

In this edition...

Markets have a tendency to favour certain sectors above others and within sectors favour certain stocks above others, regardless of fundamentals. But this is what investing is about – finding out what is being missed by the market, which despite certain theories is not perfect. Thus we present the case again for one stock that we regard as offering exceptional value, Cytopia, which this week released results of a Phase I trial of its cancer drug CYT997.

We also introduce a new stock wrap section to improve our coverage and communication to readers on less frequently discussed stocks

The editors

Companies covered: ACG, BIT, CYT, DIA, GIA, MVH, PPB

	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 (from 4 May '07)	-10.0%
Cumulative Gain	194%
Av Annual Gain (6 yrs)	26.8%

Bioshares is published by Blake Industry & Market Analysis Pty Ltd. The company also provides market and company analysis of the Australian pharmaceutical and biotech industries for local and international funds management institutions, venture capital funds and other related industry groups. For further details contact David Blake (see details below).

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) 9671 3633
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

Individual Subscriptions (48 issues/year)
\$320 (Inc.GST)
Edition Number 241 (16 November 2007)
ISSN 1443-850X

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Bioshares

16 November 2007
Edition 241

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

With Three Phase II Trials Planned, Cytopia Offers Exceptional Value

As Cytopia (CYT: 51 cents) continues to drive its drug discovery and development engine room, its share price fails to respond to the progress being made. The company is capitalised at only \$38 million with \$14 million in cash at June 30, a ridiculously low market valuation that seems to contradict a general perception that company's work is well respected amongst peers and by institutional investors and investment managers active in the sector. However, we are confident that with three Phase II cancer trials to be launched in the next 12 months, it is difficult not to see a revaluation occurring with this stock over the coming year.

In a snapshot, Cytopia has one drug, CYT997, ready to move into Phase II clinical testing in cancer (multiple myeloma). It has a drug development partnership with **Novartis** in the area of auto-inflammatory diseases, which has a potential deal value of up to \$274 million. Only a handful of Australian companies, including Cytopia, have ever struck deals with large international pharmaceutical partners, and in our view the market has missed the point of how such a deal validates the capabilities of the company. Cytopia has two other patented preclinical assets in development: compounds that hit the JAK2 pathway, for the treatment of a range of cancers, cardiovascular disease and myeloproliferative disorders; and it has a program to find drugs that intercept and modulate the FMS kinase pathway.

Inflexion point approaching

Cytopia is approaching a large value inflexion point. Within 18 months, it should by our estimates, have three drug candidates in clinical trials (CYT997, FMS candidate, JAK2 candidate) with Phase II results from at least one cancer indication.

What makes the Cytopia drug engine room so appealing is that a major focus on proteins involved in 'signal transduction pathways' (excluding CYT997). These are signaling pathways inside cells. The blocking of these lines of communications with very specific acting drugs represents a novel way to treat disease. The highly successful Gleevec drug from Novartis works on a kinase pathways and is about 95% effective in treating cancer (chronic myeloid leukemia). It perhaps explains the interest by Novartis in Cytopia, but Novartis also has a very important franchise in auto-immune disease.

Cytopia's Kinase Inhibitor Assets

- JAK3 (rheumatoid arthritis, transplantation rejection, psoriasis, asthma) - Partnered with Novartis
- JAK2 (blood-based cancers, cardiovascular disease such as congestive heart failure, myeloproliferative diseases such as thrombocytopenia which is categorized by an increased level of blood platelets)
- FMS (oncology and bone degradation)

Cont'd over

Cytopia's Lead Drug Candidate

CYT997, a vascular disrupting agent and tubulin inhibitor, completed Phase I clinical study in 31 patients with solid tumours.

Phase I CYT997 results

This week Cytopia reported Phase I results in 22 evaluable patients with a range of solid tumours. The aim of the trial was to establish the maximum tolerable dose of the drug. Patients started on very low doses (7 mg/m²) to the maximum dose (358 mg/m²). The patients enrolled in the trial had failed all other treatments.

A number of indicators in the trial suggests there is strong reason to continue development of this drug candidate, and in fact evidence that the drug is working in some patients.

CYT997 works by disrupting the tumour vasculature. In one patient with a mesothelioma tumour that had advanced to the abdomen, a MRI scan clearly showed that the blood vessel feeding the tumour were destroyed after only a few days of treatment with the drug. Using a biomarker (plasma von Williebrand factor) that measures blood vessel wall disruption, there was a clear increase on average in patients on the higher dosage groups. CYT997 works by breaking up blood vessels in solid cancers whilst leaving healthy blood vessels intact.

Of the 22 patients, five had progressive disease with the remainder seeing their best response (not over the entire treatment time but the period between MRI scans) stabilise disease. Two patients recorded a reduction in tumour size. The pharmacokinetic data from this intravenous infusion study, which measures the length of time and the level of active drug maintained in the bloodstream, was very consistent with all patients.

Upcoming Phase II CYT997 trials

Cytopia plans to begin a Phase II trial in patients with multiple myeloma at the **Alfred Hospital** in Melbourne. It plans to commence two other Phase II trials with CYT997 next year in solid tumours, possible melanoma and mesothelioma, although this remains undecided.

In laboratory studies using samples from patients with multiple myeloma, CYT997 was shown to stop the uncontrolled division of plasma cells that characterizes the disease, as well as overcoming the resistance mechanism often seen in patients being treated for multiple myeloma. Drug resistance is common in this disease and the possibility of stopping drug resistance with this drug (as well as potentially being an effective standalone therapy)

may make it a useful drug to add to the current therapy regimes.

The multiple myeloma study will include an interim analysis after 11 patients have been treated, using an adaptive design process to help better guide the remainder of the trial. Cytopia has an open IND for CYT997. Other Phase II programs are likely to include trial sites overseas as well as in Australia.

Cytopia is also completing a Phase I trial with CYT997 dosed orally. This is an accelerated trial that allows patients to reach maximum dose more quickly. We estimate results should be available in the first half of next year.

Comparative valuations

The table on this page shows a number of international oncology companies that are connected by their targeting of intracellular function. There is a spectrum of companies included. If biotech companies are successful in this area to develop first line oncology treatments, and if they maintain some marketing rights, an enterprise value in the order of US\$3 billion can be achieved, as achieved by **Onyx Pharmaceuticals**. (**Imclone Systems** is another example, having developed the chimeric monoclonal antibody. It co-markets with BMS and has a enterprise value of US\$3.4 billion).

Companies that have developed powerful drug discovery engine rooms, such as **Exelixis**, can generate considerable value. The company has 14 different drugs in Phase I and Phase II and has an enterprise value of US\$761 million. A promising Phase III program can be worth around US\$300 million (**Ariad Pharmaceuticals**). Companies such as **Kosan Biosciences** and **Infinity Pharmaceuticals** developing drugs against the Hsp-90 (heat shock protein 90), which acts a molecular 'chaperone', appear to reflect a lower value.

Selected small molecule drug developers - oncology focus

Company	Phase I	Phase II	Phase III	Market drugs	Comments	Enterprise Value (US\$M)
Onyx Pharmaceuticals				1 (Nexavar)	Co-marketed with Bayer, raf kinase inhibitor	\$2,840
Exelixis	8	6			One of best kinase drug discovery engines	\$761
Ariad Pharmaceuticals			1		Hits mTOR protein kinase	\$306
Rigel Pharmaceuticals	1	1			Oncology & JAK3 pathway for autoimmune	\$153
Kosan Biosciences		4	1		Hsp90 inhibitors	\$130
Infinity Pharmaceuticals	1				Collaborations with Astrazeneca, J&J and Amgen, Hsp90 inhibitors	\$71

Selected Australian oncology companies

Company	Phase I	Phase II	Phase III	Marketed drugs	Comments	Enterprise Value (\$M)
Chemgenex Pharmaceuticals		1	1		Expected to file for approval within 12 months	\$186
Progen Industries			1		Angiogenesis inhibitor	\$59
Cytopia		1			Collaboration with Novartis	\$24

Note: the above table indicates the number of drugs in trials,

not the number of trials being conducted for different disease indications.

Of closer interest in this table for assessing Cytopia is **Rigel Pharmaceuticals**. It has one drug (a spleen tyrosine kinase inhibitor) in three Phase II trials for indications including rheumatoid arthritis and oncology (B-cell lymphoma). It has one preclinical program focused on the JAK3 pathway to treat transplant rejection and rheumatoid arthritis (the same pathway and indications as Cytopia), and it has a Phase I program to treat solid tumours (an aurora kinase inhibitor) which is partnered with **Merck Serono**. It also has a preclinical development program with **Pfizer**. Rigel has an enterprise value of US\$153 million.

Considerably undervalued

With a technology value of only \$24 million, Cytopia is considerably undervalued. A technology value *in excess* of \$80 million for Cytopia would arguably be easily justified for the company, which translates to \$1.25 a share. The company has the challenge ahead to deliver on its milestones over the next 12 months, and delivering on these milestones will help its share price better reflect the value within the company.

Milestones for the next year include:

- Start of Phase II multiple myeloma study
- Interim results from multiple myeloma study
- Final results from oral Phase I CYT997 study
- Start of two further Phase II studies with CYT997
- Possible collaboration for JAK2 program

Another surprising market value at present is that on **Progen Pharmaceuticals**, which has a technology value of only \$59 million. This may have to do with major milestones (results) for the Phase III liver cancer program being at least two years away. It also represents very good value for investors at its current price, although this stock is much more a binary play than Cytopia.

Management and Board Changes

The founder of Cytopia, Dr Andrew Wilks, will be moving to a consulting and advisory role with the company in the new year. The company also announced changes to the board, with director John Hasker stepping down. The company would benefit from more international drug commercialisation experience at the board level.

Summary

Cytopia has long been acknowledged as having a valuable drug discovery pipeline and this pipeline is now beginning to bear fruit for the company and its shareholders. It should be a pivotal period ahead for the company and at its current market value, it is an exceptionally attractive investment opportunity.

Bioshares recommendation: **Speculative Buy Class A**

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Probiotec – Right on Target

Probiotec continues to deliver results right on company forecasts, confirming management has a solid grasp of its business and a capability to outperform. The company listed in December last year at \$1.00 share, was added to the Bioshares Portfolio at \$1.12 and the share price has had a strong run recently, finishing this week at \$1.50.

Probiotec is a manufacturer, distributor and seller of over-the-counter pharmaceuticals and nutraceuticals. This is a competitive business where strict business disciplines are required to succeed. Probiotec's approach has been to acquire distressed businesses, consolidate them and then in-license other products or internally develop new products to leverage its manufacturing and marketing and distribution infrastructure.

The company forecast in its prospectus a pre-tax profit for FY2007 of \$6.0 million, which was met. It then forecast pre-tax profit growth of 30%. In the first four months of this year it generated a pre-tax profit of \$2.75 million, indicating it is well on track to meet its profit target, excluding costs associated with litigation action which it is defending. We believe this action is not a significant threat to the underlying business.

Based on current profit forecasts supplied by the company, Probiotec is trading on a 2008 prospective PE of 13 times. With strong growth anticipated to be maintained, this stock remains an attractive investment option. Probiotec is capitalised at \$72 million.

Bioshares recommendation: **Buy**

Bioshares

Five Stocks in Brief

Recently a reader asked if there was a way we could provide more comments on some of the stocks we rarely, or perhaps have never looked at. We understand that such analyses can help investors even if the recommendations by and large say “don’t go here”. So beginning in this edition we have included a specially formatted table summarising five stocks. We expect to regularly include this table, covering different companies, to keep Bioshares readers up to date on some less frequently examined stocks.

Company	Atcor	Code	ACG	CMP	\$0.11	Cap'n (\$M)	\$11.0	Cash (\$M)	\$5.61	SI	1.2
<ul style="list-style-type: none"> Markets the Sphygmocor device, which non-invasively measures central blood pressure (versus radial or cuff pressure) Several major clinical studies support the technology as superior in predicting cardiovascular problems ACG gaining traction in the clinical trials market - current contracted revenue at \$3.5M; No. of contracted companies now 10 '07 revenue \$4.8 M [Gross margin: 79%] Rev. split is 66% hardware and 33% services; also split 50% pharma and 50% research ACG is well-managed and communicates proactively 											
<ul style="list-style-type: none"> Milestone: develop improvements in wave form capture technique/technology [ease of use at poc must be greatly improved] Another milestone is to complete data analysis to derive hazard ratio statistics 											
Comment: Major challenge is gaining coding and reimbursement, which depends in part on completion of more data analysis											
Bioshares recommendation: Speculative Buy Class B						Timing Considerations - None					

Company	Biotron	Code	BIT	CMP	\$0.185	Cap'n (\$M)	\$16.6	Cash (\$M)	\$0.72	SI	0.2
<ul style="list-style-type: none"> BIT225 Phase Ia trial successfully completed in August; indications include HIV and HCV Announced 16/11 an SPP, of which \$2.5 million is underwritten by Martin Place Securities While BIT225 offers a novel approach for treating HIV, the practicalities of HIV clinical trials are very demanding BIT's HCV program will deliver more relevant data ahead of HIV trial, and has chance to overtake HIV program While BIT has been focused on core operational goals, it has neglected development of communication channels with the market 											
<ul style="list-style-type: none"> Milestone: Will commence a Phase Ib/Ia dose finding and efficacy study in HCV patients (Q1-08); results mid-2008 Will commence a Phase Ib repeat dose study in HIV patients (Q1-08); results mid-2008 											
Comment: Company has a major challenge to fund programs, which has been hampered by an exceedingly low profile											
Bioshares recommendation: Speculative Hold Class C						Timing Considerations - HCV data in mid-08 a key test					

Company	Medic Vision	Code	MVH	CMP	\$0.15	Cap'n (\$M)	\$14.0	Cash (\$M)	\$2.6	SI	0.6
<ul style="list-style-type: none"> MVH is a distributor of surgical simulation training devices and services into Aust., UK, China and now India MVH now has a clearer focus and cleaned-up register since spin-out of KarmelSonix The business model generates income from subscriptions to training centres and courses, and consultancies to set up centres The main driver is a global trend to move to surgeon training that is more efficient, consistent, standardised and measurable MVH's strength stems from its building of key relationships, and depth in consulting and designing and operating training centres 											
<ul style="list-style-type: none"> Milestones to monitor include signing of new contracts in Asian markets 											
Comment: Conversion of initial agreements with several Indian and Chinese hospitals into growing revenue will drive investor interest											
Bioshares recommendation: Speculative Buy Class C						Timing - monitor quarterly sales trend to adjust weighting					

Company	Giaconda	Code	GIA	CMP	\$0.39	Cap'n (\$M)	\$28.5	Cash (\$M)	\$1.3	SI	0.5
<ul style="list-style-type: none"> GIA is developing Myoconda, a combination antibiotic therapy for Crohn's disease; Hepaconda for HCV; Heliconda for h.pylori infection Myoconda now under US IND submission; two Phase III trials planned, one US, one European Myoconda previously completed Phase III trial in Australia, but prospects impacted by advent of biologics such as Remicade Market opportunity exists because Myoconda addresses cause rather than symptoms 											
<ul style="list-style-type: none"> 55.67 million shares were released from escrow on 27/9 											
<ul style="list-style-type: none"> Milestone: Myoconda European Phase III trial expected to commence Q1-08, complete +52 weeks; filing with UK MHRA Q3 2009 Secure US licensee for Myoconda 											
Comment: Register is dominated by founder (70%); register composition is an issue dampening investment appeal											
Bioshares recommendation: Speculative Hold Class B						Timing - Wait for signif. decrease in founder stake					

Company	Dia-B	Code	DIA	CMP	\$0.08	Cap'n (\$M)	\$13.1	Cash (\$M)	\$1.38	S.I	0.5
<ul style="list-style-type: none"> Has now completed a Phase Ia and Phase Ib for ISF402, a tetra-peptide which acts as an insulin sensitising agent Announced that the metabolite (HTD-amide) of ISF402 can be detected in plasma (blood) Has 87 million \$0.20 quoted options expiring 31/12/10 											
<ul style="list-style-type: none"> Milestone: Phase Ib data for ISF401 expected this quarter (Q4-07) 											
<ul style="list-style-type: none"> DIA is yet to finalise an FDA registration strategy for ISF402, prior to US IND submission Pending above mentioned milestone and funding, will commence a Phase II trial in 2008 H2 											
Comment: Board and management need strengthening; must address of key issue of near-term funding											
Bioshares recommendation: Speculative Hold Class C						Timing - Wait for funding situation to be resolved					

Notes: SI - Survival Index - refer to Bioshares 240 for explanations

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Bioshares Model Portfolio (16 November 2007)

Company	Price (current)	Price added to portfolio	Date added
Ventracor	\$0.65	\$0.625	October 2007
Sirtex Medical	\$5.30	\$3.90	October 2007
Clinuvel Pharmaceuticals	\$0.43	\$0.66	September 2007
Progen Pharmaceuticals	\$2.65	\$3.52	September 2007
Starpharma Holdings	\$0.40	\$0.37	August 2007
Pharmaxis	\$4.12	\$3.15	August 2007
Circadian Technologies	\$1.20	\$1.45	June 2007
Universal Biosensors	\$1.65	\$1.23	June 2007
Biota Holdings	\$1.37	\$1.55	March 2007
Tissue Therapies	\$0.45	\$0.58	February 2007
Probiotec	\$1.50	\$1.12	February 2007
Phylogica	\$0.21	\$0.42	January 2007
Peplin Inc	\$0.80	\$0.83	January 2007
Arana Therapeutics	\$1.16	\$1.31	October 2006
Sunshine Heart	\$0.16	\$0.19	September 2006
Chemgenex Pharma.	\$1.10	\$0.38	June 2006
Cytopia	\$0.51	\$0.46	June 2005
Optiscan Imaging	\$0.31	\$0.35	March 2005
Acrux	\$1.35	\$0.83	November 2004
Alchemia	\$0.69	\$0.67	May 2004

Portfolio Changes – 16 Nov 2007

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, NeuroDiscovery, Biotech Capital, Cygenics, Cytopia, Biodiem, Peptech, Starpharma Holdings, Cogstate, Xceed Biotechnology, Incitive, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Medical Therapies, Circadian Technologies, Biota Holdings, Stem Cell Sciences, Halcyon Pharmaceuticals, Peplin, BioMD, Impedimed

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