Insights to Fibrosis Drug Discovery & Development

Gary Phillips, Pharmaxis CEO
Bioshares Biotech Summit, July 2017
Presentation Overview

- Mechanism of action - NASH
- SSAO inhibitor (anti inflammatory)
- LOXL2 inhibitor (anti fibrotic)
  - Why target LOXL2?
  - Differentiation against antibody
  - Pre candidate Profile
- What does Big Pharma want?
Drugs targeting NASH → Cirrhosis

- Virus / bacteria
- Diabetes
- High-fat diet

Potential Insults

Quiescent State (healthy liver)

Inflammatory State

Fibrotic State

- Neutrophils
- Macrophage
- Endothelial cells

- PXS4728 SSAO inhibitor
- Reactive oxygen species
- LOXL2 inhibitor

- Activated stellate cell
- Chemo/cytokines

- Collagen
- LOXL2
- MMPs
- TIMP

Collagen Fibrils

- Cross links

Hepatocytes
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SSAO for NASH

SSAO inhibitor PXS4728A sold to Boehringer Ingelheim in May 2015

PXS-4728A

- **Mechanism based inhibitor of SSAO**
  - Small molecule oral drug
  - Important pathway in several inflammatory diseases of the liver, kidney, heart, eye and CNS.

- **Development status**
  - Pharmaxis discovery – patent filed 2012
  - Effective in pre clinical models of NASH and airway inflammation
  - Phase 1 study reported
    - orally bioavailable
    - long lasting enzyme inhibition after single dose
    - progressive dose response
  - Phase 2 NASH trial scheduled Q3 2017

End of Phase 1 deal with Boehringer Ingelheim

- **Potential milestones to approval:** €418.5m (~A$600m)
  - Upfront (May 2015): €27.5m (~A$39m)
  - 1\(^{st}\) Indication (NASH)
    - Commencement of phase 2: €18m (~A$27m) and phase 3: €37m
    - Filing, regulatory & pricing approvals: total €140m (~A$200m)
  - 2\(^{nd}\) indication (commercial in confidence)
    - Commencement of phase 2: €10m
    - Total milestone payments to approval: €195m (~A$280m)

- **Earn-out payments on annual net sales**
  - Tiered percentages increasing from high single digits
  - Plus sales milestones

External validation of PXS drug discovery and ability to negotiate valuable global deals
Boehringer NASH study

Recruitment open

- 150 patients with moderate to severe steatosis
- 4 doses placebo controlled
- 12 week duration
- proof of mechanism and support of dose finding
- safety evaluation in patients with clinical evidence of NASH
- 1\textsuperscript{st} patient in triggers €18m milestone payment.
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Targeting LOXL2 for cardiac interstitial fibrosis and heart failure treatment

Overwhelming link of LOXL2 and fibrotic diseases in humans. Aim is to BLOCK LOXL2 with small molecule.
Simtuzumab versus PXS small molecule

PXS molecules are fast-acting, mechanism-based selective inhibitors
- with higher potency and achieving complete inhibition
- good tissue/cell penetration

PXS-3rd series


Enzyme: R&D Systems recombinant human LOXL2
DAB: diaminobutane
DAP: diaminopentane
Pharmacology: Lead-candidate

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>Pre-candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinact/K_\text{i} \ LOXL2 (h recom)</td>
<td></td>
</tr>
<tr>
<td>Kinact/K_\text{i} \ LOX (bovine native)</td>
<td></td>
</tr>
<tr>
<td>Selectivity</td>
<td></td>
</tr>
<tr>
<td>LOXL2/LOX (Kinact/K_\text{i})</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition pIC_{50}</th>
<th>Pre-candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>r human LOXL2</td>
<td></td>
</tr>
<tr>
<td>r mouse LOXL2</td>
<td></td>
</tr>
<tr>
<td>bovine LOX</td>
<td></td>
</tr>
<tr>
<td>r human LOXL1</td>
<td></td>
</tr>
<tr>
<td>r human LOXL3</td>
<td></td>
</tr>
<tr>
<td>r human LOXL4</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Selectivity pIC_{50}</th>
<th>Pre-candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>r human AOC3</td>
<td></td>
</tr>
<tr>
<td>r human MAO-A</td>
<td></td>
</tr>
<tr>
<td>r human MAO-B</td>
<td></td>
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</tbody>
</table>

100x selectivity vs LOX / LOXL1
No activity against other amine oxidase enzymes
# In vitro ADME: Lead-candidate

<table>
<thead>
<tr>
<th></th>
<th>Pre-candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma stability; Remaining @1hr</td>
<td>Human, Rat, Dog</td>
</tr>
<tr>
<td>Plasma protein binding; % bound</td>
<td>Human, Rat, Dog</td>
</tr>
<tr>
<td>Microsomal stability; Remaining @ 1hr</td>
<td>Human, Rat, Dog</td>
</tr>
<tr>
<td>Hepatocyte stability; Remaining @ 1hr</td>
<td>Human, Rat, Dog</td>
</tr>
<tr>
<td>Cyp inhibition (1A2; 2C9; 2C19; 2D6; 3A4)</td>
<td>Human</td>
</tr>
<tr>
<td>Cell Health Assay: highest conc. survival</td>
<td>HepG2</td>
</tr>
<tr>
<td>Pgp substrate</td>
<td>No development flags</td>
</tr>
<tr>
<td>Permeability (CaCo, MDCK2)</td>
<td>Excellent in vitro ADME properties</td>
</tr>
</tbody>
</table>

Available under CDA
## In vivo ADME: Lead-candidate properties

<table>
<thead>
<tr>
<th></th>
<th>Pre-candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability</td>
<td>Dog – Rat</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>Dog – Rat</td>
</tr>
<tr>
<td>Vss</td>
<td>Dog – Rat</td>
</tr>
<tr>
<td>Excretion urine (parent)</td>
<td>Dog</td>
</tr>
<tr>
<td>Dose linearity in oral absorption</td>
<td>Dog</td>
</tr>
</tbody>
</table>

**Excellent in vivo properties**

**No development flags**
Summary of in vivo studies

• Liver fibrosis
  – CCl₄-induced (Pharmalegacy, Shanghai)
    • 6 wk mouse
    • 4 – 9 wks rat
  – Thioacetamide-induced (Pharmalegacy, Shanghai)
  – Stelic NASH model (SMC, Tokyo)
• Kidney fibrosis
  – Diabetic nephropathy (Kolling Institute, Sydney)
• Cardiac fibrosis
  – Carotic aorta occlusion (CL Laboratory, Baltimore)
  – Ischemia/reperfusion (HRI, Sydney)
• Lung fibrosis
  – Bleomycin-induced (Aragen, San Francisco)
  – Ad-TGF-β-induced (McMaster University, Toronto)
• Cancer
  – Oral cancer (Boston University)

- Studies have shown a consistent reduction in the area of fibrosis.
- Efficacious compounds are from different chemical series, using prophylactic and therapeutic doses between 3-30 mg/kg by once a day, oral gavage.
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Drugs in the clinic targeting NASH

Several large Pharma companies seeking to build competitive portfolios

<table>
<thead>
<tr>
<th>Company</th>
<th>Metabolic modifiers</th>
<th>Anti-inflammatory</th>
<th>Anti-fibrotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>Ph 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genfit</td>
<td>Ph 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galmed</td>
<td>Ph 2/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergan</td>
<td>Ph 2</td>
<td>Ph 2</td>
<td></td>
</tr>
<tr>
<td>Gilead</td>
<td>Ph 2 x 2</td>
<td>Ph 2</td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>Ph 2</td>
<td></td>
<td>Ph 1</td>
</tr>
<tr>
<td>Galectin</td>
<td></td>
<td></td>
<td>Ph 2</td>
</tr>
<tr>
<td>Novartis</td>
<td>Ph 2</td>
<td></td>
<td></td>
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<tr>
<td>AstraZeneca</td>
<td></td>
<td></td>
<td>Ph 2</td>
</tr>
<tr>
<td>Shire</td>
<td>Ph 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td></td>
<td></td>
<td>Ph 1</td>
</tr>
<tr>
<td>Other</td>
<td>Ph 2 x 3</td>
<td>Ph 2 x 4</td>
<td></td>
</tr>
</tbody>
</table>
What program elements add value in a partnering deal for an anti fibrotic?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value Drivers</th>
<th>Pharmaxis LOXL2 program status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease target</td>
<td>Independent validation</td>
<td>Multiple references including Pharma company authored. No clinical PoC.</td>
</tr>
<tr>
<td>Pre clinical proof of concept</td>
<td>2 or more different animal models</td>
<td>9 different models across 5 different diseases. Combination studies planned</td>
</tr>
<tr>
<td>Drug like qualities</td>
<td>No flags</td>
<td>Clean profile</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Ease of use</td>
<td>Oral once a day tablet or capsule</td>
</tr>
<tr>
<td>Patent</td>
<td>Uncomplicated</td>
<td>100% Pharmaxis owned</td>
</tr>
<tr>
<td></td>
<td>Composition of matter</td>
<td>Composition of matter</td>
</tr>
<tr>
<td></td>
<td>As long as possible</td>
<td>2016 filing date</td>
</tr>
<tr>
<td>Cost of Goods</td>
<td>Low</td>
<td>Small molecule with easy synthesis</td>
</tr>
<tr>
<td># Compounds</td>
<td>1 plus backups</td>
<td>2 lead candidates plus back ups</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Wide therapeutic window</td>
<td>Work in progress</td>
</tr>
<tr>
<td></td>
<td>As long as possible</td>
<td>28 day</td>
</tr>
<tr>
<td>Clinical phase</td>
<td>Phase 1 or 2</td>
<td>Planned for phase 1 in 2H 17</td>
</tr>
</tbody>
</table>

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Shareholders & trading

ASX code: PXS

Shareholders (26 May 17)
- Shares on issue: 319m
- Employee options: 10m
- Institutional shareholders ~50%:
  - Australia/NZ: Australian Ethical (10%); Allan Gray (8%); Other (1%)
  - US - BVF Partners (19%); Other (2%)
  - UK - Montoya Investments (6%); Other (3%)

Shares traded to 26 June 17
- Three months: 35m
- Six months: 49m
- Twelve months: 84m

Market capitalisation
- A$80m (26 June 17)