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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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Bioshares

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

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 vary 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

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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 Pharmaceucitals** 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

Bioshares Model Portfolio (8 June 2007)

Company	Price (current)	Price added to portfolio
Acrux	$1.34	$0.83
Alchemia	$1.00	$0.67
Biodiem	$0.35	$0.29
Biota Holdings	$1.72	$1.55
Circadian Technologies	$1.43	$1.45
Cytopia	$0.65	$0.46
Chemgenex Pharma.	$0.95	$0.38
Optiscan Imaging	$0.41	$0.35
Neuren Pharmaceuticals	$0.43	$0.70
Peplin	$0.85	$0.83
Peptech	$1.52	$1.31
Phylogica	$0.38	$0.42
Probiotec	$1.11	$1.12
Starpharma Holdings	$0.37	$0.37
Sunshine Heart	$0.19	$0.19
Tissue Therapies	$0.60	$0.58
Universal Biosensors	$1.16	$1.23

Amgen's Little Shopping Spree…

Amgen has very recently and in a very short space of time announced acquisitions of two privately held biotech firms. It intends to acquire **Ilypsa**, based in San Francisco, for US$420 million and **Alantos Pharmaceutical Holdings**, headquartered in Cambridge, Massachusetts for US$300 million. These two transactions were announced on June 4 and June 6 respectively.

Selected Pharma and Biotech Companies
Capitalisations

Company	Market Cap ($US B)
Pfizer	$185
Johnson & Johnson	$180
Glaxosmithkline	$143
Novartis	$129
Sanofi-Aventis	$122
Merck	$109
Abbott Laboratories	$83
Genentech	$79
AstraZeneca	$78
Amgen	**$66**
Bristol-Myers Squibb	$57
Gilead Sciences	$33
Biogen Idec	$17
Genzyme	$17
CSL	$13

Amgen is capitalised at US$66 billion and is among the top ten of US listed firms that sell branded therapeutic products. It posted a net profit of US$3 billion for the year ending December 31, 2006, implying a P/E ratio of 22. Amgen's revenues are built on the sales of five products, including Aranesp (US$4.1 billion; 30% of product sales), Neulasta (US$2.7 billion; 20%), Neupogen (US$1.2 billion; 9%), Epogen (US$2.5 billion; 18%) and Enbrel (US$2.9 billion; 21%).

A major feature of the global life sciences sector is the very high level of transactions that take place on an annual basis. These transactions include the merger and acquisition of firms and the licensing of products, technologies and IP. For a major biotech firm such as Amgen to announce two acquisitions so close together, the question of why the acquisitions have occurred is all the more interesting, because broader company motives may be more clearly seen and analysed.

What is noticeable about the Ilypsa and Alantos transactions is that both companies appear to have been bought because they have Phase II drug development programs. Ilypsa is a developing an oral therapy, ILY201, for chronic kidney disease, with a Phase II trial completed. Alantos is developing ALS 2-0426, an oral diabetes drug candidate, with a Phase II trial underway.

Cont'd over

Amgen's Acquisitions History

Date Completed	Target Company	Ownership Status	Acquisition Price ($US M) Total ; (Net to Amgen)	Rationale or asset of interest
July, 2002	Immunex	Public	$17,800	To gain full rights to Enbrel (ie buy out royalties)
August, 2004	Tularik	Public	$1,500	5 clinical programs and small molecule expertise
April, 2006	Abgenix	Public	$2,200	To gain full rights to Vectibix (panitumumab)
October, 2006	Avidia	Private	$290 ($275)	C326 - Phase I Crohns Disease (an IL-6 pgm) and Avimer technology (novel class of binding proteins)

Avidia Funding History
Jul 2003 -Spun out of Maxygen, which invested $500K, retained a 46.9% stake
May 2005 - Series B $28.5 M [Amgen Ventures participated in this round]
Sept 2006 - Series C $43.8 M
Total fundings (est.) >$73M

Date Announced			Amount To Be Paid ($US M)	
June, 2007	Ilypsa	Private	$420	ILY101 -Phase II completed - oral tx for chronic kidney disease

Ilypsa Funding History
May 2003 - founded as Symyx Therapeutics; Series A $8M
Jul 2005 - Series B $36 M
Total fundings (est.) $44M

June, 2007	Alantos Pharmaceutical Holdings	Private	$300	ALS 2-0426 Phase II u'way (Diabetes - oral DPP-IV inhibitor)

Alantos Funding History
1999 - Founded as Therascope AG
July 2003 -name change to Alantos Pharmaceuticals AG
July 2003 -Series B $27.7 M [Cum. Funding $31 M]
Mar 2005 -Series B (2) $20 M
Total fundings (est.) $51M

The Fit

Importantly these programs also fit with existing programs being managed by Amgen. Amgen has two oral drug candidates AMG837 and AMG221 in Phase I trials for Type II diabetes, and ALS 2-0426, a DPP-IV inhibitor complements these two earlier stage drugs. However, there are now nine classes of drugs covering thirty medicines available to treat diabetes, which begs the question as to why Amgen devotes resources to drug development in this disease area. The answer is that while many medicines do exist, the challenge still exists to make an orally available drug that outperforms insulin, which much must be injected.

The acquisition of Ilypsa and its drug for chronic kidney disease does appear to be a sensible fit. Amgen sells Aranesp, a drug that is approved to treat patients suffering from anemia associated with chronic renal failure and also for the treatment of chemotherapy-induced anemia in patients with non-myeloid malignancies. Presumably, Amgen has strong marketing links into the clinics of kidney specialists, and such existing channels would be used to efficiently market a drug such as ILY201. This compound is a polymeric agent that works by preventing the absorption of ingested phosphate. Excessive levels of phosphorous can weaken bones, and patients undergoing dialysis usually are prescribed a phosphate-absorbing drug. Ilypsa has other similar drugs in development.

A link of sorts

There is a link of sorts between Amgen's nephrology franchise and its oral diabetes drug program. The link is that both can stand to benefit from the massive increase in diabetes that is expected to occur globally. Diabetes, characterised by higher levels of blood sugars, can contribute to kidney failure.

These two acquisitions, and two others that occurred in 2006 (**Avidia** and **Abgenix**), are of interest to Australian investors because they reveal much about the tensions inside a major biotech firm and its requirements to fill its pipeline, even though its current financial position appears solid.

When 'follow-on' clinical trials for its current marketed drugs are removed from its development pipeline, the company's Phase III program looks thin. It is developing AMG531 to treat immune thrombocytopenic purpura (ITP) and denosumab, a fully human monoclonal antibody to treat a variety of cancer-related bone disorders and also osteoporosis. It is possible that developing a monoclonal antibody, such as denosumab, to treat osteoporosis that is not quickly reversible may not result in the greatest commercial success. It would appear that baseline levels of a biomarker associated with denosumab are returned to at six months after a single dose of less than 60mg. A six months period of reversibility may not be considered helpful by physicians who prefer the flexibility that could be obtained from a shorter-acting drug.

Amgen is well endowed with Phase I drug programs, which total 15 in number and are spread fairly evenly across its main areas of interest. So it then has become an obvious need to boost its Phase II line-up of compounds in development, where its has five different drugs in eight clinical studies. Its Phase II line is also heavily dominated by oncology trials (six of eight). With its latest acquisitions, the company has rounded out its Phase II programs. In fact, it would be more accurate to say that it has acquired a Phase III-ready program in the form the Ilypsa phosphate binding compound.

Observations

The long term

There are several observations that can be made for the benefit of Australian investors from Amgen's shopping activities. The first is that large biotech and pharma firms pay a great deal of attention to the long term horizon. Amgen is clearly sensitive to the potential threat to its earnings outlook that can come in the form of biosimilar competitors in Europe to Epogen and other forms of competition to Enbrel. Although Enbrel has been a raging success for Amgen (which it obtained the full rights to through its acquisition of Immunex for $17.8 billion in 2002), Enbrel's future earnings growth is more likely to weaken rather than increase as competition intensifies.

Will buy assets at any stage

Amgen's recent activities suggest there is no rule that bigger firms will only look at 'pre-clinical companies', or 'Phase I companies', or 'Phase II companies' or 'Phase III companies'. Rather they will buy assets that meet their requirements, of which the main one is a focus on an improved approach to treating a disease. And companies such as Amgen will pay a premium over funds invested by founders and others, and they are willing to pay cash.

Heating up?

Another observation is that these two acquisitions may be an early sign that the global market for biotech assets is heating up, when considered in the context of **AstraZeneca's** $15 billion move this year on **Medimmune** and **Genzyme**'s acquisition of **Bioenvision** for $345 million.

A textbook play

Ilypsa looks to be a textbook play for biotech entrepreneurs, with its founders and financiers collecting an almost 10-fold return, for a company founded in 2003, simply because they identified a particular opportunity in a relatively low-key area of specialist medicine.

Stock Briefs

Chief Medical Officer Appointments

One sign of maturity of a biotech company is when it appoints an appropriately credentialled person to the position of Chief Medical Officer (CMO). This week Progen Pharmaceuticals (PGL: $5.18) appointed Dr James Garner to the position of Vice President of Medical and Clinical Affairs (equivalent to a CMO) and Peptech (PTD: $1.52) appointed Dr David Fuller as Chief Medical Officer.

The role of the CMO is typically to oversee the design and management of clinical programs. A CMO will also typically be medically qualified. Although many smaller Australian biotechs could benefit from appointing a CMO at early stage in a drug development program, they usually can't afford such a dedicated high level management function. Another difficulty is that finding and attracting CMOs is a challenging task almost anywhere in the world. Another company that has appointed a CMO is Peplin, which appointed an interim CMO in 2006, but more recently appointed a permanent CMO, Dr Arthur Bertolino.

Progen Pharmaceuticals is capitalised at $277 million and Peptech is capitalised at $249 million.

Bioshares recommendations:
Progen Pharmaceuticals – **Speculative Hold Class A**
Peptech – **Buy**

Aridol Receives European Approval

Pharmaxis' (PXS: $3.34) Aridol lung function test is now approved for sale in fourteen European countries. This is an important step for the company in its roll-out of Aridol into major markets around the globe. Pharmaxis expects to file a US marketing application in the current quarter or the following September quarter. It will be interesting to follow sales of Aridol as they emerge.

Pharmaxis is capitalised at $593 million. As of March 31, the company held $80 million in cash. Pharmaxis is a well managed company with a strong sense of discipline and focus.

Bioshares recommendation: **Speculative Hold Class A**

Founder Sells Down in Cygenics

The CEO of Cordlife (CBB: $0.48) (formerly Cygenics), Steven Fang, recently sold down his stake in Cordlife, selling over $1 million of shares, leaving him with an 8% interest in the company. Fang was a founder of Cordlife Pte Ltd in Singapore and negotiated the earlier merger with Cytomatrix, which did not work out as planned with the company now focusing on the cord blood storage business.

It's always a concern to see CEOs of speculative development companies sell down significant holdings in the listed entity. The market, including investors and analysts, rely on these spokespeople/promoters for much of the information on the progress of the company, which often can not be assessed by financial statements and company announcements alone, and where company activities are focused particularly on commercialising technologies in areas that can, because of their distance from Australia, be difficult to monitor.

We recommend investors follow Fang's lead and reduce their exposure to this stock.

Bioshares recommendation: **Sell**

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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