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In this edition...
M&A is starting to become a central issue for the global biotech and pharmaceutical industry. Japanese pharma is escalating its advance on the international pharmaceutical sector, this week announcing a bid of up to US$4.6 billion for the Indian generics business Ranbaxy. The last 12 months has seen frenetic M&A activity for international assets by Japanese Pharma. There are likely to be implications for Australian biotech which has links with Japan on several fronts.
We cover the leading developments at ASCO this year. We look at Peplin's plans to acquire a private US biotech business. And we update readers on NeuroDiscovery, which is approaching significant milestones.

The editors
Companies covered: ACL, CYT, NDL, PEP

	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)	-9%
Cumulative Gain	**90%**
Av Annual Gain (7 yrs)	**17.8%**

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Bioshares

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

ASCO 2008 – Progress in Lung Cancer Treatments

The annual meeting of the American Society of Clinical Oncologists was held recently (May 30 - June 3, 2008) in Chicago. The meeting is an important event on both oncologists' and investors' calendars because of the volume and scope of clinical research results that are presented. More than 30,000 people attend and several thousand abstracts are published.

Many biotech companies developing cancer treatments or related technologies, through their clinical investigators, present the results of trials. The focus on this conference means that good results can become more widely known and discussed. In fact the last great catalyst the biotech sector received was the release of trial data in 2003 for **Genentech's** anti- VEFGR monoclonal antibody Avastin (bevacizumab), which in combination therapy was shown to be significantly superior to the control arm.

ASCO 2008 Highlights

So what were the highlights of ASCO 2008? Perhaps the leading story was in connection to cetuximab (Erbitux), a monoclonal antibody developed by **Imclone Systems** and marketed in North America by Imclone and **Bristol Myers Squibb**, and in Europe by **Merck KgaA**.

Cetuximab binds to the EGF (epithelial growth factor) receptor and shuts down cancer cell growth and induces cell death. A rival to cetuximab is Amgen's panitumumab (Vectibix), which also targets EGFR. Cetuximab is an IgG1 mab whereas panitumumab is an IgG2 mab.

Cetuximab was approved in February 2004 by the FDA for the treatment, in combination with irinotecan, of EGFR expressing metastatic colorectal cancer (mCRC) where irinotecan-alone treatment had failed. It was also approved as a single agent treatment for EGF- expressing mCRC for patients intolerant to irinotecan.

However, a study led by principal investigator Dr Robert Pirker of the Medical University of Austria suggests that cetuximab may be beneficial as a treatment for patients diagnosed with non-small cell lung cancer (NSCLC). NSCLC accounts for 80% of lung cancers and 80% of NSCLC express EGFR. Current standard of care for lung cancer is the administration of a platinum based drug such as carboplatin or cisplatin in combination another chemotherapeutic such as gemcitabine or paclitaxel. These regimes deliver a one-year survival rate of 35%-40%

Cont'd over

The Phase III study in NSCLC compared cetuximab in combination with established chemotherapy drugs cisplatin and vinorelbine (CV) versus CV alone. The study evaluated 1125 patients, with 557 receiving cetuximab and CV (Arm A) and 568 in the CV alone arm (Arm B).

A statistically significant median one year survival of 11.3 months in the cetuximab arm against 10.1 months in Arm B was reported (p=0.044). The one-year survival rate was 47% in the cetuximab arm versus chemotherapy alone (42%). On the down side, levels of febrile neutropenia were higher in the cetuximab arm (22%) compared to the chemotherapy arm (15%), which Dr Thomas Lynch from the Massachusetts General Hospital said "was unacceptably high for a first-line therapy". Higher frequencies of acne-like rash, diarrhoea and infusion related reactions were also reported. Readers may recall that **Progen Pharmaceuticals'** Phase II trial of PI-88 in prostate cancer patients recorded a 27% incidence of febrile neutropenia.

The study is worth noting because it is one of two trials to demonstrate a survival benefit of a targeted antibody in combination with platinum based chemotherapy in advanced NSC lung cancer. A trial of bevacizumab (Avastin) in combination with carboplatin and paclitaxel (BCP) has also shown a benefit: one year survival of 12.3 months for BCP v 10.3 months in the CP arm; however alarming bleeding events were reported for this trial - 7 fatal. Up until now there have been 15 Phase III trials in more than 12,000 patients that have evaluated combinations of new agents such as monoclonal antibodies in conjunction with chemotherapy, with no overall increase in survival obtained.

The KRAS marker

Another element of cetuximab treatment is that the antibody is only active in a segment of patients. Dr Eric Van Cutsem of the University Hospital, Gasthuisberg, Belgium, revealed that post-hoc tumour analysis of patients with colorectal tumours that expressed the normal version of protein called KRAS showed a improved response when administered cetuximab as a first line treatment.

Patients that tested positive for the normal KRAS marker recorded one-year progression free survival rates of 43% when administered cetuximab and the FOLFIRI regime (fluorocil, leucovorin, irinotecan) versus 25% for the FOLFIRI regime alone. Median survival rates were 9.9 months versus 8.7 months respectively (p= 0.017). There was no difference in PFS for KRAS negative patients in either arms.

KRAS now appears to be valid marker for categorising metastatic colorectal cancer patients according to likelihood of benefit of treatment by the EGFR targeted antibodies, panitumumab and cetuximab. A logical extension of the Van Cutsem study would be the analysis of the Pirker study using the same marker.

Adverse event profiles

As previously mentioned the adverse event profiles of cetuximab and bevacizumab are not without some serious issues. Another session at ASCO discussed the side effect of targeted therapies (presumably both antibody and small molecule), including side effects specific to the emerging treatments. These side effects include an interstitial-like lung disease, pleural effusions, increases in pancreatic enzymes and elevation of tryglyscerides. Established chemotherapeutics are noted for side effects that include nausea, vomiting, and reduction in platelets and white blood cells.

In the case of new targeted therapies, a bevy of cardiovascular side effects appear to be emerging, including hypertension, coronary syndromes and left ventricle dysfunction and QTc prolongation. According to the ASCO presenter who highlighted these issues, Dr Remick, these side effects are presenting at a time when the population is aging and which is experiencing increased cardiovascular health issues.

Australian companies

Several Australian companies submitted abstracts to ASCO, including **Cytopia** and **Novogen**. A conclusion of Cytopia's Phase I dose finding study of CYT997, a vascular disrupting agent (VDA), was a maximum tolerated dose of 202mg/m^2 . This was recommended as the Phase II dose. Amongst other maximum doses of VDAs discussed at the conference, **Oxigene's** OXi4503 (CA4P) was well tolerated up to a dose of 11mg/m^2, the maximum tolerated dose of Epicepts EPC2407 was 13 mg/m^2, and **Nereus Pharmaceuticals** NPI-2538 recommended Phase II dose was 30 mg/m^2. Oxigene also reported the results of a dosing trial of CA4P in combination with bevacizumab. The recommended Phase II doses were 63mg/m^2 for CA4P and 10mg/kg for bevacizumab. What the dosing figures for competitor drug candidates suggest for CYT997 is that it has a wide therapeutic window i.e. a dosing profile as much as 20 times greater than its rivals, and hence one with more benefits. It is also a dosing profile which is more comparable to the taxane drug, paclitaxel, which is dosed above 200 mg/m^2.

Summary

Several themes stand out from studying the presentations delivered at ASCO. There continues to be an enormous number of studies reported that involve the tubulin disruptors (e.g. docetaxel, paclitaxel) and DNA alkylating agents (e.g cisplatin). However, headway continues to be made with new drugs, but more often in combination with established drugs.

The defining long-term trend in cancer is the continued categorisation of cancers into many more sub-groups, as defined by biomarkers as and when they emerge and are validated. What follows from this is that there will be an increasing demand for the facilities and services that offer and process tests.

Another theme is that new drug classes invariably bring with them new side-effect issues. Some of these class related side effect issues may emerge only after new cancer medicines i.e. targeted therapies, have become widely used, with the consequence that seemingly effective drugs have restrictions imposed on their use.

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Peplin Makes Acquisition and Withdraws US IPO

As uncertainty in financial markets prevails, the negative impact on drug development companies continues to be felt. In the first quarter of this year, only $40 million was raised, compared to an average of $235 million a quarter in 2007, although the current quarter should offer some improvement.

Neosil acquisition

Peplin (PLI: 40 cents) this week announced it would acquire an early-stage, private drug discovery company also operating in the dermatology field, called **Neosil**. Whilst the acquisition is a good fit for the company, beefing up Peplin's development pipeline, the reason behind the move at this stage was largely to access that company's cash of $6.7 million, which is the same as the acquisition price. Peplin will pay for the company with Peplin shares.

Perhaps not surprising is that investors in Neosil include **MPM Capital**, which is also a substantial investor in Peplin (although not the same fund within MPM). Other investors in Neosil include **Burrill & Company**. Neosil raised $32 million in 2004 in a Series A funding round. The acquisition would suit MPM as it places the Neosil programs in a safe holding position until capital markets improve, and it gives Peplin some further funding. Including the funds from Neosil and the US$15 million loan facility, we estimate Peplin has access to approximately $30 million in funding.

Neosil has two early clinical programs. The first is a treatment for hair loss and the second broad spectrum antimicrobial for the treatment of acne. On the completion of the acquisition, existing Neosil shareholders will own 7.3% of Peplin.

The perilous nature of equity markets at the moment are causing biotech companies, that by nature require continuous access to funding whilst their businesses are being built, to be heavily discounted. Peplin is a quality biotech company and the main risk remains funding.

The company has withdrawn its plans to list in the US and raise up to $75 million in the process, due to the current financial conditions.

Final testing protocol for PEP005

Peplin also announced this week that it had received a Special Protocol Assessment for its Phase III trial from the FDA which brings with it some surety over the final stage of its clinical trial process. To bring PEP005 to market, the company will need to conduct three further trials. These are:

– A 250-person Phase III trial for the treatment of actinic keratosis (AK) on non-head lesions (dose 0.05%)
– A 250-person Phase III trial for the treatment of AK on the head and neck
– An open label safety study, in approximately 200 people, to reach the set level of patient usage on this New Chemical Entity.

The company is currently completing a dose ranging study for the head and neck AK trial which will govern the dose for the Phase III trial above (either 0.005%, 0.0010% or 0.015% of active ingredient). The trials are not difficult to conduct nor does in take long to recruit patients, having recruited 100 patients per month for previous AK trials.

Peplin currently has funding to conduct complete the dose ranging Phase II study, the first Phase III study and the safety study. However, it will need to raise further funding to complete the second Phase III study for head and neck AK. By removing its IPO registration, the company is now in a position to raise further funds in alternative means, which it was unable to so with its IPO filing in place.

The capital markets are taking their toll on many biotechs. Peplin has the backing now of two major VCs and we are confident the company will secure sufficient funding for its product to reach the market. However the state of capital markets moving forward will dictate how dilutive that process will be.

Bioshares recommendation: **Speculative Hold Class A**

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Japanese Pharma Goes Shopping – Part II

Two weeks ago we looked at the increasing interest from Japan in the international pharmaceutical industry. This was triggered by an announcement in April this year that **Takeda** would acquire **Millennium Pharmaceuticals** in the US for US$8.8 billion in cash. This followed on from the US$3.9 billion acquisition by **Eisai** of **MGI Pharma** in December last year and a number of smaller acquisitions and several major in-licensing deals.

This interest is starting to appear like a full assault with an announcement this week that **Daiichi Sankyo** made a bid of up US$4.6 billion for a majority stake in the Indian generics group, **Ranbaxy Laboratories**. There is a suggestion that **Pfizer** might enter a bidding war for Ranbaxy.

There are signs that the US dominance of the global pharmaceutical industry is beginning to lose hold. A weaker US currency has seen an escalating number of US acquisitions by foreign companies in pharmaceutical and biotech industries.

Several Australian biotech companies have collaborations/partnerships with Japanese biotech and pharmaceutical groups. These include **Biota Holdings** (with Daiichi Sankyo), Patrys (with Takeda), **NeuroDiscovery** (with Sosei), **Arana Therapeutics** (with Kyowa Hakka) and **Optiscan Imaging** (with Hoya-Pentax). Some of these companies, particularly Biota Holdings, Arana Therapeutics and Optiscan Imaging, may well become takeover targets amidst the shifting sands of the global pharmaceutical business.

Stock Updates

NeuroDiscovery – Milestones approach

NeuroDiscovery (NDL: 10 cents) is approaching a period in which key data expected to be released. This includes results from two Phase II studies with its natural product candidate, NSL-101. The studies involve dental applications, one for reduction of pain following wisdom tooth extraction, going up against Lidocaine, and the second for patients being treated for gum disease (periodontitis). Positive results will put the company in a position to license out the technology.

The company is also conducting a Phase I multiple ascending dose study with NSL-043. This drug candidate is a key asset for the company. The compound is being developed for the treatment of neuropathic pain.

There are a number of points to be remembered about this program. There have been very few advances in the treatment of neuropathic pain in the last 20 years, other than the somewhat serendipitous discovery that the drug gabapentin for epilepsy also works in 30%-50% of people suffering this pain condition. It's a billion dollar market and any compound with a hint of efficacy should draw fierce interest from major pharmaceutical groups.

NSL-043 has previously been in late stage clinical trials for an anti-inflammatory condition but failed to achieve efficacy. There is a belief this drug may work in neurpathic pain, with a battery of preclinical testing showing the drug is a very encouraging drug candidate. This and the clinical experience with this drug is the basis for the strong interest in this program from NeuroDiscovery and Sosei, who jointly share the rights to the compound.

The Phase I multiple ascending trial is looking at drug doses ten times the level dosed in the previous anti-inflammatory trials, suggesting a potential wide therapeutic window. These results are expected after the end of the current quarter. Whilst the trial is looking only at safety and finding the maximum tolerable dose, any signs of early efficacy may give the companies an option of conducting even a Phase I licensing deal.

A Phase IIa trial with NSL-043 is expected to begin in the second half of this year and be completed by around mid 2009. Positive results in that trial could see a significant licensing deal involving a large up from payment and large milestone payments. For billion dollar markets such as neuropathic pain, there is a tendency to load the deal more towards the front (up front and milestone payments) with lower (small single digit) royalties from sales.

NeuroDiscovery is capitalised at only $5.7 million with $2.4 million in cash at the end of March this year. The company also has a service business that has high level expertise in conducting electrophysiology testing in neuropathic pain for the pharmaceutical industry. This business is profitable and generates annual sales in the order of $2 million and growing at around 25% a year. NeuroDiscovery recently appointed the former **GlaxoSmithKline** worldwide head of pain research, Iain Chessell, as its CEO.

Bioshares recommendation: **Speculative Buy Class A**

Alchemia – Still awaiting major milestone

Data emerged this week that showed Arixtra sales for the month of April returned to similar levels two months earlier of US$12.8 million. This follows a surge in Arixtra sales in March to just over US$20 million following heparin safety concerns. Alchemia is developing a generic to the synthetic heparin drug Arixtra. We place a **Speculative Hold Class A** on the stock until the company's partner, **Dr Reddy's**, files an Abbreviated New Drug Application with the FDA, which we have been expecting to occur by mid-2008.

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Bioshares Model Portfolio (13 June 2008)

Company	Price (current)	Price added to portfolio	Date added
Cellestis	$2.61	$2.27	April 2008
IDT	$2.05	$1.90	March 2008
Circadian Technologies	$0.93	$1.03	February 2008
Patrys	$0.27	$0.50	December 2007
NeuroDiscovery	$0.10	$0.16	December 2007
Bionomics	$0.32	$0.42	December 2007
Cogstate	$0.11	$0.13	November 2007
Sirtex Medical	$3.50	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.35	$0.66	September 2007
Starpharma Holdings	$0.32	$0.37	August 2007
Pharmaxis	$1.51	$3.15	August 2007
Universal Biosensors	$0.88	$1.23	June 2007
Biota Holdings	$0.93	$1.55	March 2007
Probiotec	$1.24	$1.12	February 2007
Peplin Inc	$0.40	$0.83	January 2007
Arana Therapeutics	$1.15	$1.31	October 2006
Chemgenex Pharma.	$1.00	$0.38	June 2006
Cytopia	$0.22	$0.46	June 2005
Optiscan Imaging	$0.19	$0.35	March 2005
Acrux	$0.93	$0.83	November 2004
Alchemia	$0.40	$0.67	May 2004

Portfolio Changes – 13 June 2008

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, 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

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