OPT-302: 
a VEGF-C/VEGF-D ‘Trap’ for wet AMD

Ophthalmology Innovation Summit, Nov 12 2015

Circadian Technologies
(ASX:CIR, OTCQX:CKDXY)

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Opthea Pty Ltd

- Opthea Pty Ltd is a 100% owned subsidiary of Circadian Technologies (Melbourne, Aust)
- Extensive IP portfolio around members of the Vascular Endothelial Growth Factor (VEGF) family
  - VEGF-C
  - VEGF-D
  - VEGFR-3
- Lead compound OPT-302 inhibits VEGF-C and VEGF-D
  - Potent inhibitor of angiogenesis & vascular leakage
- OPT-302 in development for treatment of wet AMD
- Potential in a range of eye diseases as a monotherapy or in combination with approved anti-VEGF-A therapies
- Phase 1/2A trial actively recruiting wet AMD patients under IND at US clinical sites

<table>
<thead>
<tr>
<th>Key Financial Details</th>
<th>ASX: CIR</th>
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<tbody>
<tr>
<td>Ticker Symbol</td>
<td>ASX:CIR</td>
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<tr>
<td></td>
<td>OTCQX: CKDXY</td>
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<tr>
<td>Share Price</td>
<td>A$0.29</td>
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<td>(Nov 10 2015)</td>
<td></td>
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<tr>
<td>Market Capitalisation</td>
<td>~A$43M (~USD 30M)</td>
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<td>(Nov 10 2015)</td>
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![Pie chart showing investment distribution](chart.png)
Resistance to anti-VEGF-A monotherapy

- Long-term single-agent therapy with VEGF-A inhibitors is associated with sub-optimal response
  - Sub-optimal improvements in VA (<15-letter gain)
  - Persistent fluid on OCT
- Resistance to VEGF-A monotherapy may be related to other VEGF family members
- VEGF-C and VEGF-D bind and activate VEGFR-2 and VEGFR-3
- Complete blockade of VEGFR-2 requires VEGF-A, VEGF-C and VEGF-D inhibition
- VEGFR-3 also stimulates angiogenesis via a VEGF-A independent pathway

- OPT-302 combination therapy with an anti-VEGF-A inhibitor achieves more complete suppression of the VEGF/VEGFR pathway
- Targets functional redundancy and mechanisms of sub-response to VEGF-A inhibition
VEGF-C stimulates angiogenesis and vascular permeability

VEGF-C is required for retinal vascular development

*Tammela et al., Nature Cell Biology, 2011.*

![Image of retinal vascular development with Vegfc⁺/⁻ and Vegfc⁺/⁺ comparisons](image1)

VEGF-C is a potent inducer of vascular leakage

*Cao et al., Circ Res., 2004*

![Image of vascular leakage with FGF-2, VEGF-A, and VEGF-C comparisons](image2)
‘Sub-responsiveness’ to anti-VEGF-A therapy is associated with upregulation of VEGF-C and VEGF-D

- Sub-responsiveness to anti-VEGF-A therapy is associated with upregulation of VEGF-C and VEGF-D expression
  - Lieu et al., 2013; Li et al., 2013; Zhao et al., 2006; Rose et al., 2010; Fan et al, 2011, Grau et al., 2011

- VEGF-C is elevated in the plasma of wet AMD patients compared to healthy volunteers and patients with dry AMD
  - World Congress on Angiogenesis, Boston, 2015, #1509

- VEGF-C is expressed in the RPE of healthy eyes.
- In wet AMD, VEGF-C is expressed in RPE and endothelial cells associated with CNV.
- VEGF-C levels in the retina increase with disease severity.
  - World Congress on Angiogenesis, Boston, 2015, #1509

Mean Plasma Levels of VEGF-C

- Control
- Dry AMD
- Wet AMD

VEGF-C

World Congress on Angiogenesis, Boston, 2015, #1509
OPT-302

- OPT-302: a soluble form of VEGFR-3
- Comprises the extracellular domains 1-3 of VEGFR-3 and the Fc Fragment of human IgG1
- Potent inhibitor of VEGF-C (~5pM) and VEGF-D (~0.5 nM)
- A ‘trap’ that binds and neutralises the activity of VEGF-C and VEGF-D, blocking binding to the receptors VEGFR-2 and VEGFR-3
- OPT-302 PK in rabbit and cyno vitreous humor following IVT similar to aflibercept, prolonged exposure in posterior and anterior segments
- Completed IND enabling safety toxicology studies in cyno & rodents to support Ph 1/2A (IV and IVT administration, single and repeat-dose, monoTx & Lucentis combination)

**ELISA**

**VEGFR-2 bioassay**

**VEGFR-3 bioassay**
OPT-302 has comparable single-agent and additive activity with Eylea® in mouse AMD

Combined inhibition of VEGF-A (Eylea®), VEGF-C and VEGF-D (OPT-302) is more effective than inhibition of VEGF-A alone

Control  
EYLEA™

OPT-302  
OPT-302 + EYLEA®

\[ \text{CNV Area} \]

- Control Antibody
- OPT-302
- Eylea
- Eylea + OPT-302

\[ \begin{align*}
\text{Control} & : 600,000 \\
\text{OPT-302} & : 400,000 \\
\text{Eylea} & : 200,000 \\
\text{Eylea + OPT-302} & : 70,000
\end{align*} \]

* Pairwise comparison: OPT-302 vs Eylea + OPT-302 (p<0.02)
  Eylea vs Eylea + OPT-302 (p<0.05)
A Phase 1/2A Dose Escalation Study Evaluating the Safety, Pharmacokinetics and Pharmacodynamics of OPT-302 in combination with Ranibizumab in subjects with wet AMD

Two stage Design

Part 1 Dose escalation – Open Label

Part 2 Dose expansion - Randomized

Subjects with active CNV associated with wet AMD including those that are either treatment naive or have received prior therapy will be eligible for the study.

IND #: 122162
Sterling IRB study #: 5123 (Approved)
ClinTrials.gov ID#: NCT02543229
OPT-302 Phase 1/2A: Protocol: OPT-302-1001

Dose-escalation & dose-expansion of repeated IVT injections

Phase 1: Dose-escalation (Open-label)

- Cohort 1: OPT-302 (0.3 mg) + Lucentis® (0.5 mg) IVT Q4W x 3
- Cohort 2: OPT-302 (1.0 mg) + Lucentis® (0.5 mg) IVT Q4W x 3
- Cohort 3: OPT-302 (2.0 mg) + Lucentis® (0.5 mg) IVT Q4W x 3
- Cohort 4: OPT-302 (2.0 mg) Monotherapy* IVT Q4W x 3

Phase 2A: Dose-expansion (Randomised)

- 28 Day DLT window

- Follow-up to week 12
- Long term follow-up at Week 24

- OPT-302 (2.0 mg) Monotherapy* IVT Q4W x 3, ~n=15 pts

- *Access to rescue anti-VEGF-A Tx

- Comprises of 4 treatment cohorts of 5 subjects each.
- Should a dose limiting toxicity (DLT) occur, 3 additional subjects will be enrolled in that cohort.
- OPT-302 and ranibizumab given as separate IVT injections (each 0.05 mL) once every 4 weeks at day 1, 29 and 57.
- When used in combination, the ranibizumab IVT injection will be given 30 mins prior to sequential IVT OPT-302.
Primary Objectives:

- To evaluate the safety and establish the dose of OPT-302 administered by intravitreal (IVT) injection in combination with IVT ranibizumab in subjects with wet AMD

Secondary Objectives:

- mean change in central retinal thickness from baseline (SD-OCT)
- mean change in CNV lesion area from baseline (FA)
- mean change in BCVA (ETDRS) from baseline
- mean time to, and number of, retreatment injections of anti-VEGF-A therapy during long term follow-up (week 12 to 24)
- need for ‘rescue therapy’ with ranibizumab in subjects receiving OPT-302 monotherapy
- pharmacokinetics (PK) of OPT-302
- incidence of anti-OPT-302 antibody formation

Exploratory Objective(s):

- To evaluate changes in systemic levels of angiogenesis-related biomarkers
Clinical Advisory Board of internationally recognised and experienced key opinion leaders from Australia and US

Extensive experience in development of novel and FDA approved therapeutics for wet AMD, including Macugen™, Fovista™, Eylea™ and Lucentis™

- Pravin Dugel MD (Retinal Consultants Arizona, Keck School of Medicine USC)
- Mark Gillies MD (Save Sight Institute, Sydney Uni.)
- Peter Campochiaro MD (Johns Hopkins, Wilmer Eye Institute)
- Kameran Lashkari MD (Schepens Eye Research Inst., Mass.Eye & Ear)

Actively recruiting

ClinTrial.gov ID#: NCT02543229
In combination with a VEGF-A inhibitor, OPT-302 achieves more effective VEGF suppression

- OPT-302 is a novel ‘trap’ that blocks the alternative VEGF-C/VEGF-D pathway
- Used in combination, OPT-302 can achieve more effective VEGF suppression and target a key mechanism of sub-responsiveness to existing therapies
- Combination OPT-302 + a-VEGF-A therapy may improve visual acuity outcomes, reduce retreatment rates and lead to larger treatment free intervals for patients
  - Potential for:
    - Improved patient responses
    - Reduced treatment burden
Thank-you

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