Dementia Consortium

Launch event presentation
Agenda (London)

• January 30th, British Library Conference Centre

• 10:30  Registration opens w/ tea+coffee
• 11:00  Dementia Consortium presentation
• 12:00  Q&A session
• 12:30  Networking lunch and close
Welcome

Dr Eric Karran, ARUK
Alzheimer’s Research UK

• ARUK Strategy – past, present and future.

• Dementia Consortium
What is Alzheimer’s Research UK doing?

• ARUK is the major AD funding charity in the UK (second to the US Alzheimer Association world-wide).

• We have spent >£50million to fund 480 projects

• Our current expenditure is £21million on 121 projects

![Bar chart showing the number of publications on dementia research in 2012 for various organizations.](chart.png)
ARUK research strategy: 2012

- Basic research into disease mechanisms
- Brains for Dementia Research
- Clinical research to find better ways to assess and diagnose dementia diseases

ARUK funding

Patient benefit
ARUK research strategy: 2013

Basic research into disease mechanisms

Targeted research into critical disease mechanisms

Clinical research to find better ways to assess and diagnose dementia diseases

New potential targets for drugs

Seeding drug discovery initiatives on new targets

Longitudinal study of AD to define disease trajectory and identify subjects suitable for entering trials for new and existing drugs

Clinical proof on concept study in selected populations

New ways to assess drug effects on disease

Effective drugs for Alzheimer’s disease and other dementias – *right drug, right patient, right time.*
Basic research into disease mechanisms

Targeted research into critical disease mechanisms

Clinical research to find better ways to assess and diagnose dementia diseases

New potential targets for drugs

New potential targets for drugs – world wide

Investigational drugs

ARUK Dementia Consortium

ARUK Stem Cell Institute

Crack-it Untangle

Longitudinal study of AD to define disease trajectory and identify subjects suitable for entering trials for new and existing drugs

Clinical proof on concept study in selected populations

ARUK Drug Discovery Institute

Effective drugs for Alzheimer’s disease and other dementias – *right drug, right patient, right time.*
Dementia Consortium
Advancing New Targets In Neurodegeneration

• To accelerate bringing benefit to patients
• To close the gap between academia and Pharma
• To connect the ARUK and MRC-T academic networks with drug discovery expertise and enabling tools and reagents plus quantitative biology.
• To enable academic researchers to advance their innovation towards patient benefit
• To enable academics and pharma to establish a relationship based on shared understanding of data to facilitate future interactions
Role of ARUK

• To fund the Dementia Consortium, and catalyze funding from pharma

• To assist with logistics and publicity

• To help bridge the gap
Introduction: Eisai

Dr Lee Dawson
Eisai Global Network

- Japanese company founded in 1941
- Global presence with R&D sites in Japan, UK & USA
- Major therapeutic areas Neuroscience and Oncology
Eisai in Europe

- Coverage throughout E.U.
- Regional Headquarters for EMEA&R region sited in the UK

European Knowledge Centre
  - Commercialisation, Manufacturing
  - Neuroscience & General Medicine

Product Creation Unit (NGM-PCU)
  - Global Open Innovation
Eisai Statistics & Products

• R&D expenditure: 126 Billion Yen* (approx. 1 Billion GBP)
  * March 2012 annual report

• Worldwide employees: ~10,000
  – UK employees: ~400

![Aricept](image1.png)
![Halaven](image2.png)
![Zonegran](image3.png)
![Fycompa](image4.png)
Current collaborations in the UK/EU

- Studentships
- Research Collaborations
- Consortia

- Bristol
- Imperial College London
- Kings College London
- Leeds
- Manchester
- Nottingham
- Strathclyde
- York

- Pharmacog
- Innovative Medicines Initiative
Open Innovation
Collaborative Opportunities for academic-industrial partnerships

- UK based Open Innovation team is a dedicated group looking to form truly collaborative alliances

- Academic and SMEs researchers across the UK and EU at all stages of research and drug development

- Disease areas: neuroscience, metabolism, inflammation and general disease processes

- Entrepreneurial alliances to translate basic research into targets to be developed into truly novel therapeutics for patients.
Introduction: Lilly

Dr Michael Hutton
Lilly in the Dementia Consortium

Michael Hutton
CSO Neurodegenerative Diseases
Neuroscience Research at Eli Lilly and Erl Wood

- Neuroscience at Eli Lilly is focused on three areas:
  - Neurodegeneration (Alzheimer’s)
  - Psychiatry (Schizophrenia and Depression)
  - Pain

- Erl Wood is Lilly’s biggest research operation outside of the US. We have invested more than £120M in the site in the past 10 years.

- Today, the site is a centre of excellence for Neuroscience (Alzheimer’s and Psychiatry).

- There are 650 staff at Erl Wood, from over 50 different countries, including 400+ scientists.
Alzheimer’s Disease
Current Portfolio Strategy

1. Highest priority: Aβ and β-Amyloid

2. Target Tau as a second approach to disease modification

3. Identify and develop targets for symptomatic relief
Disease Modification
Targeting multiple stages in the amyloid cascade

APP

BACE

BACE inhibitors

Production of Aβ

γ-secretase

Aβ42 monomers

Oligomers

β-amyloid deposits

Tau targets (pathogenesis)

Tau antibodies

Small molecule targets

Anti-Ab mAb: Soluble Aβ

Anti-Ab mAb: Selective targeting of deposited β-amyloid

Clearance mechanisms

Neuronal loss

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Lilly in the Dementia Consortium

What are we interested in?

- Targeting the Aβ-tau interaction
- Mechanisms of Neurotoxicity
  - Aβ related toxicity
  - Tau related toxicity
  - Other mechanisms
- Tau pathogenesis and spreading
  - Accumulation of misfolded/aggregated tau
  - Trans-synaptic spreading
- TREM2/TYROBP and related “inflammatory” mechanisms
- Targets for improved symptomatic therapies
  - Cognitive symptoms
  - Psychiatric symptoms
- **Less interested in:**
  - Targets to block Aβ or β-amyloid production/generation
26 years of Lilly Alzheimer’s Research
1988-2014

- 1906 Describing AD
- 1984 Amyloid Hypothesis
- 1988 Lilly Enters AD
- 1991 Genetic Validation of Amyloid Hypothesis
- 1995 APP Transgenic Mouse
- 1999 Abeta Vaccination
- 2000 Semagacestat Enters Pipeline
- 2004 Solanezumab Enters Pipeline
- 2008 BACE Inhibitor I Enters Pipeline
- 2010 BACE Inhibitor II Enters Pipeline
- 2012 Amyvid™ Approved in U.S.
- 2012 Solanezumab Phase III Results

- 1982 Cholinergic Hypothesis
- 1987 Cloning APP
- 1990 Xanomeline Work
- 1995s Gamma & Beta Secretase Inhibitors
- 1998 Tau Mutations
- 2000 Scios Collaboration
- 2004 In Vivo Understanding of AD
- 2004 Avid is Founded
- 2009 BACE Inhibitor I Terminated
- 2010 Semagacestat Results
- 2012 Genetic Validation for Blocking BACE
- 2013 Amyvid™ Approved in EU
- 2013 Lilly Announces Tau Programs
Introduction: MRCT

Dr Justin Bryans
Forming partnerships to drive early stage scientific research to the patient.

- MRC heritage established 2000
- CHARITY status
- 120+ staff
- MRC
- DRUG DISCOVERY
- PHARMACEUTICAL BIOTECHNOLOGY Markets
- ACADEMIC AND NON PROFIT Institutions
- 2 DRUGS On market
- 11 drugs in clinic
- SM and Ab research
- UNMET NEED
- NEW Partnerships
- 2 drugs On market
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- MRC
- DRUG DISCOVERY
- PHARMACEUTICAL BIOTECHNOLOGY Markets
- ACADEMIC AND NON PROFIT Institutions
FORMING PARTNERSHIPS

RESEARCH

COLLABORATION

UNMET HEALTHCARE NEEDS

PATIENT

MRCT

PHARMA / BIOTECH
EARLY DRUG DISCOVERY SPECIFIC CAPABILITIES

Assay development and high quality compound collection
Cellular pharmacology
Medicinal chemistry plus in silico and ADMET
Antibody Engineering
Structural biology and CRO network
Collaborative ethos
Project management

Increasing knowledge and compound sharing since 2010
Provided 69 screening libraries
29 Virtual screens
480 Probe compounds
54 Publications and 42 podium talks
CENTER FOR THERAPUTICS DISCOVERY

WHY US?

- Assay Development
- Screening
- Medicinal chemistry and Therapeutic Antibody group

- 2 marketed drugs
- 11 in clinical development
- Tool compounds and Abs
- Publications
- Grant applications

- De-risking the target
- Access to the best techniques for positive outcomes
- Compound library, diversity sets and pharmacy links

- Constructing a pharma quality data package
- Profile of compounds and antibodies
- Work in collaboration

UNMET NEED

Academic research translation
De-Risking Dementia Targets
Patient Benefit

COLLABORATION

COLLABORATION

ADDING VALUE

Intellectual Property

Scientific Development

Commercial

Key Outputs
Outline of the Dementia Consortium

Dr Eric Karran, ARUK
Goal of the Dementia Consortium

• £3m fund to generate and advance novel targets for the treatment of neurodegenerative disease towards the clinic
  – >10 years since last treatment approved
  – Many Pharma withdrawing from area
  – Find new ways to bring together charity and industry sectors to ultimately see new therapies benefit patients
  – New model of collaborative drug discovery
Model for Consortium–funded Projects

- DC aims to support precompetitive collaborative target validation and drug discovery
- Not a typical grant-funded work; applications are to *collaborate* with DC
  - Academic brings novel biology, disease expertise and reagents/resources
  - ARUK provides grant funding and oversight
  - MRCT provides drug discovery resources and project management
  - Eisai and Lilly provide Pharma insight, tools and potential (pre)clinical drug discovery and development
- Projects typically up to 2 years in duration

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Target validation for drug discovery

• Target validation:
  – Robust demonstration of link between modulation of a target and proposed therapeutic benefit

• Preclinically, this means answering
  1. How is the target implicated in disease or disease models? What evidence supports this?
     – siRNA, KO/rescue, GWAS, SNPs
  2. Is the target druggable?
  3. Can ligands be identified that will modulate the target as desired, avoiding off-target effects?
  4. Do the ligands possess drug-like characteristics for further development?
  5. Can the target be modulated in vivo models of disease
  6. Does modulating this target show promise over competing approaches existing on the market or in development?
Resources for Target Validation

Dr Justin Bryans, MRCT
Target validation for drug discovery

- Drug discovery framework
- Route to and through the clinic
- Focus on antibody and small molecule approaches
  - Others not excluded but will be discussed on case-by-case basis for collaboration with CRO network

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Small molecule drug discovery resources

- Consortium resources available:
  - 20 MRCT chemists on staff; 25 biologists
  - Assay development
  - Cellular pharmacology
  - HTS robotics
  - Compound collections (diversity set; target focussed sets, fragment libraries)
  - Hit-to-Lead, Lead optimisation chemistry
Antibody drug discovery resources

• Consortium resources available:
  – Experienced antibody engineering team (15 people)
  – Antibody generation
  – Humanisation and development of monoclonals
  – Biophysical characterisation
  – Affinity maturation
Drug discovery resources

• Consortium resources available:
  – *in silico* modelling and screening
  – ADME testing e.g. microsomal stability, permeability etc.
  – Collaborations with structural biology expertise

• Network of CROs
  – Can use CROs to supplement existing capabilities
  – Can project manage grants that require different capabilities e.g. peptides, delivery etc. from CROs
What do we mean by ‘druglike’?

- Suitable properties for scaled up production, administration to man, bioavailability in man, access to the target at relevant site of action, potency at target modulation

- Small molecules
  - Lipinski compliant
  - No toxicophores
  - Good ADME properties

- Antibodies
  - Good affinity
  - Biophysical characteristics
Project Outcomes - deliverables

• Goal is to provide the Pharma partners with robust collaborative projects to enter preclinical pipelines
  
  – Proof of concept in accepted models of disease
  – Demonstration of target modulation and association with therapeutic effect
  – Tools and reagents to feed into full scale drug discovery programme
  – Opportunities for publications to progress science
  – Opportunities for funding for further development

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Project Outcomes – benefits

• Seeing basic research translated towards the clinic

• Ultimately leading to patient benefit

• All parties sharing in the revenue from successful projects that progress into the clinic
The Application Process

Dr Duncan Young, MRCT
Applicant Eligibility

• Lead applicant
  – Should have contract which will cover their salary for at least the duration of the grant

• Principal Investigators as co-applicants should have a tenured position
Application Process

Step 1: Talk to us!

- Contact us to discuss outline of project, suitability, and how we might help

  - info@dementiacconsortium.org
  - 0207 391 2826

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Application Process

- **EoI**: 6-8 weeks
- **Full**: 2-3 months
- **Feasibility**: ~6 months

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Expression of Interest

• Open, ongoing application process
• Panel meet every 6-8 weeks
• Representation from MRCT and ARUK with input from Eisai/Lilly

• Brief look at the target, evidence linking to disease, resources available to support programme

• Page 1 non-confidential, shared with Pharma
• Questions 1-8 can be treated as confidential from Pharma if desired at this stage

• Feedback and Project fostering – if not successful, may still provide advice and tools to get project to a point where it is ready

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Full Application

- Written in collaboration with MRCT scientific and due diligence teams

- Detailed analysis of science, commercial and intellectual property aspects of the proposal

- Project plan and progression strategy
  - Broken down by milestones
  - Full path to take project to proof-of-concept in animal model
  - Who is required to do the work (University, MRCT, CRO...)

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Application Guidance and Costing

• Projects typically up to 2 years in duration
  – May be less; goal is for focussed assessment of the target/opportunity

• Focus on small molecule and antibodies
  – Other approaches not excluded, but considered case-by-case, where Consortium feels it is able to contribute

• Project Costs
  – Will be more fully fleshed out at full application stage
  – Anticipate typical costs £100-250k
  – Notional limit £500k, for exceptional cases
Feasibility

• Initial phase of all approved projects
• Putting agreements in place with host institutions
• Agreeing terms for commercial development
• Getting hold of key materials
• Independently reproducing key background experiments
• Reassurance for project plan
Launched Projects

- Projects run on milestone basis
- Collaboration – all results and reagents shared
- Goal will be for publication of results, with appropriate protection in place
- Project management shared between PI and MRCT
- Frequent update meetings (quarterly)
- Reports shared with Consortium partners
Intellectual property

• Foreground IP jointly owned
• MRCT take on patent costs
  – Potential to take on background IP too
• IP made exclusively available to Consortium for further development

• Revenue shared with all parties
(Pre)Clinical Development

- Pharma Dementia Consortium members have exclusive option to progress projects

- But all parties can progress projects

- May want further collaboration with academic for support and expertise on biology

- Successful project in clinic see rewards shared with Consortium and applicants
**Triage panel:** 2 ARUK reps + external experts + ARUK SAB Chair + MRCT chair

**ARUK/MRCT EoI proposals entry point**

**ARUK/MRC-T Expert Panel Triage process.**

- Pharma Members assess proposal
  - Pharma member does not participate in any subsequent discussion of target

- Pharma Members assess full proposal
  - Pharma deselected targets

**Project scope and flow-scheme delineated and agreed between MRCT/ARUK, Pharma and academic at project scope meeting**

- Budget, resource need and timeline agreed. ARUK awards grant and is responsible for post-award administration including funding allocation.

**ENTRY STAGEGATE**

**Start of Project**
Formal project review meetings held quarterly with all party representation. Chaired by MRCT.

Project fails.

Tool/Lead Declaration:
Outputs offered to Pharma consortium. Academic and Pharma free to negotiate collaboration terms if appropriate. All parties free to access reagents and take project forward.

Project termination meeting. All reagents generated made available to all parties if required.
Approval criteria

- Global scheme looking to support best science
- Promising, novel biology
- Academics with strong desire to engage in translational process
- Acceptance of grant terms and conditions
Possible reasons for failure

• Not talking to us first!
• Early stage vs. early stage
  – Levels of evidence to support disease association
• Availability of models/assays for confirmation of activity and relevance to disease
• ‘Druggability’ of target
  – Certain classes more difficult to screen/assess
  – Activators vs. inhibitors
  – Allosterism – how to assess?
  – Protein:NA or Protein:Protein difficult with small molecules
• Competitive advantage target offers over existing / emerging approaches

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Example Applications and Questions

• What kinds of questions might the DC consider when reviewing the following?
  – Not all questions need to be answered upfront – but should be aimed to be answered by the end of the project...

• Novel DUB implicated in regulation of aggregate clearance

• Amyloid aggregation inhibitors

• Muscarinic potentiators in cognition enhancement
Example Applications and Questions

• Novel DUB implicated in regulation of aggregate clearance
  – DUBs not proven as druggable targets
  – But emerging novel interesting area
  – What is the evidence linking DUB to clearance?
    • siRNA/CRISPR, polymorphism associated with increased incidence of AD?
  – Can you express DUB and relevant substrate for assay development? Could this be outsourced?
  – Is DUB KO mouse viable and protected?
  – Could aggregate clearance in other indications provide advantage for route through the clinic?
  – Is there structural information available to support medicinal chemistry?
Example Applications and Questions

• Amyloid aggregation inhibitors
  – Academic has already performed screen
  – How relevant is the primary screen to disease pathophysiology?
  – How drug-like are the compounds?
  – Is there SAR? Is there scope to improve?
  – This has been tried many times before, with no success
    – what is unique about this approach?
  – What is the stoichiometry of drug to target?
  – Is this achievable in vivo?
  – What selectivity assays would be used?
Example Applications and Questions

• Muscarinic potentiators in cognition enhancement
  – Large literature supporting this
  – What is novel? What hasn’t been done before?
  – New way of modulating known target (allostery)?
  – What advantages over other cognition enhancement approaches?
  – What animal model would be used to show cognitive benefit translatable to man?
  – What is the face, predictive and construct validity of the model?
  – What is the clinical experience of this mechanism to date?
What next?

- Phone or email the team
- Talk to us over lunch
- Departmental visits and presentations
- 1:1 discussions on potential projects
Questions?

info@dementiaconsortium.org

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