ISSN 1443-850X

In this edition...
After much effort and consideration, Hunter Immunology has decided to merge with Sydney-based Probiomics. Hunter Immunology has an interesting potential therapeutic for the treatment of COPD, which is a massive market opportunity.
Circadian's relatively new structure as an oncology business is starting to take shape, with its Phase I clinical trial due to start soon. The company potentially has some very valuable and unique assets and is capitalised at only $21 million. And Mayne Pharma has received a setback from the European drug regulator.
The Editors
Companies Covered: CIR, MYX, PCC-Hunter Immunology Merger

	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 - May '09)	-7.3%
Year 9 (May '09 - May '10)	49.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 now commenced	-27.2%
Cumulative Gain	**206%**
Av. annual gain (10 yrs)	**21.2%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.
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AFS Licence
No. 258032

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Individual Subscriptions (48 issues/year)
$375 (Inc.GST)
Edition Number 437 (16 December 2011)
ISSN 1443-850X

Bioshares

16 December 2011
Edition 437

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

Probiomics and Hunter Immunology to Merge via Public Offer

The privately-held Hunter Immunology is preparing to merge with Probiomics (PCC: $0.01), complete a capital raising and re-list as Bioxyne by March 30, 2012.

Probiomics is conducting a public offer to raise a minimum of $2.2 million and a maximum of $4.4 million, with shares issued at 1.1 cents. The market capitalisation of the merged group at the offer price is $37.2 million. A 20:1 consolidation is expected to occur on completion of the merger.

Probiomics markets proprietary probiotics to treat irritable bowel syndrome, diarrhea, intestinal health and atopic dermatitis in infants. It also has an agreement with Chr. Hansen of Denmark to manufacture, market and supply its proprietary probiotic strain in dietary supplements, OTC drugs, in sports nutrition, clinical nutrition and slimming products.

Probiomics and Hunter Immunology [founded 2003] share a common founder, with Professor Robert Clancy from the University of Newcastle co-founding Probiomics when it was formerly called VRI Biomedical [founded 1998, listed 2000]. VRI Biomedical was responsible in its earlier days for the development of several immunotherapy programs that are similar to those developed by Hunter Immunology.

Hunter Immunology has received as net proceeds from financing a little over $17 million since FY2006.

The Oral Immunotherapy Program

Hunter Immunology has developed an oral vaccine that has the potential to treat sufferers of chronic pulmonary obstructive disease (COPD) by reducing exacerbations and hospitalisations.

COPD is linked to rates of smoking and is a large and growing market with a pronounced medical and economic burden.

Hunter's immunotherapy is based on the observation that most frequently isolated bacteria from the sputum of patients with smoking related lung disease is *haemophilus influenza*.

The company's treatment theory is that oral vaccination with killed inactivated *haemophilus influenza* will stimulate a mucosal immune response, leading to reductions in exacerbations.

The Results of the Phase IIa COPD Trial

Hunter Immunology has conducted several clinical trials of its lead therapeutic vaccine candidate, HI-164OV. The results of a Phase IIa trial were published in the journal *CHEST*.

A limitation of this trial was that the trial was underpowered due to less than expected recruitment and the loss of a study site.

The placebo controlled, randomized trial enrolled 42 patients with 38 subjects being analysed. The patients were classified as severe COPD patients, having had two or more acute episodes in a two year period. It was this 'consecutive years' selection rule which became an impediment to reaching the minimum number of 100 subjects required to properly power the study.

Subjects received two 45 mg tables of HI-164OV twice a day for three days at the beginning of each month, for three months, then were followed for four months, creating a study period of six months.

Total exacerbations in the treatment group decreased by 16%. However this result was not statistically significant. One the other hand moderate-to-severe exacerbations, defined as those treated with cortico-steroids, were reduced by 63%, a result that was statistically significant (p=0.05).

Perhaps the most striking result from this trial was the reduction on hospitalisations that were due to the administration of HI-164OV. There were 11 respiratory-based admissions for the placebo group against three admissions in the treatment group, a statistically significant 90% reduction in hospital admissions (p=0.4).

According to the Probiomics's public offer document another Phase II trial in 102 patients with less severe disease, HI-164OV did not show any clinical benefit.

However, the Phase IIa trial gave the company confidence to proceed with a larger Phase IIb trial, designed to deliver appropriate statistical power.

The Design and Plan of the Phase IIb COPD trial

The Phase IIb trial in moderate to severe COPD subjects is similar in design to the earlier randomised, placebo controlled Phase IIa trial, following the same dosing regime. The trial has now recruited its planned 320 trial subjects across 21 sites in Australia.

The primary endpoint is the rate of exacerbations requiring oral or parenteral cortico-steroid treatment or hospitalisation.

Some secondary endpoints include the proportion of participants per group requiring oral or parenteral cortico-steroid treatment or hospitalisation, the time to steroid use or hospitalisation, or time to antibiotic use. The total number of exacerbations defined as mild, moderate or severe will also be an endpoint.

In contrast to the inclusion criteria for the Phase IIa trial, inclusion criteria included patients with a history of one moderate or severe COPD exacerbations in the last twelve months. Subjects were also to have a COPD severity status defined by FEV <60% of predicted, in contrast to a FEV <50% inclusion score for the Phase IIa trial.

Results of the trial are expected to be available in April, 2012.

Earlier Problems with the IND

Hunter Immunology had filed an Investigational New Drug (IND) application with the US FDA July, 2008. The FDA placed a Clinical Hold on this application until the company was able to satisfy a number of concerns, including the completion of certain toxicology studies and the provision of GMP commercial scale manufacturing information.

The company has been addressing these concerns, receiving correspondence from the FDA accepting some toxicology data.

However, without an IND the company cannot conduct US clinical studies which are often required, although not technically obligatory, for US drug applications. This would appear to be one of the company's current investment weaknesses.

– Cont'd on page 4

Selected Hunter Immunology Clinical Trials Summary - HI164OV
[Inactivated, Whole Cells of Non-Typeable Haemophilus Influenza, isolate 164]

Trial Code	Status	Phase	Description	Num. Pts Planned	Num. Pts Actual	Inclusion Criteria	Dose
HI-H005	Active	Phase IIb	Reducing the Rate and Severity of Exacerbations in Pts with Moderate to Severe COPD	340	320	1 moderate or severe acute COPD exacerbation in last 12 months; FEV1 <60% predicted	2x45mg/ 3 cons days/ each month for 3 months
?	Completed	Phase IIa	Reducing the Rate and Severity of Exacerbations in Pts with Moderate to Severe COPD	>100	38	2 acute COPD exacerbation each year in last 24 months; FEV1 =< 50% predicted	2x45mg/ 3 cons days/ each month for 3 months
Published: CHEST 137 4 April 2010							
HI-H003	Completed	Phase I	Smokers at Risk of Recurrent Bronchitis	64	64	Have smoked at least 10 cigarettes/day for last 2 years	2x45mg/ 3 cons days/ each month for 3 months
Published:Clinical and Experimental Immunology, 161:127-133							

Circadian – Excellent Value for the Longer Term Biotech Investor

The Chief Executive of ASCO (American Society of Clinical Oncology) made an interesting point at this year's ASCO conference; the field of cancer therapy is going to need to learn how to combine two or more targeted therapies to "block the main road, the side road and the dirt road."

This is a very relevant statement for Circadian Technologies (CIR: $0.45). One of the most successful cancer drugs in recent times, Avastin, generated sales of US$7.2 billion last year. This treatment blocks the formation of new blood vessels which are crucial to allow solid tumour growth. However for 25%-50% of patients on this drug, their tumours work about how to bypass this system, turning on other angiogenic (blood vessel growth) factors.

Avastin blocks what is called the VEGF-A signaling pathway. Circadian's core technology covers blocking other pathways in this family of growth factors, namely VEGF-C and VEGF-D.

A study conducted at the prestigious MD Anderson Cancer Center and published last year specifically proved the technology that Circadian is seeking to commercialise. In that study patients on chemotherapy and Avastin therapy showed that as their disease moved from stable to progressive, the circulating levels of the VEGF-C protein were increasing at precisely the same time. What this indicates is that whilst Avastin is successful in shutting down one pathway, another pathway (VEGF-C) opens to allow the tumour to start growing again.

Two Opportunities for Circadian's VEGF-C IP

Two distinct roles for VEGF-C are presented in cancer therapy. The first is the opportunity to use VEGF-C drugs in combination with Avastin, either immediately with Avastin, or one once the patient starts to relapse and tumour growth starts up again.

The second application is to use VEGF-C as a diagnostic, to give patients and doctors an early sign that is easily measurable for when Avastin therapy is failing.

First Application – VGX-100

Circadian is looking to start a Phase I trial with its first VEGF-C inhibitor, an antibody drug candidate called VGX-100. The first part of that trial will be looking at the safety of VGX-100 on its own (in three cohorts), and then will look at the safety profile when delivered in combination with Avastin. That second part should start around June next year. The aim is to complete the Phase I trial by November 2012.

The company is looking at getting this product to market the fastest way possible. Its current plan is to accelerate trials in patients with glioblastoma, for which Avastin is currently approved. Avastin was approved for this use following only a 167 patient Phase IIb study.

Circadian believes that the side affect profile for its VGX-100 should be better than Avastin's. There is a 1.7% risk of a perforated bowel with Avastin use (although most (around 80%) can be treated without surgery). There is also an increased risk of bleeding and hypertension with Avastin. VEGF-A inhibitors cause a lot of vascular permeability but VEGF-C inhibitors do not, according to Circadian CEO Robert Klupacs. "Our tox profile is remarkably clean," believes Klupacs.

On the efficacy side, VGX-100 should not only block blood vessel growth but also restrict growth of lymphatic vessels which facilitate the spread of tumours throughout the body.

Faster Acceptance of Combination VEGF-C therapy

The rational for combining a second VEGF drug that works to block a different pathway appears very clear. Both Avastin and Circadian's VGX-100 are antibody drugs. Their side effect profiles should be similar, and Circadian believes its drug's side effect profile should be even better than Avastin. The forthcoming Phase I trial will shed light on that. If combination use of the two drugs can be shown to be safe, then there should be a very strong chance of an improved therapeutic outcome. This rational should not be lost on oncology clinicians who have a lot of experience with using VEGF type drugs and thereby we expect adoption of an approved VEGF-C therapy, such as Circadian's, should be quite rapid, if the drug can get onto the market.

Tackling diseases such as glioblastoma, where the disease is almost always fatal, should see keen interest to trial VCX-100 and a potentially fast track approval if effective. Circadian believes approval of this drug candidate, if is successful, could occur within four years (late 2015).

Second Application

Circadian's VEGF-C technology could also be used to monitor for Avastin resistance or for when disease progression begins. Testing patients every two months at $200 per test represents, by our estimates, a potential global market of around $160 million a year.

Third Application

Another application for VGX-100 is for use in the treatment of eye diseases. One particularly interesting use is for people undergoing a corneal transplant. A problem with corneal transplants is that blood vessel and lymphatic vessel growth in the eye can prevent successful binding. An increased expression of the VEGF-C protein has been found where corneal transplants have been rejected.

There is the risk of blindness in this procedure and the use of immune system modulating drugs is required to help prevent rejection. However they have little effect.

There is a very good case for trialing VGX-100 in this indication. Over 10,000 corneal transplants occur each year in the US and Circadian believes this presents a unmet clinical need worth over $300 million a year.

Circadian is looking to start a clinical trial in early 2013 in this indication and if all goes well could file the drug for approval for

Cont'd over

– *Circadian cont'd from previous page*

this indication by the end of 2015. It's an attractive indication for Circadian because the patient numbers to gain approval for this indication may not need to be high. It could also potentially take the drug to market on its own, being a narrowly distributed market.

Other Diagnostic Tests

In the first half of next year, Circadian's partner Healthscope is expected to launch a test for Cancer of Unknown Primary origin. Circadian licensed the test to Healthscope in 2009 for Australia, New Zealand, Singapore and Malaysia.

In February this year Circadian's partner Cincinnati Childrens launched a diagnostic involving a VEGF-D test for a degenerative lung condition in women. This represents potential future revenue to Circadan of between $1-$2 million. That same test however could potentially be used for a much larger market, that being to test the effectiveness of a particular class of cancer therapies (mTOR drugs including Affinitor).

Funding

At the end of November Circadian had $19 million cash. It has assets in its shareholding of Antisense Therapeutics (11%, currently worth $3 million) and Optiscan Imaging (7% currently worth $0.8million). Circadian expects to receive royalty from its diagnostic products, those being a VEGF-D test which is being sold in the US, and a test for Cancers of Unknown Primary which is expected to be launched in early 2012. These tests could initially bring in revenue of $1 million a year. The company is also seeking to gain grant funding for some of its programs and will also be eligible for an Australian Government R&D rebate. The company believes it has sufficient funding to get to early 2014.

Summary

Circadian has a number of commercial opportunities available around its franchise of VEGF-C and VEGF-D assets. Its clinical trial due to start with VGX-100 should deliver key aspects around the safety profile of the drug candidate, both for use on its own and more importantly, in conjunction with Avastin. If this combination therapy is safe, then there's a very good chance it will become a viable commercial product to be used with the $7 billion Avastin blockbuster drug.

Circadian is capitalised at $21 million.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

– *Hunter Immunology merger cont'd from page 2*

HI-164OV Strategy

Hunter Immunology does not envisage HI-164OV being used as a standard on care in its targeted patient groups, rather it would be used to lift the clinical outcomes from existing medicines.

The company's existing commercialisation strategy is to partner, license or sell product candidates at completion of the proof of concept stage.

Competition Risk

Although Hunter Immunology has filed patents covering its vaccine specific strains and for use in COPD and severe allergic asthma, with its key patent expiring in 2029, the company faces the risk that a variation of the above approach could be adopted by rivals who successfully patent different bacterial strains or antigenic material.

Summary

The logic of merging Probiomics with Hunter Immunology is that a common scientific heritage and focus on mucosal immunity is joined together in a company with an strengthened ability to develop, commercialise and market products. Hunter Immunology brings to the merged entity other vaccine opportunities based on administering inactivated forms of *P. aeruginosa*, *S. Aureu*s and *C. Albicans*.

The clinical development of HI-164OV is now at a point where clear proof-of-concept data can be gained. The upside for the product in treating COPD patients is potentially very large and attractive. However, the commercialisation strategy for HI-160V is incomplete while the US IND commands a Clinical Hold status.

Given that the company's strategy is to license once it has achieved proof-of-concept data, an issue is that the licensing terms would be arguably less than optimal for HI-164OV in the absence of data derived under a US IND protocol.

Investors are required to read the prospectus before subscribing to the offer. A copy of the prospectus can be downloaded at:
http://www.probiomics.com.au/index.php?option=com_content&task=view&id=30&Itemid=54

Bioshares

Bioshares Model Portfolio (16 December 2011)

Company	Price (current)	Price added to portfolio	Date added
QRxPharma	$1.25	$1.66	October 2011
Mayne Pharma Group	$0.400	$0.435	September 2011
Genetic Technologies	$0.12	$0.18	August 2011
Acrux	$2.98	$3.37	June 2011
Bioniche	$0.69	$1.35	March 2011
Somnomed	$0.91	$0.94	January 2011
Phylogica	$0.045	$0.053	September 2010
Biota Holdings	$0.79	$1.09	May 2010
Tissue Therapies	$0.40	$0.21	January 2010
Atcor Medical	$0.08	$0.10	October 2008
Impedimed	$0.57	$0.70	August 2008
Bionomics	$0.54	$0.42	December 2007
Cogstate	$0.24	$0.13	November 2007
Sirtex Medical	$4.35	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.51	$6.60	September 2007
Pharmaxis	$1.05	$3.15	August 2007
Universal Biosensors	$0.80	$1.23	June 2007
Alchemia	$0.315	$0.67	May 2004

Portfolio Changes – 16 December 2011

IN:
No changes

OUT:
No Changes

Mayne Pharma Receives Setback to SUBACAP

Mayne Pharma (MYX: $0.40) has hit an obstacle with its SUBACAP program as it moves towards gaining European approval. Its 175 patient comparative study compared its version of the antifungal drug itraconazole (SUBACAP) to the market leader Sporanox and a placebo.

It was an excellent result for Mayne from the perspective that SUBACAP showed clear benefits at only half the dose over Sporanox. The problem however was that Sporanox was no better (not statistically significant) than the placebo.

This has resulted in the European regulator questioning the validity of the trial – "No conclusions on the non-inferiority of SUBACAP compared to the reference drug can be made".

Mayne has three options. The first is to argue its point with the European regulator. The second is to conduct another pharmacokinetics study, which may take another nine months, where it will pick the right dose to deliver the same result as Sporonox, which has a very poor bioavailability.

The third is to wait around two years for its Phase III study in the US to be completed and to use that data.

This is another questionable decision from the European regulator. SUBACAP has an obvious safety and efficacy benefit over Sporonox. Yet to get the drug approved remains difficult.

The issue with option two is that if it gets a dose that only matches Sporonox, then it likely won't have any label claims of superiority over Sporonox, only an implied benefit from using a lower dose.

Doryx Update

Mayne has provided an update on its partner Warner Chilcott's patent dispute around the oral antibiotic, Doryx. In summary, the generic company Mylan may be able to launch its generic version of Doryx before the patent dispute goes to court, which should be around February next year. In our view, we don't expect Mylan to launch 'at risk' as there are large penalties if it loses the patent case.

Mayne and Warner Chilcott are still trying to stop Mylan being in a position to launch 'at risk' before the patent case goes to court. Warner Chilcott has also introduced a double score version of the 150mg dose, which is another small, and somewhat different tactic to slow its competitors. So the generics drug game continues.

Mayne Pharma is capitalised at $61 million.

Bioshares recommendation: **Hold**

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. 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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