

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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Extract from Bioshares –

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 speciality 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.

Mesoblast- 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 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 patients 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.

Mesoblast & Angioblast Stem Cell Trials

Indication	Type of cells	Trial	Status
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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 failure	Autologous	Phase Ib, 6 pp	Completed successfully
Congestive heart failure	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

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**

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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