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In this edition...
We provide coverage of Steve Burrill's 'State of the Industry' address at the BIO conference held in Chicago last week. In a 200 slide rapid fire presentation, Burrill provides an excellent snapshot of the key trends and events that have occurred in the global biotech industry.
We also update readers on Circadian Technologies, a biologics oncology company with a key position in the VEGF cancer drug development space. Within 12 months the company expects two of its technology applications to be in the clinic in the oncology area.
And BioMD has started what could be a key feasibility study with a major medical device group to apply its technology to the manufacture of tissue heart valves.

The Editors
Companies Covered: BIO coverage, BOD, CIR

	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)	49.2%
Cumulative Gain	**190%**
Av Annual Gain (9 yrs)	**18.5%**

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Bioshares

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

2010 BIO State of the Industry Report

The 2010 conference of the Biotechnology Industry Organisation (BIO) was held in Chicago last week. An unconfirmed figure of 14,500 attendees put the event slightly ahead of the 14,300 attendees at the Atlanta convention in 2009. In 2007, 22,000 people attended.

This year's traditional 'State of the Industry' address by Steve Burrill, CEO of Burrill & Company, was delivered in his typical rapid-fire style, backed by a deck of more than 200 slides. The content was, and has come to be expected, rich in data and opinion. Burrill & Company is a merchant banking, VC investment and media firm, based in San Francisco.

Burrill commenced his presentation by looking back to the state of the industry a year ago when the economic downturn prevailed and the Dow Jones Index was down about 3000 points from where it is today. "Capital markets were closed. We had concerns about pandemic flu. We were active in discussion about healthcare reform but we didn't have leadership at the FDA or CMS", he said.

"If you had left this meeting a year ago, we were cautiously optimistic that things were going to turn around. The general thesis was quite pessimistic. I was criticized for being too pessimistic. This year I am going to be far more optimistic. And I hope you conclude that at the end."

In summing up the progress for the year, Burrill said that healthcare reform was achieved in the US, and nearly $50 billion dollars was raised by the biotech sector. "In the worst year of the capital markets, we raised more money than at any other time" he said. The market cap of the (biotech) sector grew by more than a third from a year ago, 10 IPOs were completed, although concerns about gene patenting hung over the industry. Burrill said that while sales for the sector fell 8%, there was a marked slow-down in R&D spend, which fell 18.7%, "with companies putting things in the refridgerator".

US Healthcare Reform
What did healthcare reform in the US achieve, Burrill asked? "We don't have a healthcare system in the USA. We have a totally dysfunctional system. All we did was to change how we pay for a dysfunctional system. What it did was to put 32 million people into the insurance system. It didn't add any hospitals, it didn't add any doctors, it didn't add any drugs." Burrill said that when you add 30 million people on the demand side and nothing on the supply side, the costs will go up. The situation is worse not better."

And with a framework for comparative effectiveness being introduced, Burrill saw this as being both a positive but also a negative, generating "a horrendous burden". The issue is that comparative effectiveness will be a third hurdle to be overcome to get a product through to the market place.

What concerned Burrill about healthcare reform the most was that it didn't get to any fundamental issue. From an economics standpoint he said "it probably bent the curve the wrong way". An enormous challenge he argued is the conflict that exists between wanting more healthcare and coverage but at lower cost. He added that such a dialogue will continue in this USA and around the world.

Finance

Burrill emphasized that it is important to remember that the biotech industry is a capital dependent industry – it has been for the last 40 years and will be for years to come. However, he noted that capital markets today have very high demand for liquidity and transparency. One thing recent economic chaos did do was to scare the investors away from long term investments. "We need capital for decades, not two years. We are de-linked from where the investment community is."

Burrill also discussed the issue of company stature. "Last year, I said that both the buy side and the sell side have no interest in the micro cap land. Micro caps in Wall Street terms are stocks under a US$1 billion (in capitalization) but only 59 companies in our industry have market caps over a billion dollars. We are marginalised by Wall Street. The consequence is that there is very little interest from the investment banks, although they will help the big cap stocks, those close to $1 billion."

On the buy side, the hedge funds, the institutional investors and the VCs have moved to larger cap stuff and so early stage funding is hard to find. Although some IPOs were achieved he observed that the first one that got away had $1 billion in sales."

And in referring back to his statement that it was "was a fabulous year for raising money" he queried why in the worst year was the industry able to raise more money. "It was actually very simple. We had no choice. We didn't like the terms. A year ago people were writing the obituary for this industry. We financed because we had to, not because we wanted to." The biotech sector raised $20 billion from the capital markets and took in about $30 billion in partnering capital.

One point made by Burrill is that in terms of overall VC financing across all industry sectors over the last decade, between 10% and 15% has gone to biotech, the implication being that the proportion of funds is relatively low. Nevertheless, a lot of what happened in the public equity markets affects private equity markets, with IPO activity an issue for VCs. Looking back, the 104 IPOs completed prior to 2010 are still under water by 50% Burrill noted. However, the seven IPOS completed this year have been marginally successful.

Burrill claimed that the bankers (behind the IPOs) have played a heavy role in buying the stock of these companies. However, the public markets are paying the same price that previous investors paid. An issue has been that previous investors by and large have not being rewarded. "The VC is not getting a premium for the risk they take for the time they were invested. New investors can say 'why should I buy a VC's offering' when it will be cheaper tomorrow. This explains why VCs are in trouble", said Burrill.

With capital inflows, Burrill suggested that money has tended to go towards later stage companies and a gap has formed between the seed investment stage and where VCs are now entering. Companies have begun to reach more heavily for governments and disease advocacy groups for early stage funding. Such funding has been cheaper than what could be achieved from VCs.

Burril observed that VCs have become more likely to put in $20-$40-$50 million in a company in one go to get to proof-of-concept, whereas once they put in $5 -$10 million on a sequential basis. This is because of the uncertainty of the money being available to VCs. "So you see a strange phenemona of larger VC rounds, albeit with some constraints."

Burrill concluded his discussion on finance stating that "there is capital available at all stages – it's just more expensive."

Other matters addressed by Burrill included the problems that continue to confront the healthcare system in the US, which suffers market distortions, where there is no incentive to move from a cost-based system to a value-based system. He noted that 75% of costs go to chronic care. Medicine today is not a "one-size-fits-all arrangement but we live in a one-size-fits-all world." According Burrill, personalized medicine is now a major dialogue, predicting the $1000 genome will occur within 12 months time.

A related trend suggested by Burrill is the digitization of healthcare, with a whole new set of technology or technology-enabling businesses becoming involved in consumer digital health. Linked to this is the phenomena of the mobile phone and its potential for adaption as a healthcare digital tool. "There are more people who have access to mobile phones than to clean water and electricity" he said, noting 4 billion phones are used the world over, in a population of more than 6 billion. This factor will be "violently transformative of healthcare".

Burrill challenged the audience to move from thinking about molecules and understanding pathways as the way to build a company to building companies with the patient in mind, and then proceed to understanding the molecules and pathways.

The address concluded with several predictions being offered, including growth in the stem cell and regenerative medicine areas, increased pharmaco-vigilance from regulators, growth in generics and emergence of bio-similars, and more biotech-pharmaceutical consolidation.

Bioshares

Circadian Technologies – Progressing Its Biologics VEGF Franchise

Circadian Technologies (CIR: 71 cents) has transformed itself into predominantly a cancer drug discovery and development company. It has secured a key intellectual property position around the VEFG angiogenesis pathway. Angiogenesis is the growth of new blood vessels. Choking the blood supply to tumours has proven to be a successful way of stopping cancer growth and even regressing tumour vasculature. The wildly successful Avastin product from Genentech generated sales of $6.1 billion, up 21% over the previous year.

Blocking more than one pathway

Avastin, a monoclonal antibody, only blocks one part of the VEGF family pathway (binding with the VEGF-A protein in the blood stream and/or tumour and preventing it activating the cell receptor VEGFR-2 and therefore blood vessel growth).

But there are other proteins which can also stimulate angiogenesis (blood vessel growth) by activating the cell receptor VEGFR-2 which is a potential reason for limited response rates to Avastin in certain settings or why some patients become resistant to Avastin over time. Two of these best characterised alternate VEGFR-2 signalling proteins are VEGF-C and VEGF-D.

Positive preclinical results

Last month Circadian released positive results from several preclinical studies in mice. In a prostate cancer model, that by adding its lead drug candidate, VGX-100, to Avastin (and the chemotherapy drug docetaxel), tumour inhibition increased from 35% with Avastin and docetaxel to 83% with VGX-100.

In a brain cancer model in mice, Avastin and Circadian's VGX-100 showed very little effect alone, but when combined, a 43% drop in tumour growth was seen.

In a pancreatic cancer model in mice, Avastin and VGX-100 showed a similar positive effect in slowing tumour growth when used independently.

This program is a long way from reaching the market. However these early studies highlight the benefit of the potentially, very valuable intellectual property position Circadian has established around VEGF inhibition outside of the Avastin space.

The results also highlight the cancer treatment potential of Circadian's lead candidate, VGX-100, and give early indication of the potential benefit in stopping tumour blood vessel growth on more than one front through combination with Avastin.

Other shots on the same goal

Circadian is working on shutting down the VEGF pathway in different ways. There are two main receptors that are the main targets to inhibit tumour blood vessel growth, called VEGFR-2 and VEGFR-3. Avastin and the proteins VEGF-C and VEGF-D both hit the receptor VEGFR-2. However Avastin doesn't block the receptor VEGFR-3.

Imclone Systems (which was acquired by Eli Lilly in 2008 for US$6.5 billion) is developing an antibody to bind to the receptor VEGFR-3. This drug candidate is expected to be in clinical trials by year's end. Circadian stands to receive a royalty from any potential sales.

Circadian is working on a soluble VEGFR-3 receptor (a fusion protein) that would soak up the VEGF proteins that normally would bind to the receptor and facilitate blood vessel growth in the tumours. This program, called VGX-300, is about 12 months behind VGX-100.

And further away is an antibody program to bind to the VEFG-D protein, called the VGX-200 series program. Circadian's lead program, VGX-100, an antibody which binds to the VEGF-C protein, is expected to move into the clinic in the first half of next year.

Inhibiting cancer metastases?

Circadian believes that one of the VEGF pathways might also be involved in forming lymphatic vessels that help spread the cancer to other parts of the body. The receptor is VEGFR-3, which Avastin does not bind to.

Manufacturing progress

With antibody's, getting the compounds into the clinic is difficult, as manufacturing is very costly. Once in the clinic, the specific acting nature of this drug class has seen a better rate of achieving clinical success and in a quicker time. The average time for clinical development of antibodies is 6.7 years.

Antibodies, which are classified as biologics, are also a hot area at the moment following the health care reform bill in the US, which has seen biologics given 12 years market exclusivity.

– Cont'd over

Free Bitoech Investor Forum

The ASX is holding a free investor forum featuring six listed Australian biotech companies. The forum will be held on Thursday 20 May in Sydney. Companies presenting will be Chemgenex Pharmaceuticals, Living Cell Technologies, Alchemia, QRxPharma, Starpharma Holdings and Acrux.

To register visit: www.asx.com.au/spotlight

Circadian is prepared to move one of its programs to achieve proof-of-concept Phase IIa results before partnering. It is also looking to partner one of its early-stage assets or programs.

Ark Therapeutics

In October last year, Circadian terminated its license to Ark Therapeutics for access to operate in the VEGF-D space for its gene therapy Trinam product. The license was terminated because Ark Therapeutics was not paying its fees. Ark will now need to renegotiate with Circadian if it wants to commercialise its product.

Ark Therapeutics currently has many problems, including unsolicited bids for the business and products, and funding. The CEO is to step down, and the Phase III Trinam program is being downgraded to a Phase IIb program, with the view of partnering it after results are released next year.

Circadian expects that an arbitration proceeding will be conducted early next year. However it looks like Ark Therapeutics has several other issues to resolve as well.

Competitors

There are very few competitors with clinical programs in the VEGF space, largely because of the secured intellectual property nature of this area, of which Circadian has a firm central position. Imclone (Eli Lilly) expects to move into the clinic with an antibody to VEGFR-3 as mentioned (called IMC-3C5) which Circadian enjoys rights to, and it also has a Phase III antibody program (IMC-1121b) against VEGFR-3 which is in Phase III trials for a range of solid tumours.

Regeneron (with Sanofi-Aventis) has a Phase III program in a range of solid tumours using its VEGF-A fusion protein that works as a trap to soak up VEGF-A proteins in the blood (see table below).

Summary

By around this time next year, Circadian is expecting to have two programs in the clinic that utilise its technology. These are the Imclone antibody and its own antibody, VGX-100. Over the last 12 months Circadian has made considerable progress on the manufacturing side with VGX-100 that should not be underestimated.

The company is capitalised at $32 million with $34.8 million in cash at the end of last year, sufficient for around two and a half years of funding. The company's wide intellectual property position in the VEGF area is potentially a very valuable asset that has been amplified by the recent changes relating to extended market exclusivity of biologics in the USA.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

VEGF Cancer Drugs and Drug Programs

Company	Compound	Target	Approach	Phase
Roche	Avastin	VEFG-A	Antibody	Approved for renal, brain, breast, colon & NSC lung cancers
Imclone	IMC-1121b	VEGFR-2	Antibody	Phase III
Imclone/Circadian	IMC-3C5	VEGFR-3	Antibody	Preclinical
Regeneron (Sanofi-Aventis)	Aflibercept	VEGF-A	Fusion protein trap to absorb VEGF-A	Phase III
Circadian	VGX-100	VEGF-C	Antibody	Preclinical
Circadian	VGX-300	VEGF-C&D	Soluble VEGFR-3 fusion protein to absorb VEGF-C&D proteins	Preclinical

BioMD starts feasibility study with major heart valve group

BioMD (BOD: 3.4 cents) this week announced it is conducting a feasibility study with an undisclosed leading global tissue heart valve company.

BioMD has developed a tissue processing technology that it believes delivers a superior process for the preparation of biologic tissues that are derived from animal sources and used for human medical implants. One of the leading applications is the replacement of leaking heart valves.

The existing market for biologic (tissue) heart valves is currently estimated at US$700 million a year. The tissue heart valve market should see accelerated growth following the approval in January this year by the FDA of the first tissue heart valve that can now be implanted through a catheter rather than requiring open heart surgery. The valve, developed by Medtronic's and called the Melody valve, is made from a cow's jugular vein valve that is sown onto a metal scaffold.

The problem with existing tissue processing techniques is that the harsh chemical treatment used to render the tissue non-immunogenic lends itself to calcification of the tissue and reduced elasticity over time. Tissue heart valves need to be replaced every 10 – 15 years as a result. The approval of a valve system that can

Bioshares Model Portfolio (7 May 2010)

Company	Price (current)	Price added to portfolio	Date added
Tissue Therapies	$0.18	$0.21	January 2010
Biodiem	$0.16	$0.15	October 2009
QRxPharma	$1.12	$0.25	December 2008
Hexima	$0.30	$0.60	October 2008
Atcor Medical	$0.12	$0.10	October 2008
CathRx	$0.18	$0.70	October 2008
Impedimed	$0.65	$0.70	August 2008
Mesoblast	$1.94	$1.25	August 2008
Circadian Technologies	$0.71	$1.03	February 2008
Patrys	$0.11	$0.50	December 2007
Bionomics	$0.30	$0.42	December 2007
Cogstate	$0.26	$0.13	November 2007
Sirtex Medical	$4.99	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.24	$0.66	September 2007
Starpharma Holdings	$0.60	$0.37	August 2007
Pharmaxis	$3.08	$3.15	August 2007
Universal Biosensors	$1.42	$1.23	June 2007
Probiotec	$1.48	$1.12	February 2007
Acrux	$1.91	$0.83	November 2004
Alchemia	$0.55	$0.67	May 2004

Portfolio Changes – 7 May 2010

IN:
No changes.

OUT:
No changes.

be delivered via a catheter is a major advance in this field.

BioMD's ADAPT process was used in a 30 patient trial in young children (around four years of age) to treat heart deformities using a bovine-derived, heart tissue patch. Interim data has shown the patch has performed well with no calcification in the first six patients at 12 months. The full 12 month follow-up data should be available later this year. Calcification of heart patches in children is generally seen early on (within the first 12 months) due to children's rapid growth.

The tissue heart valve application is a major market for BioMD's technology. The first milestone in the feasibility study is expected to be completed by September this year. The feasibility study is a non-exclusive arrangement.

Last month BioMDs clinical study in Sydney in pelvic floor reconstruction using its ADAPT treated tissue was discontinued following infection complications. Whether the infections were caused by the BioMD patch or not has not been confirmed.

BioMD is capitalised at $4 million. At the end of March it had $0.3 million in cash and has since raised just under $1.3 million.

Bioshares recommendation: **Speculative Buy Class C**

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

Corporate Subscribers: Pharmaxis, Starpharma Holdings, Cogstate, Bionomics, ChemGenex Pharmaceuticals, Circadian Technologies, Biota Holdings, Halcygen Pharmaceuticals, Impedimed, QRxPharma, Patrys, Labtech Systems, Hexima, Tyrian Diagnostics, Mesoblast, Atcor Medical, CathRx, BioMd, Tissue Therapies, Viralytics