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

Extract from Bioshares –

Circadian Briefing Report

Circadian Technologies' (CIR: \$0.18) CEO Megan Baldwin gave an update to investors recently, confirming that the direction for the company is now very much the development of ophthalmic applications of the company's technology.

Last year, Circadian raised \$17.4 million. It is now funded through 2017, allowing it to generate clinical data from its Phase I and Phase IIa clinical studies of OPT-302 in wet AMD. US and European funds own 41% of the company, with Australian funds owning 33%.

Circadian's core technology is around inhibition of blood vessel growth, specifically the VEGF-C and VEGF-D pathways. Inhibition of the VEGF pathways has applications in oncology as well as ophthalmic diseases. Circadian has completed a Phase I trial with its compound VGX100 in oncology but the company will now partner this program and concentrate on development of its lead eye drug candidate, OPT-302.

At the moment there are only two targeted drugs for the treatment of wet AMD, Lucentis and Eylea, which inhibit VEGF-A new blood vessel formation pathway. Circadian's strategy is to combine its drug with Lucentis first up, thereby potentially providing a more effective and longer lasting therapy by inhibiting three VEGF pathways (A, B and C).

Circadian intends to start a Phase I trial in patients with wet AMD before mid year. The trial will assess OPT-302 both on its own, and in combination with Lucentis. Primary data from this trial is expected in the first quarter of next year.

Phase II Trial Readout In 2017

The Phase IIa study will start next year with results out in 2017 Q2. The trial will compare OPT-302 against OPT-302 and Lucentis. It will also look at the effect of OPT-302 in those patients who are not responding well to Lucentis, which is in more than 50% of patients.

A Very Clear Investment Proposition

Circadian has become a clear investment proposition. Within one year, investors will have some idea of the efficacy of OPT-302 in treating wet AMD. In just over two years time, the company will have randomised Phase II data on the efficacy of its OPT-302 against Lucentis, when used in combination. If that data is clearly positive and clinically meaningful, then Circadian will have a very valuable asset in its possession. This potential outcome is presumably what has attracted US and European investment funds to the company last year.

Clinical Endpoints

Baldwin said that what is very appealing about the wet AMD application are the short clinical endpoints. Early data can be obtained within three to six months said Baldwin, and Phase III trials only need to follow patients for 12 months.

Cont'd over

Companies covered: CIR, MSB, RNO

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May '11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - May '14)	26.6%
Year 14 (May '14 - current)	5.4%
Cumulative Gain	375%
Av. Annual gain (14 yrs)	16.5%

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Another benefit of developing drugs for ophthalmic conditions is that measurement of efficacy is conducted using routine but high sensitive visual acuity tests.

Anatomical tests using Optical Coherence Tomography also provide very good measurement of retinal thickness, fluid volume, retinal detachment and hemorrhage said Baldwin. These measures of drug effectiveness form another very appealing and not insignificant investment consideration with Circadian.

Market Characteristics

Baldwin said that wet AMD is the leading cause of blindness in the western world and is on the increase with an aging population. In Australia between 17,000-20,000 people develop a severe form of wet AMD each year. However, existing drugs only have an effect in half of those patients.

Baldwin said that what the market is really looking for is to reduce the treatment burden. This can be explained because Eylea and Lucentis are injected into the eye every one to two months.

Preclinical Data

In a mouse model of wet AMD, Circadian showed that OPT-302 is very effective in reducing the area of blood vessel formation (70% drop), as is Eylea (78% drop). Combining the two compounds delivered a better result (91% drop) than using Eylea alone. This data is what got investors very interested in the company in the US and Europe said Baldwin.

Clinical Advisory Board

Circadian has put together a highly relevant and reputable Clinical Advisory Board which includes clinicians who have been involved in the development of the leading ophthalmic drugs including Macugen, Fovista, Eylea and Lucentis.

Wet AMD – Comparable Programs And Companies

If Circadian can generate positive results in its clinical trials over the next 12-24 months, then there is substantial upside for investors. Baldwin presented a comparison with other biotechs with clinical development programs in wet AMD.

Leading the list is Ophthotech, which has an anti-PDGF drug candidate in clinical development. Its compound, Fovista, has completed a Phase II, six month trial in combination with Lucentis in 449 patients. The trial showed that the combination delivered a statistically better improvement in visual acuity than Lucentis alone.

In May last year, Novartis, which sells Lucentis outside of the US, licensed ex-US rights to Fovista only in a deal that included US\$330 million in upfront and short term milestone payments (start of Phase III trial), US\$300 million on marketing approvals, US\$400 in sales milestones plus royalties from sales.

Ophthotech has started its Phase III study. It is capitalised at US\$1.7 billion. Although Fovista is effective in combination with Lucentis, it does not have single agent activity in wet AMD.

Other biotechs with clinical programs in wet AMD include Avanche Biotech (gene therapy approach in Phase I/II), Aerie Pharmaceuticals (small molecule in Phase III), Ocular Therapeutics (Phase III), AGTC (gene therapy in Phase I/II), and OHR Pharmaceuticals (Phase II).

Circadian is capitalised \$27 million and retained cash of \$20 million at the end of January.

Bioshares recommendation: **Speculative Buy Class A**

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. For both groups, the rating “Take Profits” means that investors may re-weight their holding by selling between 25%-75% of a stock.

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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