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In this edition...
This week we focus on three well positioned companies that biotech investors can do well to monitor. Arana, an antibody drug developer, is proving more and more it is a well positioned company in one of the the hottest areas in the world of drug development. Biota, has, we argue developed a sustainable model for drug development and, despite its litigation blow-up with GSK, has a viable future. Cellestis is a profitable company that looks to be set for a year of strong growth in sales and profits, thanks to non-cyclical, recession proof demand for TB testing and the publication of 230 scientific papers.

Companies covered: AAH, BTA, CST

	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)	-39.0%
Cumulative Gain	**26%**
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.

Biota Holdings – A Sustainable Business Established

Investors in Biota Holdings (BTA: 37.5 cents) have experienced a disappointing year following the capitulation by the company's board of litigation initiated against **GlaxoSmithKline** for failure to properly market the influenza drug Relenza.

Biota ended up settling with GSK, for a payment from the pharmaceutical giant of $20 million, with $7.5 million of that having been paid out, presumably to its lawyers in the first quarter of this financial year. The result was disappointing , given the company had previously received but rejected a settlement offer from GSK in 2006, valued by the Biota in the order of $80 million. There were two previous offers, also rejected, of $11 million at the commencement of the litigation and one in 2005 for $25 million.

On the positive side, Biota has now become a sustainable true biotech business. The company is generating sufficient revenue from Relenza royalties and from product development collaboration that should see the company run now a near cash flow neutral business.

The company aims to create value through drug discovery and development but mitigates risk through a portfolio of development programs that are partnered early with collaborators.

At the end of the first quarter of this financial year, the company had an estimated $70 million in cash assets following the final litigation receipts and expenses. We estimate the company has a further $80 million in revenue from Relenza royalties to flow over the next five years, with its patent expiring on 26 July 2013 in the US according to a Wilson HTM report, which includes a 633 day patent extension.

The company now has five main assets, those being Relenza and four drug development programs. These are a long acting neuraminidase inhibitor (LANI) program which is partnered with **Daiichi Sankyo,** Japan's third largest pharmaceutical firm, and is ready to move into Phase III clinical testing as a once a week flu drug; a Phase I RSV (respiratory syncytial virus) program which has been partnered with **MedImmune** (now part of **AstraZeneca)**; a preclinical hepatitis C program that has been partnered with **Boehringer Ingelheim**; and a Phase IIa human rhinovirus (common cold) program which the company is seeking to partner.

Relenza Royalties

The seasonal flu drug market is now almost entirely dominated by the competing drug Tamiflu, sold by **Roche**. It is now a US$600 million a year market. GSK is focusing its efforts on selling Relenza into the government stockpiling market. This market is made up of governments completing, increasing, and replenishing of stockpiles, which have a five year shelf life.

Cont'd over

Biota cont'd

Biota estimates the replenishment market is worth around US$1 billion a year, with Relenza gaining between 15%-20% of that market. As of March this year, the US stockpile had reached 50 million courses of flu drugs from a target of 81 million courses. These stockpile levels are arguably still very low and would provide protection to a small percentage of the population over an extended period.

LANI Program

Biota's LANI program, which could be described as a next generation longer lasting version of Relenza, is progressing well. The LANI program involves the development of a prodrug of a Relenza active compound (zanamavir) that is taken into the lungs and converted over time into the active neuraminidase inhibitor, which allows the drug to be effective over a longer period (at least one week). The lead compound is called CS-8958.

A Phase II study was conducted by Daiichi Sankyo in several hundred patients who naturally acquired a flu infection. The study compared a once only dose of CS-8958 against Tamiflu taken twice a day over five days. It found the two treatments to be statistically indistinguishable. In the laboratory, the drug candidate was found to be effective against influenza A and B and against the pandemic strain, H5N1.

Last week Biota and Daiichi Sankyo announced that the Phase III study will start in Asia (Japan, Taiwan, Hong Kong and Korea) in the current flu season. Daiichi Sankyo will conduct the trial and will also run a Phase II/III trial with CS-8958 in Japan in children less than nine years old. Daiichi Sankyo will pay for the Asian trials and Biota will be entitled to a royalty from sales.

For areas outside of Asia, it is likely that a development partner will be secured to run the Phase III study/studies, and market the drug. Depending on the size of the Asian trials and the results, it's possible only one or two small western supplementary trials may be required to get the drug approved. Biota has US$2.5 million available in NIH funding to run Phase I studies with the compound in western studies.

Depending on the severity of the current Asian flu season, if sufficient numbers of patients who have contracted the virus are enrolled, then the company may be in a position to file for approval in Asia in 2009 if the results are positive. Once again, the control arm will be Tamiflu taken twice daily for five days.

The LANI program has the potential to become a valuable asset for Biota and Daiichi Sankyo. Daiichi Sankyo has the rights to the drug in Asia, from which Biota will receive a royalty, and both companies will equally share the rights outside of those Asian markets. The seasonal Japanese flu market alone is worth US$100 million a year with Tamiflu having secured most of that market. Tamiflu has shown to have side effects in adolescents and a once-a-week version would be very competitive against Tamiflu if shown to be as effective.

Stock holding advantage

If CS-8958 is shown to be as effective as the current flu drugs Relenza and Tamiflu, there would be considerable advantages gained from stockpiling a drug that only needs to be taken once a week versus twice daily, both from a storage perspective but also from compliance and distribution of the drug during any possible pandemic.

One possibility for the companies would be to partner the drug for seasonal use but maintain rights to sell the drug for government stockpiling. There is an extremely narrow distribution path for stockpiling that could be managed by even a small company and out-source manufacturing similar to the major pharmaceutical companies. Biota has indicated that its role as a biotech company is not to be involved with later stage drug development or sale and distribution.

RSV Program

Another of the very attractive assets that Biota is developing is its respiratory syncytial virus (RSV) infection therapeutic. Biota's scientists first started work on this program in 1998/1999, when there was no blockbuster market for this viral infection. In 1998 MedImmune released its drug Synagis, a monoclonal antibody used as a prophylactic for RSV infection in at risk infants. In 1999, that drug achieved sales of US$352 million. (Synagis replaced MedImmune's Respigam, a polyclonal antibody drug approved in the US in 1996).

Sales of Synagis have increased steadily over the last decade. Synagis remains the main drug for RSV and last year generated sales of US$1.15 billion. Ribavirin is used for treatment of RSV in high risk cases. It is a dangerous drug to handle, being an aerosol that is teratogenicity, or its ability to cause birth defects in pregnant women.

The commercial success of Synagis has encouraged several groups to become active in the RSV space. Biota, because of its interest in flu virus research and because RSV infection is often mistaken for influenza infection, has been early into RSV research and development. With MedImmune, it is now placed as one of only two other companies with major clinical programs underway in RSV (according to an earlier Wilson HTM report), the others being **Alnylam** with an RNAi approach, and **Novartis/Arrow Therapeutics**. Both Novartis/Arrow Therapeutics and Biota/MedImmune are developing fusion protein inhibitors, the same target as Synagis. AstraZeneca/MedImmune has also developed the antibody motavizumab (MEDI-524), for which it has filed a NDA with the FDA and a marketing authorization application is expected to be filed with the EMEA in 2009 H1.

Biota's program is progressing particularly well. The drug candidate has shown excellent potency and looks to be very competitive aganst other drugs in development. AstraZeneca/MedImmune appears to be very committed to the collaboration. Biota had received US$8 million in upfront and milestone payments between December 2005 and July 2007, then in August this year, AstraZeneca paid an additional US$3.5 million to expand the license deals to parts of Asia not previously covered in the agreement. This brings the total to US$11.5 million received to date from AstraZeneca/MedImmune, of which US$8.5 approximately covers Biota's initial investment in the program.

Biota cont'd

The Phase I trial is being conducted by Biota. It's expected the program will move into Phase II studies in late 2009. At some point during Phase II development, AstraZeneca will take control of the program. Biota continues to work on second and third tier back-up compounds that will be used as either a follow-on drug should the first drug be successful, or as a back-up should the lead fall over. This is a strategy adopted by many drug developers.

Another appealing aspect of the program is that there is an extremely strong patent position around the program, with patents going out to 2024 with back-up compounds out to 2028.

Even though both Synagis and Biota's compound hit the same target, it is expected the Biota/AstraZeneca drug candidate will be used as a therapeutic. Synagis does not work well as a therapeutic for which the reasons are not well understood. It is used as a prophylactic treatment.

There is a very large market for children who are not eligible for Synagis. There is a high RSV disease burden in the elderly and untreated RSV infection is almost fatal in organ transplant recipients because of their immuno-compromised position from transplant rejection therapy. **AstraZeneca**, **Novartis**, **Johnson & Johnson**, **Bristol Myers-Squibb, Merck** and **GSK** all have RSV programs underway suggesting this is a major market opportunity for drug developers that remains poorly served.

Hepatitis C Program

The Hepatitis C program was licensed/partnered with Boehringer Ingelheim in November 2006. Biota received a US$3 million technology access fee. The program is still in preclinical development. Boehringer Ingelheim is funding development costs.

Rhinovirus Program

The human rhinovirus program has moved into Phase IIa studies. The company will seek to complete the current study before finding a partner to finish development. The Phase IIa study will test the drug as a prophylactic in 200 health volunteers challenged with the virus.

Summary

The focus on Biota's failed litigation against GSK and the continuing Relenza stream has resulted in the progress of Biota's other development programs progressing somewhat unnoticed. The LANI and RSV programs will be well worth monitoring over the next 18 months and have the potential to become valuable assets. The RSV program alone has already paid for itself with US$11.5 million received from AstraZeneca/MedImmune.

The biotech model is proving successful with Biota. Over the next five years, the company would like to double the number of programs it is working on, partnering early with partners funding much of the clinical development costs.

Biota has an estimated $70 million in cash. It is capitalised at $66 million with up to $80 million in further royalties and four main programs, three of which are in clinical stages of development and three of which have been partnered or are in co-development. At current prices, Biota Holdings is yet another of a number of very appealing investment options available as a result of the turbulent market conditions.

Bioshares recommendation: **Speculative Buy Class A**

Cellestis' Stellar Start To Financial Year 2009

Cellestis (CST: $1.88), which markets tests for latent tuberculosis, provided an update on operations to shareholders at its AGM this week. The company has had a very strong first four months in this financial year due to increasing product sales and a favourable movement in exchange rates.

Sales for the first four months precisely doubled sales for the previously corresponding period, up from $4.9 million to $9.8 million, with the company increasing its cash position by $2.6 million to $16.7 million in the four months from the end of June. The company's profit before tax in this first half is expected to surpass the profit before tax for all of FY2008, which was $2.26 million. In *Bioshares* 286, we estimated that Cellestis' profit before tax could exceed $10.4 million for this financial year at current exchange rates.

The company expects lower distributor sales in November and December, although sells directly in Australia, the main parts of Europe and the US. The company indicated there has been no obvious effect yet from the world economic downturn although stated this remains a wildcard for its business, presumably if healthcare spending is reduced. We would rate the likelihood of this occurring as low, given the relative importance that is placed on TB testing.

Cellestis is currently selling more than 1 million tests a year into a developed world market that is 60 times its current market share. The company reported that the number of publications regarding the diagnostic technology has almost doubled in the last year from 120 to 230. The company also indicated that it is in a strong position to consider local and international M&A opportunities.

Cellestis made reference to a US Army memorandum in September this year that specifically listed the three available options for latent tuberculosis testing, being the tuberculin skin test and the two Cellestis interferon-gamma release assays, being QuantiFERON-TB Gold and QuantiFERON-TB Gold-In-Tube, and that changes to choice of test should be made at local levels.

Cellestis is capitalised at $180 million. We expect strong growth to continue with this business with profit margins expected to increase, with the company having built and secured a global distribution infrastructure.

Bioshares recommendation: **Buy**

Arana Therapeutics – Antibodies Are Prime Space

This week Arana Therapeutics (AAH: 77.5 cents) officially opened its new facilities in Parkville, the Melbourne district that is home to the headquarters of **CSL**. The focus of the facility is on antibody engineering, including humanization and optimization. Also this week, in Boston, global pharmaceutical company **Novartis** held a Research Day.

Are the two events linked? While there is no direct link, when one considers the fact that the number of biologic drugs under development at Novartis has grown from six (we estimate) in 2005 to 25 as of the third quarter 2008 – biologics now represent more than 25% of drugs in development at Novartis – the importance and perceived value of biologic drugs comes into its own. There are perhaps as many as 400 antibody drugs in development across the global drug development world. So for one company with a history as a small molecule drug developer to increase its exposure to that technology class that much in such a short period of time, then an event of significance has occurred.

It helps also to reflect on the statement made by the President of the **Novartis Institute for BioMedical Research**, Mark Fishman, at the Research Day. "We went into biologic therapies for a few reasons. First of all, they are very specific reagents, so that we know once that we get efficacy we are less likely to be troubled by toxicity and that is born out secondly in the clinic by fact that biological therapeutics tend to fail less often going through clinical trials than low molecular weight compounds and this is held up to be true".

While the specificity and development certainty is higher for biologic drugs (read antibody drugs) relative to small molecule medicines, there is another very compelling reason for allocating resources to their development. The reason is that it will be much harder for rivals to develop biosimilar's or biogenerics of approved antibody medicines compared to the development of generic small molecule drugs. At least in the drug product marketing territory of the USA, the possibility exists that a period of 14 years exclusivity may be legislated, although this is not certain. Further to that, biogeneric manufacturers are likely to find themselves conducting expensive patient studies trials to confirm comparability. Biologic class molecules are large and complex molecules and variations in chemical groups such as sugars that decorate antibodies can effect the functionality of the molecule.

Arana Therapeutics has and continues to grow and add value as an antibody drug developer. It is arguably the leading company in its class listed on the ASX, not least because it holds cash resources of $182 million. The company's lead molecule, the domain antibody compound ART-621, is now in a Phase II trial in psoriasis and a Phase II trial in rheumatoid arthritis is expected to commence by the end of 2008, now that an Investigational New Drug application has been accepted by the FDA. Behind ART-621 is ART-104, in pre-clinical development as a treatment for colorectal cancer, ART-010 for cancer-related bone disease, ART-150 for lung cancer and melanoma and PMX-52 for ocular diseases.

It is worth noting in particular Arana's co-development program which it initiated with **Kyowa Hakko** (now **Kyowa Hakko Kirin**) in April 2008, to gain access to that company's Potelligent technology. The deal resulted in a joint ownership development program being established for ART-104, with both parties to share equally in development costs.

The Potelligent technology

The Potelligent technology is an antibody engineering technology that controls or manipulates the fucosylation of antibodies. It is known that if a particular fucose sugar group is removed from an antibody, then antibody-dependent cellular cytotoxicity (ADCC) is greatly enhanced. This is more relevant for anti-cancer antibodies, which unlike for other disease states where simple blocking of binding sites might be all that is required to modulate a disease, in the case of cancer therapy, it is generally desired to generate a cyto-toxic (killing) effect on cancer cells. A prime benefit of the technology is that potency is enhanced, and with improved potency, smaller doses can administered to achieve a particular effect. Up to a 100-fold difference has been observed between unoptimised and fucosylated antibodies and their optimised and defucosylated counterparts.

Arana Therapeutics received a $US4 million up-front payment in respect of the deal with Kyowa Hakko, with a milestone payment of US$4 million to follow. To put this in another context, in December 2006 Arana Therapeutics acquired the ART-104 antibody along with a portfolio of 25 other antibodies from **Scancell** (UK) for approximately $5 million (GBP 2.85 million is to be paid in cash or shares when ART-104 enters a Phase I trial), with Scancell offloading its antibody assets so as to preserve funds for the development of its lead programs. Thus, it is apparent that Arana is roughly in a neutral position, cost-wise, on the development of ART-104 up to now, a fact not generally recognised by the market.

Cont'd over

In June, Arana announced another collaboration with **Greenovation Biotech GMBH**, from Germany. This collaboration gives Arana access to Greenovation's Bryotechnology, a technology derived from bryophytes (mosses), which like the Biowa technology enables the removal (engineering) of selected fucose sugar groups on antibodies, to enhance antibody dependent cellular cytotoxicity. The deal with Greenovation is covers up to five antibodies, and grants access for Greenovation to Arana's optimisation platform.

CSL Licenses Biowa Potelligent Technology

BioWa, the US subsidiary of Kyowa Hakko Kirin, announced that **CSL** had entered a license agreement for use of the Potelligent technology in October. It can be further noted that Arana Therapeutics has completed two antibody humanisation and optimisation projects for CSL, with the most recent being completed in June. It can also be noted that CSL's most advanced antibody in development is CSL-360, for AML. But the connection to be made with the contract work completed Arana and the signing of the licence agreement with BioWa is that CSL is probably developing more antibodies in the cancer field. **Novartis**, **MedImmune**, **Genentech**, **KaloBios**, **Medarex** and **GlaxoSmithKline** have also licensed the Potelligent technology.

Opportunity

Although the Arana share price has fallen as equity markets have weakened this year, the company is well placed to take advantage of the opportunities that will emerge as some biotech companies run out of funds. The company should be looking to snap up validated drug targets that are protected by sound IP, where antibodies are the most likely form of technology used to drug the target. The company will also be in a position to expand its focus beyond cancer and inflammatory disease targets, which may be more achievable while asset prices are depressed, should it so desire. The company has a requirement to strengthen its asset base by increasing the diversity of drug targets it has title to.

Summary

There are many different points of positive validation available for investors studying Arana Therapeutics. The company's optimisation and humanisation technology and services have delivered outcomes successfully at least five times for three companies, including CSL, **GlaxoSmithKline** and **Vegenics**. The progression of CSL into the antibody field has been achieved with the aid of Arana's technologies, and no doubt with insights gained from working with Arana scientists. The proximity of the two companies in Parkville should not be ignored. We continue to rate Arana as an exceptional but speculative investment opportunity.

Arana is capitalised at $182 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (21 November 2008)

Company	Price (current)	Price added to portfolio	Date added
Hexima	$0.40	$0.60	October 2008
Atcor Medical	$0.14	$0.10	October 2008
CathRx	$0.65	$0.70	October 2008
Impedimed	$0.55	$0.70	Aug-08
Antisense Therapeutics	$0.03	$0.07	Aug-08
Mesoblast	$0.85	$1.25	Aug-08
Cellestis	$1.88	$2.27	April 2008
IDT	$1.75	$1.90	March 2008
Circadian Technologies	$0.54	$1.03	February 2008
Patrys	$0.10	$0.50	December 2007
Bionomics	$0.21	$0.42	December 2007
Cogstate	$0.17	$0.13	November 2007
Sirtex Medical	$1.80	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.22	$0.66	September 2007
Starpharma Holdings	$0.22	$0.37	August 2007
Pharmaxis	$1.01	$3.15	August 2007
Universal Biosensors	$0.56	$1.23	June 2007
Biota Holdings	$0.38	$1.55	March 2007
Probiotec	$1.26	$1.12	February 2007
Peplin Inc	$0.30	$0.83	January 2007
Arana Therapeutics	$0.78	$1.31	October 2006
Chemgenex Pharma.	$0.47	$0.38	June 2006
Cytopia	$0.17	$0.46	June 2005
Acrux	$0.42	$0.83	November 2004
Alchemia	$0.15	$0.67	May 2004

Portfolio Changes – 21 Nov 2008

IN:
No changes.

OUT:
No changes.

Note:
An out of date version of the Bioshares Model Portfolio was shown in last week's edition of Bioshares. We apologise for this error.

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, 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, Tyrian Diagnostics (Proteome Systems), Mesoblast

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