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In this edition...
Drug repositioning is starting to gain wider acceptance as a strategy to be incorporated into drug development by Big Pharma. Escalating costs and ironically fewer drugs reaching the market are driving the need to add clever ways to improve drug development efficiencies. Smaller biotech companies have also been quick adopt this approach, including several Australian biotechs that are covered in this edition.
We also provide readers with an update on Tissue Therapies. It may be time to take a closer look at this company. And Select Vaccines has secured a valuable partnership with Avant Immunotherapeutics that provides important validation and funding to that company.
The editors
Companies covered: BNO, CXS, MBP, MTY, NDL, SLT, TIS

	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 (from 5 May '06)	24.2%
Cumulative Gain	**246%**
Average Annual Gain	**27.9%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd. The company also provides market and company analysis of the Australian pharmaceutical and biotech industries for local and international funds management institutions, venture capital funds and other related industry groups. For further details contact David Blake (see details below).

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Bioshares

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

Australian Biotechs Quick to Move on Drug Repositioning Trend

Drug repositioning is a term that Australian biotech investors should be become acquainted with as it becomes a more accepted and successful method in reducing risk and improving commercialisation outcomes in drug development, including in the Australian landscape.

Drug repositioning is a broad term that refers to the re-development, re-formulation or re-engineering of existing drug molecules for new indications or for specific patient groups in existing indications. Drug re-positioning can be applied to marketed compounds or to compounds that have been discarded from the development process.

The most notable and successful example of drug repositioning in recent years comes from a compound called sildenafil citrate, which was being developed in the early 1990s as a potential therapeutic for the treatment of chest pain. However, trial clinicians discovered that this compound displayed a curious side effect, and the drug has since been commercialised for the treatment of erectile dysfunction. Known as Viagra, the drug generated sales last year of about US$1.6 billion.

A recent article in the journal *Drug Discovery World* discussed the trend towards drug repositioning. The costs of drug development continues to increase and yet the high failure rates in the clinic – due to the focus on complex and late onset chronic disease, according to DDW – are responsible for declining new drug entity (NCEs) approvals from over 50 in 1996 to just 14 last year. The drug development industry is looking at ways to improve efficiencies in the process and reduce the number of clinical failures. Drug repositioning potentially offers one of the solutions.

There are statistics detailed in the DDW article that explains why drug repositioning is a strategy that is becoming more appealing and an increasing number of drug developers are incorporating this approach to their drug development programs. It is estimated there are over 2000 compounds sitting on the shelves that have failed later stage clinical trials, with many of these having failed because they have not achieved set efficacy levels. Each year, about 200 drugs stall in clinical trials. Approximately 90% of approved drugs are generating meaningful sales for indications other than originally anticipated. Incorporating across the board drug repositioning into development programs can increase portfolio value by at least 10%.

Extended patent protection of repositioned drugs also adds appeal to this strategy. By filing a new 'use patent' application before a compound enters Phase II can add three years or more onto the patent life of that asset.

The DDW article suggests that the successful application of genomic technologies and

Cont'd over

Drug Repositioning cont'd

improvements in screening techniques are delivering 'druggable targets with weaker disease hypotheses', which as a result is contributing to a higher ratio of clinical failures. Therefore it would make sense to include a repositioning strategy into standard drug development programs which would balance the higher failure rate.

Australian Drug Repositioners

It seems that Australian biotechs have been quick to acknowledge the merits of drug repositioning.

Chemgenex Pharmaceuticals

In 2004, Chemgenex Pharmaceuticals (CXS: 74 cents) acquired a US biotech, Chemgenex Therapeutics Inc (Chemgenex Inc). That company had acquired two compounds from the **National Cancer Institute** in the US for which the company was attempting to reposition.

The first compound, Ceflatonin, was in development for the treatment of chronic myeloid leukemia (CML). However with the stunning success of **Novartis**' Gleevec for the same indication, Ceflatonin was dropped until Denis Brown, the founder of Chemgenex Inc, picked it up for the treatment of CML for patients resistant to Gleevec. About 20% of patients treated with Gleevec for CML become resistant to the drug and in a quarter of these patients it is because of a particular genetic mutation (T315I). It is in patients with this mutation that Ceflatonin is initially being tested.

Chemgenex is currently completing what may be a registration trial for the drug. Initial results are due out in the second quarter of this year with full results at the end of the year.

With the Chemgenex Inc acquisition came a second oncology product, Quinamed, for the potential treatment of a range of solid tumours. The drug was shelved initially because of toxicity issues. However, by the genetic profiling of patients, the company has been able to reposition the drug with dose adjusted for the patient's metabolism based on their DNA (the NAT2 genotype).

The drug is currently in a Phase IIa trial in 50 patients with a range of tumour types. Results will be released at ASCO (June 1-5) this year and the assumption is that the results will be positive. A Phase IIb trial is expected to start in the second half of this year.

Through repositioning the drugs, albeit in the same indication although through patient stratification (or personalised medicine), Chemgenex has relatively quickly placed itself in a position where it may be ready to file its first drug for approval with the FDA towards the end of this year.

Bioshares recommendation: **Speculative Buy Class A**

NeuroDiscovery

NeuroDiscovery (NDL: 22.5 cents) listed on the ASX in 2005. It is specializing in developing therapeutics for the treatment of pain and the base of its business has been built around classic drug repositioning. Its lead compound, NSL-043, previously completed Phase III studies in treating an inflammatory disease by a Japanese pharmaceutical company but failed because of poor efficacy.

The safety profile of this drug had been well established. Another Japanese pharmaceutical company, **Sosei**, gained access to this compound and approached the scientists at NeuroDiscovery to test this compound (and several others) for potential treatment of pain. Neurodiscovery identified this compound (called NSL-043) as a potential pain therapeutic, after it showed strong evidence of efficacy in several preclinical models used by the company (Neurodiscovery's subsidiary, Neurosolutions specialises in providing contract preclinical electrophysiology testing).

The compound is expected to move into Phase I clinical testing in coming months with Phase II studies expected to begin early next year. NeuroDiscovery owns 50% rights to the compound, shared with Sosei, although a small royalty stream is payable to the originator.

Neurodiscovery has a similar agreement for a second compound, NSL-036, which was also trialed as an anti-inflammatory compound in a preclinical setting by another group. This compound has shown positive results when tested by the Neurodiscovery scientists. Neurodiscovery is also working on a natural pain therapeutic compound from Peru that it is seeking to commercialise in western markets.

Bioshares recommendation: **Speculative Buy Class B**

Metabolic Pharmaceuticals

Metabolic Pharmaceuticals' (MBP: 78.5 cents) lead program is a high profile obesity treatment based on a human growth hormone fragment to promote weight reduction. However the company has a drug repositioning/expansion strategy, investigating the potential of the compound to prevent osteoporosis and as a drug transport vehicle. The compound has a favourable known safety profile, having been tested in over 1000 people and it's a sensible strategy to investigate other uses for the drug candidate, should the lead program fall over, or to simply to add value to this asset. Results from Metabolic's obesity trial are expected next month.

Bioshares recommendation: **Speculative Hold Class A**

Cont'd over

Drug Repositioning cont'd

Medical Therapies

Medical Therapies (MTY: 23.5 cents) listed on the ASX last year at 20 cents a share. Its lead compound is a variation on the existing drug Indomethacin used to treat inflammation. The company is developing a variation on this drug – a copper complex of Indomethacin – that has a similar efficacy but an improved long term use safety profile. Indomethacin is classed as a Non-Steroidal Anti-Inflammatory Drug (NSAID), as is aspirin, and this class of drugs represent a massive existing market valued in excess of US$11 billion.

However long term use of NSAIDs has been linked to gastrointestinal bleeding and stomach ulcers. Medical Therapies believes its variation on indomethacin may reduce the health risk of long term use. The new composition gives the company a proprietary position on this compound. The compound is moving into clinical trials in this half of 2007.

Bioshares recommendation: **Under review**

Bionomics

Bionomics (BNO: 32 cents) is developing several compounds using its MultiCore technology to improve known compounds (to the point of fresh patentability). BNC105 is an improved and modified version of a cancer drug candidate called CA4P, and its anxiety compound BNC210 is a modified version of an already publicly disclosed compound.

Bioshares recommendation: **Speculative Buy Class A**

Share Trading Volumes

Liquidity can be an issue that needs to be considered when investing in Australian biotech shares. It's helpful to note which stocks are gaining broader investor attention so we have complied a list of the share trading volume (in net value of shares traded) for January of the top 30 biotech stocks by capitalisation, excluding the large cap biotech and device stocks such as CSL and Resmed. The details are listed in the table below.

Company	Value of January Trades
Ventracor	$36,656,390
Metabolic Pharmaceuticals	$32,990,106
Avexa	$31,871,799
Progen Industries	$25,654,753
Pharmaxis	$18,789,722
Peptech	$12,294,111
Biota	$10,925,197
Fermiscan Holdings	$10,054,809
Life Therapeutics	$9,917,056
Clinuvel Pharmaceuticals	$8,624,255
Novogen	$6,870,229
pSiVida	$6,829,761
Mesoblast	$5,355,916
Heartware	$4,108,638
Alchemia	$4,107,373
ChemGenex Pharmaceuticals	$4,052,123
Evogenix	$3,749,595
Phosphagenics	$3,489,326
Blackmores	$3,358,987
Peplin	$3,225,399
Cellestis	$3,195,227
Sirtex Medical	$2,986,741
GenePharm Australasia	$2,188,019
Acrux	$1,886,496
Southern Dental Industries	$1,636,684
Lipa Pharmaceuticals	$1,551,689
Starpharma Holdings	$1,344,403
Institute of Drug Technology	$900,436
Genetic Technologies	$859,323
Apollo Life Sciences	$559,603

Select Vaccines Secures Important Partnership

Select Vaccines (SLT: 3.4 cents) this week signed a major licensing deal with a US-based vaccine developer, **Avant Immunotherapeutics**. The deal initially covers the development of an influenza vaccine using Select's Virus Like Particle platform. Importantly, it included an upfront equity investment in Select and also ongoing funding for the influenza vaccine program for the next two years.

Select Vaccines is commercialising a range of vaccines from discoveries and development at the **Macfarlane Burnet Institute**. However, the researcher's discovery of the VLP technology has seen the company move with an increasing focus to vaccine development where the commercial rewards are substantially higher.

Select's VLP technology

The technology uses proteins from a hepatitis B virus from ducks as a scaffold which has been found to act as a virus like particle. Combining antigens from a particular virus has been shown to elicit both an antibody and T-cell immune response in preclinical studies and this forms the basis of the invention.

Avant will invest US$735,000 (at 3.2 cents a share) in Select as equity and will fund up to three vaccine development programs with Select incorporating the VLP technology.

The first program will look at an influenza vaccine for both seasonal and pandemic forms and Avant will have the right to exercise an exclusive option to commercialise these applications. Total deal value for the first target could reach US$34 million if the influenza vaccine reaches the market, although that will take as long as 10 years.

Avant also has the right to develop two other vaccines using the technology over the next two years, excluding the applications of hepatitis C, HIV and a malaria vaccine.

There is a growing appeal to the use of VLPs in vaccine development. The success of hepatitis B vaccines, that use a VLP approach and also with Merck/CSL's Gardisil vaccine for HPV has heightened interest in this area.

Avant's head of R&D, Ron Ellis, was formerly with **Merck** and involved with the in-license of Gardisil from **CSL**. His interest in VLP technology is strong. Ellis is also Editor-in-Chief of the recently formed journal, *Human Vaccines*.

Avant's investment in Select Vaccines is important for a number of reasons. Firstly in provides an equity investment into Select. Avant will also fund the development of the influenza vaccine program, which will reduce costs. It will also provide Select researchers with an added commercial focus for its R&D programs. Avant is not a comparatively large company, with a market capitalisation of US$106 million, however the company is spread across three locations in the US, including a GMP facility (very useful for vaccine manufacture) and has 73 employees.

Avant also represents a potential exit strategy for Select shareholders. If R&D progresses well, it is a strong possibility the company might acquire Select, which currently has a capitalisation of $7.5 million. Events to monitor in over the next 12-24 months include triggering of milestone payments from Avant for the influenza vaccine program, and a decision from Avant to develop two other vaccines using VLP technology.

Bioshares recommendation: **Speculative Buy Class C**

Bioshares

Bioshares Model Portfolio (16 February 2007)

Company	Price (current)	Price added to portfolio
Acrux	$1.07	$0.83
Alchemia	$1.20	$0.67
Bionomics	$0.32	$0.21
Cogstate	$0.21	$0.18
Cytopia	$0.67	$0.46
Chemgenex Pharma.	$0.74	$0.38
Optiscan Imaging	$0.52	$0.35
Metabolic Pharmaceuticals	$0.79	$0.53
Neuren Pharmaceuticals	$0.56	$0.70
Peplin	$0.81	$0.83
Peptech	$1.80	$1.31
Phylogica	$0.41	$0.42
Prima Biomed	$0.050	$0.09
Probiotec	$1.15	$1.12
Progen Industries	$6.90	$3.40
Sunshine Heart	$0.21	$0.19
Ventracor	$0.93	$0.92

The Bioshares 20 Index

Change from June 30, 2006	**48.1%**
Change from Dec 31, 2006	**17.3%**
Change - week ago	**0.6%**

Nasdaq Biotech Index

Change from June 30, 2006	**11.0%**
Change from Dec 31, 2006	**3.2%**
Change - week ago	**0.5%**

Tissue Therapies Poised to Start Three Efficacy Trials

Tissue Therapies (TIS: 64 cents) was founded in September 2002. The company listed on the ASX in March 2004 with the intent of commercialising the VitroGro technology licensed from the **Queensland University of Technology**. VitroGro is a complexed (joined together) set of proteins, which include an extracellular matrix protein called Vitronectin, a protein known for its very 'sticky' properties. Other proteins in the complex include growth factors such as insulin-like growth factor and a protein called the growth factor binding protein.

VitroGro has a number of potential uses including as a compound used to treat burns and wounds, where a property of VitroGro to promote cell migration appears to provide an important benefit.

Another application area for VitroGro is as replacement for human and animal serum in cell culture media, particularly in media used to grow stem cells.

In 2006, Tissue Therapies reported on progress in several different areas that quite convincingly support the commercial development and success of VitroGro. Firstly, in May the company announced that it had been able to culture human embryonic stem cells and support more than 20 passagings (generations) without differentiation occurring. This development no doubt contributed to the successful signing in January 2007 of an exclusive laboratory supplies agreement for the VitroGro platform with a major life sciences supplies firm **Invitrogen** (Cap'n ~ US$3 billion). This agreement is the most useful indicator of the potential of the VitroGro technology, since large life science firms have a technology and market due diligence capability that exceeds most other investors.

In August 2006, the company reported that it had developed a new version of VitroGro, termed VitroGro-1. This is a fusion of the active regions of the different proteins that constitute VitroGro. This 'cut down' version of the larger complexed molecule means that Tissue Therapies can produce a cheaper product, with a new layer of patent protection.

In November 2006, Tissue Therapies completed a pre-clinical study of synthetic VitroGro and confirmed that it worked as well as VitroGro made from purified proteins. The trial also provided information on doses of VitriGro that could be used in forthcoming human trials.

The problems with animal derived media

A necessary element of experimental research across a number of medical research disciplines is the culturing of cells, such as liver, endothelial or stem cells. Culturing refers to the generation, growth and maintenance of cell culture populations.

There are numerous cell culture media products on the market, provided by large companies such as **Sigma Aldrich Fine Chemicals** (SFAC), **Becton Dickenson** (BD), **Invitrogen**, **Millipore** and other smaller firms. These cell culture products are differentiated by the cells they are often designed and optimised for use with (eg blood stem cells or brain stem cells), as well as the scale of use, such as research or for large-scale manufacturing.

An emerging trend has been the introduction of one, chemically defined and two, animal component free cell culture media. The factors driving the trend include problems stemming from the use of components such as animal sera (eg foetal bovine calf serum), which are complex mixtures of hundreds of proteins. While the use of such accessible and cheap research materials such as FBS has aided researchers in the past, the variability that stems from using such components impacts on the quality of research efforts. Variability comes in several forms, including the sourcing and mixing of serum from many different animals. And even where the use of complex mixtures delivers favourable results that can be reproduced consistently, identification of the appropriate active agents within the mixture is likely to remain unknown.

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Selected Examples of Defined Cell Culture Products

Company	Product	To be used with/for	Description (from product label)	Components
Irvine Scientific	IS CHO-CD	Chinese Hamster Ovary (CHO) cells	A chemically defined medium…the formula contains only defined components of non animal origin	Not stated
Hyclone	HyQ CDM4NS0	Monoclonal antibodies	A chemically-defined medium containing no animal derived components	Not stated
Stem Cell Technologies	StemSpan Serum Free Expression Medium (SFEM)	Human hematopeietic progenitor cells	Serum-free medium optimized for the expansion of hematopoietic cells in the presence of various cytokines	Bovine serum albumin, rh insulin, h transferrin, 2 mercaptoethanol, L-glutamine, Iscoves MDM
Millipore (developed by **Stem Cell Sciences**)	HEScGRO hES Cell Medium	Human embryonic stem cells	The first, animal-component free medium that is specially formulated to meet the unique requirements of human embryonic stem cell culture	Not stated
R&D Systems	StemXVivo	Adult stem cells	Defined mixtures of supplements and growth factors	Not stated

Such lack of definition does not sit well with the increasing bias of regulatory authorities to seek therapeutic product developers to define as precisely as possible the chemicals and processes used in product development.

Another demand factor pushing for defined animal component free media specially emanates from studies of stem cells, which sit at the top end of cost in terms of research dollars. Although advances have been in made in the study of stem cells, still much more knowledge of how stem cells grow needs to be established.

A primary concern relating to use of foetal bovine calf serum or other mammalian products or even human components is the risk of transmission of viruses or prions. Clinical, regulatory and commercial success of stem cell products is more likely to succeed where defined and reproducible systems that do not involve animal products are adopted, and preferably synthetic materials are used.

Coupled to these trends is the introduction of products that are claimed to be chemically defined and free of animal components, yet anecdotes from conference meetings indicates that some products do not deliver on their expected performance. The table on the previous page provides some examples of products that are ostensibly chemically defined and are free of animal components. However, for only one product were components listed and interestingly this product included an animal component (albumin protein from bovine serum).

Clinical Trials

Tissue Therapies is planning to conduct three clinical trials of VitroGro this year, one each in the areas of burns, diabetic ulcers and venous ulcers. Each trial will be double-blinded, enrolling a total of 80 patients with 40 in the treatment arm and 40 in the control arm, where the control arm is the current standard of care, and the treatment arm includes VitroGro with the current standard of care. Results from these trials should be available well before the end of the year, because the time from treatment to measurement (of burns or wounds) is short and the wound measurement procedure is straight forward. Formal trial protocols have not yet been released.

Funding

Since listing Tissue Therapies has raised $8 million, with the company's current cash sitting at a little over $1 million. The three clinical trials the company is planning to conduct this year will require somewhere between $1 million to $1.2 million in funding. Tissue Therapies is likely to raise funds soon. Medium-term working capital requirements would mean the overall funds sought by the company would probably be closer to $3 million. (The company currently has 20.2 million shares on issue.)

Risks and Issues

Funding

If Tissue Therapies is unable to garner funds to support its activities, its prospects will be considerably dampened. However, the company is now in a much more solid position since its last raising to seek additional funds and the forthcoming clinical trials may quickly and cheaply generate data that may indicate the effectiveness of VitroGro as an agent for treating wounds and burns.

Patents

Patents from Tissue Therapies' three patent families have yet to be granted in the jurisdictions covering the major markets of USA, the EU and Japan . Until patents are granted in these major markets then a major risk continues to sit over the stock.

Competition

While Tissue Therapies licensee Invitrogen may be able to successful develop and market a chemically-defined animal-component free VitriGro product or suite of products targeting the stem cell research market, it will face competition from a number of products such as Millipore's HEScGRO hES Cell Medium, a product developed by the soon-to-list (on the ASX) **Stem Cell Sciences**. What is often not known about some of these competing products are their components and the degree of chemical definition.

Corporate

Tissue Therapies is a small company. Investors should remain aware that as with the majority of small companies, Tissue Therapies capacity to deal with unexpected corporate difficulties is less that possessed by larger, better resourced firms.

Summary

Since it listed in 2004, the company has developed GMP standards for the manufacture of VitroGro, enlisted a manufacturer in Canada, developed a freeze dried version of VitroGro, completed a dosing study, inked a laboratory markets distribution arrangement and uncovered the technical fault that saw an animal dosing study fail. We consider that Tissue Therapies has made excellent progress in the last twelve months.

There is significant upside in Tissue Therapies should it succeed in at least one of its clinical trials, of which results will be known in the second half if this year. VitroGro may prove to be a surprising product capable influencing a range of biological activities or at least offering its functional properties to be exploited to treat a range of diseases.

Tissue Therapies is capitalised at $13 million.

Bioshares recommendation: **Speculative Buy Class B**

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

Corporate Subscribers: Phylogica, Neuren Pharmaceuticals, Pharmaxis, NeuroDiscovery, Prima Biomed, Biotech Capital, Cygenics, Cytopia, Biodiem, Peptech, Starpharma Holdings, Cogstate, Xceed Biotechnology, Healthlinx, Incitive, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Medical Therapies

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