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In this edition...
Validation for the field of oncolytic virotherapy took place this year when Amgen acquired Biovex, for a down-payment of US$425 million. Being well advanced in a Phase III trial no doubt set the attractive terms. Viralytics is one of a just a few companies in the same area. If it gets an IND agreed to by the FDA, it could see some significant value creation uphead.
Circadian has been honing its clinical development strategy for its anti-angiogenesis antibody VGX-100, influenced by opportunities to work in combination with the blockbuster antibody drug Avastin but also where Avastin has failed.
We also present six stocks capitalised at under $50 million with the potential to deliver alpha returns.
The Editors
Companies Covered: ACG, CGS, CIR, PABPYC, SHC, SOM, VLA

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 - May '09)	-7.3%
Year 9 (May '09 - May '10)	49.2%
Year 10 (May '10 - Current)	43.5%
Cumulative Gain	**316%**
Av Annual Gain (9 yrs)	**18.5%**

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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) 9329 3350
Email: info@bioshares.com.au

David Blake
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
Mark Pachacz
Ph:03 9348 9317
Email: pachacz@bioshares.com.au

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

Viralytics Waits for IND Greenlight

Viralytics (VLA: 5.1 cents) is developing a novel cancer therapy, called Cavatak, based on delivering a common virus (the cocksackivirus) at a very large dose directly into tumours, as well as systemically. The virus lyses (breaks apart) and kills the tumour cells. However a secondary, longer lasting effect stems from cellular material being presented to the immune system to power-up a longer-lasting immune response to the tumour cells. The cocksackivirus causes mild upper respiratory track infections.

Oncolytic viruses may be effective on tumours because tumour cells lack the defence mechanisms to deal with viruses, allowing oncolytic viruses to grow in, and disrupt, the tumour.

A potential benefit from using a relatively benign virus is that harsh side effects of traditional chemotherapies can be avoided or reduced.

Viralytics has completed a dose escalation Phase I study in patients with melanoma, showing that highest dose was tolerated, that five out of nine patients experienced reductions in tumour volume and that Cavatak was detected in three of five injected lesions at the end of the trial, despite neutralising antibodies being present.

It has a further two Phase I studies underway, one of which is evaluating the intravenous delivery of Cavatak in nine head and neck cancer patients and the other is evaluating the intratumoral delivery of Cavatak in nine patients with breast and prostate cancers and melanomas.

IND Questions Outstanding

The company held a pre-Investigational New Drug (IND) meeting with the FDA in 2009, which was followed by a face-to-face meeting in 2010.

Viralytics submitted its IND application to the FDA in November 2010. An IND filing includes detailed clinical protocol, manufacturing, pre-clinical and toxicology information. However, the FDA has asked Viralytics a set of further questions, which must be answered together. Once Viralytics has answered these questions, then once again the FDA has thirty days to accept the IND, or come back to the company with further questions.

– Cont'd over

The Phase II late stage melanoma trial Viralytics has planned for 63 patients will comprise four intra-tumoral injections over eight days (when antibodies to Cavatak have not been developed and where a systemic effect is possible) and then injections every twenty one days in the Cavatak-antibody-positive state, for a total of six cycles. In the second component, Viralytics anticipates continuing tumour destruction through viral replication and boosting the T-cell response.

The planned endpoint is disease control measured by immune related RECIST criteria which measures changes in tumour burden and kinetics over time. It should be noted that the protocol is still subject to FDA agreement.

The Biovex Acquisition

In January 2011, **Amgen** acquired privately held **Biovex** for a US$425 million up-front payment and contingent payments of $US575 million. This deal is the most significant commercial validation to date of the virotherapy approach. It follows the licensing of the privately held Jennerex's oncolytic virotherapy JX594 to French company **Transgene** in September 2010. Transgene acquired the European, CIS and Middle East rights for an upfront payment of an undisclosed milestone and a total potential payments of US$116 million, in addition to double digit royalties.

Until its acquisition, Biovex was the most clinically advanced of the four main companies in the oncolytic virotherapy field. Biovex was founded 1999. **Oncolytics Biotech**, which is capitalised at US$411 million, was founded in 1998, Viralytics (as Virotarg) in 2001 and **Jennerex** in 2006.

Biovex raised US$70 million in 2009 for a Phase III study (the second largest private raising of that year), aiming to enrol 430 patients in a controlled unblinded trial, in which patients would be randomised 2:1 in their investigational product (OncoVEX) to the comparator GM-CSF. The trial is not fully recruited with about 380 patients enrolled to date. The trial is being conducted under a Special Protocol Assessment with the FDA.

Success in this trial could be very positive for all the oncolytic virotherapy companies if it is successful in being approved by the FDA.

Leading Oncolytic Virotherapy Companies

	Biovex	Oncolytics Biotech	Jennerex	Viralytics
Virus "Platform"	Herpes Simplex Virus - 1 (HSV1)	Reovirus Serotype 3 - Dearing Strain (REO: **R**espiratory and **E**nteric **O**rphan virus)	Poxvirus	Coxsackievirus A21
Genetic Engineering	ICP34.5 and ICP47 deletions; GM-CSF added	None (wild type)	Thymidine Tyrosine kinase deletion; GM-CSF added	None (wild type)
Code/Product name	OncoVEX (GM-CSF)	REOLYSIN	JX-594	CAVATAK
Stage of Development	Phase III	Phase III	Phase II	Phase II - pending
Capitalisation ($M)	Acq jan 2011 for US$425 M - upfront; US$ 575 M	US$411 million	Private	$29
Founded	1999	1998	2006	2001

Amgen looks to have paid attention to the fact that Biovex may be in a position to have Oncovex approved for late stage melanoma because its endpoint is demonstration of durable response, defined as the rate of complete response or partial response lasting for more than six months, and the comparator is GM-CSF. This is a low bar compared to the two year survival rate end point in its second Phase III trial in head and neck cancer patients. [In a Phase II trial in late stage melanoma, Biovex reported a durable response rate of 92% as defined above.]

However, the bar for other melanoma therapy developers may have been raised higher with the approval of ipilimumab (Yervoy) from **Bristol-Myers Squibb** for melanoma in March 2010. In stage III and IV melanoma patients, ipilimumab generated a medial survival of 10.1 months compared to 6.4 months for the control (statistically significant), although the response rate was about 10%. One implication is that other therapeutic approaches for the treatment of late stage melanoma may need to be evaluated in combination with ipilimumab as well as a side-by-side comparison. Since Viralytics is still at the Phase II stage of development, such considerations can still be built into its development plans.

The four main companies in the oncolytic virotherapy space each utilise a different virus, however two companies (Biovex and Jennerex) have engineered theirs to express the GM-CSF cytokine and delete several other proteins, hopefully improving the effectiveness of the therapies. Oncolytics Biotech and Viralytics both use wild-type viruses, conferring an element of development efficiency over the other two. (See table below)

The main issue for the oncolytic virotherapy is the degree to which patients have previously been infected the virus. For example, Viralytics estimates that the rate of cocksackievirus infection in the general population is about 25% i.e. are antibody positive. This means there is a reasonable pool of antibody negative cancer patients (at least 75%) for which the treatment could be applied. However, neutralising antibodies begin to be raised about a week after administration. At the same time, Viralytics has shown that Cavatak continues to maintain a presence in tumours despite the neutralising antibodies being produced.

Another issue that is being explored is whether systemic injections are viable. Its worth noting that Biovex has stuck with the intratumoral injection approach, given the high incidence of HSV serotype positive in the general population.

Summary

The field of oncolytic virotherapy is beginning to heat up with three large Phase III trials underway or pending (see table on page 3). The number of patients in clinical trials in the field completed, underway or planned now exceeds 1,700. As pharmaceutical companies search for promising new approaches to treating cancer, and especially those that harness the immune system's power to fight cancer,

– Cont'd on page 5

Selected Clinical Trials - Oncolytic Viro-Therapies

Phase	Disease Class	Design	Primary Endpoint	Num Pts	Start	Data Completion	Study Completion
Biovex - Clinical Trials of OncoVEX GM-CSF							
Ongoing							
Phase III	Melanoma (Unresectable) Stage IIIa, IIIb and IV	Randomized; Comparator: GM-CSF	Durable response rate*	430	Apr-09	Jun-11	Jun-12
Phase III	Head and Neck Cancer	Randomized;Comparator: Radiation/Cisplatin	2 year event free survival	528	Dec-10	Oct-14	Dec-17
			Sub-total Pts	958			
*defined as the rate of CR or PR lasting continuously for 6 or more months							
Completed							
Phase II	Melanoma - Stage IIIb and IV	Open label	Efficacy - tumour response rates	60	Oct-05		
			Sub-total Pts	60			
			Total Pts	**1018**			
Jennerex - Clinical Trials of JX-594							
Ongoing							
Phase II	Liver cancer	Open label; prior to Sorefinib	Safety and tolerability	10	Aug-09	Mar-11	Jan-12
Phase II	Liver cancer	Open label	Delivery and replication within tumours	20	NA	NA	NA
Phase I	Advanced cancers	Open label	Max. tolerated dose	24	Jun-08	Mar-10	
Phase II	Liver cancer	Open label	Dose finding	30	Apr-08	Mar-11	Jul-11
Phase I	Solid Tumours - Pediatric pts	Open label	Safety and tolerability	15	Aug-10		
			Sub-total Pts	99			
Completed							
Phase I/II	Melanoma (S3, S4)	Open label	Response rate for injected tumours	15	Feb-07	Dec-09	Dec-09
Phase I	met. Liver cancer	Open label	Max. tolerated dose	14	Jan-06	Jul-07	Aug-07
			Sub-total Pts	29			
			Total Pts	**128**			
Oncolytics - Clinical Trials of REOLYSIN							
Ongoing							
Phase III	Head & Neck cancer (after platinum therapy)	Randomized; REOLYSIN plus Carboplatin and Paclitaxel (C+P); Control - C+P	Efficacy - Overall survival	280	Jun-10	Jun-12	Dec-12
Phase II	met NSC Lung cancer (KRAS +ve, EGFR)	Open label; REOLYSIN plus C+P	Efficacy - Objective response rate	36	Mar-09	Jul-11	Sep-11
Phase II	Small Cell Lung Cancer	Open label; REOLYSIN plus Carboplatin and Paclitaxel	Efficacy - Objective response rate	55	Oct-09	Apr-11	Jun-11
Phase II	met Melanoma	Open label; REOLYSIN plus C+P	Efficacy - Objective response rate	43	Sep-09	Apr-11	Jul-11
Phase II	Advanced Pancreatic cancer	Open label; REOLYSIN plus Gemcitabine	Efficacy - Objective response rate	33	Oct-09	Apr-11	Jul-11
Phase 1	Colorectal cancer - refactory to oxaliplatin and mut. KRAS +ve	Open label; REOLYSIN plus Folfori	Safety and efficacy; dose finding	12	Dec-10	Dec-11	
Phase II	Head & Neck cancer	Open label; REOLYSIN plus plus C+P	Safety and efficacy; dose finding	14	Aug-08	Mar-11	May-11
			Sub-total Pts	473			
Completed							
Phase II	Bone cancer met. to lung	REOLYSIN	Efficacy - Objective response rate and disease stabilization	53	Jun-07	Jan-11	Oct-10
Phase I/II	malignant Glioma	REOLYSIN	Safety and efficacy; dose finding	18	Jul-06	Apr-10	Jul-10
			Sub-total Pts	71			
			Total Pts	**544**			
Viralytics - Clinical Trials of CAVATAK							
Planned							
Phase II	Late stage melanoma	CAVATAK (IT)	Efficacy	63	NA	NA	NA
Ongoing							
Phase I	Head & neck cancer	CAVATAK (IT)	Safety & tolerability	9	Jan-09	Jun-11	
Phase I	Breast, prostate and melanoma	CAVATAK (IV)	Safety & tolerability	9	Mar-08	Jul-11	Dec-11
			Sub-total Pts	81			
Completed							
Phase I	Late stage melanoma	CAVATAK (IT)	Safety & tolerability	9	Feb-07	Sep-09	Jan-10
Phase I	Late stage melanoma	CAVATAK (IT)	Safety & tolerability	5			Jan-10
IV - intravenous (systemic); IT - intratumoural							
			Sub-total Pts	14			
			Total Pts	**95**			

Seeking Alpha….Six Stocks Under $50 Million on the Move

The interest from investors in biotech stocks is spreading from the Tier-1 stocks, which have been in strong demand over the last two years, to quality smaller cap stocks. Below are six quality biotech stocks that have just started to move on the market.

Sunshine Heart – Capitalisation $45 million

Sunshine Heart is developing the C-Pulse Heart Assist system. It has just completed a 20 patient feasibility trial in the US. Venture capital groups GBS Venture Partners and CM Capital own half of the company. Presumably they will want to exit in the 12 months. So for GBS, it may be its third public company exit after the sales of Peplin and Chemgenex (pending).

Key points

- Low market cap compared to Heartware, which is valued at in excess of $1 billion and operates in a similar field although addressing heart failure quite differently
- VC stakeholders will likely seek exit in next 12 months
- Results from 20 patient feasibility trial due out in third quarter 2011. This will be major a driver of the stock price.

Bioshares recommendation: **Speculative Buy Class B**

Patrys – Capitalisation $34 million

Patrys is the global leader in the commercialisation of human antibodies for the treatment of cancer. It recently commenced its first clinical trial in the treatment of patients with melanoma. The company has recently removed its convertible note financing facility, which will reduce selling in the stock, and larger cap investment bank, Wilson HTM, has recently initiated coverage, attracting new investors into the stock.

Key points

- Results from Phase I melanoma study expected my mid year, with trial update in coming weeks
- Convertible note removed so less stock sellers
- Wilson HTM has initiated coverage and raised funds for company this year

Bioshares recommendation: **Speculative Buy Class A**

Somnomed – Capitalisation $46 million

Somnomed is commercialising an oral device that is custom fitted by dentists to prevent snoring, teeth grinding and the treatment of obstructive sleep apnea. The company has just moved into profitability and the CEO has recently moved to the US with strong growth expected in that market.

Key Points

- 23,000 units currently being sold per annum based on latest annualised data
- Sales tracking at $12 million a year
- Unit sales growing at 25% pa
- Set to benefit from recent US reimbursement changes

Bioshares recommendation: **Speculative Buy Class A**

Cogstate – Capitalisation $13 million

Cogstate has built up a business around providing cognitive testing for clinical trials of pharmaceuticals, mainly in the area of Alzheimer's disease and schizophrenia. It recently expanded into iron deficiency in anemia. The blue sky for the company is the trend underway to better manage concussion in sport. Through its joint venture in the US, the company is seeking to convince a number of the 60 million sports players in the US to take a baseline cognitive test each ear, which represents an addressable market of $420 million a year $7 per test.

Key points

- ARL has mandated Cogstate test in Australia and all but one AFL club has adopted Costate baseline testing
- Concussion in sport in USA a major public issue
- Cogstate through JV Axon Sports has first mover advantage with easily accessible test

Bioshares recommendation: **Speculative Buy Class A**

Atcor Medical – Capitalisation $16 million

Atcor Medical is commercialising the Sphygmocor, non-invasive central blood tressure test. It has developed the gold standard technique. This week the company announced **Sonic Healthcare** would use the test in its insurance candidate evaluation business. This is the first time insurers will use the test. Insurers were also the first in 1917 to adopt commercial use of the standard cuff pressure test that is widely used today. The awareness of this technology continues to grow.

Key points

- First insurer has adopted Atcor's central blood pressure test
- Recognition of test's benefits continues in pharmaceutical and medical industries
- Company generates around $9 million sales a year. Profitability forecast in FY2012

Bioshares recommendation: **Speculative Buy Class A**

Phylogica – Capitalisation $20 Million

Phylogica's drug discovery library of peptides is generating strong interest from leading global pharmaceutical companies. Its first project with **Roche** was successfully completed and the company is looking to move into a second collaboration with that company. Its other two programs with **Pfizer** and **AstraZeneca** are progressing well and the company is aiming to enter into other drug screening deals with existing partners and other companies.

Key points

- More drug screening deal flow expected in 2011 with new and existing partners
- Second project with Roche will be a major milestone for this year
- First Roche deal successfully hit all milestones

Bioshares recommendation: **Speculative Buy Class A**

Circadian Technologies Moves Towards Clinical Trials

Circadian Technologies (CIR: 72.5 cents) is moving towards the clinical phase of development, now that it has secured the intellectual property around the VEGF-C, VEGF-D and the VEGFR-3 receptor biological pathways. Circadian has a potentially valuable IP asset around this technology that is used to prevent the formation of new blood vessels, primarily as a way of preventing cancer growth, which specifically needs to generate new blood vessels rapidly to grow.

The leading compound in this market is the highly successful Avastin, which blocks the VEGF-A pathway. Avastin sales in 2009 were US$5.7 billion.

Imclone Systems Commences Phase I Trial

This week the one of the company's licensees of the technology, **Imclone Systems** (subsidiary of Eli Lilly), announced that it had started a Phase I trial with its drug candidate that hits the VEGFR-3 receptor protein. That trial, which will take between 12-15 months, will look at the safety of that compound in patients with advanced solid tumours. However with imaging, information should also become available on whether the compound has an effect on tumour growth and size. Circadian receives a 'significant' annual payment from Imclone (more that $100,000 a year) and stands to receive a royalty around 5% from any future drug sales.

Circadian has been working on its commercial strategy for its own drug candidate, called VGX-100, which is a monoclonal antibody that hits VEGF-C. It expects to be in a position to reveal its clinical program for this drug in the next two months, with its own Phase I trial anticipated to start in the second half of this year. Whilst the Imclone approach blocks only the VEGFR-3 receptor, VGX blocks this pathway and also another, hitting VEGFR-2.

Getting the strategy right behind this drug is crucial at an early stage. This week the company also released more preclinical data from mouse studies that showed that adding VGX-100 to Avastin delivered a clear added benefit to using Avastin alone, and more benefit still when used in conjunction with chemotherapy.

This type of data will likely direct the clinical development pathway for VGX-100, which is likely to be explored for use in conjunction with Avastin, although initially will look at how VGX-100 works alone. VGX-100 is believed to be active in inhibiting angiogenesis (blood vessel formation) in the lymph glands, which means it might play a role in inhibiting cancer metastases. This may have a synergistic effect when used with Avastin, which works primarily on the solid tumour. While some cancer is spread through the blood, it is mostly spread through lymph glands in the body.

Avastin therapy currently is very expensive, at $75,000 per year of treatment. It is currently approved for five different cancer indications. However it is expected that at some stage generics will surface to this drug, at which point the price will drop substantially, and combination with another cancer antibody drug would be affordable to payors. Potentially VGX-100 could be a life cycle management option for Genentech for its highly successful Avastin product.

Another of the strategies for Circadian is to trial VGX-100 in cancer indications where Avastin has failed.

Assuming positive progress for Circadian, its lead drug candidate VGX-100 could be in Phase II trials by mid 2013.

There is also the opportunity to take VGX-100 into clinical studies for the treatment of front-of-the-eye diseases, where both VEGF-C and VEGF-D are over abundant in people with eye diseases.

Circadian is currently capitalised at $34 million. It had $22 million in cash at the end of last year and is receiving just over $600,000 a year in ongoing royalties. To support its clinical programs, the company will likely need to raise cash in the next two years.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

– *Viralytics continued*

then the prospects for companies such as Viralytics can expect to improve. What is very much in Viralytics' favour is that there are only a few companies in the space.

The acceptance of its IND application by the FDA will be very significant step forward for the company.

While Viralytics is not as clinically advanced as Biovex and Oncolytics Biotech, the company's successful passage through its Phase II program should warrant a major uptick in valuation.

Viralytics is capitalised at $28 million and held cash of $4.5 million at December 31, 2010. It also has access to a US$1.5 million convertible note.

Bioshares recommendation: **Speculative Buy Class B**

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Bioshares Model Portfolio (8 April 2011)

Company	Price (current)	Price added to portfolio	Date added
Bioniche	$1.28	$1.35	March 2011
Somnomed	$1.24	$0.94	January 2011
Phylogica	$0.062	$0.053	September 2010
Sunshine Heart	$0.042	$0.036	June 2010
Biota Holdings	$1.38	$1.09	May 2010
Tissue Therapies	$0.69	$0.21	January 2010
QRxPharma	$1.69	$0.25	December 2008
Hexima	$0.46	$0.60	October 2008
Atcor Medical	$0.12	$0.10	October 2008
Impedimed	$0.72	$0.70	August 2008
Patrys	$0.13	$0.50	December 2007
Bionomics	$0.52	$0.42	December 2007
Cogstate	$0.19	$0.13	November 2007
Sirtex Medical	$5.32	$3.90	October 2007
Clinuvel Pharmaceuticals	$2.10	$6.60	September 2007
Starpharma Holdings	$1.36	$0.37	August 2007
Pharmaxis	$2.80	$3.15	August 2007
Universal Biosensors	$1.28	$1.23	June 2007
Acrux	$3.23	$0.83	November 2004
Alchemia	$0.70	$0.67	May 2004

Portfolio Changes – 8 April 2011

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. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

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

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