

In this edition...

Cytopia's decision to merge with YM Biosciences is a watershed moment for drug development companies in Australia. Cytopia had gone down the path of *de novo* small molecule drug discovery, which in the fragmented world of cancer drug development, is arguably more costly and more difficult than the strategies adopted by other firms to improve or re-purpose known drugs.

In contrast, new technology approaches, such as antibody drugs or cellular therapies, have the potential to offer new levels of therapeutic performance. We highlight recent local and global trends in the world of cell therapies and suggest that a new commercial phase of this therapeutic approach is imminent.

We also discuss recent trends in debt financing obtained by local biotechs.

The Editors

Companies Covered: CYT, Cellular Therapies, Debt Financing

	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 - May '09)	-7.3%
Year 9 (May '09 - Current)	54.0%
Cumulative Gain	187%
Av Annual Gain (9 yrs)	19.1%

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Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence
No. 258032

Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9329 3350
Email: info@bioshares.com.au

David Blake

Ph: (03) 9326 5382
Email: blake@bioshares.com.au

Mark Pachacz

Ph: (03) 9671 3222
Email: pachacz@bioshares.com.au

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Bioshares

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

Extract from Bioshares –

A Wave Of Cell Therapy Products Approaching Market

Over the next 18 months cellular therapies, including stem cell therapies, will arrive on a commercial basis in western healthcare markets. This will be the beginning of a new era in modern medicine, which takes its cue from when many of the opportunities in small molecule drug development have been exhausted or are becoming increasingly difficult to capture (as highlighted by falling small molecule drug approvals), when the antibody therapeutics field looks to have reached a plateau, as antisense technologies are still seeking clinical and commercial success, and RNAi technologies remain in their clinical infancy.

All Eyes on Dendreon

In the next nine months, **Dendreon** is expected to launch its cancer treatment Provenge product, an autologous therapeutic prostate cancer immunotherapy/vaccine. The therapy harnesses a patient's own immune system to fight the cancer using reprocessed or 'super-charged' dendritic cells that are specific to the cancer cells. These immune cells are expected to remain active in the body to continue fighting the cancer cells. Dendreon is expecting to submit an amendment to its regulatory submission for approval with the FDA (BLA submission) in mid November and the company is anticipating product launch in mid 2010.

Dendreon currently has 25% of its future expected manufacturing capacity at its New Jersey facility, in the heartland of US pharmaceutical manufacturing territory. This facility will increase to 48 work stations in the first half of 2011, and in the second half of 2011 two additional facilities, in Los Angeles and Atlanta, are expected to come on line. Each of these facilities will have 36 work stations.

Dendreon will then seek to expand the applications of Provenge by conducting clinical trials in breast cancer (late 2010/early 2011), metastatic renal cell carcinoma (2011) and colon cancer in 2012. The company's aim is to start one new cancer cellular immunotherapy trial every year. Those that said an autologous cell therapy product could not be profitable look to be in the minority with Dendreon now capitalised at US\$3.1 billion.

In Australia, Prima Biomed has seen its share price surge with its activities in therapeutic cancer vaccines. The company has received clearance to begin its Phase II trial in 60 women with ovarian cancer with its own therapeutic cancer vaccine, called CVac.

Current Cell Therapy Products

There has been little progress (in western markets) in cellular therapy products. One of the most successful to date is a product called Carticel, sold and processed by **Genzyme**. This product is used to repair cartilage damage. The product was approved for use in the US in 1995 and to date over 13,000 patients in the US have been treated with this therapy.

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The treatment involves taking a biopsy of chondrocyte cells from a patient's own healthy cartilage, having those cells grown in a laboratory by Genzyme Tissue Repair, and then implanted to repair the cartilage. The current cost for this autologous cell therapy product is on average US\$26,000.

Adult Stem Cell therapies - Osiris Therapeutics Receives Major Setback

The leader in commercialising adult stem cell technologies has been **Osiris Therapeutics**. Using its mesenchymal stem cells, the company was well advanced in Phase II and Phase III trials in several applications. In November last year it struck a major partnering/licensing deal with Genzyme Corporation. The deal involved a US\$130 million up-front payment to Osiris with a potential total deal value worth US\$1.4 billion for Genzyme to access ex-North American rights alone.

However, last month Osiris reported disappointing results from its two Phase III trials where its lead product candidate, Prochymal, failed to reach primary endpoints in graft versus host disease involving around 450 patients. Osiris believes its stem cells have anti-inflammatory properties and with the ability to prevent scar tissue formation and regenerate specific tissue structures. This was the first phase III adult stem cell trial *ever* completed.

In a subset of the patients, those with liver and gastrointestinal GvHD, statistically significant positive results were achieved (in the steroid refractory group). This mirrored earlier pilot data. However for some reason in the Phase III trials the company broadened its patient group, including skin GvHD, which is linked to 80% of cases, and preliminary results showed the trials failed to meet primary endpoints. The company is now seeking to focus on severe GvHD of the liver.

In another setback in March this year, Osiris stopped a 210 patient Phase III trial with Prochymal in Crohn's disease after a trial flaw was revealed showing a higher than expected placebo response rate.

Osiris is also conducting clinical trials with Prochymal in lung tissue repair (COPD), type 1 diabetes (protection of islet cells) and in patients following heart attack. The company has also completed enrolment in Phase I/II with Chondrogen, a similar stem cell therapy to improve regeneration of the meniscus following knee surgery.

As with many highly successful technologies, including Avastin and SSRI drugs (that now includes antidepressants such as Prozac) which generate billions of dollars in annual revenue, late stage clinical setbacks have needed to be overcome to find suitable applications for the technologies.

Opportunity for Mesoblast to become Dominant Adult Stem Cell Group

Osiris stumbling presents an opportunity for Mesoblast to become the dominant adult stem cell company. Where Osiris uses mesenchymal stem cells, Mesoblast is using the precursor to these cells, called mesenchymal precursor stem cells (MPCs). It argues

it has a purer and more potent population of adult stem cells than Osiris.

Mesoblast is developing orthopedic applications of these stem cells. It is conducting two Phase II trials in the US in spinal fusion, one trial in Melbourne in knee osteoarthritis, and it is planning to introduce a product in Australia for the treatment of non-union long bone fractures. The company is also seeking to file an IND in the US for the repair of intervertebral discs, with positive preclinical results recently achieved.

The company's CEO, Silviu Itescu, argues that Mesoblast has conducted more thorough preclinical studies in large animal models before it has embarked on clinical trials, which should reduce the chance of disappointing clinical outcomes with its cells. So far that has proven to be the case.

Its sister company, Angioblast Inc, in which Mesoblast owns a 38% interest, is currently recruiting for three Phase II trials in the US – two in heart disease and one in bone marrow therapy (expansion of hematopoietic stem cells used in bone marrow transplants) – and in conjunction with LVAD (heart pump) implants in a Phase II trial which is not yet recruiting. One of the advantages of working in cardiovascular disease is that any improvements in disease can be measured quickly and accurately.

Mesoblast has decided to file one of its products for regulatory approval in Australia. This is a strategic decision that looks to be well founded because it should result in the generation of revenue for the company, and will also increase the profile of the product (and technology) through clinical use. This product will be an autologous stem cell therapy for the treatment of non-union long bone fractures.

This product could generate a niche income stream of \$5 million - \$10 million a year in Australia from only 200 procedures, even if the procedure was not reimbursed. Patients who have fractures that are not healing can face amputation of the limbs. And high performance sports people may seek the technology to reduce healing times, allowing them to return to their sports sooner and stronger than without stem cell-assisted bone repair.

Cell Therapies in Melbourne will reprocess the cells. Cell Therapies is positioning itself to capitalise from this accelerated introduction of new cell therapy products that is anticipated.

Progress in the global stem cell arena

According to a summary prepared by Robin Young covering the Stem Cell Summit held in January in New York this year, the stem cell field looks set to break out in the next few years. "There is no doubt whatsoever we that clinicians are standing at the dawn of the cellular phase in therapeutic history."

In China autologous stem cell therapies are now generating in excess of US\$50 million a year. In the US around 30,000 patients have been treated with allogeneic stem cell therapies in the last four years and over 2,000 people with autologous stem cell treat-

Cont'd over

ments. Most of the controversy over stem cell use has related to embryonic stem cells. Ironically, any therapies derived from these stem cells remain a very long way from clinical use and most of the therapies will involve adult stem cells. Adult stem cells are being derived from many new sources including human testes, skin and placenta.

And some of the breakthroughs may occur in less regulated markets which is also a risk for the technology. Hospitals in China are currently claiming to provide autologous stem cell therapies for over 25 different diseases or disorders. At the controversial **Xcell-Center** in Cologne, Germany, they are using autologous stem cells to treat patients for at least 12 different applications, including treatment of spinal injuries, stroke and Alzheimer's disease. Cases of stem cell therapies in India to treat spinal cord injury, with some success, are also being cited.

Stem cell therapy lends itself to niche market applications in some cases, where for up to \$50 million a viable commercial operation can be built. Locally developed and processed stem cells that are delivered in stem cell hospitals may be the way some of these treatments are introduced. This is distinct from a pharmaceutical development model, where several hundreds of millions of dollars are required to bring a new therapeutic to market.

These niche businesses will offer unique therapies that will be taken up with or without reimbursement in cases. One example cited at the Stem Cell Summit was of Australian Graham Barnell who travelled to the US and paid \$1.3 million for a life saving stem cell transplant to treat his leukemia.

Future Stem Cell Treatments?

HIV is another area that may benefit from stem cell research. One theory being pursued (at the City of Hope Medical Center in California) is to deliver replacement stem cells into the bone marrow that can produce white blood cells that are resistant to attack from the virus.

ReNeuron in the UK has received regulatory and conditional ethics approval to trial its allogeneic stem cells (derived from adult tissue) for the treatment of disabled stroke patients via a direct injection into the brain. The first patients will receive two million stem cells and this will be scaled up to 20 million cells as the trial progresses.

Stem Cell Therapy Market

Mesoblast and Angioblast have certainly selected the right markets for which to develop its products. By 2018, it is expected that stem cell products will be generating revenue in the order of US\$8 billion a year in the US, in 2 million annual procedures, from \$65 million revenue in 2008. Almost half of that revenue is expected to come from orthopedic applications (US\$1.5 billion) and cardiovascular therapy uses (\$2.3 billion).

Summary

The appeal with cellular therapies is that they seek to enhance the natural processes of the body; the most powerful system in the body, immune system cells, or the multifunctional stem cells that are distributed throughout the body and curiously perform their set tasks as and when required. It does appear that an exciting new dawn involving cellular therapy is approaching.

Dendreon's anticipated launch of Provenge next year will draw much attention to the field. And stem cell therapies are making very strong progress with local company Mesoblast on track to become one of the leading global adult stem cell companies, if clinical advances are an accurate measure. There will be setbacks in the process with Dendreon (having previously knocked back by the FDA for approval of its Provenge product) and Osiris Therapeutics examples to note.

The success in the future will depend of the right business model being chosen, forming strategic partnerships where required, and having the capacity, both financial and in management, to effect the commercialisation of the technologies. But it would seem that investors and the broader population have much to look forward to from the introduction of these novel therapies.

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.

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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