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Bioshares

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

In this edition...
While a number of biotech stocks are doomed to be investment failures, others, especially those building businesses in the biologics (proteins and peptides) space appear to be almost guaranteed investment winners. The proviso is that they have a platform technology or similar assets locked away with good IP. Another international acquisition this week looks to have increased demand for biologics companies yet again.

We also initiate coverage on tissue engineering in company bioMD and introduce readers to a private company and potential IPO play in 2008, TGR Biosciences.
The editors
Companies covered: BOD, PTD, PYC, TGR Biosciences

	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)	-8.6%
Cumulative Gain	**198%**
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).

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BMS Acquires Adnexus; Demand for Biologics Companies Remains Strong

External events continue to play an important role in shaping the destiny of several Australian biotech companies, including Peptech (PTD: $1.24) and Phylogica (PYC: $0.28).

This week, **Bristol Myers Squibb** announced its intention to buy the US-based **Adnexus**, a privately-held biologics company for a net price of US$415 million. Adnexus is not an antibody company, but has been using a design engine to develop targeted drugs based on fragments of the common structural protein fibronectin.

5-fold return

Owners of Adnexus stand to gain up to US$75 million if certain development and regulatory milestones are met. Since it was founded in 2002, Adnexus has received around $76 million in funding, mainly from venture capital investors, who own about 85% of the company. Adnexus' investors look set to achieve in the vicinity of a 5-fold return on their investment. This is not dissimilar to the return **Peptech** made on its investment in **Domantis**, which was acquired late in 2006 by **GlaxoSmithKline** for US$453 million.

The parallels between Adnexus and Domantis are striking. Both had been developing a technology platform to generate small protein fragments that are a tenth to a fifteenth the size of an IgG antibody. Both offered a fresh patent position that could overcome incumbent antibody binding and antibody engineering patent estates. Both offered a class of compound that could potentially be more flexible in dosing and administration, and possibly cheaper to manufacture, but neither had validated their technology in proof-of-concept human trials.

Domantis (originally Diversys) was founded in 2000, whereas Adnexus was originally founded as **Compound Therapeutics** in 2002. However, Adnexus did acquire **Phylos**, the original creator of the core protein display technology called PROfusion, in 2004. Phylos was founded in 1997.

A steady flow of M&A

There has been steady flow of M&A in the global biologics space, with the Peptech merger with **Evogenix** one the of most recent. Another major acquisition for 2007 was **Eisai**'s acquisition of the US-based privately held **Morphotek** in March for US$325 million, net of cash. These transactions follow on from **AstraZeneca**'s purchase of **Cambridge Antibody Technologies** (US$1.3 billion), **Merck**'s purchase of **Abmaxis** (US$80 million) and **GlycoFi** (US$400 million) in 2006. And the early September announcement of a collaboration between **Boehringer Ingelheim** and **Ablynx**, covering its antibody-derived proteins, which also included an equity investment, may set the scene for another acquisition in the next year or so.

The ongoing demand for biologics companies with either novel proprietary platform technologies and/or novel protein engineering skills and/or protein drug development skills means that Peptech and Phylogica stand a very strong chance of being acquired by larger pharmaceutical firms in the medium term. Phylogica is similar to Adnexus in that it has a powerful dis-

Cont'd on page 5

BioMD Approaches Clinic with its ADAPT Tissue Engineering Technology

BioMD (BOD: 14 cents) listed on the ASX in 2004 to commercialise its safety syringe technologies (the POP safety injection needle and the prefilled safety syringe). The priority for the company now is the commercialisation of its tissue engineering technology. BioMD is seeking to license the prefilled safety syringe prototype to syringe manufacturers.

In November 2005, bioMD acquired its initial interest in a tissue engineering technology company, **Celxcel Pty Ltd**, which has developed the ADAPT tissue processing technology. The technology is due to be tested in clinical trials in South Africa for the repair of cardiac tissue repair. Biological tissue implants are generally accessed from bovine or porcine sources. However, the harsh chemical treatment to render the implanted tissue immunologically inactive results in reduced lifespan of the tissue. bioMD is seeking to extend the life span if implanted tissue with its ADAPT technology.

bioMD has increased its ownership of Celxcel to 76%. Over the last 12 months the company has delivered a number of positive preclinical data supporting its tissue engineering technology, culminating in the presentation of its results at a major heart valve disease conference earlier this year.

History of the ADAPT technology

One of the pioneers of the ADAPT tissue engineering technology is Celxcel's Chief Scientific Officer, Dr Leon Neethling. Neethling had worked on tissue engineering technologies in South Africa for approximately 10 years before moving to Australia to continue his work. Between 2000-2005 the final product development on the ADAPT process technology was completed with Celxcel being formed in 2001.

The standard process for treating implantable tissue from animal sources has involved the use of the chemical glutaraldehyde that allows crosslinking (stabilisation) of the tissue matrix. DNA is removed from the tissue prevent any immune responses and the end result is a neutral collagen matrix that can facilitate rejuvenated tissue repair.

However, the problems with using large volumes of glutaraldehyde are its cytotoxic properties and the increased level and rate of calcification of the implanted tissue that reduces the elasticity and lifespan of the tissue.

The ADAPT tissue treatment process reduces the amount of glutaraldehyde used by around 90% and preclinical results have shown the not only does the process reduce calcification (and hence stiffening) of the tissue, but provides suitable environment within the collagen matrix that allows tissue rejuvenation, including the migration of fibroblasts and even capillary formation in transplanted tissue.

Results from preclinical studies

Study I

Over the last year, BioMD (Celxcel) has generated several positive preclinical data using the ADAPT process. In March, the company reported data from a preclinical study in 45 young rats (15 in each group), where a bovine pericardial (the tissue cavity that surrounds the heart) was treated with the ADAPT process and compared with the two commercially available bovine pericardial tissue patches. The patches were implanted subcutaneously for 200 days.

The results showed that two commercially available patches became densely fibrotic after 200 days with one showing only limited fibroblast infiltration into the patch and the second patch degenerated showing signs of inflammation.

In contrast, the ADAPT treated patches were free from any dense fibrotic tissue and showed signs of capillary formation with red blood cells circulating in the patches. There was also formation of

Cont'd over

Biological versus Mechanical Heart Valves

Mechanical and biological heart valves were first developed in the 1960s. Mechanical heart valves generate global sales in the order of US$1 billion a year. While these types of valves have been more popular in the past, making up as much as 80% of the total valve replacement market, today biological heart valve implants from pigs, cows or donated human valves such as the one received by Opposition Leader Kevin Rudd, are approaching 60% market share and growing at 11% compared to the near stagnant growth of mechanical valves. BioMD is targeting the treatment of porcine and bovine heart valves. Over 170,000 valve replacement procedures are conducted worldwide every year.

Whilst mechanical valves should last the life of the patient and biological valves last only 10 -15 years, there are downsides to the mechanical valves. These include the requirement to receive continued anticoagulant therapy with regular monitoring of blood properties; the audible noise of the mechanical device; and the risk of excessive bleeding from a major injury.

Opposition Leader Kevin Rudd: Recipient of a donated human heart valve

fat tissue within these patches which was also a positive sign of tissue rejuvenation. Some of the rats within this study were followed for a full 12 months where the positive remodelling properties in the ADAPT treated tissue were maintained.

Study II
In this trial, 14 implants of ADAPT treated kangaroo pericardial tissue and ADAPT treated bovine pericardial tissue were implanted into sheep, into the jugular vein to form a vascular roof. The aim was to investigate the possible use of these tissue implants for possible use in heart valve leaflets.

The results were very successful, showing no calcification after 200 days and the presence of fibroblast cells with evidence of endothelial cell and capillary formation.

In the same trial, positive results were also obtained in three implants of ADAPT treated kangaroo carotid artery grafts indicating the potential to use this tissue and process in heart bypass surgery. Kangaroo tissue has appealing qualities because of the animals have almost no cholesterol, where in comparison pigs have a high cholesterol level.

Forthcoming clinical trial

These positive preclinical results have paved the way for a 50 person clinical trial to be conducted at the Universitas Hospital in Bloemfontein, South Africa. Unconditional ethics approval from the hospital has been received. The trial is anticipated to start early next year. It should take about six months to recruit the patients and the patients will be followed for 12 months after the procedure. Final results can be expected by the end of 2009 if the trial runs to schedule.

The patients to be recruited will be young adults who have a congenital heart defect, being either a hole in an internal wall of the heart or to reconstruct deformities in the aorta. The patients will receive an ADAPT treated bovine patch. Bovine pericardial tissue is used because it is the right thickness (about 0.7mm) and also is consistent in thickness. South Africa has been selected because of the high rate of congenital heart defects. Celxcel's CSO, Leon Neethling also has strong ties to the teaching hospital where the trial is to be conducted, having previously worked at the university and maintains a position as a visiting professor to the university. He is employed by the company for four days a week at the University of Western Australia. Commencement and completion of the trial will be major milestones for the company.

The implant material will be sourced from local (WA) bovine pericardial tissue. It will be treated at a third party GMP manufacturing facility although that site has yet to be confirmed.

Applications of the technology

The company is looking to develop the ADAPT technology for five distinct areas of use. Its aim is to outlicense the process to different commercial parties. The five commercial applications selected are:

- Cardiovascular repair, which is to be investigated in the forthcoming clinical trial
- Treatment of biological heart valves
- Repair of the abdominal wall, such as repairs to the pelvic floor or hernia
- Orthopedics, for repair of ligaments or rotator cuffs in joints
- Plastic surgery, as a dermal filler that will regenerate into living host tissue or for use in mastectomy reconstruction

Over the next 12 months, the objective is to secure at least one and potentially two licensing deals.

Risks

Patents
BioMD's patent position over its subsidiary's ADAPT technology has not been secured in major regions. A patent has been granted in Australia and an international patent application has been lodged. However, the ADAPT tissue treatment process is one of five processes that makes up the technology and some of the other processes will be maintained as trade secrets.

Copycats
The company's commercial model is to outlicense the technology to different parties for separate uses. However, being a processing technology, it may be difficult to ensure this technology is used by only licensed parties.

Funding
At June 30, the company had cash assets of $2.1 million. The company's loss for the previous year was also $2.1 million. With clinical trials due to begin in coming months, bioMD will likely need to raise further funds in this time.

Competition
There are competing process technologies that can reduce calcification in implanted tissue. BioMD will need to prove its process results in material that is superior to current available treated material. Preclinical results to date support the development of the ADAPT technology.

Summary

BioMD through its investment in tissue engineering company Celxcel is moving towards major milestones in clinical trials in coming months. The last 12 months has generated very positive preclinical data that supports the decision to progress to the clinical phase of development. The market for biological implant patches is valued in excess of $1 billion a year and the growing popularity of biological heart valves is certain to sustain interest in improvements that can emanate from tissue processing technologies.

The company is current capitalised at $12 million

Bioshares recommendation: **Speculative Buy Class B**

Private Company Profile – TGR Biosciences Pty Ltd

On occasion *Bioshares* reports on private companies that have indicated that at some stage they will seek a listing on the ASX, if not some other exchange. One company in this category is **TGR Biosciences**, which is based in Adelaide.

TGR Biosciences has flagged its intention to seek an IPO in mid-2008. However, such an action is contingent on the company successfully achieving several milestones and also securing funding through a pre-IPO round by December, 2007. A list of other potential IPOs can be found on the next page.

TGR Biosciences was founded in 2001 as a spin-out from the **CRC for Tissue Growth and Repair.** The firm employs 20 people.

Revenues for FY2007 were $2.5 million, level with the previous year's figure. Product and service income for FY 2006 was $1.5 million, up from $1 million in FY2005. Product and service income for FY 2007 has not been disclosed.

The TGR Biosciences Business

TGR Biosciences has two business units, one encompassing therapeutic product development, the other focused on the manufacture and sales of proprietary cell-based screening assays, marketed as the 'SureFire' assay kits and distributed by partner **Perkin Elmer.**

Products under development

Therapeutics

The company's lead therapeutic product candidate is Lactermin, a medical food treatment for oral mucositis (mouth ulcers), a side effect from chemo- and radio-therapy. Lactermin is a growth factor derived from milk and is currently in a Phase II trial. Recruitment is currently 50% complete. The company is also studying wound healing and dermal regeneration product possibilities.

'Surefire' Assay Kits

The company has now brought 14 'Surefire' assay kits to market and has secured a contract with a pharmaceutical company for the development of a further 20 kits.

Funding History and Outlook

TGR Biosciences has raised an estimated $9 million since its inception in 2002. The company has also been successful in obtaining government grants, including a $1.35 million Commercial Ready grant in the June quarter of 2006. TGR Biosciences is looking to raise approximately $5 million in a pre-IPO funding round.

Board and management

The MD and CEO of TGR Bioscience is Leanna Reed, with other board members being Bob Moses (Chair), John Bastian and Mike Hirshorn (Kestrel Capital).

Summary

TGR Biosciences is a well managed company with clear focus and it is supported by a solid board. The company has built a track record as an effective communicator. Should the company's lead product Lactermin obtain trial results sufficient to support marketing activities, then a worthwhile investment opportunity may became available through an IPO.

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Bioshares Model Portfolio (28 September 2007)

Company	Price (current)	Price added to portfolio
Acrux	$1.38	$0.83
Alchemia	$0.83	$0.67
Biota Holdings	$1.67	$1.55
Circadian Technologies	$1.23	$1.45
Clinuvel Pharmaceuticals	$0.45	$0.66
Cytopia	$0.55	$0.46
Chemgenex Pharma.	$1.05	$0.38
Optiscan Imaging	$0.40	$0.35
Peplin	$0.86	$0.83
Peptech	$1.24	$1.31
Pharmaxis	$4.05	$3.15
Phylogica	$0.28	$0.42
Probiotec	$1.20	$1.12
Progen Pharmaceuticals	$3.39	$3.52
Sirtex Medical	$3.95	$3.90
Starpharma Holdings	$0.32	$0.37
Sunshine Heart	$0.18	$0.19
Tissue Therapies	$0.49	$0.58
Universal Biosensors	$1.28	$1.23

Portfolio Changes – 28 Sept. 2007

IN:
No changes

OUT:
No changes

Pool of potential biotech floats
(in the next 12 months)
(revised and updated from **Bioshares** 192 - 10 Nov. 2006)

Possible IPOs	
Hatchtech	
Immune System Therapeutics (formerly Pacmab)	– likely
Continence Control Systems	
Mimetica	
Genera Biosystems	– likely
Cleveland Biosensors	
TGR Biosciences	– flagged mid - 08
Opal Therapeutics	
Ecobiotics	
CNS Bio	
Cryptopharma	
Kayban	
Vegenics	– strong possibility
Sienna Diagnostics	– flagged Q1 08
Sleep Diagnostics	– possible, 08
Mems-ID	
Underway/pending	
Impedimed	
Actinogen	
Oncaida	

– 'Biologics Transactions' , from page 1

covery engine with which to generate novel scaffolds. Peptech is a currently running the first clinical trial of a domain antibody compound (PN0621), but also possesses antibody humanisation and optimisation technologies. Triggers for such moves might include the generation of data from human clinical trials or highly validated preclinical studies.

Peptech is capitalised at $290 million, and retains an estimated $165 million in cash resources. Phylogica is capitalised at $40 million, with an estimated $7.5 million in cash assets.

Bioshares recommendations:
Peptech – **Speculative Buy Class A**
Phylogica – **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, Neuren Pharmaceuticals, Pharmaxis, NeuroDiscovery, Prima Biomed, 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, Halcygen Pharmaceuticals, Peplin, BioMD

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