

## Developing biological therapeutics for cancer

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## From the CEO

Dear Shareholders,

One of the most rewarding aspects of leading Circadian Technologies is knowing that our company, despite its small size, is at the forefront of a major transformation of healthcare – the development of antibody-based therapeutics for cancer.

In contrast to traditional pharmaceuticals, antibodies offer two compelling advantages – they are much more specific, meaning they are more effective in targeting pathways contributing to a disease, and they are generally much less toxic.

An appreciation for these advantages is what led us to enter the field. And I would like to share with you some recent data that illustrates the growing promise of our commercial opportunity.

One reference point comes from EvaluatePharma, a leading industry market research organisation. EvaluatePharma predicts that by 2014, four of the six best-selling drugs in the world will be antibodies, and three of these will be anti-cancer drugs.

So Circadian's antibody therapy-based approach is arguably the most promising (and lucrative) technology platform in the pharmaceutical industry.

Our programs are also unique in the exceptionally promising field of angiogenesis therapy. Within this field, we are aware of approximately 60 products targeting the VEGF/VEGFR family. This large number of competitors, most of which are major international pharmaceutical companies, reflects the significant interest in this promising target family. One of these drugs, Avastin® from Genentech, is forecast to be the world's top selling drug in 2014.

However, only about ten of these products are antibodies. And a remarkable fact is that four of these are owned by or licensed from Circadian Technologies.

How has a small Australian company established a leading position in such a competitive area?

The key reason is patent rights. Circadian controls an extensive portfolio of over 320 patents or patents pending that afford us unique rights to develop antibody-based drugs in this field.

And I am pleased to report that we have taken another step forward in strengthening our intellectual property in this area. Circadian has recently been granted a significant patent covering the use of the VEGF-D protein. Details are provided elsewhere in the newsletter.

Of course, the key to our long term success will be the successful marriage of commercial and scientific outcomes – in this newsletter we give some insight into the role of our unique Product Development Review Committee (PDRC), an experienced group of experts that provide advice to Circadian on our drug development strategy to meet our commercialisation objectives. The Circadian PDRC is helping to ensure that we capitalise upon the great potential of our intellectual property.

We hope you find this edition of our shareholder newsletter to be informative. Thank you, as always, for your support.

Best wishes,

Robert Klupacs  
CEO



## Snapshots of recent milestones

*These findings are highly promising and, because of their related mechanism, they reinforce the potential of Circadian's own VEGF-C and VEGF-D antibody programs.*

Circadian Research Scientist David Phelan, Ph.D. in the Circadian laboratory located at the Ludwig Institute for Cancer Research in Melbourne.

### Promising data from licensee ImClone reported at AACR

At this year's American Association for Cancer Research (AACR) annual conference, scientists from US biotechnology company ImClone Systems released data demonstrating that an antibody developed under license from Circadian was effective in two models of cancer.

The data showed that, in an animal model of human head and neck cancer, treating mice with a combination of a monoclonal antibody targeting the Vascular Endothelial Growth Factor Receptor 3 (VEGFR-3) plus the chemotherapy drug docetaxel gave significantly better results than treatment with docetaxel alone.

In a second animal study, ImClone showed that the same antibody also combined with the chemotherapy drug cisplatin to more effectively treat human lung tumours than cisplatin alone.

These findings are highly promising, and because of their related mechanism, they reinforce the potential of Circadian's own VEGF-C and VEGF-D antibody programs.

ImClone Systems and Circadian announced in October 2008 that the VEGFR-3 antibody, IMC-3C5, has been designated as a formal pre-clinical development candidate for oncology indications.

### First patient enrolled in Phase III clinical trials for Trinam®

Another of Circadian's licensees is also advancing its trials. Ark Therapeutics Group plc (LSE:AKT) has enrolled the first patient into its US Phase III study for Trinam®, a novel treatment to improve quality of care and quality of life for kidney dialysis patients.

Trinam® is a gene-based medicine to prevent blood vessels from blocking in kidney dialysis patients who have undergone vascular access graft surgery. Rights to employ the VEGF-D gene in Trinam® are licensed from Circadian to Ark.

Trinam® has already demonstrated considerable benefits for patients undergoing kidney dialysis. In Phase II trials, the lifetime of a dialysis access graft was increased to 17 months from 4.5 months, which reduces the need for repeated surgery and may increase the survival time of patients undergoing dialysis.

If successful, this Phase III study is expected to be the final stage of clinical trials and thus marks a significant milestone on the path to commercialisation of Trinam®, and yet another reflection of the significant commercial value of our VEGF intellectual property.

Under the terms of the license agreement, Circadian is entitled to receive milestone payments on clinical development achievements and royalties on product sales.

### European VEGF-D patent further strengthens IP portfolio

Securing patent protection is a key element of Circadian's strategy to become a leading developer of therapeutic antibody drugs for cancer. Last month, Circadian was granted European Patent 1749836, covering the use of VEGF-D protein and antibodies to VEGF-D in a broad spectrum of therapeutic indications, including the treatment of cancer – a very important development towards executing our strategy.

Together, with similar patent rights in the US that had already been granted in 2008, these patents provide Circadian with a major commercial advantage and protection of its VGX-200 program, as well as other possible product applications in the world's two largest pharmaceutical markets.

Circadian Scientific Advisory Board Chairman, Professor Kari Alitalo receives the InBev-Baillet Latour Health Prize from Princess Mathilde of Belgium.



## Industry leadership

### Sponsorship of International Angiogenesis Conference

Circadian Technologies is keeping good company: We joined Astra Zeneca and Roche Pharmaceuticals, two of the world's top ten pharmaceutical companies, as a principal sponsor of the European School of Haematology Interdisciplinary Conference on Angiogenesis. The meeting was held in Helsinki on June 6 and 7.

The conference is a highly regarded meeting of leading international angiogenesis researchers from the pharmaceutical industry and academia. Sponsorship of such a conference helps to reinforce our reputation as one of the leaders in next-generation inhibitors of angiogenesis as treatments for cancer. It's also a valuable opportunity for Circadian to raise its profile within the industry and connect with potential future customers and partners, and remind them of the recent change in strategy

of Circadian Technologies to focus on drug development in this area.

The conference was chaired and hosted by Professor Kari Alitalo of the University of Helsinki. Professor Alitalo also serves as Chairman of Circadian's Scientific Advisory Board.

### Chair of Circadian's Scientific Advisory Board awarded top scientific prize

The therapeutic importance of Circadian's technology has received international recognition. Professor Kari Alitalo, Chairman of Circadian's Scientific Advisory Board, was named the co-recipient of the prestigious InBev-Baillet Latour Health Prize for 2009. The InBev-Baillet Latour prize is one of the most prestigious awards in European science. It is awarded annually for contributions in biomedical research, particularly its practical application.

In granting the award to Professor Alitalo, the InBev-Baillet Latour Fund cited his "cloning and characterizations of the first specific growth factor receptor of the lymphatic system, VEGFR-3," and his demonstration that VEGFR-3 plays a key role in the spread (metastasis) of tumour cells via the lymphatic system.

Circadian Technologies owns world wide patent rights to develop Professor Alitalo's work covering VEGFR-3 for biomedical applications. Professor Alitalo serves as a collaborator and advisor to the company for these programs.

### Focus on commercialisation:

## The role of Circadian's Product Development Review Committee

An important resource to many small biotechnology companies, Circadian included, is a Scientific Advisory Board. Such a group, usually composed of academic scientists, serves to help identify new project opportunities and to evaluate early stage projects.

While the role of the Scientific Advisory Board is very important, Circadian has established a second panel of experts known as our Product Development Review Committee (PDRC). This body, made up of former senior executives from some of the worlds' most respected pharmaceutical companies, assists management so that every product development program in Circadian's

portfolio is conducted to the highest standards in the industry.

Circadian's PDRC comprises six people who collectively have experience in developing over 150 drug candidates. The committee members have had diverse, operational responsibility for all of the key areas of drug development including pharmacology, toxicology, regulatory affairs, clinical development and commercialisation. Employing their vast experience, the PDRC assists Circadian management in making well informed choices relating to investment in the company's drug development programs – both pre-clinical and human clinical.

### 60 seconds with Russell Howard, CEO of Maxygen and member of Circadian's PDRC

Russell Howard is the CEO of Maxygen, a US-based, NASDAQ listed biotechnology company. On a recent trip to Australia, he spoke at an industry luncheon hosted by Circadian and Deacons law firm to share his views on the US biotech industry. Russell comments on his role on the Circadian Product Development Review Committee.

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### Why did you join CIR's PDRC?

For me, the fact that Circadian's Product Development Review Committee was established in the early stages of drug development was a critical factor in joining. Circadian has an excellent portfolio of technology, intellectual property and drug leads, and by getting involved early there is a greater opportunity to shape and influence the drug development program strategy and design. The calibre and experience of the other members of the PDRC also made this role very appealing to me.

### What expertise do you bring to the committee?

While the ultimate goal of Circadian's development programs is to bring new drugs to market, Circadian plans to partner with major international pharmaceutical companies for the costly later stages of clinical trials. In order to achieve this, Circadian needs to develop a compelling "package" of supporting data for each program. As a CEO of a US biotech that has discovered drugs using a technology platform, advanced them into clinical trials and partnered with large pharma companies, I've been through this process several times. I can provide advice from both sides of the fence, so to speak, on what makes up a high quality package.

### Why is a committee such as PDRC important to a company like Circadian?

Drug development is a long-term and complex business. It's important to have in mind the end-goal as well as value inflection points for investors along the way when making decisions. The PDRC helps the company to remain focused on the commercial goal, guide the development towards a desired end-point – be that selecting a disease application for the product or gearing towards partnership with a pharmaceutical company. Importantly, the PDRC allows Circadian to validate its benefit from the collective knowledge the group members have built throughout their careers.

## Circadian's Product Development Review Committee



### Dr Errol Malta (Chairman)

Former Product Development Team Leader at Amgen Inc, the world's largest biotechnology company.



### Mr Carlo Montagner

CEO of Specialised Therapeutics. Former senior executive with major international pharmaceutical companies Sanofi-Aventis and Bayer-Schering.



### Dr Russell Howard

CEO of US Nasdaq listed Maxygen Inc, a company focused on human therapeutics with several programs in protein pharmaceuticals.



### Mr Ralph Smalling

Former head of Amgen Regulatory Affairs. 23 years drug development experience with Amgen.



### Dr George Morstyn

Former Senior Vice-President and Head of Development at Amgen and Head of the Clinical Program of the Ludwig Institute for Cancer Research in Melbourne.



### Dr Richard Morgan

More than 25 years experience in pharmaceutical research and development including Head of Toxicology at GlaxoWellcome (now GlaxoSmithKline).