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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
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
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

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Discovery</th>
<th>Development</th>
<th>Clinical Phase 1</th>
<th>Clinical Phase 2</th>
<th>Clinical Phase 3</th>
<th>Indication</th>
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<tr>
<td>VGX-100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Solid tumours</td>
</tr>
<tr>
<td>VGX-200 series</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Solid tumours</td>
</tr>
<tr>
<td>VGX-300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Solid tumours and eye diseases</td>
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<tr>
<td>VEGFR3 Abs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Selected tissue tumours - Head &amp; Neck cancers</td>
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<tr>
<td>(ImClone - licensee)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>likely first target</td>
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<tr>
<td>Trinam®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graft patency in dialysis</td>
</tr>
<tr>
<td>(Ark - licensee)</td>
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<td></td>
<td></td>
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</table>

[ImClone Systems Incorporated](#)

[Ark Therapeutics](#)
### Anti-Angiogenic Agents Targeting the VEGF/VEGFR Family

*Competitive environment reflects clinical/commercial potential*

<table>
<thead>
<tr>
<th>Company</th>
<th>Agent/Program</th>
<th>Company</th>
<th>Agent/Program</th>
<th>Company</th>
<th>Agent/Program</th>
<th>Company</th>
<th>Agent/Program</th>
<th>Company</th>
<th>Agent/Program</th>
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</thead>
<tbody>
<tr>
<td>Genentech</td>
<td>Avastin</td>
<td>Regeneron / Aventis</td>
<td>VEGF-Trap</td>
<td>UCB</td>
<td>CDP-791</td>
<td>Pfizer</td>
<td>Suant (Sunitinib)</td>
<td>Taisho*</td>
<td>TSU-68 (SU-9668)</td>
</tr>
<tr>
<td>Circadian</td>
<td>VGX-100 (anti-Veg-F)</td>
<td>Boehringer Ingelheim</td>
<td>BIBF-1120</td>
<td>Taiho</td>
<td>TSU-68 (SU-9668)</td>
<td>Merck</td>
<td>KGaA Anti-VEGF Mab</td>
<td>Bayer Yakuhin</td>
<td>BAY-57-9352</td>
</tr>
<tr>
<td>Circadian</td>
<td>VGX-200 (anti-Veg-D)</td>
<td>Exelixis</td>
<td>XL-880</td>
<td>Bayer Yakuhin</td>
<td>BAY-57-9352</td>
<td>Pfizer</td>
<td>Avitinib</td>
<td>AstraZeneca</td>
<td>Zactima (ZD 6474)</td>
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<tr>
<td>Circadian</td>
<td>VGX-300 (VEGFR-3-Fc)</td>
<td>GlaxoSmithKline</td>
<td>Pazopanib</td>
<td>Merck</td>
<td>L-21649</td>
<td>Pfizer</td>
<td>Brivanib Alaninate</td>
<td>Kirin Brewery</td>
<td>KRN-633</td>
</tr>
<tr>
<td>Novartis / Schering</td>
<td>Vatalanib (PTK787)</td>
<td>Exelixis</td>
<td>XL-880</td>
<td>Bayer Yakuhin</td>
<td>BAY-57-9352</td>
<td>Pfizer</td>
<td>Brivanib Alaninate</td>
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<td>KRN-633</td>
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<tr>
<td>Pfizer</td>
<td>L-21649</td>
<td>Pfizer / Sugen</td>
<td>SU-14813</td>
<td>Novartis / Schering</td>
<td>Vatalanib (PTK787)</td>
<td>GlaxoSmithKline</td>
<td>Pazopanib</td>
<td>Bayer</td>
<td>Dual VEGFR-2 &amp; -3 Inhib.</td>
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<tr>
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<td>Boehringer Ingelheim</td>
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<td>Hoffman-La Roche</td>
<td>RO-4383596</td>
<td>BMS</td>
<td>SU1-408514</td>
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<td>Exelixis</td>
<td>XL-620</td>
<td>Exelixis</td>
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</tr>
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</table>

**Note:** The table above lists companies and their anti-angiogenic agents targeting the VEGF/VEGFR family. The competitive environment reflects the potential clinical and commercial significance of these agents.
Anti-Angiogenic Agents Targeting the VEGF/VEGFR Family

Competitive environment reflects clinical/commercial potential

- Of 58 agents on the market or in development, only 10 are antibody-based drugs
- Avastin is the market leader with >US$7 billion sales
Anti-Angiogenic Agents Targeting the VEGF/VEGFR Family

Competitive environment reflects clinical/commercial potential

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

58

Anti-angiogenic agents marketed or in development

10

Only 10 are antibody-based drugs

4

Are owned or licensed from Circadian
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)

Go to Company video at www.circadian.com.au
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
• 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)
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®
  - 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.

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

“I think this deal will surprise the years, will help pathology laboratories identify the hidden source of secondary cancers.

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.
• 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
Company with strong financial position & shareholder base

Top 10 shareholders: 51.8%

<table>
<thead>
<tr>
<th>Investor</th>
<th>% of issued shares</th>
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</thead>
<tbody>
<tr>
<td>Packer and Co Limited</td>
<td>17.1</td>
</tr>
<tr>
<td>Select Asset Management Ltd</td>
<td>8.1</td>
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<tr>
<td>Ludwig Institute for Cancer Research</td>
<td>5.7</td>
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<tr>
<td>Licentia Ltd</td>
<td>5.6</td>
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<td>Leon Serry</td>
<td>4.6</td>
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<tr>
<td>HSBC Custody Nominees</td>
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<td>Chemical Trustee Limited</td>
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<tr>
<td>Jagen Pty Ltd</td>
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<td>JFF Steven Pty Ltd</td>
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<tr>
<td>Audivac Pty Ltd</td>
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</table>

Total 10 shareholders own 51.8%

Total 20 shareholders own 58.9%

Financial Summary @ 9 July 09

<table>
<thead>
<tr>
<th>Stock code:</th>
<th>CIR</th>
</tr>
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<tbody>
<tr>
<td>Share price:</td>
<td>75c</td>
</tr>
<tr>
<td>Shares issued + deferred issue:</td>
<td>46,396,928</td>
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<tr>
<td>Market cap:</td>
<td>~ $35 mill</td>
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<td>Cash holdings:</td>
<td>$39M</td>
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<tr>
<td>Listed investments:</td>
<td>$5.6M</td>
</tr>
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</table>

Total number of shareholders: ~3,500

Institutions/Funds: ~ 31%
Retail investors: ~ 41%
Professional investors: ~ 28%
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 experiments - all programs

• Updates from key collaboration partners Stanford and Harvard on non-cancer applications

• Key patent grants: USA, Europe, Japan
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