



# new horizons

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Developing biological  
therapeutics for cancer

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## From the CEO

Dear Shareholders

I'm pleased to share with you, in this second edition of Circadian's newsletter, details regarding the strong inroads we are making in executing our new strategy to become a world class developer of drugs for cancer therapy and other diseases.

Perhaps the most significant recent event is that, in January, our licensee Ark Therapeutics was granted FDA approval to commence Phase III trials of Trinam®. Trinam® is a novel treatment to improve quality of care and quality of life for kidney dialysis patients and is the most advanced product in our pipeline. Contingent upon the success of this trial, Trinam® could be on the market within as little as two to three years. Circadian is due to receive royalties from sales of this product as well as product approval-based milestones.

Another major commercial achievement for the company was the deal announced with Healthscope Ltd, one of Australia's leading clinical pathology service providers, to clinically validate and commercialise our diagnostic technology for Cancers of Unknown Primaries (CUP). This technology has been developed in conjunction with

the Peter MacCallum Cancer Centre over the past three years and has the potential to improve cancer treatment for the many people worldwide affected by this form of cancer, as well as deliver substantial revenue to Circadian.

These tangible milestones demonstrate that, despite the difficult economic and market conditions, Circadian is very well positioned to prosper. Our strong position is based upon a foundation of comprehensive intellectual property, a promising product pipeline, prominent commercial partners, a strong cash position, and the potential, as outlined by the recent Healthscope deal, to generate licensing and royalty revenues in the near term.

Amongst international investors, the mood towards biotech companies that can demonstrate credentials such as ours is optimistic. This sentiment is reinforced by recent research from the major US biotechnology body BIO and Thomson Reuters<sup>1</sup> which found that 70 per cent of investors expect biotech to outperform the rest of the market. The same research found that 67 per cent of investors stated that the best investment opportunities are in oncology.

Many of you will be aware of the recent takeover bid for Arana Therapeutics Limited, another developer of antibody based therapeutics, at a substantial premium to market price. We believe that this bid reflects the value of antibody development companies and highlights the investment appeal of your company.

Thank you for your support.

Robert Klupacs  
CEO

<sup>1</sup> 2009 BIO Thomson Reuters Investor Perception Study

The Circadian team at the Lorne Cancer Conference



*The CUP diagnostic is an important adjunct to our core business. It has the ability to improve cancer treatment plans for many people globally as well as potentially deliver substantial revenue*



## Snapshot of recent milestones

### Circadian signs deal with Healthscope to bring new cancer diagnostic technology to market

Cancers of Unknown Primaries (CUP) is generally less well known and publicised than other cancer types. However, it is actually more common than leukaemia and is the fourth most common cause of cancer deaths in Australia. CUP refers to a complex form of cancer in which the site of origin of a tumour cannot be identified using standard techniques. The inability to identify a primary site of cancer poses many challenges, given that the primary

site of cancer usually dictates the treatment, expected outcome, and overall prognosis.

Last month, Circadian signed an agreement with Healthscope Limited, one of Australia's largest healthcare providers, to commercialise a world-first diagnostic technology for CUP.

Under the agreement terms, Healthscope will further develop, clinically validate and market the test throughout Australia, New Zealand, Malaysia and Singapore. Circadian will earn an upfront fee, development milestones and a royalty on sales of the test. A potentially even larger financial return may arise because Circadian retains exclusive rights to commercialise the test throughout all other countries in the world including the lucrative US diagnostics market.

The diagnostic method was developed in collaboration with the Peter MacCallum Cancer Centre, a leading specialty cancer hospital and research institute in Australia. The software-based methodology identifies a patient's tumour type by comparing its pattern of gene expression to a database of known tumours.

Dr David Bowtell, Director of the Peter MacCallum Cancer Centre and a co-inventor of the diagnostic methodology said, "We hope the assay will lead to earlier diagnosis, improved treatment outcomes and enhanced quality of life for patients."

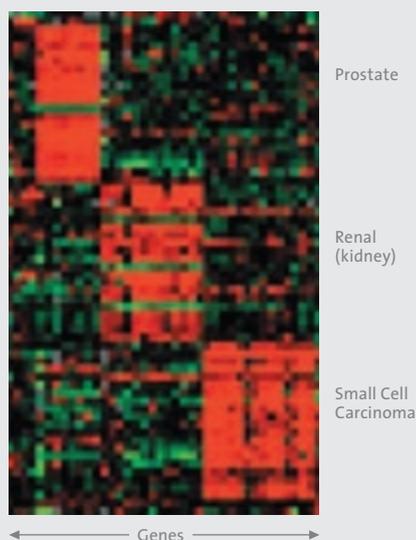
### Trinam® receives FDA approval for Phase III clinical trials

A major milestone for the company is the announcement that Circadian's licensee, Ark Therapeutics Group plc, has received clearance by the US Food and Drug Administration (FDA) to commence Phase III human clinical trials of Trinam® which is based on our Vascular Endothelial Growth Factor-D (VEGF-D) intellectual property.

Trinam® is a novel treatment that prevents the vascular grafts from blocking. Vascular grafts are used to insert dialysis tubes for patients undergoing kidney dialysis. More than 275,000 patients receive regular hemodialysis in the US alone.

In earlier Phase II trials, patients given Trinam® achieved up to a three-fold increase in the time that access grafts remained functional, as compared to untreated controls. If these results can be confirmed in larger Phase III trials, this would represent a significant benefit to patients.

The commencement of Phase III trials represents a major valuation milestone for Circadian, with the potential to generate royalty income in two to three years time if trials are successful.



An image representing distinct gene expression patterns from different types of tumors. Red pixels indicate high expression of a gene, green represents low expression. The pattern of gene expression obtained from a tissue biopsy is a "fingerprint" that can be used to identify the organ of origin, allowing more appropriate treatment. The Circadian CUP diagnostic employs a sophisticated algorithm to interpret these patterns of gene expression.



## Industry leadership

Emma Gordon receiving the Circadian Award for Excellence in Angiogenesis Research from CEO Robert Klupacs.

### Circadian sponsors Lorne Cancer Conference

In February, 400 leading cancer scientists and academics from Australia and around the world gathered in the Victorian coastal town of Lorne for the 21st Lorne Cancer Conference. In keeping with its emerging role as an Australian leader in the field of cancer therapeutic development, Circadian was a principal sponsor of the conference. This was a valuable opportunity for us to

raise our profile and engage with members of the global cancer research community, as well as demonstrate our support for the industry.

A significant theme of the conference was the important role of angiogenesis in tumour growth and spread, and the potential to block these processes as cancer treatments. This, of course, is the focus of Circadian's drug development programs.

*The annual Circadian Award for Excellence in Angiogenesis Research has been created to reflect the company's role as an emerging world leader in the field.*

### Circadian Award for Excellence in Angiogenesis Research

As part of our sponsorship and desire to raise the profile of angiogenesis research in Australia, we created the Circadian Award for Excellence in Angiogenesis Research. We would like to extend our congratulations to Ms Emma Gordon for winning this year's award in recognition of her research paper "Defining the Role of Macrophages in Embryonic Lymphangiogenesis."

Emma Gordon is a graduate student in the laboratory of Dr Natasha Harvey in the Centre for Cancer Biology at the Hanson Institute in Adelaide, South Australia.

### Take a look at our new website: [www.circadian.com.au](http://www.circadian.com.au)

We've updated our branding and website to reflect the new Circadian. We're pleased to unveil our new website [www.circadian.com.au](http://www.circadian.com.au) which contains a range of new resources and information including new fact sheets, latest news

and an overview of our pipeline and technology.

We invite you to visit the site and take a look at an informative corporate video which provides a succinct overview of Circadian, our technology and the concept of anti-angiogenesis therapy for cancer.



(Above) The new look of the Circadian website. (Right) The new corporate video explains how the company works and the technology of Circadian.

# Summary of recent research papers

A large body of data has emerged over the past 10-15 years from research groups around the world implicating VEGF-C, VEGF-D and/or their receptor, VEGFR-3 in cancer progression and tumour growth.

A number of research papers continue to be published reinforcing the important role of these molecules in cancer. Summarised

below are two, among many, recent reports from leading international laboratories.

## VEGFR-3 melanoma link

In a report from the respected Salpêtrière Hospital in Paris, the authors demonstrated a strong correlation between circulating levels of VEGFR-3 in blood and cancer

progression in melanoma. They noted "... Our data indicate that high expression of VEGFR-3 in the blood is significantly correlated to poorer prognosis for melanoma patients. This suggests that VEGFR-3 is

*"... Our data indicate that high expression of VEGFR-3 in the blood is significantly correlated to poorer prognosis for melanoma patients. This suggests that VEGFR-3 is a promising drug target for melanoma disease..."*

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Mouawad, R et al, European Journal of Cancer, 2009 (Epub)

## VEGF-C in lung cancer

The authors of another paper investigated the roles of VEGF-A and VEGF-C in the spread of tumours in patients with non small cell lung cancer. They identified two

different types of lung cancer which spread, one mediated by VEGF-A and the other by VEGF-C.

They noted that the drug Avastin might be effective for tumours expressing

VEGF-A. On the other hand, some tumours expressed VEGF-C, but not VEGF-A.

The authors

recommended, "Therefore, new molecular target agents against VEGF-C should be developed to control these VEGF-C positive tumours in the near future..." Circadian's drugs VGX-100 and VGX-300 are intended to do just this.

Kadota, K et al, European Journal of Cancer, 2008, 44 p1057

## Profile: Megan Baldwin, PhD

Head of Pre-Clinical Research and Development (R&D)

**Megan Baldwin was appointed in January 2008 as the Head of Pre-Clinical R&D of Circadian Technologies. With a scientific background of more than 10 years focused on angiogenesis and therapeutic strategies for oncology indications, Megan has the ideal experience to guide the pre-clinical research program of Circadian's promising product pipeline.**

Megan oversees Circadian's internal research laboratory as well as directing third party relationships with contract research organisations and academic groups, both locally and internationally.

"My role as Head of Pre-Clinical R&D is central to Circadian's new business model as a developer of therapeutics. My responsibilities involve implementation of activities and management of relationships required to move our products forward through development."

"My ultimate goal in this role is to witness the success of the molecules that we are developing and see them enter the clinic and improve the lives of patients."

Prior to joining Circadian, Megan spent five years at Genentech, the world leader in the field of angiogenesis-based therapies for cancer and other diseases. For the first three years, she worked as a postdoctoral fellow in the Research division on VEGF/VEGFR biology. The following two years Megan worked in the Commercial division within the Market Planning department, with responsibility for corporate competitive intelligence activities to support the company's oncology programs. In this role, she developed extensive knowledge of the angiogenesis and cancer fields.

Megan holds a PhD in Medicine from the University of Melbourne, having conducted her doctoral studies



at the Ludwig Institute for Cancer Research.

Outside of the office, Megan enjoys outdoor activities with her family and is a keen swimmer.