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In this edition...
One company that has been very much on the perimeter of biotech investment interest has been Antisense Therapeutics. This week it announced a licensing deal with global generics business Teva Pharmaceuticals for its multiple sclerosis drug, ATL1102. The deal is more significant for the fact that Teva has a major interest in the MS drug space, with its drug copaxone netting US$1.7 billion a year in sales. The positive news is that Teva looks like it will develop drug further even if the Phase II results of ATL1102 are at best ambiguous.
In other developments Circadian is trading at less than its cash backing and looking very attractive, Stem Cell Sciences has reorganised its business and Progen's board is in urgent need of renewal.
The editors
Companies covered: ANP, CIR, PGL, STC, TIS

	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)	-32.0%
Cumulative Gain	**119%**
Av Annual Gain (6 yrs)	**26.8%**

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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) 9671 3633
Email: info@bioshares.com.au
David Blake
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
Mark Pachacz
Ph: (03) 9671 3222
Email: pachacz@bioshares.com.au

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

Antisense Therapeutics Lands MS Licensing Deal With Teva

Two years ago, when financial markets were humming along nicely, including in the biotech sector, Antisense Therapeutics (ANP: 6.3 cents) received a rude shock when **Biogen Idec's** drug Tysabri was pulled from the market. Antisense's lead compound, ATL1102, targets inhibition of the same protein, and as a result, its share price plummeted, with even viability of the company in doubt at the time. Tables have turned considerably with Antisense being one of the best performing stocks in the sector this year, having just signed a licensing deal with **Teva Pharmaceuticals**.

A surprising deal

Antisense Therapeutics has signed a licensing deal with Teva for its lead multiple sclerosis program. At first glance it's a surprising deal because it's done with a company that has been built from a generics base, and also the agreement was negotiated before the release of data from a significant Phase II study underway, expected around mid 2008. But looking further into the rationale behind the deal, it appears to work well for both companies involved.

Deal terms

Under the terms of the deal, Antisense will receive a US$2 million up front payment with a total deal flow valued potentially as much as US$100 million if the drug candidate is successfully commercialised. Antisense will also receive low double digit royalties which are tiered and based on net future sales.

Antisense Therapeutics licensed the antisense target and the lead compound from **Isis Pharmaceuticals** in the US, and as a result is obliged to pay them one third of any licensing fees and a percentage of future royalty payments.

Deal rationale

Teva Pharmaceuticals is now a US$35 billion company with over 20,000 employees. It was formed as a generics company and in 2006 acquired another major generics business, **Ivax**. Teva is expanding its branded pharmaceutical product range with a particular specialty in multiple sclerosis.

The upfront payment made by Teva is not large but it gives the company an option (Teva has licensed the program) over the Antisense MS program. The main emerg-

The Teva MS franchise

The first drug developed in Israel and approved for use by the FDA was Teva Pharmaceuticals' Copaxone for the treatment of relapsing-remitting MS. The drug was first approved in the UK in 2000, in the US in 2002, in a pre-filled syringe formulation, and is now sold in 47 countries. In 2007, Teva generated sales of copaxone (in-market) of US$1.7 billion, a 21% increase over the previous year. Efficacy of the drug was demonstrated in three key trials involving 50, 211 and 239 patients.

The company is about to launch a Phase III program with its next MS drug candidate, Laquinimod, which was acquired from Active Biotech in Sweden. Antisense Therapeutic's ATL1102 will be the second clinical MS research program for Teva and may become, if successful, a useful competing drug to Tysabri (Biogen-Idec) which inhibits the same protein as ATL1102, called VLA-4.

ing competitor in the MS market is Biogen Idec's Tysabri, which last year generated sales of US$343 million and growing rapidly. Tysabri and Antisense's drug candidate ATL1102 both seek to inhibit excess production of the immune system molecule VLA-4.

So for Teva it's not just a tactic to build its market in the MS space, but also potentially protect it from competition from Tysabri should ATL1102 be successful. And signing the deal before the release of the Phase II results will no doubt be considerably cheaper for the company if the deal was done after a positive Phase II trial result.

Teva also gets an option to trial the compound in asthma, which has been flagged by Antisense as another potential application. Teva has a large respiratory franchise now through its acquisition of **Ivax**, which makes the deal a nice fit on many levels for Teva. According to the Antisense, discussions prefacing this deal started 18 months ago and were in fact initiated by Teva.

Benefits to Antisense Therapeutics

For Antisense Therapeutics it brings a number of benefits. Firstly there is the small upfront payment and potential future payments that could be considerable if the technology is successful. The out-licensing of the program will free up Antisense management time to focus on subsequent programs in development. And a very important aspect of the deal is that it may see continuation of the Antisense MS program should the current Phase II study fail to produce meaningful results.

Teva has already purchased ATL1102 material to conduct further trials, suggesting the result from the current study may not be crucial to the continuation of this program - speculation on our part. The 'option' Teva has taken over this program through the licence agreement may likely include the price of the upfront, cost of material, and the cost of conducting perhaps a different/larger Phase II study, which would might be a broader approach to establish drug efficacy, including various dosing levels and dosing schedules.

Teva planning the next trial?

An advantage for both companies to negotiating the deal now is that Teva can immediately begin planning the next trial. Had Antisense waited until after Phase II results, it would have received a larger upfront, but the royalty rate negotiated would not have been overly different, and it would have taken up to 12 months to complete a deal, delaying the start of the next trial by at least 15 months. Antisense had always intended to partner this program early and it allows the company to now focus its efforts on ATL1103 for the treatment of acromegaly.

Antisense technology hits a purple patch

The leader in the antisense field, from whom Antisense Therapeutics has licensed its compounds, is **Isis Pharmaceuticals**. Over the last 12 months Isis has sealed some major licensing deals and delivered arguably some of the most impressive results yet seen with this novel approach to disease management. In particular the results Isis has achieved in a Phase II trial in around 200 patients for its lipid lowering drug mipomersen. The drug reduced cholesterol levels by 50% in patients with stable cholesterol levels already receiving statin class drugs.

This result is largely responsible for **Genzyme** paying US$175 million up front and a US$150 million equity investment in Isis to license the program in January this year. This follows on from a deal with the **Johnson & Johnson** company **Ortho-McNeil** in September last year for access to some antisense compounds to treat Type II diabetes (US$45 million up front) and in May last year **Bristol-Myers Squibb** entered into a collaboration with Isis in the cardiovascular space (US$15 million up front) for some of Isis's antisense compounds.

A key point in these deals is that they all involve antisense compounds that target liver cells. And liver cells are the target of the ATL1103 program for Antisense Therapeutics. This is important because antisense compounds have largely failed to deliver over the last 10 years, probably because of inadequate delivery to the target site. It is now being demonstrated that the liver is an excellent target for antisense drugs, which is likely because the liver's function is to filter the blood that carries drugs in circulation in the body.

ATL1103 – The next focus for Antisense Therapeutics

The next cab off the rank for Antisense is ATL1103, which is an antisense compound that inhibits growth hormone receptor and thereby seeking to reduce IGF-1 levels in the blood. It's a very interesting program. ATL1103 has a direct potential application in treating acromegaly which is characterised as an uncontrolled enlargement of body tissues.

Growth hormone is produced in the pituitary gland. In patients with acromegaly – 40,000 in North America – 90% of cases are caused by a benign tumour compressing this gland generating

excessive growth hormone. The action of the growth hormone is mediated through a growth hormone receptor in the liver involved in producing IGF-1. Reducing IGF-1 levels is the accepted clinical endpoint for treating acromegaly.

ATL1103 works by inhibiting the growth hormone receptor in the liver. It's a validated target, with the drug Trovert on the market that also inhibits this receptor. Trovert is a pegulated peptide drug. However, it is an expensive drug, costing around US$60,000 a year, and to their advantage, antisense drugs have potential cost and dosing benefits.

This is an excellent application for the antisense technology because it targets the liver. Antisense technology has been slow to achieve clinical success but has recently delivered very promising results in a number of programs by Isis Pharmaceuticals where the target has been the liver (see side bar).

What is also appealing with this program is that biomarkers for judging efficacy are easily measured – IGF-1 levels. And importantly, Antisense has already proven in primate studies that IGF-1 levels can be controlled using ATL1103. There is also an application for this technology to treat retinopathy. This program is now moving into preclinical toxicology with clinical studies expected to begin in 2009.

The royalty obligations to Isis are less onerous with this compound because the target was not licensed from Isis, only the drug candidate. It is also worth noting that the ATL1103 target, like that for ATL1102, is a target validated by other products on the market. The market for existing drugs to treat acromegaly is around US$1 billion.

IP position

Patents over ATL1102 begin to expire in 2018 with up to five years extension possible in the US. Isis Pharmaceuticals has some other patents over the technology which go out to 2023.

Summary

The licensing deal with Teva significantly reduces the risk in Antisense stock. The funding risk has been reduced, albeit marginally at this stage with the upfront payment; and the continuation of the ATL1102 program we speculate is almost certainly assured regardless of the outcome of the current Phase II trial. Antisense can now focus on other programs, particularly ATL1103, where it will likely retain more of the potential upside.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Progen Pharmaceuticals: From bad to worse

Progen Pharmaceuticals (PGL: $1.775) delivered disappointing news to the market this week, announcing that its investigator-initiated trial of its lead drug candidate, PI-88, in combination with Taxotere for the treatment of hormone refractory prostate cancer had to be stopped because of adverse events in 27% of patients. The trial result was announced as delivering a positive efficacy outcome with 70% of patients (from a total of 55) achieving greater than a 50% decrease in PSA levels, a marker for prostate cancer. In the registration trial of Taxotere alone, 45% of patients met the same endpoint. [The trial had anticipated enrolling 90 patients.]

The structure of this announcement was disappointing, just as the result. With the trial having to be prematurely stopped due to side effects, it was clearly a negative result regardless of the efficacy outcome.

This result comes on the back of a failed Phase II result for PI-88 in lung cancer in combination with docetaxel, announced in September last year. The company is continuing a Phase II trial in patients with melanoma although recruitment is likely to be slow.

The company also announced this week the planned Phase III study in patients with resectable liver cancer has yet to begin recruitment. Failure to begin a pivotal Phase III trial on time is a sign a worrying sign of possible deeper issues within the firm.

In light of recent and not so recent events, concerns over the board and management have moved to the forefront with greater clarity. The board needs to accept responsibility for the decision to not partner PI-88 in recent years and the increasingly negative consequences this will have on the company's future . The Executive Chairman had said in November last year he would step down as chairman and additional directors appointed although no appointments have been made.

The board, in our view, is in desperate need of refreshment. The chairman, Stephen Chang, has been on the board cumulatively for 14 years, John Zalcberg has been a director for almost 13 years, and Patrick Burns and Malvin Eutick have been directors for the last nine years. Justus Homburg was appointed CEO and director in 2006.

The Executive Chairman and the CEO last year were remunerated in total approximately $650,000 (excluding share options) and yet neither are principal contacts on recent press releases. The failure to start the Phase III trial on time reflects poorly on the board and management of the company. And communication with the market needs to be improved, particularly when a Phase II study with the lead compound is halted due to safety issues.

Progen may be one of the best funded companies in the sector but its future is suddenly looking bleak and with results from this trial at least three years away, there will be few Phase III trial related drivers for this stock. *Bioshares* has downgraded its recommendation to **Sell**.

Bioshares

Managing Circadian's Listed Investment Portfolio

Circadian Technologies (CIR: $1.025) released its Half-Year Report for the period ended December 31, 2007, this week. Circadian reported a loss of $0.495 million for the half-year period.

Circadian reported cash reserves of $32.8 million. Together with its share of cash held by investee company Vegenics of $9.6 million, total cash accessible by the company amounted to $42.4 million, or the equivalent of $1.06 per share. This excludes $14 million on investments in other listed companies and other intangible unlisted investments such as Vegenics.

Perhaps the most significant element of the company's accounts was the fact that the company had sold down further its shareholding in Avexa. At June 30, 2007 Circadian held a 3.4% stake in Avexa. The company has sold 5.6 million shares to gain a net $2.6 million. It retains a 2% shareholding of 8 million shares valued at the current market price for Avexa shares of $3 million.

In FY2007, Circadian sold 22.5 million shares for a net gain of $13.9 million. Circadian has therefore reduced its shareholding in Avexa from a total of 36.1 million shares, a gain of approximately $16.5 million.

Circadian's principle focus going forward is the management of Vegenics, in which it holds a 67% interest. However, it is also managing a number of other early stage research projects and maintains investments in several other listed biotech companies.

It is evident from Circadian's sell-down in Avexa that it has taken a proactive interest in its portfolio of listed investments . Regarding the other three listed investments (Antisense Therapeutics, Metabolic Pharmaceuticals, and Optiscan Imaging), Circadian's portfolio management challenges are significantly different to the Avexa investment.

Circadian's Listed Investments

Listed Company	CMP	Shares (M)	CIR shares (M)	Market Value of Investment ($M)	%'age share-holding
Avexa	$0.38	406.0	8.09	$3.0	2.0%
Optsican Imaging	$0.25	104.2	6.40	$1.6	6.1%
Metabolic Pharm.	$0.04	301.0	36.01	$1.4	12.0%
Antisense Therap.					
Direct	$0.06	533.4	102.74	$6.5	19.3%
Through Syngene	$0.06	533.4	23.07	$1.5	4.3%
Combined				$7.9	23.6%
Total				$14.0	

For **Antisense Therapeutics**, it is likely that Circadian will maintain its investment now that Teva Pharmaceuticals has licensed the MS project (see Antisense analysis on page 1). This partnering event has de-risked the Antisense investment considerably, with the deal giving an indication that Teva will continue with further trials of ATL1102 even in the current Phase II trial delivers ambiguous or luke-warm results.

For **Metabolic Pharmaceuticals**, a company in which Circadian is the largest shareholder (12%), there is an emerging need for the shareholder base, perhaps led by the major shareholders, to ensure that the remaining funds in the company (~$17 million) are not squandered on meaningless projects.

For **Optiscan Imaging**, the investment challenge is made all the more difficult by the fact that Circadian is the largest single shareholder, despite only a 6.1% shareholding holding. In contrast to a number of peer companies by capitalisation (see table at left), the median ownership percentage for the top shareholder is 17%. Circadian came into Optiscan as a founding shareholder with a direct 25% stake in 1994, which reduced on Optiscan's listing in 1998 to 15%. (Circadian also had a 15% (2/4/2004) stake in Axon Instruments which in turn had held a 12% stake in Optiscan but which it disposed of in February 2004.)

The exceptional spread of the Optiscan register makes it difficult for an investor such as Circadian to optimally exit its investment, which has remained essentially unchanged in terms of number of shares held since at least 2000. Optiscan's weak share register could be another factor that explains its relatively weaker share price, in addition to problems stemming from its Pentax partnership. Interestingly, it is stocks in which Circadian has had much higher investment positions such as Zenyth Therapeutics (22.6%), Axon Instruments (15%) and Avexa (17.6% at de-merger) that it has crystallised excellent investment returns.

Company	Code	Cap'n ($M)	CMP	Top 20 Shh.	Top Shh.
Brain Resource Corp	BRC	$37	$0.40	73%	12%
Cytopia	CYT	$35	$0.40	56%	12%
KarmelSonix	KSX	$34	$0.14	46%	12%
Benitec	BLT	$32	$0.11	65%	19%
Adv. Surgical Design & Man.	AMT	$31	$0.85	85%	22%
Sunshine Heart	SHC	$31	$0.15	79%	24%
Halcygen	HGN	$28	$0.37	46%	13%
Proteome Systems	PXL	$27	$0.15	71%	15%
Apollo Life Sciences	AOP	$27	$0.14	79%	54%
Optiscan Imaging	**OIL**	**$26**	**$0.25**	**35%**	**6%**
Clovercorp	CLV	$26	$0.16	59%	29%
Cyclopharm	CYC	$25	$0.18	64%	13%
Eastland Medical Systems	EMS	$23	$0.14	53%	14%
IM Medical	IMI	$23	$0.019	35%	10%
Giaconda	GIA	$21	$0.29	86%	69%
ITL	ITD	$21	$0.17	55%	19%
Life Therapeutics	LFE	$20	$0.17	39%	10%
Avantogen	ACU	$19	$0.03	92%	87%
Bone Medical	BNE	$19	$0.25	92%	57%
Phylogica	PYC	$17	$0.12	59%	21%
Average		**$26**		**64%**	**26%**
Median		**$26**		**62%**	**17%**

Summary

With $42 million in cash resources, Circadian Technologies is in a very strong cash position and is extremely attractive investment given that it is trading at less than its cash backing.
Bioshares recommendation: **Speculative Buy Class A**

Stock Briefs

Stem Cell Sciences

Stem Cell Sciences (STC: 51 cents) announced the results of the corporate review that follows the appointment of Dr Alistair Riddell as CEO in late 2007.

The company said it would streamline operations by consolidating commercial operations and all senior management into facilities in Cambridge, UK. Facilities in Edinburgh would be closed and the Melbourne facilities would become a centre for research excellence.

One of the company's aims is to build revenues through increasing the number of research collaborations it engages in with pharmaceutical companies. These partnerships would generate licence fees and research income.

Stem Cell Sciences also intends to increase revenues by pursuing licence fees from companies that are using its proprietary technologies without permission, similar to **Genetic Technologies** strategy to pursue companies that have been illegally exploiting its non-coding DNA patents. The company intends to hire a US law firm on a commission basis to support this task.

Stem Cell Sciences will also consider its involvements in the stem cell media business. The company is capitalised at $17 million and $8.9 million in cash at the end of last year.

Bioshares recommendation: **Speculative Buy Class B**

Tissue Therapies

Tissue Therapies (TIS: 20 cents) has been heavily sold down in recent weeks. The company's long awaited trial for the treatment of a range of skin ulcers (diabetic, venous and pressure ulcers) has been beset by a number of delays. However, the trial should now start at the end of this month. The trial is expected to take one month to complete and results should be available in April. Around 60 people are expected to be recruited for the trial in Canada, with recruitment not expected to be difficult once the trial is allowed to proceed. Our expectation is that the trial should produce positive results, which will allow the company to register the product in Canada and form a marketing and distribution alliance.

The company now has a capitalisation of $7 million with $0.9 million in the bank at the end of last year and an additional $500,000 convertible loan facility arranged in January. Tissue Therapies has sufficient funds to complete the trial (if there are no further significant delays) although will need to raise more money following the completion of the trial. Positive news flow is expected over the next two months however the market is aware of company's low cash position and the need to raise further cash subsequent to the release of results from the forthcoming trial. At is current low market capitalisation, the company is exposed to the risk of a takeover over the coming months.

The stock has been downgraded to a **Speculative Buy Class C** because of its low cash position.

Bioshares Model Portfolio (15 February 2008)

Company	Price (current)	Price added to portfolio	Date added
Circadian Technologies	1.025	1.025	February 2008
Patrys	$0.35	$0.50	December 2007
NeuroDiscovery	$0.16	$0.16	December 2007
Bionomics	$0.37	$0.42	December 2007
Cogstate	$0.13	$0.13	November 2007
Ventracor	$0.42	$0.625	October 2007
Sirtex Medical	$3.85	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.35	$0.66	September 2007
Starpharma Holdings	$0.35	$0.37	August 2007
Pharmaxis	$2.95	$3.15	August 2007
Universal Biosensors	$0.95	$1.23	June 2007
Biota Holdings	$1.24	$1.55	March 2007
Tissue Therapies	$0.20	$0.58	February 2007
Probiotec	$1.22	$1.12	February 2007
Phylogica	$0.12	$0.42	January 2007
Peplin Inc	$0.70	$0.83	January 2007
Arana Therapeutics	$1.09	$1.31	October 2006
Chemgenex Pharma.	$0.72	$0.38	June 2006
Cytopia	$0.40	$0.46	June 2005
Optiscan Imaging	$0.25	$0.35	March 2005
Acrux	$1.02	$0.83	November 2004
Alchemia	$0.50	$0.67	May 2004

Portfolio Changes – 15 Feb 2008

IN:

With $42 million in cash resources, Circadian Technologies is in a very strong cash position, is extremely attractive given that it is trading at less than its cash backing, and it has sold down its stake in Avexa considerably.

OUT:

Progen Pharmaceuticals has been removed from the portfolio (see coverage on page 3)

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

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