



# Corporate Presentation

26 August 2009



Robert Klupacs, CEO & Managing Director  
Circadian Technologies (ASX.CIR)

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# New direction in cancer therapies

- Developing antibody therapies to treat cancer
  - a major global opportunity
- Break through technology
  - anti-angiogenic approach
- Partnered programs
  - leading international biotechs
- Deep pipeline of products
- Other disease applications
- Dominant IP position

# Company with strong financial position & shareholder base

## Top 10 shareholders: 51.8%

Investor	% of issued shares
Packer and Co Limited	17.1
Select Asset Management Ltd	8.1
Ludwig Institute for Cancer Research	5.7
Licentia Ltd (Helsinki)	5.6
Leon Serry	4.6
HSBC Custody Nominees	2.7
Chemical Trustee Limited	2.3
Jagen Pty Ltd	2.2
JFF Steven Pty Ltd	1.8
Audivac Pty Ltd	1.7
<b>Total 10 shareholders own</b>	<b>51.8%</b>
<b>Total 20 shareholders own</b>	<b>58.9%</b>

Institutions/Funds: ~ 31%

Retail investors: ~ 41%

Professional investors: ~ 28%

## Financial Summary @ 30 June 09

<b>Stock code:</b>	<b>CIR</b>
Share price:	73c
Shares issued + deferred issue:	46,396,928
Market cap:	~ \$35 mill
Cash holdings:	\$39M
Listed investments:	\$5M

Total number of shareholders: ~3,500



# Circadian - An investment with significant upside

## ✓ Deep Diverse Product Pipeline

- One product at Ph 3
- Four drug development programs targeting different mediators of cancer - three antibody drugs

## ✓ Partnership Opportunities

- Two existing deals
- Antibodies - major focus of big pharma
- High value space for early deals & M&A: eg Roche/Bioinvent \$700 million (Ph 1)

## ✓ Product Advantages

Compelling advantages over existing treatments:

- Trinam®: 4-fold increase in kidney dialysis graft lifetime
- VGX products: Angiogenesis significant product opportunity validated



# Circadian - An investment with significant upside



## **Competitive IP**

Dominant IP position over key mediators of angiogenesis and tumour spread



## **Revenue stream**

Existing *and increasing* royalty flow possible within 24-36 months



## **People**

Track record of deal making & drug development success



## **News flow**

Potential for upcoming product development/partnership milestones



## **Strong financial position**

\$44m » cash of \$39M plus listed investments of \$5M

# Therapeutic Antibodies

## A major development opportunity

- Exquisite targeting-improved probability of success (compared to small molecule drugs)
- Major successes in cancer treatment: Avastin®, Herceptin®, Erbitux®, Mabthera®
- Extremely large markets
- Major focus of big pharma
  - High value early stage deals
  - M&A opportunities
- Significant product opportunity in angiogenesis inhibition (Avastin®)

# Antibodies: A rich deal environment

- Antibodies are one of the most valuable sectors of the market
  - 21 antibody drugs on the market
  - Mostly in cancer and inflammation
  - Current sales of top ten antibodies > \$US20B pa
  - Total sales growing by >30% annually
  - Greater competitive barrier to entry
  - Targeted profiles = cost vs health economic advantage

By 2014 it is expected that 4 of the top 6 best-selling drugs will be antibodies & the top 10 selling drugs will come from biotech (source: EvaluatePharma®)

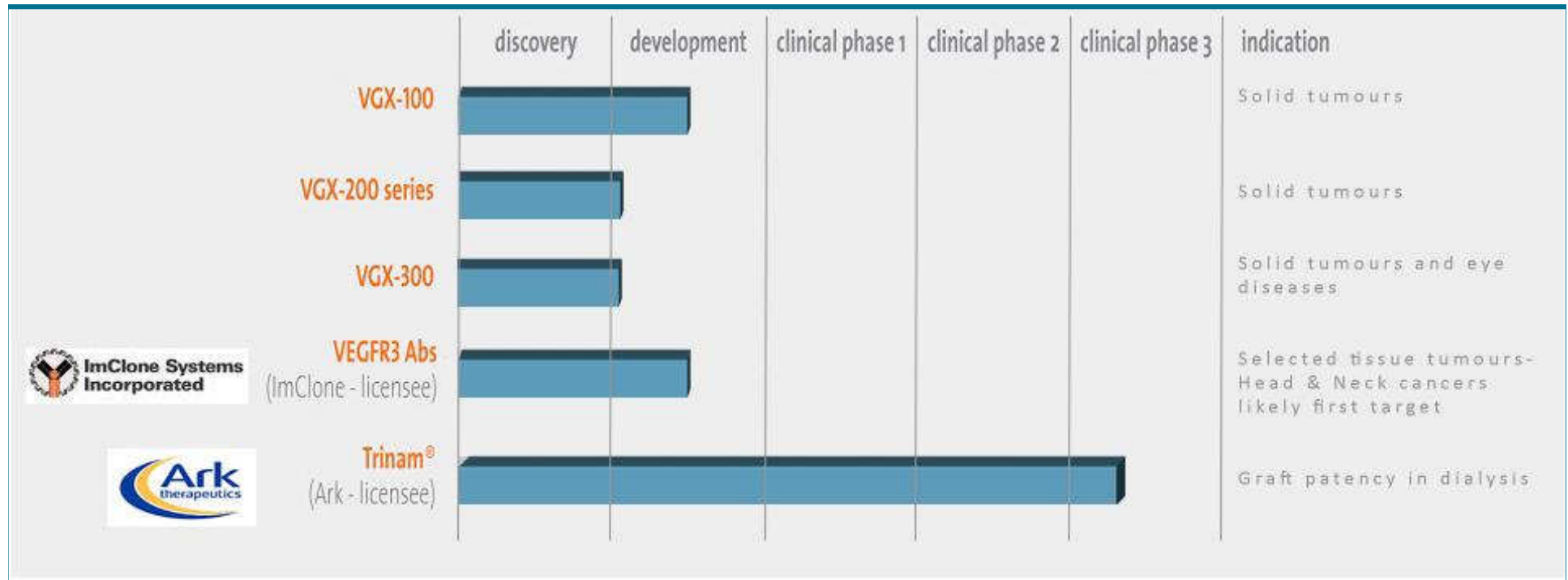
# Antibodies: A rich deal environment (cont)

- Strong interest in antibodies from pharma in M&A and early stage licensing:
- M&A over last 2 years:
  - Medimmune/AstraZeneca - US\$15.5b
  - Cambridge Antibody Technologies/AstraZeneca - US\$1.3b
  - Domantis/GSK - US\$435m
  - Adnexus/BMS - US\$425m
  - Morphotek/Eisai - US\$325m
  - Cephalon/Arana - US\$215m

# Oncology Antibodies: Pre-clinical Deals

Parties	Date	Size	Technology
BiolInvent/Thrombogenics /Roche	Jun 08	\$US800M	Exclusive licence to PlGF Abs in oncology. \$US75M upfront. \$US700M milestones. Double digit royalties
Micromet/Bayer-Schering	Jan 09	\$US396M	Option to Ab against undisclosed oncology target
Abbott/LICR	Nov 08	\$US150-200M	Exclusive licence to 2 <sup>nd</sup> generation EGFR Ab in oncology which has completed 8 person Phase 1 study
Dyax/Sanofi-Aventis	Feb 08	\$US500M	Exclusive licence to Tie-1 Ab DX-2240 and phage display in selected applications
GSK/OncoMed	Dec 07	\$US1.4B	Exclusive licence/co-development of 4 selected stem cell Abs in cancer

# Circadian's Deep Therapeutic Products Pipeline



# Circadian's Deep Product Pipeline

- Four drug development programs
  - Including three antibodies
  - Target different mediators of the process of angiogenesis
  - Focus is on treatments for cancer
- One late stage clinical asset, Trinam®
  - Phase 3 clinical trials commenced Jan 2009

# Technology centred on anti-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 (anti-angiogenesis) leading to tumour starvation



# The role of Vascular Endothelial Growth Factor (VEGF)

- Our technology is centred on two members of the VEGF family of proteins: VEGF-C & VEGF-D and their activation on VEGF receptors VEGFR-2 and VEGFR-3
- These proteins promote blood and lymphatic vessel development
- Targeting this process has the potential to limit tumour growth and spread
- VEGF technology also has applications in other diseases such as eye diseases

# The role of Vascular Endothelial Growth Factor (VEGF)

How does  
Circadian's technology work?

# An exciting commercial opportunity

- Anti-angiogenesis drugs arguably the most significant recent advancement in cancer therapy
- Potential to treat virtually all cancer types with minimal side effects
- Avastin®: Fastest sales growth of any drug
  - First anti-angiogenesis drug, approved Feb 2004
  - Antibody that blocks angiogenic protein VEGF-A
  - Developed and sold by Roche/Genentech Inc.
  - 2008 sales: \$US2.7B in US; \$US7.5B worldwide
  - Global sales forecast to surpass \$US10B in 2009



# An exciting commercial opportunity (cont)

- Avastin®: Effective but not across the board
  - Not all patients respond to therapy (30-50% response rate)
  - 25-50% of responders become “resistant” within 12 to 18 months
  - Likely reasons:
    - Tumour growth due to factors other than VEGF-A; and/or
    - Other angiogenic factors being turned on when VEGF-A blocked (i.e. VEGF-C, VEGF-D)

Avastin  
effective but  
has limitations

= Major  
opportunity for  
CIR

Our technology  
builds upon the  
Avastin application



# Strategy for extracting pipeline value

- Objective is to secure pre-clinical partnerships for one or more of our therapeutic programs
- Retain development of one selected therapeutic to proof of efficacy in humans - partner thereafter
- Selectively exploit / commercialise other aspects of portfolio:
  - therapeutics outside oncology area
  - clinical diagnostics and reagents for early revenues

# Existing partnered programs

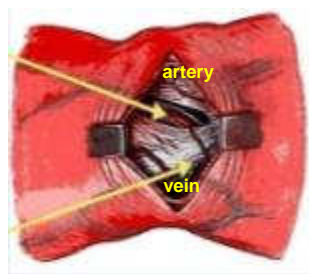
- Established partner programs with leading international biotechs in their fields
  - Ark Therapeutics plc (LSE:AKT) - Phase III clinical trial for Trinam<sup>®</sup>
  - ImClone Systems Inc (recently acquired by Eli Lilly & Co) (NYSE:LLY) - developing anti-cancer drug
  - Healthscope Limited (ASX:HSP) - developing cancer diagnostic test



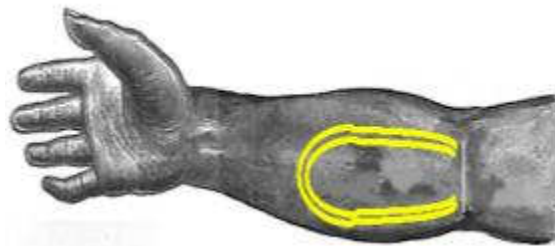
# Phase III product Trinam®

## Significant benefits for kidney dialysis patients

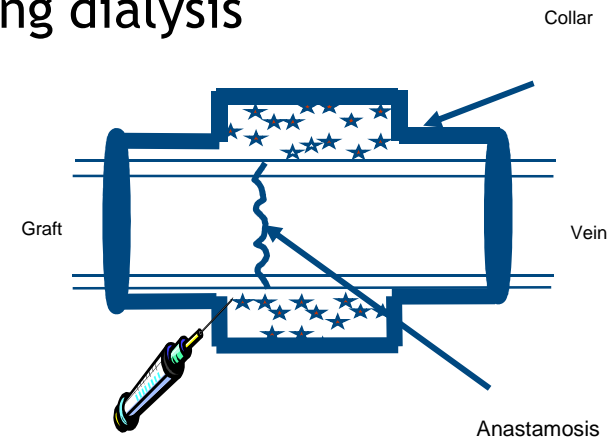
- Phase 3 trials commenced Jan 2009 under SPA
  - Expected recruitment 250 patients over 18 months
- VEGF-D gene therapy product - license under Circadian patents
- Extends lifetime of dialysis access grafts:
  - Phase 2 trials 17 months vs 4.5 months
- Major patient impact - reduced need for repeated surgery; increased survival time of patients undergoing dialysis
- Market estimates > \$US750M+ 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) for cancer

*ImClone/Eli Lilly*

- Formal internal product development candidate
- IND planned H1 2010
- Currently completing manufacturing development and animal safety testing
- Wide range of peer reviewed literature
  - Significant results presented at AACR 2009
- Likely first indication head & neck cancer

# Other potential revenue generating assets

- Cancers of Unknown Primaries (CUP) Molecular Diagnostic
  - Ownership and exclusive commercialisation rights in US, Europe and Japan; partnered with Healthscope for other territories
  - US incidence of CUP 60,000 to 100,000 per annum
  - Test to sell for between AU\$1,000 and AU\$2,000 due to significant health cost savings

## Landmark trial for cancer tool

**Olga Galacho**  
**EXCLUSIVE**

CIRCADIAN Technologies last night signed on major private hospital operator Healthscope to test and market a breakthrough cancer diagnostic tool.

years, will help pathology laboratories identify the hidden source of secondary cancers.

Circadian chief executive Robert Klupacs said he expected the company to make other similar announcements in coming months, leveraged off last year's acquisition of Ludwig Institute Vegenics assets.

"I think this deal will surprise the

was confident the potential partnerships in Circadian's pipeline were impressive.

One of the most cash-rich life science companies in Australia with more than \$42 million in the bank, Circadian owes its financial position in part to a \$25 million investment by the late Kerry Packer about 10 years ago.



# Dominant and protected IP position

- 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
- Freedom to operate in respect of competitors
- Over 500 granted and pending patents worldwide

# Experienced and talented management team

- Robert Klupacs (CEO)
- Natalie Korchev (CFO & Head of Operations)
- Dr Alex Szabo (Head Business Development)
- Dr Megan Baldwin (Head Pre-clinical Development)
- Dr Mike Gerometta (Head CMC Development)
- Dr Richard Chadwick (Head Intellectual Property)
- Sue Foran (Head Toxicology & Project Management)

# Product Development Advisory Committee

- Vast experience in international drug development and oncology. Collective experience in over 150 drug developments
  - Errol Malta (Chair): ex Amgen
  - George Morstyn: ex CMO Amgen
  - Russell Howard: CEO Nasdaq listed Maxygen
  - Ralph Smalling: ex Amgen Reg Affairs
  - Richard Morgan: ex Glaxo-Wellcome
  - Carlo Montagner: ex Aventis, Schering, Abraxis

# Expected events next 12 months

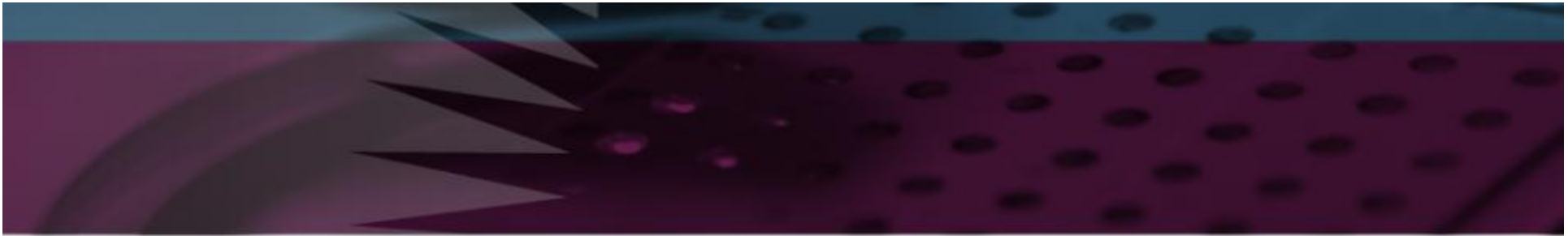
- Trinam® (licensee Ark Therapeutics)
  - Phase 3 trial: enrolment update
- VEGFR3 Abs IMC-3C5 for cancer (licensee ImClone)
  - IND filing
- CUP molecular diagnostic
  - Validation of diagnostic test completed by Healthscope

## Expected events next 12 months (cont)

- VGX cancer drug development program
  - VGX-100 commencement of GLP toxicology
  - VGX-200 lead drug candidate selection
  - VGX-300 manufacturing milestone achieved
  - Publication of data from animal tumour model experiments - all programs
- Updates from key collaboration partners Stanford and Harvard on non-cancer applications
- Key patent grants: USA, Europe, Japan

# An investment with significant upside

- Therapeutic antibodies
  - Major focus of big pharma
  - High value early stage deal opportunities and M&A opportunities
- Deep diverse product pipeline
  - One product at Phase III (partnered & fully funded)
  - Potential multi-million dollar royalties
  - Royalty flow possible within 24-36 months
- Angiogenesis - significant product opportunity validated
- Dominant and protected IP position
- World-class drug development expertise and management
- Strong financial position



# APPENDICES

# 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
- 45,241,928 shares on issue; further 1.155M to be issued Aug 10 2010 (Top 10 control approx 53.5%)

# Anti-Angiogenic Agents Targeting the VEGF/VEGFR Family

*Competitive environment reflects clinical/commercial potential*

Circadian  
VGX-200 (anti-VegF-D)

Circadian  
VGX-300 (VEGFR-3-Fc)

Circadian  
VGX-100 (anti-VegF-C)

ImClone (Circadian Licensee)  
HF3-3C5 MAb

- Circadian controls rights to nearly half the products in the field

58



10



4

Anti-angiogenic agents marketed or in development

Only 10 are antibody-based drugs

Are owned or licensed from Circadian



# 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 H1/2011.
- 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.

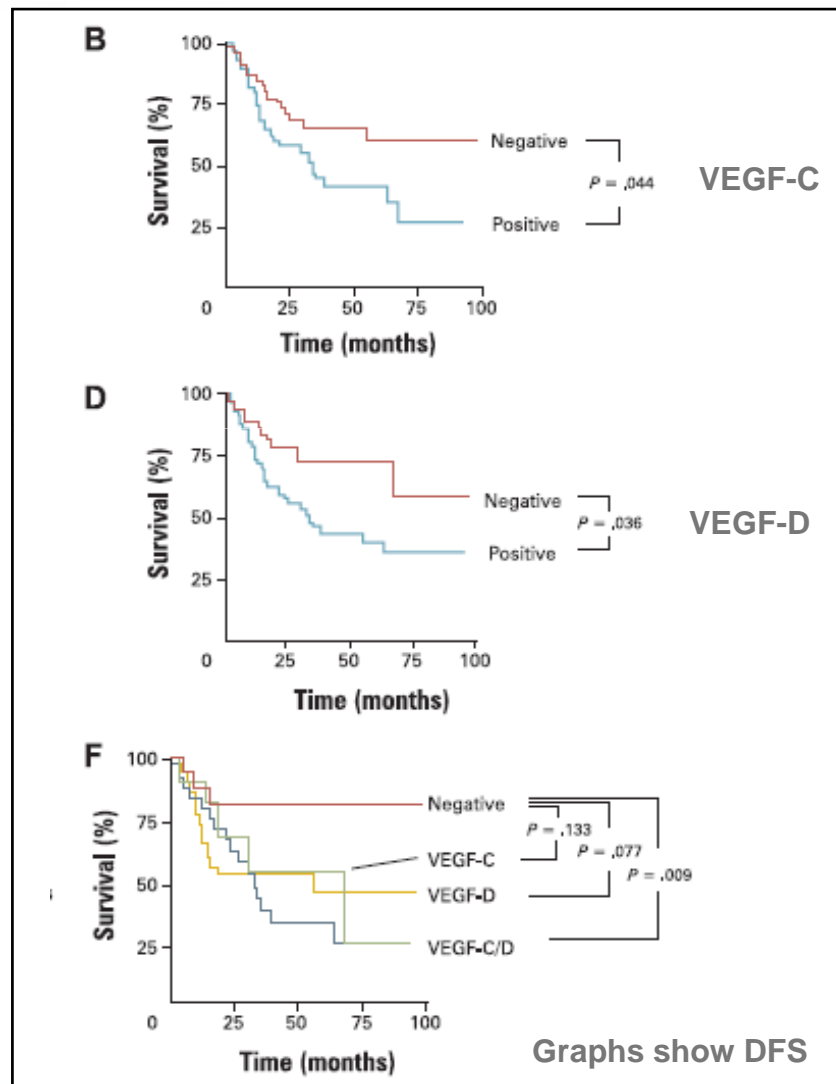
# VGX-200 Program Summary

- Humanisation and affinity maturation program complete
- Lead hlgG1 mAbs identified based on fold-improvement in KD relative to murine parental VD1 antibody
- Formal lead identified by Dec '09 based on *in vivo* efficacy
- IND anticipated H2/2011
- 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 lymph node mets and decreased survival in gastric cancer



91 Gastric Adenocarcinomas

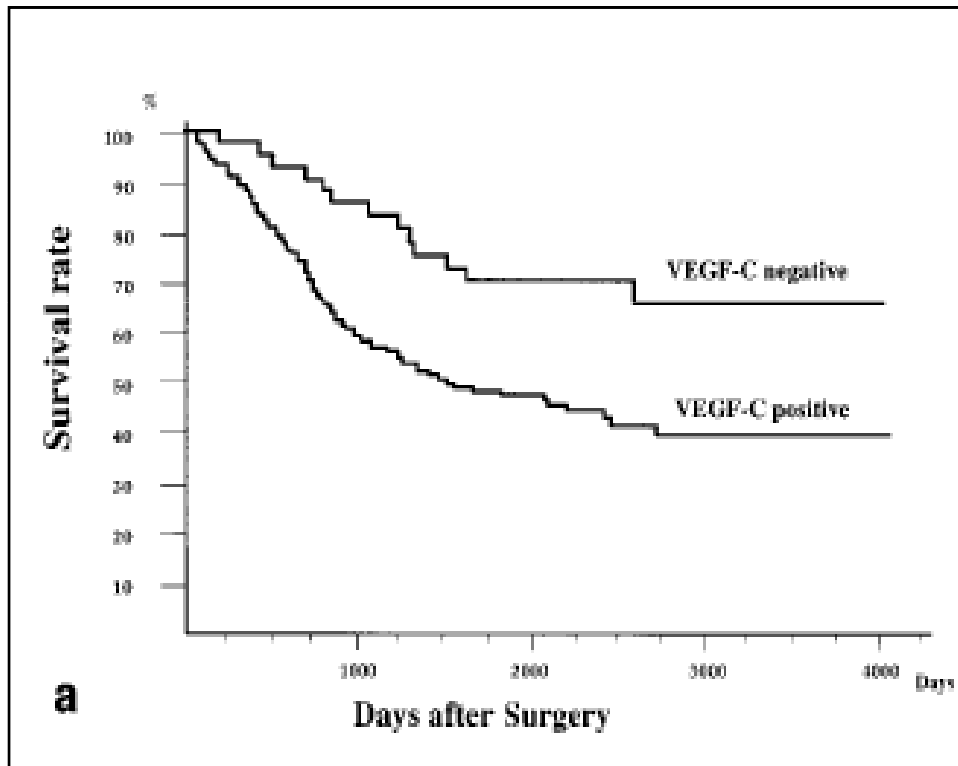
**VEGF-C and VEGF-D correlated with:**

- 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%

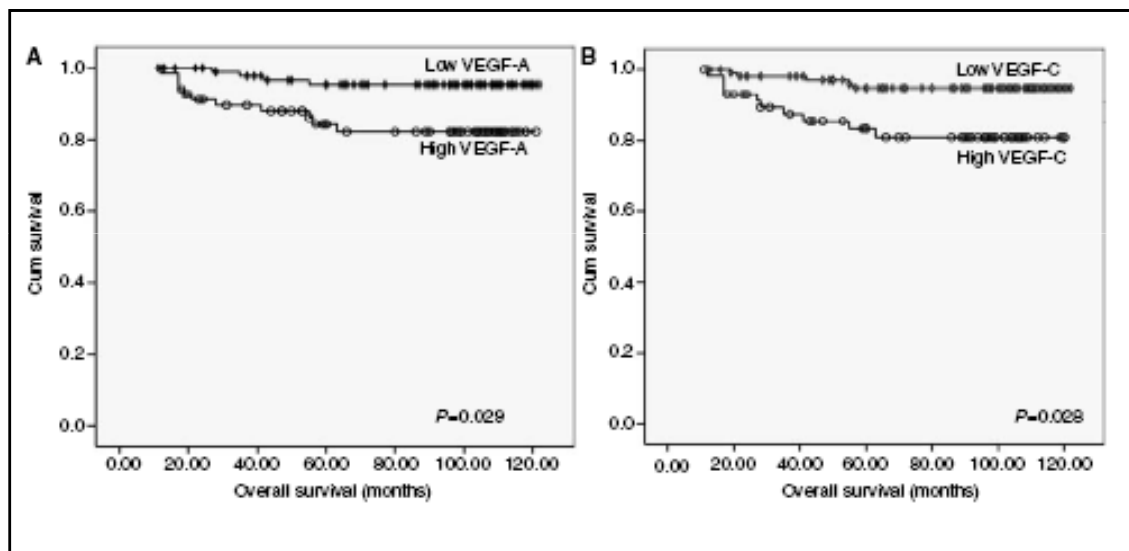
VEGF-C negative: 70%

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

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



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



117 invasive breast cancer

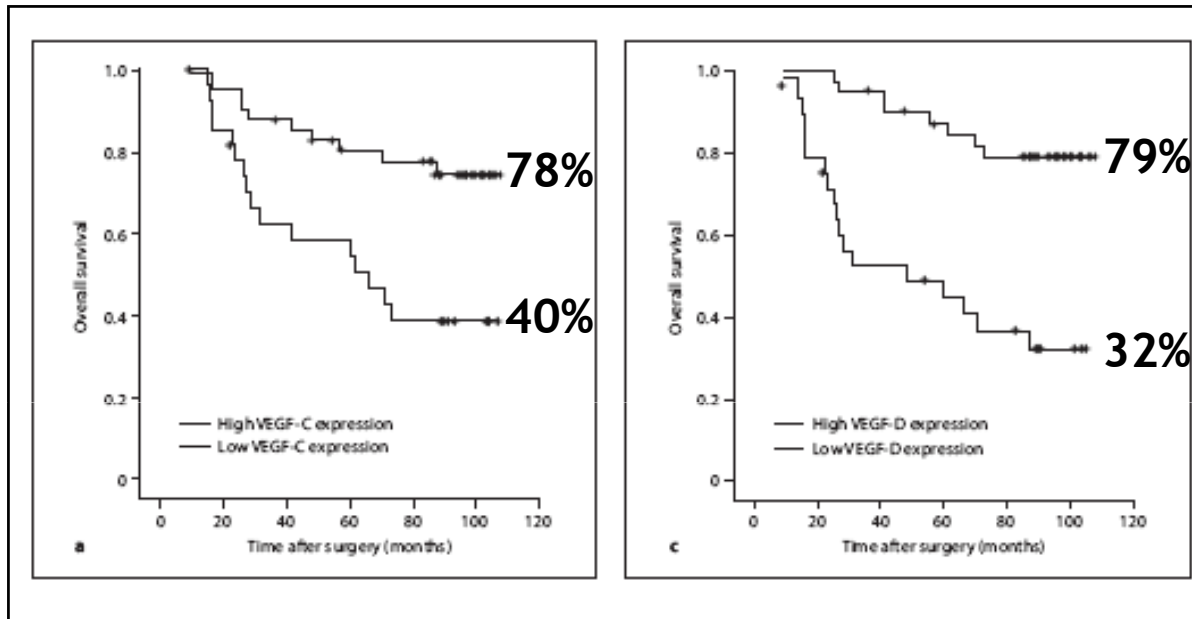
***VEGF-C correlated with:***

- 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

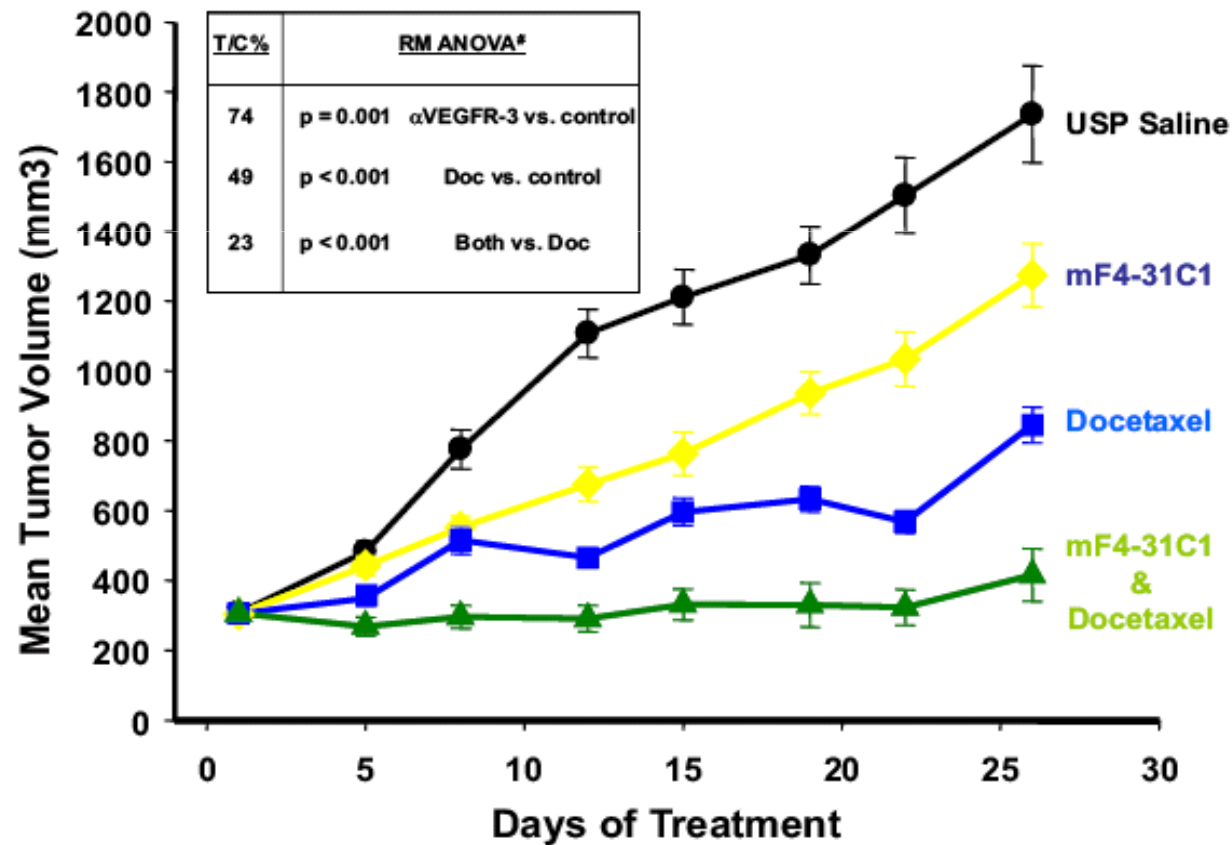


Hu et al., Eur Surg Res, 39: 229-238, 2007.

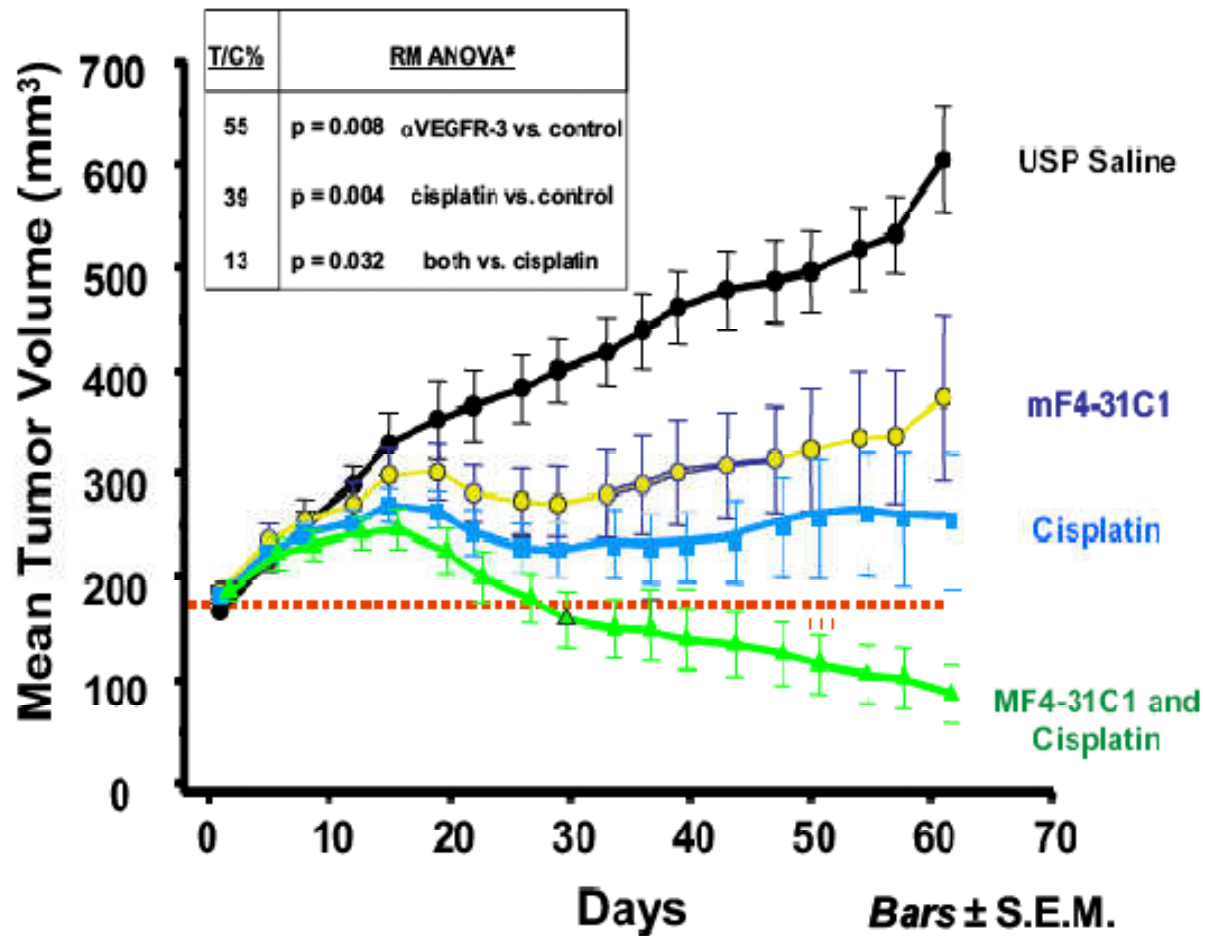
# Circulating VEGF-C & VEGF-D levels are elevated in cancer patients

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>

# VEGFR3 Ab +/- chemotherapy in Non-Small Cell Lung Cancer xenograft model (NCI-H292)

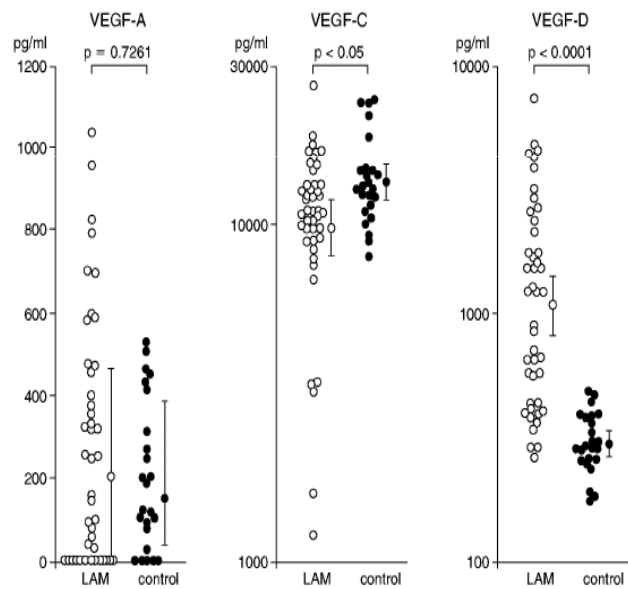


# VEGFR3 Ab +/- chemotherapy in head and neck cancer carcinoma xenograft model



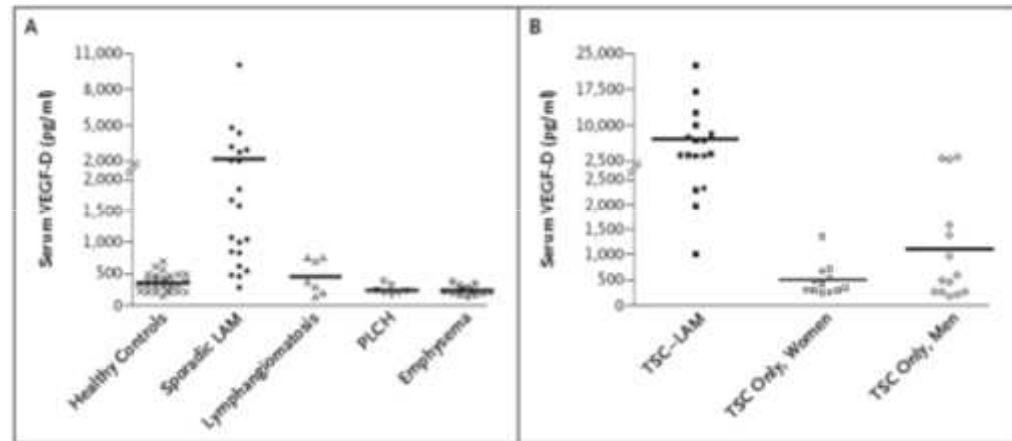
# LAM - Orphan Development Opportunity for VEGF-D Antagonists

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