



# Corporate Presentation

26 March 2009



Robert Klupacs, CEO & Managing Director



# Disclaimer

Investment in Circadian Technologies Limited ('Circadian') is subject to investment risk, including possible loss of income and capital invested. Neither Circadian nor any other member company of the Circadian Group guarantees any particular rate of return or performance, nor do they guarantee the repayment of capital.

This presentation is not an offer or invitation for subscription or purchase of or a recommendation of securities. It does not take into account the investment objectives, financial situation and particular needs of the investor. Before making any investment in Circadian, the investor or prospective investor should consider whether such an investment is appropriate to their particular investment needs, objectives and financial circumstances and consult an investment advisor if necessary.

This presentation may also contain forward-looking statements regarding the potential of the Company's projects and interests and the development and therapeutic potential of the Company's research and development. Any statement describing a goal, expectation, intention or belief of the Company is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercialising drugs that are safe and effective for use as human therapeutics and the financing of such activities. There is no guarantee that the Company's research and development projects and interests (where applicable) will receive regulatory approvals or prove to be commercially successful in the future. Actual results of further research could differ from those projected or detailed in this presentation. As a result, you are cautioned not to rely on forward-looking statements. Consideration should be given to these and other risks concerning research and development programs referred to in this presentation.





## Circadian Technologies Limited

*A cashed up company developing novel anti-angiogenic therapeutics for cancer and other serious diseases*

*With a dominant IP platform*

*And the potential for generating significant revenues in the near term.*

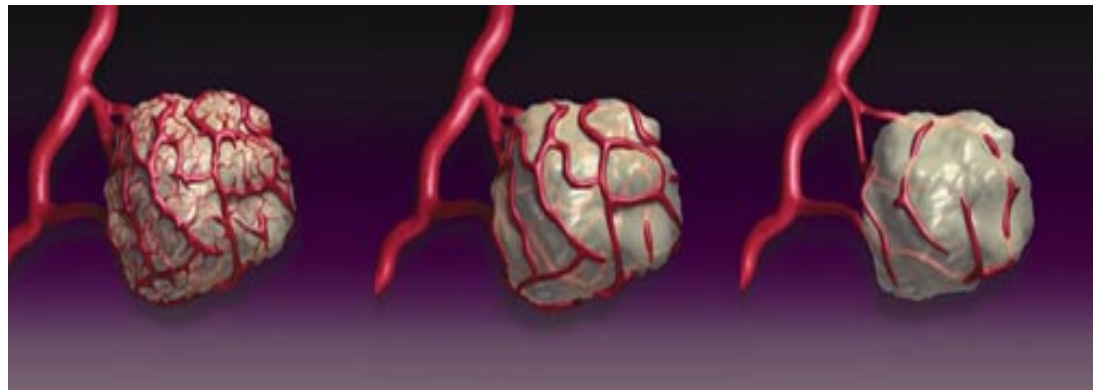


# Developing therapeutics for cancer and other serious diseases

- Developing **angiogenesis-based therapies** for cancer and other serious diseases
- World's **most comprehensive patent** estate covering key angiogenesis targets VEGF-C, VEGF-D and VEGFR3
- **Partnered programs** with leading international biotechs in their fields providing existing cash flows
  - Ark Therapeutics plc (LSE:AKT) - Phase 3 clinical trial
  - ImClone Systems Inc (NSDQ:IMCL) - developing anti-cancer drug
  - Healthscope Limited (ASX:HSP) - developing cancer diagnostic test
- **Strong financial position** - \$46 million in cash & listed investments
- **Existing royalties and potential for future significant royalty income** from Ark, cancer diagnostic test and ImClone (Lilly) as well as other applications of portfolio.

# What is angiogenesis?

- Angiogenesis is the growth of new blood vessels
- Tumour growth is caused by stimulation of new blood vessel growth by proteins (e.g. proteins VEGF-A, C, D)
- Blocking these proteins blocks blood vessel growth, leading to tumour starvation

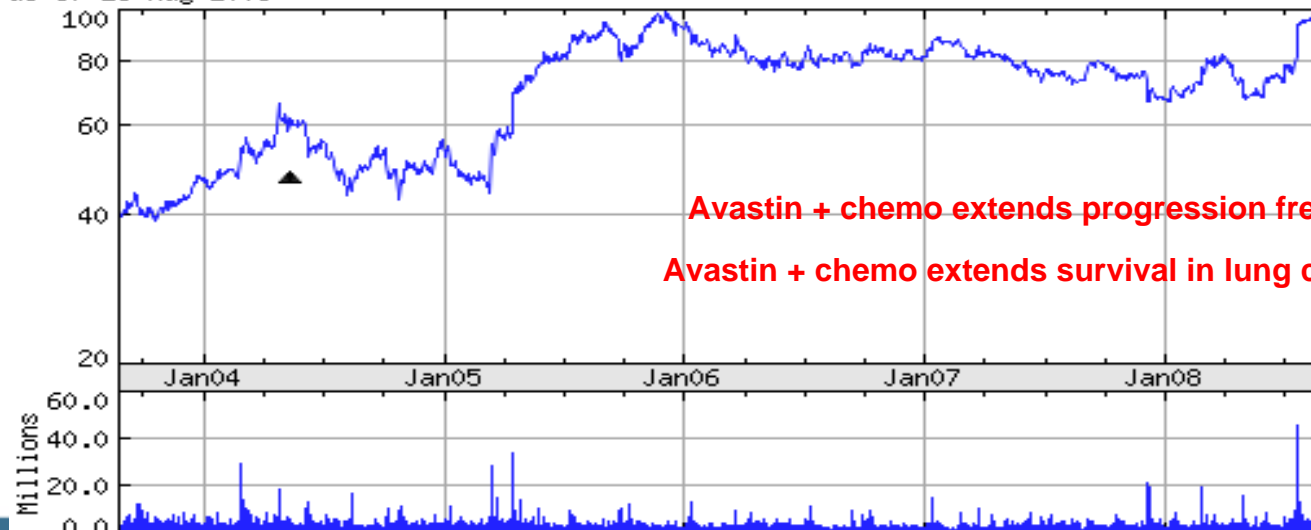


# Avastin® Story

- First targeted anti-angiogenesis therapy to become drug (developed & sold by Genentech Inc and Roche)
- Antibody that blocks angiogenic protein VEGF-A
- First approved Feb 2004
- 2007 sales: in US \$US2.3B, worldwide: \$US6B (\$10B+ 2009)
- Fastest sales growth of any drug

GENENTECH INC  
as of 25-Aug-2008

Splits: ▼



Avastin + chemo extends progression free survival in breast cancer

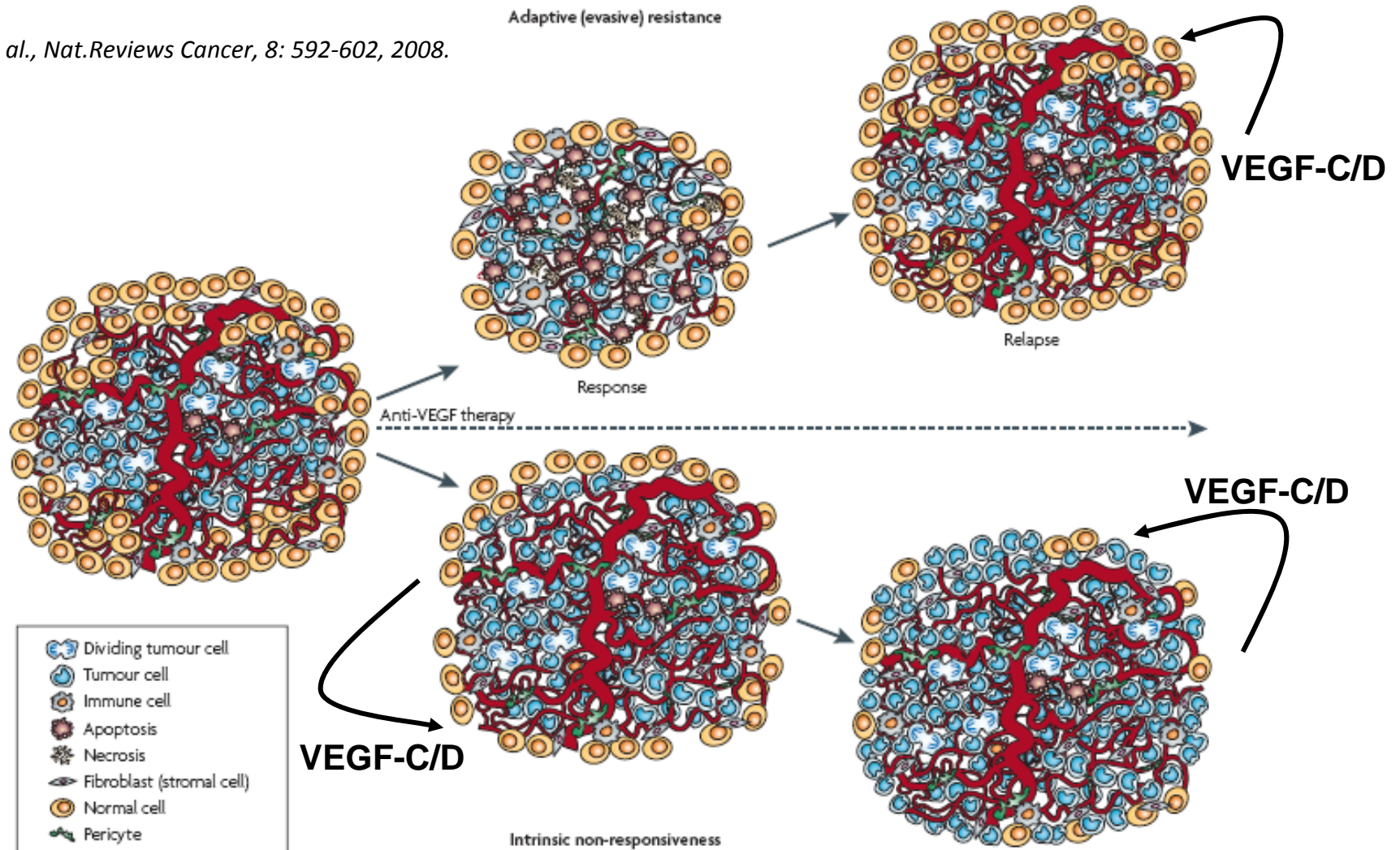
Avastin + chemo extends survival in lung cancer



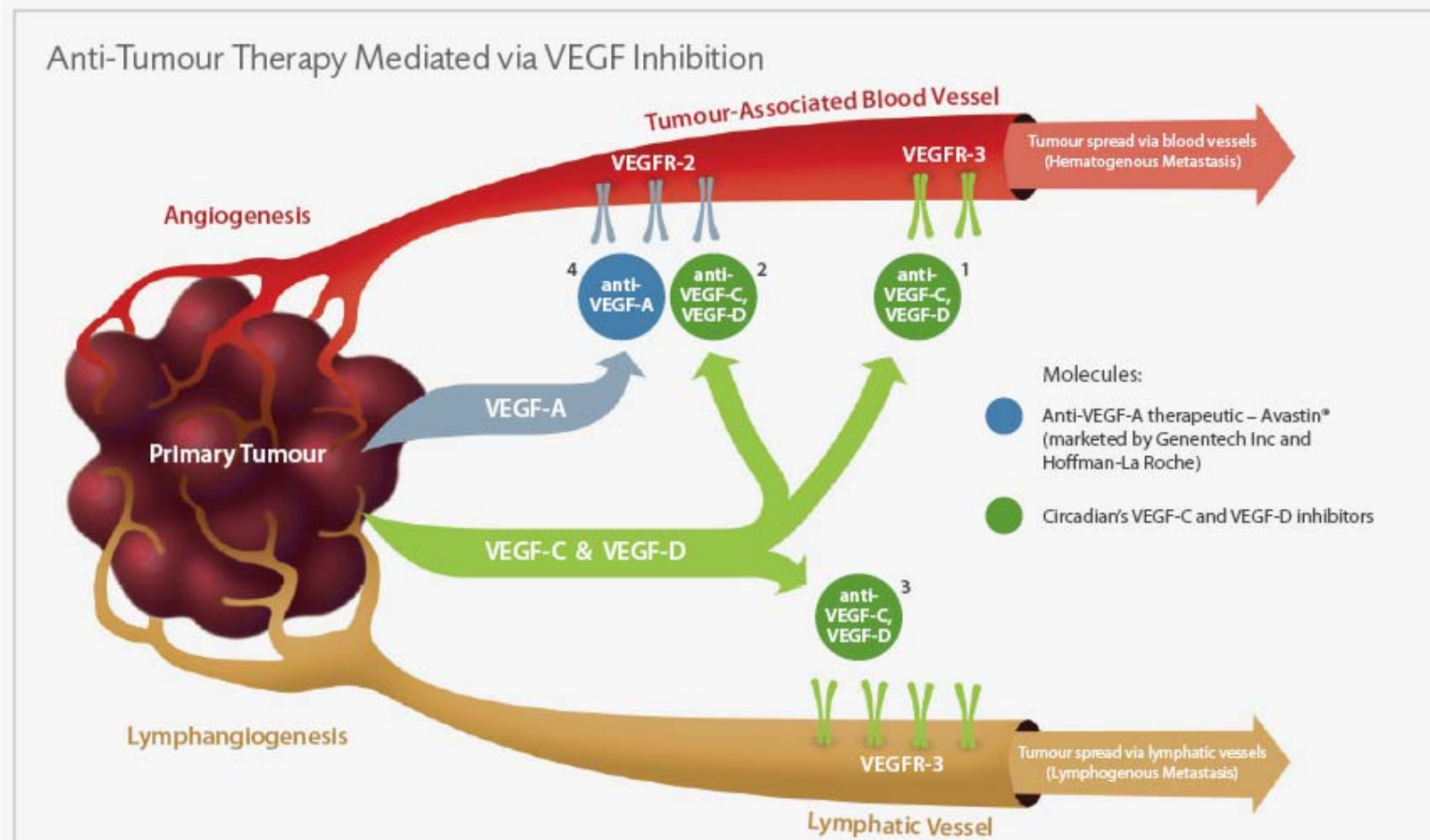


# $\alpha$ -VEGF Therapy (Avastin®): Effective but not across the board.....

Bergers et al., *Nat.Reviews Cancer*, 8: 592-602, 2008.



# Activity of Circadian's VEGF-C/D Inhibitors





# Circadian's approach and technology

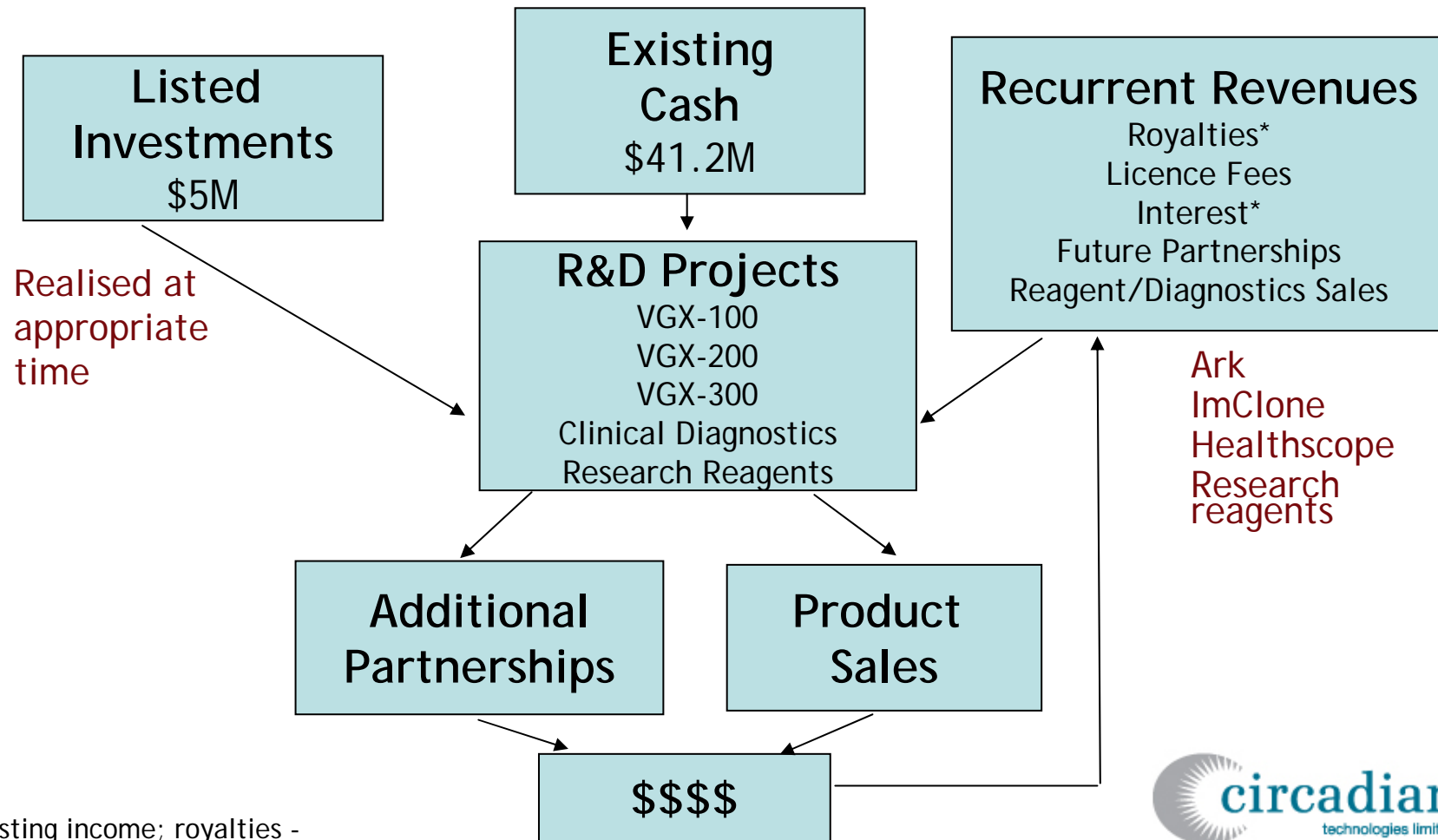
- Developing blockers of the two other angiogenic VEGF proteins (VEGF-C & D) - involved in tumour growth as well as in tumour spread (metastasis)
- Blocking VEGF-C/D - not only starves tumours but additional major therapeutic potential for inhibiting tumour spread through lymphatic system
- Cancer first therapeutic target
- Circadian's products capable of targeting multiple indications enabling multiple partnering and/or early revenue generating opportunities
- Product development secured by dominant IP position for VEGF family members VEGF-C/D and VEGFR3.



# Our strategy

- Develop selected therapeutics to proof of efficacy in Phase II trials
- Subsequent clinical development with partners - large pharmaceutical/biotechnology companies
- Seize opportunity for earlier therapeutic partnerships if appropriate
- Selectively exploit/commercialise parts of therapeutic portfolio not in angiogenesis area at earlier stages
- Divest listed investments as soon as practicable and appropriate to liberate cash.
- Exploit clinical diagnostics and reagents for early revenues

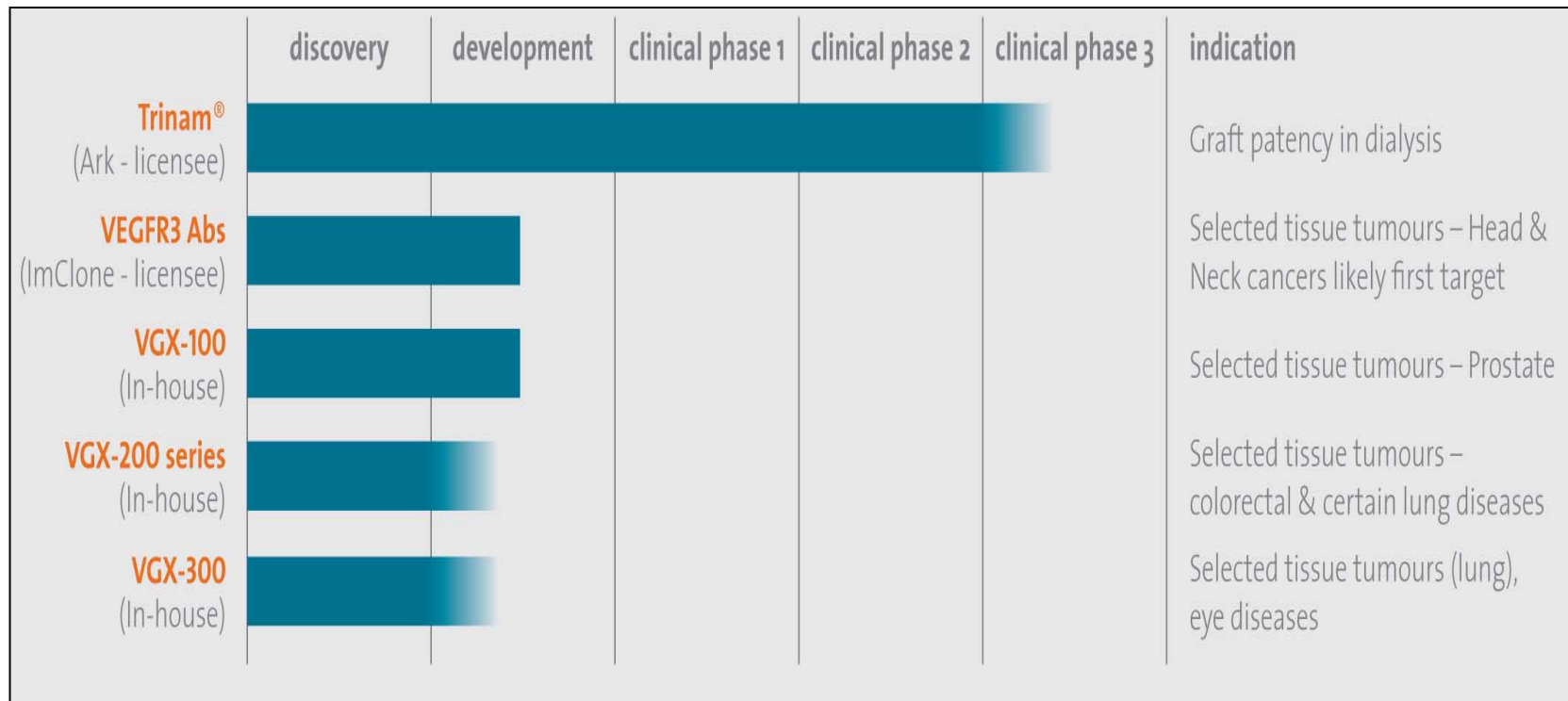
# CIRCADIAN'S BUSINESS MODEL



\* Existing income; royalties - potential for significant increase



# Deep Product Pipeline with mechanistically distinct mechanisms



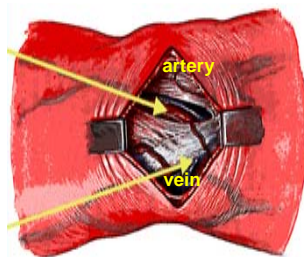
# Other Potential Revenue generating assets

- **VEGF-C, VEGF-D ligands** as research reagents, therapeutic development in wound healing, cardiovascular disease, lymphedema, neurodegenerative disease
- Ownership and exclusive commercialisation rights to **molecular diagnostic for Cancers of Unknown Primary (CUP)** in US, Europe, Japan; partnered with Healthscope for other territories
  - US incidence of CUP 60,000-100,000 per annum
  - Test to sell between \$500-1500 due to significant health cost savings

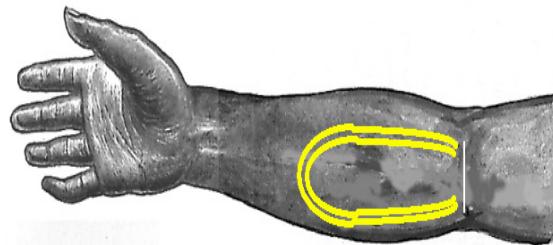


# Phase 3 Product Trinam® - Ark Therapeutics

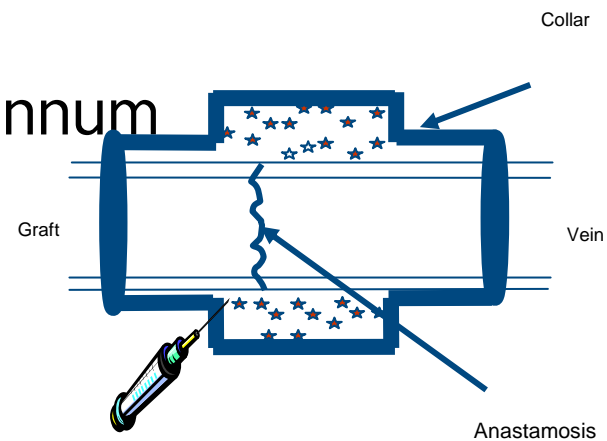
- Commenced Phase 3 trials Jan 2009 under SPA. Expected recruitment 250 patients over 18 months.
- VEGF-D gene therapy product.
- Extends lifetime of dialysis access grafts. Phase 2 clinical trials 17 months v 4.5 months.
- Major patient impact by reduced need for repeated surgery and increased survival time of patients undergoing ongoing dialysis.
- Market estimates > \$US500M+ per annum



Step 1: Surgical isolation of vein and artery



Step 2: Insert flexible plastic tube graft to provide access for dialysis



# IMC-3C5 (human anti-VEGFR-3 mAb)

*ImClone/Lilly*

- Formal internal product development candidate
- IND planned H1 2010
- Currently completing CHO cell line development and process
- Wide range of peer reviewed literature
- Confidential data in range of xenograft models
- Likely first indication head & neck cancer

# Circadian has dominant IP rights in respect of VEGF-C/D antagonists

- Granted IP rights in major territories to VEGF-C/D proteins and VEGFR-3 and blockers
- Applications in cancer and certain other diseases
- IP rights over product candidates extend beyond 2020
- Further strategic IP filings being made to extend patent life

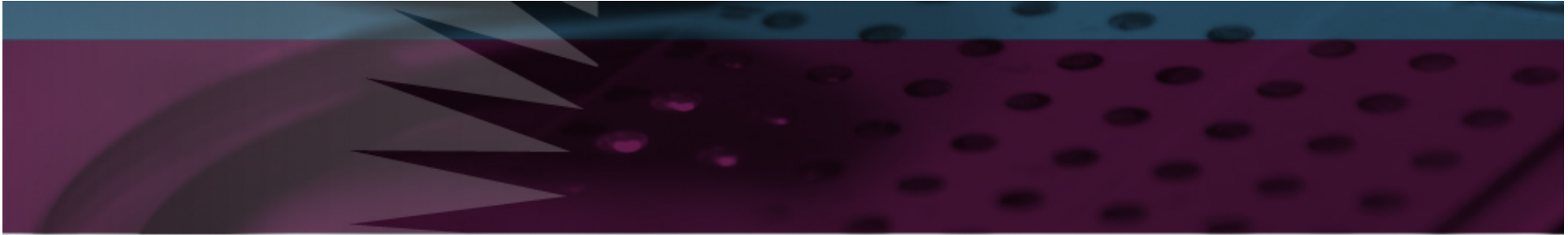
# Deal-making drug development and operational track record

- **Robert Klupacs (CEO)** Founder and former CEO, ES international and six other early stage companies. Entrepreneur and IP expert with extensive history of industry deals including Sanofi, Baxter, Aventis, Pharmacia, Novartis, Alexion, Pfizer.
- **Dr Alex Szabo (Head, Business Development)** Formerly Bionomics, Beckman-Coulter, Affymetrix, Pharmacia. Recent deals include Aventis, Eisai, Genmab, LabCorp, Merck-Serono.
- **Natalie Korchev (CFO & Head of Operations)** ACA Formerly Ernst & Young, global finance, risk management experience. Over 10 years experience in biotech industry.
- **Product Development Advisory Committee** The nine members together bring vast experience in international drug development and oncology. Past roles have included positions with Amgen, GSK, Aventis, Schering, Affymax, Maxygen. Over 150 drug development experience.

# An investment with significant upside

- Dominant IP position over key mediators of angiogenesis.
- Phase 3 product partnered and pipeline of product opportunities-multi-million royalty flow possible within 24-36 months.
- Strong financial assets to support development/deal making
- Extremely high value space for partnerships (Roche/BioInvent \$500M+)
- World class drug development expertise and management
- Share price currently trading at 45% below cash with no apparent value ascribed for our IP assets or existing and future royalty flows.





# APPENDICES

# VGX-100 Program Summary

- VGX-100 is a fully human, high affinity, neutralising monoclonal antibody for VEGF-C
- Development and clinical program designed to address resistance and non-responsiveness to anti-angiogenic therapies for cancer
- Orphan drug designations likely
- IND expected Q1 2011.
- Preclinical data demonstrating dose-responsive inhibition of primary tumor growth in several mouse xenograft models
- Sound scientific rationale and pre-clinical data demonstrating potential as anti-tumorigenic and anti-metastatic agent.

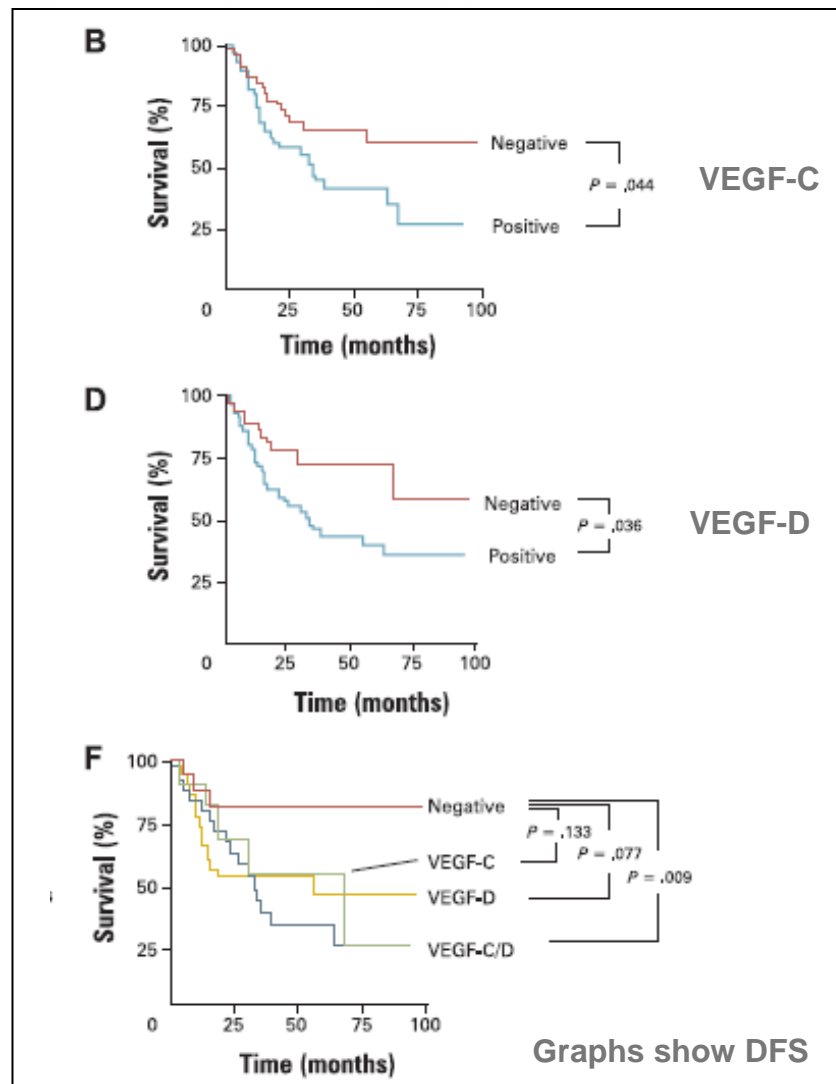
# VGX-200 Program Summary

- Humanisation and affinity maturation program complete
- Lead hIgG1 mAbs identified based on fold-improvement in KD relative to murine parental VD1 antibody
- Formal lead identified by Nov '09 based on *in vivo* efficacy
- IND anticipated H1/2011
- Orphan drug designation likely
- Proof of concept model demonstrates potential as anti-tumorigenic and anti-metastatic agent.

# VGX-300 Program Summary

- Soluble receptor protein consisting of the first 3 Ig-like domains of hVEGFR-3 linked to the Fc region of hIgG1
- Neutralises *both* VEGF-C and VEGF-D
- Stable CHO cell line expressing levels sufficient for research grade production
- IND anticipated H2/2011
- Orphan drug designation likely
- Proof of concept established using adenoviral gene delivery
- Several peer-reviewed articles demonstrating potent anti-metastatic activity

# VEGF-C & VEGF-D levels correlate with LN mets and decreased survival in gastric cancer



91 Gastric Adenocarcinomas

*VEGF-C and VEGF-D correlated with:*

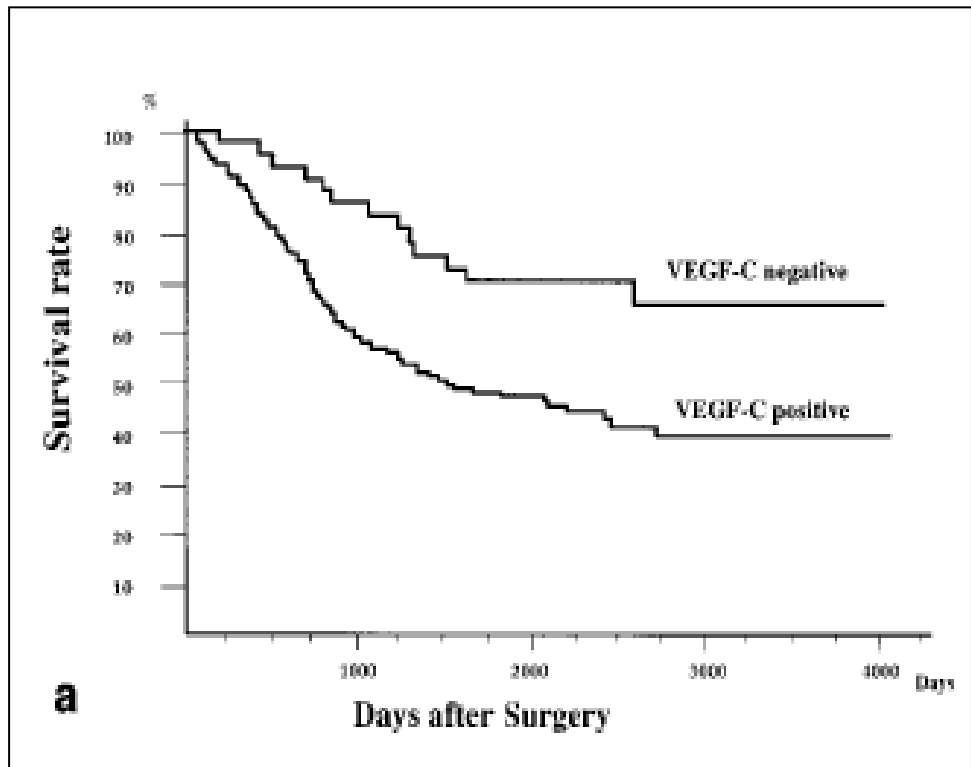
- LN metastases
- Decreased survival

*VEGF-D and VEGFR-3 are independent prognostic markers*





# Poor prognosis for Non Small Cell Lung Cancer patients expressing VEGF-C and VEGFR-3



180 NSCLCs

5yr survival rates for patients:

VEGF-C positive: 47%

VEGF-C negative: 70%

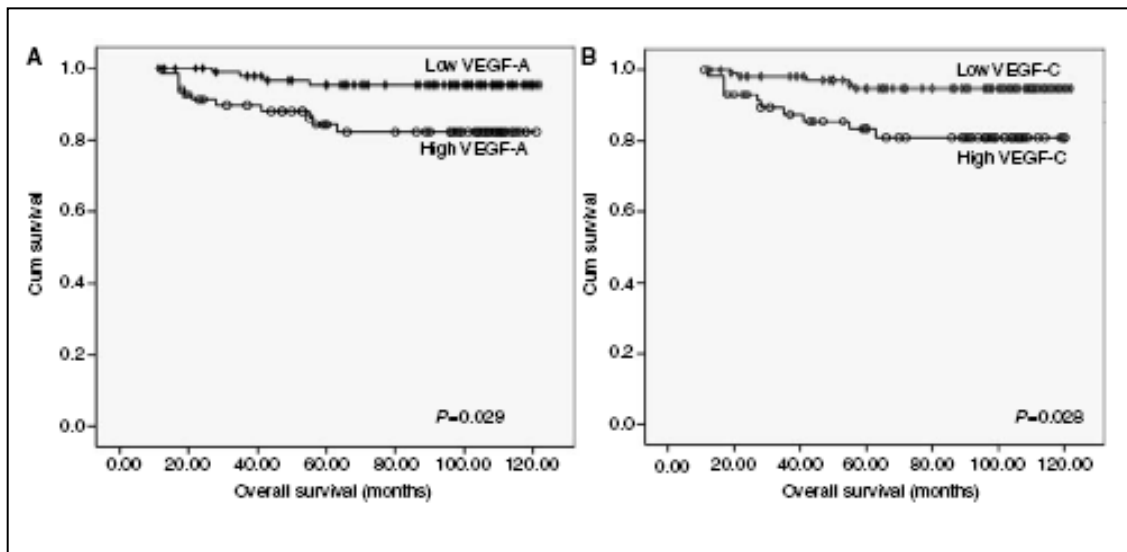
*VEGF-C and VEGFR-3 correlated with:*

- Decreased survival
- Pts with positive staining for both had poorest prognosis



Arinaga et al., *Cancer*, 97(2): 457-464, 2004.

# Poor survival of breast cancer patients with high VEGF and VEGF-C levels



117 invasive breast cancer

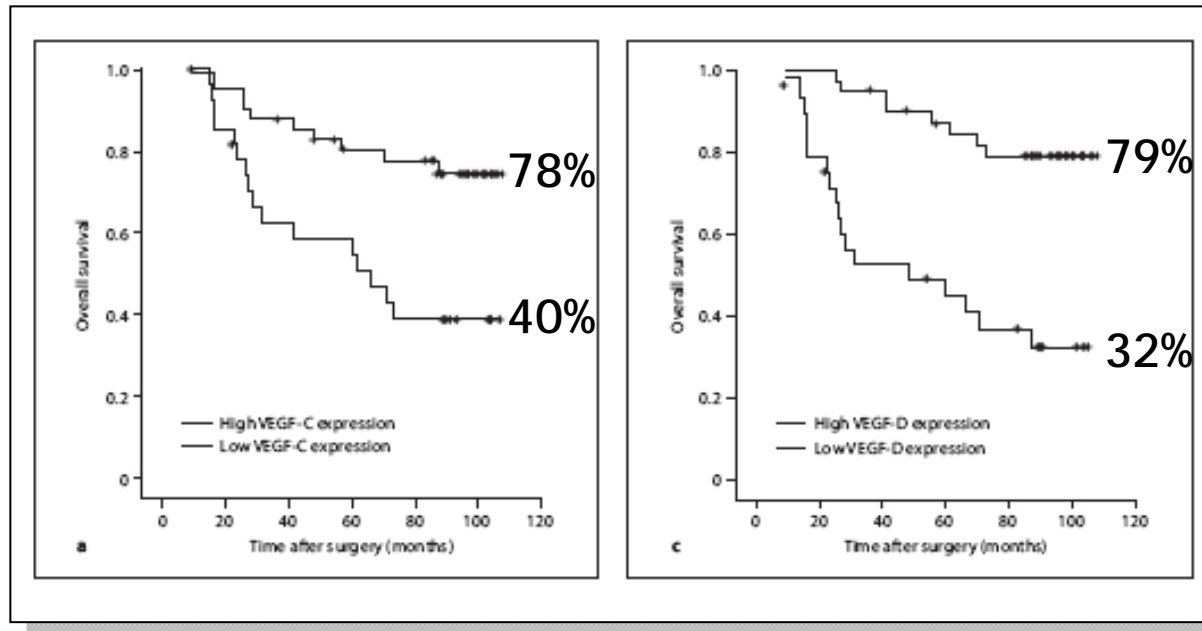
*VEGF-C correlated with:*

- LVD
- LN Metastases
- Decreased OS

Pts with high VEGF-C & VEGF levels have worst prognosis



# VEGF-C and VEGF-D are risk factors for colorectal cancer



Overall Survival Rates:  
High VEGF-C/VEGF-D: 28%  
Low VEGF-C/VEGF-D: 84%

69 CRC

*VEGF-C correlated with:*

- LN Metastases
- Clinical Stage

*VEGF-D correlated with:*

- LN Metastases
- Depth of Tumor Invasion

*Elevated VEGF-C and VEGF-D associated with:*

- Decreased DFS
- Decreased OS



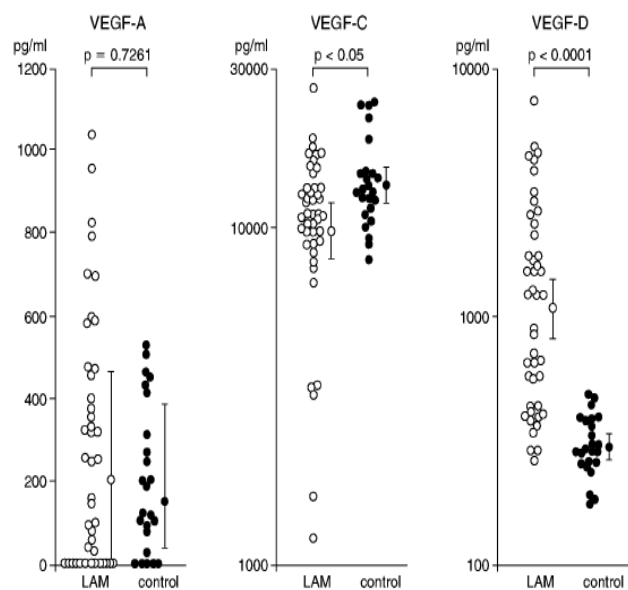
Hu et al., Eur Surg Res, 39: 229-238, 2007.

# Circulating VEGF-C & VEGF-D levels are elevated in cancer patients

Indication	VEGF-C	Median or Mean Level (pg/ml by ELISA)	Reference
CRC	HIGH vs Healthy Controls	35 U/ml vs 11.5 U/ml	<i>Duff, Int. J. Oncol., 2003.</i>
NSCLC	HIGH vs Healthy Controls	1726 vs 941.2	<i>Tamura, Cancer, 2003</i>
NSCLC	HIGH vs non-metastatic	2046.7 vs 1419	<i>Tamura, Ann.Surg.Oncol., 2004</i>
NSCLC	HIGH vs non-metastatic	2009.2 vs 1465.5	<i>Tamura, Chest, 2004</i>
CERVICAL	HIGH vs Healthy Controls	11885 vs 9594	<i>Mitsuhashi et al., Cancer, 2005</i>
CERVICAL	HIGH in Adv vs Early vs Healthy	6678 vs 3505 vs 1561	<i>Mathur , Gynecol Oncol., 2005</i>
GASTRIC	HIGH vs Healthy Controls	595 +/- 201 vs 360 +/- 97.4	<i>Wang, World J. Gastroenterol., 2007</i>
MELANOMA	HIGH in Adv vs Local Mets	2584 vs 1643	<i>Vihinen, Acta. Oncologica, 2007</i>
PAPILLARY THYROID	HIGH in Recurrent vs Benign	6433 vs 5289	<i>Yu et al., Surgery, 144: 934-41, 2008</i>
PAPILLARY THYROID	HIGH vs Benign	7433 +/- 230 vs 5289 +/- 296	<i>Yu et al., Surgery, 247(3): 483-89, 2008</i>
Indication	VEGF-D	Median or Mean Level (pg/ml by ELISA)	Reference
NSCLC	HIGH vs Healthy Controls	N/A	<i>Wojciech, Oncology Res., 16(9): 445-451, 2007</i>
SCLC	HIGH vs Healthy Controls	N/A	<i>Wojciech, Oncology Res., 16(9): 445-451, 2007</i>
Angiosarcoma	HIGH in Adv vs Early vs Healthy	667 +/- 463 vs 273 +/- 58	<i>Amo, Brit.J.Dermat., 150, 160-161, 2004</i>
Prostate	HIGH in Adv vs Early	436 vs 332	<i>Kaushal, Clin.Canc.Res., 11: 584-593, 2005</i>

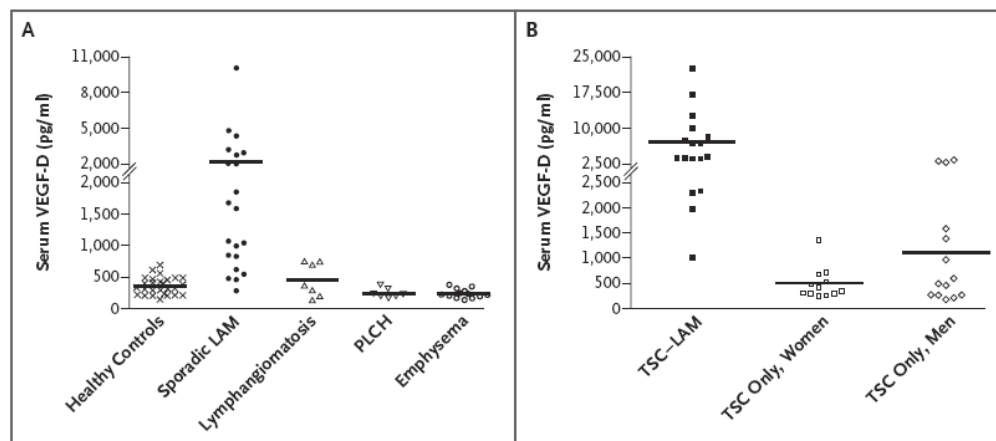
# LAM – Orphan Development Opportunity for VEGF-D Antagonists

VEGF-D is increased in serum of patients with LAM



Seyama et al. *Lymphatic Res & Biol.*, Vol 4, #3, 143-152, 2006

Serum VEGF-D levels distinguishable from other cystic and chylous lung diseases



Young et al. *NEJM.*, 358(2), 199-200, 2008

VGX-200 as therapeutic?  
VEGF-D diagnostic?



# LAM – Orphan Development Opportunity for VEGF-D Antagonists

- Lymphangiomyomatosis (LAM): cystic lung lesion, lymphatic abnormalities, abdominal tumors
- Proliferation of abnormal smooth muscle cells
- Often degenerative requiring lung transplant
- Frequently fatal
- Primarily affects women of reproductive age
- Estimated 300,000 cases worldwide
- No effective treatment
- No surrogate markers to predict severity or clinical course

# Circadian Background

- Listed on the ASX in 1985
- In 2006, Circadian acquired 50% of Vegenics Limited.
- In 2008 Circadian acquired 100% of Vegenics Limited put in place new leadership and transformed its business model to focus on the development of biologics-based therapies for cancer through inhibition of angiogenesis
- 12 person management and scientific team supported by international advisors, contracted testing agencies and relationships with leading academic researchers
- Cash at bank and listed investments at 25 March 2009 \$A46.2M
- 45,241,928 shares on issue; further 1.155M to be issued Aug 10 2010 (Top 10 control approx 53.5%)
- Market Cap approx \$32M @25 March 2009