Exceptional pipeline of new medicines targeting G protein-coupled receptors

Breakthrough chemistry for validated, yet previously hard-to-drug, biology

Multiple Phase 1 & Phase 2 clinical programs reporting data during 2014-16

Indications: Alzheimer’s, Schizophrenia, Chronic Migraine, Diabetes, ADHD

World’s leading structure- & fragment-based GPCR discovery platform

Proprietary StaR® technology enables small molecule & biologics discovery

Deals include: Cubist, MorphoSys, AstraZeneca, MedImmune, Takeda

Investors: Clarus Ventures, MVM, Novartis, Takeda, Stanley Foundation

Experienced leadership team in UK & USA / Boston
# Heptares Team

**Directors**
- John Berriman
  - Algeta, Alnylam, Celltech
- Eric Bednarski
  - MVM Life Science Partners
- Richard Henderson
  - MRC LMB, co-founder
- Anja Koenig
  - Novartis Venture Funds
- Michael Steinmetz
  - Clarus, MPM, Roche
- Malcolm Weir
  - Inpharmatica, GSK

**Management**
- Malcolm Weir, CEO & co-founder
  - GSK, Inpharmatica
- Fiona Marshall, CSO & co-founder
  - GSK, Millennium
- Daniel Grau, President
  - CombinatoRx, Cortria
- Barry Kenny, CBO
  - Pfizer, Biofocus, Takeda
- Tim Tasker, CMO & VP Development
  - GSK, Evotec
- Miles Congreve, VP Chemistry
  - GSK, Astex

**Advisors**
- David Brown
  - Pfizer, GSK, Roche
- Elliot Ehrich
  - Alkeremes, Merck
- Richard Hargreaves
  - Merck
- Duncan Higgons
  - Agios, TransForm
- Patrick Humphrey
  - GSK, Theravance
- Paul Leeson
  - AstraZeneca
- Beverly Lybrand
  - Merck
G Protein-Coupled Receptors (GPCRs) Super Family

- Most important family of drug targets in industry
- 375 GPCRs in 3 major subfamilies
- 225 with known ligands, 150 orphan targets
- Compelling biology across wide range of diseases
- Many valuable yet challenging targets still untapped

Many Top-Selling Drugs Hit GPCRs
Heptares Structure-Based Drug Design (SBDD) Approach

- SBDD required to drug notoriously challenging targets
  - HCV protease (Vertex), BRAF (Plexxikon), BACE, HIV Integrase (Merck), BCL3 (AbbVie)
- Previously not applicable to GPCRs due to GPCR protein instability
- Heptares StaR® technology now enables SBDD for GPCRs
  - Unlock un-druggable targets; identify previously inaccessible chemotypes
### Heptares Corporate Deals

<table>
<thead>
<tr>
<th>Company</th>
<th>Description</th>
<th>Deal Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubist Pharmaceuticals</td>
<td>Up to 2 GPCR drug targets for undisclosed indications in acute care</td>
<td>1st target: $5.5M upfront cash + $4M research funding, milestones, royalties</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Small molecule &amp; antibody drugs in multiple therapeutic areas</td>
<td>$180M: $6.25M upfront cash, research funding, milestones, royalties</td>
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<tr>
<td>MedImmune, Inc.</td>
<td>StaR® antigens for antibody discovery, multi-target alliance</td>
<td>Upfront, milestones, royalties</td>
</tr>
<tr>
<td>Shire</td>
<td>Preclinical option deal in CNS</td>
<td>$190M value + royalties; option grant &amp; exercise payments received</td>
</tr>
<tr>
<td>Morphosyn</td>
<td>StaR® antigens for antibody discovery, multi-target alliance</td>
<td>Upfront, milestones, royalties, + retained rights to an antibody drug</td>
</tr>
<tr>
<td>Takeda</td>
<td>Small molecules targeting single GPCR linked to CNS disorders</td>
<td>$100M deal with $7M upfront + milestones &amp; royalties</td>
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<tr>
<td>Novartis</td>
<td>Small molecules targeting a single GPCR nominated by Novartis</td>
<td>$200M deal, including upfront + milestones &amp; royalties</td>
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<tr>
<td>MRC Centenary</td>
<td>Trans-membrane stabilisation &amp; structure determination technologies</td>
<td>Founding &amp; on-going strategic partnership</td>
</tr>
</tbody>
</table>

Additional scientific collaborations with leading academic institutes & disease foundations
## Heptares Product Pipeline

Clinical portfolio of GPCR drugs advancing internally & through new partnerships

<table>
<thead>
<tr>
<th>Program</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
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<tbody>
<tr>
<td>M$_1$ Agonist</td>
<td>Phase 1 + Imaging + Human Cognition Study</td>
<td>Phase 2 Alzheimer’s Disease</td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s / Cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M$_4$ or Dual M$_1$/M$_4$ Agonist</td>
<td>Preclinical</td>
<td>IND Enabling</td>
<td>Phase 1 + Imaging / Pharmacodynamic Model</td>
</tr>
<tr>
<td>Schizophrenia / Psychosis</td>
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<td></td>
</tr>
<tr>
<td>A$_{2A}$ Antagonist</td>
<td>Phase 1 + Imaging + Human Attention Study</td>
<td>Phase 2 ADHD</td>
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</tr>
<tr>
<td>ADHD / Attention Disorders</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CGRP Antagonist</td>
<td>Preclinical</td>
<td>IND Enabling</td>
<td>Phase 1 + Capsaicin Pharmacodynamic Model</td>
</tr>
<tr>
<td>Severe Headache Prophylaxis</td>
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<tr>
<td>GPR39 Agonist</td>
<td>Preclinical</td>
<td>IND Enabling</td>
<td>Phase 1 + Glucose PoC</td>
</tr>
<tr>
<td>Diabetes, Beta Cell Protection</td>
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<tr>
<td>GLP-1 Agonist</td>
<td>Preclinical</td>
<td>IND Enabling</td>
<td>Phase 1 + Glucose PoC</td>
</tr>
<tr>
<td>Diabetes, Oral Small Molecule</td>
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</tbody>
</table>

### Additional Preclinical & SBDD Assets:
- Orexin Antagonists
- mGlu Modulators
- Chemokine Receptors
- Extensive StaR® & Structure Library
Selective Muscarinic Receptor Agonists

- Holy grail profile for 30+ years: activate M₁ and/or M₄ without M₂, M₃
- Activating post-synaptic M₁ in hippocampus & cortex improves memory
  - Dementia in Alzheimer’s, Parkinson’s, Lewy Body dementia & Schizophrenia
- Activating presynaptic M₄ in striatum, cortex & hippocampus treats psychosis by reducing dopamine & glutamate release
  - Schizophrenia, AD Psychosis, PD Psychosis, Tic disorders
- M₁/M₄ dual action for co-morbid cognitive impairment + psychosis
  - Mod-Severe AD (with behavioural/psychological symptoms), Schizophrenia
Muscarinic $M_1$ Agonist for Alzheimer’s Disease

- First-in-class, entered clinical development in 2013
- Clinically validated target; previous pharma compounds discontinued due to insufficient selectivity
- Current SoC prevents breakdown of acetylcholine, yet endogenous levels decline as disease progresses
- $M_1$ agonist targets post-synaptic receptors, independent of endogenous cholinergic input
- Practical strategy vs. recent disease modifying efforts: breakthrough chemistry for target with clear symptomatic efficacy advantage over SoC
- AD: #1 cause of dementia; no cure/prevention; major economic burden; only 2 MoAs approved
- Clinical strategy: Human cognition study + imaging during Phase 1; Phase 2 in Alzheimer’s disease

Multiple X-ray structures drive design of potent & selective agents
**Selective M₁ Agonist Preclinical Cognition Models**

- Scopolamine mimics ACh loss in AD, producing memory loss
- This memory loss is reversed by the Heptares novel M₁ agonist
- *In vivo* PoC for cognitive enhancement
- Donepezil (Aricept) & Heptares M₁ agonist both active
- Cognitive improvement with combination is superior to individual components
- Opportunity as add-on therapy

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**Reversal of Scopolamine Deficit in Passive Avoidance**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Latency (s)</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>200 ± 10</td>
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<tr>
<td>Scopolamine</td>
<td>300 ± 20</td>
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<tr>
<td>Scopolamine + 3 mg/kg</td>
<td>250 ± 15</td>
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<tr>
<td>Scopolamine + 10 mg/kg</td>
<td>220 ± 10</td>
</tr>
<tr>
<td>Scopolamine + 30 mg/kg</td>
<td>200 ± 10</td>
</tr>
<tr>
<td>Aricept (IP)</td>
<td>200 ± 10</td>
</tr>
</tbody>
</table>

**Reversal of Scopolamine Deficit in Passive Avoidance**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>24th recall latency (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine (1mg/kg) IP</td>
<td>-</td>
</tr>
<tr>
<td>HTLB (S) (mg/kg) PO</td>
<td>-</td>
</tr>
<tr>
<td>Donepezil (mg/kg) IP</td>
<td>-</td>
</tr>
</tbody>
</table>

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Muscarinic $M_4$ & Dual $M_1/M_4$ Agonists for Psychosis

- Novel Heptares chemistry unlocks highly validated target for psychosis
- Xanomeline trials in AD & Schizophrenia + KO models validate $M_4$ MoA
- Psychosis in AD, PD, LBD: no drug approved; off-label antipsychotics avoided
- Schizophrenia: urgently needs new MoA with efficacy + superior tolerability
- Co-morbid psychosis + cognitive impairment: ideal setting for dual $M_1/M_4$ agent
- Clinical strategy: Phase 1, Phase 2a Imaging + cognition in Schiz patients

Xanomeline in AD: Significant improvement in vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, compulsiveness, mood swings
**A₂A Antagonist: Novel Non-Stimulant for ADHD**

- Novel non-stimulant agent that selectively enhances dopamine transmission in brain regions linked to ADHD
- Fresh indication for the MoA, with validation in clinical trials, animal models, known receptor biology
- Heptares next-generation A₂A antagonist uniquely combines once-daily QD optimized receptor kinetics, selectivity, potency & novel chemotype advantages
- Older-generation compounds limited or discontinued due to weak potency, poor PK, chemotypes with known furan toxicity risk & other liabilities
- TPP: fast-acting, high efficacy, no titration, unscheduled, safety/tolerability suitable for children & adults
- Projected 20M+ ADHD sufferers in US
- #1 unmet medical need = more effective & better tolerated alternatives to scheduled stimulant drugs
Selective A\textsubscript{2A} Antagonist Validation in ADHD

- Compelling \textit{in vivo} + direct clinical evidence for selective A\textsubscript{2A} antagonism in ADHD
- A\textsubscript{2A} knockout mice have improved working memory in the radial arm maze model
- A\textsubscript{2A} antagonists speed up reaction time in 5CSRT test of attention & impulsivity
- Caffeine & A\textsubscript{2A} antagonist in highly-validated SHR rat model of ADHD reverse deficit in social recognition; A\textsubscript{1} antagonist no effect
- Caffeine benefit mediated by A\textsubscript{2A} yet side-effects due to A\textsubscript{1}, PDEs, GABA
CGRP Antagonists: Prophylaxis for Severe Headaches

- CGRP antagonism disrupts key vasodilation & neuro-inflammation pathway
- Clinically validated in both rescue & prophylaxis
- Heptares potential to deliver first-in-class non-injectable agents: oral and/or intranasal
- Potential for both superior prophylaxis efficacy + superior safety/tolerability vs. current agents
- Chronic migraine: ~25% of migraine patients have 1-3 attacks per week; 5-10% have 3+ attacks per week
- Cluster headache: aka “suicide headache,” multiple excruciating attacks daily for periods of 6-12 weeks; 2-3 bouts per year; chronic form unremitting
- Additional rare/orphan diseases
- Clinical strategy:
  - Capsaicin forearm vasodilation model during Phase 1
  - Efficient Phase 2 enrolling high frequency population
Non-Injectable GLP-1 Agonist for Diabetes

- Injectable GLP-1 agonists offer impressive HbA1c + weight loss efficacy
- Invasive / injectable route of administration remains major barrier to broad use
  - Fear or distaste of needles; reluctance to fill scripts; needles conjure insulin & advanced disease
  - #1 liability cited by physicians, payers, patients
- Non-invasive: 1\textsuperscript{st} choice for new GLP-1 starts
- Heptares first to solve Family B GPCR structures
- Structural insights directly applicable to GLP-1
- NCE agonists identified
- Clinical strategy:
  - Phase 1 includes insulin response to graded glucose infusion in volunteers vs. T2DM patients
GPR39 Agonist: Disease Modification in Diabetes

- New mechanism to stop or reverse beta cell failure in T1DM & T2DM
- Disease modification the #1 unmet medical need & next major frontier in diabetes
  - All diabetes drugs fail, even in combination
  - Diabetes pandemic & disease progression driving significant mortality, morbidity, cost
- Heptares positioned for first-in-class GPR39
  - Novel binding site revealed with StaR® SBDD
  - Low molecular weight agonists identified
- Clinical strategy:
  - Phase 1 includes insulin response to graded glucose infusion in volunteers vs. T2DM patients
  - In vivo models for beta cell mass & function; sustained glycaemic control during washout
Selective Orexin-1 Antagonists for Addictive Craving

- Orexin-deficient narcoleptics do not show modulation of VTA by monetary reward (fMRI)
- OX-1 regulates dopamine in reward pathways
- OX-1 structure with novel Heptares lead agent

- Novel GPCR mechanism to directly inhibit pathological / addictive craving
- Craving the #1 cause of relapse in addiction & compulsive disorders
- Current agents mainly replacement therapies, high failure rates
- Markets with high morbidity & mortality: nicotine, alcohol, binge eating disorder
- Heptares has the first & only crystal structures of OX-1 & OX-2 receptors
- First-in-class industry position with highly potent & selective leads
mGlu5 Antagonists & Family C GPCRs: Neurology

- Radar plot of Heptares mGlu5 PCC properties. A perfect compound hits the bull’s eye
- Heptares has X-ray structures of mGlu5 – defines drug binding
- Heptares agent: QD/low dose with tight PK:PD relationship to avoid Cmax-driven AEs seen in competitors

- New mechanism for broad range of neurological & psychiatric diseases
- Clinically validated in Autism, Dyskinesia, Depression/Anxiety, Migraine
- Heptares leadership in SBDD for mGlu Family C (8 important GPCRs)
- High-resolution X-ray structures of mGlu5 in complex with multiple ligands
- Creation of novel allosteric modulators using antagonist StaR® proteins
- Highly differentiated next-generation drugs with best-in-class properties
- Advantages: superior control over PK:PD; enhanced oral BA; cleaner chemistry lacking toxicity alerts / sites of metabolism; excellent affinity & potency
Superior Drugs Using Heptares SBDD Technology Platform

Perfect Drug Hits “Bull’s-Eye”

- **Heptares $A_{2A}$ Antagonist**
- **Heptares $M_1$ Agonist**
- **Heptares Chemokine Antagonist**
- **Preladenant Phase 3 $A_{2A}$ antagonist**
- **Xanomeline Clinical-stage agonist**
- **Launched Chemokine antagonist**

\[ IC_{50}, \text{ selectivity, LE (Ligand Efficiency), HAC, LLE (Lipophilic Ligand Efficiency)} & \text{ ClogP normalized where } 0-1 \text{ are very good drug-like properties & 4-5 are poor drug-like properties} \]
StaR® Technology For Antibody Discovery

- Scarcity of GPCR mAbs: only one mAb approved to date
- StaR® technology solves key problem: offers stable, quality antigen in pharmacologically specific conformation
- 100 previously untapped mAb GPCR targets across range of diseases (cancer, fibrosis, inflammation, respiratory, pain)
- Leveraging via partnerships; phage + in vivo technology

Unique Structural Insights

In Vivo Efficacy

Stable in Adjuvant

Antibody Partners

MedImmune, Inc.

Morphosys
Pioneering GPCR Antibody Deal with MorphoSys

- Cutting-edge GPCR antibody alliance unites Heptares StaR® antigens with MorphoSys Ylanthia® antibody library and antibody engineering technologies.

- Technology PoC achieved & highlighted in MorphoSys key presentations
  - Stable, correctly folded StaR® antigen greatly increases yield of diverse, specific antibodies

- Highly productive alliance on track to deliver pipeline of novel GPCR-targeted antibody medicines

Flow cytometry screening on target GPCR-CHO cell line to select for primary hits:

- >10 fold over background
- 5-10 fold
- 2-5 fold
- Background

Flow cytometry screen on CHO cell line expressing an irrelevant GPCR to deselect non-target or non-specific antibodies:

© MorphoSys, BPA 6th Annual Congress of Antibodies; 25th-26th April 2014
Heptares Technology Platform

Stabilised Receptor (StaR®)

- Validated pharmacology
- Increased stability

GPCR Structure Determination

- Landmark structure reveals new drug-binding site in Family B GPCRs

GPCR Fragment-Based Design

- FBDD of mGlu modulator; sub-nanomolar affinity with superior PK

Controlling Receptor Kinetics

- Drug kinetics by StaR® using SPR related to X-ray crystal structures

Antigens for mAb Discovery

- Functional or blocking mAbs generated using StaR® antigens
Heptares Technology Platform Highlights

StaR® Technology Validated Across GPCR-ome

33% of World’s GPCR Structures use StaR® Technology

- Antagonist (Inactive state) Conformations
- Agonist (Active state) Conformations

Ligand-stabilised fusions

StaR: Heptares, LMB, LMB/NIH

November 2013
## GPCR Pipeline & Partnership Opportunities

<table>
<thead>
<tr>
<th>Approved, But Superior NCE Needed</th>
<th>Only Injectable Approved, Oral Needed</th>
<th>Clinically Validated, No Drug Yet</th>
<th>Emerging: Biological Validation</th>
<th>New Biology: De-Orphaned</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEUROSCIENCE</strong></td>
<td>D2, S1P1, 5HT1a, GABA-B</td>
<td>M1, M4, A2a, OX1/2, mGluf, D1, 5HT6, H3, Kappa opioid, OT, CRF1, 5HT2c</td>
<td>mGluf2, 4,7, OX1, NPS, GPER, V1a, GalR1, GPR37, ET1</td>
<td>GPR4, GPR7, GPR17, TAAR1</td>
</tr>
<tr>
<td>AD, Sz, PD, LBD, Depression, MS, Insomnia</td>
<td></td>
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<tr>
<td><strong>PAIN &amp; MIGRAINE</strong></td>
<td>Mu opioid, 5HT1D</td>
<td>CGRP, Kappa opioid, AT2, OT, mGluf5</td>
<td>GalR2, EP4, PAR2, LPA1, NMU, NPFF</td>
<td>LPA5</td>
</tr>
<tr>
<td>Migraine, CH, FMS, OA, Neuropathic Pain</td>
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<tr>
<td><strong>METABOLIC</strong></td>
<td>5HT2c</td>
<td>GIP, GCPG, CB1, GPR119, NPY2</td>
<td>GPR81, RXFP3, T1R, NMUR1,2</td>
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<tr>
<td>Diabetes, Obesity</td>
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<tr>
<td><strong>ONCOLOGY</strong></td>
<td>Smo, CCR4, GnRH</td>
<td>FZD7, Kisspeptin</td>
<td>OX1, CCR1,2,5,6 GPER, CCR1,2,7, S1P1, CD97, MC1, CCR5</td>
<td>BBR1-3, LGR5, mGluf5, GPR6A, GPR65, U28, BILF1</td>
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<tr>
<td>Multiple Cancers</td>
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<tr>
<td><strong>CARDIO</strong></td>
<td>AT1, β1, IP, P2Y12, ETA</td>
<td>V1a/V2, GHRH</td>
<td>Urotensin CCR5</td>
<td>Apelin, MAS</td>
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<tr>
<td>HT, Lipids</td>
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<tr>
<td><strong>RESPIRATORY</strong></td>
<td>β2, M3</td>
<td>CRTH2, CCR2, CCR4</td>
<td>P2Y2, VPAC2, FPR1-3</td>
<td>NPS</td>
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<td>COPD, Asthma</td>
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<tr>
<td><strong>INFLAM / GI / GU</strong></td>
<td>M3,β3, CCK, GLP-2</td>
<td>GHRH, CCR1, 2, 9 C5a, 5HT4, Motilin</td>
<td>PAR2, CCR5, FPR2, VPAC1,2, H4, CX3CR1, CCR6, LPA1</td>
<td>CXCR5,6,7, LPA6, GPR35, EBI2</td>
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<tr>
<td>RA, IBD, IBS</td>
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<tr>
<td><strong>BONE</strong></td>
<td>CaSR</td>
<td>PTH, Calcitonin</td>
<td>EP2</td>
<td>RXFP2</td>
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<td>OP, Dental</td>
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<tr>
<td><strong>OPHTHALMOLOGY</strong></td>
<td>FP2α, α2</td>
<td>EP2, CB1/2, SSTR2, FZD4</td>
<td>S1P2, CX3CR1, CCR2,3</td>
<td>GPR91</td>
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<tr>
<td>AMD, Glaucoma</td>
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<tr>
<td><strong>WOMEN’S HEALTH</strong></td>
<td>GnRH</td>
<td>Kisspeptin, NK3, FSHR, OT</td>
<td>GPER, FPR2, CXCR6, PAR2, EP2/4</td>
<td>GPR18, LPA1</td>
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<tr>
<td>Endometriosis, PCOS, Dysmenorrhea</td>
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</table>
Heptares Business Strategy

- Goal: Build the world’s leading GPCR products & platform biotech company
- Comparative advantage: access to previously unattainable GPCR chemistries
- Well positioned: $60M in financing from leading investors; $1B+ in deals with pharma; rich pipeline of high-value drugs
- Now entering next major growth & value inflection phase
- Key priorities:
  1. Portfolio of clinical programs with multiple Phase 1 & Phase 2 milestones over next 24-36 months
  2. Balanced model for both licensing & retaining selected products in clinically tractable specialty indications
  3. Additional deals to harvest StaR® technology into non-dilutive revenue
  4. Spearhead GPCR science & technology for small molecules & biologics
Heptares Therapeutics

**Platform for GPCR SBDD**

- **StaR® Technology**
  - Stable Receptors
  - Any GPCR in any conformation

- **GPCR X-Ray Structures**
  - Library of structures/co-structures

- **Controlling Kinetics**
  - Exquisite on / off-rate control

- **StaR® for Antibody Discovery**
  - StaR® as antigen
  - Overcomes key roadblock
  - Phage + in vivo
  - Functional agonist mAbs
  - Orphans

**Pipeline of Novel GPCR Medicines**

- **Selective Muscarinic Agonists**
  - FIC M1, M4, dual
  - Cognition in AD
  - Psychosis in AD, SZ, DLB
  - Clinical Phase 1
  - Dominant position

- **Adenosine A_{2A} Antagonists**
  - ADHD novel non-stimulant MoA
  - BIC unique A_{2A} antagonist
  - Clinical candidate

- **Oral GLP-1 Agonists**
  - “Victoza in a pill”
  - FIC small molecule agonists
  - Allosteric sites
  - Unique structural insights

- **Selective Orexin Antagonists**
  - BIC Dual Ox1/Ox2 w/ optimised kinetics

- **Small Molecule CGRP Antagonists**
  - Prophylaxis severe headache
  - Cluster, migraine
  - Highly potent & slow dissociating antagonists

- **Selective Mucosterin Agonists**
  - FIC Ox1Selective
  - Anti-craving
  - Addictions

- **mGlu Modulators**
  - BIC mGlu5 NAM
  - Depression, Autism, Addictions
  - QD & optimised PK
  - Fam C GPCRs: mGlu 5, 2, 4, 7
  - Movement disorders, psych

**Pharma Partnerships**

- **Leading capability for structure-guided design of GPCR drugs**
- **Externally validated with both NCE & antibody pharma deals**

**Pipeline of Novel GPCR Medicines**

- **Clinical portfolio of Phase 1-2a programs with data 2014-16**
- **Discovery wave of products in rare/orphan & oncology GPCRs**
Thank You

www.heptares.com

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