



Update Report

CIRCADIAN TECHNOLOGIES LIMITED

IND filed for VGX-100 in cancer, strong financial position



Date: 7 October 2011

Name:	Circadian Technologies
Country:	Australia
Price:	AUD 0.47
ISIN Code:	AU000000CIR6
Reuters Code:	CIR.AX
Market Cap (AUD m):	21.8
EV (AUD m):	4.2
Cash & cash eq. (AUD m):	25.8
Shares outstanding (m):	46.396
Volume:	37,500
Free float:	100%
52-week Range:	0.41-0.78

AUD m (1 USD = AUD 0.94)	2009A	2010A	2011A	2012E	2013E
Revenues	3.1	2.3	1.8	5.5	23
Net Loss/Profit	-9.9	-6.9	-10.3	-10.5	1.3
Net loss per share (cents)	-22.2	-15.4	-22.2	-22.6	2.8
R&D costs	-4.5	-4.3	-6.6	-12.5	-12.9
Cash increase/(decrease)	-7.3	-6.9	-10.4	-11.9	12.8
Cash and marketable sec.	38.8	31.9	22.1	10.1	22.9

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Executive Summary

CIRCADIAN TECHNOLOGIES LIMITED

- Circadian Technologies Limited (CIR) is an Australia-based listed biotechnology company having a strong product pipeline which includes VGX-100 (a fully human antibody against VEGF-C), VGX-200 (a humanized antibody against VEGF-D) and VGX-300 (a soluble recombinant form of VEGFR-3). Circadian develops and commercialize therapies primarily for cancer, as well as for other serious diseases.
- The Company is engaged in the development of biological drugs, including antibodies, for the treatment of cancer, targeted against Vascular Endothelial Growth Factors (VEGF) C, D and the VEGFR-3 receptor as well as developing a range of in vitro diagnostics. During the fiscal year ended June 30, 2010 the Company developed a production manufacturing process for VGX-100 and completed the production of drug compound for use in animal pharmacokinetic and toxicology studies. Data demonstrates efficacy of VGX-100 with other therapeutic agents in mouse models of lung, brain, ovarian and prostate cancers. Besides, VGX-100 significantly reduces the metastatic spread of prostate cancer in a mouse model. VGX-100 is covered by a variety of US and international patents extending beyond 2022.
- End of last month the company announced that it has submitted an IND application to the FDA to initiate clinical studies of VGX-100. The Phase I dose escalation study will involve the treatment of a variety of different cancer types in patients with late stage cancer. . Circadian intends to initiate clinical trials of VGX-100 in Q4 2011.
- Earlier last month, the company announced the publication of data, which showed that VGX-100 significantly reduced inflammation and corneal epitheliopathy in Dry Eye Disease (DED). DED is a complex immune mediated disorder that has multiple causes and affects about 5 million Americans above the age of 50 years. Currently, topical cyclosporine-A is the only approved treatment for DED.
- With more than AUD 22 million in cash, the company continues to have a strong financial position. This should be enough to take its lead drug VGX-100 through Phase I and Phase II trials. With the start of clinical trials, the company expects for 2012FY a cash burn of AUD 10-12.5 million.
- Based on sum-of-the-parts valuation, we believe Circadian is gravely undervalued at the current share price of AUD 0.47. Using our valuation model, the Company's total value is AUD 91 million, or AUD 1.97 per share. This represents more than 300% upside from the current share price.

1. Company Overview

Circadian Technologies Inc. (ASX: CIR) is an emerging Australian biotechnology company developing innovative, biologics-based therapies. The Company's principal activity is to develop and commercialize therapies primarily for the treatment of cancer and other serious diseases. Circadian owns an extensive portfolio of products and intellectual property related to Vascular Endothelial Growth Factors (VEGFs), a class of proteins that regulates tumour blood supply and growth of the lymphatic system. These programs are conducted through Vegenics Ltd, a wholly-owned subsidiary of Circadian.

Circadian has a strong product pipeline which includes VGX-100, VGX-200 and VGX-300. Last month, Circadian filed for an IND to enable Phase I studies with VGX-100. A dose ranging phase I trial of 27 to 33 patients would simultaneously examine the safety and tolerability of VGX-100 as a mono therapy and in combination with Avastin. A subsequent Phase II trial in glioblastoma of more than 100 patients will very likely be a pivotal registration trial. Phase II is expected to start one year after the start of the Phase I trial.

Moreover, the company maintains commercial partnerships with other leading biotechnology companies such as Ark Therapeutics and ImClone Systems for the development of products based on Circadian's own technology. Circadian, in collaboration with Healthscope Limited (one of Australia's largest pathology companies) is developing a novel diagnostic technology, which identifies a patient's primary tumour type when they present with metastatic cancers with Cancer of Unknown Primary, by comparing its pattern of gene expression to a database of known tumours.

2. Recent Developments

Circadian files for IND application on VGX-100 with the FDA

Last month, Circadian announced that it submitted an Investigational new drug (IND) application to the US FDA to start clinical studies with VGX-100. The first Phase I trial will involve the treatment of a variety of different cancer types in patients with late stage cancer.

Preclinical data (see also Chapter 4, Pipeline) have shown that VGX-100 combined with Avastin and chemotherapy, can significantly reduce tumor growth and tumor spread as well as significantly improve tumor inhibition. These data show much better results than treatment with Avastin and/or chemotherapy alone.

Circadian expects to start Phase I trials by the end of this year and to see results from the study in the second half of 2012. A dose ranging phase I trial of 27 to 33 patients would simultaneously examine the safety and tolerability of VGX-100 as a mono therapy and in combination with Avastin. A subsequent Phase II trial in glioblastoma of more than 100 patients will very likely be a pivotal registration trial.

An IND is a request for authorization from the FDA to administer an investigational drug to humans. During a new drug's preclinical development, a company focuses on generating scientific data and information necessary to establish that the product will not expose humans to unreasonable risks when used in clinical studies.

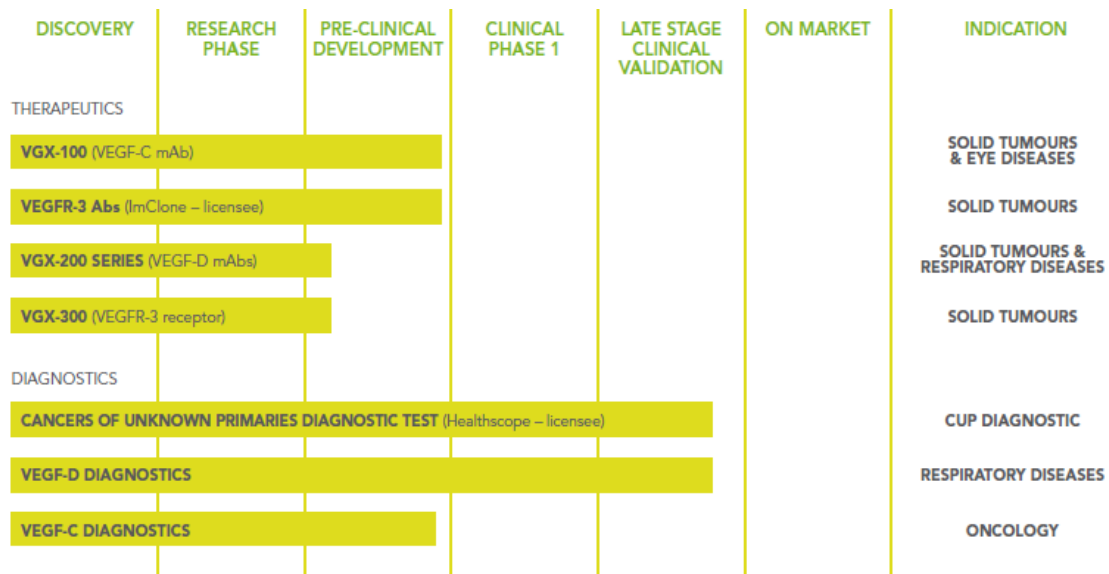
Once the IND is submitted, the applicant must wait 30 days before initiating any clinical trials. During this time, the FDA reviews the data in the IND and determines the conditions under which human trials can commence.

A combination therapy with Avastin has become more interesting as a result of clinical data that show that the effect of Avastin in inhibiting angiogenesis is only partial. Hence there is a need for auxiliary or improved anti-angiogenesis agents. Next to that, key patents of Avastin will expire in 2017 which makes it very attractive to companies to look for combination therapies with generic Avastin.

VGX-100 potential new therapy for Dry Eye Disease

In September, Circadian also announced the publication of data in the scientific journal Archives of Ophthalmology that showed that VGX-100 significantly can reduce inflammation and corneal tissue damage associated with Dry Eye Disease (DED). These data would indicate that next to the treatment of a variety of cancers, VGX-100 also offers a therapeutic treatment for DED. Currently, only topical cyclosporine-A is approved to treat DED.

3. Pipeline



Source: Company reports

VGX-100

VGX-100 is a fully human monoclonal antibody targeting the VEGF-C protein. Preclinical studies data have demonstrated that VGX-100 inhibits the growth of a variety of tumour types including prostate, pancreatic, lung, ovarian and glioma. Additionally, VGX-100 has been shown to dramatically reduce the frequency of tumour metastatic spread in certain animal models. Preliminary toxicology studies have identified no serious adverse effects of VGX-100 treatment in animals. VGX-100 is covered by a variety of US and international patents extending beyond 2023. An IND with the FDA to enable Phase I studies, was filed earlier last month. Clinical trials are expected to commence in Q4 2011. If clinically validated, VGX 100 has the potential to be a major new treatment for some types of cancer.

Highlights of preclinical studies data are as follows:

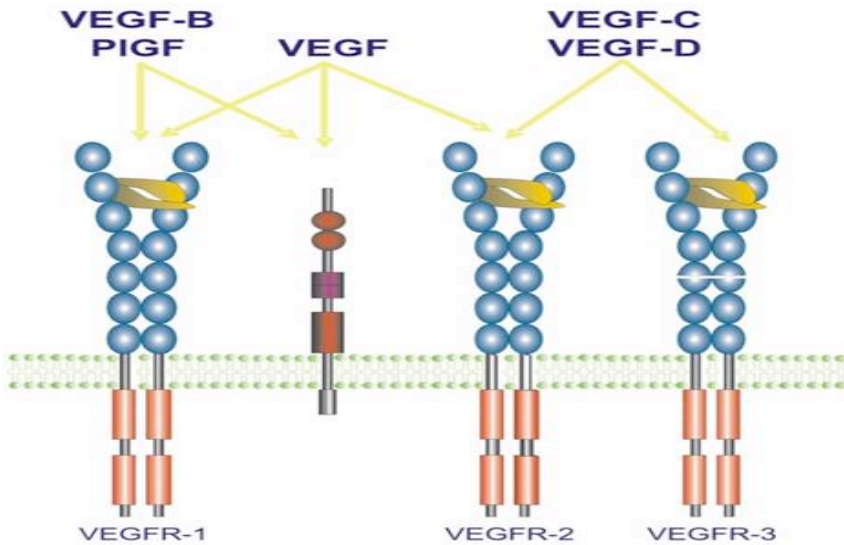
1. In a mouse model of human prostate cancer, treatment of animals with a triple combination of VGX-100, Avastin and docetaxel inhibited tumour growth by 83.4%, as compared to only 35.8% in animals treated with Avastin plus docetaxel alone.
2. In the same study, animals treated with the triple combination were four times as likely to survive until the end of the study as animals treated with docetaxel alone. Survival was increased 2.7 times

over animals treated with docetaxel plus Avastin.

3. About 40% of animals treated with the triple combination were tumour-free at the conclusion of the study (tumours had been eradicated). This compares to none (0%) that were tumour free among the animals treated with docetaxel plus Avastin and 20% among animals treated with docetaxel alone.
4. In a glioblastoma animal model, VGX-100 added to Avastin achieved a statistically significant improvement in tumour growth inhibition compared to untreated animals. The tumours in animals treated with VGX-100 plus Avastin were on average 42% smaller than untreated control animals.
5. In a pancreatic cancer model, treatment with VGX-100 inhibited tumour growth similar to that achieved in animals treated with the drug Avastin.

This was the first substantial data to directly demonstrate that blocking the VEGF-C pathway by VGX-100 can inhibit tumour growth in mouse models of lung, ovarian and prostate cancer. Moreover, data indicate that VGX-100 can act either by itself or in combination with approved drugs can significantly slow the growth of several different tumour types including prostate, pancreatic, and glioblastoma. This can be a possible future use as a new cancer treatment option. The data suggest that there may be some cancer indications for which VGX-100 is superior to Avastin, one of the world's leading anti-cancer drugs or may be effective where Avastin isn't. Also there may be cases where adding VGX-100 to Avastin may significantly improve existing therapies. Highlights of the data are as follows:

- Addition of VGX-100 to bevacizumab (Avastin®) + docetaxel therapy reduces tumour burden in prostate, ovarian and lung cancer models
- In an orthotropic mouse model of human prostate cancer (a model where tumours are inoculated directly into the prostate) single-agent VGX-100 significantly inhibited primary tumour growth by 59% compared to a control antibody
- In the same orthotropic model of human prostate cancer single agent VGX-100 significantly reduced the incidence of metastasis (tumour spread) to local lymph nodes by 55%VGX-100 neutralizes VEGF-C and prevents VEGF-C binding and activating both VEGFR-2 and VEGFR-3



VGX-100 can block angiogenesis driven by VEGFR-2 and VEGFR-3 resulting in better control of tumor growth. This can be achieved either by combining bevacizumab plus VGX-100 therapy or combining therapy with VEGFR-2 and VEGFR-3 antibodies. VGX-200 series is a set of humanized monoclonal antibodies targeting the VEGF-D protein. Circadian is currently evaluating a number of lead candidates with high binding affinity for VEGF-D (Kd below 1nM). Patent coverage of the VGX-200 series extends beyond 2025. This program is still at research phase.

VEGFR-3 as an anti-cancer target

Circadian's partner, ImClone Systems, is developing a VEGFR-3 antibody as treatment for solid tumours. In 2008, the antibody was formally designated a product development candidate. It was demonstrated that anti VEGFR-3 antibodies significantly inhibited blood vessel supply to tumours and blocked tumour growth. Circadian receives annual milestone payments and royalties on the sale of the VEGFR-3 antibody product. ImClone commenced Phase I studies with its lead candidate IMC-035 in April 2011. According to the licence agreement, Circadian is entitled to annual licence fees, product milestone payments and royalties on sales.

VGX-200 series

The VGX-200 series is a set of humanized monoclonal antibodies targeting the VEGF-D protein. Circadian is currently evaluating a number of lead candidates with high binding affinity for VEGF-D (Kd below 1nM). Patent coverage of the VGX-200 series extends beyond 2025. This program is still at research phase.

VEGF-C/D/R3 pathway and cancer

The commercial success of Avastin®, clinically validated anti-angiogenic drugs as an effective means of inhibiting solid tumour growth. By blocking the interaction of VEGF-A with its receptors, primarily VEGFR-2, the multi-billion dollar cancer therapeutic slows tumour growth by inhibiting blood vessel recruitment into the tumour, effectively starving tumours of essential nutrients and oxygen required for growth. Avastin, which is sold by Genentech (now part of Roche), recorded a worldwide sales of USD 7.3 billion.

VEGF-C and VEGF-D inhibitors, VGX-100, VGX-200 and VGX-300, are key therapeutics in the portfolio of Circadian's unlisted subsidiary Vegenix, which block these alternative stimulators for VEGFR-2. As such, they have the potential to block blood vessel growth in tumours resistant to anti-VEGF-A therapy and, when used in combination with drugs like Avastin®, may completely shut down angiogenesis (the growth of blood vessels) mediated by VEGFR-2, resulting in greater clinical efficacy.

VEGF-C and VEGF-D are also the only known proteins to bind and activate VEGFR-3 which drives lymphatic vessel and tumour-associated blood vessel growth. Inhibitors of VEGF-C, VEGF-D and VEGFR-3 thus have therapeutic potential to inhibit not only primary tumour growth through their anti-angiogenic activities, but to also inhibit tumour spread or metastasis via the lymphatic vessels - a mechanism of tumour dissemination that is often the deadliest aspect of many tumour types and a mechanism that is not effectively blocked by anti-VEGF-A or anti-VEGFR-2 therapeutics. VGX-300 is a recombinantly produced protein comprising the soluble form of the VEGFR-3 molecule linked to an immunoglobulin. It is designed to capture and block the activity of the proteins VEGF-C and VEGF-D.

4. Technology

Circadian is developing a variety of drugs to block the interaction between VEGF Receptor-3 (VEGFR-3) and its ligands VEGF-C and VEGF-D. Drugs blocking this pathway would represent a novel and potentially revolutionary treatment approach for cancer patients as well as potentially in diseases of the cornea. VEGFR-3 pathway inhibitors may treat cancer by two mechanisms: First, inhibition of the ligands VEGF-C and VEGF-D blocks tumour angiogenesis, suppressing blood vessel development, starving tumours of oxygen and nutrients needed to grow. Second, tumours are known to metastasize through the lymphatic system. Tumour metastasis is often the direct factor leading to patient mortality. Blocking VEGFR-3 activation stops lymphangiogenesis, which in turn reduces the ability of tumours to spread. This approach to cancer treatment is potentially more effective than chemotherapy and may have greatly reduced side-effects. Circadian holds an extensive intellectual property position protecting its rights as the exclusive developer of this class of drugs.

VEGF

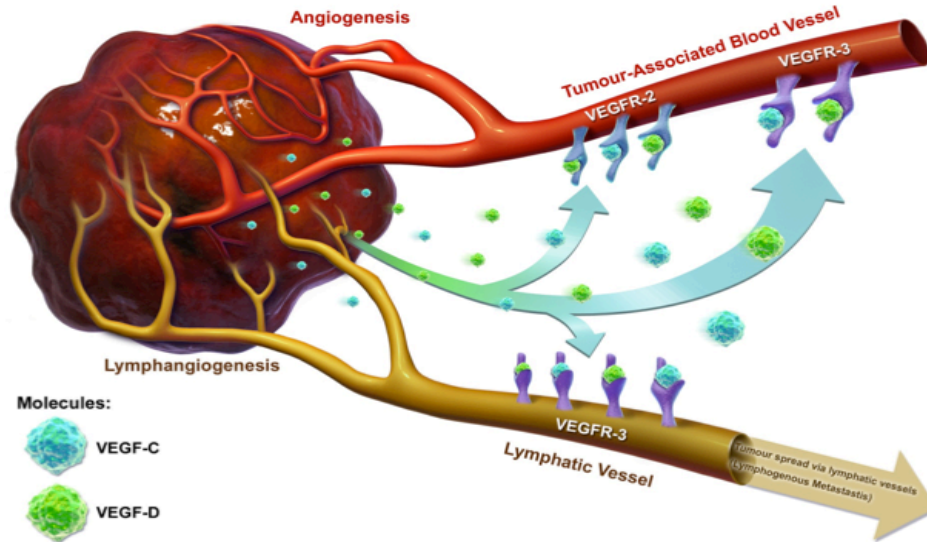
In 1989, Napoleone Ferrara, M.D., and a team of scientists at Genentech first isolated human vascular endothelial growth factor (VEGF), a protein now believed to be one of the most potent sources of angiogenesis. The need for oxygen and nutrients triggers tumor cells to produce and release the VEGF protein, which leads to the formation of new blood vessels to feed the tumor. In addition to supporting tumor growth, these new vessels provide a "highway" along which tumor cells can travel through the bloodstream to other parts of the body. This may lead to the formation of new tumors and spread of cancer (metastasis). Sustained angiogenesis is a hallmark of most, if not all cancers. Without angiogenesis, a tumor would not likely grow beyond a few millimetres, the size of an average pencil eraser.

Anti-Angiogenesis

As researchers gained a greater understanding of VEGF and its role in angiogenesis, they turned their focus to creating therapies that could interfere with angiogenesis by targeting the VEGF protein, one of the most potent and predominant regulators of angiogenesis. Therapies that inhibit VEGF may have multiple effects on angiogenesis, tumor growth and delivery of other types of therapy. These effects may include:

- Reducing the tumor's blood supply by potentially causing existing small blood vessels in the tumor to die.
- Preventing the development of new blood vessels in the tumor.
- Facilitating the delivery of chemotherapy to the tumor cells by potentially making mature tumor vessels, which tend to be leaky, behave more like normal vessels

By inhibiting the VEGF protein, the blood supply to a tumor may be gradually reduced.



Source: Company data

Avastin: The First Anti-Angiogenesis Treatment for Cancer

In 1993, Dr. Ferrara and his team at Genentech produced a monoclonal antibody that specifically binds to the VEGF protein, preventing it from promoting new blood vessel growth.⁷ In 2004, after seven years of human clinical trials, the U.S. Food and Drug Administration (FDA) approved the antibody, known as Avastin® (bevacizumab), in combination with intravenous 5-fluorouracil (FU)-based chemotherapy for the first-line treatment of patients with metastatic colorectal cancer. Avastin is the first approved anti-angiogenesis treatment for cancer. Avastin was initially approved based on the results of a Phase III study of the drug plus chemotherapy in previously untreated metastatic colorectal cancer patients. This study provided the first Phase III clinical validation of the long-standing hypothesis that targeting a tumor's blood supply via angiogenesis could be used as a cancer therapy. While Avastin® has been demonstrated to be effective in fighting cancer, clinical results indicate that its effect in inhibiting angiogenesis is only partial. Hence there is a need for auxiliary or improved anti-angiogenesis agents.

VEGF-C and Lymphangiogenesis

The metastatic spread of tumor cells is responsible for the majority of cancer deaths, and with few exceptions, all cancers can metastasize. Clinical findings have long suggested that by providing a pathway for tumor cell dissemination, tumor-associated lymphatics are a key component of metastatic spread. It is not known,

however, whether pre-existing vessels are sufficient to serve this function, or whether tumor cell dissemination requires de novo lymphatic formation (lymphangiogenesis) or an increase in lymphatic size. Lymphangiogenesis has traditionally been overshadowed by the greater emphasis placed on the blood vascular system (angiogenesis). This is due in part to the lack of identification of lymphangiogenic factors, as well as suitable markers that distinguish blood from lymphatic vascular endothelium. This scenario is changing rapidly after the identification of the first lymphangiogenic factor, vascular endothelial growth factor C (VEGF-C). Increased expression of VEGF-C in primary tumors correlates with increased dissemination of tumor cells to regional lymph nodes in a variety of human carcinomas.

With few exceptions, all cancers can metastasize. Metastasis unequivocally signifies that a tumor is malignant, and the metastatic spread of tumor cells is responsible for the majority of cancer deaths. Tumor dissemination may occur through a number of pathways:

- direct seeding of body cavities or surfaces
- local tissue invasion
- hematogenous spread and
- lymphatic spread

Clinical and pathological observations suggest that for many carcinomas, transport of tumor cells via lymphatics is the most common pathway of initial dissemination, with patterns of spread via afferent lymphatics following routes of natural drainage. Sentinel lymph nodes are a variable but limited set of nodes that are the first to receive drainage from any given location. As a rule, carcinomas preferentially metastasize to these lymph nodes, although intralymphatic tumor cells can pass directly into the blood vascular system through venolymphatic communications, and vice versa. Sentinel lymph node biopsy and histopathological examination improve tumor staging and facilitate the planning of therapeutic strategies.

Lymphangiogenesis has traditionally been overshadowed by the greater emphasis placed on the blood vascular system (angiogenesis). This is due in part to the lack of identification of lymphangiogenic factors, as well as suitable markers with which to distinguish blood from lymphatic vascular endothelium. However, this scenario changed rapidly following the discovery of the first lymphangiogenic factor, VEGF-C.

VEGF-C

VEGF-C is a member of the VEGF family of growth factors, which are highly conserved secreted glycoproteins that regulate vasculogenesis, hematopoiesis, angiogenesis, lymphangiogenesis, and vascular permeability and are implicated in many physiological and pathological processes. To date, the VEGF family is comprised of VEGF-A, -B, -C, and -D and Orf virus VEGFs (also called VEGF-E). Of the three VEGF tyrosine kinase receptors identified thus far (VEGFR-1, -2, and -3), VEGFR-1 binds VEGF-A and -B, VEGFR-2 binds VEGF-A, -C, -D, and -E, and VEGFR-3 binds VEGF-C and -D. VEGFRs differ with

respect to mechanisms of regulation and patterns of expression. For example, VEGFR-1 and -2 are expressed almost exclusively by vascular endothelial cells and hematopoietic precursors, whereas VEGFR-3 is widely expressed in the early embryonic vasculature but becomes restricted to lymphatic endothelium at later stages of development and in postnatal life.

VEGF-C displays a high degree of similarity to VEGF-A, including conservation of the eight cysteine residues involved in intra- and intermolecular disulfide bonding. The cysteine-rich COOH-terminal half increases the length of the VEGF-C polypeptide relative to other members of this family. Like VEGF-A, both human and murine VEGF-C are alternatively spliced. In addition, VEGF-C mRNA is first translated into a precursor from which the mature ligands are derived by cell-associated proteolytic processing after secretion. Unprocessed VEGF-C binds to VEGFR-3. Removal of its NH₂- and COOH-terminal extensions increases the affinity of VEGF-C for VEGFR-3 by approximately 400-fold. Processing also allows VEGF-C to bind to VEGFR-2. Processed VEGF-C induces endothelial cell proliferation and migration, as well as increased vascular permeability in the Miles assay. However, the respective roles of VEGFR-2 and -3 in mediating the biological effects of VEGF-C are incompletely understood. Unlike VEGF-A, VEGF-C expression does not appear to be regulated by hypoxia.

VEGF-D, an additional member of the VEGF family, contains the eight conserved cysteine residues characteristic of the VEGF family and has a cysteine-rich COOH-terminal extension similar to VEGF-C. Like VEGF-C, VEGF-D is proteolytically processed after secretion, and it binds to and activates VEGFR-2 and -3. Clearly, this VEGFR-3 ligand also plays a role in (tumor) lymphangiogenesis.

In summary, in normal adults, VEGF-C appears to be a lymphangiogenic factor, and VEGFR-2 is restricted to lymphatic endothelium. VEGFR-3, in contrast, is expressed by both blood vascular and lymphatic endothelium. However, VEGF-C also induces the formation of new blood vessels, but this appears to be restricted to early development and certain pathological settings such as tumorigenesis; in both of these settings, VEGFR-3 is also expressed by blood vascular endothelium. Although there is currently no explanation for the selective effects of VEGF-C on lymphangiogenesis versus angiogenesis, this may depend on the repertoire of VEGFRs expressed (including heterodimers between the different VEGFRs) or on the extent of VEGF-C proteolytic processing.

A number of reports have described a correlation between VEGF-C expression, tumor lymphangiogenesis, and the formation of metastasis in regional lymph nodes. Thus, a significant correlation has been described in a variety of cancers (including thyroid, prostate, gastric, breast colorectal, and lung cancer) between VEGF-C levels in primary tumors and lymph node metastases. Recent data published by Circadian scientists at AACR 2011 has indicated that inhibition of VEGF-C can significantly inhibit the spread of prostate cancer in an animal model of metastatic diseases, as well as significantly reduce the growth of a range of different tumour types when used in combination with Avastin and chemotherapy.

Several recent findings have further enhanced interest in VEGFR-3 as an important new drug target for cancer. These include:

- VEGF-D correlates with poor prognosis in a variety of cancer types
- Circadian and its collaborators have shown that blocking VEGFR-3 or VEGF-C and VEGF-D inhibits tumour growth in various animal models. In addition, the VEGFR-3 pathway has certain properties that make it especially attractive as a drug target
- VEGFR-3 is expressed at the cell surface, so it is accessible to biotherapeutics such as antibodies or soluble receptor drugs and
- The signalling pathway of VEGFR-3 is well understood, which facilitates the evaluation or ruling out of potential side-effects or toxicities.

Inhibitors of VEGF-C, VEGF-D and VEGFR-3 block the activity of these proteins in a similar, but alternative, way to the multi-billion-dollar drug Avastin®. As such, inhibitors of VEGF-C and VEGF-D have the potential to block blood vessel growth in tumours that are resistant, or have developed resistance, to anti-VEGF-A therapy. When used in combination with drugs like Avastin®, inhibitors of VEGF-C and VEGF-D may more effectively shut down angiogenesis. Inhibitors of VEGF-C, VEGF-D and VEGFR-3 also have the potential to limit the spread of tumours which is often the fatal event in cancer progression through their effect on lymphangiogenesis. Anti-VEGF-A therapeutics have not shown efficacy in blocking the spread of tumours through the lymphatic system.

Summary

Increased expression of VEGF-C in spontaneously arising human tumors has been reported to correlate with increased lymphangiogenesis and dissemination of tumor cells to regional lymph nodes. However, it is not known whether pre-existing lymphatics are sufficient to serve this function, or whether metastasis requires the de novo formation of lymphatic capillaries (lymphangiogenesis) or lymphatic enlargement. Some authors have suggested that it is not necessary to invoke lymphangiogenesis in this setting and that pre-existing peritumoral lymphatics that enlarge in response to VEGF-C in tumors will suffice. If this hypothesis is correct, it may be necessary to invoke non-lymphangiogenic functions of VEGF-C to account for the increase in lymph node metastasis. This might include the production of trophic, mitogenic, or chemotactic factors for tumor cells by VEGF-C-stimulated lymphatic endothelium or alterations in lymphatic endothelial-tumor cell adhesion. To date, nothing is known about these potential interactions.

In contrast to its sister field, angiogenesis, much less is known about the mechanisms and mediators of lymphangiogenesis. With regard to angiogenesis, an extensive effort is currently being directed worldwide to identify antiangiogenic agents, particularly for use in anticancer therapy, and many potentially useful compounds have progressed beyond preclinical studies into the early phases of clinical trials. This is largely due

to the identification of key molecular mediators. The fast increasing interest in lymphangiogenesis, after many decades of dormancy, will undoubtedly ensure that we move rapidly to attain similar objectives in the lymphatic system. Circadian's pipeline aimed to inhibit both lymphangiogenesis and angiogenesis by blocking the pathway between VEGFR-3 and VEGF-C & VEGF-D promises to be a realistic therapeutic strategy for inhibiting tumor cell dissemination and the formation of metastases.

5. Financials

For the FY2011 figures, published in June, Circadian reported revenues of AUD 1.8 million. Net loss increased 50% to AUD 10.3 million, with the increase in research & development costs, higher occupancy charges, a substantial increase in impairment losses and an increase in net foreign exchange losses. The preparation of and manufacturing for the upcoming clinical trials started to kick in.

The Company has a strong financial position with substantial cash reserves of AUD \$2 million as at 30th June 2011. According to management this should be ample enough to finance the clinical trials for VGX-100 till Phase II.

Financial Summary

AUD millions	2011 FY	2010 FY	change
Income Statement			
Gross Revenue	1.8	2.3	-21.7%
Selling, General	4.8	5.5	-12.7%
Research & Development	6.6	4.3	53.5%
Net Income (Loss)	(10.3)	(6.9)	49.3%
Balance Sheet			
Cash & Cash Equivalents	22.1	31.9	-30.7%
Current Assets	22.4	32.3	-30.6%
Current Liabilities	2.4	2.7	-11.1%
Long-term Debts	-	-	-
Shareholders' Equity	21.8	31.8	-31.5%
Retained Earnings	(13.2)	(3.0)	-
Cash Flow			
Depreciation & Amortization	-	-	-
Cash from:			
Operating Activities	(9.4)	(7.7)	22.1%
Investing Activities	(0.1)	0.7	-
Financing Activities	-	-	-

Source: Company filings

6. Valuation

We valued Circadian using the sum-of-the-parts valuation approach for each drug in the pipeline, adjusted for corporate overheads. We adopted the Net Present Value (NPV) Approach to value each drug, considering each drug under development as a separate project. We arrive at a fair value of AUD 1.96 per share using the SOTP valuation method.

Product	NPV (AUD M)	NPV per share
IM3C5	7.1	0.15
VGX-100 Cancer	43.0	0.93
VGX-100 Eye Disease	17.5	0.38
Cup Test	14.0	0.30
VEGF-D Diagnostic	9.4	0.20
NPV based fair value per share		1.96

■ SOTP Valuation

Source: Van Leunenboeck Research

Assumptions

To calculate the value of the Company, we estimated market size for each indication, expected market share of each drug, average medication cost, and life cycle of all drugs. Probability of approval is also considered to incorporate the chances of failure while calculating the NPV of the drug.

Cost of capital and terminal growth rate assumptions: For valuation purposes, we estimated the cost of capital at 15%. We have calculated the cost of capital as the weighted average of cost of equity and debt. To derive the cost of equity, we assumed a 14.9% equity risk premium and a 3.5% risk-free rate (10-year T-bond yield). A beta of 1.0 was assigned to Circadian; we believe this adequately reflects the risks associated with the Company. We used a 1.5% growth rate to arrive at the terminal value in the DCF.

We also use different probabilities of success dependent on the development stage. Once a partnered product comes on the market we assume that Circadian receives a 5% royalty on sales.

Probabilities of success

	Individual	Cumulative
Preclin-Phase I (IND)	80.0%	80.0%
Phase I-Phase II (Commencement Phase II)	70.0%	56.0%
Phase II-Phase III (Commencement Phase III)	50.0%	28.0%
Phase III-NDA (success Phase III)	50.0%	14.0%
NDA-Market	90.0%	12.6%
BLA Approval	90.0%	11.3%

Valuing IM-3C5

We valued the VEGFR 3 antibody that Imclone licensed in by using the NPV approach. The drug recently started Phase I and we expect it to be commercialized by 2020. The total NPV for the drug came out to be AUD 7.1 million (i.e. AUD 0.16 per share) after applying the probability of approval. We assume that Circadian will get a 5% royalty when the product will be on the market as well as an annual maintenance fee as agreed upon in the contract with Imclone. We note that Circadian has not disclosed actual value of the royalty percentage other than to say 'good single digit' and so the actual rate may be higher than 5%.

Valuing VGX-100

We valued VGX-100 also using the NPV Approach for both cancer treatments and treatments for eye diseases. We expect the start of clinical trials in cancer later this year. A partnership is expected with the start of Phase II trials, which we estimate to be in 2013. With a partner we expect VGX-100 to be on the market in 2019. Our assumptions indicate that VGX-100 has the potential to generate peak sales of AUD 3 billion (USD 2.8 billion) in 2025 for the cancer treatments and AUD 600 million (USD 565 million) for treatments in eye diseases. We have assumed that the company will be able to enter a partnership agreement for the development for VGX-100 and the partner will take care of the development expense and Circadian will get upfront and milestone payments as well as high single digit royalties. The total NPV for the drug came out to be AUD 43 million (i.e. AUD 0.93 per share)for cancer and AUD 17.5 million (i.e. AUD 0.38 per share)for eye diseases after applying the probability of approval.

Valuing Cup Diagnostic Test

In February 2009, Circadian signed a deal with Healthscope Ltd (ASX: HSP) to develop and commercialize a diagnostic technology for “Cancers of Unknown Primaries.” Under the terms of the agreement, Healthscope, through its subsidiary, Clinical Laboratories Pty Ltd, will further develop, clinically validate and market the test throughout Australia, New Zealand, Malaysia and Singapore. Circadian will retain rights to market the test in the remainder of the world. Healthscope will pay Circadian an upfront fee, development milestones and a royalty on sales of the test. We expect Circadian is getting low double digit royalties as of 2011. We believe the

test has the potential to generate peak sales of AUD 35 million in 2017. The total NPV for the test came out to be AUD 14 million (ie AUD 0.30 per share).

Valuing VEGF-D Diagnostic

In February 2011, Circadian launched its first diagnostic product, a serum based test to detect VEGF-D as a marker for respiratory disease. We expect a licensing deal in the next year as well as the start of product sales. Our assumptions indicate that the VEGF-D diagnostic has the potential to generate peak sales of AUD 20-25 million in 2022. The total NPV for the test came out to be AUD 9.4 million (i.e. AUD 0.20 per share) after applying the probability of approval.

Valuing Circadian

We valued Circadian using two approaches: SOTP and DCF valuation. Using SOTP, we arrived at a valuation of AUD 91 million (i.e., AUD 1.96 per share), which makes the Company significantly undervalued as compared to the current market price of AUD 0.60.

7. Forward Looking Statements

Circadian Technologies key events for the next 12-24 months include:

- completion of the first phase of development of CUP diagnostic test by Healthscope
- completion of Phase 1 studies by ImClone in respect of the VEGFR-3 antibody designated IMC-3C5 and subsequent commencement of Phase 2 clinical trials
- IND filing in respect of VGX-100 and subsequent commencement of clinical trials in corneal disease
- generation of additional data in animal models on non-cancer-related diseases to support development in non-cancer disease settings
- development of tests for the measurement of VEGF-C, VEGF-D and/or VEGFR-3 in blood as diagnostic assays for particular clinical conditions and
- extension of marketing partnerships throughout the world in respect of VEGF-D diagnostics

Analyst: Marcel Wijma MSc

Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starline as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.

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