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In this edition...
Denmark has a population of 5.5 million people. Necessity has driven this small country to develop a medical products industry. What can Australian investors learn from the Danish approach to wealth creation, especially since Denmark has developed a taste for Australian biotech, acquiring Gropep and Peplin?
We also continue our coverage of AGMs. At the Cellestis AGM, the emphasis was on the need to invest in marketing.
Circadian is now into its third year as dedicated biologics drug developer, and headed for the clinic in 2011. Genera Biosystems may be close to partnering its next-generation HPV test, with acquisition of the firm also a prospect. We also note compelling data from Mesoblast's trial of its cell therapy product in heart failure patients.
The Editors
Companies Covered:CIR, CST, GBI, MSB

	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 - Current)	82.7%
Cumulative Gain	**255%**
Av Annual Gain (9 yrs)	**22.2%**

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Bioshares

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

The Danish Connection

Denmark sent its biotech business development team to Sydney this week to further build relationships between Danish and Australian biotech. Denmark is taking an increasing interest in the Australian biotech sector, with the acquisition of Gropep in 2006 by **Novozymes** and more recently the acquisition of **Peplin** by **Leo Pharma**. The Australian biotech sector is becoming better regarded internationally, not just by US investment fund managers but now by the Danish biotech sector, perhaps looking for more hidden treasures.

Denmark does not boast the natural energy and mineral assets that Australia has access to. Its key exports including food products such as pork and cheese, machinery, and products from a well established pharmaceutical industry. From medical devices and pharmaceuticals, the country generates revenue of $18 billion a year.

Its largest pharmaceutical company is **Novo Nordisk**, which employs 27,000 people worldwide, producing 40%-50% of the world's insulin. The company generates revenue of $10 billion a year and spends $1.6 billion a year on R&D. The insulin market has doubled in the last five years with diabetes becoming a massive global problem. Novo Nordisk continues to enhance its insulin product, ensuring potential generic competitors are kept at bay. This year the company will trial its first dose of oral insulin.

Wound care company **Coloplast** employs around 7,000 people. Denmark has two billion dollar plus biotechs in **Genmab** and **Novozymes**, and successful pharmaceutical companies Leo Pharma (with 3,000 employees) and CNS group **Lundbeck**, which generates $2.5 billion a year in sales.

Denmark and Sweden also share the Medicon Valley biotech hub, which is home to 150 biotechs, 170 medtech companies and six large R&D-based pharmaceutical companies. The region employs 44,000 people in life science companies.

The Danish Business Forum held described the similarities between the Danes and Australians in terms of culture and the country is clearly looking to build further ties with Australia. Most Danes speak English very well making it easy to do business with. Its trade representatives made it clear that Denmark is very keen to assist Australian biotechs looking to form a European base in Denmark as the first entry into the Euro-

Danish Interests in Australian Biotech

2009	**Novo Nordisk** licenses from St Vincent's in Sydney Macrophage Inhibitory Cytokine program for obesity & diabetes
2009	**Leo Pharma** Acquires Peplin for US$287 million
2008	**Novo Nordisk** negotiates option over Cbio Xtoll program
2006	**Novozymes** acquires Gropep for $96 million.
2006	**Novo Nordisk** collaboration with G2 Therapies for US$6M upfront & up to $102M total deal value

AGM Report – Genera Biosystems

Genera Biosystems (GBI: $0.89) has had an exceptionally good year as judged by its trial development progress. At the company's AGM this week, the interest was very strong with the focus now on completing a commercial transaction by the end of January next year. The transaction could be a licensing deal for the company's novel HPV (human papillomavirus) diagnostic, called PapType, or more likely an outright acquisition of the company.

The HPV test is used as a screening tool to prevent occurrence of cervical cancer. The test was pioneered by **Digene**, which in 2007 was sold to **Qiagen** for US$1.6 billion. In June 2008, **Third Wave Technologies** was sold for US$580 million for access to its **Cervista** HPV test, after 12 potential acquirors approached the company with eight conducting due diligence. The current market is worth US$350 million a year and is expected to grow to US$1-2 billion a year.

Genera has developed a test that arguably has the best product attributes of all existing tests on the market. Compared with the leading Digene (HC2 test) and the Third Wave Technologies test (Cervista), the Genera (PapType) test requires a much smaller volume of sample (0.8 ml compared to 4 ml and 2 ml respectively). About 7% of samples are too small to use with the 4ml required by the HC2 test. Compared to HC2 and Cervista, the Genera test is the only one that tells you the type of virus subtype. And the Genera and Cervista test has an internal control, where the HC2 test does not. This internal control tells you whether any human material is present and helps safeguard against false negatives.

At least two other tests, the Amplicor test from Roche and the Linear Array test, have been approved in Europe, with only the HC2 test and the Cervista test approved in the US. This week, Genera filed its test for approval with the TGA in Australia, with approval then expected in Australia and Europe early in 2010.

Whilst Pap smear testing has significantly reduced the incidence of cervical cancer, 32% of cervical cancers occur in women who regularly undergo Pap smear testing. In terms of accuracy, the Genera test has shown to have around half (8.9%) the number of false negatives than the HC2 test (18.9%). That is 18.9% of women who walk out the door with undetected cervical precancer. The Genera test has also shown 95% reproducibility of the same test.

The increased sensitivity of the Genera test should also work in the company's favour, according to CEO Allen Bollands, when the level of vaccination against HPV continues to increase and the number of cases of cervical disease reduces, which will require a more sensitive test such as PapType.

Licensing – In Advanced Discussions

In terms of licensing the technology, Bollends indicated at the AGM that the company was in very advanced discussions with at least one company. One licensing deal for global rights would be ideal, however it appears that some shareholders may be interested in a trade sale within coming months, with that expectation well known to the board.

Genera is capitalised at $55 million with $4.1 million in cash at 6 November.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Denmark – from page 1

pean market or form collaborative ventures. According to Danish representatives at the business forum, the Peplin acquisition has generated a lot of interest in Denmark.

The interest in Australian biotech from Denmark has helped Australians, particular the wider investment community, to appreciate the value that can be generated from biotech. Denmark has a significantly more established drug development industry. The lack of natural resources has been a factor in Denmark placing such a priority in continuing to build its biotech and pharmaceutical industry. The above pharmaceutical and biotech statistics are impressive, considering that Denmark is 180 times smaller than Australia and its population is only 5.5 million people.

As the Australian biotech sector moves through arguably the busiest and most important period in its 20-year history, with a record number of drugs in later stage clinical trials (nine in Phase III studies with Peplin now deleted from this list), it is perhaps an appropriate time to consider where the Australian biotech sector is heading.

Further acquisitions of Australian biotechs will almost certainly occur in the next 12 months by off-shore companies. Although this is a clear immediate measure of success that will encourage more investment into the sector, is does not build a sustainable, Australian-based pharmaceutical industry. To date only three pharmaceuticals have been developed by Australian companies; Gardasil from CSL, Relenza from Biota Holdings and Evamist from Acrux.

This year has seen two $300 million plus acquisitions (of **Arana Therapeutics** and **Peplin**). Smaller biotechs **Cytopia** and **Stem Cell Sciences** were acquired, or are being acquired, because they could not fund their own programs.We suggest that Peplin's skin cancer treatment drug candidate will likely generate $300 - $500 million in export revenue a year for Denmark. If Australia is to expand its international pharmaceutical presence past that of CSL, then some consideration should be given as to how the drug and medical product development successes that are currently occurring can be enjoyed more fully by Australian biotechs and Australian investors. Perhaps the Danish perspective is a useful starting point.

(Readers' comments are welcome on this topic).

Bioshares

Cellestis AGM Report

Cellestis (CST: $3.46) held its AGM in Melbourne, on Monday November 16, drawing attendance of , we estimate, 150 people, to a meeting room at the RACV Club in the Melbourne CBD.

The CEO of Cellestis, Tony Radford, crafted his AGM address around several themes, one of which was the need to invest in marketing.

In discussing the full year results (to June 30, 2009), in which sales increased by 83% from $18.8 million to $34.5 million, and profit rose by 391% from $1.7 million to $8.2 million, Radford pointed out a significant increase in expenditure on marketing and business development expenses. Compared to an expenditure of $6 million in 2008, spending on marketing and business development in 2009 was $9.9 million, a 63% increase.

"If you take away a message it is that we invest heavily in marketing", said Radford. The company now has a team of seven devoted to marketing and business development.

The company has employed a medical writer and commenced the publication of Quantiferon News, which serves as an information resource for customers. Another marketing tool to be launched by Cellestis in 2010 is a digital compendium of scientific publications and presentations stored on a USB stick. This searchable information resource, called Gnowee, will contain all the scientific articles on Quantiferon produced to date. The Gnowee resource can be updated through the internet. Gnowee is an answer to the problem of distributing a large and voluminous resource that now amounts to 400 publications.

IGRA Symposium

As part of its marketing efforts, the company sponsored a second international conference on interferon-gamma release assays (IGRA), held in Dubrovnik following the European Region of the International Union Against Tuberculosis and Lung Disease conference in June 2009. This enabled the company to learn much more about its markets and customers and meet with key opinion leaders from around the world. One outcome, previously highlighted in *Bioshares* 316, was the finding that 16 countries had guidelines in place covering the use of IGRA's. Cellestis subsequently reported at the AGM that this figure had increased to 18.

Sales by Region

The US remains the largest market and is likely to continue that way, representing 40% of sales. However, currency effects are likely to have an impact on earnings from that region. Europe, the Middle East and Africa account for 35% of sales and Japan and the rest of the world account for 24%.

For the first four months of FY2010, sales were up 37% from the previous corresponding period. However, year to date sales have fallen in Japan and are likely to be flat for the first half, due to issues that arose with the introduction of Cellestis' third generation product, Quantiferon Gold In-Tube. Apparently translation errors on product instruction sheets were to blame for problems that occurred as it was rolled-out. These problems have caused a five month delay for the product, with a re-launch to occur.

In terms of major new sales regions, Cellestis expects to receive approval in Taiwan for Quantiferon Gold In-Tube in the second half of 2011.

CDC Guidelines

In a recent development that opens up a new testing market for Cellestis, the US Center for Disease Control's Department of Global Migration has released guidelines that recommend interferon-gamma release assays (i.e. Quantiferon) for assessing latent TB infection in 2-14 year old subjects, in addition to the Mantoux skin test. This is a 500,000 strong market, according CEO Radford. Most of this new market segment is likely to have received the BCG vaccination, which is meant to protect against TB infection. However, because a high rate of false positives from the Mantoux test is associated with BCG vaccinated subjects, immigration applicants may be more likely to opt for the more reliable IGRA test (e.g. Quantiferon), in order to avoid significant out-of-pocket expenses on X-rays and sputum tests that are mandatory following a (false) positive reading.

Summary

Cellestis continues to impress with its unwavering focus on its business, its strong sense of discipline and the balance it brings to rewarding shareholders but at the same time making necessary investments in marketing efforts that will help the company increase its market share from the 4% it currently holds.

Cellestis is capitalised at $332 million. The company is trading on a PE of 40 and we estimate a prospective PE of 29 assuming net profit for FY2009 increases by 40%, which is more or less in line with its current growth in sales.

Bioshares recommendation: **Hold**

Bioshares

Circadian Technologies – A Solid Year of Progress

The Circadian Technologies (CIR:$0.72) AGM, held on November 19, was the company's 25th annual meeting, but the second since the company announced its transition from being an early stage seed investor to being a focused developer of biologic cancer therapies.

Circadian controls IP over the VEGF-C and VEGF-D growth factors and the VEGF Receptor 3 protein. These proteins are involved in development of blood vessels. However, controlling or regulating their function in the setting of tumour growth is one development objective, as is regulating the development of lymphatic vessels.

CEO Robert Klupacs reported on the objectives the company set for FY2009. These were to extend and strengthen the company's core IP covering VEGF based therapeutics, continue the development of its product pipeline, increase the number of partnerships and strengthen the company's management team.

The company established a product and development review committee (as opposed to the more common scientific advisory board). The company added Errol Malta to the board and also appointed Alex Szabo as head of business development, Mike Gerometta as head of chemistry manufacturing and control and Mark Sullivan (formerly with GlaxoSmithKline and Gilead Sciences) as head of clinical development.

VGX-100

Product development achievements for FY 2009 included the development of a cell line for manufacturing VGX-100, which is a VEGF-C antibody and is Circadian's most advanced biologic. Cell line development is a critical step in the manufacture of biologic drugs. The next step will be to manufacture material for (pre-clinical) toxicology studies. The company has conducted 45 experimental studies with the VGX-100 compound and has 11 underway.

Milestones to monitor for VGX-100

- Evaluate animal model data H1 2010
- FDA pre-IND meeting H1 2010
- Complete toxicology studies H2 2010
- FDA IND filing H1 2011

VGX-200

A VGX-200 series antibody (a VEGF-D antibody) was humanised and optimised by Arana Therapeutics (now Cephalon).

VGX-300

One other milestone achieved in FY2009 was working out how to make quantities of VEGF Receptor 3 protein in cell culture, a precursor step to developing commercial scale manufacturing methods and a step towards supplying material for lab studies. The VEGFR3 protein is soluble, which means that as a circulating protein it can bind to and mop up VECG-D and VEGF-D antibodies before they find and bind to the membrane-bound VEGFR3 protein.

Strategy

CEO Klupacs described the company's commercial strategy, which is to secure a pre-clinical deal for one of its programs but progress one under its own management through to clinical proof-of-concept, after which the goal would be to seek a partner for further development. The strategy also includes selectively exploiting the company's IP in areas outside of oncology and in the area of clinical diagnostics and research tools.

Cancers of Unknown Primaries Project (CUP)

Circadian obtained the world-wide rights to the **Peter MacCallum Cancer Centre's** CUP diagnostic technology in 2003. In February, 2009 Circadian reached an agreement with **Healthscope** to develop the product in Australia, New Zealand, Malaysia and Singapore. Circadian retains rights to the rest of the world.

The CUP diagnostic, which is based on gene expression profiling, is expected to be launched in the second half of 2010 and may become a valuable new aid to cancer diagnosis. In the US, for example, there are between 60,000-100,000 cancers diagnosed for which the primary tissue or organ is not known. Identification of the primary source of a tumour can mean more effective treatment is possible. Circadian expects a CUP diagnostic would sell for between US$2,000-US$4,000.

In October 2009, a US company, Prometheus Labs, launched its own CUP test, which can identify the tissue of origin of 25 different tumour types and is based on the measurement of the expression levels of 48 microRNA biomarkers.

While this product may represent a commercial threat to Circadian's CUP project, it may in fact break open the market for the Circadian CUP product, and offer insights into how the product can be priced and distributed.

Commentary

Circadian has made very solid progress in the last twelve months or so, and the expansion of its management team is an action that investors can gain great deal of confidence from. Getting the right skill sets to manage both protein drug development *and* clinical development can mean development risks are properly addressed.

The company's strategy to partner out a program at the pre-clinical stage but also to take one through to proof-of concept is a sensible and realistic plan given that the company has healthy but not unlimited cash resources. Furthermore, partnering of antibody assets has been shown to be lucrative, with antibody assets in high demand by pharmaceutical companies.

Circadian held unaudited cash assets of $35.5 million as of November 18, 2009 and recorded operating expenses of $13 million for FY2009. Circadian is capitalised at $33 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Mesoblast - More Positive Data With Major Inflexion Point Approaching

Data from an ongoing adult stem cell trial by conducted by Mesoblast's associate company, Angioblast, of which Mesoblast owns 38%, continues to be very positive. In the first group of 20 patients with moderate-severe congestive heart failure injected with the lowest dose of the proprietary adult stem cells, the 20 patients achieved a 22% mean increase in injection fraction at six months (37% increase at three months) compared to a 18% mean decline in the control group at six months (11% decline at three months).

The data was presented at the annual **American Heart Association** conference in Florida, by the lead investigator, Dr Nabil Dib, the Director of Cell Therapy at the **University of California – San Diego** (and the Director of Cardiovascular Research at the Mercy Gilbert and Chandler Medical Centers in Arizona).

The safety profile was reported as excellent to date in the first 40 patients. The second 20 patient cohort has now been dosed. This patient group has received a higher dose of the stem cells than the first 20 patients. The data from this second cohort, which we expect by the end of January, may be the most important data released to date by Mesoblast/Angioblast. If it continues to be positive, it will place Angioblast in a strong position for partnering this program prior to Phase III studies – which could be a large partnering deal – and should allow the company to start designing its Phase III program which could begin in 2010.

The current trial involves a third active arm (20 patients again) which will receive the highest dose of stem cells. It is expected these patients will all receive treatment by early 2010. The stem cells being used are allogeneic cells where the same set of cells is used to treat all patients.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (20 November 2009)

Company	Price (current)	Price added to portfolio	Date added
Biodiem	$0.20	$0.15	October 2009
QRxPharma	$0.85	$0.25	December 2008
Hexima	$0.57	$0.60	October 2008
Atcor Medical	$0.22	$0.10	October 2008
CathRx	$0.70	$0.70	October 2008
Impedimed	$0.85	$0.70	August 2008
Mesoblast	$1.44	$1.25	August 2008
Circadian Technologies	$0.72	$1.03	February 2008
Patrys	$0.15	$0.50	December 2007
Bionomics	$0.36	$0.42	December 2007
Cogstate	$0.31	$0.13	November 2007
Sirtex Medical	$6.75	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.29	$0.66	September 2007
Starpharma Holdings	$0.58	$0.37	August 2007
Pharmaxis	$2.34	$3.15	August 2007
Universal Biosensors	$1.95	$1.23	June 2007
Probiotec	$2.53	$1.12	February 2007
Chemgenex Pharma.	$0.93	$0.38	June 2006
Acrux	$2.21	$0.83	November 2004
Alchemia	$0.74	$0.67	May 2004

Portfolio Changes – 20 November 2009

IN:
No changes.

OUT:
No changes.

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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