

In this edition...

Global financial markets are doing it tough, so it comes as something of a surprise to see several local biotechs raise \$150 million in the last month. However, capital has been raised because the funds are being directed towards later stage development goals.

Mesoblast will now move its cardiovascular product Revascor into Phase III trials, now that the full data from its Phase II trial has been released. Impedimed and Biota are two companies with important news to post in the next two weeks. We also discuss the range of opportunities being addressed by Benitec's gene silencing technology, with the company's freshly articulated development plan a pleasing step forward. And Mayne will look at improving efficiencies.

The Editors

Companies Covered: BLT, BTA, IPD, MSB, MYX

	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	-24.5%
Cumulative Gain	218%
Av. annual gain (10 yrs)	21.2%

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Bioshares

25 November 2011

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

Extract from *Bioshares* –

Benitec – Building Proof of Concept Data in Four Diseases

Benitec gave a clinical investigator group update recently on its gene silencing programs. As an emerging therapeutic drug class, RNAi has under-delivered, largely due to delivery issues. However Benitec believes its approach, using a DNA-directed RNAi, is superior and is advancing four core programs to prove its case and in the process, aiming to deliver substantial shareholder value.

Core Programs

Benitec's four core programs are in:

- Non-small cell lung cancer (NSCLC), which accounts for about 85% of all lung cancers
- Cancer-associated pain
- Hepatitis B
- Oculopharyngeal Muscular Dystrophy

Three Elements to RNAi Drug Development

There are three parts to the process of developing an RNAi drug candidate. The first is to know or find the target. The second is to fine the gene that you want to silence. And the third is to build the RNAi construct.

Lung Cancer

In the NSCLC program, the target, the BetaIII tubulin protein has been shown to be associated with chemotherapy drug resistance in NSCLC i.e. those patients with higher levels of the BetaIII tubulin protein had a worse response to chemotherapy and a lower overall survival.

Professor Maria Kavallaris and her team at the University of NSW believe they have found the right gene, that if 'knocked down' or suppressed, using Benitec's gene silencing, will better expose the cancer cells to chemotherapy.

Benitec has made one of its gene silencing constructs, called shRNAi (short hair pinned RNAi) to block this gene. In initial studies in mice, the team has shown it can knock down the gene in human lung cancer cells grafted onto mice.

The beta-III tubulin protein is also expressed in other cancers, including breast and prostate cancer, and glioblastoma.

The next step is to more mice studies, and then more mouse preclinical studies in combination with chemotherapy to see whether chemosensitivity has been improved.

Cont'd over

Cancer-associated Pain

Benitec is making good progress on a potential RNAi therapy for the treatment of chronic pain, particular that associated with cancer. It has looking at two possible targets, and has selected an enzyme called PKCgamma which it believes is an excellent target. In a rat model of neuropathic pain, it has achieved an 86% hit rate to block pain by turning off the PKCgamma enzyme. Turning this off has also shown to overcome morphine tolerance. The PKCgamma enzyme is increased in the spinal cord when patients are experiencing cancer associated pain.

In this program, Benitec has identified the target, identified the best gene, and has also developed the right sequence to block this gene. The target is patented in China and it has freedom to operate in the rest of the world. It owns IP around its gene silencing approach, but also around the DNA sequence it has found to best block this target.

The company will use a lentiviruses to deliver its DNA (that will produce the RNAi in the cell), which works well against non-dividing cells.

Hepatitis B Program

Benitec is working on the proof-of-concept for its hepatitis B program with a Chinese company, Biomics Biotechnologies.

The challenge here is to deliver the therapy to the liver, however the company's technology has had success through its hepatitis C program through its spinout company, Tacere Therapeutics. (Tacere had a major collaboration with Pfizer in this area.) Benitec's partner in China has shown it can achieve close to 100% transfection of all liver cells using this technology.

Its researchers have found the best gene sequence and then Benitec built 14 short hair-pinned RNAi constructs with the best three to make up a triple cassette. The constructs work, says the company.

This is potentially a curative therapy for hepatitis B. It uses the AAV8 virus, the same as Tacere's hepatitis C program. Benitec has leverage a lot from its hepatitis C work, saving it many years, believes CEO Peter French.

The next steps for this program are to build the triple cassette, conduct preclinical studies, and then prepare for clinical studies. The risk with this program, and what the company will be wary of, is if it produces too much of a therapeutic effect then it can lead to toxicity.

Muscular Dystrophy

Benitec is working with scientists in London and Paris to develop a gene silencing approach for the treatment of oculopharyngeal Muscular Dystrophy, one of the nine types of MD. This is a disorder that occurs in people between the ages of 40-70. The condition often leads to swallowing difficulty and choking.

The condition is a good one for Benitec to apply its technology for a number of reasons. The genetic mutation is small and located

Benitec's Technology

Benitec's approach to gene silencing has some distinct advantages over the short double stranded RNA interference (siRNA) approach, which is the approach used by all of its competitors. What Benitec has secured is the intellectual property and freedom to operate around the use of DNA directed RNA interference (ddRNAi).

The powerful discovery, only 13 years ago, was that if you can introduce double stranded RNA into the cell cytoplasm, then it is processed by the cell machinery. The cell machinery separates the two strands and produces a very powerful silencing tool that binds to the messenger RNA which is about to signal specific protein production. Using RNAi, the concept is to stop the production of unwanted proteins responsible for disease.

The common approach is to introduce the double stranded RNA into the cell, usually by incorporating it with liposomes. But this delivery issue remains a major hurdle.

Benitec's approach is to use DNA that is introduced into the cell (nucleus) with a benign virus, such as the lentivirus or the adeno-associated virus (AAV8). Delivering a specific code into the DNA of a person's cell this way, the cell nucleus can be programmed to produce the RNA of choice using Benitec's approach. The problem is that the nucleus only makes a single stranded RNA. And this is where it gets even more complicated.

To turn the single strand into a double strand of RNA (remember the discovery 13 years ago was for the use of double stranded RNA), Benitec uses a 'hair pin' which allows the single stranded RNA to fold back on itself and thereby cleverly form a double stranded RNA, the same that competitors have difficulty getting into cells. Because the DNA is now part of the cell, the double stranded RNA is continuously produced, continuously blocking the messenger RNA. This achieves a very strong and everlasting effect.

For Benitec's competitors, they can't use viruses to deliver the RNA, because only DNA, not RNA, can be incorporated into the virus. That's why delivery for them remains a major stumbling block.

On the risk side, because it is a sustained effect, the issue then becomes ensuring long term safety, with it difficult to reverse or neutralize the action.

on a small gene (called PABPN1). The condition is also localized around the throat which makes it more accessible for delivery.

The company will use either the AAV8 virus as a vector to deliver the DNA or stem cells in combination with the lentivirus.

Cont'd over

HIV Program

Perhaps one of the most encouraging signs for this technology is from a trial in four patients with HIV. This trial has shown, using a combination of three technologies including Benitec's ddRNAi, that after three years, three of the four patients continue to carry the inserted gene in their immune system, and one patient continues to express the shRNAi developed by Benitec.

A long term expression of this gene silencing could lead to a cure for HIV the company believes. However how the delivery of this therapy is very difficult and remains one of the core challenges in this application. Work is being progressed at the City of Hope National Medical Center in California under grant funding. The head researcher with this program has described the results as spectacular. However likely due to the level of difficulty with this program, Benitec is not funding it further. Importantly, the trial is the first clinical evidence that Benitec's RNI interference approach can actually work in people.

Summary

Benitec's technology has the potential to achieve curative therapies for a number of diseases, however its technology risk is very high.

Over the next year the main goals for the company are to build its proof-of-concept data in its four disease programs (cancer pain, hepatitis B, lung cancer and muscular dystrophy) and to form licensing/collaborative agreements around its technologies.

Benitec is capitalised at \$13 million and had \$5.6 million in cash at the end of September. Last year it generated a loss of \$3.5 million.

Bioshares recommendation: **Speculative Buy Class C**

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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