

In this edition...

Investment opportunities in the Australian biotech sector continue to offer increasing appeal as global credit market weakness continues. In recent editions we have highlighted some core biotech holdings investors should consider closely. This week we look at a profitable biotech company (IDT) paying a 5% dividend yield with expectations of strong growth ahead and arguably Australia's strongest drug discovery engine (Cytopia) that has fallen to extraordinary low share price levels that in no way reflects progress at the company. We also update readers on BioMD, which is ready to move into Phase II studies for the testing of its tissue processing technology.

The editors

Companies covered: BOD, CYT, IDT

	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)	-40%
Cumulative Gain	94.7%
Av Annual Gain (6 yrs)	26.8%

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

Extract from *Bioshares* –

Cytopia Builds its Pipeline

Cytopia (CYT: 29 cents) is a developer of small molecule drug candidates. The company has made steady progress in building a pipeline of drug candidates that target a class of proteins called kinases. However, it should be noted that Cytopia's lead compound, CYT997, has a different mechanism of action. CYT997 is a vascular disruption agent that works by disrupting tubulin polymerisation. Tubulin is a component of cellular architecture. CYT997 is also thought to be capable of initiating cell death in cancer cells.

Cytopia recently announced that it had selected a compound, CYT387, for formal pre-clinical development. CYT387 is a potential treatment for myeloproliferative diseases (MPDs), a group of diseases of the blood in which the over-production of blood cells occurs. In turn, the prospects for arterial or venous clotting or severe bleeding increase, as does the likelihood for strokes and heart attacks.

There are two main groups of MPDs, those termed 'Philadelphia chromosome positive' (Ph. +), which include chronic myeloid leukemia (CML), and are distinguished by the causative effects of the bcr-abl fusion gene. The other group of MPDs is termed 'Philadelphia chromosome negative'.

The most common Ph. negative MPDs include polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis. These in turn are characterised by the presence of a mutation on the JAK2 kinase, termed the V617F mutation. (A mutation on the JAK2 gene causes the substitution of phenylalanine for valine at position 617 in the JAK2 protein.)

The mutation is found in about 95% of polycythemia vera cases, 50%-60% of essential thrombocythemia cases and idiopathic myelofibrosis cases. In fact the discovery of the V617F mutation has now shifted the definition of the disease so that an MPD (excluding CML) is now V617+ or V617-, with V617+ polycythemia vera and V617+ thrombocythemia regarded as the chronic phase myelo-fibrosis seen as an accelerated phase of the disease. This is similar to how CML is broken down into chronic, accelerated and blast phases.

The very strong correlation of the mutation to the disease marks the MPDs out as an attractive drug opportunity because treatment of the disease is arguably mechanistically simple. Blocking the effect of the mutation should theoretically result in disease remission in a clear-cut way. The more specifically it is addressed or blocked by a drug, then the more likely the side effects are contained.

Cont'd over

The development pathway for CYT387 is extremely attractive because once satisfactory dosing information is obtained in Phase I studies, then efficacy studies will fairly rapidly reveal the effectiveness of the drug candidate because the effectiveness of disease treatment can be measured simply and quickly by blood analysis. Cytopia expects to lodge a US IND in by Q4 2008.

CYT387– Competitive Opportunity

Current treatments for MPD's are limited. They include phlebotomy (the centuries old practice of therapeutic bleeding) and the use of myelosuppressive agents such as radioactive phosphorus and hydroxyurea.

Currently there are at least five other companies that have initiated JAK2 programs targeting MPDs (see table below). **Incyte**, a genomics company that morphed into a drug developer in 2002, has the most advanced candidate in clinical trials, INCB18424. Incyte is testing the compound not only in myelofibrosis, but also in rheumatoid arthritis, psoriasis, multiple myeloma and prostate

have been exhausted and also because current treatments such as Velcade, Revlimid and Thalomid exhibit certain toxicities.

Recent research has revealed that aberrant signalling in the NF-kappa B pathway is implicated in multiple myeloma. It would be of no surprise if researchers ascertain that point mutations are involved in multiple myeloma, and in fact patients who respond to Velcade are thought to be respond positively because of mutations in proteins in the NF-kappa B pathway.

Cytopia intends to commence a Phase I/II trial of CYT997 in glioblastoma multiforme, a cancer of the brain. Glioma's are currently treated with surgery, radiotherapy and drugs including Temodar and platin class cancer agents. These tumours are highly vascularised, which means they may be amenable to treatment with vascular disruption agent such as CYT997. The Phase Ib dosing component to determine the optimal dose will see CYT997 administered in combination with carboplatin and one other chemotherapeutic on a 21 day cycle, with CYT997 being administered by

infusion for 24 hrs on day 2 of the cycle. A two-stage phase II part of the trial will follow. Between 25 and 30 patients will be enrolled overall in the trial.

JAK2 Drug Developers - Myeloproliferative Disorders

Company	Num. Drug Cand. (all indications)	INDs filed (all indications)	Founded	Employees	Cap'n (\$M)	JAK2 Candidate	Status
Cytopia	3	1	1998	46	\$25	CYT387	Pre-clinical
Exelixis	11	14	1994	735	US\$710	XL019	Phase I ongoing
Incyte	11	12	1991*/2002	196	US\$866	INCB18424	Phase II
TargeGen	3	2	2002	~60	Private	TG101348	Phase I/II
Astex	8	?	1999	~100	Private	AT9283	Discovery
S*Bio (Singapore)	5	?	2000	~50	Private	SB1518	Pre-clinical

*Founded as a genomics company; refocused as a drug developer in 2002

cancer. The strategy to test the drug in so many non-MPD indications as well as myelofibrosis (which is an advanced stage MPD disease) suggests that company has developed a less specific agent, compared to Cytopia's CYT387 or indeed even others in development by other companies.

The competition objective being addressed by Cytopia is to develop a highly specific drug that delivers a more favourable safety profile than its competitors.

Although Cytopia is not a current leader in the JAK2 MPD drug development group of companies, in reality the numbers of competitors are few, with as far as *Bioshares* can ascertain, no significant involvement to date by large pharmaceutical firms. This fact lends support to Cytopia's strategy to license out CYT387, when sufficient and appropriate data has been gathered, to a pharmaceutical partner.

Update on CYT997

Cytopia has moved CYT997 into a Phase II trial with multiple myeloma patients. Multiple myeloma is a cancer of the platelet blood cells. This indication (as a blood-based cancer) is outside the original focus on solid tumours. Cytopia has selected this development option because of data gained in pre-clinical studies of the compound. An opportunity exists for drug developers to find compounds that can treat multiple myeloma once other options

are being explored. Cytopia has been focusing on building a drug development pipeline with both breadth and depth. The company's strategy has been to harness a drug discovery engine that is based on understanding of a special class of proteins called kinases, which are involved in cell signalling.

Cytopia's objective is to develop a steady stream of drug candidates, and with the selection of CYT387 for advanced pre-clinical studies, the company has demonstrated its comprehensive drug discovery skills.

What makes Cytopia attractive, and even more so at its current valuation of \$25 million, is that it is structured to accommodate the high risk of failure in drug development, by building the capacity to develop many compounds. It has partnered out drug development pertaining to the JAK3 kinase for transplant-rejection with **Novartis**, and now has two compounds in development, over which it holds 100% ownership. The company has the capacity to bring forward more compounds, although development is constrained by funding. Our expectations are that the company will bring forward into pre-clinical development a JAK2 targeted candidate for the condition of pulmonary arterial hypertension and a second generation follow-up to the FMS inhibitor CYT645 in the near future.

Cont'd over

The very poor state of equity markets has seen many biotech stocks driven to very, very low prices. In the case of Cytopia, its share price is offering exceptional value at present and the stock sits well under the value range that biotech investors have regularly awarded companies that have drug candidates at the Phase II stage of development.

Milestones to monitor

- Commence glioma trial Q2 2008
- Conclusion of CYT997 Phase I Oral H1 2008
- Interim analysis multiple myeloma trial Q3 2008
- Filing of IND for CYT387 Q4 2008

Bioshares recommendation: **Speculative Buy Class A**

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

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

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