ISSN 1443-850X

In this edition...
Could the way cancer therapies are applied be improved simply by timing their administration to fit the cycling of the immune system? That is a theory being explored by Adelaide oncologist Dr Brendon Coventry who discussed this topic at last month's Thredbo Biotech Summit. QRxPharma continues to make solid progress in the development of its combination opioid MoxDuo, most recently completing a Phase II study of the analgesic administered intravenously. Patrys has appointed a CMO who comes with a high level investment banking qualifications. And Universal Biosensors blood glucose meter system partner Lifescan has announced a September launch for its One Touch Verio diabetes management system in Australia.

The Editors
Companies Covered: PAB,QRX, UBI

	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 - Current)	-4.0%
Cumulative Gain	**178%**
Av Annual Gain (9 yrs)	**18.5%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.

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Individual Subscriptions (48 issues/year)
$350 (Inc.GST)
Edition Number 372 (13 August 2010)
ISSN 1443-850X

Bioshares

13 August 2010
Edition 372

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

Are We Ready for the World's Biggest Paradigm Shift in Cancer Therapy?

Potentially one of the biggest paradigm shifts in the history of cancer treatment was discussed in a presentation at Thredbo last month that fascinated many but also was treated with healthy scepticism by others.

Professor Brendon Coventry, a senior surgical consultant and practising surgeon at Royal Adelaide Hospital and Associate Professor of the Department of Surgery at the University of Adelaide, is putting into practise a discovery made by Melbourne-based scientist and previously a healthcare biotechnology analyst, Martin Ashdown.

The basis of that theory is that like many other aspects in the body functions, the immune system operates according to a cyclic rhythm. If chemotherapy or other cancer treatments can be timed to coincide with the optimum phase of this oscillating immune system cycle, then a very effective treatment can be achieved. This would explain why some patients achieve a complete response (where all cancer disappears) and others do not, when treatments are 'randomly given' without consideration to their individual immune cycles.

"A cure for cancer is not about killing dividing cancer cells the way we have been thinking about it in the past, but appears to be the way immune cells are being killed, depending on the timing of the administrations of our therapies," said Coventry.

Chemotherapy has a range of side effects, including nausea and vomiting, but it is immune depression that stops cancer therapy more than anything else according to Coventry. But Coventry believes the manipulation of the immune system is actually the 'main game' and we've been missing it all along – it's been 'right under our noses' for years!

A New Paradigm Required for Cancer Treatment

Coventry said that around US$32 billion is being spent globally each year on cancer drugs yet the cancer mortality rate in the US is over 11,000 people *per week* and over 700 people *per week* in Australia. In a *Science* publication from August 2006, an analysis of cancer statistics from the American Cancer Society showed that remarkably the rate of mortality from cancer has changed very little over the last 50 years. "That is telling us that somehow we have all got this remarkably wrong," claimed Coventry.

"It doesn't matter which way we're attacking advanced cancer, we still can't increase the (complete) response rates above 5-10% for almost all advanced cancers. This is biologically very unusual despite trillions of dollars and hours invested in cancer research world-wide."

Coventry pointed out that the immune system's role in fighting cancer progression had been highlighted as early as 1903, when William Coley noticed a 5-10% complete response rate in patients with late stage cancer when those patients had acquired a sys-

– Cont'd over

temic infection. Coventry believes that we have been missing something right under our noses, something very simple, as simple as the discovery of penicillin, which was "just that stuff that grows on our oranges if you leave them for too long on your sink."

Immune System Cycles like Other Biological Systems

"Most of our biological systems go through cycles," said Coventry. Conception can only occur at a very narrow three to four day window every 28 days and why the menstrual cycle is 28 days in length is still unknown. There is also a 24-hour cortisol (a steroid hormone) cycle in the body.

"And the immune system undergoes a cycle as well," said Coventry. "When a stimulatory antigen is presented in the immune system, you can get an expansion of active 'effector' cells that can act against that stimulus. The stimulus then decays, or the immune response is brought down homeostatically by an expansion of inhibitory cells about three days after the initial effector expansion. This immune response can be 'paralleled' or measured in the body by changes in C-Reactive Protein (CRP), which is a well-established marker of inflammation".

No Doubt Immune System Starts to Respond to Aberrant Cancer Cells

The immune system is finely balanced between responsiveness and tolerance. Unfortunately, in cancer the immune system is overly swayed to tolerance. The immune system starts to respond to aberrant cells (cancer) and it seems to be in no mistake that this is an aberrant cell believes Coventry.

However, this response occurs only during a very finite window, and then the opportunity for the immune system to react is lost. "If you go in with therapy at the right time you can engineer a effector response if you want that (when the immune system response is activated); if you go in at the right time you can engineer an regulatory response if you want that (when the immune system is being inhibited causing tolerance); or, if you happen to get it wrong, you engineer the wrong response at the wrong time, and we are very concerned that has been happening with most chemotherapies."

A 7% Complete Response Keeps Turning Up

"For some reason the complete response (from cancer therapies) has been locked at about 7% and we've not understood why. That is a fact that is biologically remarkably unusual," believes Coventry. Coventry said that despite the investment of trillions of dollars, we have not been able to get the complete response rate above 7% for most advanced cancers. This is after every type of approach to treating cancers. "Our collective wisdom world-wide has not been enough to shift this (complete response) above 7%. This includes chemical therapies, biological therapies and pathway blockers," said Coventry.

What is peculiar is that this 7% figure keeps recurring as a complete response rate in advanced cancers. That figure can be explained according to Ashdown's theory because the immune system cycles approximately every seven days, and for around 12 hours of that weekly cycle there is a time when the inhibitory cells of the immune system are rapidly expanding and are therefore more susceptible to killing by chemotherapy drugs. This optimum 12-hour treatment window occurs about once every week and if the patient comes into the clinic at the right time then chemotherapy is more effective. So, each patient has a one in 14 chance of getting it right randomly, which equates to that recurring 7% complete response rate.

Timing Cancer Treatment Shown Effective in Animal Models

Coventry said that the phenomenon of timing chemotherapy has been proven in a mouse model by Robert North in the late 1980s, and by David Klatzmann in France last year. If the chemotherapy is delivered to 'knock-off' T-effector cells (immune response expansion) then the tumour kept growing. However, it the chemotherapy was delivered to 'knock off' the T-Regulatory cells (immune system inhibition), then the tumour dies said Coventry. So dosing the chemotherapy too early would not actually be effective. However, in mouse models the starting point for the immune system was known because of when the tumour was implanted. For people, that is where mapping of the cycling immune system plays a key role.

So What is the Answer?

The optimum timing to deliver cancer treatment, according to Coventry, is for chemotherapy drugs to be given just at the point at which immune system response effector cells are finishing expanding, and just before immune system inhibition begins (around a 12 hour window). If you mistakenly start dosing the chemotherapy when the immune system cells (which are active against the cancer) are expanding/dividing, then those cells are killed and the chemotherapy will actually produce a block in the natural immune system response against the cancer cells according to Ashdown. And this cycling of the immune system can be easily measured using the CRP marker. For vaccines, the best point to treat appears just when the effector cells are starting to expand, providing a much needed 'boost' to the active response against the cancer.

Coventry and Ashdown believe that cancer therapy can be designed to coincide with the optimum point in this immune cycle. Coventry says patients could measure their CRP levels up to three times a day using a diagnostic such as that being developed by **Universal Biosensors**. Such tools should allow the therapy to be timed more accurately to each patient's own immune system cycle.

Summary

"The immune system is not ignorant of tumours, it sees them only too well," said Coventry. "The literature also strongly supports this view. Immune suppression is caused through normal homeostatic mechanisms that damp-down the whole anti-cancer response. But these homeostatic mechanisms can be subverted using IL2 cytokines, CTLA4 monoclonal antibodies and vaccines." Coventry argued that standard chemotherapy appears to manipulating the immune system subtly to breaking tolerance and this has been occurring accidentally in random therapies (if delivered at the right time of the cycle). Disturbingly, if it's delivered at the wrong time, immune tolerance can be increased and the cancer can grow.

– Cont'd on page5

QRXPharma – Solid Progress Continues

QRxPharma (QRX: $0.95) has announced the completion of a Phase II study in which a formulation of morphine and oxycodone (MoxDuo) was administered intravenously (IV) to 20 patients who had undergone hip replacement surgery. A control group of 20 patients was administered solely morphine. The trial commenced in the second half of 2009 and was conducted in Germany.

There were two components to the trial. The first half evaluated anesthetist-assisted control of analgesia. Patients received doses of drug (1.5 mg morphine or 0.75 mg morphine/0.75 mg oxycodone) titrated at five minute intervals by an anesthetist over a 65 minute period until pain relief was achieved.

The next component involved patients self administering either 1.0 mg of morphine or 0.5mg morphine/0.5mg oxycodone, up to three doses per hour (with a gap of 5 minutes between doses) and 60 mg of morphine over 24 hours.

The primary endpoint for the first component was a difference in the sum of pain intensity scores (SPID) from baseline. The MoxDuoIV group achieved a 50% better analgesic effect that the morphine alone group.

Across the full 48 hours of the study period MoxDuoIV SPID scores were 10% better than the morphine alone group. However, the medium number of MoxduoIV doses administered was 13 compared to 17 for morphine alone.

Adverse Events

In terms of opioid related adverse events, 37% of patients receiving morphine alone experienced nausea compared to 24% who were administered MoxDuo IV. MoxDuoIV delivered a superior side effect profile in all other categories bar one – a greater percentage of MoxDuoIV patients (19%) recorded constipation as a problem compared to 16% of morphine only patients.

The trial produced outcome consistent with previous studies which demonstrate that MoxDuoIR achieves equivalent pain control with lower doses of combinations of morphine and oxycodone compared to either morphine or other drugs such as Percocet, and also delivering at the same time a greatly improved side effect profile.

With the Phase II complete, QRxPharma will assist Aoxing Pharma of China with the design of Phase III trials. Aoxing Pharma has licensed the marketing rights to Mox DuoIV in China, in exchange for funding of a Phase III program. Rights outside of China are retained by QRxPharma.

MoxDuo IR Phase III Study

MoxDuoIR (Immediate Release) is QRxPharma's most advanced formulation of MoxDuo, which is being developed for the initial indication of moderate-to-severe post-surgical pain. The company intends to file a New Drug Application for MoxDuoIR with the FDA in Q1 2011.

A Phase III study (008) in bunionectomy patients was completed in April 2010, with a second Phase III study (009) in 140 total knee replacement patients nearing completion. Data is expected to become available in Q4 2010.

Study 009 is comparing the highest dose formulation of MoxDuoIR (12 mg morphine; 8 mg oxcydone). QRxPharma believes this dose is equivalent to either 24 mg of morphine or 16 mg of oxycodone, but Moxduo is expected to deliver an equivalent analgesic effect but with a superior side effect profile.

Summary

QRXPharma is making solid and convincing progress. The latest study results are consistent with earlier studies and add to the increasingly robust body of data regarding its proprietary formulations of morphine and oxycodone.

QRxPharma is capitalised at $97 million and held cash assets of $13 million at June 30, 2010.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Key Appointment At Patrys

Patrys (PAB: $0.105) , a developer of anti-cancer therapies derived from naturally occurring antibodies, has announced the appointment of its first Chief Medical Officer, Dr Marie Roskrow.

Roskrow is a significant appointment for Patrys since she brings not only her experience as an oncologist with a specialisation in hematology, but a valuable career as an investment banker at **Lazard**, where she was a Senior Director of Investment Banking in their Healthcare Group. Given her dual responsibilities at Patrys, of which the second area will include corporate strategy and global business development, Roskrow has also been appointed to the position of President of the company.

Patrys has made progress in two other areas this month: it has regained ownership of the drug candidate PAM-1 from **Debiopharm**; and it has secured funding from **Advance Opportunities Fund**, based in Singapore, of up to $15 million available for working capital and clinical trial requirements.

The next milestone for investors to monitor is the dosing of its first patient in a 10 patient Phase I trial of PAT-SM6 in melanoma patients, now that ethics approval has been received.

The appointment of Roskrow has allowed the company to access two high level skill sets in the one person. It is a very significant step forward to building a very strong managment team at the company. Patrys is capitalised at $20 million.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Bioshares Model Portfolio (13 August 2010)

Company	Price (current)	Price added to portfolio	Date added
Sunshine Heart	$0.032	$0.036	June 2010
Biota Holdings	$0.97	$1.09	May 2010
Tissue Therapies	$0.19	$0.21	January 2010
QRxPharma	$0.95	$0.25	December 2008
Hexima	$0.28	$0.60	October 2008
Atcor Medical	$0.13	$0.10	October 2008
CathRx	$0.19	$0.70	October 2008
Impedimed	$0.69	$0.70	August 2008
Mesoblast	$1.91	$1.25	August 2008
Circadian Technologies	$0.64	$1.03	February 2008
Patrys	$0.11	$0.50	December 2007
Bionomics	$0.30	$0.42	December 2007
Cogstate	$0.30	$0.13	November 2007
Sirtex Medical	$5.00	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.22	$0.66	September 2007
Starpharma Holdings	$0.53	$0.37	August 2007
Pharmaxis	$2.11	$3.15	August 2007
Universal Biosensors	$1.57	$1.23	June 2007
Probiotec	$1.27	$1.12	February 2007
Acrux	$1.95	$0.83	November 2004
Alchemia	$0.50	$0.67	May 2004

Portfolio Changes – 13 August 2010

IN:
No changes.

OUT:
No changes.

Universal Biosensors – One Touch Verio Australian Launch

Universal Biosensors' (UBI: $1.565) marketing partner **Lifescan (Johnson & Johnson)** will launch the One Touch Verio blood glucose test meter in Australia in September 2010. This follows the first European territory launch of the system in the Netherlands in January 2010. The Netherlands was chosen as a launch market as a dozen systems compete for market share. According to UBI CEO Mark Morrisson, the One Touch Verio system launched in the Netherlands has "exceeded expectations" and has taken market share.

The meter is used as a diabetes management tool. The system includes a lancing unit that draws very small amounts of blood, which when placed or touched onto a disposable test strip developed by UBI, delivers a reading in about five seconds. The system offers accuracy of +/-15% compared to a current industry standard of +/- 20%. The system requires a blood sample of 0.45 microlitres, which is a significant improvement on existing systems offered by LifeScan, and which also brings it in line with blood sample requirements of a number of rival systems.

Between 16-18 billion strips are sold each year by the various suppliers of glucose test meters, including Abbott, Bayer, Roche and Johnson & Johnson. Universal Biosensors currently has the capacity to manufacture 750 million strips per annum, which can be expanded to 1.5 billion. Under its agreement with Lifescan, UBI stands to receive US one cent per strip it manufactures, regardless of where the strip manufactured. With Lifescan selling 4 billion strips per annum, and if the One Touch Verio system emerges as a product that displaces other models in Lifescan's suite of blood glucose sensors, the likelihood of Lifescan commissioning another strip manufacturing plant also increases. The receipt of marketing clearances and roll out of One Touch Verio progresses in various territories would also boost the need for an additional facility.

In addition to the US one cent per strip payment, UBI also receives a margin on manufacturing and R&D payments.

UBI continues to provide research and development services to LifeScan in the area of diabetes management to develop other and improved products. For example, the parties could be looking to develop a sensor system with an accuracy of +/- 10%.

Milestone Alert

Universal Biosystems expects to complete a product deal based on its proprietary technology outside of the area of diabetes before the end of CY 2010.

Universal Biosensors is capitalised at $246 million and held cash assets of $27 million at June 30, 2010. For the first six months on this calendar year, UBI increased revenue by 145% to $6.1 million over the previous corresponding period, and its loss was reduced to $3.6 million from $7.0 million over the same period.

Bioshares recommendation: **Speculative Buy ClassA**

Bioshares

– Coventry cont'd from page 2

The balance as to whether you are attacking the cancer or the immune system or both is vitally important in the clinical result for the patient. Coventry suggested that random timing of pharmaceutical intervention has the capacity to drive the disease in either direction. Coventry said his team along with two other groups, in Melbourne and at the Mayo Clinic, are looking seriously at timing cancer interventions, but this work is unique in its use of timing to synchronise therapy accurately. A flurry of articles recently published from other renowned labs around the world have implicated timing with treatment success, although they do not yet synchronise therapy.

"How right we are, we're not sure," said Coventry, "but it's beginning to look remarkably interesting."

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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48 issues per year (electronic distribution): **$350**

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