Corporate Overview

2012
Heptares Therapeutics

- Breakthrough medicines targeting previously undruggable GPCRs
- $40M from leading venture investors since 2009
- Major R&D partnerships with multiple large pharma companies
- Structure-Based Drug Design for GPCRs, enabled for the first time by StaRs® (Stabilised Receptors)
- Leading GPCR capability in industry, integrating chemistry & structural biology
- Engine creating both small molecule NCEs and antibody therapeutics
- Exceptional pipeline of investigational medicines for serious diseases
GPCRs: Target Superfamily Linked to Many Disorders

- 375 GPCRs across 3 Major Subfamilies (A, B, C)
- 225 with Known Ligands, 150 Orphan Targets
- Linked to Many Diseases Across Therapeutic Areas
GPCRs: Important Source of Important Drugs

Top 200 Brand Name Drugs by US Retail Sales in 2010

2010 Top Selling Drugs:
6 of Top 10 Hit GPCRs
60 of Top 200 Hit GPCRs
Untapped Opportunity: Historically Undruggable GPCRs

- No successful NCEs to multiple validated & high-value targets
  - M₁, Ox₁, CGRP, D₁, GLP-1, Glucagon, VIP, FSH, PTH
- Scarcity of quality drug-like chemotypes \(\rightarrow\) high failure rates
  - Ox₁/₂, mGlu₅, mGlu₂, CRF₁, MC₄, Neuropeptides, C3a, GnRH, Lipid
- Poor yield from conventional empirical screening paradigm
  - HTS yield low quality
    - Only 1 GPCR drugged per year in last 10 years
- Structural information suggests GPCRs intrinsically druggable
- Structure-Based Drug Design (SBDD) approach needed, yet historically blocked by protein instability
StaRs® Enable Structure-Based Drug Design Approach

- Receptor embedded in cell membrane, highly unstable when removed
- Aggregates and loses function when purified in detergent
- Stabilised StaR® receptor purified and used for drug design (like a kinase)
Heptares Solves First Family B GPCR Structure

- 50-receptor Family B includes many important drug targets
  - GLP-1, PTH, Glucagon, CGRP
- CRF-1 (anxiety/depression) 7TM domain solved at high resolution with bound antagonist
  - Major differences to Family A
  - Useful modelling of Family B enabled for the first time
- Fundamental advance opening up new avenues for drug design
  - Driver for in-house GLP-1 agonist programme

X-ray diffraction to 2.6Å
Leading GPCR Discovery Capability in Industry

First GPCR SBDD Candidate
Adenosine $A_{2A}$ Antagonist for Neurology

First Biophysical Map
Biophysical Mapping: ZM241385 bound to $A_{2A}$

First Fragment Screens

First Leads from Fragment Screens (e.g. Intractable Peptide GPCR)
Heptares Major Partnerships

**Heptares Achieves Key Milestone and Receives Payment from GPCR Drug Discovery Agreement with Novartis Option Fund**

StaR® Technology Provides First-Ever Stabilisation of GPCR Target Nominated by Novartis and Enables Structure-Based Drug Discovery Programme

Welwyn Garden City, UK, 25 January 2011 – Heptares Therapeutics Ltd, a drug discovery company creating new medicines targeting G-protein coupled receptors (GPCRs), announced today that it has successfully generated a stabilised receptor (StaR®) to a GPCR target nominated by Novartis using Heptares’ proprietary StaR technology. For the first time, this important target will be accessible to structure-based drug discovery technologies and approaches, thereby presenting opportunities to discover completely novel drug leads against the target. By achieving this drug discovery milestone, Heptares will receive its first milestone payment from the Novartis Option Fund, under the terms of the option agreement signed by the two companies in 2009.

**Heptares and Takeda Initiate Drug Discovery Collaboration Focused on GPCR Linked to CNS Disorders**

Deal includes £4.5 million upfront cash and equity, up to £80.5 million in future milestone payments, and royalties on product sales

UK and Japan, 11 April 2011 – Heptares Therapeutics and Takeda Pharmaceutical Company today announced the formation of a two-year drug discovery collaboration focused on a single G-protein coupled receptor (GPCR) that plays an important role in the pathology of central nervous system disorders. This GPCR has proved intractable using historical drug discovery efforts, due to its instability when removed from cell membranes and the resulting lack of insight into its structure. A new medicine targeting this GPCR would be first-in-class.

**Heptares Therapeutics Grants Shire an Exclusive Option to License Novel Adenosine A2A Antagonist**

Best-in-Class Candidate with Potential in Treatment of CNS Diseases

Welwyn Garden City, UK, 9 May 2011 – Heptares Therapeutics today announced it has signed an exclusive option agreement with Shire Pharmaceuticals for a novel adenosine A2A antagonist discovered by Heptares and currently in preclinical development. Adenosine A2A is a G-protein coupled receptor (GPCR) involved in the regulation of dopaminergic pathways in the brain. Recently, inhibition of the A2A receptor has been proved to be clinically effective in treating symptoms of Parkinson’s disease and may offer benefits in additional CNS diseases.

**AstraZeneca and Heptares Collaborate to Investigate Important GPCR Drug Targets**

Alderley Park and Welwyn Garden City, UK, May 31, 2011 – AstraZeneca and Heptares Therapeutics today announced they have entered a four-year collaboration focused on the potential discovery and development of new medicines targeting G-protein coupled receptors (GPCRs).

- New drug discovery + product licensing deals
- Small molecule + antibody applications
- Significant non-dilutive capital to advance pipeline
# Heptares Product Pipeline

<table>
<thead>
<tr>
<th>GPCR</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Indication(s)</th>
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<tbody>
<tr>
<td>Muscarinic M1</td>
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<td>Alzheimer’s Disease, Schizophrenia</td>
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<tr>
<td>Orexin 1</td>
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<td>Binge Eating, Nicotine Addiction</td>
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<td>Chronic Insomnia</td>
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<td>GLP-1</td>
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<td></td>
<td>Type 2 Diabetes (First Oral NCE)</td>
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<td>GPR39</td>
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<td>Type 2 Diabetes (Disease Modifying)</td>
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<td>mGluR5</td>
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<td>Autism, Dyskinesia, Depression</td>
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<td>CGRP</td>
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<td>Migraine Treatment &amp; Prophylaxis</td>
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<td>Adenosine A2A</td>
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<td>CNS Disorders</td>
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<td>Takeda</td>
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**Non-Confidential**
First GPCR Candidate Wholly Derived from SBDD

- Superior adenosine A$_{2A}$ antagonists
- Entirely novel chemotypes
- Candidate licensed to Shire
- Treatment of multiple neuro disorders
- Radical binding mode with highly optimised receptor interactions

- Features
  - Non-furan, non-xanthine
  - Very low molecular weight
  - Relatively polar

- Benefits
  - Attractive safety profile
  - Improved oral bioavailability and PK
  - Excellent *in vivo* efficacy

Alzheimer’s Disease

- Most prevalent form of dementia in elderly
  - Leading cause of disability, nursing home admissions, death
  - Aging boomers driving epidemic: >10M in G7 by 2020
  - Presently no cure, no prevention
  - Familial / Early Onset AD strikes in prime of life (5-10% of AD)
  - 30-50% with co-morbid psychosis symptoms

- Acetyl-cholinesterase inhibitors (AChEIs) are SoC
  - Inhibit breakdown of ACh, an endogenous non-selective muscarinic agonist
  - Multiple $B class used by patients desperate for improvement

- AChEIs exhibit modest and transient efficacy
  - Require presence of ACh, which declines as neurons die

- AChEIs exhibit dose-limiting side effects
  - GI disturbances (pain, nausea, diarrhoea, vomiting)
  - Largely mediated via activation of M_2 and M_3 subtypes
  - M_2 activation may also impair cognition (↓ ACh release)

New York Times: A photo taken at the Reiswig family reunion in Perryton, TX., in August 1959. Of the 14 siblings, 10 carried a genetic mutation that causes early-onset Alzheimer’s, and all 10 died from it. The odds that their children will also have the mutation are 1 in 2.
Opportunity for Selective Muscarinic Agonist

- Activate desirable subtypes (M₁, M₄), without activating undesirable subtypes (M₂, M₃)
- Holy grail profile in neuroscience for 30 years
- Superior efficacy:
  - Independent of endogenous cholinergic input
  - Not constrained by dose-limiting side effects
- Superior safety and tolerability:
  - No M₂ and M₃ mediated side effects
  - No non-muscarinic receptor side effects
- Emerging evidence of disease modification
- Strong reimbursement -> delay nursing home
- Projected sales = 1-3 x Aricept peak = $4-12B

**Potential Indications**
- Alzheimer’s disease
- Schizophrenia
- PD dementia
- Lewy body dementia
- MS cognitive impairment
- Mild cognitive impairment
- Down syndrome
- Traumatic brain injury
- Vascular dementia
- Biswanger’s dementia
- ADHD
- Autism
Heptares Selective Muscarinic Agonists

- Activation of $M_1$ w/out $M_2$ or $M_3$
- Dial up or down $M_4$ (anti-psychotic)
- Confirmation in animal models
- Excellent PK and safety profile
- Multiple chemotypes, SAR insight

Phospho-ERK1/2 in CHO-hMX cells

HTL-B reverses scopolamine-induced deficit in passive avoidance in rats ($ED_{50} \sim 10$ mg/kg)
Heptares Management Team

- **Malcolm Weir, CEO and Founder**
  - CEO Inpharmatica
  - Glaxo, VP Molecular Sciences Division

- **Fiona Marshall, CSO and Founder**
  - GSK, Millennium
  - Expert in GPCR biology and pharmacology

- **Daniel Grau, President**
  - CEO Cortria, COO CombinatoRx
  - Corporate and Commercial Development

- **Barry Kenny, CBO**
  - Pfizer, Biofocus, Takeda Cambridge
  - CNS and GPCR drug discovery

- **Miles Congreve, Head of Chemistry**
  - GSK, Astex Director of Chemistry
  - Leader in structure/fragment-based design

- **David McGibney, CMO and Head of Development**
  - Pfizer, SVP & Head of EU R&D
# Heptares Board of Directors & Advisors

## Directors

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<thead>
<tr>
<th>Name</th>
<th>Company/Institution</th>
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<tr>
<td>John Berriman (Chair)</td>
<td>Algeta, Alnylam, Celltech</td>
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<td>Malcolm Weir (CEO)</td>
<td>Inpharmatica, Glaxo</td>
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<td>Michael Steinmetz</td>
<td>Clarus, MPM, Roche</td>
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<td>Eric BednarSKI</td>
<td>MVM Life Science Partners</td>
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<td>Anja Koenig</td>
<td>Novartis Option Fund</td>
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<td>Richard Henderson</td>
<td>MRC LMB</td>
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## Advisors

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<tr>
<td>Richard Henderson</td>
<td>MRC LMB, Founder</td>
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<tr>
<td>Beverly Lybrand</td>
<td>Merck</td>
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<tr>
<td>David Brown</td>
<td>Pfizer, GSK, Roche</td>
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<tr>
<td>Jon Mason</td>
<td>Lundbeck, Pfizer, BMS</td>
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<td>Elliot Ehrich</td>
<td>Alkermes, Merck</td>
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<td>Gebhard Schertler</td>
<td>Paul Scherer Institute</td>
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<td>Mike Tarbit</td>
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<td>Patrick Humphrey</td>
<td>Glaxo, Theravance</td>
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<td>Chris Tate</td>
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<td>Paul Leeson</td>
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<td>Mervyn Turner</td>
<td>Merck</td>
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