

# CEO Lunch Series

## *The New Circadian - Transforming from Biotech Incubator to Biologicals Drug Developer*

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**Hosted by: Mr James Cherry**

Partner, Freehills Patent & Trade Mark Attorneys



**BioMelbourne  
Network**

Progressing BioIndustry



Presentation to  
Biomebourne Network

Friday, 24 April 2009



Robert Klupacs, CEO & Managing Director



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# CIRCADIAN-Leader, Adapter, Survivor

*CIRCADIAN-AN EVOLUTIONARY JOURNEY :  
FROM DEVELOPER,  
TO EARLY STAGE INVESTOR,  
TO INCUBATOR, TO FUND,  
TO BIOLOGICALS DEVELOPER*

# Mr Leon Serry



## Circadian History -Melatonin phase

- 1984: Leon Serry partners with Monash Uni to develop melatonin jet lag project
- 1985: Circadian Listed on the ASX with \$1M raising
- 1985-1994: Additional investments in early stage projects
- 1994: Eli Lilly granted exclusive licence to develop melatonin agonists

# Circadian History -Melatonin phase

- Eli Lilly sued for non performance in early 98
- Settled Xmas 1998
- \$US3M settlement payment

# Circadian Listings/Investments

- Optiscan listed on ASX Aug 1997
- Metabolic listed on ASX Nov 1998
- Axon listed on ASX Mar 2000
- Initial investment in AMRAD May 2000
- ANP listed on ASX Nov 2001
- AVX obtained from AMRAD demerger 2003

# Circadian Listings/Investments/Proceeds Stage

- Proceeds realised on investments
  - Axon \$31M (Gain \$29.9M) acquired by Molecular Devices May 2004
  - AMRAD \$30M (Gain \$7.5M) acquired by CSL Nov 2006
  - Metabolic \$16.2M (Gain \$15.7m)
  - Avexa (from AMRAD demerger) \$18.3M (Gain \$4.8m)
- 2 Significant placements in 2000 (\$37M)
- Capital return and dividends of \$20M Oct 2004/Feb 2005

# Circadian VEGF-C/D Biologicals Developer

- JV formed with Ludwig Institute and Licentia to commercialise VEGF-C, VEGF-D in Apr 2006
- Leon Serry announces retirement in Dec 2007
- New CIR leadership from Mar 2008
- New directions launched with 100% ownership of VEGF J/V company in Aug 2008

# CIRCADIAN TODAY

*A cashed up company developing novel anti-angiogenic therapeutics for cancer*

*With a dominant IP platform*

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

# CIRCADIAN TODAY

- Focused on the development of VEGF-C/D antibodies as biologics-based therapies for cancer through tumour starvation (“anti-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 23 April 2009 \$A45M approx
- 46,396,928 shares ; 1.155M to be issued Aug 10 2010 (Top 10 control approx 53.5%)
- Market Cap approx \$38M @23 April 2009

# WHY DID WE CHANGE STRATEGY TO BECOME BIOLOGICALS DRUG DEVELOPER?

Major focus of big pharma

High Value early stage deals and M&A

Exquisite targeting-improved probability of  
success

Extremely large markets

Avastin®

Significant product opportunity in angiogenesis

Unique, Deep and Dominant IP



## Antibodies represent significant market opportunities

- Strong interest in antibodies from pharma in M&A and early stage licensing:
- M&A over last 2 years:
  - Medimmune/AstraZeneca - US\$15.5b
  - CAT/AstraZeneca - US\$1.30b
  - Domantis/GSK - US\$435m
  - Adnexus/BMS - US\$425m
  - Morphotek/Eisai - US\$325m
  - Cephalon/Arana - US\$200m

# Oncology Antibodies: Preclinical Deals continuing

<i>Parties</i>	<i>Date</i>	<i>Size</i>	<i>Technology</i>
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.
Bioinvent/Thrombogenics/ Roche	Jun 08	\$US800M	Exclusive licence to PIGF Abs in oncology. \$US75M upfront. \$US700M milestones. Double digit royalties
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

# Antibodies represent significant market opportunities

## 19 antibody drugs on the market

- Current sales of top ten antibodies > US\$20bn p.a;
- Total antibody sales growing by >30% annually
- greater competitive barrier to entry
- targeted profiles can provide cost v health economic advantage
- probability of success is higher

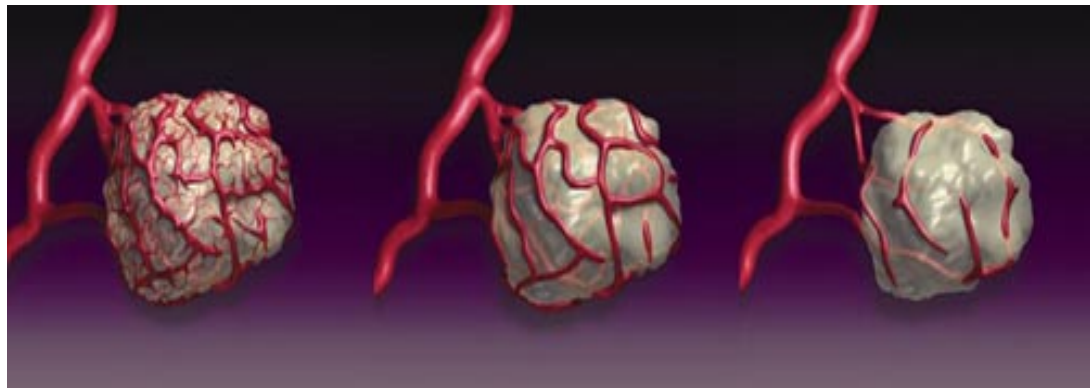
# Avastin® Story

- 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



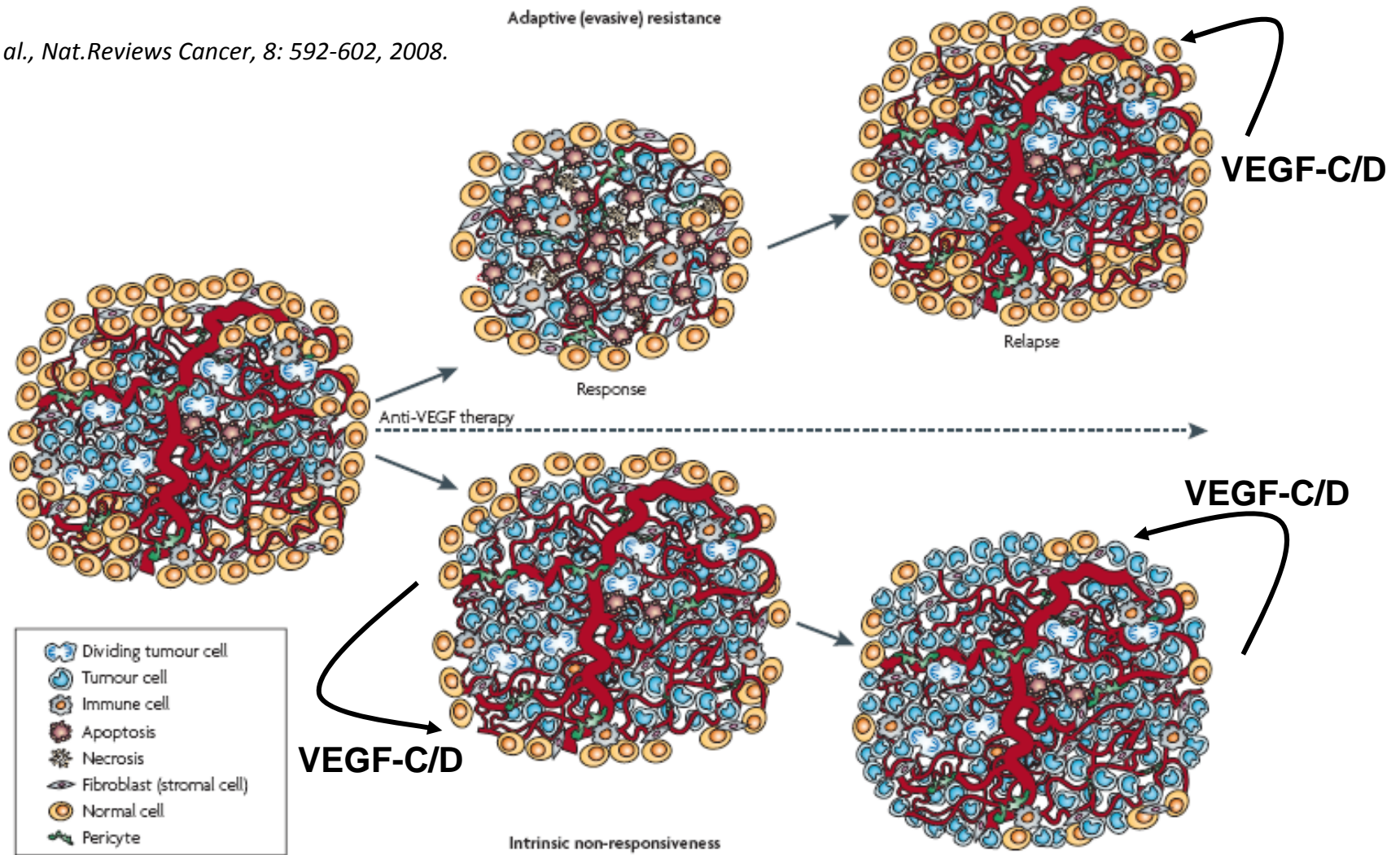
# What is angiogenesis?

- 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



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

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

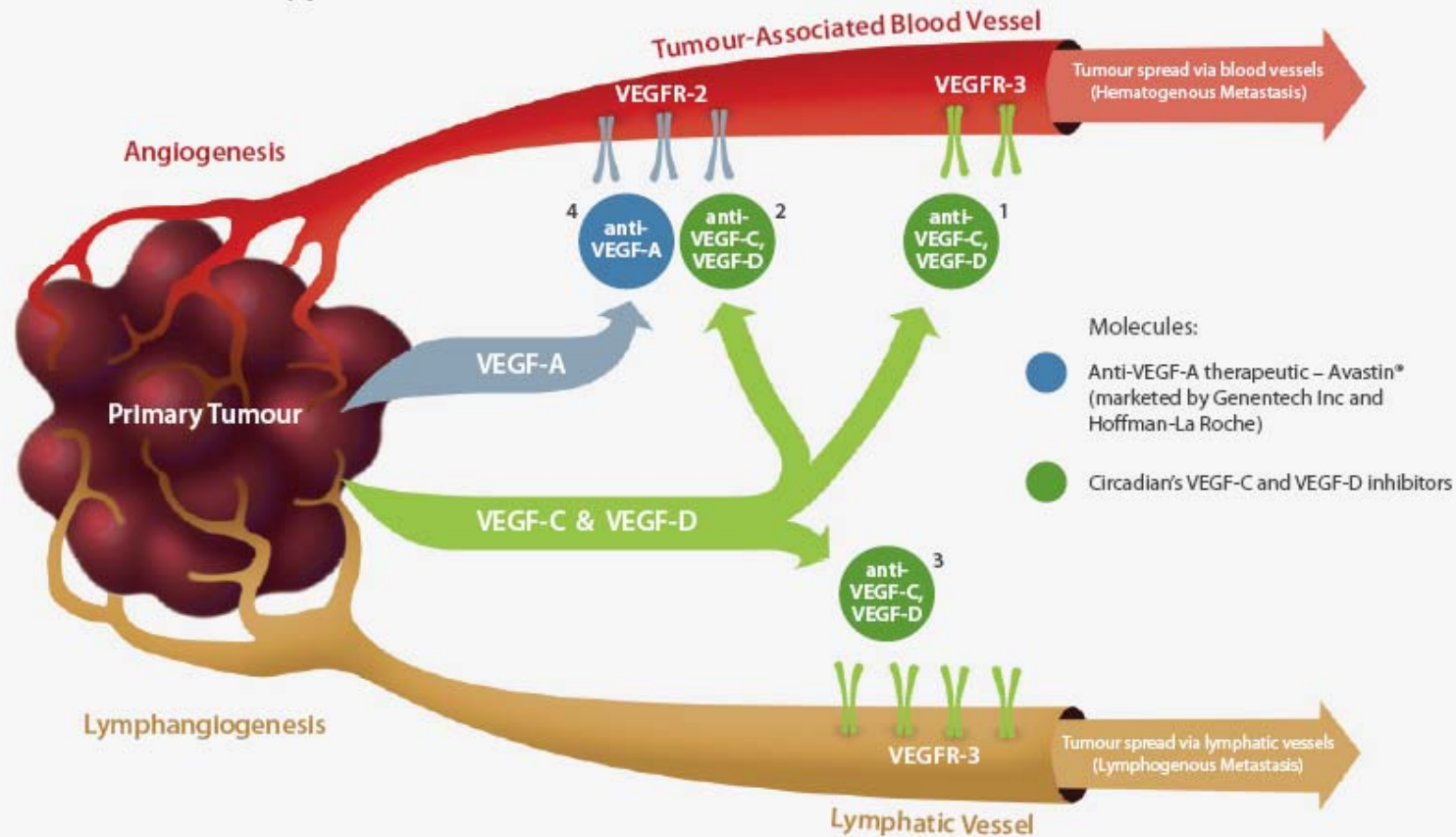


# The Product Opportunity

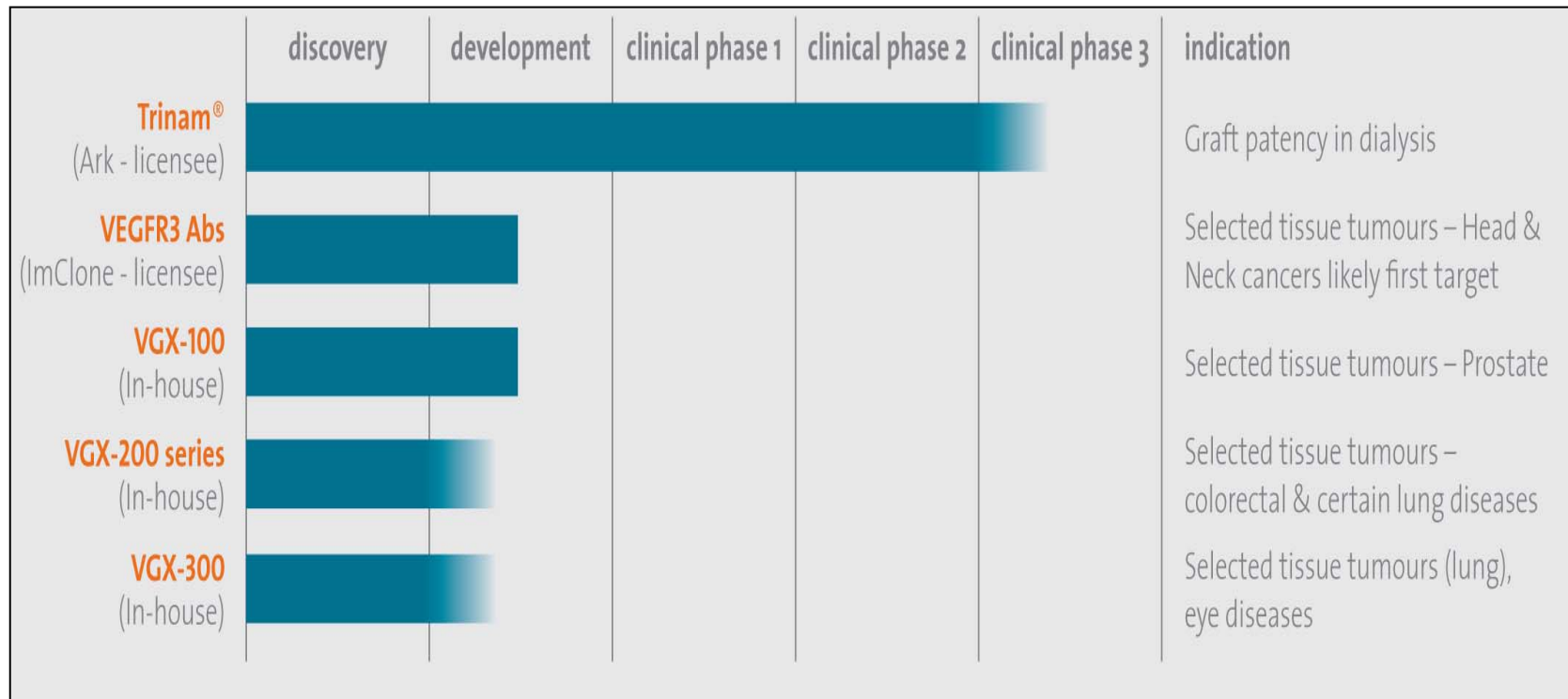
Opportunity to develop a new class of antagonists to address resistance and/or non-responsiveness to anti-angiogenic therapies in cancer.

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

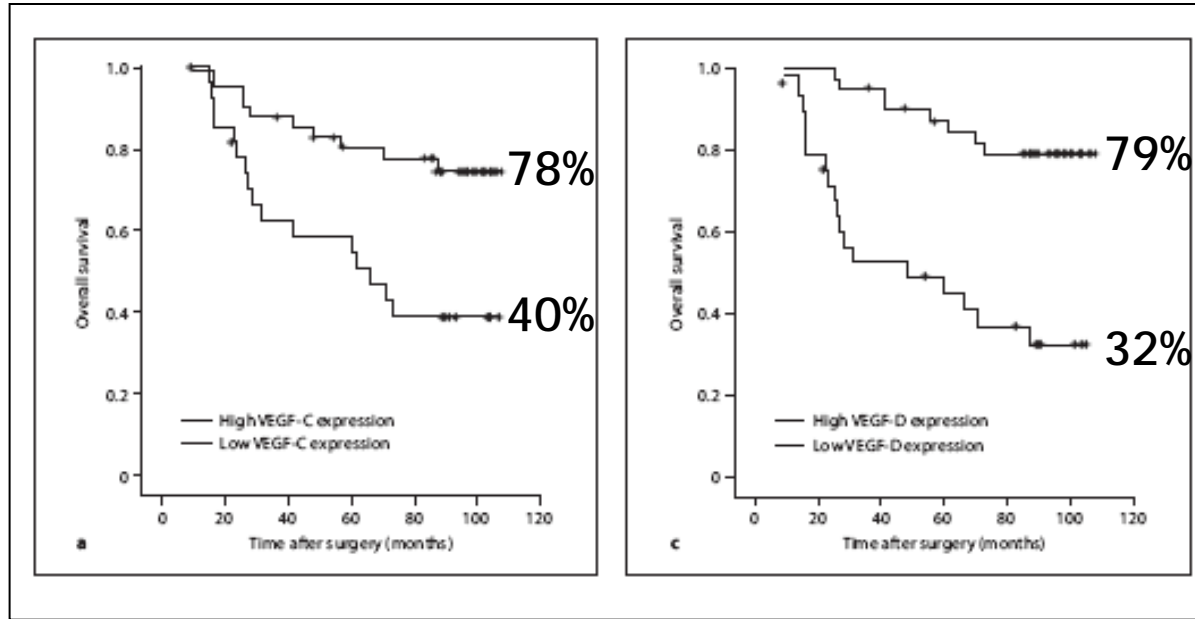
Anti-Tumour Therapy Mediated via VEGF Inhibition



# Deep Product Pipeline with mechanistically distinct mechanisms



# 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



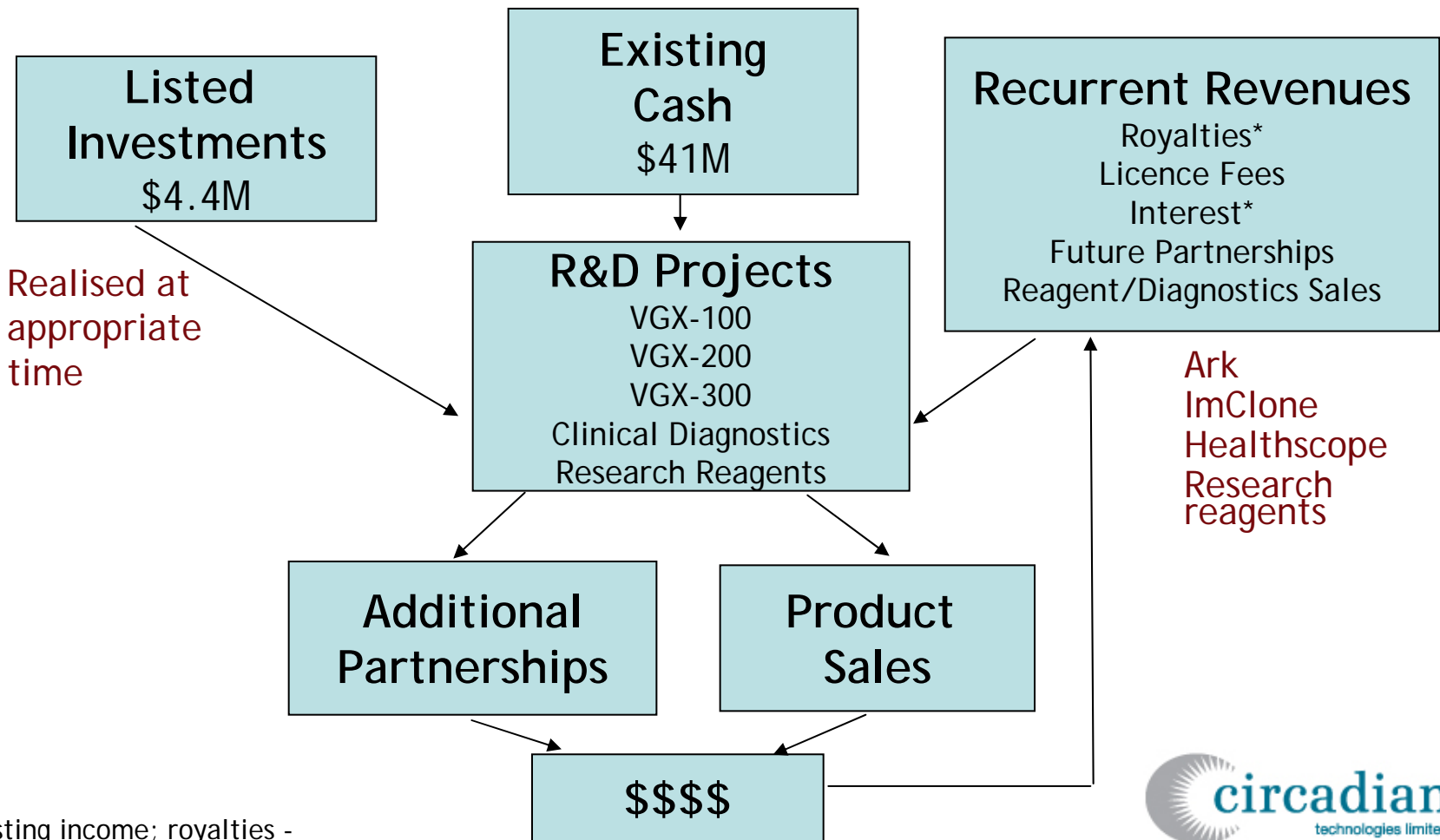
# Developing therapeutics for cancer and other serious diseases

- 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 field 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** - \$45 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.

# 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

# CIRCADIAN'S BUSINESS MODEL - MAINTAINING CASH FOR R&D



\* Existing income; royalties - potential for significant increase

# 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.

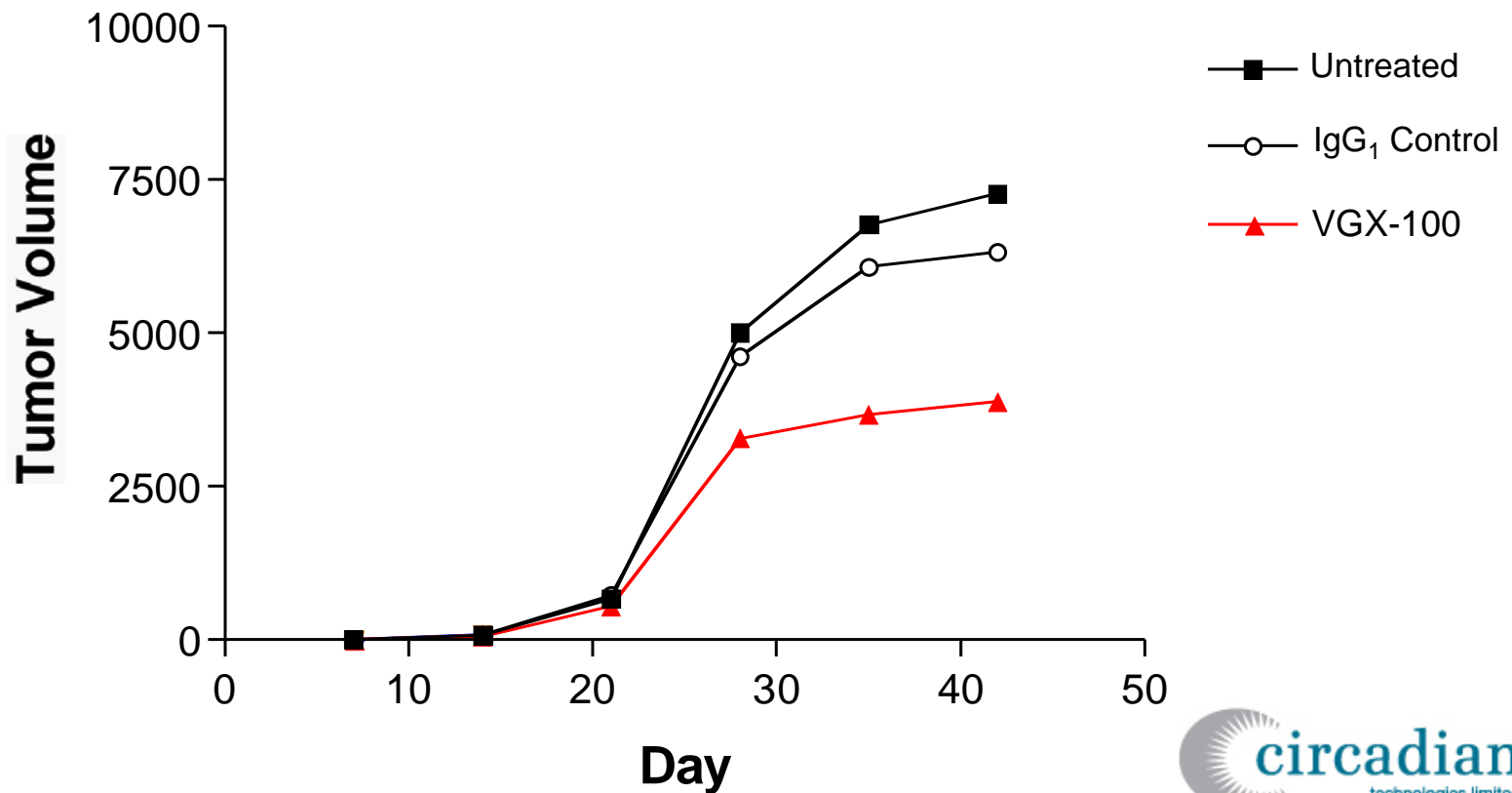


# Our strategy

- 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
- Exploit clinical diagnostics and reagents for early revenues

# VGX-100 slows growth of orthotopic prostate tumors

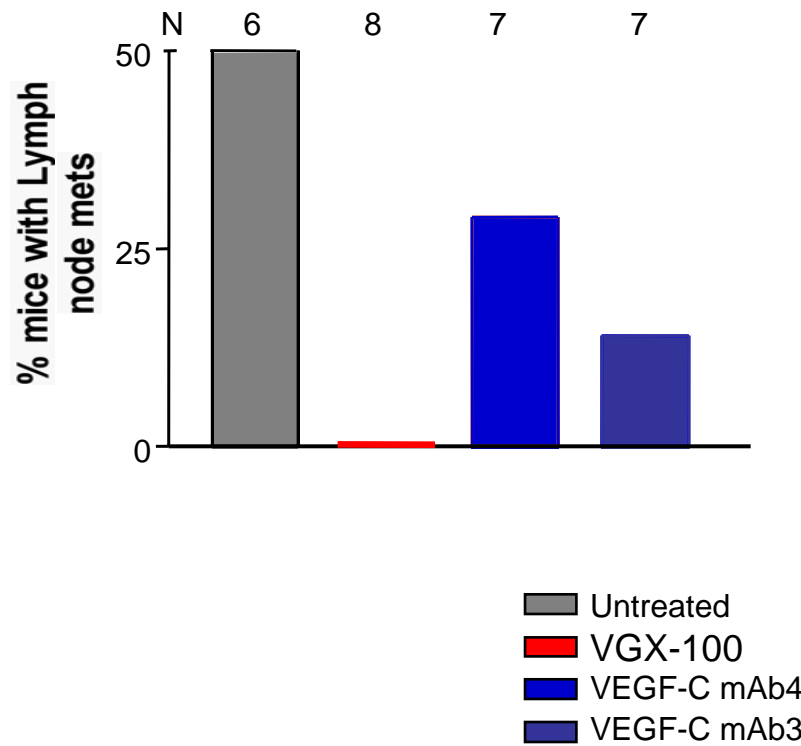
## PC-3 Growth rate



Dosing: 20 mg/kg every 7d.

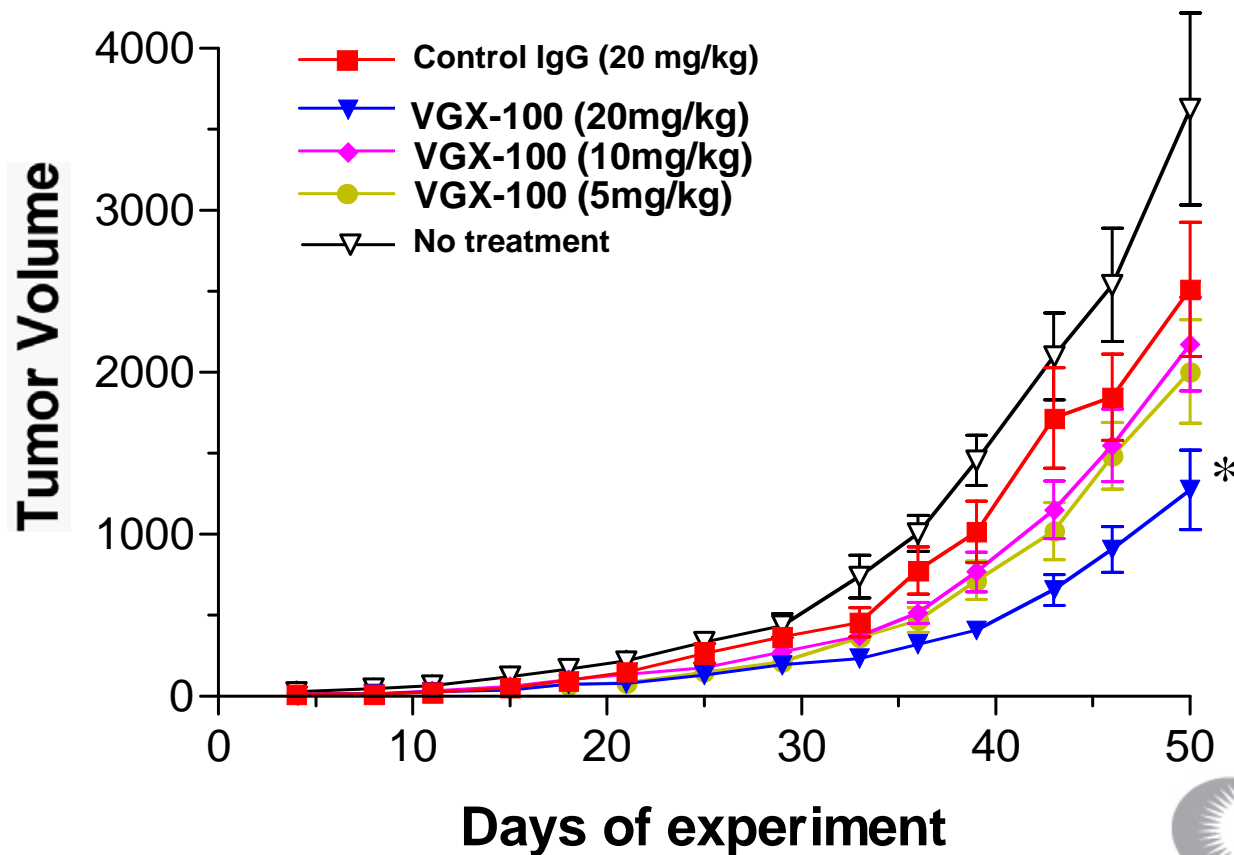
# VGX-100 inhibits PC-3 metastasis

Lymph Node Metastatic Frequency

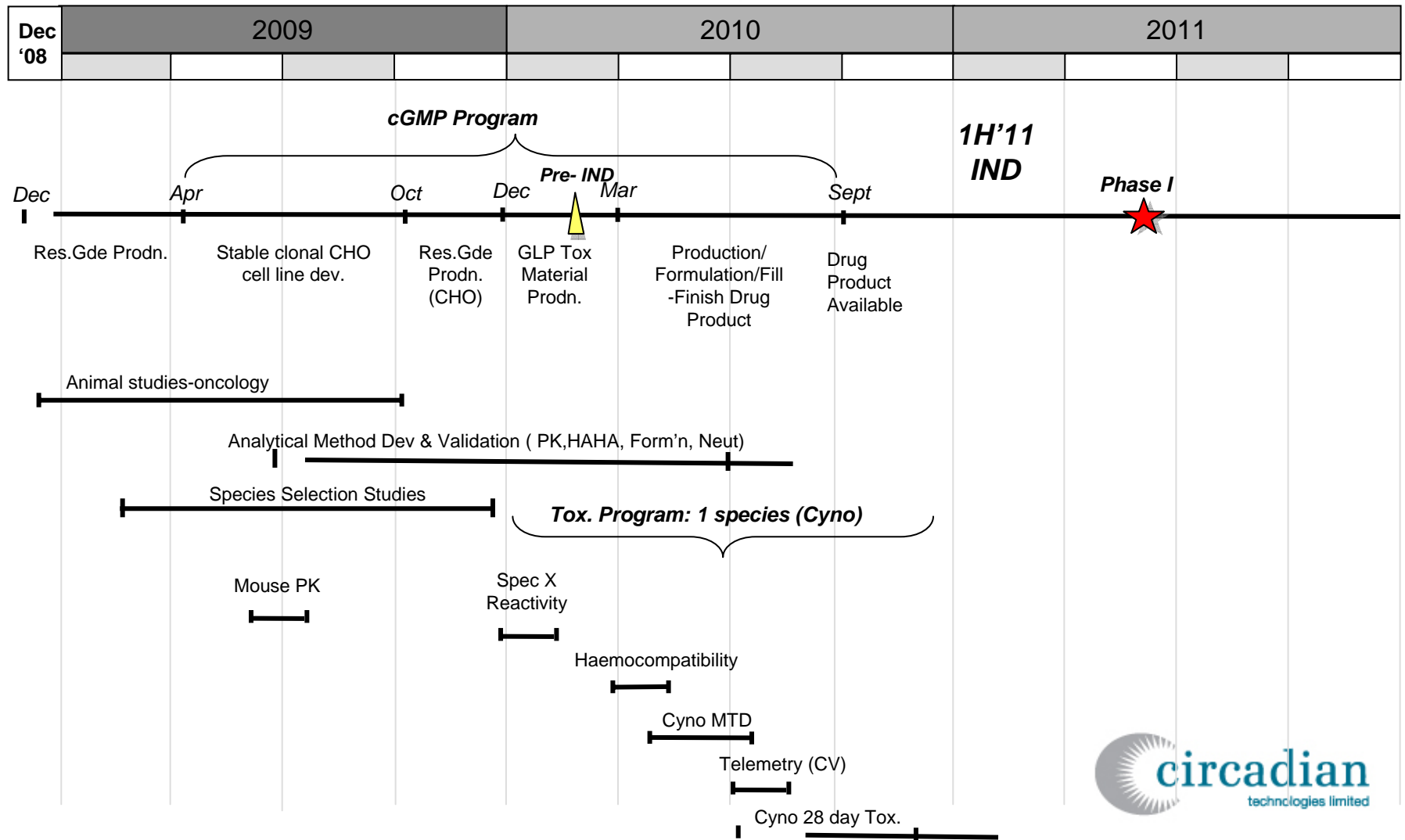


# Dose-dependent inhibition of breast cancer xenografts

## MDA-MB-231 Growth

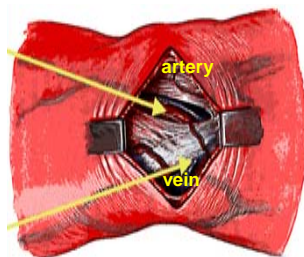


# VGX-100 Development Program

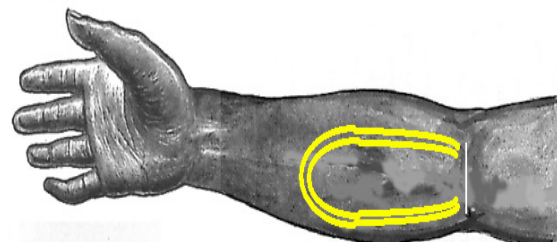


# Phase 3 Product Trinam® - Ark Therapeutics

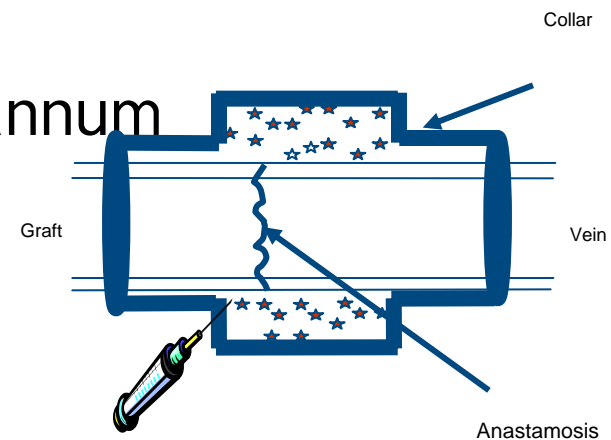
- Commenced Phase 3 trials Jan 2009 under SPA. Expected recruitment 250 patients over 18 months.
- VEGF-D gene therapy product.
- Extends lifetime of dialysis access grafts. Phase 2 clinical trials 17 months v 4.5 months.
- Major patient impact by reduced need for repeated surgery and increased survival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



Step 1: Surgical isolation of vein and artery



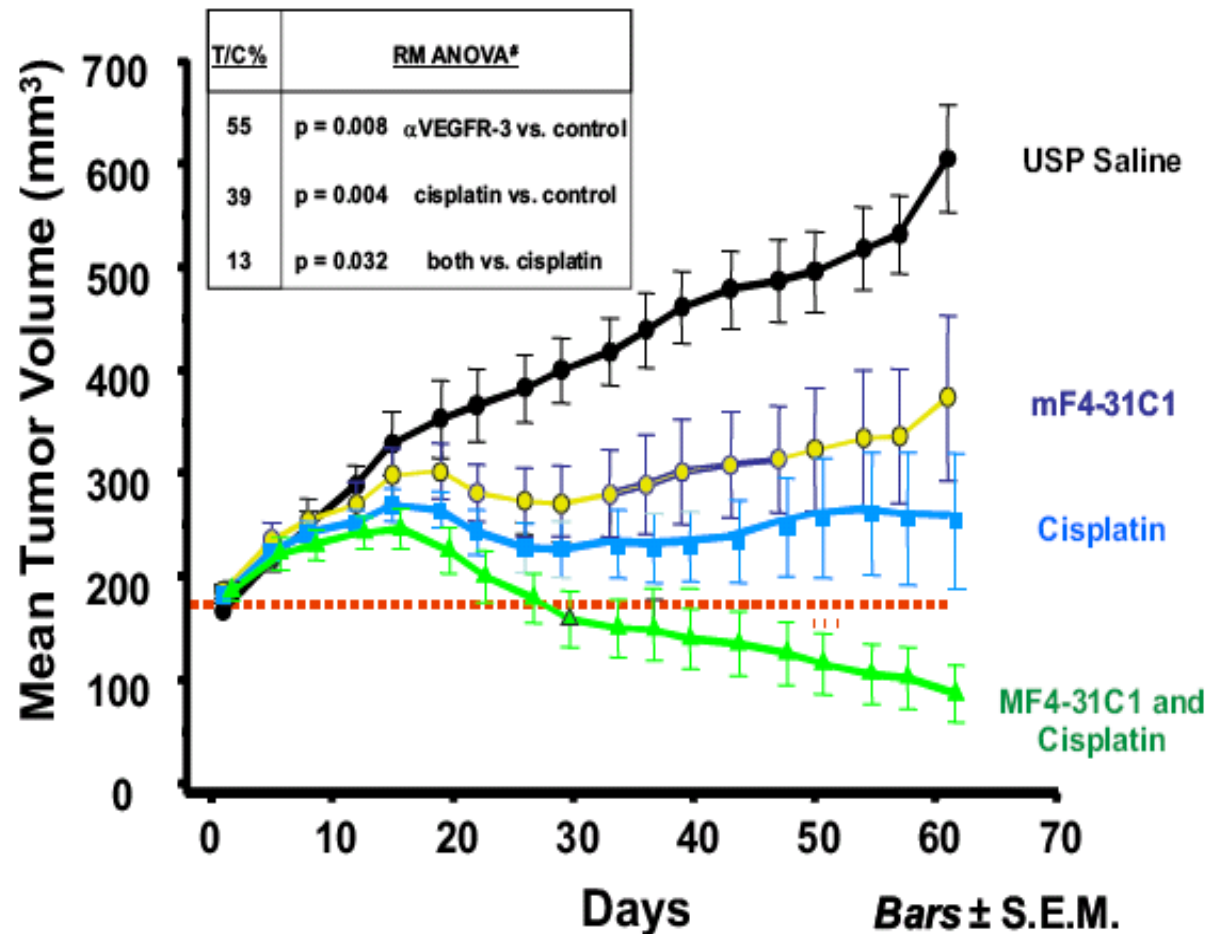
Step 2: Insert flexible plastic tube graft to provide access for dialysis



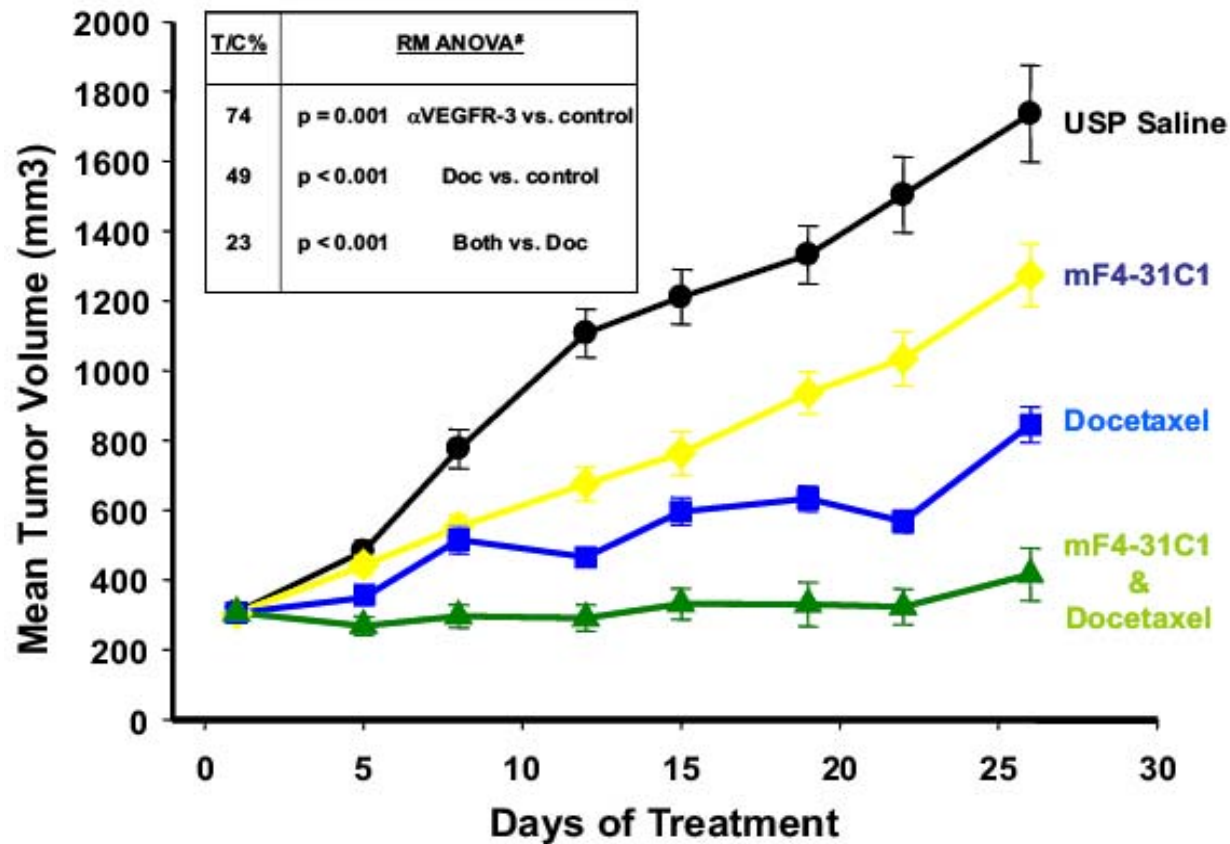
# IMC-3C5 (human anti-VEGFR-3 mAb) *ImClone/Lilly*

- 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

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



# VEGFR3 Ab +/- chemotherapy in NSCLC xenograft model (NCI-H292)



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

- Over 500 granted and pending patents worldwide
- 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

# Experienced and talented management team

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

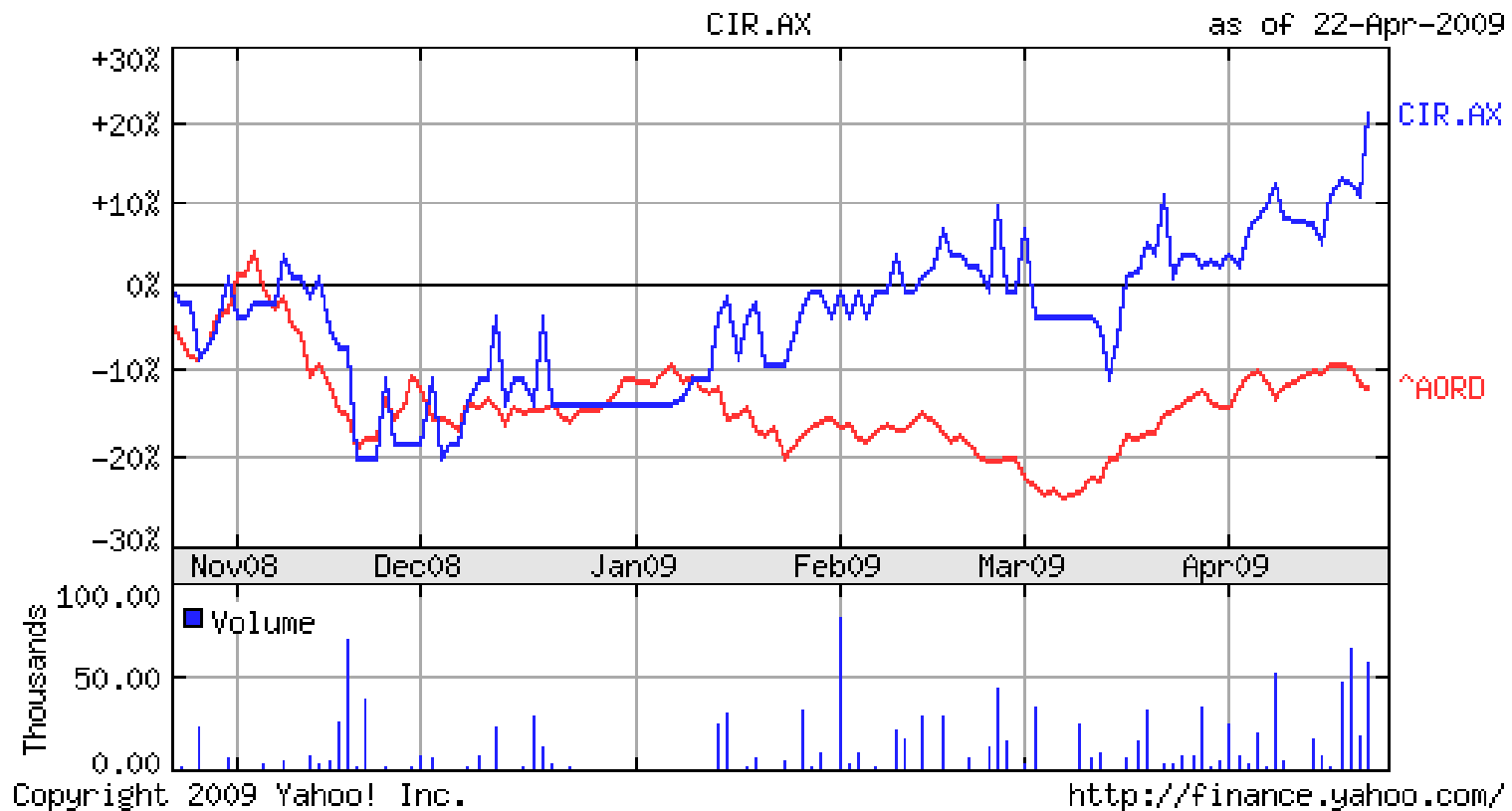
# Product Development Advisory Committee

- Team with experience in over 150 drug developments
  - Errol Malta (Chair): ex-Amgen
  - George Morstyn: ex-CMO Amgen
  - Russell Howard: CEO Maxygen
  - Ralph Smalling: ex-Amgen Reg Affairs
  - Richard Morgan: ex Glaxo-Wellcome
  - Carlo Montagner: ex Aventis, Schering, Abraxis

# Scientific Advisory Board

- World leaders in angiogenesis research
- Prof Kari Alitalo (Chair): Finnish Academy of Sciences
- Assoc Prof Marc Achen: Ludwig Institute
- Assoc Prof Steve Stacker: Ludwig Institute

# Last 6 months



## NEXT 12 Months

- Expand management and scientific team
- Complete cell line development and manufacturing of VGX-100, VGX-200 and VGX-300
- Complete initial rounds of xenograft experiments
- Develop serum based assays for VEGF-C/D
- IMC-3C5 commences clinical studies
- Partner(s) identified

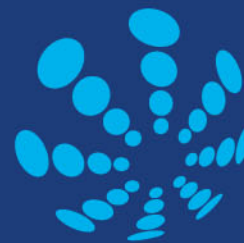
# An investment with significant upside

- 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 below cash with no apparent value ascribed for our IP assets or existing and future royalty flows.

# BIOBREAKFAST

Tuesday, 12<sup>th</sup> May

**‘How can Biotech Companies  
Navigate the Current USA Patent  
Climate?’**



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