ASX and Media release

6 April 2011

Circadian's VGX-100 Inhibits Tumour Growth in Models of Lung, Ovarian and Prostate Cancer

- Data demonstrates efficacy of VGX-100 with other therapeutic agents in mouse models of lung, ovarian and prostate cancers.
- VGX-100 improves the efficacy of Avastin® in a lung cancer model and further inhibits tumour growth when combined with Avastin® plus docetaxel in mouse models of human lung and ovarian cancer. Data expand on previous anti-cancer effects seen with VGX-100 in prostate, pancreatic and brain cancers (glioblastoma).
- In addition to the effect on primary tumour growth, VGX-100 significantly reduces the metastatic spread of prostate cancer in a mouse model.
- IND Filing for VGX-100 in oncology applications on track for filing Q3 2011

Circadian Technologies Limited (ASX.CIR) today released data at the American Association for Cancer Research (AACR) annual conference in Orlando, Florida (U.S.A.) demonstrating that its lead anti-cancer therapeutic, VGX-100, significantly inhibits tumour growth and spread in a variety of different mouse models of human cancer. These data indicate that, if clinically validated, VGX-100 has the potential to be a useful new treatment for some types of cancer.

VGX-100 is a fully human monoclonal antibody targeting the VEGF-C growth factor. VGX-100 inhibits the development of blood vessels that are required for tumour growth. Additionally, VGX-100 may inhibit cancer spread (metastasis) by suppressing the development of both blood and lymphatic vessels.

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 orthotopic 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 othotopic model of human prostate cancer single agent VGX-100 significantly reduced the incidence of metastasis (tumour spread) to local lymph nodes by 55%.

The poster entitled "The novel therapeutic monoclonal antibody VGX-100 neutralises VEGF-C and inhibits tumour growth and metastasis in subcutaneous and orthotopic models of human cancer" and a more detailed description and data figures are contained in the Appendix that follows.

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"This data further demonstrates that blocking the VEGF-C pathway by VGX-100 can inhibit tumour growth in mouse models of cancer. Moreover, our data indicates that VGX-100 can act either by itself or in combination with approved drugs to slow the growth of several different tumour types including prostate, ovarian, lung, pancreatic, and glioblastoma. The observed effects on inhibiting the effects of metastatic spread in the prostate cancer model are especially exciting" commented Dr. Megan Baldwin, Head of Preclinical Research and Development and senior author.

Robert Klupacs, CEO of Circadian stated that "This data, in addition to the data we have previously released publically, continues to build the strong case for clinical evaluation of VGX-100 and its possible future use as a new cancer treatment option. We are very excited by the prospect of commencing clinical development later this year."

Circadian controls exclusive worldwide rights to an extensive intellectual property portfolio enabling it to commercially develop antibodies targeting VEGF-C.

Circadian intends to file an Investigational New Drug (IND) application with the US FDA in the third quarter of 2011 in order to begin human clinical trials of VGX-100. This is subject to successfully completing the VGX-100 animal safety/toxicology studies which evaluate whether VGX-100 is safe to be studied in humans.

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About Circadian Technologies Limited

Circadian (ASX:CIR) is a biologics drug developer focusing on cancer therapies. It controls exclusive worldwide rights to a significant intellectual property portfolio around Vascular Endothelial Growth Factor (VEGF) C and D. The applications for the VEGF technology, which functions in regulating blood and lymphatic vessel growth, are substantial and broad. Circadian's internal product development programs are focussed on novel anti-cancer therapeutics for large unmet needs. Circadian has also licensed rights to some parts of its intellectual property portfolio for the development of other products to ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, including the antibody-based drug IMC-3C5 targeting VEGFR-3.

About Circadian's pipeline of treatments for cancer

The clinical and outstanding commercial success of Avastin®, an antibody that blocks the activity of VEGF-A, 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, had U.S. sales in 2009 of US$5.7 billion and worldwide sales in excess of US$8.6 billion. Avastin® is approved by the US FDA in the following indications: metastatic colorectal cancer, non-squamous-cell lung cancer, metastatic breast cancer, glioblastoma, metastatic renal cell carcinoma.

The VEGF-C inhibitor, VGX-100, a key therapeutic in Circadian's portfolio, block this alternative stimulator for VEGFR-2. As such, it has 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 along with the molecule 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 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.

Inherent risks of Investment in Biotechnology Companies

There are a number of inherent risks associated with the development of pharmaceutical products to a marketable stage. The lengthy clinical trial process is designed to assess the safety and efficacy of a drug prior to commercialisation and a significant proportion of drugs fail one or both of these criteria. Other risks include uncertainty of patent protection and proprietary rights, whether patent applications and issued patents will offer adequate protection to enable product development, the obtaining of necessary drug regulatory authority approvals and difficulties caused by the rapid advancements in technology. Companies such as Circadian are dependent on the success of their research and development projects and on the ability to attract funding to support these activities. Investment in research and development projects cannot be assessed on the same fundamentals as trading and manufacturing enterprises. Thus investment in companies specialising in drug development must be regarded as highly speculative. Circadian strongly recommends that professional investment advice be sought prior to such investments.

Forward-looking statement

Certain statements in this ASX announcement may contain forward-looking statements regarding Company business and the therapeutic and commercial potential of its technologies and products in development. Any statement describing Company goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of developing technology and in the process of discovering, developing and commercialising drugs that can be proven to be safe and effective for use as human therapeutics, and in the endeavor of building a business around such products and services. Circadian undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Actual results could differ materially from those discussed in this ASX announcement.

Appendix: Key data for presentation at American Association for Cancer Research Annual Conference, Orlando Florida U.S.A., APRIL, 2011.

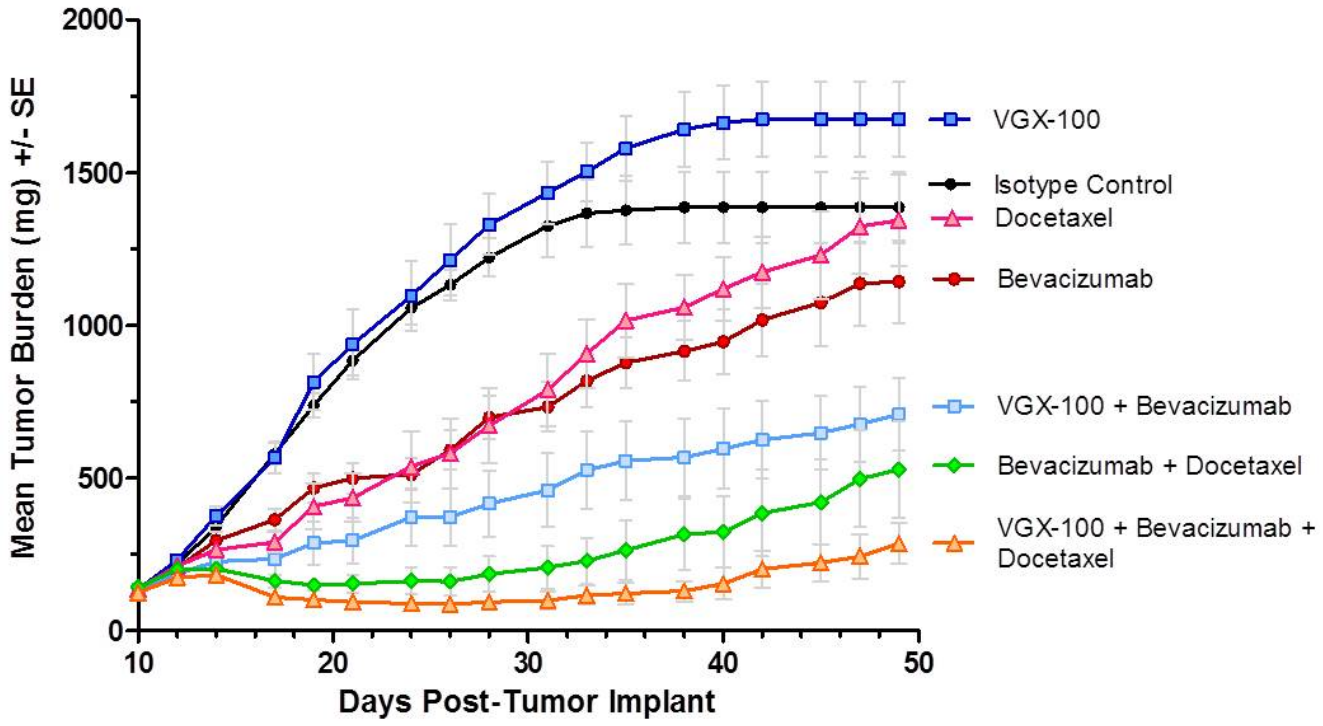


Figure 1. VGX-100 Enhances the Anti-Tumour Efficacy of Chemotherapy and Bevacizumab (Avastin®) in a Lung Cancer Model. The figure presents the mean lung cancer tumour size in animals receiving various treatments. Adding VGX-100 to bevacizumab therapy (light blue symbols) significantly improves tumour growth inhibition by a further 38% compared to treatment with bevacizumab alone ($p<0.05$, Students t-test). Furthermore, adding VGX-100 to the combination of bevacizumab + docetaxel (orange symbols) also improves tumour growth inhibition compared to bevacizumab + docetaxel (green symbols).

How the experiments were performed: Cells from a human lung tumour line (H292) were implanted subcutaneously (under the skin) into mice and grown until the tumours reached an average size of 132 mg. At this time, the animals were placed in different groups and treatment was initiated. Mice were treated twice weekly with the indicated dosage of either VGX-100 (40 mg/kg), bevacizumab (10 mg/kg), a combination of the two, or a negative control antibody (Isotype Control, 40 mg/kg). In the groups indicated, docetaxel (10 mg/kg) was administered intravenously weekly for the first three weeks. Tumour size was measured 2-3 times weekly with calipers and tumour burden calculated using the formula: Tumour burden (mg) = $(L \times W^2)/2$, where L and W are the respective orthogonal tumour length and width measurements (mm). Vertical bars indicate the standard error of the mean for tumour weight for each time point in each treatment group. 10 animals per treatment group.

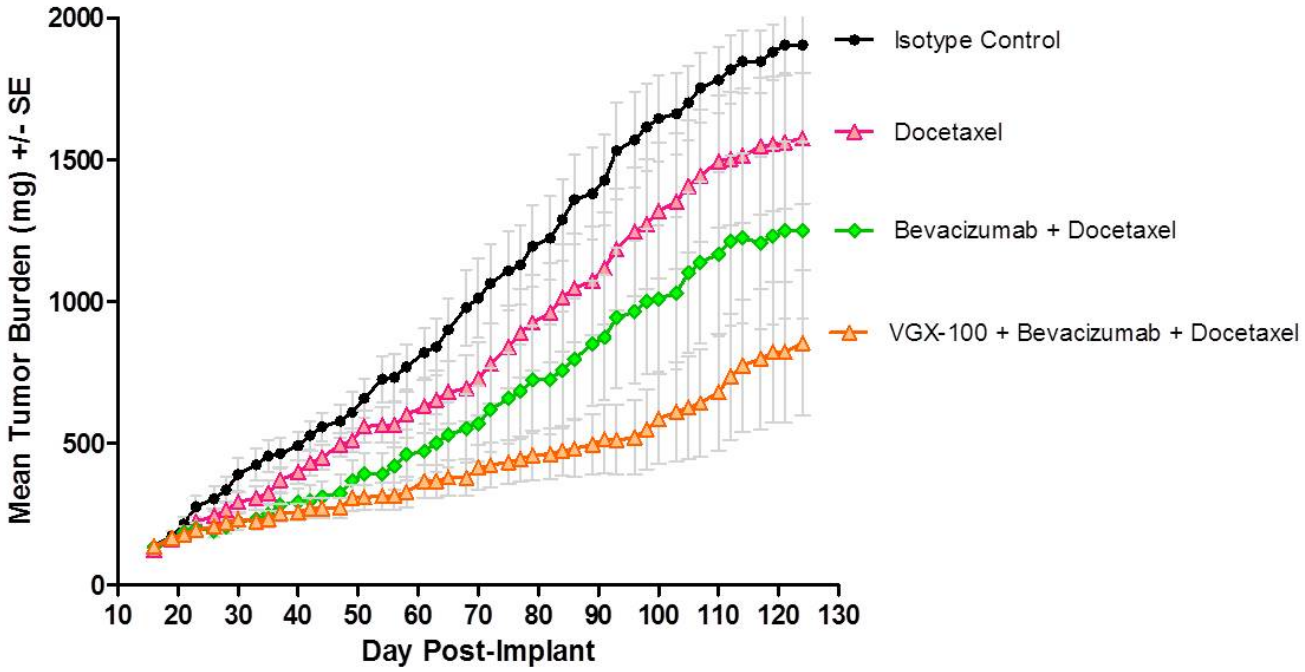


Figure 2. VGX-100 Enhances the Anti-Tumour Efficacy of Chemotherapy and Bevacizumab (Avastin®) in an Ovarian Cancer Model. The figure presents the mean ovarian cancer tumour size in animals receiving various treatments. Adding VGX-100 to the combination of bevacizumab + docetaxel (orange symbols) improves tumour growth inhibition by a further 21% at day 124 compared to bevacizumab + docetaxel treatment (green symbols).

How the experiments were performed: Cells from a human ovarian tumour line (OVCAR-8) were implanted subcutaneously (under the skin) into mice and grown until the tumours reached an average size of 129 mg. At this time, the animals were placed in different groups and treatment was initiated. Mice were treated twice weekly with the indicated dosage of VGX-100 (40 mg/kg), bevacizumab (10 mg/kg) or a negative control antibody (Isotype Control, 40 mg/kg). In the groups indicated, docetaxel (10 mg/kg) was administered intravenously weekly for the first three weeks. Tumour size was measured 2-3 times weekly with calipers and tumour burden calculated using the formula: Tumour burden (mg) = $(L \times W^2)/2$, where L and W are the respective orthogonal tumour length and width measurements (mm). Vertical bars indicate the standard error of the mean for tumour weight for each time point in each treatment group. 10 animals per treatment group.

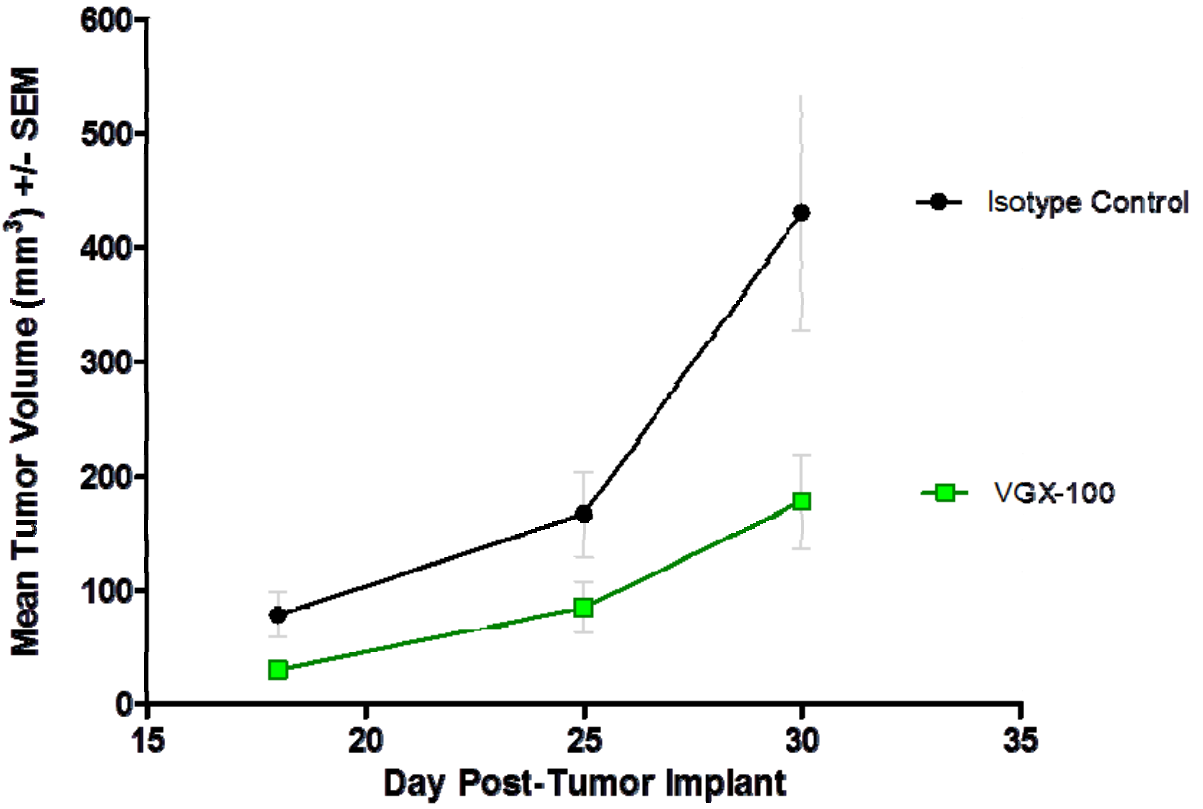


Figure 3. VGX-100 Inhibits Growth of Orthotopic Prostate Tumours. Tumour fragments of the human PC-3-GFP prostate tumour cell line were implanted surgically into the prostate of mice. Three days after surgery, treatment with VGX-100 or the isotype control antibody was initiated. At the conclusion of the study (day 30), VGX-100 significantly inhibited the growth of orthotopic prostate tumours, reducing tumour burden by 59% compared to treatment with the control antibody (p=0.019, Student's t-test).

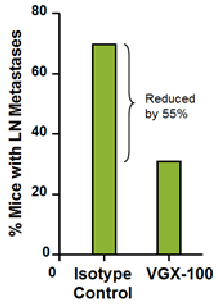
How the experiments were performed: Tumour fragments of the human PC-3-GFP prostate tumour cell line were surgically implanted between the ventral lobes of the prostate and closed by suture. Treatment was started three days after surgery (60 mg/kg, 3x/week via intraperitoneal injection). Tumour size was measured weekly with calipers. Vertical bars indicate the standard error of the mean for tumour weight for each time point in each treatment group. 20 animals per treatment group.

A.

Group	# Mice	# Mice with LN Mets	% Mice with LN Mets	p value*
Isotype Antibody Control	17	12	71%	-
VGX-100	19	6	32%	0.019

** p value by Fisher exact test.*

B.



C.

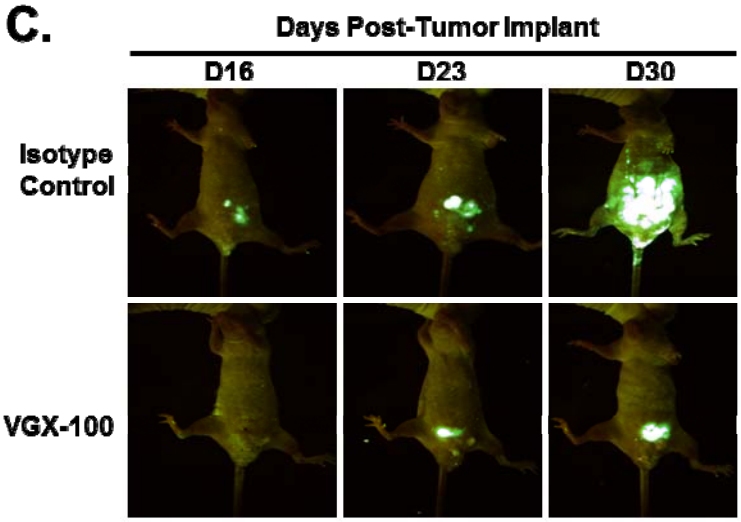


Figure 4. VGX-100 Reduces Lymph Node Metastasis of Orthotopic Prostate Tumours. Tumour fragments of the human PC-3-GFP prostate tumour cell line were implanted surgically into the prostate of mice. Three days after surgery, treatment with VGX-100 or the isotype control antibody was initiated. As the tumour cells were labeled with green fluorescent protein (GFP), tumour growth and metastasis was also monitored during the experiment by fluorescence optical tumour imaging (FOTI). At the conclusion of the study (day 30), mice were further examined for tumour metastasis to local lymph nodes and surrounding tissues.

A. Frequency of lymph node metastasis in mice with orthotopic prostate (PC-3-GFP) tumours and treated with either isotype control antibody or VGX-100. The frequency of metastasis to lymph nodes was significantly reduced by VGX-100 compared to isotype control (32% versus 71%; p = 0.019 by Fisher's exact test).

B. Graphical representation of the frequency of lymph node metastasis in mice with orthotopic prostate tumours. Treatment with VGX-100 reduced the frequency of lymph node metastasis by 55% compared to treatment with the isotype control antibody.

C. Representative series of whole-body FOTI images for one animal in each treatment group, taken on day 16, day 23 and day 30 post-tumour implantation. The PC-3 tumour cells are detected by the green fluorescent protein (green). The growth of the primary tumour and metastases to lymph nodes and surrounding tissues is evident in the mouse treated with isotype control antibody. Comparatively, treatment with VGX-100 reduced the size of the prostate tumour and markedly reduced spread to the surrounding tissues.

The novel therapeutic monoclonal antibody VGX-100 neutralises VEGF-C and inhibits tumor growth and metastasis in subcutaneous and orthotopic models of human cancer.

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Abstract

Angiogenesis and lymphangiogenesis are important processes facilitating tumor growth and metastasis. Growth factors that stimulate blood and lymphatic proliferation within tumors are therefore potential targets for anti-cancer therapies. Proof of concept of the clinical utility of anti-angiogenic drugs was first established by the FDA/EMEA-approved drug bevacizumab (Avastin®) which blocks VEGF binding to its receptors VEGFR-1 and VEGFR-2, the latter being the key receptor signaling for angiogenesis. However, patients treated with bevacizumab may be refractory or develop resistance to bevacizumab, suggesting upregulation of alternative pro-angiogenic proteins that allow tumors to bypass the inhibition of VEGF signaling. VEGF-C is a logical candidate for inducing resistance to bevacizumab via this mechanism since it is also a ligand for the angiogenic receptor VEGFR-2 and for VEGFR-3 which is upregulated on tumor-associated vascular endothelium.

VGX-100 is a highly specific, fully human monoclonal antibody for VEGF-C that blocks VEGF-C binding to both VEGFR-2 and VEGFR-3. Here we demonstrate that VGX-100 has an additive effect in combination with docetaxel and/or anti-VEGF (bevacizumab) in several tumor models, suggesting that VEGF-C may be an important mediator of the resistance to existing anti-VEGF therapies. Further, we demonstrate that in an orthotopic model of prostate cancer, that inhibition of VEGF-C alone by VGX-100 monotherapy is sufficient to inhibit tumor growth and significantly reduce the incidence of tumor metastasis to local lymph nodes. These data indicate that VGX-100 has exciting potential as a cancer therapeutic by targeting a key factor involved in angiogenesis, lymphangiogenesis and tumor metastasis and is expected to complement chemotherapy and/or other anti-angiogenic compounds in the clinic.

Introduction

The various VEGF ligands have distinct receptor binding specificities which contribute to their diversity of function, as summarized in Figure 1. VEGF-C and VEGF-D are ligands for VEGFR-2, which signals for angiogenesis, and VEGFR-3 which mediates lymphangiogenesis and tumour-associated angiogenesis. The receptor binding specificity of VEGF-C and VEGF-D is distinct to that of VEGF, which binds VEGFR-2 but not VEGFR-3.

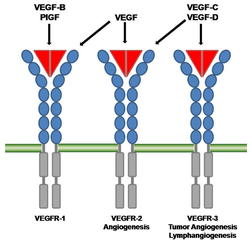


Figure 1. Receptor binding specificity of the VEGF family.

Recent publications suggest that in certain contexts, VEGF-C and VEGF-D, the alternative ligands to VEGF for VEGFR-2, can be up-regulated during VEGF blockade[1,2,3,4,5]. Furthermore, in some mouse tumor models, administration of small molecule inhibitors of the VEGFR tyrosine kinase activity can increase subsequent tumor invasion and metastasis[6,7,8]. VEGF-C and VEGF-D up-regulation during VEGF/VEGFR suppression may be a key driver of resistance to anti-VEGF/VEGFR therapies.

Expression of VEGF-C is elevated in a diverse range of tumors, including cancers of the colon, stomach, breast, ovary and prostate. Elevated levels of intra-tumoral and circulating VEGF-C frequently correlate with poor prognosis and features associated with tumor aggression (e.g. tumor depth, size, lymphatic invasion and lymph node metastasis).

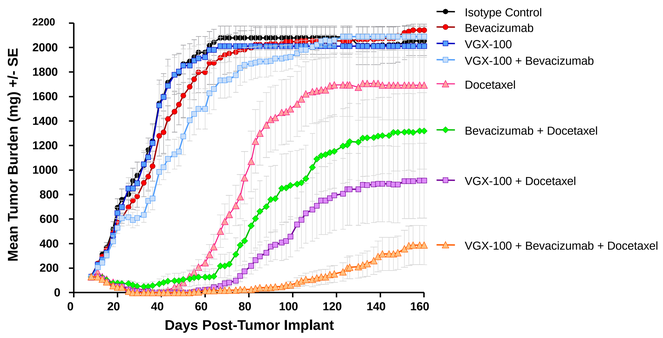
VGX-100 is a highly specific, fully human monoclonal antibody that neutralizes binding of VEGF-C to VEGFR-2 and VEGFR-3. Therefore, VGX-100 has the potential to inhibit not only primary tumor growth through its anti-angiogenic and anti-lymphangiogenic activities, but to also inhibit metastasis via the lymphatic vessels. Lymphatic metastasis is associated with poor prognosis that is not effectively blocked by anti-VEGF-A or anti-VEGFR-2 therapeutics.

We have previously reported that VGX-100 inhibits primary tumor growth as a single-agent in human pancreatic KP4 tumor xenografts, and has anti-tumor activity in combination with bevacizumab in human U87MG glioblastoma tumor xenografts. Furthermore, in the PC-3 prostate tumor model, VGX-100 significantly enhances the anti-tumor efficacy of docetaxel, and docetaxel + bevacizumab combination therapy.

Here we further demonstrate, in mouse models of human lung (H292) and ovarian (OVCAR-8) cancer, that addition of VGX-100 to chemotherapy and chemotherapy + anti-VEGF (bevacizumab) enhances efficacy and prevents the development of escape mechanisms resulting in more durable responses Furthermore, inhibition of VEGF-C significantly inhibited both primary tumor growth and metastasis of orthotopic PC-3 prostate tumors.

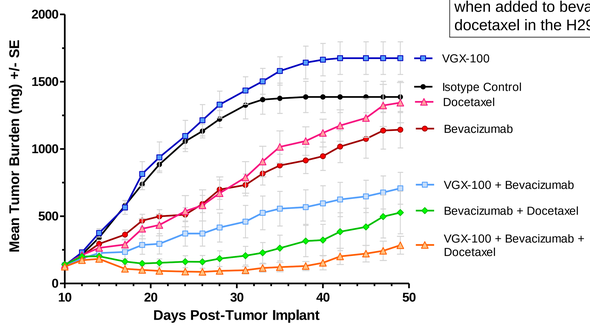
Subcutaneous Tumor Models

Prostate Carcinoma Model (PC-3)
(last observation carried forward)

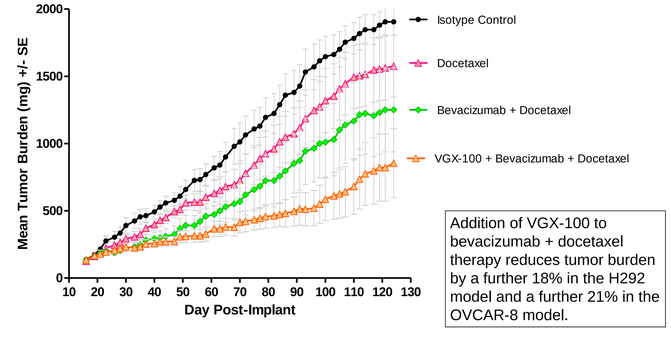


Addition of VGX-100 to bevacizumab reduces tumor burden by a further 38% compared to bevacizumab alone, and improves tumor growth inhibition by 18% when added to bevacizumab + docetaxel in the H292 model.

Lung Carcinoma Model (H292)
(last observation carried forward)



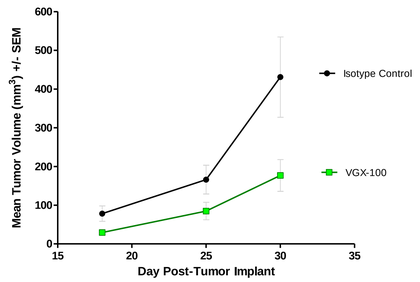
Ovarian Carcinoma Model (OVCAR-8)



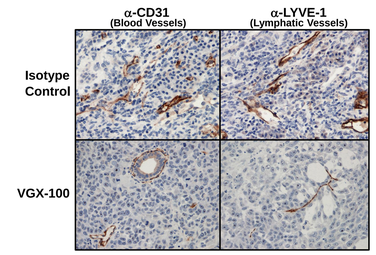
Addition of VGX-100 to bevacizumab + docetaxel therapy reduces tumor burden by a further 18% in the H292 model and a further 21% in the OVCAR-8 model.

Orthotopic Metastatic ProstateTumor Model

VGX-100 Inhibits Growth of Orthotopic PC-3 Prostate Tumors



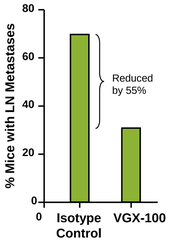
VGX-100 reduces tumor burden by 59% (at day 30) compared to control IgG.
** p=0.019 (Students t-test)*

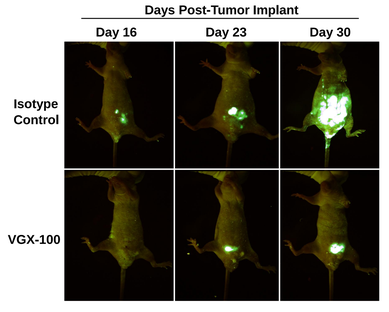


VGX-100 Reduces Lymph Node Metastasis in an Orthotopic Prostate Tumor Model

Group	# Mice	# Mice with LN Mets	% Mice with LN Mets	p value*
Isotype Antibody Control	17	12	71%	-
VGX-100	19	6	32%	0.019

** p value by Fisher exact test.*





Conclusions

- In subcutaneous mouse models of human cancer, VGX-100 has anti-tumor activity as a single-agent and in combination with chemotherapy or bevacizumab.
- VGX-100 enhances the efficacy of docetaxel and bevacizumab combination therapy in prostate, lung and ovarian cancer models.
- In an orthotopic mouse model of human prostate cancer (PC-3), single-agent VGX-100 inhibited primary tumor growth by 59% compared to an isotype control antibody, and reduced the incidence of metastasis to local lymph nodes by 55%.
- VGX-100 has the potential to affect tumor growth and invasiveness and improve patient outcomes in the clinic.
- Combination of VGX-100 with existing anti-VEGF strategies can simultaneously inhibit multiple VEGFR pathways. This may reduce redundant signalling that drives tumor resistance and limits the efficacy of currently available therapies blocking a single-target.

Materials and Methods

PC-3, H292 and OVCAR-8 subcutaneous tumor models: PC-3 (5 x 10^6), H292 (5 x 10^5) or OVCAR-8 (1 x 10^7) cells were implanted subcutaneously in nu/nu mice high in the right axilla. Mice were triaged into treatment groups (n=10/group) when the mean tumor burden was 75-175 mg. Tumor burden was estimated from caliper measurements by the formula: Tumor burden (mg) = (L x W^2)/2, where L and W are the respective orthogonal tumor length and width measurements (mm). Antibodies were administered 2x/week via intraperitoneal injection (Isotype control and VGX-100, 40 mg/kg; bevacizumab, 10 mg/kg). Docetaxel (10 mg/kg) was administered intraveneously weekly for three weeks.

Orthotopic PC-3 tumor model: PC-3-GFP human prostate cancer orthotopic MetaMouse® model was conducted by AntiCancer Inc. PC-3-GFP tumor fragments were surgically implanted between the ventral lobes of the prostate and closed by suture. Treatment was started three days after surgery (60 mg/kg, 3x/week, IP). Whole body imaging of GFP-expressing tumors was performed once a week in live animals after GFP-visible tumors were established. Primary tumor sizes were estimated once a week by caliper measurement and tumor volume (mm^3) calculated by the formula (L x W^2)/2 .

References

1. Jubb, A. et al., Clin Cancer Res., 17(2):372-81, 2011.
2. Fan, F. et al., British J Cancer, 1-8, 2011.
3. Grau, S. et al., J Neurooncol., Feb 11 2011.
4. Shojaei, F. et al., Nature Biotechnol., 25(8):911-20, 2007.
5. Moffat, B. et al., Clin. Canc. Res., 1:12(5):1525-32, 2006.
6. Ebos, J et al., Cancer Cell, 15(3):232-9, 2009.
7. Paez-Ribes M., Cancer Cell, 15(3): 220-31, 2009.
8. Loges, S., Cancer Cell, 15(3): 167-170, 2009.