

In this edition...

Starpharma is well known for its ambitious program to develop a microbicide based on dendrimers. But it has also been busy exploring other application possibilities, including the use of dendrimers to deliver siRNA constructs into cells. While initial success has been achieved in the test tube, all eyes are on Starpharma and several other companies to see whether they may hit the big time and effectively deliver siRNA into cells in diseased tissue inside the body. In a more thematic vein we discuss several acquisition recently announced by leading US biotech firm Amgen. Studying such transactions can help investors understand what big drug companies are really looking for in smaller biotech target companies.

The editors

Companies covered: CBB, PGL, PTD, PXS, SPL

	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 (from 4 May '07)	1.0%
Cumulative Gain	230%
Av Annual Gain (6 yrs)	26.8%

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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) 9671 3633
Email: info@bioshares.com.au

David Blake
Ph: (03) 9326 5382
Email: blake@bioshares.com.au

Mark Pachacz
Ph: (03) 9671 3222
Email: pachacz@bioshares.com.au

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

Extract from Bioshares –

Starpharma – Has it found the ‘Holy Grail’ for siRNA Drug Developers?

At the NZBio conference earlier this year, a technology scout from **Merck, Sharp & Dohme** in New Zealand (part of **Merck & Co**) suggested that one leading technology big pharmaceutical companies were on the look-out for was delivery technologies for short interfering RNA (siRNA). In November last year, Merck & Co acquired siRNA (also known as RNAi) group, **Sirna Therapeutics** for a stunning \$1.3 billion, in cash. There has been very strong interest in siRNA, which has the potential to provide very effective therapies by controlling gene expression. But the missing piece to the puzzle is delivery of the RNA strand into the cell.

In February this year, Starpharma signed a reagent license and supply agreement with a subsidiary of **Merck KgaA** (the German Merck, which is quite distinct from the US-based Merck & Co), called **EMD Biosciences**. This agreement was for Starpharma's subsidiary **Dendritic Nanotechnologies** (DNT) to supply its cell transfection reagents, called Priofect. The reagents will be used to transfect siRNA into cells in laboratory work. Importantly the use of DNT's Priofect compounds, which are made using the company's core dendrimer technology, for *in vivo* work including human therapeutics, is maintained by Starpharma.

Potentially an extremely valuable asset

In laboratory studies, Starpharma's Priofect compounds have been shown to be significantly better than an existing reagent at the task of entering cells to silence RNA within the cell and thereby reduce protein expression from malfunctioning genes. If this technology can be extended for use within the body, then it is a potentially very valuable asset for the company.

The application of siRNA therapy in clinical trials has been largely focused on the treatment of diseases where the target tissue is relatively accessible, because the siRNA therapy can be injected directly to the site. Also, retina cells have been shown to preferentially take up siRNA.

What makes this technology potentially very useful is not only that the cells take up these Priofect compounds, but because they are based on the dendrimer scaffold, the potential exists to add targeting compounds onto the scaffold that will seek out the target cells, such as cancer cells, and then transfect the cells and block RNA signaling within the cell.

Transfection mechanism unclear

What allows the Priofect compounds to transfect the cells remains unclear, but it is thought to relate to the size and charge of the compounds, and the rigidity and shape that allows the compounds to be absorbed by the cells. The Priofect compounds will be commercially available later this year through EMD Biosciences, and DNT will supply different sized compounds that will allow researchers to obtain the highest transfection levels. If the

Cont'd over

laboratory grade products prove to be effective by others, then expect interest in this technology to rise sharply by potential partners looking to gain access to the technology for siRNA clinical use.

A more diversified Starpharma

Starpharma has diversified the commercial application of its core dendrimer technology over the last six months. The three areas which can broadly be given equal importance now is in the microbicide clinical development, siRNA applications (discussed above), and use of dendrimers as drug delivery vehicles. There is also the reagent business based on the supply of various dendrimer scaffolds – the DNT business – that is proceeding well and last year generated sales of around US\$1 million.

Microbicide programs – Vivagel

The timeline for commercialisation of the microbicide programs was always ambitious and it is no surprise to see that the clinical program completion dates have been extended by up to two years. Starpharma has one expanded safety study for the prevention of genital herpes underway in 60 participants and another expanded safety study in 40 subjects for the prevention of HIV is expected to start shortly.

Efficacy studies in preventing genital herpes (in 1000-1500 subjects) and in HIV prevention (3000-4000) subjects are due to begin in 2008. These trials are being funded with over US\$20 million in NIH grants.

Drug delivery platform

Starpharma is now looking for multiple partnering arrangements using its dendrimer compounds as drug delivery and drug optimization platforms. That the first dendrimer-based drug candidate is now in the clinic (microbicide Vivagel) makes the dendrimer technology a more realistic tool for multiple drug developers.

Dendrimers are simply a chemical scaffold to which functional groups (drugs) can be attached or inserted. What they deliver is a spherical compound that is precise by construction, reproducible and can be manipulated for chemical attachments.

By modifying the size of the dendrimers, they can potentially be delivered to tumour sites where vascular leakage occurs as tumours grow. Attaching a cancer agent then allows targeted cancer treatment. The half life of drugs in the body can be extended by increasing the size of the dendrimer and active drug construct, which can have a major application in protein and peptide drugs that are rapidly cleared from the body. And insoluble drugs could be made soluble by attaching suitable chemical groups to the dendrimer scaffold. Changes in drug profile characteristics have become a popular tool for drug originator companies to extend their proprietary positions from generic competition as a part of life cycle management. These are some of the applications that Starpharma is now exploring through partnering discussions.

Begins trading on OTCQX

Starpharma has started trading on a new exchange in the US, called OTCQX. This exchange started operating in March this year and provides a real-time exchange for companies that have an ADR facility in the US. Approximately 20% of the company's stock is now held by US investors.

Development accelerating

Over recent years, Starpharma has been slow to leverage the wide potential application of the dendrimer chemical scaffolding technology, with only one compound in the clinic. The company is now accelerating the development of its technology. The DNT subsidiary appears to be progressing well with several dendrimer based products being sold to suppliers (**EMD Biosciences**, **Qiagen** and **Sigma Aldrich**). There is commercial potential for use of the technology as a drug delivery vehicle, although it should be noted this is a competitive area. The clinical microbicide program is progressing.

Value Driver

However the immediate value driver for this company for the delivery of siRNA therapeutics using its dendrimer Priofect compounds. There are other technologies in development by companies such as **Calando Pharmaceutics** and **Intradyme** to address this need, although Starpharma appears to be well placed. Starpharma needs to develop a package of *in vivo* data. If these compounds prove effective (positive *in vitro* data has already been generated), then expect interest in this company to accelerate rapidly.

Starpharma is capitalised at \$62 million. It had \$12.7 million in cash at the end of March this year, which increased by \$1.5 million since December with the inflow of NIH grant money.

Bioshares recommendation: **Speculative Buy Class A**

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.

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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