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# Bioshares

**13 December 2013**
**Edition 533**

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

**Companies covered: BLT, CGS, PYC, PBT Reproductive Health Science, Hatchtech**

| | 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 - May '13) | 3.1% |
| Year 13 (May '13 - Current) | 47.3% |
| **Cumulative Gain** | **425%** |
| **Av. annual gain (13 yrs)** | **18.9%** |

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Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence
No. 258032

Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9329 3350
Email: info@bioshares.com.au

**David Blake - Editor**
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
**Mark Pachacz - Research Principal**
Ph: 0403 850 425
Email: pachacz@bioshares.com.au

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## *Benitec Files IND – Last Major Hurdle Before Clinical Studies Begin*

Benitec (BLT: $0.50) this week announced it had filed its IND (investigational new drug) application with the FDA. This follows the green light from the NIH in the US in July to proceed with its gene therapy approach using RNAi to treat patients with chronic Hepatitis C infection. The filing comes in the same week that Gilead Sciences received approval for its new HCV drug, Sovaldi, which was bought for US$10.8 billion (from Pharmasset at end of the Phase II stage of development) at the end of 2011.

Sovaldi is approved for use in combination with ribavirin, an all-oral delivery treatment option for patients that removes the need for injection of interferon, which has unpleasant side effects. Sovaldi has been approved for the treatment of patients with HCV genotypes 1, 2, 3 and 4 in combination with ribavirin (delivered orally). It is a disruptive technology of its own, moving patients away from interferon injections to a daily oral treatment. Gilead's market capitalisation has increased from $28 billion when the deal with Pharmasset was announced to a staggering US$109 billion this week.

Benitec says its drug treatment is also potentially a disruptive technology, which is true. If it works, it has the potential to deliver a *once only* cure for patients as a monotherapy, where the liver cells are infected with a virus to get the DNA directed RNAi therapy to stop the virus replicating.

Benitec's IND submission was 15,000 pages in length, so it may take some time for the FDA to review the application. The FDA is required to complete the assessment in 30 days. However, the clock stops each time the FDA has any questions.

Benitec has had two previous pre-IND meetings with the FDA, although not a recent meeting. The FDA was present at the company's NIH review of the program. In a preclinical study in 80 monkeys, it was shown that the therapy could achieve complete transfection into all liver cells. The program was also successful in the standard cell culture model. However there is no good animal model for HCV.

Benitec has two sites ready to start enrolling patients. Patients are likely to be those who have failed other treatments. CEO Peter French says he is confident the company's application will be reviewed well by the regulator.

For investors, the technology risk is very high, however this is matched and very likely exceeded by the technology's potential. In a scientific paper around the technology accepted for publication this week, the author, Benitec's Senior VP of R&B, Dr David Suhy, wrote that 'researchers concluded that the likelihood of any clinically adverse effects was very low,' with Benitec's potential ddRNAi treatment for patients chronically infected with HCV. Progression into human studies will be a major milestone for the company.

*Bioshares* recommendation: **Speculative Buy Class A**

# *Backdoor Listing – Reproductive Health Science*

Adelaide-based Reproductive Health Science (RHS) is securing a back-door listing through the shell of AO Energy (AOM).

AOM will issue 200 million shares to acquire RHS. In conjunction with the acquisition, 60 million shares will be issued to raise $2.4 million. The offer will open on February 3, 2014 and shares are expected to re-commence quotation on March 3, 2014

A 1:5 share consolidation will be completed post acquisition and capital raising so that 82.7 million shares will be outstanding.

### History

The history of RHS dates back to 1994 when a precursor company NCPGG was founded by the University of Adelaide's technology transfer office. The company name was changed to Reproductive Health Science in 2003 and it began its operations in its current form in 2004.

To date, the company has received $4.2 million in venture funding and $1.3 million in grant funding.

### Chromosome Counting Technology

RHS's technology is used in a pre-implantation genetic screening (PGS) step in the IVF (in vitro fertilization) process, to more rapidly identify chromosomal abnormalities. The technology means that technicians can count the number of chromosomes inside a single cell.

According to RHT, chromosomal abnormalities are the main cause of failure in IVF cycles, which has an 80% failure rate. It is estimated that half of all embryos used in IVF have the wrong number of chromosomes (aneuploidy). Another chromosomal abnormality is polyploidy, where an organism has more than two sets of chromosomes.

According to the most recent data for 2011 published by the University of NSW, there were 66,347 IVF cycles performed in Australia and New Zealand, of which 23.1% resulted in a clinical pregnancy, 17.8% in a delivery and 17.5% in a live delivery.

Pre-implantation screening increases the chances of a chromosomally normal embryo to be selected for implantation. However, only 2% of IVF cycles in Australia (and globally) use PGS.

The fact that current PGS methods yield similar rates for clinical pregnancy (22%) and live delivery (17.8%) to the total numbers of IVF cycles indicates weaknesses and limitations with existing approaches.

### Business Plan

RHS has out-licensed its PCR know-how to Kappa Biosystems, a Boston based company which has links to more than 55 distributors. Kappa Biosystems manufactures its products in Cape Town, South Africa.

RHS intends to market several co-branded products through its partnership with Kappa Biosystems. These products include kits for single cell whole genome amplification, whole genome amplification fluorescent labeling and single cell sequencing. RHS will receive royalties on sales.

RHS will market separately to IVF clinics its microarray product, which delivers clear visual results to users, with clinicians not required to interpret the results.

The micro-array kit will incorporate a Kappa Biosystems/RHS PCR and labeling kit and the microarray kit. (Kapa Biosystems provides an enzyme for use with PCR.)

Each kit will include material sufficient for testing 20 embryos. RHS expects to price this product competitively against the single product, 24sure, from BlueGnome, which accounts for 80% of the PGS market.

Importantly, these kits will be sold on a research purpose basis, lowering the regulatory barriers for commercialization.

First product sales are expected to commence in early 2014. In the lead up to that, RHS is completing validation studies of its microarray kit, in which it will test 20 cells each from 10 cell lines. The company will seek to publish the results in a peer reviewed journal but will also aim to in effect derive a performance statement from the study which could be used to market the product.

### Investment Merits

The merits of an investment in RHS include a path-to-market that is based on almost no regulation. The company intends to sell its product (and partnered products) for 'research purposes only'. Its microarray kit is essentially a laboratory tool which would take its place alongside numerous other similar genomics tools.

RHS expects to launch it microrarray product next year and does not envisage raising additional capital before it expects to be profitable in 2017. (Although this stands as an attractive present feature, it is rare for a life sciences company to meet such expectations.)

The company's technology is supported by one patent, 'Comparative Genomic Hybridisation' which has been granted in Australia, New Zealand and China (expiring 2024), and USA (expiring 2027).

The growth drivers for the business are very strong, with two factors at play. The first is the growth in global IVF cycles of 10% per annum, the second is the potential for growth of PGS. Even without a change in the IVF growth rate, any change in the percentage of embryos subjected to screening from 2% could be the basis to build very solid revenues. It is worth noting that the current main player in the PGS business, BlueGnome, was acquired by Ilumina for $95.5 million in September 2012, although it should also be noted that BlueGnome sells other genomic-based diagnostics.

*Bioshares* recommendation: **Pending Requotation of Securities in March 2014**

## *Prana Completes Phase II Study in Alzheimer's – Results due in March*

The race to develop the first disease modifying treatment for Alzheimer's progressed this week, both locally and internationally. In Australia, Prana Biotechnology (PBT: $0.685) announced it had completed its 12 month study in 40 patients with confirmed early stage or mild Alzheimer's disease. In the US, Merck announced that it had successfully completed the first part of its Phase III Alzheimer's disease trial, that being a 200 patient opening safety arm of the trial.

Prana this week also confirmed that 33 of the 40 patients were in the extension study from the Phase II trial, which will see those patients receive the drug candidate PBT-2 for an additional 12 months in an open label setting with no placebo group.

Prana expects to announce results from its Phase II study in March next year. All patients who went into the trial were screened to confirm, with new imaging technology (the PiB imaging agent), the presence of beta amyloid deposits in the brain. The primary outcome of the trial will be changes in beta amyloid deposits in the brain. Secondary endpoints will be evidence of increased brain activity (using F-FDG PET), changes in imaged brain volume, and changes in cognition using the standard NTB suite of tests.

Merck is more advanced than Prana. It has already shown that its BACE1 inhibitor drug can reduce beta amyloid levels in the cerebral spinal fluid by 84% after only seven days. Whether this translates into improved cognitive function is what will be determined in the current Phase III study. The green light on the safety study for Merck is very important, because BACE inhibitor drugs have had safety concerns - Eli Lilly was forced to scrap its BACE inhibitor program in Alzheimer's for this reason. Merck's advanced position in the Alzheimer's disease space also explains its partnership with Cogstate, which offers a tool for identification of early stage disease in the wider population.

There have been many mid and late stage drug failures in the Alzheimer's space. The field has proven to be so difficult that the FDA has lowered the bar, now accepting that even slowing cognitive decline would be seen as a success. With failures in trying to cure late stage disease, there is now also an acceptance to focus on early stage intervention, with some success seen in the Phase III trial failures in patients with prodromal disease.

Arguably, what has really changed the field however is the advent of imaging agents, such as the one Prana is using, that allows drug developers to monitor changes in plaque levels in the brain. Previously, the only way to do this has been through an autopsy. It has taken the blind fold off for drug developers. Prana was the first company to use this test to screen patients into a clinical trial.

In an article in FierceBiotech this week, the field of Alzheimer's disease drug development was described as the biggest lottery in the industry, with success delivering an overnight fortune. It will be transformational, even for a company as big as Merck.

Prana is capitalised at $285 million.

*Bioshares* recommendation: **Take Profits**

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## *What's the Motive for Cogstate's $4M Rights Issue?*

Cogstate (CGS: $0.375) markets cognition assessment tools with applications ranging from dementia assessment and monitoring to neurological damage that has occurred on the sports field.

The company is conducting a 1 for 8 pro rata non-renounceable rights issue at $0.37 per share to raise $4.05 million. The purpose of the capital raising is to support the market development of Cognigram beyond Canada where it is conducting a pilot rollout with Merck Canada. Cogstate also intends to use the funds to expand the use of its concussion management technologies and commercialize its unique dataset of cognitive indictors. The offer closes on December 18 and is fully underwritten by Taylor Collison.

The company has a mature business supplying its test and services to pharmaceutical companies conducting clinical trials of drugs for the treatment of neurodegenerative diseases, especially Alzheimer's disease (AD). This line of Cogstate's business is dependent on the budgets for such clinical programs as determined by third parties, as well as the success and failure of drug candidates for the treatment of AD and similar conditions.

Cogstate's longer term goal is to build revenues from the assessment and monitoring of cognitive performance in the wider population. This has been a goal of the company ever since it was founded in 1999. The rationale is that earlier detection of a decline in cognitive performance, which is a common feature of Alzheimer's disease, can improve the management and treatment of the disease.

This year the FDA shifted its position on Alzheimer's disease drug development, conceding that earlier treatment was warranted regardless of what is currently known or needs to be known about the underlying mechanism of the disease.

In March 2013, Cogstate launched a pilot program with Merck Canada to evaluate the product in a discrete national setting but fundamentally in the primary care medicine (G.P.) sector. This pilot program has already been helpful to Cogstate by showing that primary care doctors are more interested in how Cognigram compares to rudimentary mental health status exams and less so how it compares to more sophisticated bio-marker tests of dementia.

A product of this discovery is that Cogstate plans to run trials which compare Cognigram to other clinical tools so that the company can present a suitable statement of purpose ( ' label claim') to health insurers and doctors.

Cogstate was motivated to raise capital to fund the expansion of Cognigram into other territories, such as the USA, but wanted to

*Cont'd over*

# *Phylogica Adjusts Business Model*

Phylogica (PYC 1.8 cents) is currently raising $6.1 million through an underwritten rights issue at 1.5 cents a share. The raising will give the company more time to progress its current partnerships with a number of major pharmaceutical companies as well as forming new deals.

Phylogica has developed an expertise in cell penetrating peptides and the company has altered its approach when selling its technology to new partners. It has also strengthened its technology this year with what the company calls an endosome escape trap.

Over the last four years, Phylogica has partnered with five major pharmaceutical companies that are assessing the capability of using Phylogica's peptide technology. What the company has found is that it has a suite of peptides that are very good at transporting other drugs into cells, which is where 80% of drug targets reside, according to the company's CEO, Richard Hopkins. All of the company's deals now are around hitting intracellular targets.

Its first collaboration with Roche, which was formed at the end of 2009, was around these cell penetrating peptides, for drugs that treat diseases of the central nervous system.

## Focus on Janssen Deal for Investors

Previously only small molecules could get inside cells. However the affinity of small molecules to targets is not as good as larger protein drugs. In December 2011, the company signed a collaboration deal with Janssen (Johnson & Johnson), specifically looking at bringing large molecules into cells.

This collaboration was expanded and extended in July this year. It's expected that additional work will be completed this year. For investors, the major investment focus will be whether Janssen decides to exercise a license for Phylogica's technology next month, and moving the drug programs into clinical trials.

## New Endosome Escape Trap Technology

With the Janssen project, Phylogica enhanced its platform technology this year with what it calls an endosome escape trap. For this technology to be effective requires three steps. The first is for the drug to bind to the cell. The second is for the drug to be taken up by the endosome inside the cell. And the last part is to exit the endosome and move into the cytoplasm.

Phylogica's endosome escape trap technology allows the company to identify when the cargo (other companies' drugs) is released from the endosome into the cytoplasm.

To date Phylogica has shown using fluorescent markers that its cell penetrating peptides can deliver cargo into the cytoplasm. The next step is to show that a functional change can occur inside the cell by delivering a toxin into the cytoplasm.

## Changed Business Model

Phylogica had previously focused on offering its peptides as alternatives to in-house drug candidates from pharmaceutical companies. However this approach was competing with in-house programs from potential partners. The company has altered its approach, where it is now focusing on delivering existing compounds from partners into cells. The company believes this approach is better received by partners.

Phylogica's most active pharmaceutical collaborations are with Janssen (cell delivery) and with Pfizer (vaccines). Other collaborations the company had formed include with MedImmune and Cubist Pharmaceuticals, both in the area of antimicrobial drugs.

## Patents

Phylogica has strengthened its patent position this year. The company was granted a US patent around synthetic versions of its peptides, taking protection out to 2027. It also filed a patent this year around its endosome escape trap technology.

## Summary

Phylogica has potentially discovered a valuable technology with multiple applications in delivering existing pharmaceutical compounds into cells and also importantly into the cytoplasm within cells where functional change can occur.

The company is improving its capital position through the capital raising underway. A key milestone to monitor over the next two months will be whether Janssen decides to license the company's technology.

Phylogica is capitalised at $18 million, assuming the full $6.1 million is raised in the current rights issue.

*Bioshares* recommendation: **Speculative Hold Class B**

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*– Cogstate cont'd*

reduce its dependency on the ebbs and flows of income from its clinical trials business.

The funds will be used to investigate the most appropriate pathway that Cogstate should use to gain regulatory approval in the US along with an analysis of reimbursement requirements. Both tasks are not trivial and will require extensive and detailed efforts over many months.

## Summary

Cogstate is making a foundation investment in market and regulatory research to secure future income that hopefully is well in excess of what it receives from its clinical trials business. Researching and characterising the US (and other markets) for Cognigram will take time, but unless the appropriate investments are made now then the longer term revenue opportunities are unlikely to eventuate.

Cogstate is capitalised at $33 million.

*Bioshares* recommendation: **Speculative Buy Class A**

**Bioshares**

**Bioshares Model Portfolio (13 December 2013)**

| Company | Price (current) | Price added to portfolio | Date added |
|---|---|---|---|
| Imugene | $0.015 | $0.022 | November 13 |
| Oncosil Medical | $0.125 | $0.155 | September 13 |
| Calzada | $0.077 | $0.073 | September 13 |
| Invion | $0.093 | $0.060 | August 13 |
| IDT Australia | $0.400 | $0.260 | August 13 |
| Viralytics | $0.325 | $0.300 | August 13 |
| Circadian Technologies | $0.210 | $0.270 | March 2013 |
| Tissue Therapies | $0.225 | $0.255 | March 2013 |
| Benitec Biopharma | $0.500 | $0.40 | November 2012 |
| Somnomed | $1.15 | $0.94 | January 2011 |
| Cogstate | $0.375 | $0.13 | November 2007 |
| Universal Biosensors | $0.49 | $1.23 | June 2007 |

### *Portfolio Changes – 13 December 2013*

**IN:**
No changes.

**OUT:**
No changes.

**Private Company Update**

# *Hatchtech Phase IIIs Cleared by FDA – Headline Results Due July 2014*

The University of Melbourne spin-out Hatchtech has received agreement from the FDA to proceed with two Phase III trials of DeOvo, its novel treatment for headlice. The company will commence these trial in the US early in the new year. Hatchtech must submit some minor amendments concerning statistical calculations to the FDA before initiating the trials.

Hatchtech is using the Special Protocol Assessment channel for DeOvo at the FDA. An SPA means that the sponsor and the FDA reach agreement in advance on Phase III clinical trial design, trial endpoints and the statistical analyses pertaining to the trial.

The outcome is that the certainty of final regulatory submission and authorization is increased, leaving the Phase III trials more as the key event for determining a drug candidate's success or failure.

## The Phase III Trial Program

Each Phase III trial will enrol 318 subjects across eight to 10 sites in the USA. The primary endpoint will be to evaluate the efficacy of one at-home treatment of De Ovo (0.74% w/v).

The efficacy measure is the proportion of index subjects who are free of headlice at day 14. Day 14 is significant because the life cycle of head lice is 14 days. Subjects will also be examined at day seven. The index subject is the youngest child in the family.

Other family members will included in the trial, and will be randomized to the same treatment group as the primary enrollee.

Children as young as 6 months will also be enrolled in the trial.

Each trial will cover a mix of geographies so that drug-resistant head lice populations can be included in the studies.

Hatchtech expects to have the results of the Phase III trials by July 2014.

The labeling objective for De Ovo is to show that it can achieve a better than 80% success rate in clearing headlice with the one application.

## Parallel Phase II Study

In parallel with the Phase III program, Hatchtech will run a Phase II study to demonstrate the ovicidal potential of DeOvo. It will do this by treating children with lice, removing the eggs and then incubating the eggs to see if any lice hatch. The object of the study to produce data to support claims of the ovicidal power of DeOvo.

## Summary

Earlier this year Hatchtech raised $12 million to support the Phase III trials, which will cost $6 million to complete. Hatchtech's progress through its Phase III trials will be well worth monitoring in 2014.

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## 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***

**Corporate Subscribers:** Starpharma Holdings, Cogstate, Bionomics, Impedimed, QRxPharma, LBT Innovations, Tissue Therapies, Viralytics, Phylogica, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Calzada, Atcor Medical, Invion, Circadian Technologies