our previous update was 3/3/2011.

Stem cells are pivotal role in Medicine's future.

Public awareness of the ability of one's own stem cells (autologous stem cells) to potentially cure a wide variety of diseases has increased dramatically in the past year. This success has been emulated and often improved, by use of allogeneic or 'off the shelf' stem cells, which is being recognised by Big and Speciality Pharma. These changing perceptions were highlighted by Cephalon's A$243m purchase of a 19.9% stake in Mesoblast in December 2010. They were validated by the decision of Cephalon's new owner, the Israeli drug major Teva, to retain the stake and indicate the importance of the Cephalon pipeline to its future growth.

MSB has stem cell technologies that work

MSB is commercialising Mesenchymal Precursor Cell (MPC) technology which allows adult stem cells to be extracted from a donor's bone marrow, grown into therapeutic quantities and administered to non-related patients. MSB initially focused on MPCs in orthopaedic and cardiovascular applications but has since expanded into inflammatory disorders and diseases of the Central Nervous System. MSB has five Phase II trials underway and is initiating a Phase III trial in Bone Marrow Transplant, with a revenue opportunity matching that of Cochlear. With the FDA requiring only one Phase II and a pivotal trial before approving a successful stem cell therapy, the company has the potential to be yielding commercial revenues by late 2013.

Mesoblast is undervalued on the heart application alone

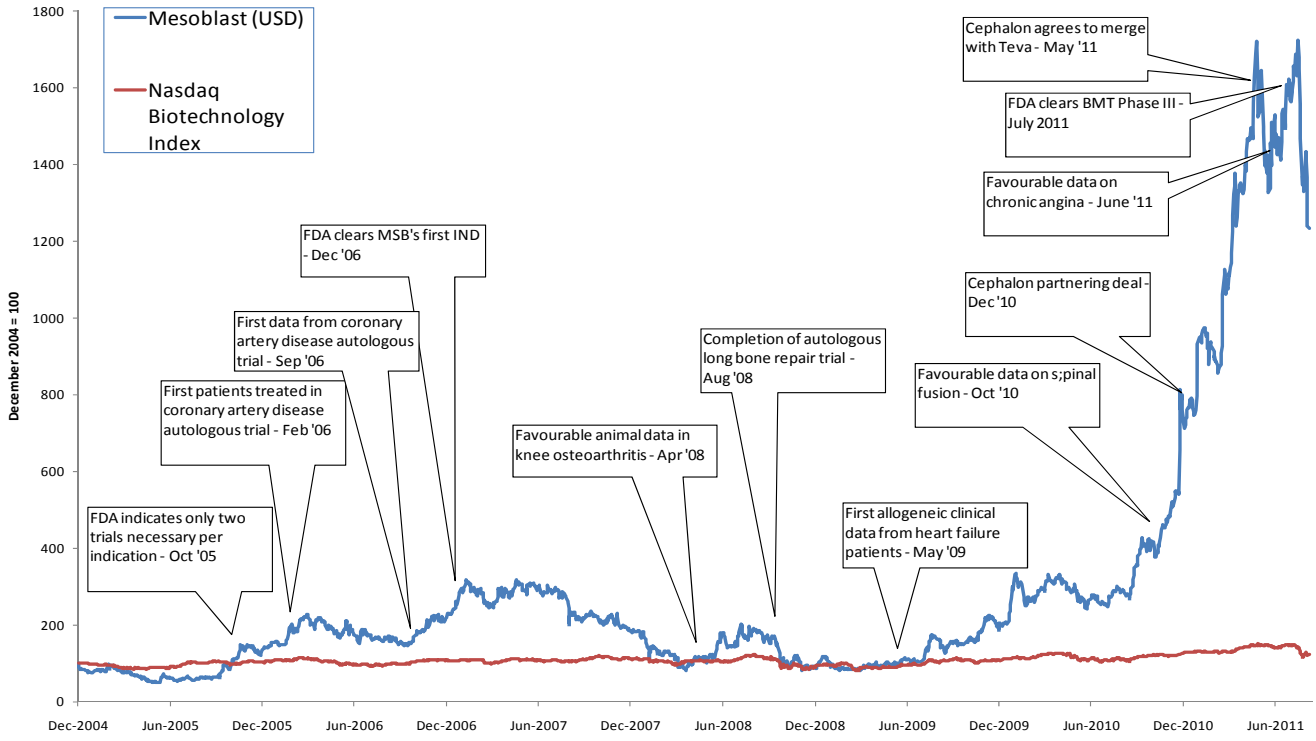
Bell Potter Securities believes Mesoblast's share price undervalues the cardiovascular applications alone. Much attention will focus on the results of the 60 patient trial of MPCs in heart failure, to be unveiled at a special session of the American Heart Association's annual meeting in November 2011. An overview of the Phase II trial released in June 2011 saw outstanding evidence that MPCs can rebuild heart muscle and improve blood flow to the heart muscle, thereby reducing adverse coronary events and hospitalisations. Applications in heart failure, in heart attacks and in chronic angina represent multi-billion dollar market opportunities.

Investment view – $16 target based on clinical success

Mesoblast's apparent Phase II success has prompted a change in valuation approach. We assume a 75% probability of clinical success for the company's cardiovascular and Bone Marrow Transplant programmes and estimate the commercial payoff from these applications using a DCF approach. This yields a valuation range of $7.35 to $14.00. Conservatively, we add a further $2.83/$6.63 per share for the opportunities in bone marrow, orthopaedic, inflammatory disease, CNS and manufacturing. Combined with cash on hand and cash from options this gives a new valuation range of target of $11.14/$21.59, and a target of $16 per share representing the midpoint of our valuation range. We assess that in the coming year many of Mesoblast's pipeline opportunities will grow into something as substantial as the cardiovascular.

Contents

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



SOURCE: NASDAQ, ASX, MSB, BELL POTTER SECURITIES

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

Since our previous note

Since our previous updated comprehensive reported Mesoblast, published on 3 March 2011, there have been five major developments:

Mesoblast now has a new major shareholder, with the announcement in May 2011 that the Israeli drug major Teva would acquire Cephalon for US$6.8bn. Cephalon owned 19.9% of Mesoblast as a result of the partnering deal in December 2010. We argue in this note that Teva's involvement in Mesoblast is likely to be positive, since the Israeli company has a strategy of growing through branded innovator drugs, and is motivated to do so given the various threats faced by Copaxone, its Multiple Sclerosis blockbuster, which loses US patent protection in 2014. We expect that Teva will seek to optimise the development pathway for Mesoblast's cardiovascular and CNS programmes, and may also use Mesoblast's technology to bolster its existing franchise in MS.

Mesoblast has announced further favourable heart failure data. Mesoblast announced in June 2011 that a subset analysis of 22 patients from its 60-patient trial in heart failure had shown that these patients, suffering from ischemic heart failure and reduced myocardial blood flow, had experienced a '*75% reduction in adverse coronary events over a mean follow-up period of 21 months compared with controls'.* This data indicated that Mesoblast's MPCs would be an effective treatment for chronic refractory angina, opening up a market which in the US alone could constitute 200,000 new patients annually and where there would be likely be little competition, except perhaps from an autologous therapy from Baxter that has completed Phase II. Mesoblast indicated that it would initiate a 150-patient Phase II trial of its MPCs in chronic refractory angina in 2012.

Mesoblast has been accepted for a special session at this year's American Heart Association meeting. The data released to date hints at the potential for a strong 12-month efficacy readout for the entire 60-patients, which is scheduled for release at the American Heart Association annual meeting in Orlando, Fl in November 2011.

Mesoblast has started its intervertebral disc repair trial. Mesoblast announced in June 2011 that it had initiated its Phase II trial in disc repair, with the clearing of the IND. The first patient was implanted in August 2011. This 100-patient trial will compare two MPC doses against placebo, with a six month endpoint. We regard regulatory approval of MPCs for disc repair in 2014 as relatively straightforward, since the primary endpoint would be reduced pain over a 12-18 month period. Disc repair represents, potentially, a US$2bn market.

Mesoblast has moved to Phase III in bone marrow transplant. Mesoblast announced in July 2011 that it was commencing its Phase III trial in bone marrow transplant, with the clearing of the relevant IND. This 240-patient trial will randomise patients to either unexpanded or MPC-expanded cord blood, with a primary endpoint of reduced time to neutrophil and platelet recovery. In our view 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, potentially opening up a US market potentially worth US$300m pa. Bone marrow transplant is Mesoblast's first application to have reached Phase III.

Sixteen 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 four Phase II trials of the technology, has completed a fifth with full data pending, and has initiated its first pivotal trial, in Bone Marrow Transplantation. Two other 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:

Mesoblast is the leading company in the stem cell sector by market cap

1. **MSB is part of a wave of the future that is capitalised at only US$3.5bn 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 ~US$3.5bn, reflecting the early stages of what we anticipate 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.

The Cephalon / Mesoblast partnering deal was the first major deal in the stem cell space

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 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 and strong financial upside. Cephalon's due diligence prior to the deal will also serve as a comfort factor for investors.
5. **Teva's acquisition of Cephalon is a plus for Mesoblast**. The Israeli drug major Teva announced that it was acquiring Cephalon for US$6.8bn in May 2011. We argue in this note that Teva's involvement in Mesoblast is likely to be positive, since that company has a strategy of growing through branded innovator drugs, and is motivated to do so given the various threats faced by Copaxone, its Multiple Sclerosis blockbuster, which loses US patent protection in 2014. We expect Teva will seek to optimise the development pathway for Mesoblast's cardiovascular and CNS

programmes, and may also use Mesoblast's technology to bolster its existing franchise in MS.

6. **MSB now has A$263m in cash.** The upfront payment and equity placement associated with the Cephalon deal has left MSB amply funded for further clinical development and negated the possibility of further capital raisings. As at June 2011 the company held $263m in cash with a burn rate of only A$2.1m per month.

Mesoblast is currently running or completing five Phase II and is moving towards its first Phase III

7. **Multiple trials are now underway with a pivotal coming soon**. As we noted above, MSB is currently conducting or working towards Phase II or Phase III trials in eight 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$318m[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	Completion optimistic case	Completion base case	Patients
Posterior interbudy lumbar fusion	II	Aug-12	Feb-13	24
Cervical spinal fusion	II	Apr-12	Oct-12	24
Intervertebral disc repair	II	Jan-13	Jul-13	100
Heart failure	II	Data out Nov-11		60
Acute myocardial infarction	II pending	Feb-14	Feb-15	25
Knee osteoarthritis	II	Jan-12	Jul-12	24
AMD / diabetic retinopathy	II pending	Feb-14	Aug-14	25
Bone marrow transplant	III	May-13	Jul-13	240

SOURCE: MSB, BELL POTTER SECURITIES. NOTE - ACUTE MYOCARDIAL INFARCTION AND AMD / DIABETIC RETINOPATHY PATIENT NUMBERS ARE BELL POTTER SECURITIES ASSUMPTIONS

8. **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 cleared IND and a Special Protocol Assessment being sought from the FDA. 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 the Australian medical device major Cochlear Ltd[2], which has a market capitalisation of A$3.9bn[3]. Also, we see the success of the Phase II trial as pointing towards a significant de-risking of the technology.

MSB's heart failure trial has generated solid interim data

9. **MSB's heart failure trial will report Phase II data in November 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 when full data is released at the American Heart Association annual meeting in Orlando, FI, in November 2011.

10. **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] 22 August close on Nasdaq.

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

[3] In FY10 COH sold 24,661 cochlear implants globally, representing around 70% of the cochlear implant market. This is around the same as the number of allogeneic bone marrow transplants performed globally each year (Source: National Marrow Donor Program).

11. **Other applications are growing in importance**. We like MSB's potential in applications such as knee osteoarthritis, AMD/diabetic retinopathy and Type I and II diabetes, where the animal data looks good.

12. **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.

The FDA only requires two clinical trials per MPC application

13. **The management is commercial.** We have a high regard for MSB's leadership team led by Executive Director Professor Silviu Itescu, who owns 24.4% 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.

14. **We expect substantial news flow in 2011 and 2012.** The next 12 months will feature some strong news flow from MSB, with potential announcements including:

- Initiation of clinical work on diabetes and AMD/diabetic retinopathy;
- Completion of the spinal fusion trials;
- Completion of the heart failure trial with results published at the American Heart Association meeting in November 2011;
- Progression to a heart failure pivotal trial;
- Completion of the disc repair trial;
- Potential completion of the knee osteoarthritis trial;
- Receipt of a Special Protocol Assessment by the FDA for the bone marrow transplant trial;
- The first patient in the bone marrow transplant Phase III;
- Approval to conduct a trial in Acute Myocardial Infarction in Europe, and the first patient in that trial;
- A strategic alliance on manufacturing; and
- Animal data on new MPC indications including Alzheimer's and Parkinson's.

15. **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;

Big Pharma likes 'off-the-shelf' business models like Mesoblast's

- *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 believe Mesoblast can yield a similar advantage today in stem cells.

16. **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 $16.00 target price for MSB is at the midpoint of our base case $11.14 / optimistic case $21.59 per share probability-weighted DCF valuation.

Valuing MSB and realising that value

We value MSB at $11.14 base case and $21.59 optimistic case

To value MSB we have previously valued seven programmes on which MSB has worked, and valued each using a probability-weighted DCF methodology where we assumed dates in which products enter the clinic and gain regulatory approval. With the apparent success of Mesoblast's MPCs in heart failure we have changed our valuation approach. We assume a 75% probability (previously ~33%) of clinical success[4] for the cardiovascular and BMT applications, and we have enlarged the prospective payoff from these applications.

Figure 3 - Our new valuation of MSB

	Base case	Optimistic case
NPV of MPCs in cardiovascular (A$m)	1,959.9	3,762.4
NPV of MPCs in Bone Marrow Transplant (A$m)	180.2	314.2
NPV of unpartnered applications (A$m)	823.1	1,929.5
Cash ($m)	263.2	263.2
Cash from options ($m)	16.6	16.6
Total diluted value ($m)	3,243.0	6,285.9
Total diluted shares	291.2	291.2
Value per diluted share	$11.14	$21.59
Valuation midpoint (to nearest dollar)	$16.36	
Share price now	$7.55	
Premium / Discount to share price	116.7%	

SOURCE: BELL POTTER SECURITIES ESTIMATES

Valuing the cardiovascular upside

Our major assumptions for cardiovascular are:

- Launch of MPCs by Teva in its first cardiovascular indication in 2015;
- A 20% effective royalty to Mesoblast ultimately rising to 30% - 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/Teva for a set transfer price out to patent expiry. The transfer pricing arrangements have not been disclosed, however we assume an initial transfer pricing arrangement of 35% of average selling price[5], offset by an MSB cost of manufacture worth 15% of average selling price. This translates to an effective royalty on sales of 20%. We see this rising to 30% within five years;
- Recept of US$700m in milestone payments from Teva over the period 2015 to 2019;
- Global sales rising to US$2bn (base case) and $4bn (optimistic case) by year five of release, late in the current decade;
- Growth of 10-20% pa after year 5;
- An eleven year time horizon;
- A terminal growth rate of 3.5%;
- Costs for MSB to run its cardiovascular franchise in the order of 4% of sales;
- A tax rate of 30%
- Conversion to AUDUSD on our long-run exchange rate assumption of 0.85.

[4] Appropriate for a large molecule drug entering phase III. DiMasi et. al. (Clin Pharmacol Ther 87: 272- 277) estimated the probability of clinical success from an analysis of the US clinical performance of the 50 largest pharma companies (by sales) in that market from the early-to-mid 1990s through to 2009.

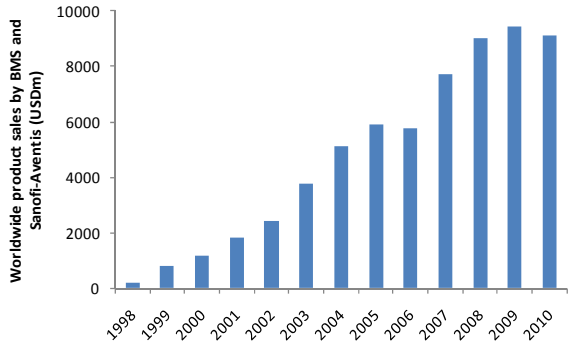
[5] We understand that Wyeth's arrangement with Medtronic for BMP, where Wyeth made the product and sells it to Medtronic, worked at a transfer price of 50% of average selling price. Wyeth merged with Pfizer in late 2009.

Our sales payoff assumption is reasonable. While some may object to the large sales numbers we have postulated for MPCs in the cardiovascular area, we believe it's worthwhile to consider the experience of two drugs that are comparable in the sense of effectively addressing large market opportunities:

Mesoblast may own the 'next Plavix'

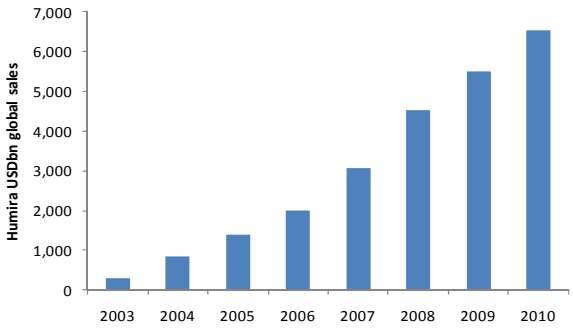
- **Plavix.** This US$9bn pa blood thinning drug, co-marketed globally by Bristol-Myers Squibb and Sanofi-Aventis[6], has been huge success since its late 1990s launch[7] mainly because of its widespread usage in patients that have been implanted with stents, but also because of the drug's demonstrated utility in treating people with Acute Coronary Syndrome[8]. Recent work has demonstrated its utility in heart failure[9]. We see Plavix as a good comparable for the cardiovascular potential of MPCs.
- **Humira.** This US$6.5bn pa anti-inflammatory antibody drug from Abbott Laboratories[10], which targets the pro-inflammatory cytokine TNF-α, has been a huge success because of its effectiveness in dealing with Rheumatoid Arthritis, and Abbott's continual pushing of the drug into new indications such as psoriasis and Crohn's disease. We see Humira as a good comparable for the autoimmune potential of MPCs.

Figure 4 - Plavix has been a huge succes in the cardiovascular space



SOURCE: SANOFI-AVENTIS

Figure 5 - Humira has been a major best-seller for Abbott



SOURCE: ABBOTT LABORATORIES

Valuing the BMT upside

We have valued the BMT application using a similar methodology to the cardiovascular approach above, assuming

- A 2014 launch;
- US$200m in milestones payments from Teva over the period 2014 to 2018;
- US$200-400m in global sales to be reached by year 5.

Valuing the Mesoblast pipeline

With this note we are retaining the pipeline valuations we used for the non-partnered applications of MPCs. These valuations were obtained by taking key pipeline programmes and valuing 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

[6] Generic name clopidogrel, see www.plavix.com.

[7] The drug loses US patent protection in 2012 and European protection in 2013.

[8] A disease situation where patients are suffering both angina and heart attack. In the US possibly 1.2 million hospitalisations a year result from ACS (source: American Heart Association, *Heart Disease and Stroke Statistics*, 2011 update).

[9] See J Am Coll Cardiol. 2010 Mar 30;55(13):1300-7.

[10] Generic name adalimumab, see www.humira.com.

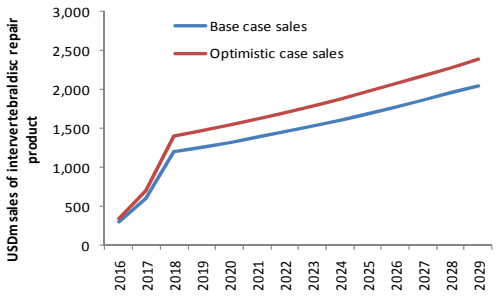
realised. We applied various probability assumptions, which give the products a roughly 1-in-3 chance of clinical success. We then calculated the NPV of the resulting cash flow at a 25% discount rate, adjusted for a 30% tax rate, and subtracted a 3% royalty for the main technology providers, the Hanson 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 0.85. The various valuation parameters used are laid out below.

Figure 6 – Key parameters for valuing MSB's deeper-pipeline 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
AMD/Diabetic retinopathy (100%)	300	500	20	10	17%	20%	2017	100	200

SOURCE: BELL POTTER SECURITIES ESTIMATES

Figure 7 - Assumed sales profile for intervertebral disc repair product



SOURCE: BELL POTTER SECURITIES ESTIMATES

Mesoblast does not need to raise further capital

We assume no further capital needs to be raised. With around A$263m in the bank after the Cephalon deal we assume that MSB is fully funded for any clinical programmes it undertakes going forward.

Target price $16.00. The result of our valuation work for MSB was base case $11.14 per share and optimistic case $21.59. We used the midpoint of our DCF as our 12-month target price for the stock.

The path to $16.00 per share

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

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 clinical 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.

The Cephalon deal has helped unlock MSB's upside

In one of the largest biotechnology transactions of 2010, MSB announced, in December of that year, a partnering deal with the American specialty pharma company Cephalon which saw that company 1) take a 19.99% stake in MSB at A$4.35 per share[11], 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.

Mesoblast's second largest shareholder is now Teva. As of this year Mesoblast has a new major shareholder. A little under five months after partnering with Mesoblast, Cephalon announced that it was being acquired for US$6.8bn by the Israeli drug major Teva Pharmaceutical Industries[12], which now becomes Mesoblast's second largest shareholder after Silviu Itescu. Let's consider first the Cephalon deal itself before looking at what Teva's involvement in the company means:

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

A transforming deal from MSB's first commercial partner

The numbers reflect the potential of stem cells. In partnering with MSB, Cephalon paid US$130m upfront and agreed to pay US$1.7bn in potential milestone payments contingent on clinical and regulatory success in the relevant programmes. Mesoblast will also share in new product sales through its retention of all manufacturing rights, which we estimate is equivalent to a double digit royalty. We see this deal as capitalising on the tremendous potential of stem cell therapies in modern medicine.

The deal leaves Mesoblast amply funded for future commercial development. Mesoblast had around ~A$281m cash after Cephalon transaction[13], 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 could take its 19.99% stake[14];
- ~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/Teva 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:

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

[12] Petah Tikva, Israel, Nasdaq; TEVA, www.tevapharm.com. Teva was the 'white knight' which bid for Cephalon after it was tilted for by the Toronto-based Valeant Pharmaceuticals, a specialty pharma company mainly focused on dermatologicals. The Valeant bid, in March 2011, led to a sell-off in Mesoblast stock on concern that Valeant, which doesn't like to do much R&D and prefers acquisitions of established products, would somehow reverse the Mesoblast/Cephalon partnering.

[13] A$263m at 30 June 2011.

[14] 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.

- Cephalon/Teva will fund the US bone marrow transplant pivotal, expected to launch in early 2011, and
- Cephalon/Teva 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 5.7 million Americans or 2.4% 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 50-60% of the heart failure market, are likely to be highly receptive[15].

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 treat these conditions[16], and given the versatility MPCs have shown, we would not be surprised to see favourable data from Mesoblast in 2011[17].

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 expect the market will value more highly as the passage into Phase III of the heart failure application lessens 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 gives Mesoblast flexibility in terms of enjoying the upside from progressively lower manufacturing costs, something that its competitor Pluristem has also recognised (see Appendix III below), with that company announcing in July 2011 that it will build a stem cell manufacturing plant in Israel. For Mesoblast's manufacturing/transfer arrangement with Cephalon we assume (and we believe this is conservative) that the arrangement allows the equivalent of at least a 17-20% royalty to Mesoblast, with Mesoblast having further upside depending on how much it can drive down production costs[18].

What Teva's involvement potentially means for Mesoblast

Who is Teva? The Israel-based Teva is a major emerging player in the global pharmaceutical industry, with US$16.1bn in 2010 revenue and US$3.9bn in EBIT and a current market capitalisation on Nasdaq of US$36.2bn[19]. The company has grown strongly over the last ten years, building from its roots as a generic drug manufacturer through various acquisitions[20], as well as, significantly, two branded innovator drugs that it

[15] It's worthwhile noting that HeartWare, 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 now has a market capitalisation of US$798m (22 August close on Nasdaq).

[16] 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.

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

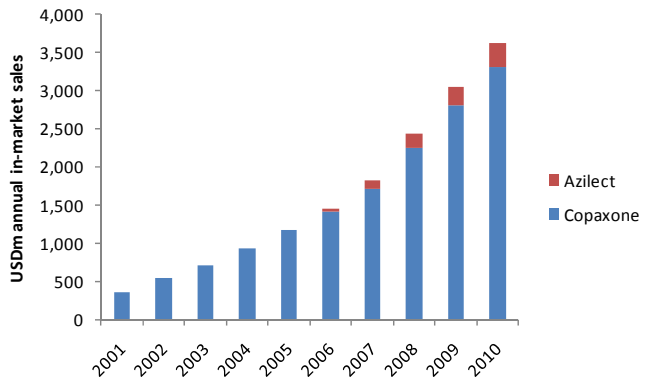
[18] The company now plans to do some work on scale up of culture processes as well as technologies for efficient use of culture media, among other things.

[19] 22 August close on Nasdaq.

[20] Most notably, prior to the Cephalon acquisition, Sicor in 2004 (US$3.4bn), IVAX in 2006 (US$7.4bn), and Barr Pharmaceuticals in 2008 (US$7.5bn), all generic drug companies.

developed from a very early stage after in-licensing from Israeli research institutions - Copaxone[21] for the treatment of Multiple Sclerosis and Azilect[22] for the treatment of Parkinson's disease[23].

Figure 8 - Copaxone has been a huge winner for Teva



SOURCE: TEVA

Figure 9 - Teva has fallen out of favour with the market

SOURCE: NASDAQ

Teva is facing challenges. Currently Teva faces three major challenges to its growth:

- *It's a tough time to be involved in generic drugs*. In revenue terms Teva is primarily still a generic drug company, and in fact remains the world's largest, having increased its involvement in the generic industry in 2010 when it spent €3.63bn acquiring the German generic drug company Ratiopharm. This acquisition now appears ill-timed given that drug prices in Europe are being cut as part of general austerity measures. Meanwhile in the US generic sales have fallen due to Teva's manufacturing problems[24] and the lack of new products[25].

Teva's Copaxone drug loses US patent protection in 2014

- *Copaxone has competition, and goes off-patent soon*. Copaxone is part of the standard 'ABC' treatment regimen for MS[26] which, while temporarily effective, can only slow the disease rather than stop or reverse it. Being part of the standard of care, Copaxone has been a huge winner for Teva since it gained FDA approval in 1996, since MS prevalence, while small[27], is primarily in Western countries with well-funded healthcare systems[28] and incidence seems to be rising[29]. Consequently Copaxone enjoyed global in-market sales[30] in 2010 of US$3.3bn, up 18% on 2009, making it the company's biggest product by far[31]. Teva's current problem with this drug is that it now has a serious competitor, with FDA approval in September 2010 of the Novartis drug Gilenya, which has the advantage of being the first orally available MS drug. Also, Copaxone goes off-patent in the US in 2014 and in most of the rest of the world in 2015, and the American biotech major Biogen Idec[32] is currently completing a Phase III study called 'CONFIRM which compares its BG-12 orally available drug candidate

[21] See www.sharedsolutions.com, which is Copaxone's home page. Copaxone is glatiramer acetate, a polymer made up of four amino acids that are found in myelin basic protein. It is believed the drug works by providing a 'decoy' to the immune system.

[22] Generic name rasagiline, see www.azilect.com.

[23] Copaxone originated from the Weizmann Institute of Science at Rehovot, while Azilect originated at Haifa's Technion. Teva picked up Copaxone after it had been rejected by J&J and the Pfizer precursor company Upjohn.

[24] The company stopped producing at a plant in Irvine, Ca. In April 2010 following a December 2009 FDA Warning Letter, and didn't restart the plant until April 2011.

[25] In the June 2011 quarter sales of generic and related drugs were down 40% YoY.

[26] Developed in the 1990s, ABC is Avonex (interferon beta-1a), Betaseron (interferon beta-1b) and Copaxone.

[27] At only 0.9 per 1,000 in the US, for example. See Neurology. 2007 Jan 30;68(5):326-37.

[28] Broadly speaking, MS tends to be a disease primarily of white people from northern latitudes. See Neurol Sci. 2001 Apr;22(2):117-39.

[29] US prevalence is around 50% higher than one estimated in 1982, suggesting the possibility of rising disease incidence (see Neurology. 2002 Jan 8;58(1):136-8) which may have something to do with the 'hygiene hypothesis' (see Ann Neurol. 2007 Feb;61(2):85-9.)

[30] That is, sales to end-users, rather than Teva's sales to distributors, which are obviously lower but not reported by the company.

[31] By comparison Azilect only enjoyed US$318m in global in-market sales in 2010. Copaxone has enjoyed average compound annual growth for the drug since 2001 of 25%.

[32] Weston, Ma, Nasdaq: BIIB, www.biogenidec.com. Biogen Idec also have an MS franchise to defend, which is based on Avonex, an interferon beta-1a product which did US$2.5bn in 2010 revenue.

to Copaxone, which, if favourable to the Biogen drug, could damage the Copaxone franchise.

- *Data on laquinimod has been equivocal.* Teva's successor drug to Copaxone had been laquinimod, an orally available drug that failed to reach its primary endpoint of reducing the annualised relapse rate in a Phase III trial, results for which were announced in August 2011. That said, Teva is still moving forward with regulatory filings for this drug, arguing that laquinimod-treated patients had a greater burden of disease at baseline which, when adjusted, demonstrated a significant reductions in the relapse rate.

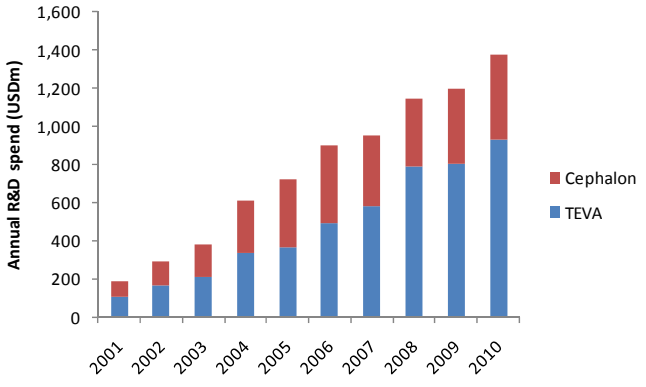
Teva stock is down 40% since March 2010

These challenges have impacted sentiment towards Teva stock, which is down more than 40% since March 2010, increasing the pressure on Teva to extract value from out of the Cephalon transaction, something it is more likely to achieve if Mesoblast's programmes perform well.

Cephalon is part of Teva's aggressive growth strategy. Teva's basic growth strategy is to stay in generic drugs and get bigger so as to benefit from the US$150bn in branded drugs that will lose patent protection between 2010 and 2015. However it also intends to grow in branded drugs, and the acquisition of Cephalon was a significant first move in that direction[33]. We see three basic elements that Cephalon brings to Teva:

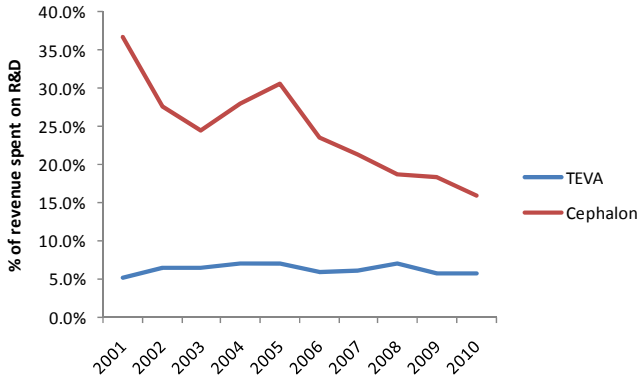
- *Established products that can offset Teva's vulnerability with Copaxone*. Cephalon was a specialty pharma company that had been built on the back of two products - Provigil, an anti-sleep drug[34] which in 2009 became a blockbuster, and Actiq, a fentanyl lozenge product[35] which continues to deliver shareholder value post patent expiry. Cephalon had been growing its top-line strongly on the back of these franchises and others. Its revenue in 2010 was US$2.8bn, up from US$2.2bn in 2009, and the company had been guiding to $3.015-$3.095bn for calendar 2011. Teva believes that it can leverage off this momentum so that Copaxone becomes less than half of Teva's branded product sales by 2015, as against 70% now.
- *A very effective 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[36].

Figure 10 – Last year Teva and Cephalon spent US$1.37bn on R&D



SOURCE: TEVA, CEPHALON

Figure 11 – Cephalon is likely to raise the R&D intensity of Teva as a company



SOURCE: TEVA, CEPHALON

[33] Teva could well afford another Cephalon or two - net debt/net debt+equity was only 22% as at 30 June 2011.

[34] 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.

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

[36] This shows that Cephalon had 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. With Cephalon Teva acquired a sales force for oncology, detailing products like the leukaemia drugs Treanda and Trisenox.

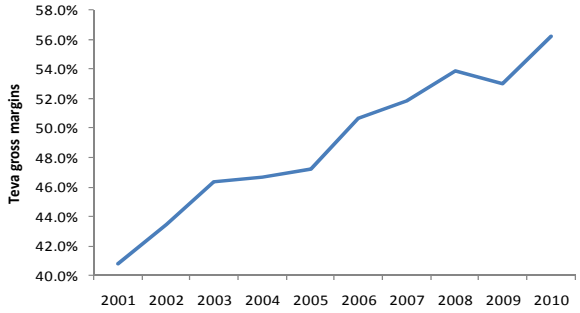
- *A serious pipeline and a strong R&D ethic*. While Teva may have established its R&D credibility with its early stage championship of Copaxone and Azilect, it traditionally lacked a 'serious' R&D budget, at only 6% of revenue over the last ten years[37]. Cephalon, by contrast, had been investing heavily in its pipeline prior to its acquisition, with average R&D spend over the decade to 2010 of 22% of revenue. In recent years the motivating factor was to offset the generic competition that had been eroding the Actiq franchise and would soon start to impact the modafinil[38] franchise. The result was multiple projects mainly in the fields of CNS, inflammation, oncology and pain[39], and in many cases focused on biological rather than small molecule drugs, with Mesoblast's MPCs one of the last to be in-licensed before Teva made its bid. With Cephalon Teva picked up something like 30 compounds in the mid-to-late clinical stage, and the Israeli company obviously expects that many of these products, such as reslizumab for asthma and obatoclax for lung cancer, can be big winners.

Figure 12 - Cephalon came with five near-term potential blockbusters

Drug	Indication	Year of launch
Nuvigil	Bipolar disorder	2013
Cinquil	Eosinophilic asthma	2014
Lupuzor	Systemic lupus erythematosus	2015
Revascor	Heart failure	2015
Revascor	Acute myocardial infarction	2016

SOURCE: CEPHALON

Figure 13 – A good branded blockbuster like Copaxone can be great for margins



SOURCE: TEVA

Two out of the five near-term blockbusters Teva got from Cephalon are Mesoblast products

Teva will seek to build on Cephalon's R&D base. We believe the price which Teva paid – effectively 17x consensus 2013 earnings[40] - suggests a premium for the Cephalon pipeline. There has been speculation that Teva intends to effectively turn Cephalon into Teva's branded products division and take advantage of the American operation's higher R&D productivity by doing more R&D there and less in Israel[41]. If that is the case then Mesoblast will be a key beneficiary since its products represent two potential near-term blockbusters (ie for heart failure and AMI) out of five which Cephalon management identified as key to its future growth out to 2016[42].

Mesoblast is well placed to contribute to key Teva franchises. We see the potential for Teva to use Mesoblast's technology to strengthen its existing franchises.

- We note below that MPCs are showing promise as potential anti-inflammatories. This suggests that they could be used in MS, which is an auto-inflammatory disorder.
- Mesoblast's technology could be used to add more products around Azilect in the CNS space.
- Teva has already invested in cord blood expansion technology, through a privately-held Jerusalem-based company called Gamida Cell[43] that is currently in Phase III with the technology, however Mesoblast at this stage has the better data (see below).

In absolute terms Teva has plenty of money to spend on R&D. Its budget may currently be only 6% of revenue on R&D but that represented US$933m in 2010.

[37] Generally Big Pharma spends 15-20% of revenues on R&D.

[38] Provigil's generic name.

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

[40] Source: Thomson One Analytics.

[41] See *Teva sets R&D layoffs in sights* by Snir Chandler, ynetnews.com, 18/7/2011. Teva has an R&D headcount of 2,700 employees, 1,000 of which are in Israel.

[42] The others were Nuvigil, the Provigil successor product as well as the above-mentioned reslizumab asthma product and Lupuzor, a lupus drug. Source: Cephalon presentation to Cowen Health Care Conference, 7-8 March 2011.

[43] www.gamida-cell.com.

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[44], 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.

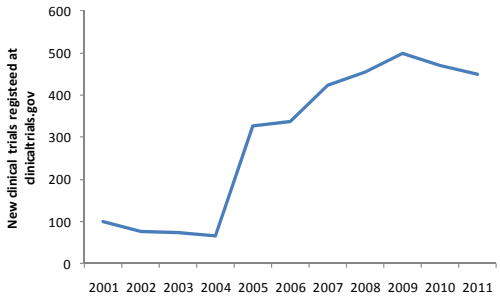
Stem cells are the wave of the future in medicine. As well as the scientific evidence there are three other reasons why stem cells will loom large in 21st Century medicine:

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 III). 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.
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.

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

For more on the background to the emergence of the stem cell field see Appendix IV of this note. We believe 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 14 - The volume of new stem-cell related trials is also increasing as the science translates to the clinic



SOURCE: CLINICALTRIALS.GOV – NOTE 2011 IS ANNUALISED

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[45].

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

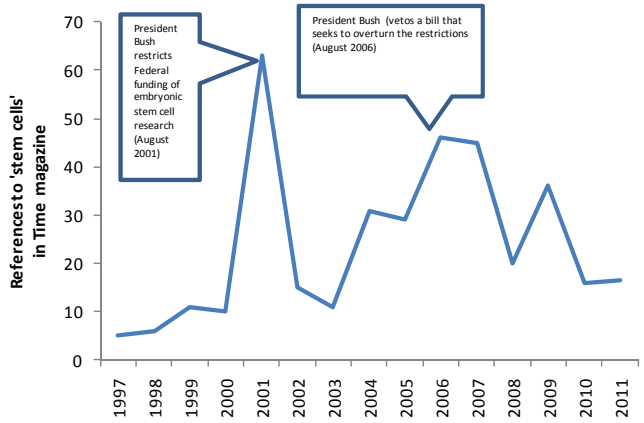
MSB knows how to get and expand mesenchymal stem cells. MSB's intellectual property, which we collectively call the MPC technology and which has primarily been obtained from the Hanson Institute in Adelaide[46] (see Appendix I), covers key methods for obtaining and then expanding 'mesenchymal precursor 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-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

[45] 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.

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

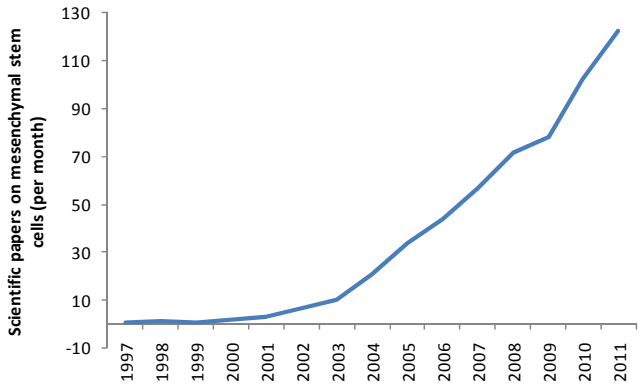
10 billion stem cells able to be produced from a starting batch of only one million cell over a six-week period[47].

Figure 15 – There has been heightened public awareness of stem cells for over ten years now



SOURCE: TIME, BELL POTTER SECURITIES – NOTE 2011 IS ANNUALISED

Figure 16 – Scientific publication on mesenchymal stem cells has been growing exponentially



SOURCE: PUBMED – NOTE 2011 IS ANNUALISED

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[48]. 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 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

[47] 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 process only involve around 20 doublings.

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

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[49], 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[50].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[51]. 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:

- 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;

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

[50] 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.

[51] 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.

- 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[52]. In 2006 MSB reported good evidence that MPCs will work allogeneically in this area[53]. 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[54].

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'[55] 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, while in June 2011 Mesoblast announced that a subgroup of patients with ischemic heart failure and chronic refractory angina had also enjoyed a superior outcome on averse cardiac events and had seen their levels of myocardial ischemia cut in half.
- In 2009 the company announced that its MPCs had helped speed the recovery of cancer patients undergoing bone marrow transplant in a Phase II trial. This was followed by favourable survival data in July 2010. This application is now going to Phase III.
- In October 2010 the company announced that its MPCs had helped speed the process of bony bridging in orthopaedics patients undergoing posterior interbody spinal fusion.

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 expect this conservatism will help boost MSB's credibility with key prospective partners of the technology.

[52] 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).

[53] 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. For a more recent animal trial see Vet Comp Orthop Traumatol. 2011;24(2):113-21. Epub 2011 Jan 11.

[54] 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'.

[55] 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 17 - 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	$200-400m

SOURCE: MSB, BELL POTTER SECURITIES

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 believe 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:

   - US$20,000 per dose in bone marrow transplantation patients;
   - US$25,000-30,000 in heart failure patients (around the level of CRT-D device reimbursement);
   - US$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', 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[56];
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[57] (see Appendix I).

[56] 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.

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

A strong lead application in bone marrow transplantation

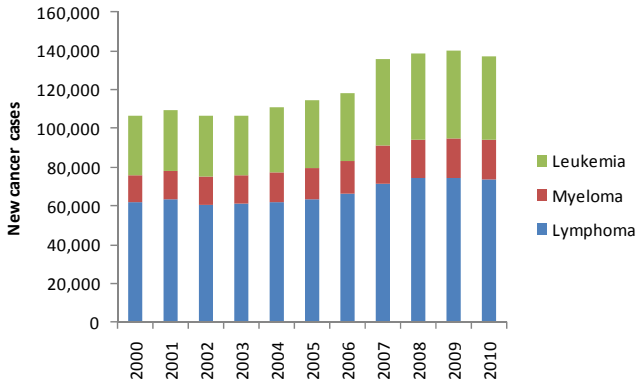
Bone marrow transplants are expensive, but MSB can make them cheaper

Demand for bone marrow transplants is rising. Bone marrow transplantation (BMT) is a procedure for the treatment of the hematologic cancers[58] – the leukaemias, the lymphomas and multiple 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 CD34+ cells (ie haemopoietic stem cells); or
- the patient's own stem cells where these have been removed prior to the treatment.

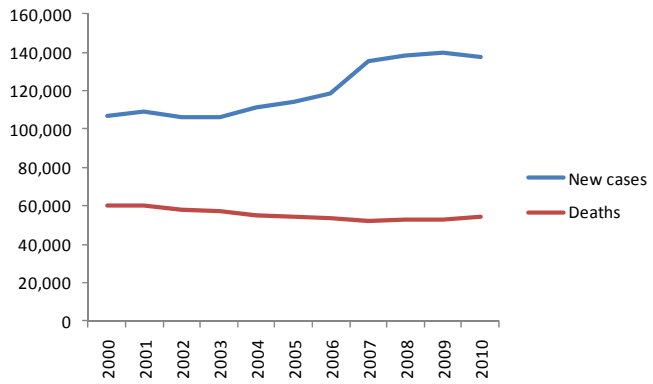
As the incidence of hematologic cancers has risen over the last decade, and clinical outcomes have improved[59], demand for BMTs has surged. Around 17,000-18,000 transplants took place in the US in 2009, up 70% on the level of 2003.

Figure 18 – Incidence of haematologic malignancies is rising



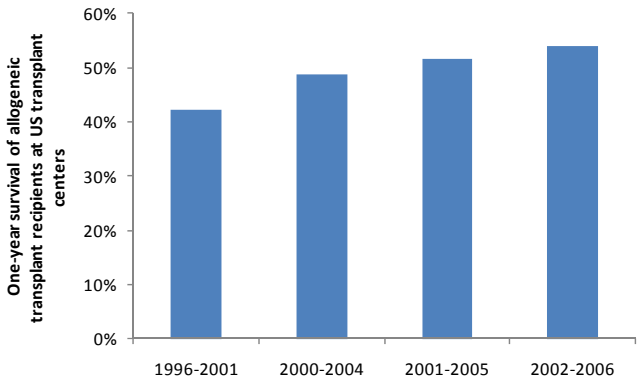
SOURCE: AMERICAN CANCER SOCIETY, CANCER FACTS AND FIGURES REPORTS

Figure 19 – Death rates from haematologic malignancies has been falling slightly due to bone marrow transplants



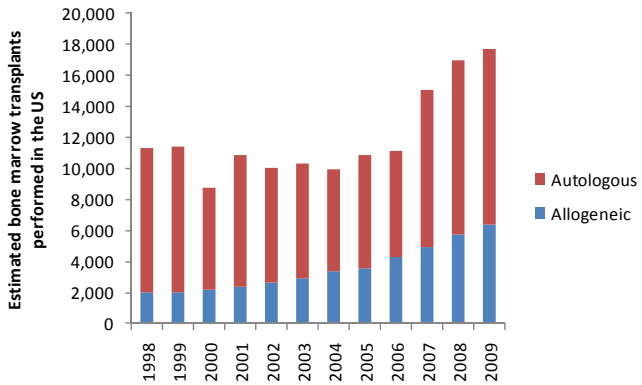
SOURCE: AMERICAN CANCER SOCIETY, CANCER FACTS AND FIGURES REPORTS

Figure 20 - Survival outcomes are improving with BMTs



SOURCE: NMDP

Figure 21 - Demand for BMTs has been rising in the US



SOURCE: HCUP, BELL POTTER SECURITIES

[58] They're also used to treat various anemias and some immune deficiency disorders.

[59] See Biol Blood Marrow Transplant. 2008 Sep;14(9 Suppl):8-15.

There are four major drawbacks with BMTs:

1. *They're expensive* - in the United States a bone marrow transplant can cost around US$250,000 in hospital charges alone, with costs having risen 7% pa over the last decade[60].
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[61]. Generally only around 25-30% of patients will be able to source marrow from a genetically matched sibling[62]. 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[63] even with rising availability of donors[64].
3. *Autologous transplants are problematic*. This issue of sourcing well-matched donor cells means that many BMTs for blood cancers are autologous transplants of previously harvested cells – we estimated around two-thirds of the market is currently autologous in terms of procedure numbers, representing around half the market in dollar value. 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[65].
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 CD34+cells[66], with those cells allowing a less rigorous genetic match in transplant situations than marrow-derived stem cells[67]. 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 blood unit[68], which is why transplant surgeons are increasingly turning to 'double cord' transplants instead[69]. The search is on for effective ways to expand the number of cells available[70].

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[71]. The trial, which was conducted at the M.D. Anderson Cancer Center in Houston[72] and funded

[60] Source: HCUP data.

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

[62] See J Clin Oncol. 1983 Sep;1(9):517-31. The probability of siblings being identical in terms of their HLA complex is 25%, since each child receives one of each parent's two HLA haplotypes. A 30% probability of HLA-matching reflects an average number of 1.25 siblings per patient (ie $1\text{-}0.75^{n}$ where n is 1.25 = 30%). Progressively smaller US family sizes in the 1970s and 1980s suggests that HLA matching rates could be lower in the future, with family sizes not bottoming out until the late 1980s at 1.8-1.9 children per family.

[63] 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*.

[64] Registered donors on the National Marrow Donor Program rose 8% pa between 2000 and 2010.

[65] 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.

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

[67] 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.

[68] 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.

[69] Interest in double cord transplants has started to emerge only in the last five years. In a Pubmed search we found a single paper in 2006 with the search term 'double cord' in the headline versus five in 2010.

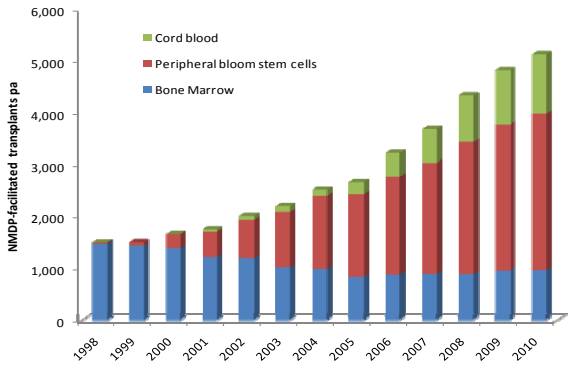
[70] One cell-saving approach that has been gaining in popularity has been 'reduced-intensity conditioning' (the use of less chemotherapy than usual so that the patient's immune system isn't completely wiped out, and can therefore rebuild with less donor cells. In this approach T-cells in the donor graft are relied on to deal with the patient's malignant cells. See Best Pract Res Clin Haematol. 2010 Jun;23(2):223-9. MPCs have potential to displace this approach.

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

[72] Rated the US's No 1 hospital for cancer care in the 2011-12 US News and World Report survey.

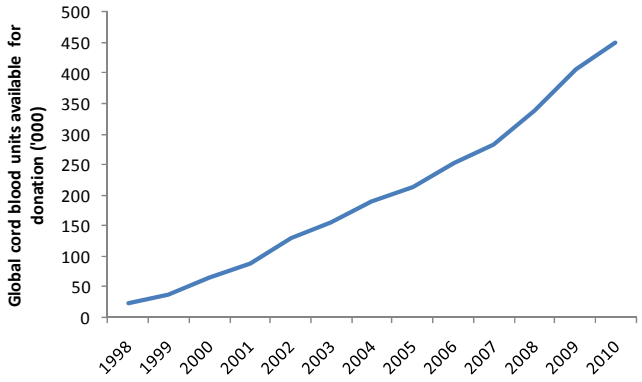
by a National Institutes of Health grant, involved double-cord transplants where one cord was unexpanded and the second expanded using MPCs, the thinking being that the expanded cord blood cells would help with the initial 'reboot' of the blood forming system, while the unexpanded cells would form the basis of the system in the long-run[73]. The trial generated some solid data in 2009 and 2010[74]:

Figure 22 – Stem cell transplants from cord blood have been rising



SOURCE: C.W. BILL YOUNG CELL TRANSPLANTATION PROGRAM

Figure 23 – Cord blood banks are growing around the world



SOURCE: BONE MARROW DONORS WORLDWIDE

- *Significant expansion of cells.* The company indicated in November 2009 that MPCs were expanding CD34+ cells available for delivery by a factor of 40. Over the whole trial the average expansion was 44-fold[75];
- *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. 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*[76]. 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[77]. For the entire trial the median time to neutrophil engraftment was 15 days[78] with 20 patients having enjoyed neutrophil recovery by day 26. This determined the final survival number for the trial;
- *Fast platelet recovery*[79]. The November 2009 18-patient data also showed median time to platelet recovery at 38 days, and while this increased to 54 days by the conclusion of the trial, we believe only a few delayed-engraftment patients were responsible for this shift. Moreover 54 days was still below the ~90 days for comparable double-cord blood studies[80]. Faster platelet recovery markedly reduced the risk of blood loss in the recovered patients.

Median time to neutrophil engraftment was only 15 days

[73] In most double-cord transplants one unit ends up as the sole source of long-term hematopoiesis (see Blood. 2010 Jan 28;115(4):757-65. Epub 2009 Oct 12) even though two units work better than one in terms of better outcomes for the patient. In a clinical trial reported at the 2008 meeting of the American Society of Hematology the M.D. Anderson scientists now working with Mesoblast demonstrated the feasibility of the expanded/unexpanded cord blood approach, with expansion at that time provided by Miltenyi's CliniMACS device (Sources: ASH 2008 Paper No 5264 abstract and NCT00067002 at www.clinicaltrials.gov.).

[74] Below are figures published by Mesoblast. The abstract for the trial result published by the M.D. Anderson scientists late in 2010 is available (See ASH 2010 Paper No 26914 abstract) however the data is complicated by the fact that the scientists also included 8 patients who received marrow derived mesenchymal stem cells from a family member. The Anderson abstract suggests 40-fold rather than 44-fold stem cell expansion.

[75] Source: Mesoblast presentation to JP Morgan conference, San Francisco, January 2011, slide 18.

[76] In bone marrow transplant the terms 'engraftment' and 'recovery' are sometimes used interchangeably. Neutrophil engraftment is defined as the first day of three consecutive days where the neutrophil count is 500 cells/mm^3 or greater.

[77] 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.

[78] Source: JP Morgan conference presentation, op. cit.

[79] Platelet recovery is defined as 20,000/mm^3 or greater.

[80] See, for example, Blood. 2010 Nov 25;116(22):4693-9. Epub 2010 Aug 4.

- *Less GvHD.* Only two of the first 18 patients experienced Grade III/IV GvHD (the most serious kinds), while for the full 25 patients the result was four patients for 16% of the total. We understand two of the patients experienced acute GvHD - ie in the first 100 days post transplant - for an 8% incidence, which is favourable[81] and reflects 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. Mesoblast has compared this to a 38% survival rate for unexpanded cord blood calculated from data made available to the company from registry searches[82] and with a 46% survival rate from a non-expanded double cord trial[83]. 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.
- *Data that was not driven by favourable genetic matches.* The abstract for the trial result published by the M.D. Anderson scientists has suggested that most transplanted cells were a 4/6 or a 5/6 match[84].

Mesoblast has better data than Gamida Cell. We noted above that Teva has invested in a cord blood expansion technology owned by the Jerusalem-based Gamida Cell. Mesoblast's Phase II BMT data is superior to that which Gamida Cell reported in a 10-patient Phase I/II trial completed in 2004 for which data was published in 2008[85]:

- Only one cord blood unit was used, that unit being split, one half being expanded, and the remainder unexpanded – in effect it was not a true 'double cord';
- There was only a six-fold expansion of CD34+ cells for the expanded half;
- While median time to platelet engraftment was 48 days versus 54 days for Mesoblast, the median time to neutrophil engraftment was 30 days versus 15 days for Mesoblast – we have previously seen that neutrophil engraftment is key to survival outcomes in these kinds of trials.

The Phase II data suggests that potential to address a market worth >$300m in the US alone. We noted above that Mesoblast would look to pricing in the order of US$20,000 per dose in bone marrow transplantation patients. This would represent outstanding healthcare economics given the halving of hospital time. Given there are around 17,000-18,000 bone marrow transplants taking place in the US this would represent peak sales for Mesoblast's product of perhaps US$350m.

Bone marrow transplant will be MSB's first pivotal trial

Phase III has commenced. 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[86]. Mesoblast's IND for a 240-patient Phase III trial was cleared in July 2011[87]. The trial will randomise patients to either unexpanded or MPC-expanded cord blood, with a primary endpoint of reduced time to neutrophil and platelet recovery. 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.

[81] 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 for the first 18 patients 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).

[82] The data came from the Center for International Blood and Marrow Transplant Research, which tracks BMT outcomes.

[83] See Blood. 2010 Nov 25;116(22):4693-9. Epub 2010 Aug 4. This trial was conducted by the same group at the M.D. Anderson Cancer Center which has conducted Mesoblast's trial.

[84] 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.

[85] See Bone Marrow Transplant. 2008 May;41(9):771-8. Epub 2008 Jan 21.

[86] 100 days is the generally-accepted point at which the outcome of a bone marrow transplant can be ascertained with certainty.

[87] Mesoblast had initially sought a 100-patient trial but with FDA guidance has put greater power into the trial in order to reduce the risk of missing the primary endpoint.

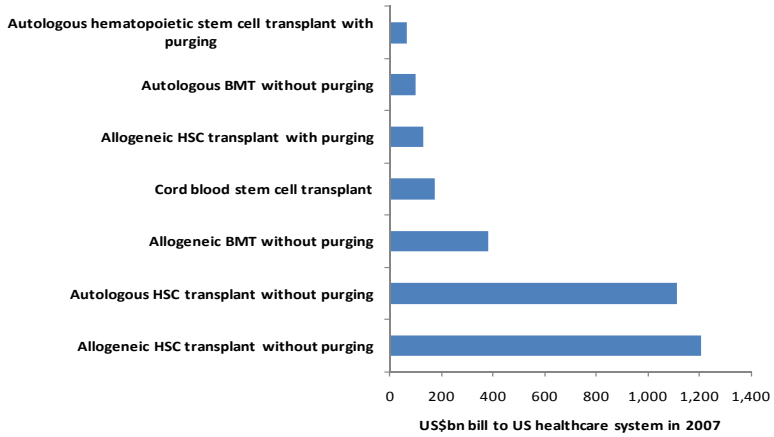
MSB is seeking Special Protocol Assessment. A Special Protocol Assessment (SPA) is a declaration by the FDA that a pivotal trial's clinical endpoints are acceptable for FDA approval of the drug. It effectively ensures that the FDA can't change its mind with regard to approval and ask for further data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

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.

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[88].

Figure 24 – 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

Mesoblast's technology is useful in both allogeneic and autologous transplants

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[89]. This suggests the potential to use MPCs in treating multiple myeloma, where autologous transplants have more successful outcomes than allogeneic transplants[90].

[88] 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).

[89] This work, by Dr Elizabeth Shpall and her colleagues at M.D. Anderson, was published in June 2011 (See Cancer Res. 2011 Jul 15;71(14):5040-9. Epub 2011 Jun 6). The total expansion of haematopoietic stem cells available for transplant was only eight-fold, but this was with a prior 3 and 4 log depletion in malignant cells, to below the limits of PCR detection.

[90] 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.

A powerful cardiovascular franchise

Mesoblast is working on three major opportunities in the cardiovascular space, in partnership with Cephalon:

- *Heart failure (*also known as congestive heart failure or CHF[91]) which is the progressive inability of the heart to pump properly due to weakened heart muscle. There are two basic types of heart failure, *ischemic heart failure* (which results from coronary artery disease, that is, the build-up of fatty deposits inside the coronary arteries, leading to occlusion or blockage which deprives oxygen to heart muscle) and *non-ischemic heart failure* (which results from other causes[92]), and Mesoblast thinks MPCs can effectively treat both types[93].
- *Chronic refractory angina*, which is chest pains associated with coronary heart disease, where partial blockage of the coronary arteries restricts the blood flow to the heart.
- *Acute myocardial infarction* (AMI – what the rest of us know as a 'heart attack'), where coronary artery disease has advanced to the point where artery blockages result 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 all these conditions is well established in both rat models and sheep models. In sheep Mesoblast has previously demonstrated recovery in heart function after a heart attack ('early CHF')[94], recovery in heart function in established heart failure situations[95], and stabilisation in heart function in non-ischemic heart failure[96]. We noted earlier that a Phase II clinical trial of MPCs in heart failure has already registered success at the six-month mark.

MPCs could be the Next Big Thing in heart failure

MPCs have performed well in heart failure

MSB's 60-patient trial in heart failure patients kicked off in October 2008[97] and measured three progressively higher MPCs doses[98] against standard of care where Ejection Fraction had dropped below 40%[99]. In the trial, 45 patients randomised to the three MPCs doses and 15 to placebo. With each dose, patients received a single injection and were evaluated for heart function recovery at three, six and twelve months. The last patient joined the trial in June 2010.

Hospitalisations and MACE are down at six months with MPCs. In January 2011 MSB reported favourable interim data from the trial[100], after all patients had reached 6 months

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

[92] Non-ischemic heart failure, or 'dilated cardiomyopathy' (the heart becomes enlarged as it weakens), is heart failure that results from conditions such as hypertension, rheumatic heart disease, alcoholism and atrial fibrillation (rapid, disorganised electrical signals that cause the atria, the two upper chambers of the heart, to 'fibrillate', that is, contract very fast and irregularly.

[93] Statistics vary but it seems that around 40% of heart failure is ischemic in etiology with the other 60% non-ischemic. See, for example, Eur Heart J. 2009 Mar;30(6):671-8. Epub 2008 Dec 24 (42.6% ischemic from a large Swedish population study) and Int J Cardiol. 2011 Feb 18 (42.5% ischemic from a large Western Australian population study).

[94] In a sheep model of heart attack MPCs were able, at low doses, to increase blood flow into the infarct area (the damaged heart muscle) by ~60% more than the controls. They were also able to 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).

[95] 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).

[96] Sheep in which non-ischemic cardiomyopathy was induced using the chemotherapy drug anthracycline saw Ejection Fraction rise 1.9% versus a fall of 6.3% for the controls. See JACC Cardiovasc Interv. 2010 Sep;3(9):974-83.

[97] After the IND was cleared in June 2008 - see NCT00721045 at www.clinicaltrials.gov.

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

[99] A normal heart has a 55-70% EF. Around 40% of heart failure patients have EFs below 40% - consider, for example, the Echocardiographic Heart of England Screening population study, which found that 41% of definite heart failure patients had an EF under 40 (see Lancet. 2001 Aug 11;358(9280):439-44).

[100] 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.

follow-up. By that time the average patient had been followed for 18 months and the data below reflects that average time period:

- 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).
- Cardiac mortality[101] dropped from 13.3% to zero. Although that outcome wasn't quite statistically significant because of the small patient numbers (p =0.059), 13.3% suggests the kind of mortality that could be expected of a well-treated cohort of Class II patients at 18 months[102].

MPCs registered no cardiac mortality over 18 months

Further favourable data in an ischemic heart failure subset analysis. The above data points to the therapeutic effect of MPCs in heart failure lasting well beyond twelve months. In June 2011 Mesoblast added some further colour to the interim data with a 22-patient subset analysis of patients in the trial suffering ischemic heart failure with reduced myocardial blood flow. This analysis suggested that MPCs can be significant in treating chronic angina, thereby opening up another potential new market for the product (see our discussion of this below). From the perspective of heart failure what was significant about this analysis was that the ischemic cohort enjoyed a *'75% reduction in the risk of MACE over a mean follow-up period of 21 months compared with controls with myocardial ischemia'*. This provided confirmation that the marked improvement in MACE risk at ~18 months didn't suddenly end at 18 months.

The reduction in hospitalisations is important from a healthcare economics perspective. At the interim analysis point the MPC patients had experienced a 48% reduction in rate of all cardiac hospitalisations and a 61% reduction in the rate of heart failure hospitalisations. Neither result was statistically significant due to the small patient numbers and time of measurement (p=0.07 and p=0.13 respectively[103]), but the data is potentially important from a healthcare economics perspective:

- Even though rates of hospitalisation have been trending down[104], in 2007 Americans with heart failure still generated close to a million hospital discharges with average length of stay of 5 days[105];
- The rate of hospitalisation increases as heart failure progresses[106];
- Each hospitalisation costs around US$19,000[107], with costs probably rising 7% pa;
- Around a fifth of all discharged heart failure patients will be readmitted to hospital within 30 days[108], which is of serious concern to hospital operators because of the potential for CMS reimbursement to be cut[109].

[101] As opposed to 'all-cause mortality'. Only around one fifth of heart failure patients die with this condition as a primary cause.

[102] See, for example, Arslan et. al. (Tex Heart Inst J. 2007; 34(2): 166–169), which registered an 11.5% mortality rate for Class II patients at two years where the patients were being evaluated for the prognostic value of the 6-minute walk test. The REVERSE study, which looked at the ability of CRT-D to reverse mild or asymptomatic heart failure, generated 18 month survival of 4.9% for the treated patients but these were only Class I and II patients (Source: *REVERSE at 18 months: Questions about CRT for mild heart failure remain*, theheart.org, 8/9/2008).

[103] The heart failure hospitalisation for MSB's control patients at ~18-months was 20%. This data is roughly borne out by Solomon et. al. (see Circulation. 2005 Dec 13;112(24):3738-44. Epub 2005 Dec 5), who studied 7,600 heart failure patients across a wide range of Ejection Fractions. That study's published incidence of heart failure hospitalisation per 100 person-years suggest an 18-month heart failure hospitalisation rate for patients with an EF below 42 of 15%.

[104] See See Int J Cardiol. 2011 May 19;149(1):39-45. Epub 2010 Jan 13.

[105] Source: CDC, National Hospital Discharge Survey: 2007 Summary.

[106] We estimated from Ahmed et. al. (Am Heart J. 2006 February; 151(2): 444–450) that perhaps 20% of all Class I patients in any one year to 25-26% of Class III and IV patients per year will be hospitalised for any cause, with worsening heart failure as a percentage of all cause hospitalisation rising from 23% of Class I patients to 44% of Class IV patients.

[107] See data from Naylor et. al. (J Am Geriatr Soc. 2004 May;52(5):675-84), updated using US CPI data on the cost of inpatient hospital services.

[108] See Circ Heart Fail. 2010 Jan;3(1):97-103. Epub 2009 Nov 10.

- Patients with low Ejection Fraction – which is the patients that were recruited into Mesoblast's trial - tend to be admitted to hospital more[110];
- Patients with Ejection Fraction below 40 also tend to cost while in hospital, and have higher readmission rates[111].
- A reduction in cardiac hospitalisations of the size registered at the interim analysis would be likely to demonstrate cost per QALY lower than cardiac resynchronization therapy using a pacemaker-defibrillator (CRT-D) device and justify the ~US$25,000 Mesoblast will be going for[112]. We discuss cardiac resynchronization therapy below.

Mesoblast's science is being presented at the American Heart Association annual meeting this year

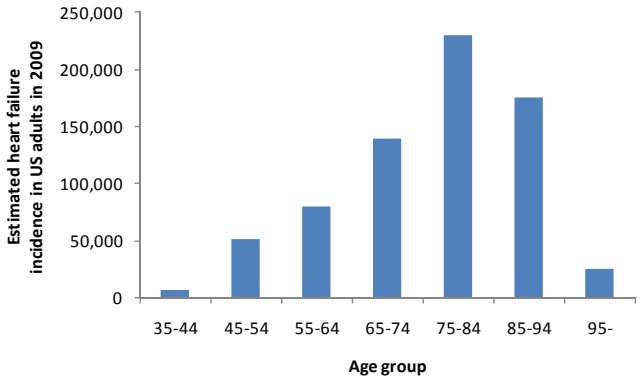
Full twelve month data for heart failure data will be available in November 2011. The data announced in January and June 2011 suggest that MPCs are potentially the Next Big Thing in mid-to-late heart failure. It's therefore appropriate that full 12-month data will be released at this year's Scientific Sessions meeting of the American Heart Association, which takes place in Orlando, Fl from 12 November to 16 November. The AHA Scientific Sessions is America's premier cardiology meeting, and presenting at Scientific Sessions is a big deal for any company developing a new treatment in the space:

- Around 17,000 professionals attend the meeting, so a presentation helps the data gain a great deal of attention in the cardiology community;
- The imminence of data is often appreciated by the equity market. In August 2010 the LVAD developer HeartWare announced that it would present its US Bridge to Transplant data at that year's AHA Scientific Sessions. The stock was $2.03 at the time, and $2.12 just prior to the meeting. It jumped to $2.21 just after the data was favourably received, and had reached $2.75 by early December.

MSB's trial will be presented in the 'Clinical Science: Special Reports' section on Monday 14 November at 9:15 AM ET by Dr Emerson Perin of the Texas Heart Institute in Houston, which was one of the trial sites[113].

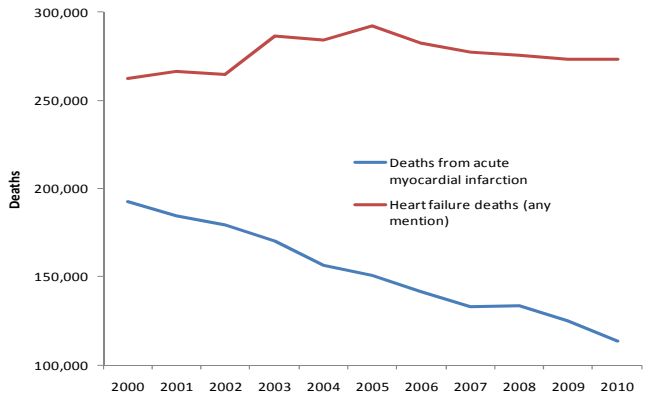
A Phase III trial in heart failure from next year. We expect that if the Phase II trial works out as expected, MSB and Teva will proceed to a >300-patient Phase III trial in 2012, with completion around mid-2014 based on 12-month follow-up from a single injection.

Figure 25 – An aging population will experience more heart failure



SOURCE: NHLBI DATA FROM FRAMINGHAM HEART STUDY, BELL POTTER SECURITIES

Figure 26 – Less Americans are dying from heart attacks, but more are dying from heart failure



SOURCE: CDC NATIONAL VITAL STATISTICS REPORTS; AMERICAN HEART ASSOCIATION, HEART DISEASE AND STROKE STATISTICS UPDATES. NOTE 2008-2010 REPRESENTS BELL POTTER SECURITIES ESTIMATES.

[109] CMS currently has the power to reduce, modify or deny payment for a hospital readmission within 30 days of discharge. From 2012, however, under provisions of PPACA (The Patient Protection and Affordable Care Act, the major healthcare reform law which President Obama signed into law in March 2010), CMS will be required to withhold payments for 'excessive' readmission rates.

[110] See Solomon et. al., op. cit., who found that rates of heart failure hospitalisations jump once Ejection Fractions is below 43%.

[111] See Clin Cardiol. 1999 Mar;22(3):184-90.

[112] See, for example, Feldman et. al. (J Am Coll Cardiol. 2005 Dec 20;46(12):2311-21), which noted a 29% drop in follow-up hospitalisation costs over two years from CRT-D. For estimated device reimbursement see *Medtronic device helps in earlier heart failure* by Susan Kelly, Reuters, 14/11/2010.

[113] Abstracts will be available online at the American Heart Association's web site from Friday, 11 November at 4:00 PM ET (ie US East Coast time).

Heart failure is a large scale opportunity for MSB. Not only is the market large in terms of patients but the current standard of care leaves a lot to be desired both in terms of cost and outcomes:

- *Prevalence of heart failure is high*. Heart failure may affect at least 5.7 million Americans adults or 2.4% of the adult population[114], which is a knock-on effect of the high prevalence of cardiovascular disease generally. Multiplying the US number by three or four may give a sense of the global patient size[115]. In Europe heart failure prevalence has been estimated at more like 3.0-3.5% of the adult population[116].
- *The costs are high and rising*. Heart failure costs the US healthcare system in the order of US$35bn pa in direct medical expenses[117].
- *Incidence probably outruns deaths.* Heart failure incidence could run north of 700,000 new cases a year in the US[118], and in our view is likely to rise in the years ahead given the aging population and the decreasing risk of dying from acute myocardial infarction[119]. In 2007, some 277,000 deaths were registered in the US where heart failure was an issue at the time of death[120].

Drug therapy can't reverse the course of heart failure. MPCs can

- *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[121], there are no drug or device therapies at present that can demonstrably reverse the muscle damage which causes and progresses heart failure, whereas there's evidence that MPCs can achieve this[122].
- *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[123] and only constitute around 5% of the heart failure population[124]. 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[125].
- *The drug market is large.* Heart failure is at least a US$3-4bn drug market in the US[126] driven mostly by off-patent products such as the ACE inhibitor lisinopril (the 2nd most

[114] Source: American Heart Association, *Heart Disease and Stroke Statistics,* 2011 update, Table 9-1.

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

[116] Data on heart failure in Europe is sketchy. One common estimate is '14 million Europeans' (J Am Coll Cardiol, 2009; 53:1960-1964), which would be ~3.3% of the population of the EU27 over 14. A comparison of population-based heart failure prevalence in Framingham, Ma (NHLBI, 2006 Chart Book on Cardiovascular and Lung Diseases, Table 5-42) and in the Dutch city of Rotterdam (see Eur Heart J. 1999 Mar;20(6):447-55) suggests roughly comparable rates of heart failure prevalence.

[117] Source: American Heart Association Heart Disease and Stroke Statistics 2010, Table 20-1. 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).

[118] Data from the Framingham Heart Study on incidence per person years for people over 35 (NHLBI, 2006 Chart Book on Cardiovascular and Lung Diseases, Table 4-28), if applied to the 2009 population structure of the US, yields this sort of incidence. The American Heart Association estimated 550,000 cases pa in the early 2000s (source: Heart Disease and Stroke Statistics 2005).

[119] There was a 35% reduction in death from acute myocardial infarction between 2000 and 2009 (Source: CDC National Vital Statistics reports) thanks primarily to devices such as stents, pacemakers and implanted defibrillators.

[120] Source: American Heart Association, *Heart Disease and Stroke Statistics,* 2011 update.

[121] 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.

[122] 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.

[123] 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).

[124] 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).

[125] MSB has been involved in an 80-patient trial studying the synergies of MPCs with LVADs – see Appendix II for more on this.

[126] See for example American Heart Association Heart Disease and Stroke Statistics 2010, Table 20-1, which postulates US$3.8bn in 'home health care' costs of the 'drugs/other' variety. We think this probably encompasses Class IV patients only. Using drug costs estimated by Hussey et. al. (Am J Crit Care. 2002 Sep;11(5):474-8) updated using BLS prescription drug price inflation data, the entire spectrum of heart failure patients could consume US$39bn in diuretics, blood thinners, COPD agents and ACE inhibitors.

prescribed generic in the US in 2010[127]), the diuretic furosemide (12th most prescribed[128]) and aspirin[129].

MPCs may represent a viable treatment for chronic refractory angina

There is improved blood flow to ischemic heart muscle with MPCs. The subset analysis to which we referred above involved 22 patients in the heart failure trial whose disease was of ischemic origin, but who, more importantly, suffered from chronic angina. While we don't have any data on angina frequency for this subgroup, the investigators found that MPC-treated patients in the group enjoyed a 51% reduction in myocardial ischemia[130] at six months whereas untreated controls with ischemic heart failure saw no change in the level of ischemia (p=0.01). This kind of reduction of ischemia is likely to have dealt with the angina symptoms as well, given Mesoblast's experience with the autologous patients trialled at John Hunter Hospital in 2006/2007 where five out of six patients saw a reduction in angina symptoms. The June 2011 data provided the first clinical evidence that MPCs could successfully build new blood vessels to supply heart muscle, something earlier rat data had indicated was possible[131]. The data has led Mesoblast to start work on a full Phase II trial of MPCs in patients that are not in heart failure but that are suffering chronic angina, which is the chest pains that result from poor blood supply to the heart whether or not the patient is experiencing a heart attack or heart failure. This represents a large market opportunity in its own right.

Chronic refractory angina incidence in the US could be 200,000 people annually

Chronic refractory angina represents a large market opportunity. Around 500,000 Americans over 45 experience 'stable' angina each year, where predictable chest pains result from exertion or stress, and around 47,000 are hospitalised each year complaining of angina[132], both stable and unstable, the latter a situation where the angina doesn't follow a pattern, can occur without physical exertion, and in 10-20% of cases is the prelude to a heart attack. For the majority of angina patients the pain goes away after they undergo an angioplasty and stenting procedure[133] or alternately a coronary artery bypass graft procedure[134], hence the high popularity of such procedures[135]. However many patients with advanced coronary artery disease are unsuitable for any further 'revascularisation'[136], leaving them with chronic refractory (ie treatment-resistant) angina. While the figures are sketchy, this could be more than 200,000 people annually in the US[137], which at US$20,000 per dose would represent a US$4bn market. Given the high cost of stenting and CABGs[138], such an intervention would likely be regarded as a relatively cost effective, especially with the lower rates of hospitalisation we noted above.

A Phase IIb will explore the angina opportunity next year. Mesoblast indicated in June that it intends to initiate a 150-patient Phase IIB trial of MPCs in chronic refractory angina

[127] The innovator drug, Merck & Co's Prinivil, went generic in 2002.

[128] Even though this drug has been FDA approved since 1966.

[129] Some heart failure drugs are still on-patent. The ACE inhibitor Diovan enjoyed US $1.4bn in US sales in 2010 for Novartis, making it that country's 18th biggest selling brand drug. Meanwhile the beta blocker Coreg CR, from GSK, was No. 128 on the US branded list of best sellers, with US$250m in 2010 sales.

[130] Presumably measured by level of 'ST depression' in electrocardiograms, where electrical activity in the heart is measured.

[131] See Example 4 in the WO 2004/084921 patent application, in which significant neovascularisation occurs in rats, with consequent improvement in ischemic myocardial tissue.

[132] Source: American Heart Association, *Heart Disease and Stroke Statistics*, 2011 update.

[133] An angioplasty is an operation to repair a damaged blood vessel or unblock a coronary artery in which a balloon is inserted into the vessel via the femoral artery using a catheter and then expanded. A stent is a mesh tube that is placed in the vessel after the angioplasty in order to keep the vessel open.

[134] Coronary Artery Bypass Graft, also known as 'CABG' or 'heart bypass surgery', involves a section of vein, usually from the patient's leg, being used to create an alternative pathway for blood to reach the heart muscle.

[135] There were around 560,000 stent operations in the US in 2007 and 400,000 CABGs. Source: CDC, National Hospital Discharge Survey: 2007 Summary.

[136] Because of factors such as chronic total occlusions (arteries closed for over a month, one of the most difficult blockage to treat), degenerated saphenous vein grafts (where the vein from the leg used in a previous CABG – the saphenous vein – has become damaged), and diffuse disease (that is, blockages in several sites in a coronary artery beyond the point where a CABG graft has previously been inserted).

[137] Mesoblast's estimate. Others estimate more like 25,000-75,000 patients annually (see Coron Artery Dis. 2009 Mar;20(2):106-11), which would still represent a large market opportunity. Baxter estimates that '*more than 850,000 patients in the United States experience refractory angina that has not responded to other therapeutic options*; (see Baxter's 11/7/2011 press release headlined *Phase Two Study Suggests Use of Adult Autologous Stem Cells May Improve Cardiac Function in Angina Patients*).

[138] A typical CABG will incur in-hospital costs in the order of US$117,000 while a stenting procedure might cost US$56,000. Source: American Heart Association, *Heart Disease and Stroke Statistics*, 2011 update, Table 21-1.

patients in the US next year. We think recruitment for the trial will be made reasonably easy by the Phase II data in heart failure as well as by the lack of alternatives.

The only competitor product will be Baxter's. In July 2011 the American medical products major Baxter[139] announced the results of a Phase II clinical trial which showed that autologous injections of CD34+ cells could reduce angina episodes by around 40% and double exercise tolerance (in terms of metres walked in six minutes on a treadmill) in patients with chronic refractory angina[140]. We think Mesoblast can potentially offer a better alternative than Baxter, since with the latter company's therapy:

- the CD34+ cells have to be mobilised from the bone marrow into the bloodstream using G-CSF[141], which may itself have cardiovascular side effects (Baxter's therapy was associated with elevated cardiac enzymes);
- there are some patients who could not tolerate the apheresis procedure[142] involved to harvest the CD34+ cells from the blood; and
- the autologous nature of the therapy may make it more expensive than Mesoblast's off-the-shelf approach.

MPCs may prevent heart failure after AMI

AMI is another large market. Around 900,000 million heart attacks happen every year in the US[143], generating drug costs around the time of the event we estimate to be at least US$350m pa[144]. It is estimated that around a third of all heart attack patients move on to heart failure over the five six years due to loss of heart muscle that started with the initial attack[145]. 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[146], 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%. This trial never yielded efficacy data due to slow recruitment, even though the safety data was favourable:

- *The EF<45 requirement limited the patient pool*, since less than 20% of heart attack patients survive a first attack but develop heart failure shortly after[147] - most enter heart failure more gradually.
- *The use of the catheter has also limited recruitment.* In this trial the MPCs were 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.

A new AMI trial is being designed

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

[139] NYSE: BAX; Deerfield, Il., www.baxter.com.

[140] See Circ Res. 2011 Aug 5;109(4):428-436. Epub 2011 Jul 7.

[141] G-CSF is a hormone called Granulocyte Colony Stimulating Factor. G-CSF promotes the growth of a kind of white blood cell known as the granulocyte, so called because it contains granules of toxic chemicals that are poisonous to microbial invaders in the body. Consequently the drug is given to patients recovering from chemotherapy to treat neutropenia, that is, abnormally low number of neutrophils. The ability to mobilise haemopoietic stem cells from out of bone marrow is its other major use in modern medicine. The best-known version of human G-CSF is Neupogen, generic name filgrastim (www.neupogen.com), from the American biotechnology major Amgen.

[142] Apheresis involves removal of whole blood from a patient or donor, with components of whole blood being separated and the remaining components being re-transfused into the patient or donor.

[143] There are some 610,000 new attacks and 325,000 recurrent attacks annually. Source: American Heart Association Heart Disease and Stroke Statistics 2009.

[144] 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 and Stroke Statistics 2006 and AHRQ Medical Expenditure Panel Survey, 2006 data.

[145] In the Framingham Heart Study the five-year incidence of heart failure post-AMI was 31.8% in the period 1999 to 1999. See Circulation. 2008 Nov 11;118(20):2057-62. Epub 2008 Oct 27.

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

[147] 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).

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[148].

Competitor data bodes well. Two competitors have announced data related to their AMI trials

- In June 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[149].
- In June 2011 Athersys reported a 4.6% absolute percentage point increase in Ejection Fraction (from 40.7% to 45.3%) at the one-year mark for heart attack patients treated with its allogeneic adult stem cell product.

This suggests the potential for MSB's trial to yield good data once the recruitment issues can be overcome, particularly since the dosing of both products 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.

MPCs will be bigger than CRT-D

Cardiac Resynchronisation Therapy provides a good insight into the cardiovascular 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[150] even though the products are only useful in the 20-30% or so of patients with conduction defects[151]

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[152], 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.

[148] 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 outperforming 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 ($p < 0.001$).

[149] 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. Osiris' trial became fully recruited as at March 2011.

[150] 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.

[151]. One large study in the UK evaluating the ability of ECG to guide therapy found 20% of suspected heart failure patients had QRS ≥120 ms, indicating a need for evaluation for cardiac resynchronisation therapy (see Eur J Heart Fail. 2007 May;9(5):491-501. Epub 2007 Jan 9).

[152] 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'[153]) or an 'osteoconductive'[154] bone substitute such as HA/TCP at the fusion site, and allowing Mother Nature to gradually join the bones together.

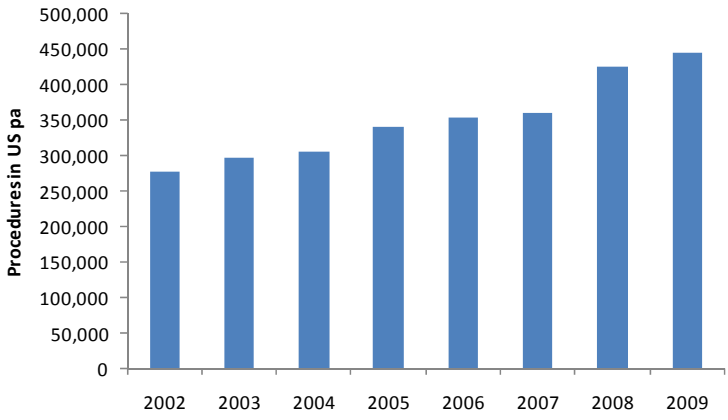
There are two basic kinds of spinal fusion...

- *Posterolateral spinal fusion*, where the bone or bone graft is places on the so-called 'transverse processes' of the vertebrae[155] to be joined.
- *Interbody spinal fusion*, where the bone graft is placed directly in the intervertebral disc area[156].

...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 27 - Spinal fusion boomed in US orthopaedic circles in the 2000s



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

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

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

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

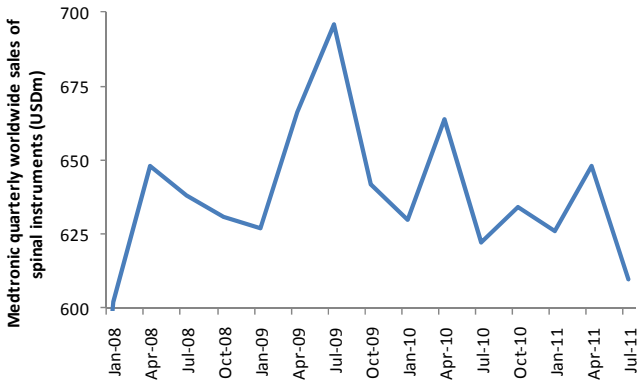
[156] Actual bone is rarely used in interbody spinal fusion.

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 has been some evidence in 2010 and 2011 that the spinal fusion market was cooling[157], 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[158];
- growing use of Bone Morphogenetic Protein as a bone graft material;
- the rise of minimally invasive spinal fusion surgery.

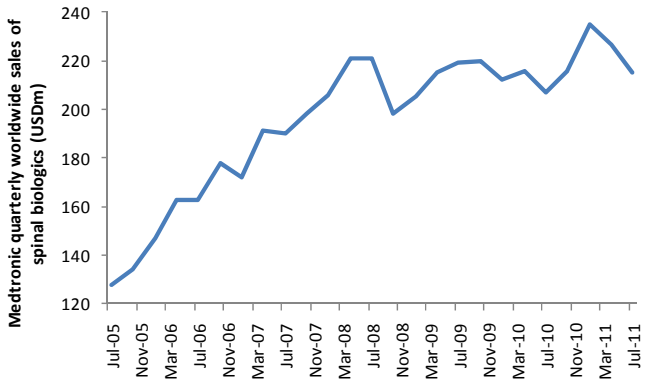
MSB has targeted its clinical programme for spinal fusion to tap into the second and third of these three trends.

Figure 28 - Medtronic has hit tough times in sales of spinal instruments



SOURCE: MEDTRONIC

Figure 29 - Spinal biologics is a US$800-900m pa business for Medtronic, driven by BMP



SOURCE: MEDTRONIC

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[159]. BMP has since proved popular with orthopaedic surgeons doing spinal fusions because it can effect fusion without any of the patient's own bone[160], 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[161] - we believe Medtronic's market penetration has continued since then;
- As a consequence of this uptake Medtronic's INFUSE is estimated to have done US$750-800m in sales in 2010/11[162];
- This growth in turn has helped grow the US market for bone graft and bone graft substitutes to an estimated US$1.5-2.0bn pa[163].

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

[157] For example, Medtronic's spine product sales declined 3% on a constant-currency basis in the year to July 2011.

[158] 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*'.

[159] 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.

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

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

[162] Medtronic discloses sales of 'spinal biologics', and INFUSE is understood to be 85-90% of this. There were US$885m in spinal biologics revenues worldwide in the year to April 2010.

[163] Source: American Association of Tissue Banks, *Bone-graft substitutes: facts, fictions & applications*, 2008.

- *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 use of BMP in cervical spinal fusion had resulted in swelling of the neck and breathing difficulties.
- *The product has been causing reputational issues for Medtronic*. In the June 2011 issue of *The Spine Journal*, an American peer-reviewed science publication, a number of articles alleged that researchers hid data on serious complications related to INFUSE when publishing on the product[164]. Also, the US Justice Department has been conducting a criminal investigation since 2008 to determine whether Medtronic illegally promoted INFUSE for off-label uses[165].

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[166]. 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[167].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[168]. The animal data looked good going into the trial[169], and for those patients that have been treated MSB has reported '*safe and robust fusion over a twelve month period*'[170]. Moreover in late April 2010, after completion of enrolment for the trial, MSB indicated that the fusion rate[171] 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[172].

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

The posterior interbody lumbar fusion trial, announced in August 2009[173], 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*

[164] The leading editorial in the publication was headlined *'A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors'*. See Spine J. 2011 Jun;11(6):463-8. The impact of this unusual move by the Spine Journal was to impact Medtronic's sales of spinal biologics, which fell 9% in the US in the July 2011 quarter.

[165] See *Use of Medtronic product being investigated by feds* by Janet Moore, Minneapolis Star-Tribune, 18/11/2008.

[166] 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.

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

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

[169] 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.

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

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

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

[173] See NCT00996073 at www.clinicaltrials.gov.

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%[174] - 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[175]. MSB unveiled favourable animal data for the use of MPCs in cervical spinal fusion in August 2008[176]. 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[177]. 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[178]. 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.[179] 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[180], however the market has yet to take off, with current US sales understood to be under US$40m[181] due to poor reimbursement[182] and concerns over method of surgical placement.

[174] This was with the first 17 patients.

[175] See NCT01106417 (for Australia) and NCT01097486 (for the US) at clinicaltrials.gov. The trial was initially intended to recruit 12 patients recruited in Australia and 24 in the US. Currently the Australian arm is not recruiting while eight sites are open in the US.

[176] 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. This work was published in 2011 (see Spine (Phila Pa 1976). 2011 Apr 15;36(8):615-23).

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

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

[179] 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.

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

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

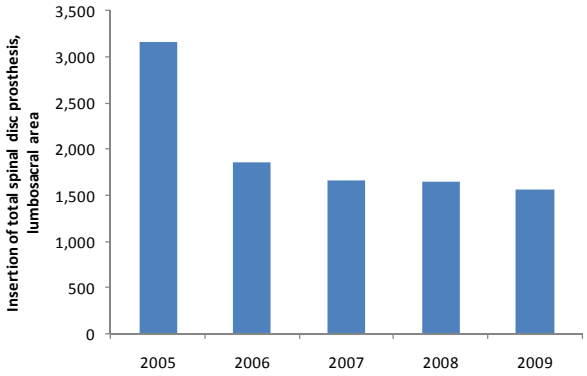
[182] For lumbar disc replacement, the Centers for Medicare & Medicaid Services, which runs Medicare and Medicaid in the US, issued a 'non-coverage decision' for beneficiaries over 60 in August 2007, due to what it considered to be a paucity of data on effectiveness.

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[183].

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[184]. 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 initiate a Phase II trial in disc repair for which the IND was cleared by the FDA in June 2011[185] and the first patient treated in August 2011[186]. This 100-patient trial will compare two MPC doses against placebo, with a six month endpoint[187]. The success of this trial would see a move into a pivotal trials 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. Moreover the ease of implantation – the first patient was implanted in an outpatient procedure that lasted less than 20 minutes with the patient fully awake and under light sedation – suggested favourable healthcare economics.

Figure 30 – 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.

[183] 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.

[184] 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.

[185] See NCT01290367 at clinicaltrials.gov

[186] The surgeon performing that procedure was Dr Kenneth Pettine, who was an inventor of Medtronic's Maverick artificial disc.

[187] We understand the trial had initially been expected to be 48-patients but Mesoblast has upped the trial numbers for better powering. 60 patients will be given MPCs with hyaluronic acid and 40 either hyaluronic acid or saline.

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.

Figure 31 - Major players in spinal fusion and artificial discs

Name	Code	Location	USDm 2010 orthopaedics revenue
J&J DePuy[188]	NYSE: JNJ	Raynham, Ma, www.depuyspine.com	5,585
Stryker	NYSE: SYK	Kalamazoo, MI, www.stryker.com	4,308
Synthes[189]	SIX: SYST	Solothurn, Switzerland, www.synthes.com	3,687
Medtronic	NYSE: MDT	Minneapolis, Mn, www.medtronic.com	3,414
Smith & Nephew	LSE: SN	London, UK, www.smith-nephew.com	2,135
Nuvasive	Nasdaq: NUVA	San Diego, Ca, www.nuvasive.com	478

SOURCE: BELL POTTER SECURITIES

Figure 32 - 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 orthopaedic partnering could attract big dollars

Kyphon demonstrates the willingness of the device companies to pay up for promising therapies. 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 seemed excessive given that Kyphon's growth slowed markedly following the transaction and the field declined in 2009[190]. 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. By extension, a licensing by Mesoblast in the orthopaedic space could attract big dollars as companies seek to control the Next Big Thing in the space without acquiring the company.

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

[189] Synthes reached agreement to be acquired by J&J in April 2011 for US$21.3bn. This deal has yet to close.

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

The knee osteoarthritis opportunity

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[191], knee osteoarthritis is common, affecting an estimated 14 million Americans or 4-5% of the population[192]. In recent years this large patient group has driven a number of major markets in the US:

- A market for knee arthroscopies[193] worth at least US$5bn. Close to one million of these were performed in the US in 2006[194] in spite of dubious therapeutic utility[195].
- A US$400-500m market for hyaluronic acid injections such the Synvisc and Synvisc One products[196] from the biotech major Genzyme[197]. 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[198].
- Increased off-label usage of Elmiron[199], a J&J drug indicated for a bladder inflammation called interstitial cystitis but with evidence of effectiveness in knee osteoarthritis demonstrated in clinical studies[200]. J&J's Ortho-McNeil-Janssen Pharmaceuticals unit enjoyed US$158m in US sales of Elmiron in 2010, the last year of its US patent protection[201].

We estimate that the hyaluronic acid and total knee replacement markets are currently growing around 9% pa[202].

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[203], 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[204]. It is possible that the study could yield data in 2011.

Knee osteoarthritis could be an early licensing candidate for MSB

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

[191] 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.

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

[193] 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.

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

[195] 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.

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

[197] Acquired by Sanofi-Aventis in 2011 for US$20.1bn.

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

[199] Generic name sodium pentosan polysulfate, see www.orthoelmiron.com.

[200] See BMC Clin Pharmacol. 2010 Mar 28;10:7.

[201] Opening up the potential of its use with MPCs. Scientists collaborating with Mesoblast have shown *in vitro* that pentosan polysulfate can promote MPC proliferation and the formation of new cartilage (see Arthritis Res Ther. 2010;12(1):R28. Epub 2010 Feb 18). They have also obtained evidence from animal models that MPCs plus pentosan polysufate can promote faster bone regrowth following anterior cervical discectomy, which is what happens in cervical spinal fusion (see Neurosurg Focus. 2010 Jun;28(6):E4).

[202] Consider that in the June 2011 quarter Sanofi-Aventis enjoyed constant currency sales growth of Synvisc and Synvisc One of 17%.

[203] 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.

[204] See NCT01088191 at clinicaltrials.gov.

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.

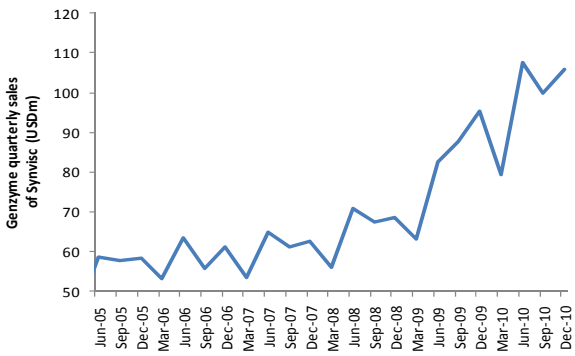
- *General knee osteoarthritis*. Given the widespread availability of orthopaedic specialists to manage knee osteoarthritis with anti-inflammatories and physical therapy, a much larger trial would be required for this indication – MSB estimates around a thousand patients.

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.

MPCs will probably represent a better product than Tigenix's

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[205] gained European approval for its Chrondocelect product, an autologous stem cell therapy with an initial application in repair of defective knee cartilage[206]. 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[207], MSB will be well-placed to license its product as a potential Tigenix competitor.

Figure 33 - Knee osteoarthritis helped Genzyme grow its Synvisc franchise



SOURCE: GENZYME

A potential big licensing is coming. We take the $100m in development milestones and $400m in sales milestones in the Genzyme/Osiris partnering deal of 2008 (see Appendix III) 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[208] 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.

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

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

[207] The product gained reimbursement in Belgium in February 2011.

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

MPCs could regenerate pancreatic cells

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)[209] , 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[210] that MPCs appear to be able to treat diabetes through PDX-1[211], 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 hormone which causes the pancreas to secrete more insulin. GLP-1 is part of the mechanism of action of three new generation diabetes drugs, one of which is a blockbuster, with another potentially on the way there:

- **Byetta**[212], co-marketed by Eli Lilly and the American biotech company Amylin Pharmaceuticals[213], gained FDA approved in 2005 as the first of the so called 'GLP-1 analogue' drugs that mimic the effect of the naturally occurring hormone. It enjoyed US$710m in global sales in 2010 although the drug has been in decline since mid-2009[214].
- **Januvia**[215] from Merck & Co, gained FDA approval in 2006. It was considered an advance on Byetta in that it works through the GLP-1 pathway – it's a DPP-IV antagonist, meaning that it can stop DPP-IV degrading natural GLP-1 – but unlike Byetta is orally available[216] Januvia and its sister drug Janumet[217] did US$3.35bn in global sales in 2010, up 31%.
- **Victoza**[218], from Denmark's Novo-Nordisk[219], FDA approved in early 2010, is considered another advance on Byetta because, while it's also a GLP-1 analogue, it's only a one-daily injection, as opposed to twice daily with Byetta. Victoza enjoyed >US$400m in global sales 2010, its first full year of release[220].

We think there is potential for MPCs to enjoy a sales profile similar to Januvia, in spite of the fact that it will be via injection whereas Januvia is orally available. Driving this will be:

[209] Islet cells 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.

[210] In WO/2010/057260.

[211] Short for Pancreatic and duodenal homeobox 1.

[212] Generic name exenatide, see www.byetta.com.

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

[214] This has been in part because of concerns over the risk of pancreatitis. In October 2010 Amylin and Eli Lilly were rebuffed by the FDA for Bydureon, a once-weekly version of Byetta, for the second time, with the FDA requesting another study to assess the cardiovascular risks. Byetta's first big advantage is that, like natural GLP-1, it quits promoting insulin production when the level of sugar in the blood reaches a normal range. Another big advantage of Byetta is that because GLP-1 slows stomach emptying and increases satiety, it actually promotes weight loss (See Cleve Clin J Med. 2009 Dec;76 Suppl 5:S12-9.)

[215] Generic name sitagliptin, see www.januvia.com.

[216] The downside is a smaller HbA1c drop than Byetta and no weight loss (but no weight gain either).

[217] Which is a combination pill of Januvia and the diabetes drug metformin.

[218] Generic name liraglutide, see www.victoza.com.

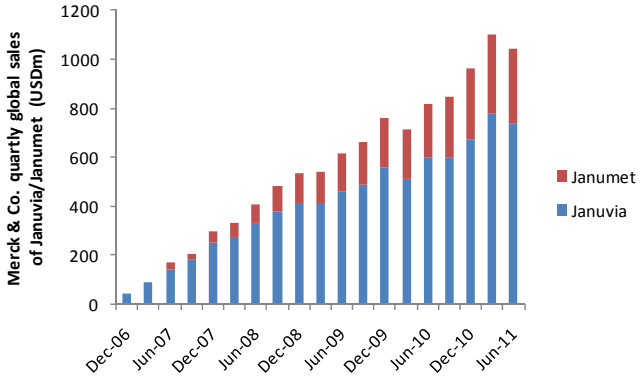
[219] Bagsværd, Denmark, OMX: NOVO B, www.novonordisk.com.

[220] In 2010 Januvia was at No. 24 on the US drug best-seller list, with US$1.3bn in sales, up 13%. Byetta was at No 78 with US$459m, down 18%. And Victoza was No 180 in its first year of US release, with US$169m in sales.

- 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.

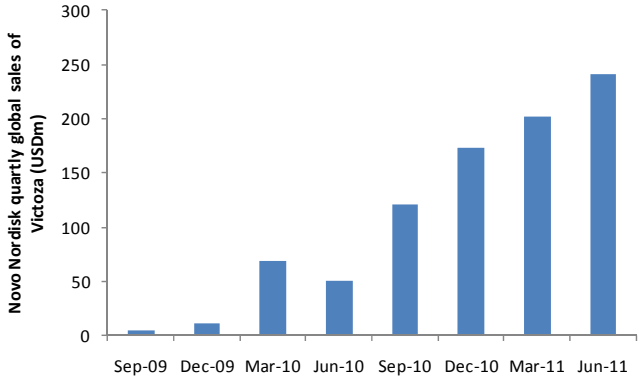
We understand that MSB has done pre-clinical work on MPCs as a diabetes treatment in non-human primates, for which results will be available later in 2011.

Figure 34 - Januvia has been a big winner for Merck & Co.



SOURCE: MERCK & CO.

Figure 35 - Novo Nordisk expects big things from Victoza



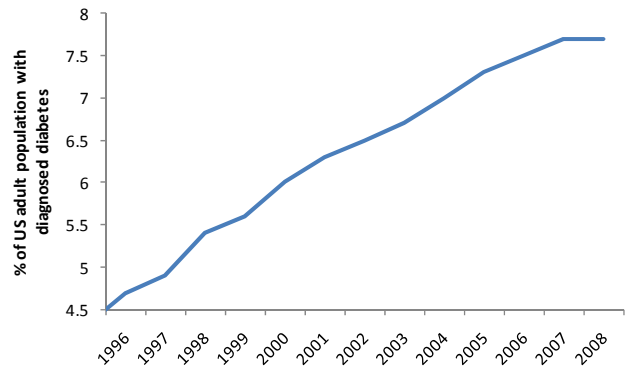
SOURCE: NOVO NORDISK

Around 8% of the US population is diabetic

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

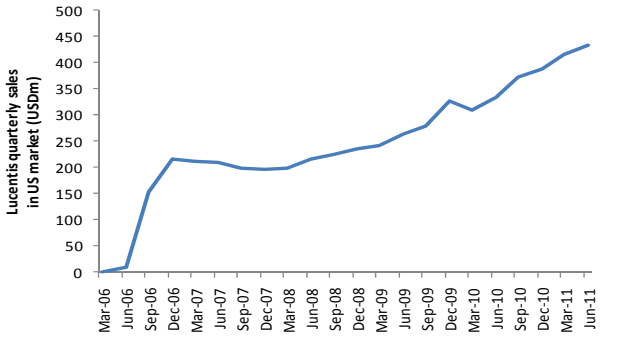
- Between 1995 and 2009 it is estimated that the age-adjusted prevalence of diagnosed diabetes in the US rose >90%, from 4.3% to 8.3% of the adult population[221].
- Another 35% of the adult population (79 million people) are estimated to be pre-diabetic or at increased risk for developing diabetes in the future[222].
- 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[223].
- Possibly close to half of all diabetics become insulin-dependent within six years of diagnosis[224], indicating lack of long-term effectiveness for existing diabetes pills.

Figure 36 - The number of Type II diabetics in America is rising fast



SOURCE: CDC

Figure 37 – Lucentis sales have been growing strongly



SOURCE: GENENTECH / ROCHE

[221] Source: CDC.

[222] Source: CDC, using NHANES 2005-2008 data.

[223] Source: International Diabetes Federation.

[224] This was a finding of the United Kingdom Prospective Diabetes Study, where 44% of subjects on sulphonylureas had failed within six years. See Diabet Med. 1998 Apr;15(4):297-303..

MPCs may be able to treat AMD and diabetic retinopathy

Age-related macular degeneration (AMD[225]) and diabetic retinopathy are similar eye conditions, in that both can be caused by neovascularisation in the eye, leading to damage of the retina and resulting impaired vision and blindness. Both conditions cost the US healthcare system around US$1bn for direct medical expenses[226]:

- **Around 1.4 million Americans have late stage 'wet' AMD**, which is AMD that results from abnormal blood vessel formation[227], as opposed to 'dry' AMD, where the light-sensitive cells in the macula slowly break down.[228]
- **There are around 4.5 million American diabetics with diabetic retinopathy,** with around 40%-45% of the total diabetic population affected[229].

Treatment is expensive, so new drugs are being sought. Until the 2006 FDA approval of the antibody drug Lucentis[230], from Genentech/Roche, there were no adequate treatments for neovascularisation in the eye beyond steroids. Lucentis is now a blockbuster[231] and still growing at > 20% pa. However the drug is expensive, costing just under US$2,000 per month.[232]. 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

A Phase II trial is pending. In September 2007 and July 2008 announced favourable animal data[233] related to both diabetic retinopathy and AMD, showing MPCs working well in conjunction with Lucentis to treat these disorders. The data appears to show that MPCs not only improve vision but reduce the frequency of Lucentis injections required to keep AMD / diabetic retinopathy in remission. 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.

Big Pharma wants new drugs to treat 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[234], 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[235] related to wet AMD and other eye diseases. For Regeneron this arrangement is worth US$75m upfront and around US$245m in milestones.

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

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

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

[228] 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.

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

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

[231] Sales in the 12 months to June 2011 were US$1.6bn.

[232] 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 (drug costs are from *Avastin versus Lucentis: Why It Matters*, Medical Research Modernization, Cleveland, Oh). Lucentis is the 'Fab fragment' of Avastin, which gained FDA approval in 2004 for colorectal cancer. Six month data from a blinded comparison trial in wet AMD shoed in 2009 that Avastin and Lucentis are equally effective (see *Am J Ophthalmol.* 2009 Oct 2. [Epub ahead of print]).

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

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

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

MPCs may be useful in 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 specific to MPCs, there is interesting evidence on the ability of similar stem cells in the CNS space. Consider:

- Arthur et. al. have shown[236] that dental pulp stem cells can begin to differentiate into functionally active neurons;
- They have also shown[237] that these cells can coordinate axon guidance, that is, the growth in a particular direction of axons on the end of nerve cells, meaning that they may play a role in promoting neuroplasticity.

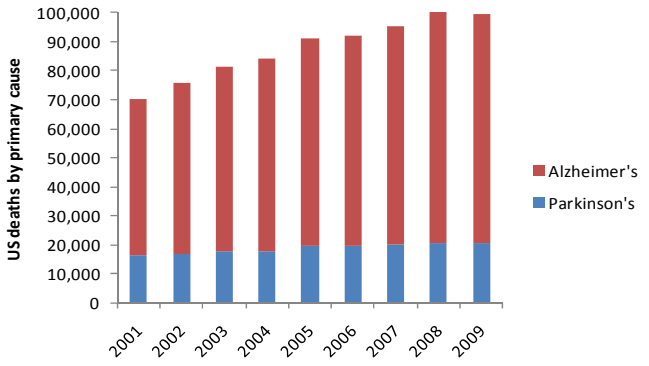
This potentially opens up two large markets:

- Around one in eight people over the age of 65 in the United States have Alzheimer's disease, making for 5.2 million patients in that country alone[238]. Globally the patient population may be 36 million once other forms of dementia are included[239]. Existing drugs to treat Alzheimer's do not appear to prevent declines in cognition beyond about 9-12 months, but in 2010 they enjoyed in excess of US$6.4bn in sales globally.

Around one million Americans have Parkinson's disease

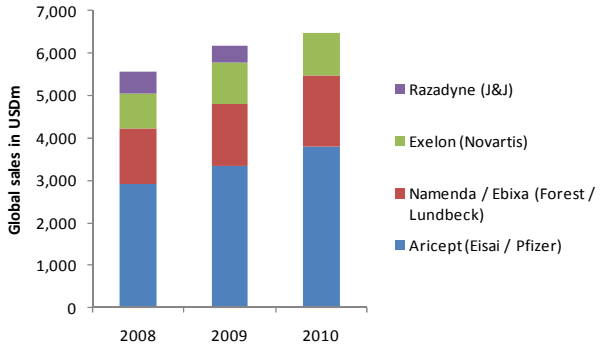
- Around 1-2% of people over the age of 55 may have Parkinson's disease, a degenerative movement disorder[240]. That would translate to around 0.9-1.0 million patients in the US alone[241], where total health care costs are estimated to be US$5-6bn and where the disease is the 15th largest cause of death[242]. What makes Parkinson's a particularly lucrative target for drug developers is the relatively long time a patient will be on medication – in many instances close to 20 years[243].

Figure 38 – Alzheimer's and Parkinson's diseases are the 6th and 15th leading causes of death in the US respectively



SOURCE: CDC

Figure 39 – Alzheimer's is a US$6-7bn drug market globally



SOURCE: J&J, NOVARTIS, FOREST, LUNDBECK, EISAI

[236] See Stem Cells. 2008 Jul;26(7):1787-95. Epub 2008 May 22.

[237] See Stem Cells. 2009 Sep;27(9):2229-37

[238] US figures come from The Alzheimer's Association, *2010 Alzheimer's Disease Facts and Figures*. There are another 200,000 people under 65 who have younger-onset Alzheimer's.

[239] Source: Alzheimer's Disease International, *World Alzheimer's Report 2010*.

[240] 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).

[241] Adapting Kaiser data from California gathered in the mid-1990s (see Am J Epidemiol. 2003 Jun 1;157(11):1015-22) to the US population structure in 2009, we estimated US incidence of ~44,000 patients per year, around twice the number of deaths where Parkinson's is a primary cause.

[242] Source: CDC, Deaths, Preliminary data for 2009.

[243] 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. Average age of onset of Parkinson's is around 60, while the average American aged 60 can expect to live to age 82 (source: 2011 Statistical Abstract of the United States, Table 103). This suggests well over a decade of life expectancy for Parkinson's patients. Pope John Paul II lived 12 years with the disease, and the Rev. Billy Graham has lived with Parkinson's for 21 years.

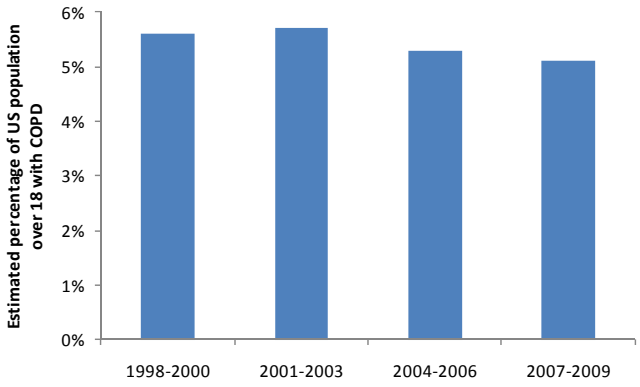
MPCs may have upside in inflammation

There is a strong body of knowledge on mesenchymal stem cells and inflammation

Mesoblast's ample funding since the Cephalon deal has motivated the company to contemplate a move into inflammatory diseases[244]. The reason for Mesoblast's interest is the compelling science. Stem cells of mesenchymal lineage have been shown to inhibit T cell and B cell proliferation[245] as well as natural killer cells[246], dendritic cells[247] and antigen-presenting cells[248]. Moreover such stem cells can down-regulate the pro-inflammatory cytokines IFN-γ and TNF-α, while up-regulating IL-4 and IL-10, known to have anti-inflammatory properties[249]. As this evidence has emerged in labs around the world so have disease-specific applications, with large market opportunities. Consider:

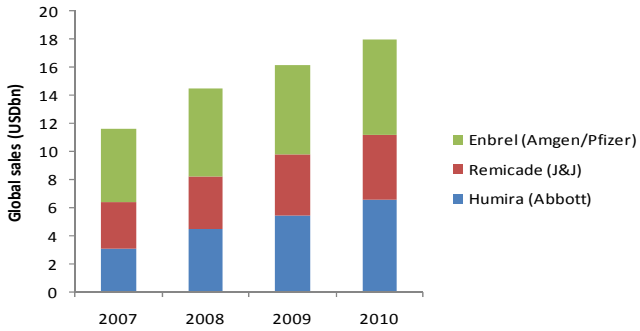
- *Arthritis and lupus* – Around 22% of the US adult population has some form of arthritis or related disorder[250]. Rheumatoid arthritis alone has created Enbrel, Humira and Remicade, three of the world's biggest-selling drugs[251]. Mesenchymal stem cells have been shown to prevent the occurrence of severe, irreversible damage to bone and cartilage in a mouse model of rheumatoid arthritis[252] while favourable results were reported in 2010 in a small clinical trial in systemic lupus erythematosus run by researchers at Nanjing University in China[253].
- *COPD* – Around 5% of the US adult population has asthma a disease driven by inflammation, as a knock-on effect of smoking. Mesenchymal stem cells have been able to repair cigarette smoke-induced emphysema in rat models[254].
- *Inflammatory bowel disease* - Around a million Americans have Crohn's disease and ulcerative colitis[255]. Mesenchymal stem cells have been shown to ameliorate the clinical and histopathologic severity of colitis in an animal model of Crohn's[256].

Figure 40 - Around 5% of the US population over 18 has COPD



SOURCE: CDC, FROM NHANES DATA

Figure 41 – Three rheumatoid arthritis drugs generate US$18bn in global sales in 2010



SOURCE: ABBOTT, AMGEN, J&J, PFIZER, BELL POTTER SECURITIES

[244] See, for example, Mesoblast's presentation to the 9/2/2011 Extraordinary General Meeting.

[245] See Leukemia. 2005 Sep;19(9):1597-604 and Blood. 2006 Jan 1;107(1):367-72. Epub 2005 Sep 1.

[246] See Stem Cells. 2006 Jan;24(1):74-85. Epub 2005 Aug 11.

[247] See Stem Cells. 2007 Aug;25(8):2025-32. Epub 2007 May 17.

[248] See Blood. 2005 Mar 1;105(5):2214-9. Epub 2004 Oct 28.

[249] See Rheumatology 2008;47:22–30.

[250] See MMWR Morb Mortal Wkly Rep. 2011 Feb 18;60(6):167-71.

[251] They were the seventh, eighth and ninth biggest selling drugs in the world in 2010. Source: IMS Health.

[252] See See Arthritis Rheum. 2007 Apr;56(4):1175-86.

[253] See Ann Rheum Dis 2010;69:1423-1429.

[254] See Am J Physiol Lung Cell Mol Physiol. 2011 May 27. [Epub ahead of print].

[255] Source: NIDDK, using prevalence figures from the late 1990s. Around 40% of prevalence is Crohn's and 60% ulcerative colitis.

[256] Gastroenterology. 2009 Mar;136(3):978-89. Epub 2008 Nov 27.

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 24.4% 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[257].
- **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[258].
- **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[259] 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.

- **The Mesoblast board** has, in our view, the expertise needed to build a world-class biotech company. In addition to Itescu it includes **Brian Jamieson** (a former Minter Ellison partner who brings corporate skills) as Chairman as well as **Michael Spooner** (a medical device entrepreneur), **Donal O'Dwyer** (who led Cordis when it gained FDA approval for the first drug-eluting stent) and **Kevin Buchi** (the outgoing Cephalon CEO who helped build the company into a highly successful specialty pharma company),

[257] See Appendix III for more on this.

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

[259] 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 eight major risks specifically related to MSB as a company and a stock:

1 **Teva risk** – There is the risk that Teva could choose to de-emphasise the MSB-sourced programmes in its pipeline, or sell its 19.9% in MSB due to a change in strategic direction.

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

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

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

5 **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.

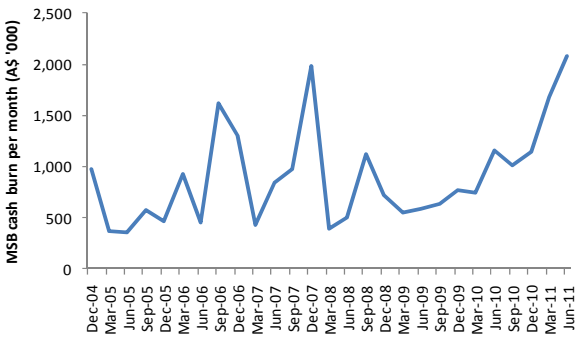
6 **Partnering risk** – There is the risk that MSB's prospective partners after Cephalon may strike too hard a bargain for MSB shareholders to enjoy a strong return outside.

7 **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$2.1m per month

8 **Burn rate** – With $263.2m 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$2.1m per month.

Figure 42 – MSB's burn rate since 2004



SOURCE: MSB

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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[260]. Itescu filed for patent protection over this treatment approach[261] and published the work in *Nature Medicine*[262], 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[263].

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[264] to pull out of the bone marrow mix mesenchymal precursors potentially capable of neovascularisation[265]. 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 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

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

[261] 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.

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

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

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

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

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[266].

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. As we noted above, until the merger of the two companies in 2010 Mesoblast owned 39% fully diluted of Angioblast[267], 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[268].
- 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[269].

Mesoblast patent applications

At present the MSB intellectual property is covered by 14 published patent applications, all filed in the name of Angioblast Systems[270], as well as various unpublished applications[271]. 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[272] 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[273]. Invented by Songtao Shi, Andrew Zenettino and Stan Gronthos with priority date 28/3/2003. This patent application 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

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

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

[268] This work was covered in MSB's sixth patent application, which was WO 2006/108229. Mesoblast scientists have demonstrated the effectiveness of STRO-3-selected MPCs in a rat model of Acute Myocardial Infarction. See J Cell Mol Med. 2010 Dec 14. [Epub ahead of print].

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

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

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

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

[273] This patent was granted in the US as Patent Numbers 7,947,266 in May 2011.

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[274], 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 neovascularisation 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.

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.

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

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.

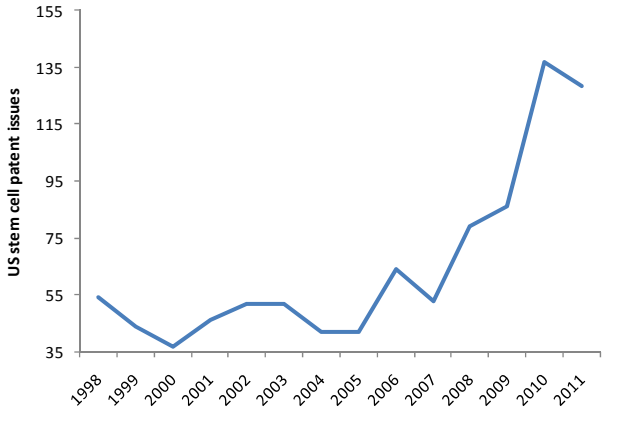
14 **Production of reprogrammed pluripotent cells**,WO/2010/105311. Invented by Silviu Itescu with priority date 20/3/2009. This patent application covers the use of the standard reprogramming techniques used in the induced Pluripotent Stem cell field to reprogram STRO-1-positive MPCs so that they could 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[275] 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 43 - 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. 2011 IS ANNUALISED.

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

Appendix II – MPCs and LVADs

MPCs could work synergistically with the other 'Next Big Thing' in heart failure. In August 2009 Mesoblast announced that its MPCs would be used in an 80-patient trial measuring two MPC doses against placebo where the patient had an LVAD implanted. We think this US-government funded trial will ultimately help build the credibility of MPCs in the cardiology community.

LVADs represent the team to beat. There are two companies pioneering the LVAD field:

- Thoratec[276] whose Heartmate II LVAD became FDA-approved in April 2008 as a 'Bridge to Transplant'[277]. 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. Heartmate II gained FDA 'Destination Therapy' approval in January 2010[278].
- Heartware[279], 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 approval in 2009 and performed well in a US Bridge to Transplant trial, 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. Many 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[280] has cast some doubt on this prospect, encouraging a continued search for agents that can reverse heart failure.

MSB's stem cells have gone through NHLBI peer review

NHLBI involvement is a key credibility boost for MPCs. The US government's National Heart, Lung, and Blood Institute (NHLBI) had been funding the Phase II LVAD study of MPCs at its expense in order to explore the synergies of LVADs and MPCs. In this trial the LVAD being used was Heartmate II. The involvement of the NHLBI suggested that MPCs had been able to pass a rigorous peer review process.

What happened to the trial? An NHLBI-funded LVAD+stem cell study had initially kicked off around 2006 with Dr Eric Rose of Columbia University as a principal investigator that explored the synergies of LVADs with haemopoietic stem cells and bone marrow mononuclear cells, but did not generate satisfactory results[281]. The five year grant was then transitioned to use Mesoblast MPCs instead[282]. The grant has since run out but we understand a new grant has been made to a physician group to continue it. It the trial 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[283].

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

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

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

[279] Nasdaq: HTWR and ASX: HIN; Framingham, Ma; www.heartware.com.

[280] 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).

[281] See NCT00383630 at www.clinicaltrials.gov.

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

[283] 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.

Appendix III– 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 companies on the list below;
- **MPCs have generated meaningful clinical data.** We think that only Osiris Therapeutics, Aastrom and Tigenix can compete with MSB on this score, and the credibility of Osiris has been impacted by some 2009 clinical issues.
- **Mesoblast has obtained the most meaningful partnering deal.** Established companies are starting to show up in the stem cell space. Pfizer partnered with Athersys in December 2009 while United Therapeutics partnered with Pluristem in June 2011. However at US$130m upfront and US$1.7m in milestone payments the Mesoblast/Cephalon deal is the only one with truly significant scale.

Figure 44 – MSB comparable companies

Company	Location	Code	Cap (USDm)	Website	Rank now	Rank March 2011	Note
Geron	Menlo Park, Ca	Nasdaq: GERN	318.6	www.geron.com	1	1	
Advanced Cell Technology	Santa Monica, Ca	OTCBB: ACTC	251.5	www.advancedcell.com	2	4	
Osiris Therapeutics	Columbia, Md	Nasdaq: OSIR	166.1	www.osiristx.com	3	3	
Cytori Therapeutics	San Diego, Ca	Nasdaq: CYTX	160.3	www.cytoritx.com	4	2	
Pluristem Therapeutics	Haifa, Israel	Nasdaq: PSTI	105.7	www.pluristem.com	5	12	[284]
Aastrom Biosciences	Ann Arbor, Mi	Nasdaq: ASTM	95.0	www.aastrom.com	6	8	
Tigenix	Leuven, Belgium	Euronext Brussels: TIG	91.8	www.tigenix.com	7	9	
International Stem Cell	Oceanside, Ca	OTCBB: ISCO	71.7	www.internationalstemcell.com	8	6	
BrainStorm Cell Therapeutics	Petah Tikva, Israel	OTCBB: BCLI	57.8	www.brainstorm-cell.com	9	13	
NeuralStem	Rockville, Md	Amex: CUR	54.8	www.neuralstem.com	10	7	
StemCells	Newark, Ca	Nasdaq: STEM	46.6	www.stemcellsinc.com	11	5	
ReNeuron	Guildford, UK	LSE: RENE	44.8	www.reneuron.com	12	10	
Athersys	Cleveland, Oh	Nasdaq: ATHX	43.2	www.athersys.com	13	11	
Bioheart	Sunrise, Fl	OTCBB: BHRT	3.0	www.bioheartinc.com	14	14	

SOURCE: BELL POTTER SECURITIES – MARKET CAPITALISATION DATA AS AT 22 AUGUST 2011

[284] The increase in ranking reflects a positive market reaction to Pluristem's June 2011 partnering deal with United Therapeutics, plus its announcement on stem cell manufacturing.

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[285]. 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';
- In June 2009 Prochymal failed in a Phase II trial in chronic obstructive pulmonary disease (COPD);
- In September 2009 there were apparent failures in two Phase III trials in GvHD[286].

The news since 2009 has been better, with the company demonstrating in February 2010 that Prochymal can generate a solid response rate when used as a rescue therapy in children suffering from severe, treatment-resistant GvHD, and this kind of market segmentation may allow Osiris to move forward commercially. Also, it appears that with Crohn's disease the company suffered bad lack. 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'.

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..04bn in revenue in 2008 and NPAT of US$427m for continuing operations;
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.

[285] Osiris gets its cells using density gradient centrifugation followed by culture expansion based on plastic adherence. Psaltis et. al. have demonstrated Mesoblast's selection of stem cells using antibodies to cell surface markers generates MPCs batches that are better at forming new heart and blood vessel cells. See J Cell Physiol. 2010 May;223(2):530-40.

[286] 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.

MSB's other listed competitors

Aastrom Biosciences is going to Phase III in critical limb ischemia

Aastrom Biosciences. 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 resulting product, called ixmyelocel-T, performed well in a Phase II trial in critical limb ischemia, generating a statistically significant improvement in the time to first occurrence of treatment failure at 12 months[287]. This indication is going to Phase III under an SPA while another indication, for dilated cardiomyopathy[288], is in Phase II.

Advanced Cell Technology. This company has a reputation for pioneering research in stem cells[289], with recent technical achievements including the 2006 derivation of embryonic stem cells without embryo destruction[290] and the 2009 creation of induced Pluripotent Stem cells via direct delivery of reprogramming proteins[291]. 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 and the trial commenced in July 2011[292]. A second IND, for dry AMD, was cleared in January 2011.

Athersys. 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 while there was favourable interim data from a Phase I in bone marrow transplant[293] in May 2011. An IND for ischemic stroke has been cleared by the FDA. There have been concerns raised in scientific circles regarding the reproducibility of the science behind MAPCs[294]. However that didn't deter Pfizer Regenerative Medicine 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.

Bioheart. 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.

BrainStorm Cell Therapeutics. This stem cell company, whose focus is the 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 cells capable of releasing neurotrophic factors, including glial-derived neurotrophic factor (GDNF), making it useful to the treatment of ALS and Parkinson's[295]. A Phase I trial in ALS commenced in June 2011.

Cytori Therapeutics. 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

[287] Critical limb ischemia is severe blockage in the arteries of the lower extremities. See Aastrom's 1 June 2011 announcement for the trial's final analysis.

[288] A severe form of chronic heart failure.

[289] 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).

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

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

[292] This indicated has been granted Orphan Drug designation in Europe.

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

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

[295] BrainStorm achieves this differentiation using, among other things, docosahexaenoic acid, an omega-3 fatty acid known to be good for nerve cells.

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 has been reported out to 18 months in heart attack patients[296]. It's also worth noting that much of its clinical work is currently conducted in Europe with no US trials at this stage.

Geron is a well known company but it's still in Phase I

Geron. 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[297]. Consequently it has attracted a lot of media attention in the US. 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 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 2010.

International Stem Cell. This company is based on technology to produce functional pluripotent stem cells through parthenogenesis[298]. 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 at an early stage. The company recently claimed to have been able to create definitive endoderm (the innermost layer of embryonic cells) from parthenogenic stem cells[299].

NeuralStem. 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[300] ('Lou Gehring's disease') while other intended applications include spinal cord injury. NSI-189, a neurogenerative small molecule drug, is in Phase I for Major Depressive Disorder.

Pluristem Therapeutics. 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, called 'placental expanded' or PLX cells, so they can be used allogeneically. The company has trialled the technology in critical limb ischemia, with favourable six months data reported in April 2011, and the company has received scientific advice from both the FDA and the EMA on a Phase II/III for this indication. In June 2011 Pluristem inked a partnering deal with United Therapeutics, the US specialty pharma company[301], with United licensing the PLX cells in order to create a cell-based treatment for pulmonary hypertension. Pluristem received US$7m upfront and will receive US$55m in milestones as well as a royalty. Like Mesoblast, Pluristem is retaining the manufacturing rights which will be sold to United for a royalty-like margin. The company announced in July 2011 that a manufacturing facility would be built in the Israeli city of Haifa. Other Pluristem targets include inflammatory bowel disease, Multiple Sclerosis, HSC engraftment in Bone Marrow Transplant and ischemic stroke.

[296] See the company's 8 June 2011 press release. 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.

[297] 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.

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

[299] See Cell Transplant. 2011 Jun 9. [Epub ahead of print]

[300] Which was granted Orphan Drug designation by the FDA in February 2011.

[301] NASDAQ: UTHR, Silver Springs, Md, www.unither.com. United Therapeutics enjoyed US$404m in 2010 revenue from three drugs for pulmonary hypertension. The company currently has a market capitalisation of US$2.8bn (22 August close on Nasdaq).

ReNeuron. This stem cell company has been built on various 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 Phase I clinical trial in disabled stroke patients in November 2010 that will evaluate changes in both motor and cognitive function over a two year period.

StemCells Inc. 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 neuronal ceroid lipofuscinosis or Batten's disease. In this trial StemCells gained some evidence of cell engraftment and long-term survival, however further work has since been discontinued due to lack of patient accrual. 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 kicked off in March 2011.

Tigenix is beginning to get reimbursement

Tigenix. 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. As of May 2011 the product has reimbursement coverage in Belgium. 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.

Appendix IV – 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[302]. 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.

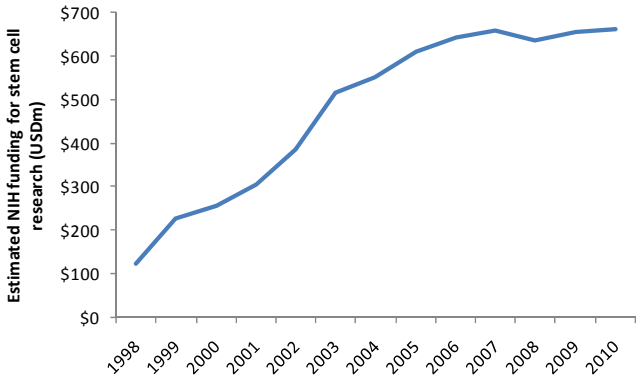
...and this has resulted in increased government funding. The US government upped its research budget considerably in 2001 to compensate for President Bush's limits on Federal funding for embryonic stem cell research, while various American states have also done some embryonic funding. The UK announced a strong increase in government funding in 2005 from around £25m pa in 2005 to more like £50m in 2007[303]. And in 2009

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

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

Korea announced a planned tripling of its spending on embryonic stem cell research by 2015, to around US$100m[304].

Figure 45 – 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 46 –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

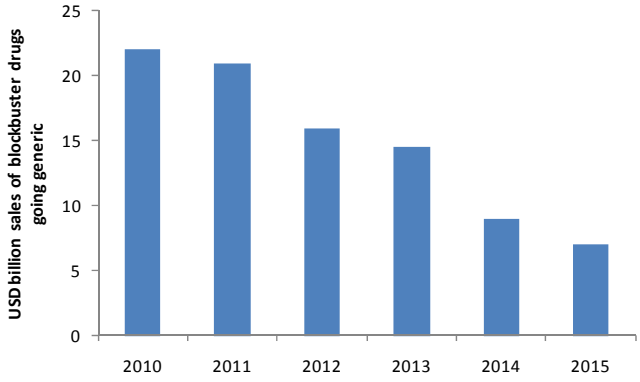
SOURCE: BELL POTTER SECURITIES

Figure 47 – 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 48 – 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[305] 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.

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

[305] Where there are no immunogenicity issues.

Widespread evidence of potential efficacy

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[306] (story reported November 2003). Spinal cord injury costs the US around US$10bn a year, with 11,000 new cases annually (source: CDC).

Many incurable diseases may be treatable using stem cells

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 [307]. 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 [308] (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[309] (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[310] (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 [311]. 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[312] (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 cells [313] (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.

[306] 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.*

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

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

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

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

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

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

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

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[314] (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[315]. The treatment involved autologous transplant of limbal cells from a remaining healthy eye (December 2009).
- Researchers at the IKEN Center for Developmental Biology in Kobe, Japan have coxed mouse embyronic stem cells to form a partial eyeball[316].

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[317] (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[318] (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[319].

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[320] (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 lethargic control mice [321] (September 2008). There are around 800,000 strokes a year in the US (source: American Heart Association).

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

[315] See *Stem Cells*. 2010 Mar 31;28(3):597-610..

[316] See *Nature*. 2011 Apr 7;472(7341):51-6.

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

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

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

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

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

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[322] (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[323] (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[324] (May 2009). Meanwhile at England's Newcastle University, researchers claim to have created human sperm cells from embryonic stem cells[325] (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[326] (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[327] (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[328] (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[329].

Gut repair – Human intestinal tissue has been engineered using pluripotent stem cells by a team at Cincinnati Children's Hospital[330]. 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[331] (January 2011). Around 85% of men over age 50 have some degree of hair loss (Source: American Hair Loss Association)

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

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

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

[325] 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.

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

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

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

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

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

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

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[332] (January 2011).

Alzheimer's disease. One of the brain cells that get hit the hardest in Alzheimer's are basal forebrain cholinergic neurons. Researchers at Northwestern University in Evanston, Illinois have managed to derive such cells from human embryonic stem cells[333] (May 2011).

Synthetic organs – Scientists at the Karolinksa Institute in Sweden made a model trachea out of a porous polymeric nanocomposite material. This model was then coated it with the patient's own marrow-derived mesenchymal stem cells before being implanted into a patients whose natural trachea had had to be removed due to cancer. The stem cells promptly turned into new tracheal cells and the result was a new trachea (July 2011[334]).

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[335]. 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[336].

  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[337].

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

[333] See Stem Cells. 2011 May;29(5):802-11.

[334] See *Cancer Patient Gets World's First Artificial Trachea* by Meredith Melnick, Time, 8/7/2011.

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

[336] 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.

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

Appendix V – MSB's capital structure

Figure 49 - MSB's current capital structure

Shares (ASX Code MSB)	280,425,258	Price (c)	755.0
Shares that may result from the conversion of options *	10,747,539	Undiluted cap ($m)	2,117.2
Total diluted shares	291,172,797	F.D. Cap ($m)	2,198.4

* Estimated option exercise price $1.55 by August 2013

SOURCE: MSB, BELL POTTER SECURITIES

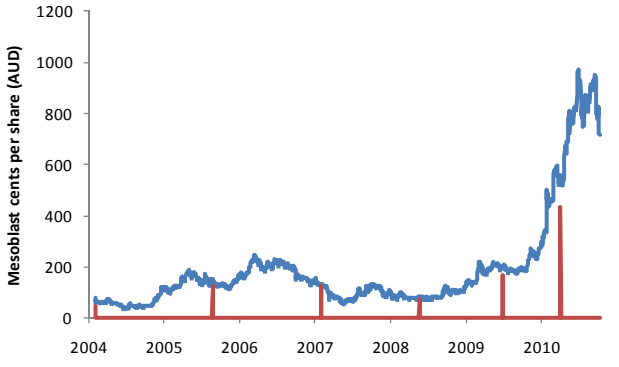
Figure 50 - MSB's capital raising history

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[338]	24.7	8.9%	$4.35	107.5	21.5%
Total	127.2	45.6%	$1.62	205.9	

SOURCE: MSB

MSB has raised $206m since its late 2004 IPO

Figure 51 – MSB has made five placements since its 2004 IPO



SOURCE: MSB, IRESS

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

Appendix VI – 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.

Amino acids - The building blocks of proteins. There are around twenty naturally occurring amino acids.

Angina – Chest pains associated with coronary heart disease. Stable angina has a regular pattern that only occurs if the heart is working harder than usual. Unstable angina doesn't follow a pattern, can occur without physical exertion, and in 10-20% of cases is the prelude to a heart attack. Chronic refractory angina is angina in patients for whom there are no treatment option available.

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.

Antigen-presenting cells - White blood cells that instruct the immune cells on what foreign thing (antigen) they should attack. They eat what they identify to be foreign substances in the blood then process (degrade) antigen into small peptides, place the peptides that indicate the characteristics of an antigen on their surface, and present the antigen to T cells so as to produce the appropriate immune system response. The class of cells called antigen presenting cells also includes dendritic cells.

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.

B-cells – White blood cells that are responsible for the production of antibodies.

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.

CABG – See Coronary Artery Bypass Graft.

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.

CMS – The Centers for Medicare and Medicaid Services (CMS), which is the US Federal agency that runs Medicare and helps coordinate Medicaid**.**

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.

Coronary arteries – The arteries that supply heart muscle with oxygen-rich blood.

Coronary Artery Bypass Graft (CABG), commonly known as 'heart bypass' surgery, in which a section of vein, usually from the patient's leg, is used to create an alternative pathway for blood to reach the heart muscle.

Cytokines - Molecules in the human body that regulate inflammation. TNF-α is a cytokine.

Dendritic cells – A types of antigen presenting cell.

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%.

EMA – The European Medicines Administration, Europe's answer to the FDA.

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.

FDA – The Food and Drug Administration, America's drug regulator.

Femur – The thigh bone.

GLP-1 – Short for Glucagon-like peptide-1, a peptide known to increase insulin secretion from the pancreas. The mechanism of action of many new generation diabetes drugs involves the GLP-1 pathway.

Glucagon - A hormone secreted by the pancreas that raises blood glucose levels.

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

Ischemic heart failure – Heart failure resulting from coronary artery disease.

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.

Leukemia – A cancer of the white blood cells.

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.

Lymphoma – A cancer of the lymphocytes which the immune system needs to create T and B cells as well as Natural Killer cells.

Major Adverse Coronary Events (MACE) - The incidence of death, heart attack or revascularisation in MSC's Phase II trial of MPCs in heart failure.

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.

Myeloma – A cancer of the B cells that the immune system needs to produce antibodies.

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.

Natural killer cells – White blood cells that are specialised to kill certain types of target cells, especially cells that have become infected with virus or have turned cancerous.

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

Neovascularisation – The formation of new blood vessels.

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.

Non-Ischemic heart failure – Heart failure resulting from causes other than coronary artery disease such as hypertension or atrial fibrillation.

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.

Peptide - Two or more amino acids linked by chemical bonds.

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.

Revascularisation – Stenting or CABG procedures.

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.

Stent – A mesh tube used to prop open an artery during angioplasty.

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.

T Cells – White blood cells that are responsible for killing cells infected by viruses (, in the case of 'Cytotoxic T cells'), and inducing B lymphocytes to produce antibodies (in the case of 'Helper T 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 2013. Mesoblast now has A$263m 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 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. The Cephalon partnering resulted in that company owning 19.9% of Mesoblast, a stake that is now held by Cepahlon's new owner, the Israeli drug major Teva. We see Teva's need for new branded drugs as a positive for Mesoblast.

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 $11.14 / optimistic case $21.59 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 5% and 15% on a 12 month view

Hold: Expect total return between -5% and 5% on a 12 month view

Reduce: Expect total return between -15% and -5% on a 12 month view

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

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