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In this edition...
Biotech investment drivers include acquisitions and deals and collaborations. And when a noteworthy deal takes place for a comparator company, then its time to pay attention to the local stock in question. In this case, Genzyme's recent deal with Osiris Therapeutics carries much significance for adult stem company Mesoblast.

Arana Therapeutics CEO John Chiplin resigned this week, a somewhat puzzling event given the progress the company had made under his leadership.

Heart assist device manufacturer Ventracor is running very short of cash and appears to have missed the opportunity to raise funds earlier in the year. The company is now in a precarious position.

Companies covered: AAH, MSB, VCR

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.0%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.3%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - current)	-28.0%
Cumulative Gain	**49%**

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Osiris Therapeutics Strikes US$130 Million Deal With Genzyme... Positive News for Mesoblast

One of Mesoblast's competitors (and comparators as flagged in earlier editions of Bioshares) in the adult stem cell field is US-based **Osiris Therapeutics**. Osiris is using mesenchymal adult stem cells (Mesoblast is working with mesenchymal precursor adult stem cells) to develop therapeutics for a raft of indications. This week Osiris signed a US$130 million upfront deal with **Genzyme Corporation** for access to two of Osiris' development products, Prochymal and Chondrogen.

This is a major deal for Osiris, which is capitalised at US$560 million. The deal not only includes a large upfront payment, but it excludes the regions of the USA and Canada, which is retained by Osiris. Osiris is responsible for development of the products for a range of disease indications up to the end of Phase II. Phase III and Phase IV clinical trial costs will be shared by Osiris and Genzyme on a 60/40 split respectively. The total deal value is worth up to US$1.38 billion.

Genzyme and Osiris entered into a collaboration in 2007 to develop one of the products, Prochymal, for acute radiation therapy under a US$225 million contract with the Department of Defense in the US. Genzyme also has a history of developing cell therapy products, having developed the first cell therapy product (Carticel) approved by the FDA. Carticel is an autologous treatment for cartilage repair. The company also makes an autologous cell therapy product (Epicel) for the treatment of burns.

Genzyme is capitalised at US$19 billion and has a history of being prepared to invest in novel technology platforms and disease areas that large pharmaceutical groups have been slow to embrace. Genzyme generated profits from developing therapeutics for rare diseases that others thought could not be profitable. This includes products such as Ceredase for the treatment of Gaucher disease, which effects only a few thousand people in the US although from which the company generated US$1.1 billion of sales in 2007, or a third of the company's product revenue. This has been an incredibly successful product for Genzyme since it was first approved in 1991.

Genzyme has spun out companies such as **Genzyme Transgenics** (see *Bioshares* 5) which was seeking to produce therapeutic antibodies in transgenic goats. Outside of rare diseases, the company also has a specialty in the treatment of renal disease.

That Genzyme seeks out opportunities that larger companies bypass and has been very successful is an important point. The company has embraced the area of cell therapy with two products on the market and now has a major collaboration with Osiris. Genzyme also made a massive investment in the antisense technology space. In January this year, Genzyme made a US$325 million investment in **Isis Pharmaceuticals** (as an equity and licensing payment) for access to Isis' mipomersen, which has delivered compelling results in the reduction of cholesterol (around 50%) in Phase II clinical studies.

Mesobast- from previous page

Implications for Mesoblast

Obviously the deal between Osiris and Genzyme has a major implication for Mesoblast. Both companies are using the same type of adult stem cells, although Mesoblast's cells arguably result in a more concentrated level of stem cells.

Osiris' Prochymal is being tested in two Phase III trials for the treatment of graft versus host disease (in bone marrow transplant) and in Crohn's disease. Prochymal is also being tested for the treatment of type 1 diabetes, acute myocardial infarction and chronic pulmonary obstructive disease (in Phase II trials). The other product candidate, Chondrogen is in a Phase II/III trial for treating osteoarthritis in the knee.

Prochymal is an intravenous infusion of the mesenchymal adult stem cells. Chondrogen is a direct injection of the cells into the knee. The mesenchymal stem cells are thought to down regulate the immune response (Crohn's disease, transplant rejection, diabetes by protecting pancreatic islet cells from immune system attack, osteoarthritis) and rebuild injured tissue by promoting the release of tissue growth factors (heart tissue repair, repair of lung tissue in chronic obstructive pulmonary disorder).

Mesoblast is using a precursor version of the mesenchymal cells (MPCs), which helps the company get around the Osiris IP portfolio, which includes 47 patents in the US alone. Both companies have proprietary IP relating to the isolation and production of their stem cells. Because the cells are not recognized by the immune system, allogeneic (other people's) mesenchymal stem cells derived from bone marrow can potentially be used in wide spread commercial therapy.

Genzyme has products on the market for transplant rejection and in orthopaedics, and combined with Genzyme's interest in cell therapy, helps explain the interest in the Osiris technology.

Mesoblast & Angioblast Stem Cell Trials

Indication	Type of cells	Trial	Status
Mesoblast			
Long bone repair	Autologous	Phase Ib, 10 pp	Completed successfully
Spinal fusion	Allogeneic	Phase IIa, 40 pp	FDA cleared, underway
Knee osteoarthritis	Allogeneic	Phase IIa	Start 2008
Invertebral disc repair	Allogeneic	Preclinical	Completed. Phase IIa in planning
Angioblast			
AMD and diabetic retinopathy	Allogeneic	Preclinical	Completed. Phase IIa in 2009
Congestive heart faliure	Autologous	Phase Ib, 6 pp	Completed successfully
Congestive heart faliure	Allogeneic	Phase IIa, 60 pp	FDA cleared, underway
Heart attack patients	Allogeneic	Phase IIa, 25 pp	FDA cleared
Bone Marrow Transplant	Allogeneic	Phase I/II, 30 pp	FDA cleared

Mesoblast currently has a number of preclinical and clinical programs underway using its precursor mesenchymal cells.

Mesoblast has rights to the stem cell technology in orthopaedic applications. Its sister company, Angioblast, of which Mesoblast owns 39%, is developing the technology for cardiac and other vascular applications such as eye diseases.

Trial details

The spinal fusion trial will involve up to 40 patients and will combine the Mesoblast allogeneic MPCs with **Medtronic Sofamor Danek** carrier granules. The study will look at three different doses of the MPCs, and will be compared to a bone autograft in the same patient as the secondary measure, with the primary measure being to assess the safety of the cells. The study is recruiting patients at the Hospital for Special Surgery in Massachusetts. No adverse effects have been reported by the company.

The Phase II congestive heart failure study will also assess three separate doses of the allogeneic MPCs in three hospitals, one in Minnesota (Minneapolis Heart Institute), one in California (University of California) and the third in Arizona ((Mercy Gilbert Medical Center). The trial has shown no adverse events in the first seven patients treated. The trial will involve up to sixty patients with efficacy to be examined at three, six and 12 months after the delivery of the cells, which is a one off procedure with the patents discharged from hospital 24 hours later. One quarter of the patients will serve as a placebo group, who will receive the current standard of care treatment with mock injection procedures.

The Phase Ib/IIa heart attack study will be smaller, with around 25 patients who have recently experienced a heart attack. Safety is the primary endpoint with secondary efficacy endpoints to be explored three different doses at three, six and 12 months after delivery. There will also be a placebo group (eight) that will receive standard of care with mock injections. The study is being conducted University of Minnesota/Minneapolis Heart Institute and at the Texas Heart Institute. The trial is currently recruiting patients.

Summary

Mesoblast is now capitalised at $120 million. The company had $11.5 million in cash at the end of September which will be sufficient for 12 months of operation. We view the company's ability to raise further funding under current conditions to be good with a solid institutional shareholder base and a stream of clinical development and commercial milestones expected over the period.

The major deal between Osiris and Genzyme helps put mesenchymal stem cell treatment on the pharmaceutical industry map and should greatly assist Mesoblast with future commercialisation negotiations.

Bioshares recommendation: **Speculative Buy Class B**

What Now for Arana Therapeutics?

With the departure of John Chiplin, the board of Arana Therapeutics (AAH: 77.5 cents) appears to once again be faced with the task of agreeing on purpose, direction and strategy. When a CEO leaves well ahead of his or her contract expiration, and when unambiguous progress has been made and continues to be made (see box at right), then clearly there must be issues over strategy that have arisen to make the CEO's position untenable.

One scenario is that the board is at odds over the direction of the company, or is unhappy with the pace of change. It could also be the case that some shareholders could also be looking to exit their holdings and no doubt many shareholders would also be unhappy about a share price that has declined from around $2.00 in 2004.

So what are some options can the board consider?

Options for Arana Therapeutics

Option – No change

Arana's first option is to continue with its current strategy of building a comprehensive drug development pipeline that generates out-licensing opportunities at the Phase II or Phase III stage. The company's latest annual report described a goal of having 2-3 assets in late stage development, 2-3 assets in early clinical development and 3-4 assets in pre-clinical development, by 2011. The current strategy is headed by the clinical evaluation of the domain antibody drug candidate ART621 in an initial proof-of-concept trial in psoriasis, to be followed by a Phase II trial in patients with rheumatoid arthritis. A US IND filing was recently receipted by the FDA, enabling the commencement of the Phase II trial before the end of 2008.

This strategy also involves the acquisition of, or active in-licensing of products, targets and technologies. From *Bioshares'* perspective, Arana has done well in building a comprehensive pipeline that is not overly stretched outside of two disease areas (inflammation and cancer) and has a strong and credible specialisation in antibody drug development.

Option B – Divest assets, return all cash

The subject of the re-distribution of cash to Arana shareholders has been a ongoing issue for some of Arana's (and formerly Peptech's) shareholders. The company currently has $182 million in cash, and a predicted license revenue to 2011 of US$55-$60 million.

If the board came to a view that the assets under is stewardship cannot be optimally exploited with the management and structures it has in place, then the an argument exists for divesting assets, by way of sale or tender, followed by a return of capital to shareholders, payment of dividends and payment of special dividends. Current market conditions make *any* cash extremely attractive to certain investors.

It is worth noting that for a number of years Arana (formerly Peptech) managed an animal health business which it sold to **Parma Corporation** in February 2008. The company also divested its joint venture with **Biosceptre International** in June 2007. What

The Arana Asset Base

At John Chiplin's Departure – November 2008

Cash
$182 million

Pipeline
ART621 (domain antibody) (small royalty to GSK)
Phase II Psoriasis underway
Phase II Rheumatoid arthritis to commence end 2008 (US IND accepted)

PMX53 (cyclic peptide;complement inhibitor)
Age Related Macular Degeneration, Osteoarthritis
Phase I/II commencing 2009 Q2

ART123 (monoclonal anitibody; anti-IL 12/23)
Inflammatory conditions
Pre-clinical (lead optimisation)

ART010 (engineered protein; variant of osteoprotegrin)
Bone cancer
Pre-clinical

ART104 (monoclonal antibody) (Co-development with Kyowa Hakka)
Colorectal cancer
Optimisation

ART150 (monoclonal antibody)
Lung cancer and melanoma
Discovery

Technologies
Superhumanization
Evogene
Synhumanisation

Other
License income stream est US$55-$60M to 2011 Q1

At John Chiplin's Arrival – January 2006

Cash
$43 million

Pipeline
PN0621 (domain antibody) – Pre-clinical
PN0615 (Anti-TNF mab) – Lead Compound

Other
Investment in Domantis 33% stake
Animal Health Business (Peptech Animal Health)
Joint Venture - Biosceptre
License income stream est $100-$130M to 2010

this shows is that the company has learnt to peel off assets that don't fit with the company's priorities.

Option C – Review portfolio
Portfolio reviews are usually conducted following the failure of a product or program, and rarely if ever mid-stream. However, the board of Arana Therapeutics could commission a wholesale review of all elements of its business, at least doing so in light of current and anticipated changes to the drug development landscape.

We anticipate that major organisational change will occur rapidly at all levels of the drug development and medical device world. (Note, we expect the fundamentals of healthcare to maintain the attractiveness of the life sciences area to investors in the medium and long term.) However, a major shakeup amongst the larger pharmaceutical companies is on the cards, in part signalled by a number of staff cuts that have been announced recently. Industry restructuring at the very minimum means that any company in the cashed-up category, such as Arana is, should have up-to-the minute plans to take advantage of sudden opportunities. And any re-orientation could mean also mean re-prioritisation of existing programs.

Option D – Expand the business through further M&A
This option may not be at the forefront of thinking within the company, following the subdued response by the market towards the Evogenix merger. However, it is worth developing for one reason. Biotech asset prices have fallen considerably, and may be set to fall further. There are a number of local M&A possibilities in the antibody space to consider, including **Patrys**, **Immune System Therapeutics** and **Circadian Technologies**.

Some of these companies may hold assets that complement the Arana pipeline, with management and technical competencies also worth adding as well.

Management Succession
The board of Arana Therapeutics has announced that an interim CEO will be appointed from a group of internal candidates, until a permanent CEO found through a search process.

With the state of employment inthe biotech sector in flux, we expect that the board will have an unparalleled opportunity to select from a very talented pool of individuals from around the world. However, the board will need to reach a strong consensus on its direction if it wishes to attract the best candidates who no doubt would want to participate in the building of a very successful biotech business.

Summary
It is disappointing that a polished and thoroughly professional CEO in the form John Chiplin has decided to discontinue his tenure at Arana Therapeutics, especially since he was instrumental in re-positioning the company as a globally competitive and globally recognised biotech company. We would hope the board continues with this ambition.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares Investment Re-ratings

The sweeping global credit crisis is making access to capital considerably more difficult for most biotech companies in the sector. In recent weeks we have started to downgrade biotech companies that may need to raise capital over the next 18 months.

Ventracor
Ventracor has put itself into a precarious position. The company has an annual cash burn of $28 million a year although has only $11.8 million in cash (five months cash). The company is currently seeking to raise $10 million through a Share Purchase Plan (up to $5000 per shareholder) and a placement of up to $3.6 million. The funding issue for this company should have been attended to at least six months ago. That it hasn't suggests the company is resorting to one of its last options, its large and somewhat loyal shareholder case.

The company is seeking to raise $10 million to get it to the end of June, by which time it hopes to secure a strategic alliance or investor, or arranging a debt facility. The problem for the company is that leaving the funding to a late stage when access to capital from equity markets is rapidly eroding and debt funding has become increasingly difficult, the terms upon which the company will seek to raise future funding will become less and less favourable, unless market conditions change significantly.

Shareholders have the option of continuing to fund the development of VentrAssist, or be harshly diluted through more costly capital. By our estimates, Ventracor needs to sell over 600 pumps a year to be profitable. It is currently selling around 240 a year, although October was a good month when 27 (324 annualised) pumps were sold, generating $2.8 million of revenue for the month (annualised at $33 million a year). We estimate the company needs to generate revenue of $60 million a year to break even.

The falling Australian dollar (currently worth US$0.67) is working in Ventracor's favour, with most costs arising from Australian manufacturing and regulatory operations. Ventracor's worrying financial position is in stark contrast to the LVAD market which is accelerating firmly following the FDA approval of market leader's **Thoratec** HeartMate II device in April this year. Thoratec has a capitalisation of $1.3 billion and is trading on a trailing PE of 75 times. It generates about half of its revenue from LVAD sales.

Ventracor expects its VentrAssist LVAD device to be approved, if all goes well, in the second half of 2010. To get to that point, the company will need at least an additional $35 million after the current capital raising of $10 million. The company still has 150 employees although has sought to reduce its burn rate by 15% to around $2.4 million a month, which assumes the company sells 20 devices a month. Leaving the capital raising to such a late stage combined with deteriorating capital markets places the company in a vulnerable position.

Cont'd over

Ventracor - from previous page

It comes at a time when its competitor, **Heartware**, has moved towards a much firmer financial position. At the end of September, Heartware had $39 million in cash and was capitalised at $160 million when it last traded. Heartware is currently redomiciling to the US and will trade as CDIs when it re-lists on the ASX.

Ironically, Ventracor is around 18 months ahead of Heartware having completed over 370 implants versus 47 from Heartware. However Ventracor is capitalised at around 20% of Heartware, at $30 million, and with a significantly lower cash position. Heartware strengthened its funding position considerably in July when it raised $31 million. Ventracor can be criticised for not securing funding at the same time.

Bringing a new LVAD to market is an enormously expensive task. Ventracor has incurred $171 million in tax losses since it was formed and may take at least another $50 million to bring the company to profitability. Ventracor may well become a takeover target however the price of this company may become even more appealing to a suitor in six months time if it cannot secure at strategic investor or partner. The current capital raising appears to be a tie-over to such time. If the company cannot secure sufficient funding it may become one of the early casualties in the sector from the current global economic crisis.

Bioshares recommendation: **Sell**

Bioshares

Bioshares Model Portfolio (7 November 2008)

Company	Price (current)	Price added to portfolio	Date added
Hexima	$0.50	$0.60	October 2008
Atcor Medical	$0.18	$0.10	October 2008
CathRx	$0.70	$0.70	October 2008
Impedimed	$0.73	$0.70	Aug-08
Antisense Therapeutics	$0.05	$0.07	Aug-08
Mesoblast	$0.99	$1.25	Aug-08
Cellestis	$2.01	$2.27	April 2008
IDT	$1.94	$1.90	March 2008
Circadian Technologies	$0.66	$1.03	February 2008
Patrys	$0.13	$0.50	December 2007
Bionomics	$0.28	$0.42	December 2007
Cogstate	$0.16	$0.13	November 2007
Sirtex Medical	$2.00	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.26	$0.66	September 2007
Starpharma Holdings	$0.28	$0.37	August 2007
Pharmaxis	$1.59	$3.15	August 2007
Universal Biosensors	$0.55	$1.23	June 2007
Biota Holdings	$0.43	$1.55	March 2007
Probiotec	$1.28	$1.12	February 2007
Peplin Inc	$0.38	$0.83	January 2007
Arana Therapeutics	$0.78	$1.31	October 2006
Chemgenex Pharma.	$0.56	$0.38	June 2006
Cytopia	$0.15	$0.46	June 2005
Acrux	$0.64	$0.83	November 2004
Alchemia	$0.21	$0.67	May 2004

Portfolio Changes – 7 Nov 2008

IN:
No changes.

OUT:
No changes.

How Bioshares Rates Stocks

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

Group A

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

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

(CMP–Current Market Price)

Group B

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

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

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

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

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Phylogica, Pharmaxis, Biotech Capital, Cytopia,Arana Therapeutics, Starpharma Holdings, Cogstate, Xceed Biotechnology, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Circadian Technologies, Biota Holdings, Stem Cell Sciences, Halcygen Pharmaceuticals, Peplin, BioMD, Impedimed, QRxPharma, Patrys, Labtech Systems, Hexima, Proteome Systems

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