ANNUAL GENERAL MEETING 20 NOVEMBER 2012

Robert Klupacs, CEO & Managing Director

Circadian Technologies (ASX.CIR)

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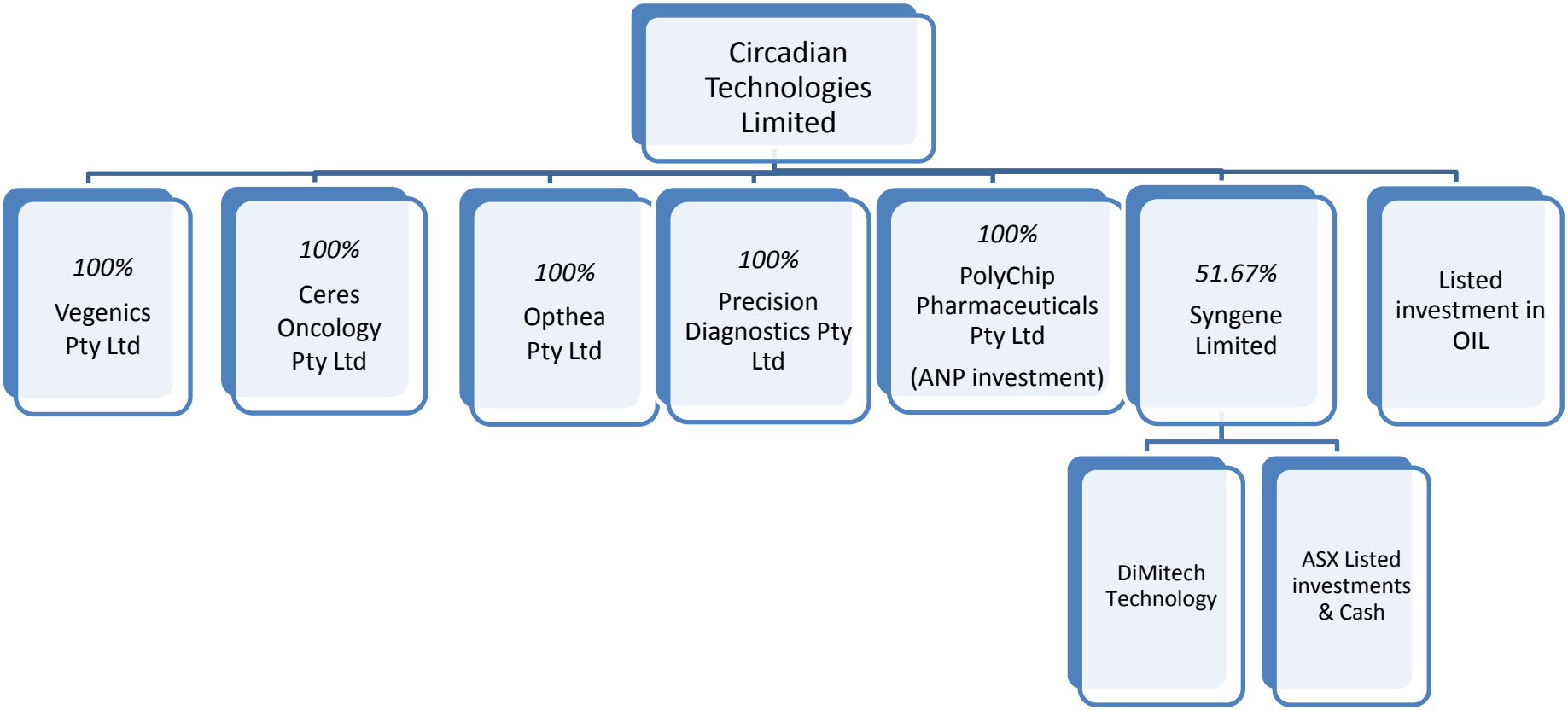
CIRCADIAN TECHNOLOGIES LIMITED- 2012 AGM PRESENTATION OUTLINE

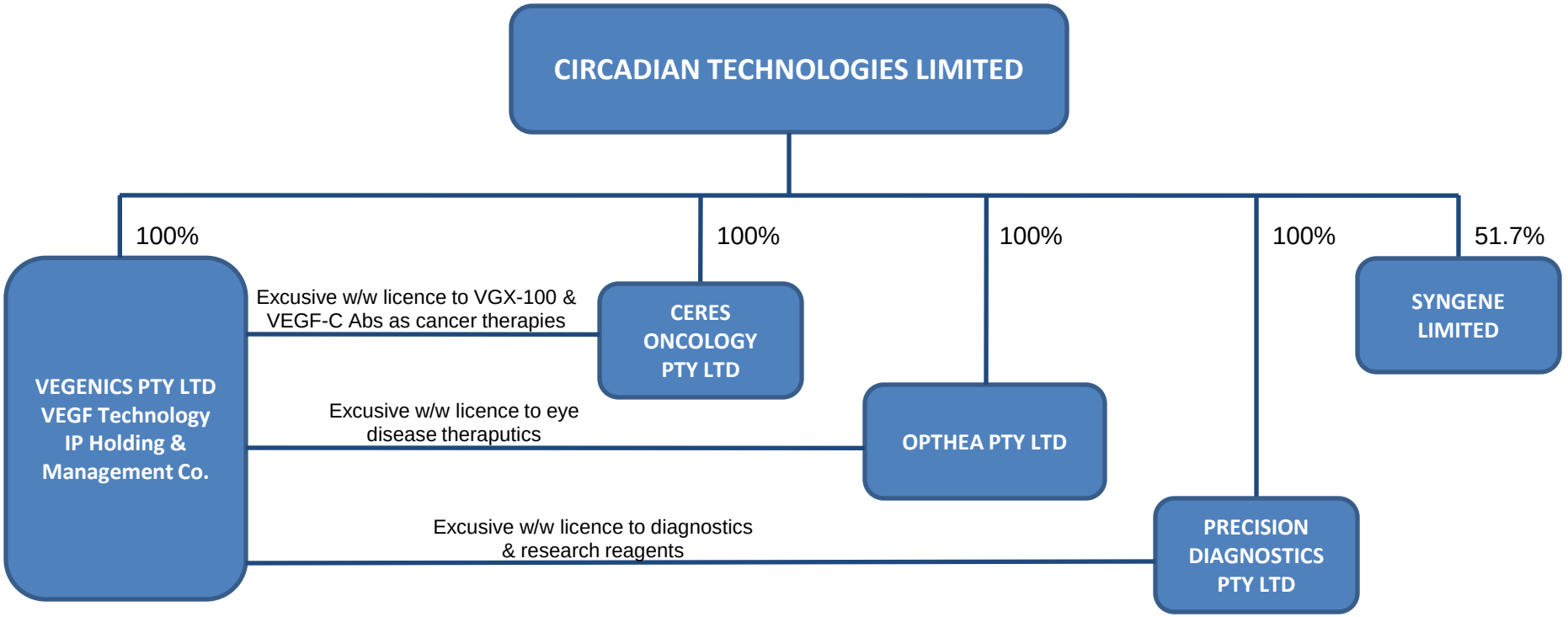
- **Corporate Snapshot & Structure**
- **Review of achievements since July 2011**
- **Therapeutic, Diagnostic & Reagent Development**
  - **Ceres Oncology Pty Ltd**
  - **Precision Diagnostics Pty Ltd**
  - **Opthea Pty Ltd**
- **Expected milestones/value adding events next 6-18 months**
- **Opthea Pty Ltd Presentation(Dr Megan Baldwin)**

CORPORATE SNAP SHOT

An Australian based emerging clinical stage company developing human therapeutic and diagnostic products from our extensive and worldwide dominant intellectual property platform in respect of VEGF-C, VEGF-D and VEGFR-3 and key relationships with leading cancer and eye research organisations.

OUR CORPORATE STRUCTURE




CIRCADIAN TECHNOLOGIES LIMITED
100%
100%
100%
100%
51.7%
VEGENICS PTY LTD
VEGF Technology
IP Holding &
Management Co.
Excusive w/w licence to VGX-100 &
VEGF-C Abs as cancer therapies
CERES
ONCOLOGY
PTY LTD
Excusive w/w licence to eye
disease theraputics
OPTHEA PTY LTD
Excusive w/w licence to diagnostics
& research reagents
PRECISION
DIAGNOSTICS
PTY LTD
SYNGENE
LIMITED

REVIEW OF ACHIEVEMENTS SINCE JULY 2011

OBJECTIVES WE SET FOR 2011/2012

- Advance drug development pipeline toward human clinical trials
- Develop partnerships for the commercialisation of our intellectual property
- Release the value inherent in our IP assets

PROGRESS ACHIEVED IN EXECUTING BUSINESS STRATEGY

Advancing our product pipeline

- Phase 1 trials commenced in USA Jan 12 with VGX-100 (human anti-VEGF-C antibody)
- Additional data generated in animal models showing combination effects with small molecule angiogenesis inhibitors
- VGX-100 and VGX-300 (soluble VEGFR-3) designated product development candidates for “back of eye” diseases
- IMC-3C5 (Imclone/Eli Lilly human VEGFR-3 antibody) Phase 1 trials continuing

PROGRESS ACHIEVED IN EXECUTING BUSINESS STRATEGY

Partnerships

- Healthscope-CUPGUIDE Test launched July 2012
- Cincinnati Children's Hospital Medical Centre – VEGF-D Diagnostic for women with respiratory disease: Product launched
- Eli Lilly-IMC-3C5: Phase 1 trials continuing
- Ark Therapeutics: Arbitration settled. Phase 2 studies with VEGF-D gene therapy commenced
- 2 new research reagent licences signed (Bio-rad, Confidential)

FINANCIAL POSITION & SHAREHOLDER BASE

Top 10 shareholders: 54.4%

Investor	% of issued shares
BNP Paribas Noms Pty Ltd	17.10
Citicorp Nominees Pty Ltd	8.78
Ludwig Institute for Cancer Research	6.43
HSBC Custody Nominees (Australia) Limited GSCO ECA	5.33
National Nominees Limited	4.73
BNP Paribas Noms Pty Ltd	3.67
Capital Macquarie Pty Limited	2.84
Chemical Trustee Limited	2.39
4 Eyes Limited	1.67
JFF Steven Pty Ltd	1.47
Total 10 shareholders own	**54.4%**
Total 20 shareholders own	**61.9%**

Financial Summary @ 16 November 2012 (unaudited)

Stock code:	**CIR**
Share price:	**37.5c** (AUD)
Shares issued:	48,481,642
Market cap:	~ A$**18.2** mill
Cash holdings: Listed investments: (ASX: ANP, OIL)	~ A$**13.1** mill A$**2.4**mill

Institutions/Funds: ~ 35%

Retail investors: ~ 37%

Professional investors: ~ 28%

KEY FINANCIALS (CONSOLIDATED)

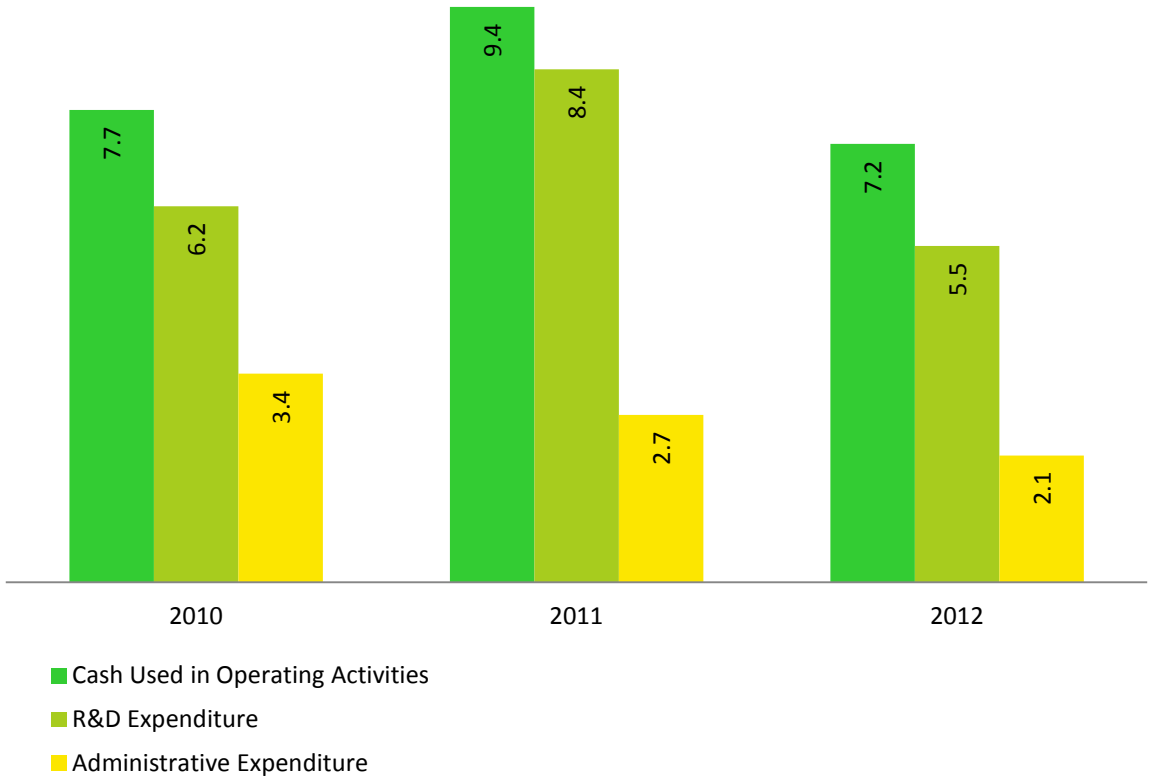
	30 June 12 $000	16 Nov 2012 (unaudited) $000 (excl Syngene)
Cash	16,439	**13,062**
Listed investments (market value)	3,652	**2,426**
Net assets	20,197	
Revenue	1,486	
Operating expenses (incl. R&D, investment related exp's)	(9,048)	
Loss before tax	(7,309)	
Net cash outflows	(5,750)	
NTA per share	**$0.41**	
Cash & listed assets per share	**$0.41**	**$0.32**
Share price	**$0.35**	**$0.38**

FINANCIALS

CASH AND EXPENDITURE

As of 30 June

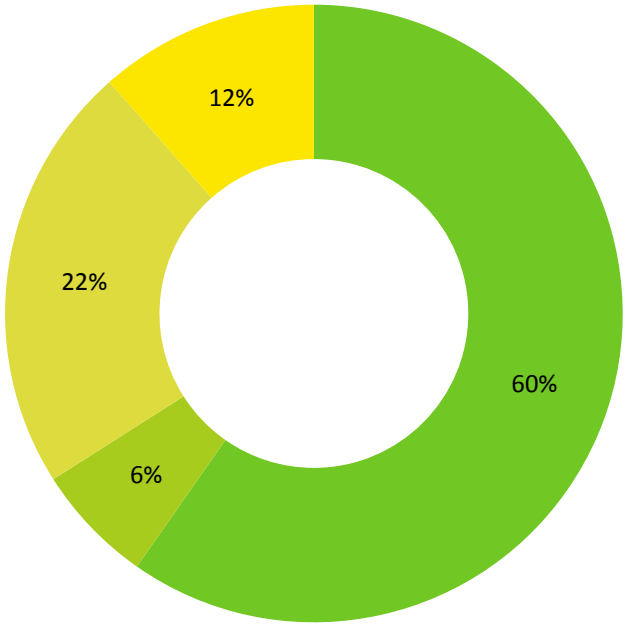
$ Million



A focus on funds going to R&D value generating activity and continued streamlining of business activities to reduce Administrative expenses

FINANCIALS

TOTAL OPERATING COSTS



Research & Development	60%
Patents	6%
Administrative	22%
Other	12%

Our goal is to have a ratio of R&D/IP Expense to Administrative/Other better than 80/20 on an annual basis

FINANCIALS – CASH FLOWS

- Current Cash - $13m (Unaudited) excluding Syngene
- Value of Listed Holdings - $2.4M (Unaudited)
- Conservative Cash Burn 2011/12 and 2012/13 - $6.0M p.a
- Well positioned to achieve key value adding milestones
- Does not take into consideration:
  - Increased R&D Tax Credit
  - Royalties on Sales of Diagnostics
  - Further partnership income
  - Income from divestment of investments

THERAPEUTIC, DIAGNOSTICS &
RESEARCH REAGENT DEVELOPMENT

Ceres Oncology Pty Ltd
Precision Diagnostics Pty Ltd
Opthea Pty Ltd


CERES
ONCOLOGY

Executive Summary

Anti-angiogenic therapies: $30B market (2011)

- Proven efficacy
- Limited by escape and relapse

VGX-100: new treatment to block VEGF-C

- Targets both blood and lymph vessel growth
  - Blocks a treatment escape route for Avastin® (anti-VEGF-A)
  - Enhances existing therapies
- Fully human, monoclonal antibody

Target Indications

- Monotherapy in lymphedema
  - Significant unmet need
  - Rapid development
- Combination with standard of care in oncology, including
  - Glioblastoma multiforme
  - Ovarian
  - Colorectal cancer

CERES ONCOLOGY

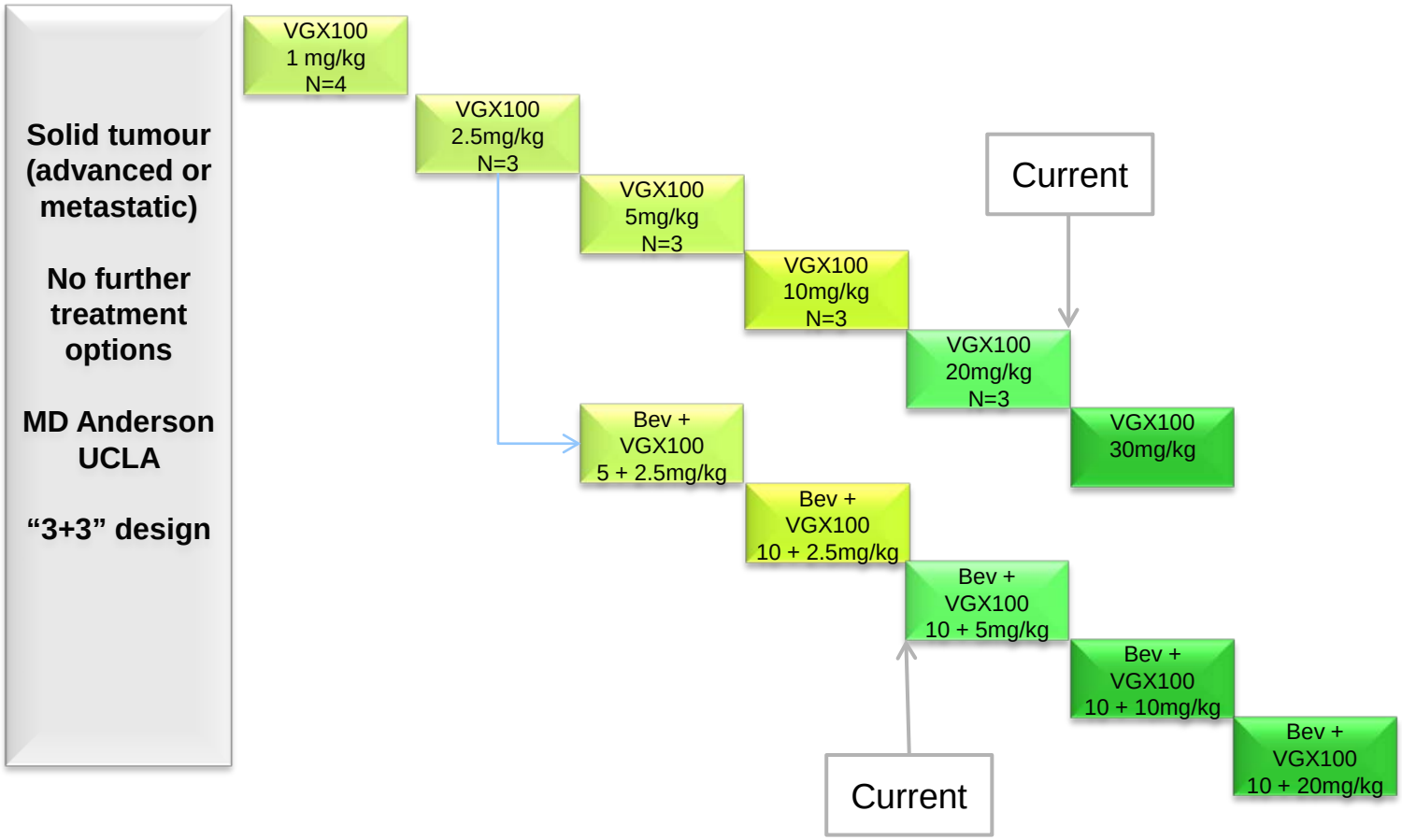
Multiple Indications with important advantages

	Lymphedema	Recurrent Glioblastoma multiforme	Recurrent Ovarian	Metastatic colorectal cancer
Rationale	++	+++	++	+++
Feasibility	+++	++	+++	++
Opportunity	++ (13-65% of breast cancer survivors)	++ (n=22,910 new cases in 2012)	+ (n=22,280 new cases in 2012)	+++ (n=149,600 new cases in 2012)
Lowest Regulatory Hurdle	+++ (likely Orphan)	++	+	++
Speed to proof of concept	+++	++	+++	++
Speed to approval	+++	++	++	+

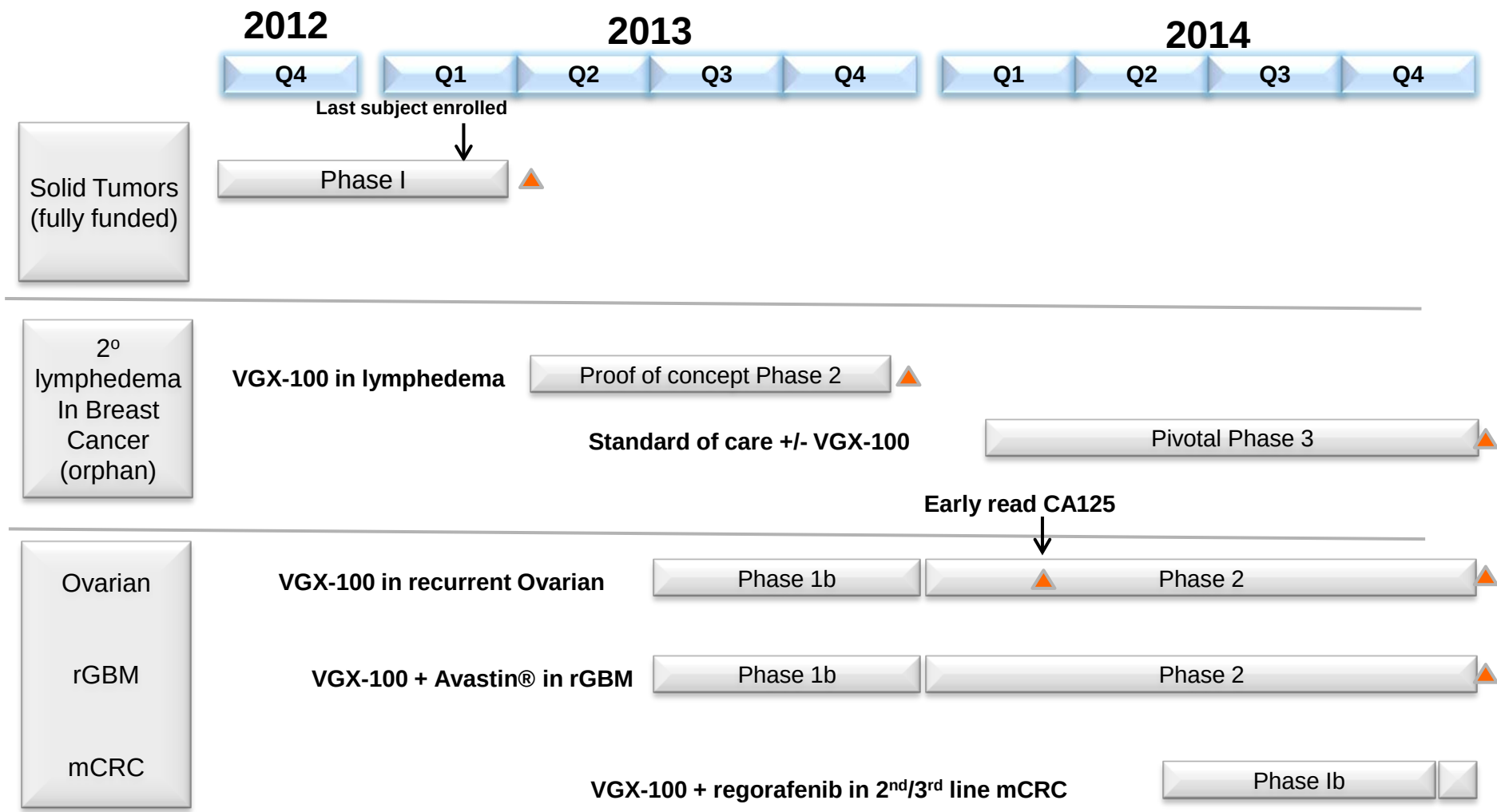
CERES ONCOLOGY

Phase Ia and Ib in a single study

Monotherapy and Avastin® combination evaluation



Forecast Timeline of Potential Value Creating Events

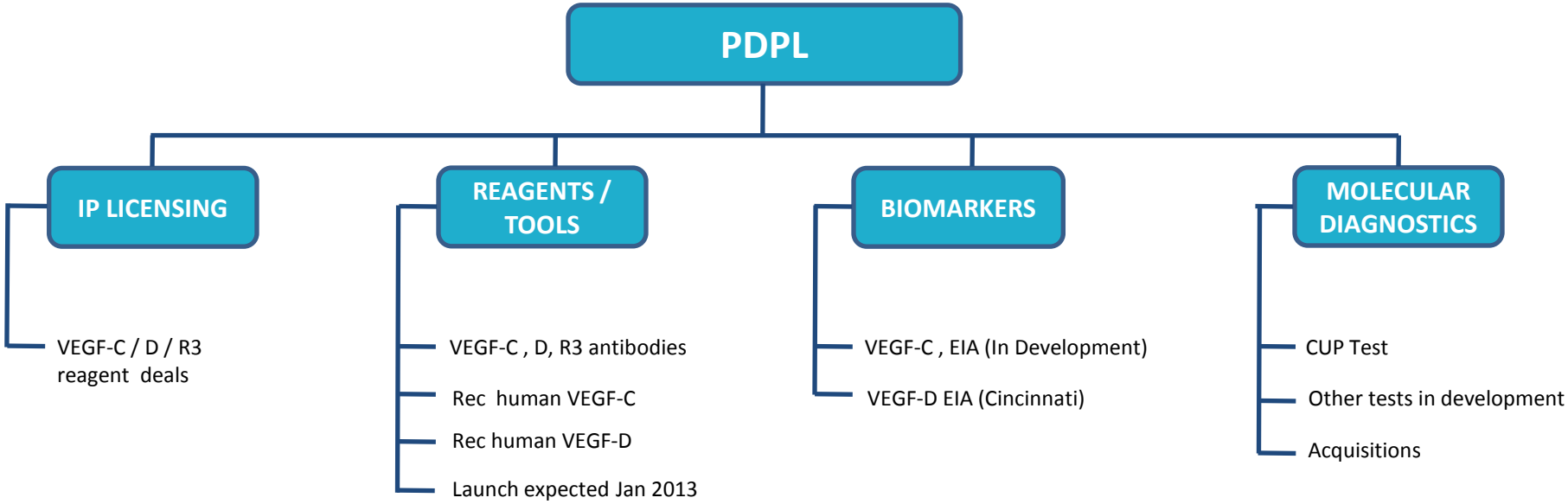


PRECISION DIAGNOSTICS PTY LTD

A research reagents and molecular diagnostics company

Precision Diagnostics
A Circadian Company

Precision Diagnostics Business Model



Development of a Gene Expression Based Assay to Determine the Origin of Metastatic Carcinomas of Unknown Primary.

Keith Byron[1], Lisa Paiman[1], Richard Tothill[2], Evangeline Buela[1], Fan Shi[3], Adam Kowalczyk[3], Robert Klupacs[4], David Bowtell[2]

[1.]Healthscope Advanced Pathology, Clayton, Vic, Australia, [2.]Peter MacCallum Cancer Centre, Melbourne, Vic, Australia, [3.]National (ICT) Australia, The University of Melbourne, Parkville, Vic, Australia, [4] Circadian Technologies Limited, Toorak, Vic, Australia.

Introduction

Carcinomas of unknown primary (CUP) account for 3–5% of all malignancies and are thus among the ten most-frequent cancers worldwide. The prognosis for patients with CUP is poor, with median survival of eleven months from the time of diagnosis. In light of the poor prognosis, morbidity and patient anxiety associated with extensive clinical investigations, the oncologist must decide how far to pursue identification of the primary tumour. However, when a primary tumour has been identified and specific treatment initiated, improved response rates and overall survival has been demonstrated.

Gene expression profiling using microarray technology has been demonstrated to be effective for the classification of cancer. A tumour's gene expression profile is believed to reflect the normal differentiated state of the cell of origin combined with the aberrant gene expression changes associated with disease transformation. It has also been shown that a tumour's gene expression signature is maintained even if the tumour has metastasised to a distant site and closely resembles that of the primary tumour.

Here we present stage one, of the development of a gene expression assay and tumour class prediction model to identify the site of origin of metastatic carcinomas of unknown primary.

Methods

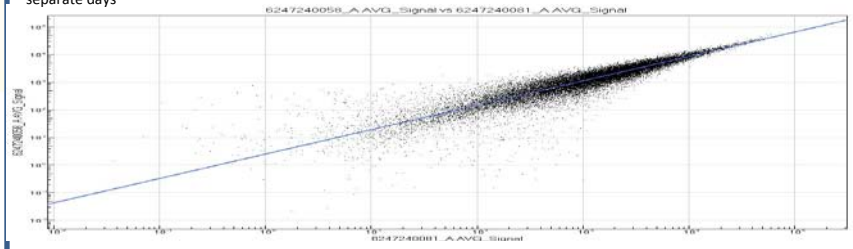
RNA extraction and processing: Seven micron sections of formalin fixed paraffin embedded (FFPE) tissue were first reviewed by a pathologist. Areas on the tissue containing the greatest amounts of tumour were macro-dissected to enrich to at least 80-90% tumour content. RNA from this tissue was then extracted using a modification of the Qiagen RNA Easy FFPE RNA extraction kit. Quantitation of RNA was then determined using the Quant-iT Ribo Green kit (Invitrogen) on a Nanodrop 3300 fluorimeter. RNA quality was assessed by amplifying a fragment (90 bp) of the highly expressed RPL13A ribosomal protein gene by reverse transcription PCR using an ABI7900.

Gene expression determination: Whole genome expression analysis was performed using the Illumina DASL humanHT-12-V4 BeadChip that is able to detect 29,285 coding and non-coding transcripts .
Data analysis: A binary Support Vector Machine was used as the basic classification method together with Recursive Feature Elimination as the feature selection method. To build a prediction model, cross validation on the training expression data was conducted, and the optimal number of genes selected, based on the greatest accuracy achieved.

Results

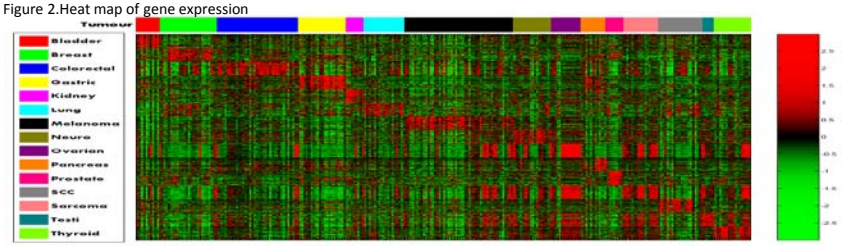
RNA was extracted from formalin fixed paraffin embedded samples containing known metastatic and primary tumours of various classes and varying degrees of differentiation. This set of samples comprised three hundred and ninety nine tumours of fifteen classes. All were analysed as described. To ensure reproducibility of gene expression detection, a control tumour sample was extracted then assayed on several occasions and on different days throughout the project. Figure 2 demonstrates representative raw intensity scatter plots of the control sample RNA run on separate days demonstrating good correlation.

Figure 1. Comparison of gene expression for the same sample extracted and analysed on separate days



To develop a classifier to predict tumour classes, we employed a one-versus-all classification strategy. For each of the 15 tumour classes considered, we built a classifier to distinguish each tumour class from all others. The discriminating probes for each of these 15 classifiers were selected by fitting the training data with a Support Vector Machine (SVM) method. In the testing phase, gene expression data from every tumour sample was tested in all of the 15 classifiers, and accordingly, one score that indicates the similarity of the test sample to a specific tumour class is produced. By comparing the similarity of the test sample to all tumour types, we are able to rank the probability of the test sample belonging to each tumour class.

Figure 2.Heat map of gene expression



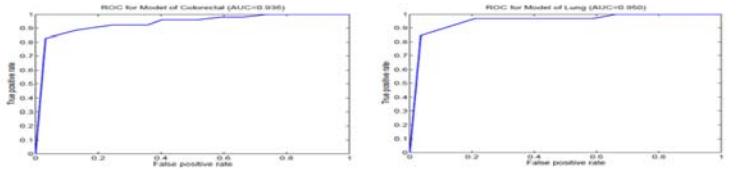
In order to evaluate the accuracy of predictions made by the classifier, we employed a cross validation strategy. To do this, the training data was split randomly into five equal sized subsets, four of which were used to develop the classifier and one is used for testing. The training and testing process strictly follow the method described above, so that we obtain the ranked predictions for each test sample. The process is repeated five times, so that each subset is used for testing once. The accuracy of the predictions was then determined by comparing them with the known tumour types. The results of this strategy are demonstrated in table 1, where both overall accuracies and class-specific accuracies can be seen for the classifiers first prediction. Also demonstrated are the accuracies of the classifier correctly predicting the samples true tumour class in the first two and three predictions.

Table 1 : Classifier accuracies and specificities.

Tumour Class	N	Correct call with first prediction	Correct call within first two predictions	Correct call within first three predictions	Specificity
Overall Average		**83%**	**89%**	**93%**	**98.5%**
Bladder	13	85%	92%	92%	99.7%
Breast	56	79%	93%	96%	96.7%
Colorectal	48	85%	92%	96%	96.4%
Gastric	26	81%	85%	89%	99.2%
Kidney	14	93%	100%	100%	99.7%
Lung	30	83%	97%	97%	97.6%
Melanoma	50	78%	84%	88%	98.8%
Neuroendocrine	18	83%	89%	89%	98.7%
Ovarian	22	77%	96%	100%	98.4%
Pancreas	18	72%	78%	83%	97.7%
Prostate	19	89%	95%	95%	99.7%
Sarcoma	29	76%	83%	86%	96.6%
SCC	27	93%	93%	93%	99.2%
Testi	8	88%	88%	88%	99.7%
Thyroid	21	91%	91%	100%	100%

Area under ROC
The calculated area under the receiver operating characteristic (ROC) curve is a fundamental tool for diagnostic test evaluation. Here we have calculated the average area under the ROC curve across all 15 tumour classes to be 0.95 indicating a test of high diagnostic value. Class examples of ROC curve for both Colorectal and Lung can be seen in figure 3.

Figure 3. ROC curves for Colorectal and Lung tumour classes



Reproducibility of Predictions
To evaluate the reproducibility of the classifier, a single colorectal adenocarcinoma was analysed on four separate occasions. The gene expression data was then submitted to the classifier for prediction scoring. For all four samples submitted, the classifier correctly predicted the class to be "colorectal".

Conclusion

Although further validation is required using a independent test cohort of known metastatic tumours, as well as a cohort of samples from patients diagnosed with CUP, our data suggests that an expression-based diagnostic test could be effective in identifying the tumour of origin in patients presenting with CUP.

PERFORMANCE OF CUPGUIDE IS EXTREMELY GOOD

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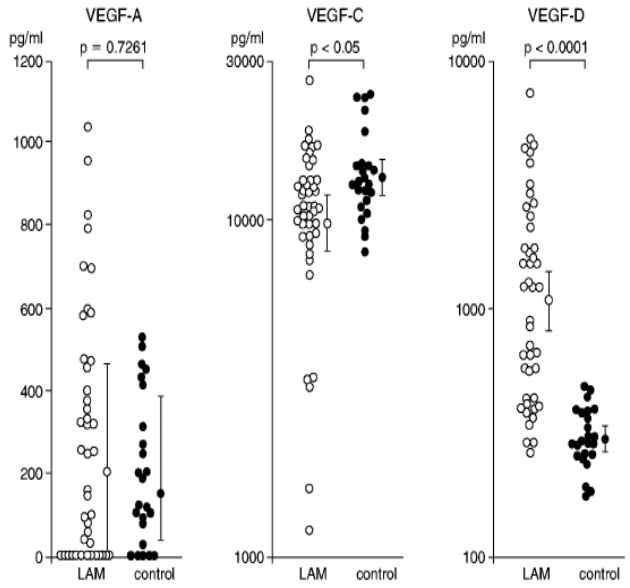
Testi	8	88%	88%	88%	99.7%
Thyroid	21	91%	91%	100%	100%

VEGF-D Diagnostics

- LAM DIAGNOSTIC TEST launched Jan 2011 in the USA under CAP/CLIA waiver.

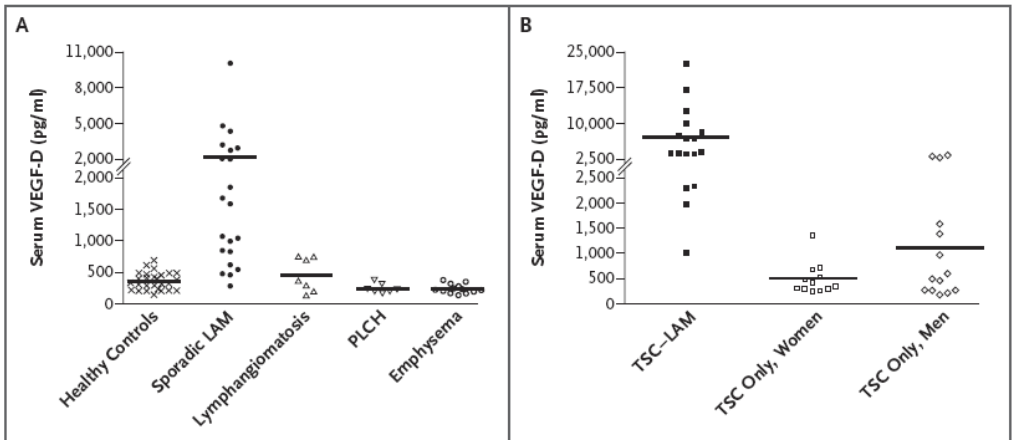
VEGF-D Diagnostics – Respiratory Disease

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

VEGF-D – A biomarker for mTOR therapy?

OPEN ACCESS Freely available online

PLoS one

Multicenter Phase 2 Trial of Sirolimus for Tuberous Sclerosis: Kidney Angiomyolipomas and Other Tumors Regress and VEGF- D Levels Decrease

Sandra L. Dabora[1]*, David Neal Franz[4], Stephen Ashwal[5], Arthur Sagalowsky[6], Francis J. DiMario Jr.[7], Daniel Miles[8], Drew Cutler[5], Darcy Krueger[4], Raul N. Uppot[2], Rahmin Rabenou[8], Susana Camposano[2], Jan Paolini[2], Fiona Fennessy[3], Nancy Lee[9], Chelsey Woodrum[9], Judith Manola[3], Judy Garber[3], Elizabeth A. Thiele[2]

1 Biogen Idec Hemophilia, Weston, Massachusetts, United States of America, **2** Massachusetts General Hospital, Boston, Massachusetts, United States of America, **3** Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America, **4** University of Cincinnati, Cincinnati, Ohio, United States of America, **5** Loma Linda University, Loma Linda, California, United States of America, **6** University of Texas Southwestern, Dallas, Texas, United States of America, **7** University of Connecticut, Hartford, Connecticut, United States of America, **8** New York University, New York City, New York, United States of America, **9** Brigham and Women's Hospital, Boston, Massachusetts, United States of America

EXPECTED NEAR TERM MILESTONES

NEAR TERM MILESTONES

H1
2013

- **VGX-100 Phase 1 trials completed**
- **Ceres Oncology partnership**
- **Reagents Launch**

NEAR TERM MILESTONES

H2 2013

- **Opthea Partnership**
- **VGX-100 Phase 2 studies commenced**
- **IMC-3C5 Phase 1 studies complete**
- **VEGF-C CLIA waivered diagnostic launched**
- **CUPGUIDE Northern Hemisphere registrations lodged**

NEAR TERM MILESTONES

H1

2014

- **VGX-100 Phase 2 oncology studies initial results**
- **VGX-300 IND Filed for “back of eye”**
- **CUPGUIDE FDA approval, CE Mark**
- **VEGF-D Diagnostic FDA approval**

OPTHEA

Development Opportunity for VEGF-C Inhibitors in Wet AMD

Megan Baldwin, PhD
megan.baldwin@circadian.com.au

Opthea Pty Ltd

- Opthea Pty Ltd is a 100% owned subsidiary of Circadian Technologies, developing VEGF-C/-D/VEGFR-3 assets for eye disease.
- 'Seed' investment from Circadian Technologies
- Actively seeking partnership/s
- Developing biologic VEGF-C inhibitors for 'wet' AMD
  - Lead candidate: VGX-300 (soluble VEGFR-3)
  - 'Back-up' programs, 'back-up' candidates

OPTHEA

Wet (neovascular) AMD

The Angiogenesis Foundation

OPTHEA

IMPROVING ANTI-ANGIOGENESIS
A Major Commercial Opportunity

"Age-related macular degeneration (wet AMD) is a worldwide epidemic with an estimated prevalence of 30-50 million that rivals that of Alzheimer's disease and that of all cancers combined."

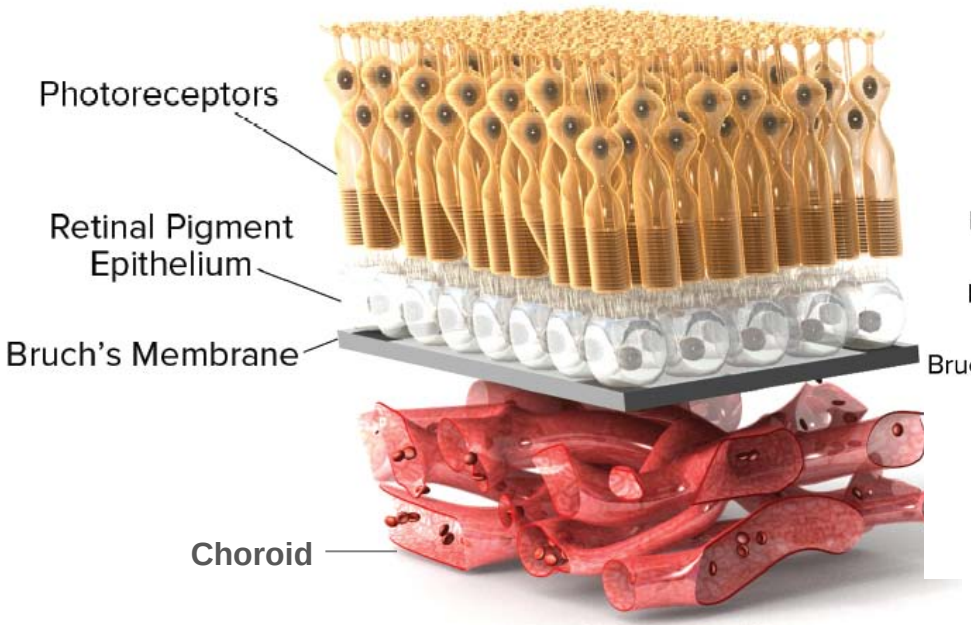
J.Ambati. The Cogan Lecture. IOVS, April 2011

Estimated $US 5 billion market opportunity p.a. in USA alone

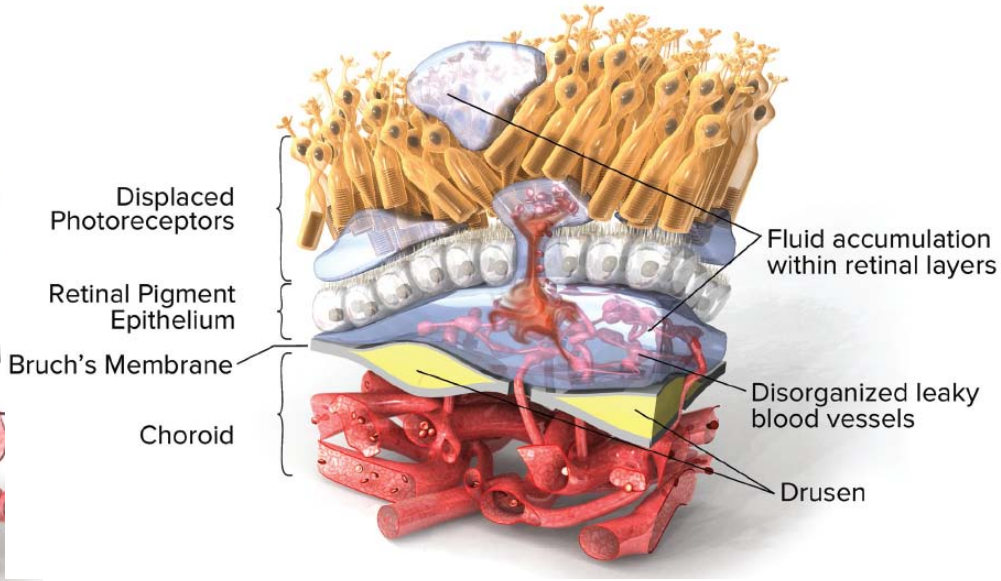
OPTHEA

The Normal Retina and ‘Wet’ (neovascular) AMD

Normal Retina



‘Wet’ AMD



The Angiogenesis Foundation

OPTHEA

IMPROVING ANTI-ANGIOGENESIS
A Major Commercial Opportunity

Existing therapies for wet AMD target VEGF-A but not VEGF-C:

- Only one-third of patients recover driving vision*
- One-sixth progress to registered blindness*

We are targeting 'sub' responders that experience no gain in vision & continue to leak:

- VEGF-C can induce angiogenesis and vessel leakage through the same receptor as VEGF-A.
- Combined VEGF-A/VEGF-C inhibition has the potential to improve patient response.

OPTHEA

* Ambati. IOVS. 52(5), 2011.

Opthea Pty Ltd

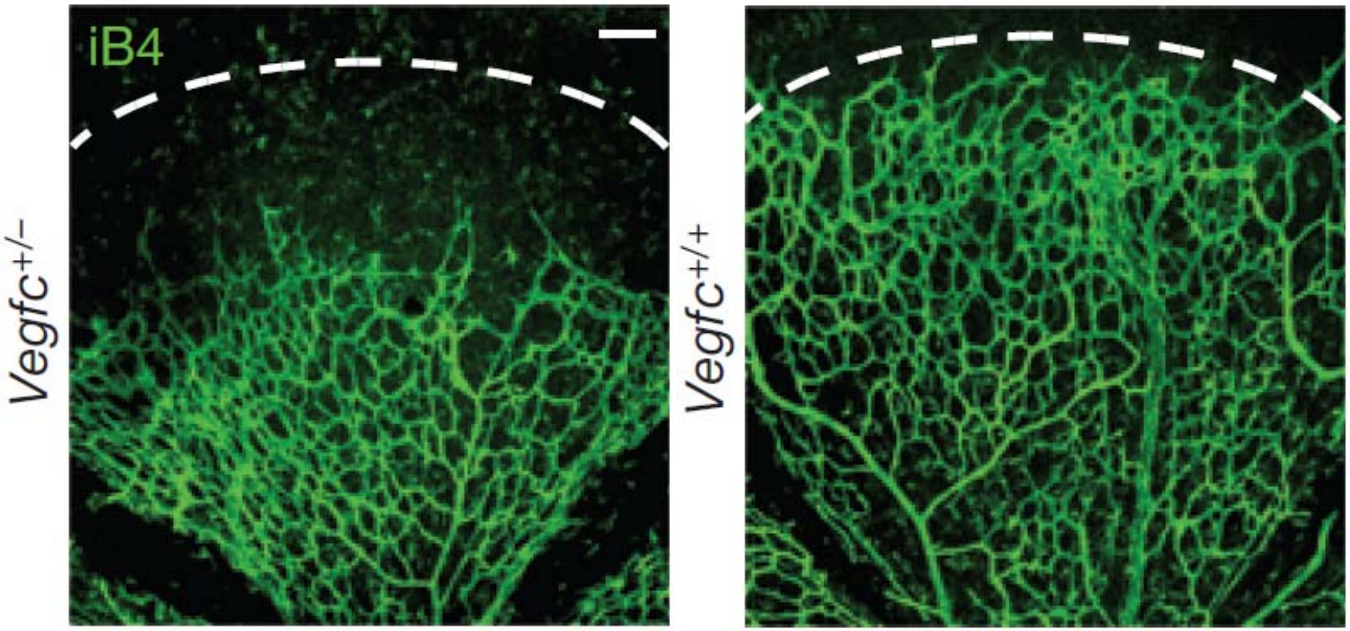
- By combining inhibition of VEGF-C with anti-VEGF-A therapies we aim to improve patient responses:
  - Vision gains
  - Reduce vascular leakage
  - Reduced dosing and visits to doctor

- **Relatively short time (3.5 yrs) to clinical proof of concept**:
  Defined clinical endpoints & efficacy measures in Phase I

- Strong scientific rationale, applicability to other eye diseases (DED, DME, corneal neovascularisation)

OPTHEA

VEGF-C is Required for Retinal Vascular Development

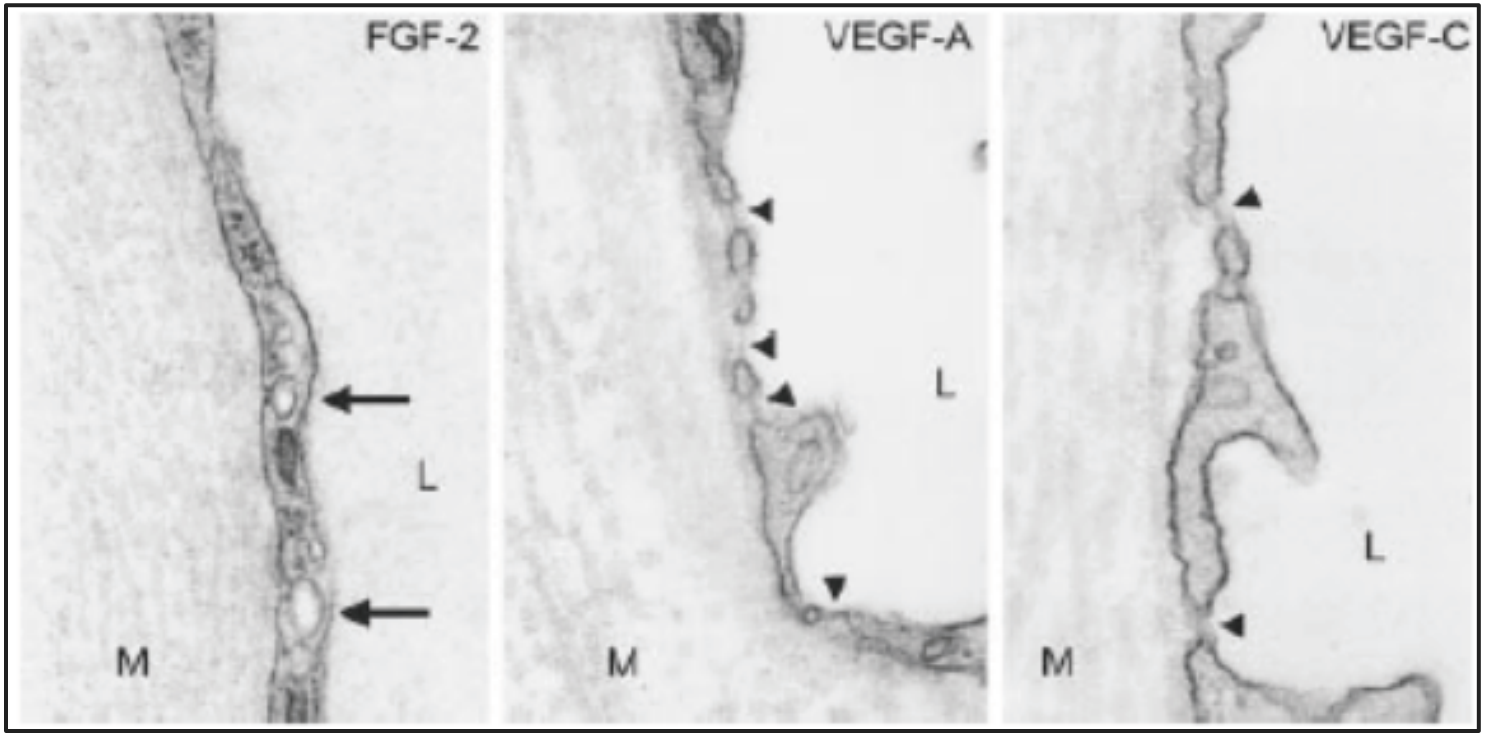


Retinas from P5 VEGF-C+/- mice have reduced vascularity.

Tammela et al., Nature Cell Biology, 2011.

OPTHEA

VEGF-C Induces Vascular Permeability - Contribution to Retinal Vessel Leakage



Cao et al,. Circ Res., 2004

OPTHEA

Development Activities

- We have demonstrated activity in rodent model of AMD
- We have shown comparable ocular biodistribution and PK profile in rabbits to marketed agents – potential for increased dosing interval in clinic
  - Fewer clinic visits & increased compliance
  - Key driver of market use
- Currently generating biomarker data for VEGF-C in ocular diseases
- Manufacture of clinical grade VGX-300 suitable for ocular administration commenced

OPTHEA

Thank-you