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In this edition...
What are the signs that a sector is undervalued? One is that M&A activity ratchets up. Another is that canny international institutional investors, or venture capitalists, enter the registers of local biotechs in a big way. This has happened and the trend is very positive for the biotech sector.

We update readers on Pharmaxis and the outcome of its Phase III trial of Aridol in the US. And at the other end of the development spectrum, we note preclinical progress with Incitive's ICV0019. We also take a look at the competitive landscape for Bionomics' and Cytopia's vascular disruption compounds.

The editors

Companies covered: BNO, CYT, ICV, PXS

	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 (from 5 May '06)	-1.6%
Cumulative Gain	**174%**
Average Annual Gain	**23.6%**

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).

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Bioshares

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

International Funds Target Australian Biotech Assets

The last 12 months has seen an upswing in interest from international funds management groups in the Australian biotech sector. A maturity of clinical programs in Australian biotech companies, the accompanying increase in valuation of these businesses, plus lower entry prices and the lack of experience from Australian institutional investors in this market, which has resulted in a shortfall of local funding, has contributed to the wave of international capital inflow over the last 12 months.

Last year, **Pharmaxis** raised $87 million in the largest single capital raising by an Australian biotech to fund commercialization of R&D programs. Approximately half of the funds were raised overseas from 15 international investment funds. Earlier this year **Peplin** raised $40 million, with the lead investor, **MPM Capital**, a specialist healthcare fund, providing the majority of the $23 million that was sourced overseas. This month **Clinuvel Pharmaceuticals** conducted a transformational funding round, rasing $35 million, with over $20 million raised from 10 European funds.

Earlier this year, the venture capital fund **Nordic Biotech** toured the country scouting for local biotech investments. Its first investment has been with **Psivida**, making a novel investment approach for Australia, although one that is more common overseas, agreeing to invest $33.7 million not in Psivida, but into one of the company's products in development.

The investment is subject to further due diligence. However the intention is for Nordic Biotech to fund the commercialisation of Medidur, which is currently is Phase III trials for the treatment diabetic macular edema. Nordic Biotech will receive initially 75% of Psivida's profit share from the commercialisation of Medidur until it recovers four times its investment. After such time, its profit share will be reduced to 50%. After cumulative revenue to Nordic Biotech totals eight times its initial investment, Nordic will then receive 20% of future profit share. Nordic Biotech will also have a right, subject to shareholder approval, to convert its rights into equity in Psivida.

Cont'd on page 4

International (selected) Capital Inflow in Last 12 Months

Company	Date of raising	Funds raised	Est. International contribution	No. Int. Funds Invested
Pharmaxis	Nov 2005	$87 million	$43 million	15
Peplin	May 2006	$40 million	$23 million	3
Clinuvel	Nov 2006	$35 million	>$20 million	10
Psivida	Nov 2006	$33 million	$33 million	1

The 'Tubulin Class' Cancer Drugs

In addition to the more established cytotoxic approaches to treating solid cancers, there now exist several newer yet now well defined, clinically and commercially validated approaches to treating solid tumours. Recently the approach of preventing the growth of blood vessels that feed tumours has achieved success, with **Genentech**'s anti-angiogenesis monoclonal antibody Avastin performing well clinically (as a combination therapy) and also in terms of sales (2005 - $US 1.1 billion).

However, another class of cancer medicine that predates the anti-angiogenesis approach is the class of tubulin inhibitors. Starting with the registration by the FDA of **Bristol Myers Squibb**'s (BMS) Taxol (paclitaxel) in 1992 and followed by **Sanofi Aventis**' Taxotere (docetaxel) in 1996, a new class of cancer treatment was established, with these drugs being progressively approved for a number of cancers. Sales for both drugs have been significant (see table - next page), although loss of patent protection, the issue of drug resistance, competition from new treatments and improved versions of taxane drugs has seen Taxol sales decline in recent years. However, these pressures have not stopped either BMS or Sanofi Aventis from developing new potentially more effective drug candidates in this class, especially to overcome drug resistance and to be less toxic.

How tubulin binding agents work

Tubulin is a protein that forms together (polymerises) with other tubulin proteins into microtubules. These microtubules are a key component of a cell's skeleton (cytoskeleton). However, microtubules have a number of other functions including controlling the formation of mitotic spindles, which are a machinery used in the process of cell division.

Tubulin binding agents can either interfere with the assembly, or the disassembly of microtubules. They may, such as Sanofi Aventis' AVE8062**, Oxigene**'s CA4 Prodrug and **Ziopharm Oncology**'s ZIO-301, inhibit polymerisation. On the other hand, the taxanes (paclitaxel, docetaxel) stabilise polymerisation (ie stop the de-polymerisation, or disassembly).

The compounds that inhibit polymerisation have been categorised as a subset, and termed *vascular disruption agents* (VDAs). When these compounds target the endothelium cells that line the blood vessels that feed tumours, the effect is to cause the cells to change shape from thin, flat and plate-like, to large and more rounded. As they balloon out, they restrict blood flow in the tumour, resulting in necrosis or cell death, and then tumour decrease or elimination.

Compounds in development

There are at least 25 tubulin class compounds in development (see table next page), including next generation taxoid class drugs and several VDAs. **Sanofi Aventis** has an extensive interest in the area, with at least six compounds in clinical and preclinical development. Of the smaller companies with more than one compound in development, **Cytokinetics** differentiates itself by developing compounds that target a protein which is active only when cells are proliferating, and not tubulin directly. This may mean its compounds are more selective than others. Cytokinetics has partnered with **GlaxoSmithKline**. The two other small companies with multiple compounds in development are **Oxigene** and **Entremed.** A table listing the capitalisations of several of these smaller US listed companies can be found on page 4.

Two Australian listed companies developing VDAs are **Bionomics** and **Cytopia**.

Bionomics' BNC105

Bionomics (BNO: $0.22), through its acquisition of Iliad Pharmaceuticals, obtained a chemistry platform and set of potential VDA leads. One of these, BNC105, is set to enter a Phase I/II trial in 2007. The company believes that BNC105 may be able to deliver competitive outcomes against similar VDAs because it takes advantage of the active (versus quiescent) state of endothelial cells. The company has reported that in *in vitro* studies, BNC105 has a 20 fold better therapeutic window than Oxigene's CA4P. Bionomics theory is that BNC105 may have a superior therapeutic window because it is more active against more of the 20 or so different sub-forms of tubulin.

A critical milestone for Bionomics' BNC105 will be its completion of preclinical toxicology studies due in the March quarter 2007. If these studies are successful then the compound will be set for a keenly observed Phase I/II trial.

Bionomics is capitalised at $42 million and held cash resources of $5.6 million at September 30.

Bioshares recommendation: **Speculative Buy Class A**

Cytopia's CYT997

Cytopia (CYT: $0.69) has been slowly completing a Phase I trial of its VDA CYT997 (intravenous administration), with the objective to find the maximum tolerated dose (MTD). Since July 2005, twenty-one patients have been enrolled to date in 9 cohorts. However, an MTD has not been established, with the dose administered to the last cohort, 20 times that given to the first. Cytopia believes that it is not far off reaching the MTD, with the eighth cohort dose similar to the lowest equivalent MTD recorded in rat and dog studies. Cytopia also intends to undertake a Phase I study of CYT997 administered orally.

This week Cytopia announced a second lead cancer drug candidate, CYT645, that inhibits the cFMS kinase. Unlike CYT997 which disrupts tumour blood vessels, CYT645 has a role in stopping the spread of cancer cells (metastasis). The company expects preclinical studies to be completed in twelve months, with CYT645 anticipated to commence a Phase I trial early in 2008.

Cytopia is capitalised at $51 million, held cash resources of $19 million at June 30. It currently employs 50 people.

Bioshares recommendation: **Speculative Buy Class A**

Selected Tubulin Class Inhibitors In Development

Company	Compound	Target/MOA	Phase	Comments
Aeterna Zentaris	ZEN-012	tubulin; topisomerase	Pre-clinical	Binds to colchicine binding domain
Bionomics	BNC105	tubulin	Pre-clinical	
Bristol Myers Squibb	ixabepilone (BMS-247550)	tubulin	Phase II, Phase III	epothilone B analogue; taxane-sensitive and resistant tumor models.
Cougar Biotechnology	CB-3304 (noscarpine)	tubulin	Phase I/II	Dev. analogues of CB3304
Cytokinetics	Ispinesib (SB-715992)	kinesin spindle protein	Phase II (x3) Phase Ib Combo (x3)	Appears to only inhibit cells that are proliferating
	SB-743921	kinesin spindle protein	Phase I/II	
Cytopia	CYT997	tubulin	Phase I	
Eisai	E7389	tubulin	Phase II	Halichondran B analog.
Entremed	ENMD-1420	tubulin (also TNF-alpha)	Pre-clinical	Prev. Celgene's CC-5079
	Panzem NCD (2ME2)	inhibits angiogenesis, micro-tubule formation,HIF-1 alpha	Phase II (x2) Phase I	Binds to colchicine binding domain
	ENMD-1198	inhibits angiogenesis, micro-tubule formation,HIF-1 alpha	Phase I	
Epicept	EPC2407	tubulin	Pre-clinical	Binds to colchicine binding domain
MediciNova	MN-029	tubulin	Phase I	Acq. from Angiogene
Myriad Genetics	MPC-6827 (Azixa)	tubulin	Phase I (x2)	potential overcome drug resistance
Oxigene	CA4 Prodrug (combretastatin)	tubulin	Phase III (Comb.) Phase II (x 3) (Mono & Comb) Phase I/II (x3) Phase I (x2)	Derived from *combetreum cafrum* tree
	OXi4503	tubulin (also cytotoxic effect)	Phase I/II	
Sanofi-Aventis	XRP9881	tubulin	Phase III	Next Gen. Taxoid
	XRP6258	tubulin	Phase IIa	Next Gen. Taxoid
	AVE8062	tubulin	Phase I	Combretastatin derivative (water soluble)
	SSR 250411	Antimitotic agent	Pre-clinical	
	SSR 97225	Antimitotic agent	Pre-clinical	
	SAR3419	tubulin	Pre-clinical	DM4 coupled to anti-CD19 Mab
Tapestry Pharmaceuticals	TPI-287	tubulin	Phase I	3rd gen. Taxane but potential overcome drug resistance
Wyeth	TTI-237	tubulin	Phase I	Intravenous admin
Ziopharm Oncology	ZIO-301	tubulin	Phase I/II	oral and nano-suspension

Source: Company websites, announcements and filings

Sales of Taxol (BMS) and Taxotere (Sanofi Aventis)

Year	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Taxol (paclitaxel) $US M	$1,206	$1,481	$1,592	$934	$857	$934	$991	$747
% change		23%	7%	-41%	-8%	9%	6%	-25%
Taxotere (docetaxel) Euros M	€ 380	€ 500	€ 744	€ 1,003	€ 1,261	€ 1,362	€ 1,426	€ 1,609
% change		32%	49%	35%	26%	8%	5%	13%

– from Page 1

The **Orbis** investment group, which entered the sector rapidly and significantly last year, is now holding local biotech investments in excess of $117 million. Of interest is that the company has been increasing its stake in **Alchemia** and **Acrux** in recent weeks. Also of interest is the activity of the US hedge fund **SAC Capital**, which has increased its holding in **Progen Industries** recently and now owns almost 7% of the company.

As the Australian biotech sector moves into a more bouyant phase of its apparent cyclical four year investment cycle, experienced international investors and local venture capital companies have been acquiring local biotech assets, signaling a positive trend for the Australian biotech sector.

Specific International Investments

Fund	Investments	Current value of investment
Orbis Group	Pharmaxis	$61.5 million
	Acrux	$17.4 million
	Alchemia	$15.5 million
	Phosphagenics	$14.6 million
	Peplin	$8 million
Nordic Biotech*	Privida	$33 million
SAC	Progen Holdings	$10.4 million

**Proposed investment*

Selected 'Tubulin Class' Small Cap Companies

Company	Code	Cap'n (US$ M)
Cytokinetics	CYTK	$285
Aeterna Zentaris	AEZS	$276
Entremed	ENMD	$156
Oxigene	OXGN	$111
Ziopharm Oncology	ZIOP	$80
Epicept	EPCT	$38
Tapestry Pharmaceuticals	TPPH	$36

Incitive Delivers Positive Initial Preclinical Result

Incitive (ICV: 15.5 cents) is one of only four biotechs to list on the ASX this year. It is an early stage R&D company specialising in diseases characterized by inflammation, autoimmune attack and organ transplant rejection. This week the company announced a significant milestone in one of its preclinical programs ahead of an anticipated busy 12-month period for the company.

The company's first program is investigating purified extracts from pineapple stems, specifically an extract termed bromelain. The lead compound identified, named ICV0019, has recently returned some positive results in mouse studies, showing that ICV0019 was able to suppress the immune system as measured by suppression of cytokine response, in an immune stimulated mouse model, compared to the use of the raw bromelain extract. The results suggest some early evidence that the lead compound may be a potential therapeutic candidate in autoimmune disease applications.

This is the first time that ICV0019 had been tested in an animal model and the company was surprised by the level of efficacy at low doses of the enzyme.

This announcement follows on from successfully manufacturing the same enzyme through recombinant means in July this year. Milestones for 2007 include the completion of animal studies in disease models in the first half of the year, followed by safety/toxicology studies in the second half of the year. The company is seeking to be in a position to out-license the lead compound/compounds in 2008.

Whilst ICV0019 works by modulating T-cells, the company's second program, of which it owns 60%, seeks to block the action of perforin which is produced by T-cells. Animal data with several inhibitors of perforin is expected by be generated beginning the first quarter of next year.

Incitive is capitalised at $6.3 million with $2.6 million in cash. The company is developing therapeutics for significant markets, and its business model initially is to out-license its programs once a positive preclinical data and package can be generated. The company is also considering M&A opportunities.

Bioshares recommendation: **Speculative Buy Class C**

Pharmaxis Releases Phase III Aridol Results

Pharmaxis (PXS: $3.12) reported the results this week from its Phase III Aridol study in the US which involved 501 people. The results showed that Aridol was as effective as an existing product in the US, methacholine, in diagnosing asthma, and was shown to be safer than methacholine. The result requires some explanation and needs to be put in some context.

Aridol was shown to identify 58% of patients with mild symptoms of asthma (compared to 54% with methacholine) and was 66% specific (proportion of healthy patients who were correctly diagnosed) compared to 70% for methacholine.

The trial was structured in accordance with dialogue with the FDA, as a direct comparison with an existing product. The patients were deemed to have asthma if they had exercise-induced bronchorestriction. The trial design was not perfect as not all patients with asthma experience exercise-induced bronchorestriction (or a narrowing of the airways). The trial showed only a 70% repeatability which confirms the less than ideal nature of the trial design.

Seek to file, Q2 2007

Pharmaxis will now meet with the FDA to discuss the trial result and pending a positive meeting, will seek to file the drug/diagnostic for approval in the second quarter of 2007.

The approach the company is taking is to gain approval for Aridol in the US as an asthma diagnostic, competing directly with the existing product methacholine. It's expected that further physician-sponsored trials will look at how Aridol performs as an asthma management tool, and will presumably seek to expand the label for Aridol use in the US.

This trial differed from the Australian and European trial (from which the product has since gained approval) which involved patients who had been diagnosed with asthma by an expert physician, rather than an exercise-induced bronchorestriction test. It was compared with hypertonic saline, which is the existing product used in those regions (methacholine is used in the US). In that trial, Aridol was 95% specific compared to expert diagnosis and 91% sensitive (ability to detect disease when present).

Diagnose and manage asthma

The different studies reflect the differences in products and procedures in diagnosing and managing asthma in those regions. Aridol is a tool not only to diagnose asthma, but more importantly a tool by which to manage treatment of the disease. Ideally the drug/diagnostic will be used to manage the level of medications such as corticosteroids. Long term use of corticosteroids should reduce the airway inflammation in response to delivery of the Aridol powder and over the long term this dosage level needs to be corrected for optimum dosing to limit the level of administration.

Whilst the result from the US was mixed, there was a clearly positive development this week for the Aridol product with endorsement by two major asthma networks, the **Global Initiative for Asthma** and the **National Asthma Council of Australia,** as a lung function test to diagnose and manage the disease.

Pharmaxis remains an excellent core investment in a portfolio oriented to a long term return. The company is now capitalised at $552 million and we place a **Speculative Hold Class A** recommendation on the stock although investors may want to capture some of the stocks strong gain in recent weeks.

Bioshares

The Bioshares 20 Index	
Change from June 30, 2005	**-3.1%**
Change from June 30, 2006	**16.2%**
Change - week ago	**-0.9%**
Nasdaq Biotech Index	
Change from June 30, 2005	**21.2%**
Change from June 30, 2006	**12.7%**
Change - week ago	**2.3%**

Bioshares Model Portfolio (17 November 2006)

Company	Price (current)	Price added to portfolio
Acrux	$0.85	$0.83
Alchemia	$0.74	$0.67
Avexa	$0.25	$0.15
Bionomics	$0.22	$0.210
Biosignal	$0.17	$0.22
Cogstate	$0.19	$0.18
Cytopia	$0.69	$0.46
Chemgenex Pharma.	$0.61	$0.38
Evogenix	$0.60	$0.47
Optiscan Imaging	$0.48	$0.35
Mesoblast	$1.75	$1.27
Metabolic Pharmaceuticals	$0.705	$0.53
Neuren Pharmaceuticals	$0.41	$0.70
Peptech	$1.23	$1.31
Prima Biomed	$0.055	$0.09
Progen Industries	$3.65	$3.40
Sirtex Medical	$2.95	$1.95
Sunshine Heart	$0.18	$0.19

Portfolio changes

We will take some profits and remove Pharmaxis from the portfolio at $3.12

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, Neuren Pharmaceuticals, Pharmaxis, NeuroDiscovery, Prima Biomed, Biotech Capital, Cygenics, Psivida, Cytopia, Biodiem, Peptech, Starpharma Holdings, Cogstate, Xceed Biotechnology, Healthlinx, Incitive, Optiscan Imaging, Bionomics, Chemgenex Pharmaceuticals

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