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In this edition...
Mesoblast has previously generated investor interest because of the potential of its MPC stem cell product to treat heart failure and because very promising clinical data in the area that secured Cephalon (now Teva) into a licensing agreement. However, interest is shifting towards Mesoblast's investigation of systemic applications of its stem cells to treat Type 2 diabetes and other inflammatory conditions. Results from a Phase II trial in 60 patients with Type 2 diabetic are expected by year end which may burst open a new arena of opportunity. A restlessness to strive to achieve high growth rates looks to be behind Somnomed's decision to restructure its management. Bioxyne is offering investors a short-term trading opportunity ahead of the release of Phase IIb results in June.
The Editors
Companies Covered: BXN, MSB, SOM

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - current)	-7.2%
Cumulative Gain	**220%**
Av. annual gain (11 yrs)	**17.8%**

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Bioshares

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Edition 455

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

Multiple Value Drivers Support Interest in Mesoblast's Share Price

Mesoblast ($MSB: 6.85) is a company that has many shots on goal for its mesenchyal precursor stem cell (MPC) technology. It has mid-to-late stage programs underway or due to start in heart failure, Type 2 diabetes, spinal fusion, invertebral disc repair, the eye disease wet AMD, and in bone marrow transplantation. Its lead program is a Phase III trial that is due to be initiated soon by its partner **Teva Pharmaceutical Industries.** The company's Phase II trial in Type 2 diabetes is open for recruitment and this trial alone could deliver a major result for the company.

Phase III Congestive Heart Failure Trial

The Phase III CHF trial clinical program is now being driven by and paid for by Teva. Mesoblast has been involved in the trial design, discussions with regulators, and it will manufacture the adult cells for the trial. Teva and Mesoblast have met with both European and US regulators. The start of this trial by Teva, expected to be in Q2 2012, will be a significant event.

Only one Phase III trial involving 1,500 patients may be required to gain product approval and the timeline for product approval for CHF remains at the end of 2015.

Phase III Interim Analysis?

Depending on the significance in the results, there is the possibility of an interim analysis of results, which could reduce development time by a year. It is anticipated that the patient population intended to be treated has a 20% chance of not living beyond 12 months. If it is observed that the overall survival of patients in the trial is much higher than the expected (i.e. suggesting that the stem cell treatment may be having a pronounced effect on survival, as seen in the 60 patient Phase II trial), then an interim analysis could occur. This could happen when 1,000 patients have been recruited. However there is a risk it could compromise the data if there is a higher than expected survival rate in the control group.

Phase II Type 2 Diabetes Trial

Mesoblast's Phase II trial in patients with Type 2 diabetes is currently open for enrollment. This will be a 60 patient trial, with three different doses and a control group (similar to its very successful heart failure trial). There will be a 12 week end point in the trial. Results should be rapid with the trial expected to be completed by the end of this year.

The three doses will be escalating, with the company anticipating the highest dose to be most effective. Each dose will be monitored by a safety committee and there may be interim data emerging from the trial.

There are a number of reasons the application of MPCs in diabetes may have merit.

Cont'd over

1. Positive preclinical studies
In preclinical studies in 17 non-human primates with diabetes (the monkeys live on sugar plantation), there was over a 60% reduction in glucose levels in the higher doses over six months following a single IV dose of the Mesoblast stem cells. There was also a drop in CRP levels (a marker of inflammation). Elevated CRP levels present a major risk of heart attack in people with Type 2 diabetes.

2. Role of Osteocalcin
What works out to be of benefit for Mesoblast is the role its population of stem cells play in diabetes. The hormone osteocalcin has been reported by others to promote beta cells in the pancreas to release more insulin, while also directing fat cells to release more of the hormone adiponectin which increases insulin sensitivity. Type 2 diabetes is characterised by not enough insulin circulating in the body and the body being resistant to insulin.

Mesoblast's mesenchymal cells are the precursor to the osteoblast cell that produces the osteocalcin hormone that promotes beta cell function. Increasing the level of insulin produced in the pancreas and increasing the body's sensitivity to insulin can both be very helpful in treating Type 2 diabetes.

3. Role of Inflammation
The second fortunate feature of the Mesoblast mesenchymal precursor stem cells is that they have an anti-inflammatory action. It's the pro-inflammatory effect in diabetes, as indicated by the high CRP levels, that can have fatal outcomes for patients with diabetes.

Other Clinical Milestones Ahead

Disc Repair
Mesoblast expects to complete its Phase II disc repair trial by the end of this year. If this is positive, Mesoblast could move into a Phase III trial, in 500-600 patients, running the trial on its own. This application is preferable over the spinal fusion use (see below) as there is no existing competition. An effective disc repair product could also reduce the need for spinal fusion procedures.

Spinal Fusion
Mesoblast is completing two Phase II spinal fusion trials. They are both fully recruited and are waiting on reaching six month endpoints. Results from these trials should also be available towards the end of this year. The spinal fusion market is more competitive with an existing product, Infuse from Medtronic, on the market. However this product has safety concerns and sales are declining.

Key Teva Advisor Joins Mesoblast board

Although it was only a one page announcement by Mesoblast, the appointment of Dr Ben-Zion Weiner to the board of Mesoblast is an important move. Dr Weiner replaced Kevin Buchi, who was formerly CFO and then CEO of Cephalon which was acquired by Teva. Buchi has now left Teva.

Dr Weiner was formerly head of R&D at Teva and is now a special advisor to the CEO of Teva. His placement on the Mesoblast board indicates Teva wants to stay very close to developments at Mesoblast.

There have been questions by some of the commitment of Teva to the Mesoblast programs following the acquisition of Cephalon. Mesoblast CEO Silviu Itescu said Teva is very committed to the Mesoblast partnership and believes it will not sell its 19.9% stake in Mesoblast.

Teva, which was built around a generics businesses, is in the process of transforming into a branded (drug development) pharmaceutical company. In January it appointed a new CEO, Jeremy Levin, who was formerly a senior executive at Bristol Myers-Squibb, which is not a generics business. Mesoblast's technology has the potential to help transform Teva into a drug discovery and development company.

We understand that what were **Arana Therapeutics'** drug discovery assets and acquired by Cephalon, were being considered for a spin out from Teva. However that option has been removed with the focus now from Teva to build its branded drug business.

Learning from the Osiris Experience

Overnight US stem cell company **Osiris** received approval from the Canadian drug regulator for its stem cell therapy Prochymal for the treatment graft-versus-host disease.

Graft-versus-host disease occurs when a patient receives a bone marrow transplant but the match is not quite exact, resulting in the transplanted immune cells in the bone marrow attacking the patient's organs. First line therapy is the use of steroids to dampen the immune system.

In 2009 Osiris failed in two pivotal late stage trials in graft-versus-host disease. The therapy is believed to be more effective in more severe cases of the disease. The Canadian regulator has approved the therapy for children who have failed steroid treatment.

Osiris is also trying to commercialise its treatment for Crohn's disease, type 1 diabetes and heart failure although has also had some setbacks here as well.

The Mesoblast technology differs from the Osisris stem cells in that its population of cells is much more concentrated. Mesoblast has learnt from Osiris' mistakes in commercializing its own stem cell technology. Osiris started with a systemic, broader acting therapy (graft-versus-host disease, Crohn's disease) and has then pursued more targeted therapies.

Mesoblast has proven first that its technology works in specific, targeted therapies such as heart failure and bone fractures. Having achieved its proof-of-concept here, it will now expand into less targeted or directed, intravenous formulations for disorders such as diabetes.

Osiris was once the commercial leader in the stem cell space with a market value of over $1 billion. It is now capitalised at only US$182 million and Mesoblast has become the global leader in the stem cell space with a market value of $2 billion.

Cont'd over

Somnomed Changes Management to Accelerate Growth

Somnomed (SOM: $0.83) has decided to make some changes in its upper management structure. The company's current CEO, Ralf Barschow, will be stepping down after five years at the helm. The new structure will be different.

The company will appoint a President of US Operations. The rest-of-world operations will be managed by the company's CFO, and its Chairman Dr Peter Neustadt. The company will not maintain a global CEO position.

There will be a change of focus for the company in respect of its direction of marketing. Over the last five years the company has focused on establishing global dental networks.

The Role of Dentists

Dentists play a crucial role in the success of this company and it's a relationship that works both ways. There are around 1,800 dentists in the US, 1,000 in Europe and around 400 in Australia who are trained to fit the Somnomed products. The dentists are important to Somnomed but the dentists can transform their businesses to service only the Somnomed product. Each dentist makes around $1100-$1200 per fitting, which involves several visits from the patient.

To date Somnomed has relied on the relationship the dentists have had with the sleep specialists and sleep centres and the company has marketed the products to the dentists. Now the company will move up the line and market the product more to sleep specialists.

The new US head of operations to be appointed will have a strength in this area. The company will also appoint a US Medical Advisory Board and a Chief Medical Officer.

The company is selling around 30,000 devices a year and to date has sold more than 70,000 units. The units sell for around $500-$600 and the price to the patient is between $1,500 – $2,000. What the company lacks at this stage is the clinical comparison data against the gold standard of CPAP. This will change in coming months with the company due to report on a 120 patient trial against CPAP systems, such as those sold by Resmed and Philips Respironics.

Somnomed is now better placed to support the marketing of its products from existing sales into what it calls the medical market (the sleep physicians).

The company indicated in its press release that the outgoing CEO had done a 'remarkable job in building a solid base' for the company. Dr Neustadt said the company is progressing well growing at 20%-25% a year. However, the company wants to grow at 30%-50% a year, and this expectation may explain the forthcoming changes to the management and management structure.

Look for Repeat Business in the Longer Term

What will also become a significant earner for the company in the next three to five years is repeat business. The Somnomed devices last for between three to five years. When the large and expanding user base starts to replace its existing units, there should be an acceleration in sales. Dr Neustadt said the company is already seeing repeat orders.

Summary

Somnomed is capitalised at $35 million. It had $3 million cash at the end of March. In the first half of this year the company generated sales of $6.8 million (up 14.6% over the previous corresponding period) with a small loss of just under $4,000.

Somnomed remains a stock with significant upside outstanding.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

– Mesoblast cont'd

Developments such as the approval of Osiris' allogeneic stem cell product in Canada, pharmaceutical group **Baxter** commencing a Phase III study in January in 450 patients with chronic myocardial ischemia using its autologous stem cell therapy (see *Bioshares* 446), and the widespread progress at Mesoblast indicates the commercial development of stem cell therapy is gaining momentum.

Summary

There are many significant milestones ahead for Mesoblast. These are summarised below. The outcome from the company's Phase II trial in diabetes could be a major event for the company. Not only does it have the potential to open up an extremely large market opportunity for the company in Type 2 diabetes, but it will support other systemic therapy applications including rheumatoid arthritis (caused by inflammation), which is over a $10 billion a year market as measured by existing product sales.

Mesoblast is capitalised at $1.95 billion. It had $226 million cash at the end of March.

Forthcoming Mesoblast Milestones

- Dosing of first patient in Phase II Type 2 diabetes trial (60 patients) – imminent
- Start of Phase III heart failure trial by Teva – Q2 2012
- Results from disc repair trial – end 2012
- Results from two spinal fusion trials – end 2012
- Interim Phase II diabetes data – end 2012

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioxyne Approaches Key Milestone in June

Bioxyne (BXN: $0.225) is the name for the company that resulted from the merger between Probiomics and the privately held Hunter Immunology.

The companies share a common scientific foundation through the research of Professor Robert Clancy from the University of Newcastle. Probiomics, which originally known as VRI Biomedical, was founded in 1998 and listed in December 2000. Hunter Immunology was formed in 2003.

Trading in Bioxyne shares commenced on April 4, 2012, opening at $0.24.

The major focus of the merged entity is the development of a novel immunotherapy for chronic lung disease, HI-164OV. A significant global market opportunity exists for novel and effective treatments for this often smoking-related medical condition (although a reasonable number of COPD sufferers have no history of smoking).

Bioxyne's Lead Program – HI-164OV

Bioxyne is developing a novel immunotherapy, or vaccine, for chronic obstructive pulmonary disease (COPD). The clinical objective is to reduce exacerbations that generally lead to costly hospitalisations.

The most frequently isolated bacteria from the sputum of patients with smoking related lung disease is *haemophilus influenzae*. Bioxyne's medical hypothesis is that vaccination (delivered in an oral tablet formulation) with a killed inactivated strain of *haemophilus influenzae* (isolate 164) can lead to an immune response in the mucosa and alleviate the rate and severity of exacerbations.

Phase IIb Trial Update

Bioxyne has completed enrolment in its current Phase IIb trial, in which 320 patients were enrolled. Trial data is being collected and readied for analysis with the results expected to become available in mid-June.

The company learnt from experience gained in its earlier Phase IIa trial in which subjects were included if they had experienced at least two moderate or severe acute COPD exacerbations in the preceding 24 months. In contrast, the current Phase IIb trial recruited subjects who had experienced only at least one moderate or severe acute COPD exacerbations in the preceding 12 months.

The Phase IIa trial needed to recruit more than 100 subjects to achieve a 37% reduction in exacerbations. However, it recruited only 42 patients, with only 38 completing the trial. These low numbers limited the statistical value of the trial. The Phase IIa primary endpoint of reduction in the severity and number of exacerbations did not achieve statistical significance, with only a 16% reduction observed.

Recruitment for the Phase IIb ran about one and half months behind schedule, and the trial recorded a drop-out rate of 9%. Of the 320 subjects enrolled, 292 completed the trial; 270 subjects were required to complete the trial in order to power the study for statistical significance. The primary endpoint of the Phase IIb trial is the rate of exacerbations requiring oral or parenteral corticosteroid treatment or hospitalisation.

The Phase IIb trial has been budgeted to cost $4.5 million.

Funding History

For the years FY2006 to FY2011, Hunter Immunology spent approximately $11.2 million on R&D activities. From 2006 and up until the merger, at least $17 million in funding had been obtained by Hunter Immunology. Included in this was $5 million of a convertible note funding obtained around January 2010.

A second tranche of $3 million convertible note funding was obtained in November 2011. In conjunction with the merger, $2.4 million in equity funding was obtained.

Major Shareholders

The major shareholders of Bioxyne are Octa Phillip Asset Management (21%), Dr Philip Comans (9.6%), Chris Cuffe (7.0%), PT Soho Industri Pharma (6.5%), Professor Robert Clancy (6.4%) and the University of Newcastle (3.2%)

Patents

Bioxyne's key patents covering HI-164OV expire in September 2029 (and in 2028 for the treatment of allergic asthma), offering a good runway in terms in-market protection.

Investment Considerations

Bioxyne's board intends to secure a trade sale of the company or out-license of HI-164OV following a successful completion of its Phase IIb trial. The company has been in discussions with more than 20 companies which have programs in the COPD area. Bioxyne expects to hire investment bankers to assist with commercialisation tasks, once the Phase IIb results are known.

However, investors should bear in mind that the company has yet to have its Investigational New Drug application, which was filed with the FDA in 2008, accepted by that regulatory authority. The FDA placed a Clinical Hold on the application because a preclinical toxicology study had not been conducted on HI-164OV to GLP standards and because there was insufficient information provided on the commercial scale and batch manufacturing of the investigational compound.

Hunter Immunology advised in its merger document that the FDA has since accepted some results from a pre-clinical toxicology study, "prior to conducting further studies". Hunter also advised that it has produced four batches of drug material which could be used to support its IND submission with the FDA.

However the merger documents indicated that Hunter could not "guarantee the FDA clinical hold will be lifted as result of (these activities) as there may be additional issues that the FDA raises that Hunter will need to address."

Cont'd over

Bioshares Model Portfolio (18 May 2012)

Company	Price (current)	Price added to portfolio	Date added
Osprey Medical	$0.40	$0.40	April 2012
QRxPharma	$1.74	$1.66	October 2011
Mayne Pharma Group	$0.335	$0.435	September 2011
Somnomed	$0.83	$0.94	January 2011
Phylogica	$0.048	$0.053	September 2010
Biota Holdings	$0.84	$1.09	May 2010
Tissue Therapies	$0.45	$0.21	January 2010
Atcor Medical	$0.07	$0.10	October 2008
Bionomics	$0.33	$0.42	December 2007
Cogstate	$0.275	$0.13	November 2007
Sirtex Medical	$5.95	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.65	$6.60	September 2007
Pharmaxis	$1.11	$3.15	August 2007
Universal Biosensors	$0.58	$1.23	June 2007
Alchemia	$0.440	$0.67	May 2004

Portfolio Changes – 18 May 2012

IN:
No changes

OUT:
No changes

– Bioxyne cont'd

The key point for investors is that the commercial development for the US market is on hold until the FDA releases its clinical hold. This status of uncertainty has the potential to reduce the company's bargaining power over HI-164OV in both the situation of a trade sale and the situation of an out-licensing transaction. Many pharmaceutical companies prefer to obtain global rights for new therapeutic products and the lack of regulatory pathway certainty could lessen potential returns available to shareholders, as things stand at present.

A second consideration for investors to keep in mind in respect of future commercial returns from HI-160V is that a Phase III trial would require the enrollment of between 1500-2000 patients. Trials would necessarily be conducted over a winter season and the earliest a Phase III trial could realistically commence would be the northern winter that commences at the end 2013. It would be more than likely that a second Phase III trial would be required and that the trials would be run over two seasons, given the scale of the programs. A Phase III trial of this magnitude would cost $35-$40 million according to Bioxyne CEO David Radford.

The implication for investors is that cost of taking HI-164OV through a Phase III program would cost an estimated $70-$80 million at a minimum for the trials alone and would not be completed until 2015 with market access achieved, assuming an EU pathway the current major option, at the earliest in 2016. The scale of these costs essentially mean that Bioxyne has almost no choice but to seek a trade sale or partner because Bioxyne has not structured itself as an integrated pharmaceutical company with internal development capabilities to progress programs to Phase III and beyond, similar to what has been achieved by Pharmaxis.

It is worth noting that the commercial strategy adopted by Pharmaxis for Bronchitol, which also may one day be used to treat COPD, has been to develop it for use first in the much smaller market of cystic fibrosis. The model adopted by Pharmaxis is to expand into larger market opportunities once smaller markets have been secured. The advantage of this strategy is that such companies can obtain leverage from safety data and manufacturing information developed for the smaller initial market, as well as using funds from product sales.

The risk for investors is that potential sale or licensing terms can be biased much more in favour of the acquirer or the licencee when companies have limited commercial options. So while a trade sale or licensing transaction for Bioxyne and/or HI-164OV is a possibility, investors' expectations of a lucrative deal should be scaled back.

Summary

Bioxyne is offering a very near term value inflexion point for investors as the Phase IIb clinical trial results are readied for public release in mid-June. Our expectation is that the outcome will be a binary result which places this as a high risk investment.

Although the trial results expected in mid-June have the potential to positively clarify the value of the HI-164OV asset, uncertainty over the products clinical development pathway in the US will continue as a brake on value creation.

Bioxyne is capitalised at $33.7 million and held cash of $2.5 million at March 31, 2012.

Bioshares recommendation: **Speculative Buy Class C – Adopt Short Term Trading Position Up Until Clinical Trial Results Are Announced in June**

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

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

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

(CMP–Current Market Price)

Group B

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

Speculative Buy – Class A

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

Speculative Buy – Class B

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

Speculative Buy – Class C

These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

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