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In this edition...
In investment circles, some investors are attuned to cyclical and sector trends, so when some Perth-based investors with an track record move from one sector to another, it pays to pay attention. Forrest Capital has now revealed its sixth biotech investment, the latest being a backdoor listing of a dormant pSivida technology into NeuroDiscovery. This investment group is taking a portfolio approach knowing full well that every investment will not pay off. Antisense Therapeutics is set to commence a Phase II trial of ATL1103 in acromegaly subjects and Invion has commenced a Phase II study of INV102 in asthma patients. What might surprise, however, is Invion's lupus program. We update readers on Alchemia and introduce private animal health company Nexvet.
Companies Covered: ACL, ANP, IVX, NDL, Nexvet

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - current)	-3.3%
Cumulative Gain	**234%**
Av. annual gain (11 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.

Another Signal from Forrest Capital that Biotech is Replacing Mining as a Destination for Speculative Capital

Forrest Capital has made its sixth investment in the biotech sector in the last 12 months, managing a backdoor listing of Enigma Therapeutics into ASX-listed NeuroDiscovery (NDL: $0.038). Through the acquisition, NeuroDiscovery accesses rights to pSivida's brachytherapy technology, for the treatment of pancreatic and other cancers.

The brachytherapy technology, called Brachysil, has been evaluated in four clinical studies. The approach is similar to Sirtex Medical's Sir-Spheres for the treatment of liver cancer, where a radioactive isotope is used to irradiate solid tumours. The difference with the Brachysil approach is that it uses radioactive phosphorus, which has a longer half-life than the Sir-Spheres at 14 days, and it is bonded with biosilicon, which is biodegradable. The therapy also differs whereby it is injected directly into the tumour, rather than delivery via the hepatic artery, which is how the Sir-Spheres are delivered.

Under the agreement, NeuroDiscovery will acquire 100% of Enigma Therapeutics for 75 million NDL shares. Forrest Capital will manage a capital raising for $1.5 million, which will give NeuroDiscovery around $3.5 million in funds.

Brachysil Phase II Trial Results

In a Phase IIa study conducted in 17 patients with pancreatic cancer, the Brachysil therapy achieved a disease control rate of 82%. A median overall survival of 10 months was achieved, which compares to 5.7 months survival with the drug Gemcitabine, the current standard of care.

In a Phase IIb trial in six patients, where the dose was increased to four times higher than in the Phase IIa trial, 100% tumour stabilisation was achieved. Early clinical studies have also been conducted in the treatment of liver cancer.

NeuroDiscovery plans to launch a Phase III open label study in 150 patients in the second half of 2013, with a single intra-tumoral injection of the therapy, which has been renamed Oncosil. It is also seeking to apply for CE Mark certification in Europe.

Forrest Capital Targets Biotech as Next Growth Sector

Forrest Capital was an active investor in the resources sector. With the resources boom having ended, it turned its focus to the biotech sector last year, with a string of initial investments. Other recent investments Forrest Capital has been involved with include Imugene, Patrys, Cynata and Sun Biomedical.

One of the drivers behind this deal is the strong success of Sirtex Medical, which has built a profitable business around the ablation of tumour cells using a radioisotope approach. Sirtex Medical is now capitalised in excess of $600 million.

Cont'd over

Antisense Therapeutics to Start Phase II Trial in Acromegaly

Antisense Therapeutics (ANP: 1.4 cents) is now ready to commence its Phase II trial of ATL1103 in patients with acromegaly. The company has sufficient funding to complete the trial, which has the potential to move the company through a significant potential value creations point.

This progress comes on the back on news of a new antisense drug approved by the FDA recently, Kynamro, an event which lends support to the development of antisense drugs.

Antisense completed a positive Phase I trial with ATL1103 in volunteers at the end of 2011. That trial showed that a 7% reduction in IGF-1 levels was achieved after three weeks of treatment (250mg four times in the first week, then once a week for the second two weeks). There was also a 19% reduction in growth hormone binding protein in the blood, which is further evidence the drug candidate was having the desired effect.

The Phase II trial due to commence will involve 24 patients with acromegaly, rather than volunteers. These patients have elevated IGF-1 levels, so if the drug is effective, it should see greater levels of reduction of IGF-1, which is not only the biomarker but also a key primary endpoint.

The trial will be conducted at six sites in the UK, Spain and France. Endocrinogist Peter Trainer will be involved with the trial. CEO of Antisense Therapeutics, Mark Diamond, said Dr Trainer is a leading authority in the field of acromegaly. Dr Trainer was involved in the trials with existing acromegaly drug Somavert.

Patients will be dosed with ATL1103 over a three month period. They will either receive 200mg once a week for 13 weeks, or 200mg twice a week over 13 weeks. There will be a one month follow up of patients following dosing. The trial will not be blinded, so there is the potential for some data to emerge before the trial has been completed. The trial is expected to be completed by the end of this year, with a report on the trial out in the first quarter of 2014.

ATL1103 will need to achieve in excess of 25% reduction in IGF-1 levels if it is to be an attractive therapeutic option. A longer term study in primates previously showed a 30% reduction in IGF-1 levels was achievable.

If the Phase II trial is positive, Antisense will look to move the drug into a Phase III setting, which may involve around 200 patients.

There are about 85,000 people in the northern hemisphere with acromegaly. About half are treated adequately with surgery. Of the remainder, around 60% are treated effectively with the drug Octeotride. However, 40% have resistance to this drug and with the remaining option being the drug Somavert. ATL1103 fits into being a more suitable treatment than Somavert. Somavert is expensive, needs to be injected daily, must be reconstituted and has shown to causes growth hormone levels to increase, rather than decrease.

Key Features of the Program

There are a number of attractive features to this program. The first is that the biomarker that measures efficacy is in fact the endpoint, so it is easily measured, compared to say progression free survival or tumour reduction in cancer patients. The company also has achieved positive results in primate studies and in the Phase I trial in volunteers, although the Phase II study will need to show greater reduction in IGF-1 levels than the 7% achieved in the Phase I study. And antisense drugs are known to accumulate in the liver, which is where IGF-1 is produced.

Kynamro Approval

The positive news for antisense drug developers last week was the approval of the first systemic antisense drug, Kynamro. Kynamro was developed by Isis Pharmaceuticals (Antisense Therapeutics' partner and technology developer) and will be marketed by Genzyme for the treatment of homozygous familial hypercholesterolemia.

An aspect of antisense drugs that needs to be monitored is the side effect profile, which includes injection site reactions, flu-like symptoms and increased liver enzymes. In Antisense Therapeutics' Phase I trial, injection site reactions were the most common, and one patient reported increased levels of the liver enzyme ALT which returned to normal during the dosing period.

Antisense Therapeutics had $5.1 million in cash at the end of 2012. The acromegaly Phase II trial is expected to cost around $2 million.

Bioshares recommendation: **Speculative Buy Class C**

Bioshares

– Forrest Capital/Neurodiscovery cont'd

Another driver is the search for alternative speculative investments following the peak of the resources sector. Forrest Capital, which was an early entrant in the resources sector at the start of the mining boom, is now hopeful it has well timed its foray into the biotech sector. What Forrest Capital also supplies is the ability to access further funds for Phase III clinical studies, which will be required.

Bioshares recommendation: **NDL – Speculative Buy Class B**

Bioshares

Invion Aims for Early POC Data for INV103 in Lupus Patients

Invion (IVX: $0.064) was formed through the merger of Brisbane-based CBio and a private US company, Inverseon in August 2012. Consideration for the acquisition was in CBio shares, amounting to 37.5% of the shares of the merged entity.

CBio's lead program was the development of Xtoll as a potential treatment for rheumatoid arthritis. Xtoll is a modified version of chaperonin 10 (CPN10), or heat shock protein 10 (HSP 10), or early pregnancy growth factor. (XToll has been rebadged as INV103)

CBio's Phase IIa trial of Xtoll was unsuccessful. As announced in July 2011, the primary endpoint of the 155 patient trial of improvement in the ACR 20 score of rheumatoid arthritis symptoms was not met. A number of other secondary endpoints were met.

Role of IL-6

Also observed was significant decrease in interleukin-6 (IL-6) levels in patients which received the higher dose used in the trial (75mg), with circulating levels reduced to levels reported in healthy subjects. This observation has now increased in importance as it contributes to the rationale for the continuation of clinical studies of XToll/INV103 in patients with systemic lupus erythematosus (SLE) ('lupus'), a chronic inflammatory disease.

CBio had completed pre-clinical studies of XToll in mice and reported that the biologic compound 'entirely prevented cutaneous lupus' and also significantly suppressed nephritis in the kidneys, an organ which often becomes critically damaged in lupus patients.

According to Invion's Chief Medical Officer, Dr Mitchell Glass, IL-6 is a marker of blood vessel inflammation (vasculitis) and lupus is fundamentally a vasculitis. The difference between lupus and rheumatoid arthritis, according to Glass is that IL-6 plays a pivotal role in lupus but has more of an associate role in RA.

Glass' thesis is that if the inflammation in the blood vessels can be blocked then a profound impact on the disease should occur.

Pre-IND Meeting

Inverseon concluded a pre-IND meeting with the FDA towards the end of 2012. The FDA confirmed that INV103 could be developed as a potential treatment for SLE, accepted the company's animal and human safety data to support a proof-of-concept strategy and accepted the clinical trial protocol, subject to a final review of the protocol.

The proof-of-concept trial may be divided into two parts, with an initial cohort of eight patients in the 24-36 patient trial, being subjected to evaluation (e.g. dose related considerations) prior to the dosing of the remaining patients.

Invion would be seeking to enroll SLE patients with less severe symptoms, in other words not end stage patients. The company would also assess subjects on the basis of bio-chemical markers (e.g. high levels of IL-6) as well as clinical symptoms (e.g. protein in the urine).

Invion's goal in the trial would be to achieve a significant difference (a definitive result) in a six-month period.

The trial protocol has yet to be agreed to by the FDA. What will be of great interest is the attitude the FDA takes towards IL-6. If it considers IL-6 is a valid surrogate bio-marker for SLE, then such an acceptance will be a very significant step forward for Invion. Blood based biomarkers can be assessed rapidly and their availability can speed up clinical development enormously.

Unmet Need in Lupus Drug Market

The market potential for INV103 in lupus is driven by unmet need, with only a few medical options available for the treatment of the disease, including corticosteroids.

Only relatively recently, in 2011, Benlysta (belimumab) was approved by the FDA. Benlysta, which was developed by Human Genome Sciences in partnership with GlaxoSmithKline. (GSK acquired HGS in 2012 for US$3.6 billion).

Benlysta blocks the effect of B-cells that produce the auto-antibodies that typify SLE, by targeting a complex known as B-lymphocyte stimulator. However, the drug is not effective with all SLE patients, a fact discovered after the failure of an earlier trial. This situation is of advantage to Invion, although there are an estimated 20 other therapies in the SLE drug development pipeline. Many of these therapies have a B-cell focus.

Potential direct competition for INV103 exists in the form of Johnson & Johnson's CNTO 136 (sirukumab) which is currently in a 25 patient Phase II trial. Results are expected in September 2013. CNTO 136 is an anti-IL-6 antibody, which is also in development as a treatment for RA.

Patent

Invion's Australian patent covering the modified form of INV103 (CPN10) expires in 2026.

The next major milestone for INV103 will be a clearance by the FDA of Invion's IND submission.

INV102 Update - Asthma Study Commenced

INV102 is the re-purposed identity for well known beta-blocker drug, nadalol. This drug has been administered to more than 8 million patients, to treat high blood pressure and chest pain. The drug is administered orally, in capsule form.

INV102 is being developed to treat respiratory conditions such as asthma and COPD. The novelty of the therapy is that rates of respiratory illness were observed in patients taking beta-blockers. The scientific founders of Inverseon discovered that chronic dosing of beta-blockers, could be effective if the dose was titrated from a small starting dose.

Invion has commenced the first of two Phase II trials planned for INV102. This first trial (the 'NIMA' study) is supported by US$4.4 million in funding from the US National Institutes of Health.

Cont'd over

Alchemia Update

Alchemia's (ACL: $0.33) CEO Pete Smith resigned suddenly and unexpectedly in late January. The company's share price has been slashed following the failed demerger/listing of the company's subsidiary, Audeo Oncology, in the US.

This week the company announced the completion of recruitment into its Phase III oncology trial, with a suggestion that results are leaning towards a positive trial outcome. But what is weighing down the company's share price the most is a widely expected capital raising, that will take the company to the end of its Phase III trial and to profitability.

By mutual agreement between the board of Alchemia and Smith, Smith decided to step down. The failed demerger/listing of Audeo Oncology was a disappointment to both shareholders and management. There were several reasons why it didn't get across the line, with a leading factor being the structure and the immediate windfall for Australian investors, which some US investors found unpalatable.

One of the points of disagreement going forward was how to proceed with the demerger. At this stage, it appears more likely that a demerger will be considered in early 2014, once the Phase III results have been released. This is a more appropriate path, where if the trial is successful, then a substantially higher technology value can be attributed to the spin out. If the trial fails, then there is no point for demerging the company because the programs will likely cease.

Alchemia had previously anticipated the Phase III HA-Irinotecan trial would have been completed in the third half of 2013. However it would appear that patients are taking longer to progress that what is historically seen.

This means either that everyone in the trial is doing better than historical outcomes in this patient group including those in the control arm, or that the HA-Irinotecan arm is delivering a better outcome for patients, extending the mean disease progression rate overall in control and treatment groups (data has not been unblinded yet so it's not known what has caused this better than expected result).

It should not immediately be assumed that the extended time for disease progression overall in the first set of patients is because the patients in the active arm (those taking HA-Irinotecan) are doing better than those in the control arm (HA-Irinotecan). But it is an encouraging sign. (Both groups are also taking the FOLFIRI chemotherapy drug regime).

Alchemia's share price has fallen 40% since it was announced the demerger would not proceed. One of the reasons the share price has fallen so far is that the market is expecting the company to raise additional funds to get the company through to profitability, and to complete the Phase III trial. Once that raise occurs, then there should be a strengthening in the company's share price.

Other factors to drive the company's share price will be increased profit share from fondaparinux sales. The company should report the December quarter profit share later this month. Of interest, GlaxoSmithKline's sales of Arixtra (fondaparinux) in the US increased to US$31 million in the December quarter, up from the low of US$25 million in the March quarter of that year. This suggests the market for fondaparinux continues to grow, with two generics on the market, one being the authorised generic sold by Apotex, the other sold by Dr Reddy's (Alchemia's partner).

Funding and the appointment of new CEO are unresolved issues of risk for Alchemia. *Bioshares'* view is that appointment of an internal candidate would not be in the best interests of shareholders.

Bioshares recommendation: **Speculative Hold Class A**

Bioshares

– Invion cont'd

This first study will enroll 60 asthma subjects across three centres in the US. Endpoints in the trial will include airway hyper-responsiveness, as well as signs and symptoms and the use of rescue medication. The primary objective will be the assessment of INV102's effect on airway responsiveness to inhaled metacholine.

A second 'smoking cessation' study will explore the potential for INV102 to ameliorate coughing in smokers needing to stop smoking. This trial is likely to enrol 120 patients with chronic bronchitis. It may include a sub-set of patients with lung cancer who are required to quit smoking. Invion is currently waiting on Investigational Review Board approvals for the trial.

Litigation

Invion is engaged in litigation with former executives of the company. Invion (under its previous banner of CBio) began legal proceedings in February 2012 in respect of a former executive chairman, CEO, CFO and company secretary. Invion is seeking to claim back payments (in the order of $1.2 million) made to these executives that were made, it is claimed, without suitable authority. However, the group of former executives has filed a counter-claim against Invion worth $1.246 million.

Summary

The opportunity to quickly ascertain the potential of INV103 as a treatment for lupus adds considerable value to the Invion investment proposition. Coupled to the INV102 program, which is now re-commencing clinical studies, Invion presents itself as a low cost of development biotech play with several value inflexion points timed to occur over the next 12-24 months.

Invion is capitalised at $25 million and retained cash of $3.4 million at December 31, 2012.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (8 February 2013)

Company	Price (current)	Price added to portfolio	Date added
Psivida	$1.43	$1.550	November 2012
Benitec	$0.015	$0.016	November 2012
Nanosonics	$0.520	$0.495	June 2012
Osprey Medical	$0.60	$0.40	April 2012
QRxPharma	$0.96	$1.66	October 2011
Somnomed	$1.00	$0.94	January 2011
Cogstate	$0.350	$0.13	November 2007
Clinuvel Pharmaceuticals	$2.22	$6.60	September 2007
Universal Biosensors	$0.88	$1.23	June 2007
Alchemia	$0.330	$0.67	May 2004

Portfolio Changes – 8 February 2013

IN:
No changes

OUT:
No changes

Private Company Profile – Nexvet

Nexvet is a Melbourne-based animal health company that investors would do well to be aware of in 2013, given that the company is a potential IPO candidate.

The company was formed in February 2010 by Mark Heffernan and brothers David and Andy Gearing. CEO Heffernan holds a biochemistry PhD from Monash University. He was a co-founder of inflammatory diseases therapeutics company Opsona Therapeutics, which is based in Ireland. CSO David Gearing was formerly Chief Research Officer and Director of Research at CSL, and a founder of Millennium Biotherapeutics. Andy Gearing is a non-executive director. He is the CEO of business development company Biocomm[2].

Other board members include Peter Howard, currently Corporate Executive and General Counsel at Mesoblast, and Andrew O'Brien, a financial adviser to the Trans-Tasman Commercialisation Fund.

Animal Biologics

Nexvet is developing a suite of biologic drugs for the treatment of pain and inflammation in dogs, cats and horses. The company is possibly the first in the world to pursue this business objective, with the economics of developing biologics for animal health previously perceived as an insurmountable barrier. Other barriers in general to developing biologics include freedom to operate issues surrounding technologies used to humanise and optimise monoclonal antibodies or other proteins (e.g receptor fusion proteins).

However, Nexvet has developed its own technology ('PETisation') which is akin to the humanisation process that is applied to monoclonal antibodies that are derived from a donor species such as mice. Nexvet claims that its PETisation process retains the binding affinity of a donor antibody better than other approaches such as CDR (complementarity determining region) grafting and can be also done much more quickly and cheaply.

Affinity is a crucial aspect of monoclonal antibody drug development. It refers to the degree to which a mab binds to an epitope. An antibody might have a high degree of specificity to an antigen, but without a strong affinity, the required biochemical activity is weak or lacking.

The company has demonstrated that its lead drug candidate does not elicit an immune response i.e. is non-immunogenic. This is an important technology development milestone that has now been achieved.

Possibly the most important issue that Nexvet has been able to address is that of cost of goods (COGS), estimating that it can develop biologic drugs that are competitive with the list pricing of certain current companion animal medicines.

Products in Development

The company has eight products in development, with the lead product NV-01 being developed to treat pain related to osteoarthritis in dogs. The drug targets Nerve Growth Factor.

In a welcome move, Nexvet will develop products aligned to the higher standards of human health (i.e. randomised, controlled studies) so that higher quality medical (and marketing) data can be created. This is a more expensive approach that is less frequently adopted in the world of veterinary medicine.

Funding

Financing of $3.5 million to date has come from sophisticated and industry-aware high net worth individuals in addition to the Trans-Tasman Commercialisation Fund. The company is open to accessing additional capital through an IPO but also will be looking to access funding through partnerships. In August 2012, Nexvet licensed a canine anti-inflammatory product to Meiji Seika Pharma on undisclosed terms.

The company would like to take two products through development to the marketing authorisations stage, a process which it estimates would cost an estimated $25 million.

Summary

As much as can be ascertained with the benefit of the more complete disclosure that comes through the issuance of a prospectus, Nexvet bears the hall marks of a quality biotech operation which has moved rapidly to build value for its founders and investors. Should the IPO market open again in Australia, Nexvet may be one of the better quality offerings to appear.

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

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