
# DEMENTIA

## Consortium

# 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

DEMENTIA Consortium

Alzheimer's Research UK
Defeating Dementia

Eisai

Lilly

MRC

# Welcome

Dr Eric Karran, ARUK

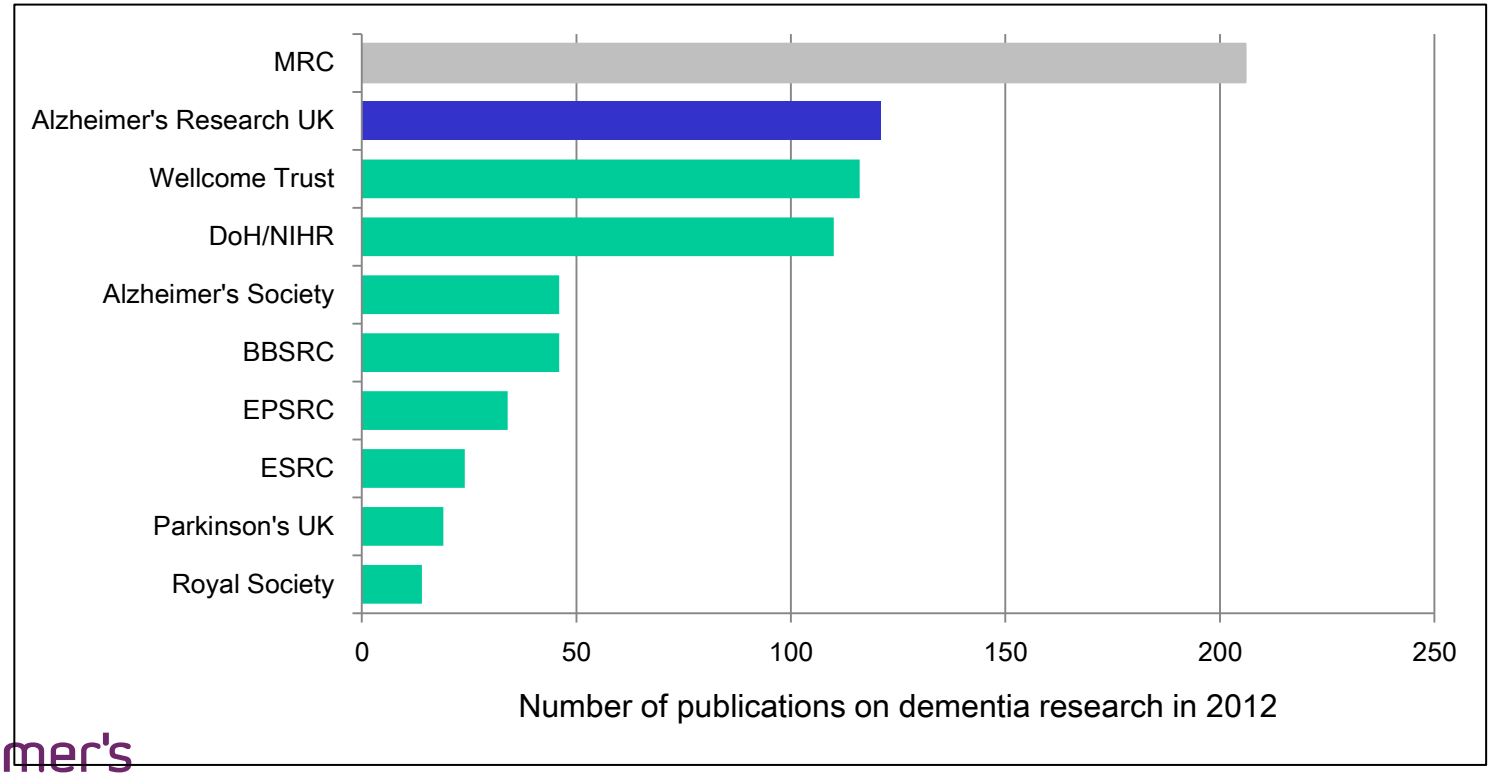
# Alzheimer's Research UK

- ARUK Strategy – past, present and future.
- Dementia Consortium

Alzheimer's Research UK
Defeating Dementia

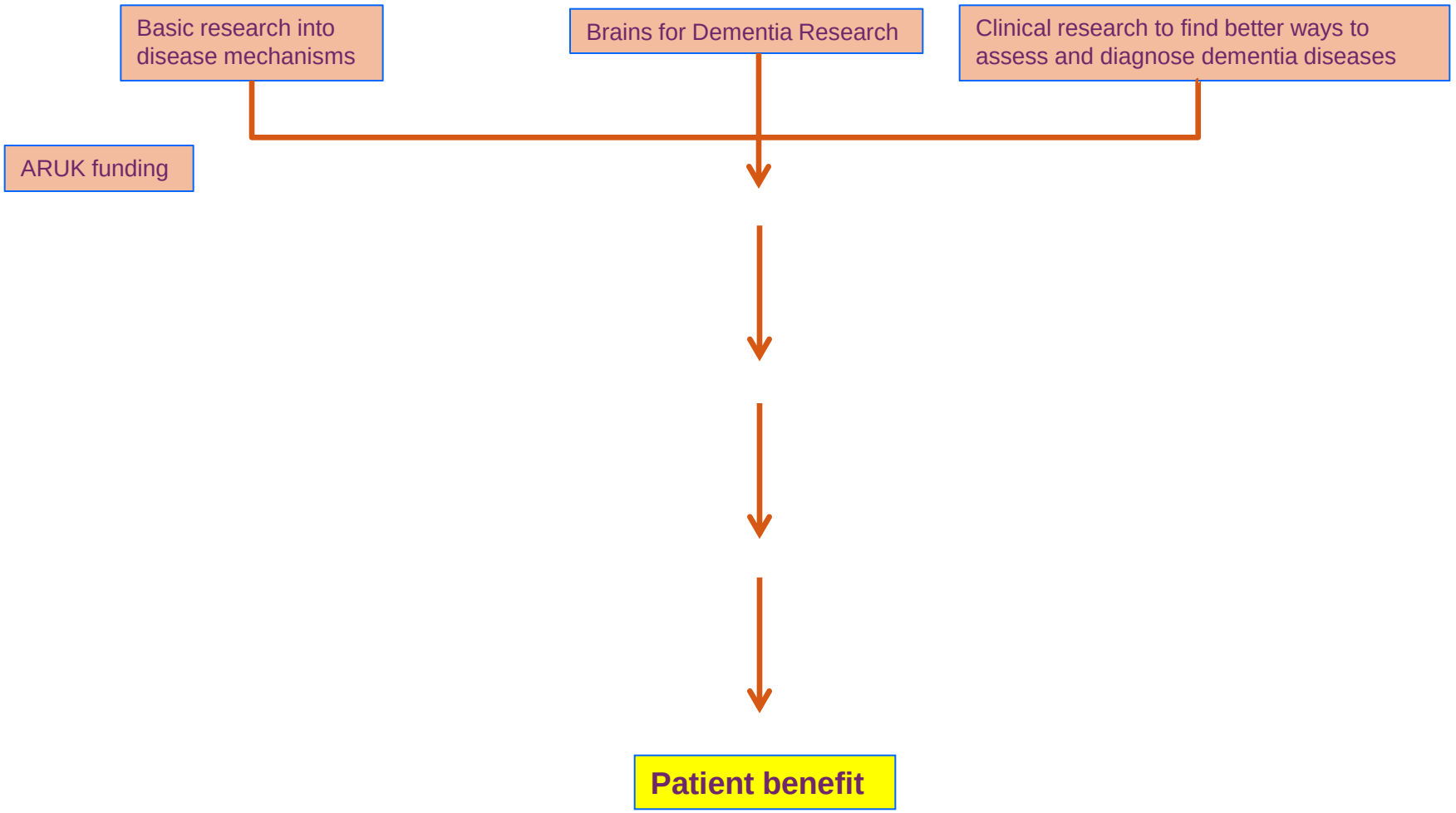
# What is Alzheimer's Research UK doing?

- 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




Alzheimer's Research UK
Defeating Dementia

# ARUK research strategy: 2012

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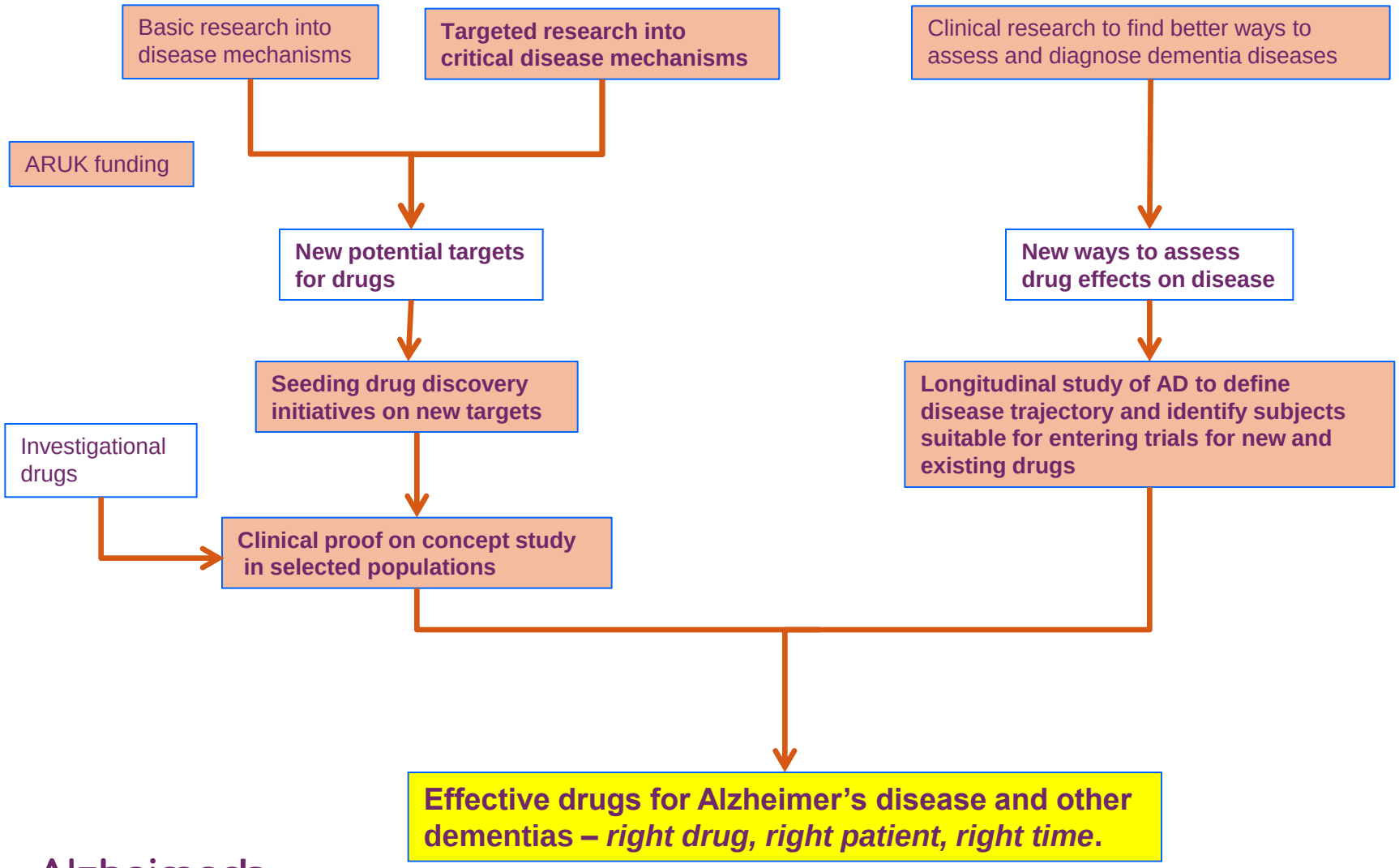
# ARUK research strategy: 2013

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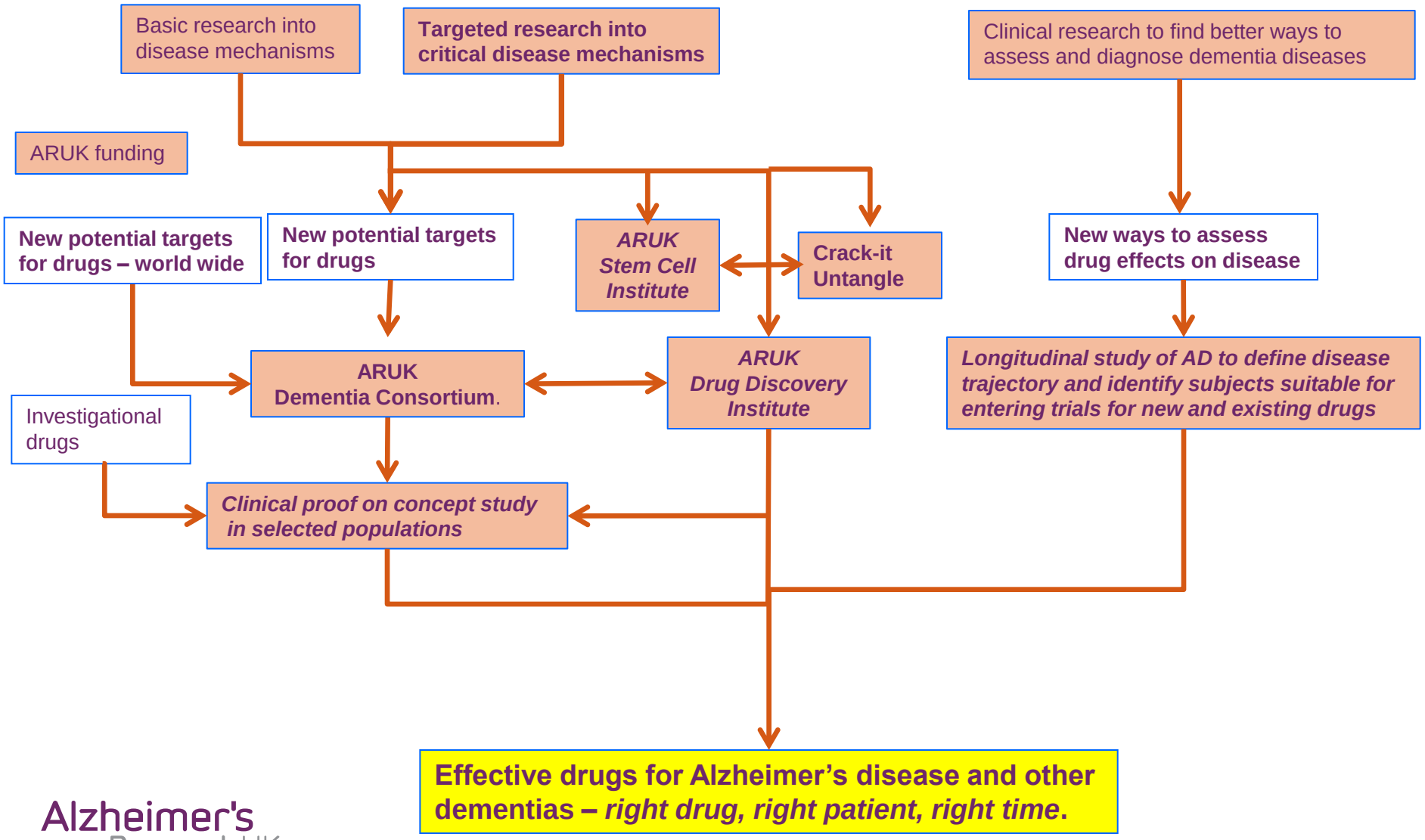
# ARUK research strategy: 2014




Alzheimer's Research UK
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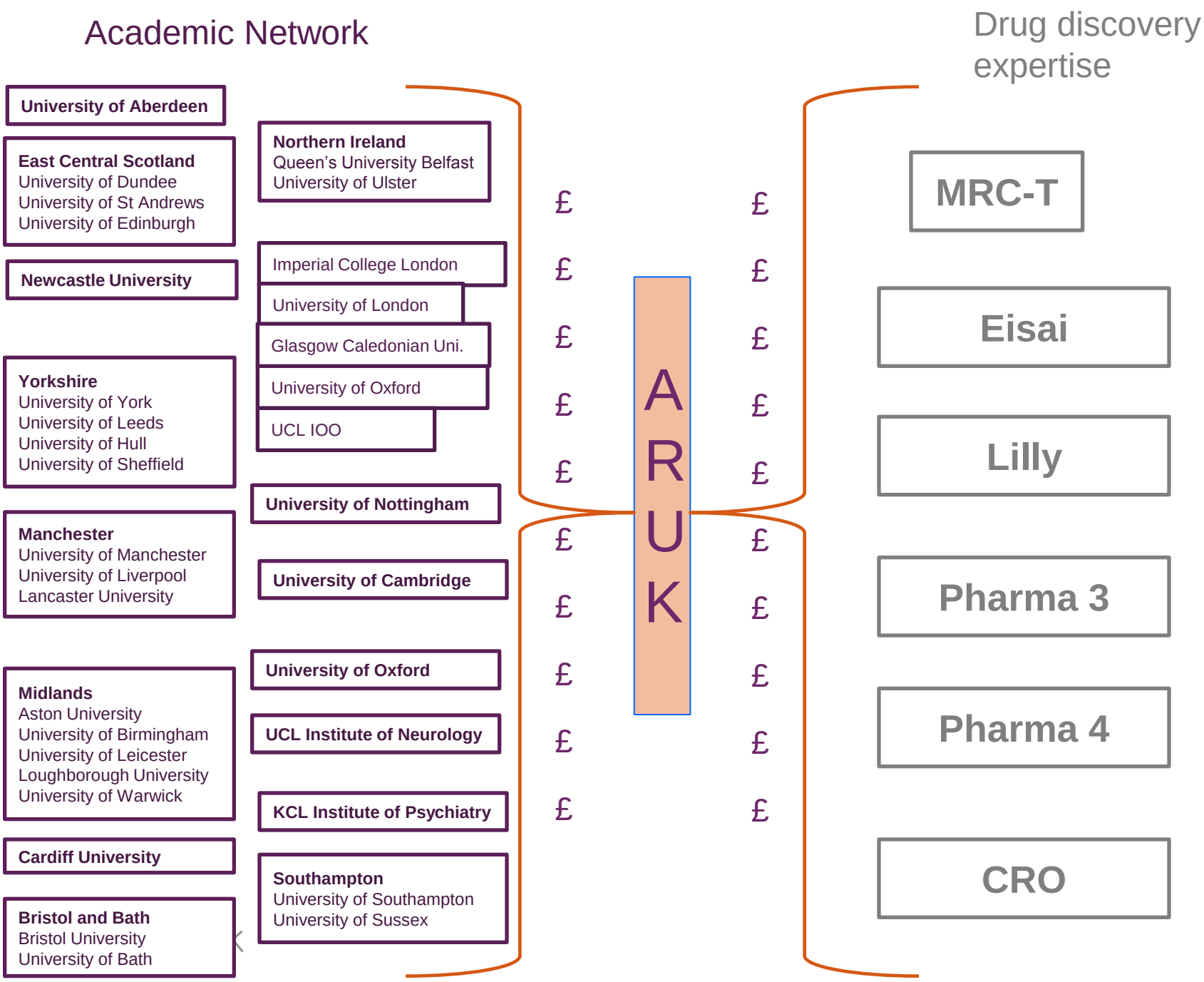
Academic Network
Drug discovery expertise
University of Aberdeen
East Central Scotland
University of Dundee
University of St Andrews
University of Edinburgh
Newcastle University
Yorkshire
University of York
University of Leeds
University of Hull
University of Sheffield
Manchester
University of Manchester
University of Liverpool
Lancaster University
Midlands
Aston University
University of Birmingham
University of Leicester
Loughborough University
University of Warwick
Cardiff University
Bristol and Bath
Bristol University
University of Bath
Northern Ireland
Queen's University Belfast
University of Ulster
Imperial College London
University of London
Glasgow Caledonian Uni.
University of Oxford
UCL IOO
University of Nottingham
University of Cambridge
University of Oxford
UCL Institute of Neurology
KCL Institute of Psychiatry
Southampton
University of Southampton
University of Sussex
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MRC-T
Eisai
Lilly
Pharma 3
Pharma 4
CRO

# 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

Alzheimer's Research UK
Defeating Dementia

# Role of ARUK

- To fund the Dementia Consortium, and catalyze funding from pharma
- To assist with logistics and publicity
- To help bridge the gap

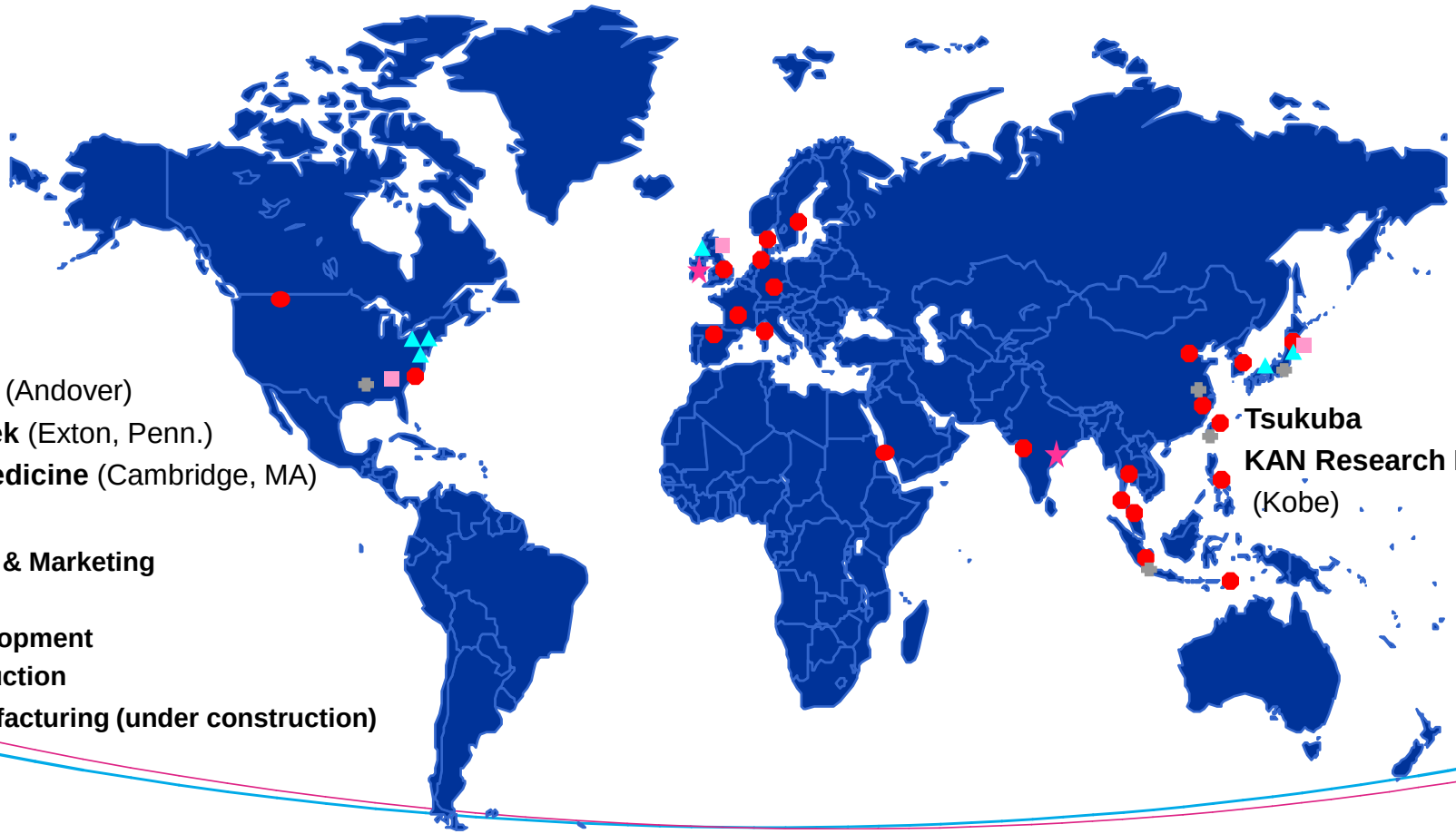
Alzheimer's Research UK
Defeating Dementia

# 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




hhc human health care

# 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**


**European Knowledge Centre** (Hatfield, UK)

# 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 donepezil hydrochloride

Halaven eribulin

Once-daily zonegran zonisamide

Fycompa perampanel

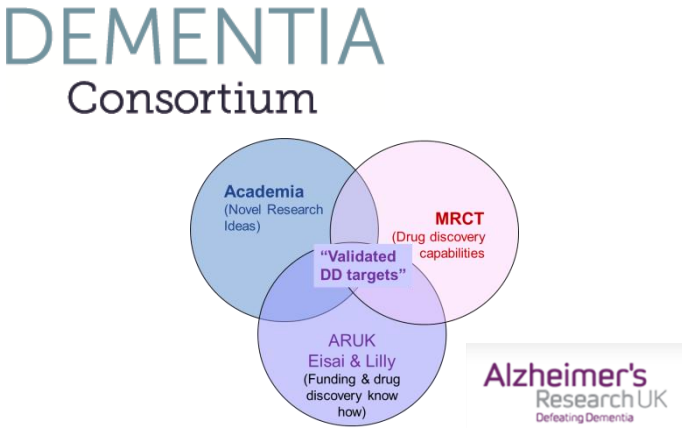
hhc human health care

# 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.

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Eisai

Lilly

MRC

# Introduction: Lilly

Dr Michael Hutton

*January 30th 2014*

# Lilly in the Dementia Consortium

***Michael Hutton***

***CSO Neurodegenerative Diseases***

Lilly

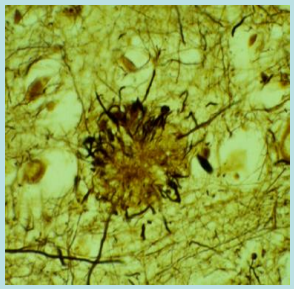
Answers That Matter.

# Neuroscience Research at Eli Lilly and Erl Wood

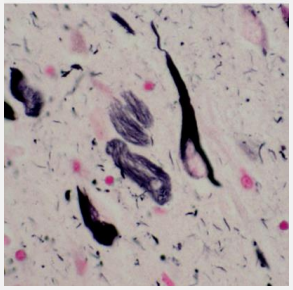
- Neuroscience at Eli Lilly is focused on three areas:
  - **Neurodegeneration (Alzheimer's)**
  - **Psychiatry (Schizophrenia and Depression)**
  - **Pain**
- Erl Wood is Lilly's biggest research operation outside of the US. We have invested more than £120M in the site in the past 10 years
- Today, 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

Answers That Matter.

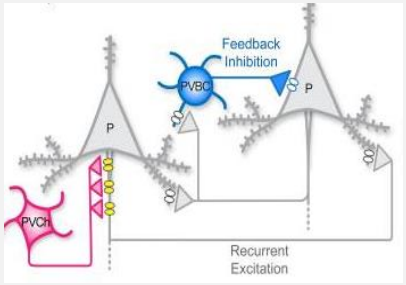
# Alzheimer's Disease
## *Current Portfolio Strategy*



**1. Highest priority: Aβ and β-Amyloid**



**2. Target Tau as a second approach to disease modification**



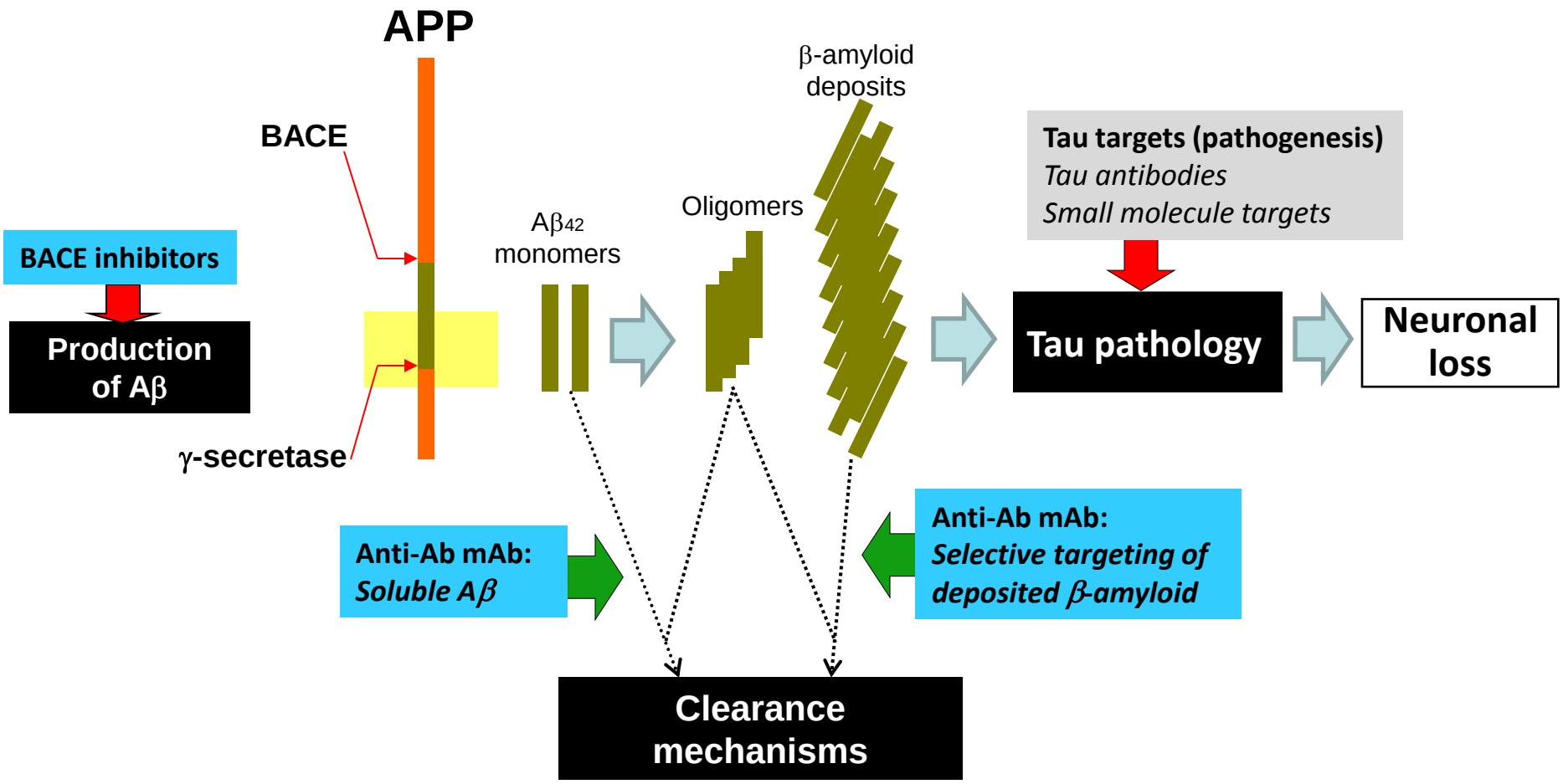

**3. Identify and develop targets for symptomatic relief**



Lilly
Answers That Matter.

# Disease Modification

## *Targeting multiple stages in the amyloid cascade*



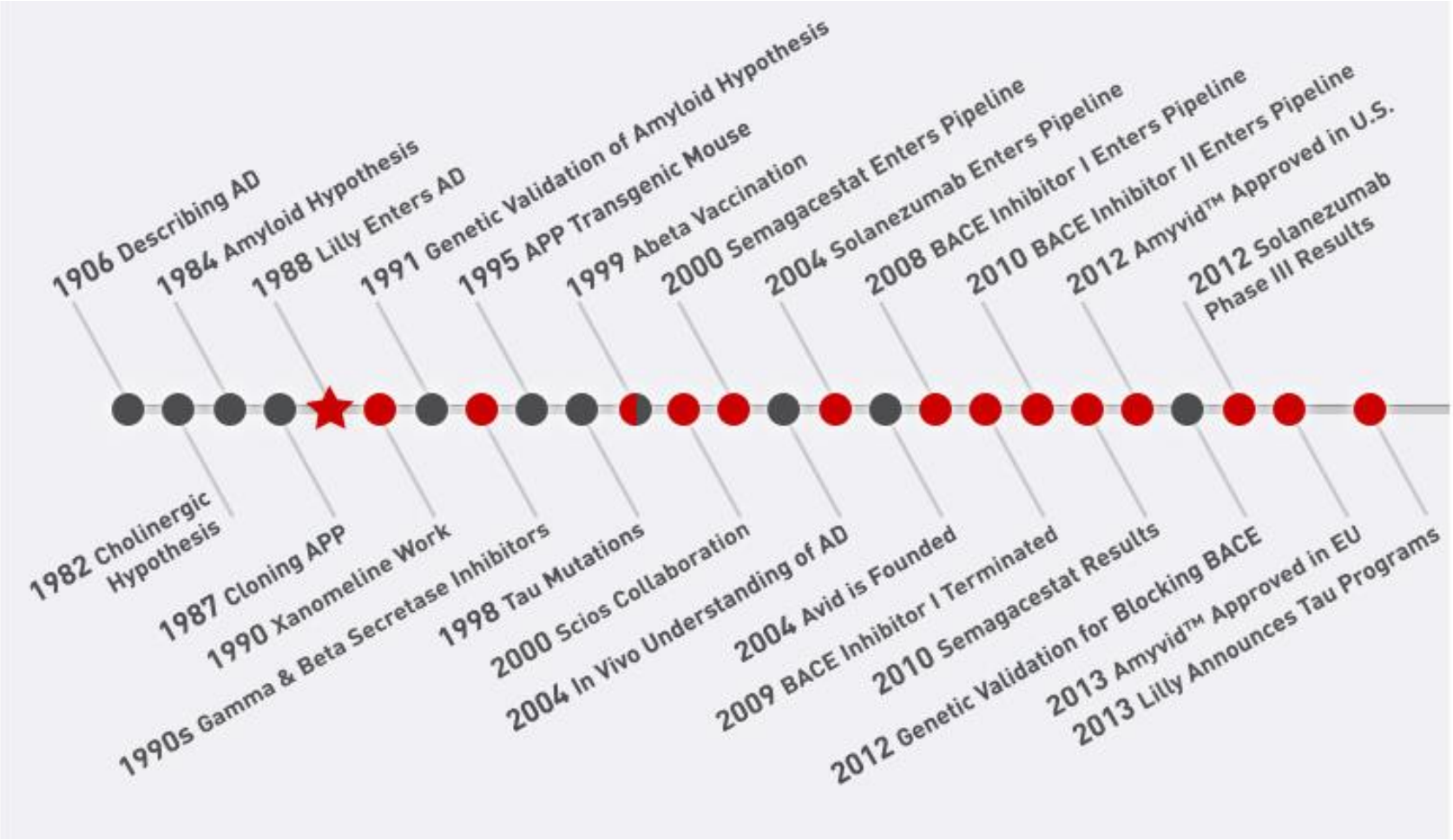



Lilly
Answers That Matter.

# 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
- ***<u>Less interested in:</u>***
  - Targets to block Aβ or β-amyloid production/generation

# 26 years of Lilly Alzheimer's Research
## *1988-2014*

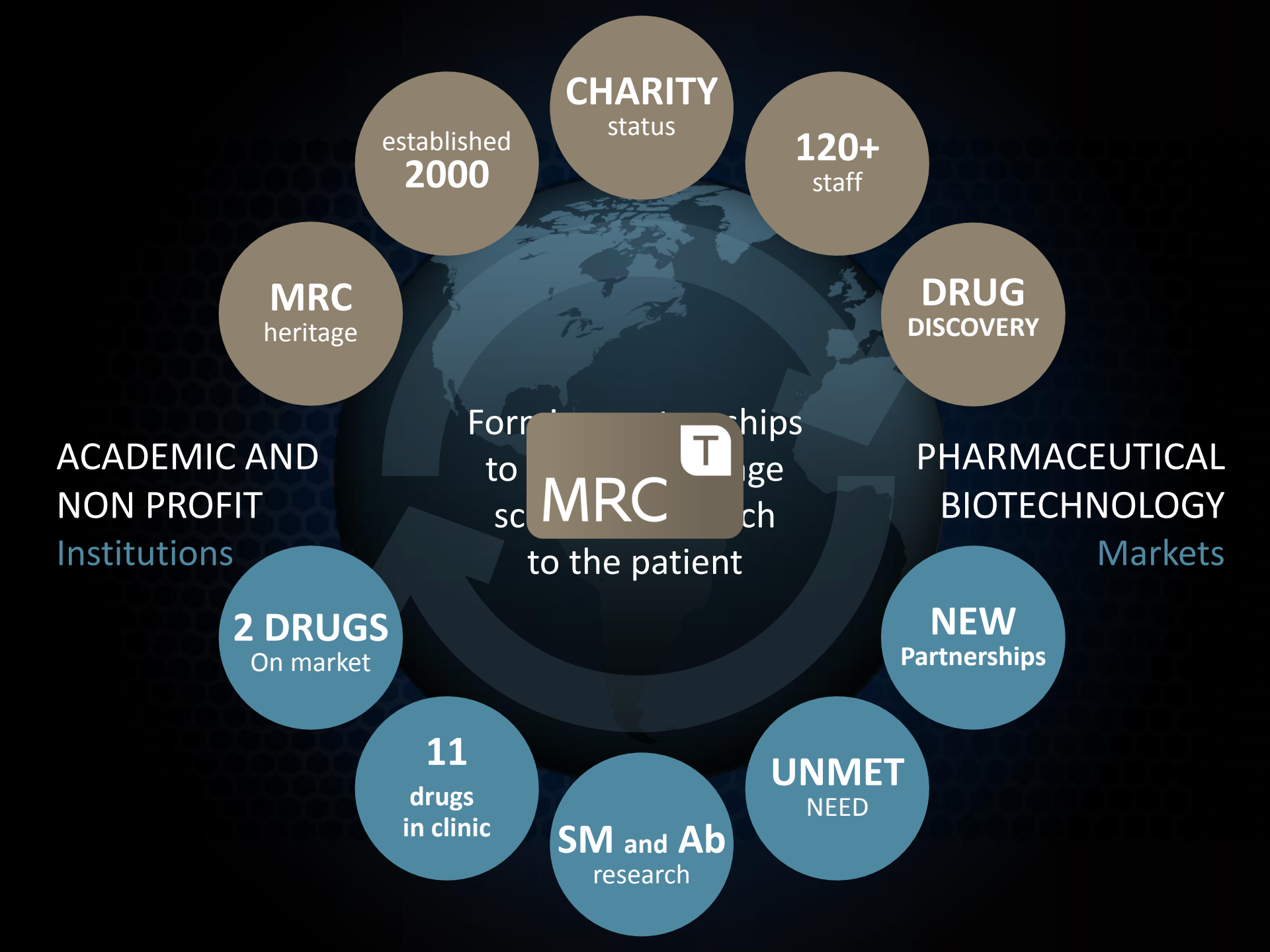





Answers That Matter.

# Introduction: MRCT

Dr Justin Bryans


CHARITY
status
established
2000
120+
staff
MRC
heritage
DRUG
DISCOVERY
ACADEMIC AND
NON PROFIT
Institutions
Forr ships
to ge
sc ch
to the patient
MRC T
PHARMACEUTICAL
BIOTECHNOLOGY
Markets
2 DRUGS
On market
NEW
Partnerships
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drugs
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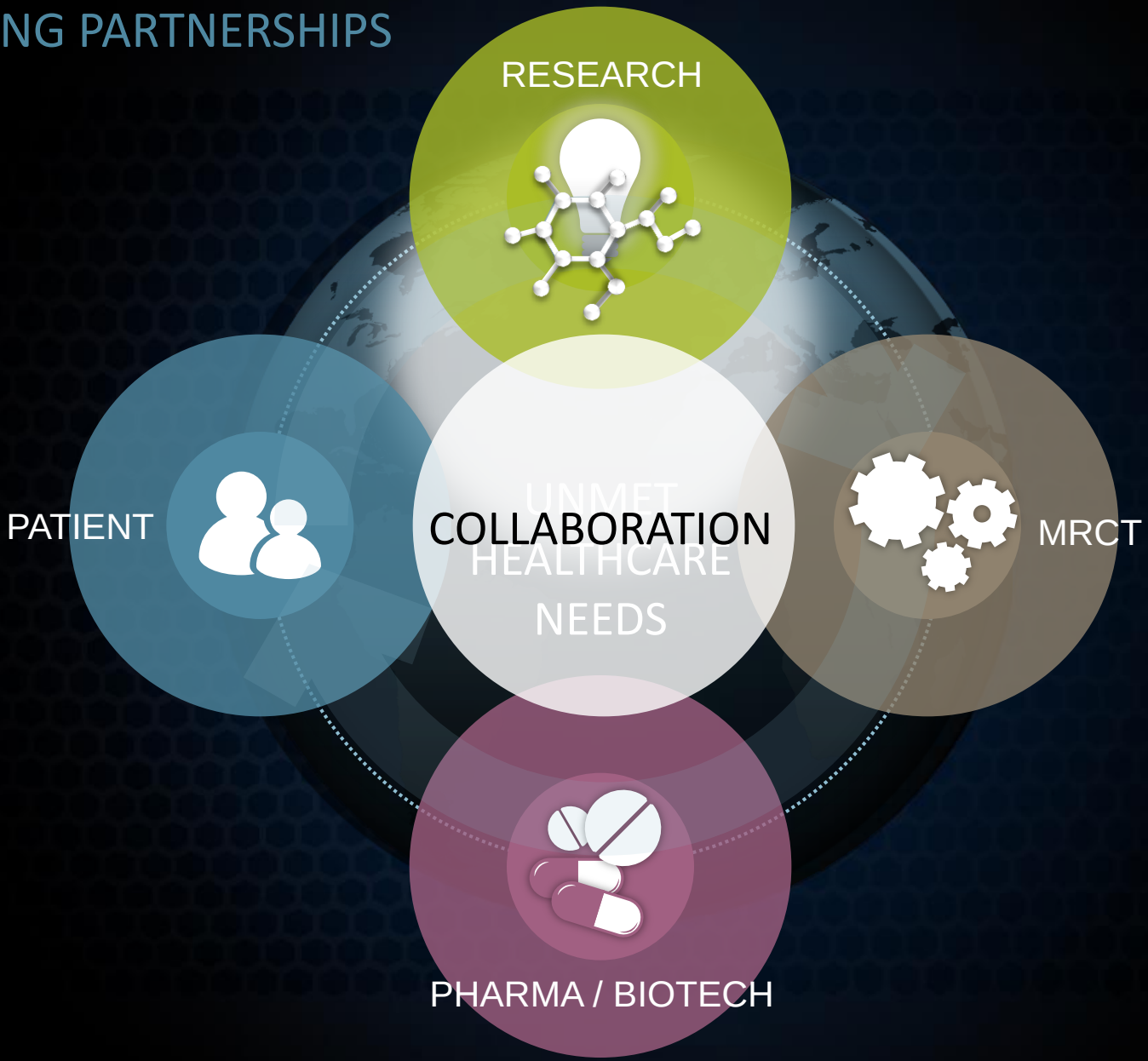
# FORMING PARTNERSHIPS

# FORMING PARTNERSHIPS



# 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

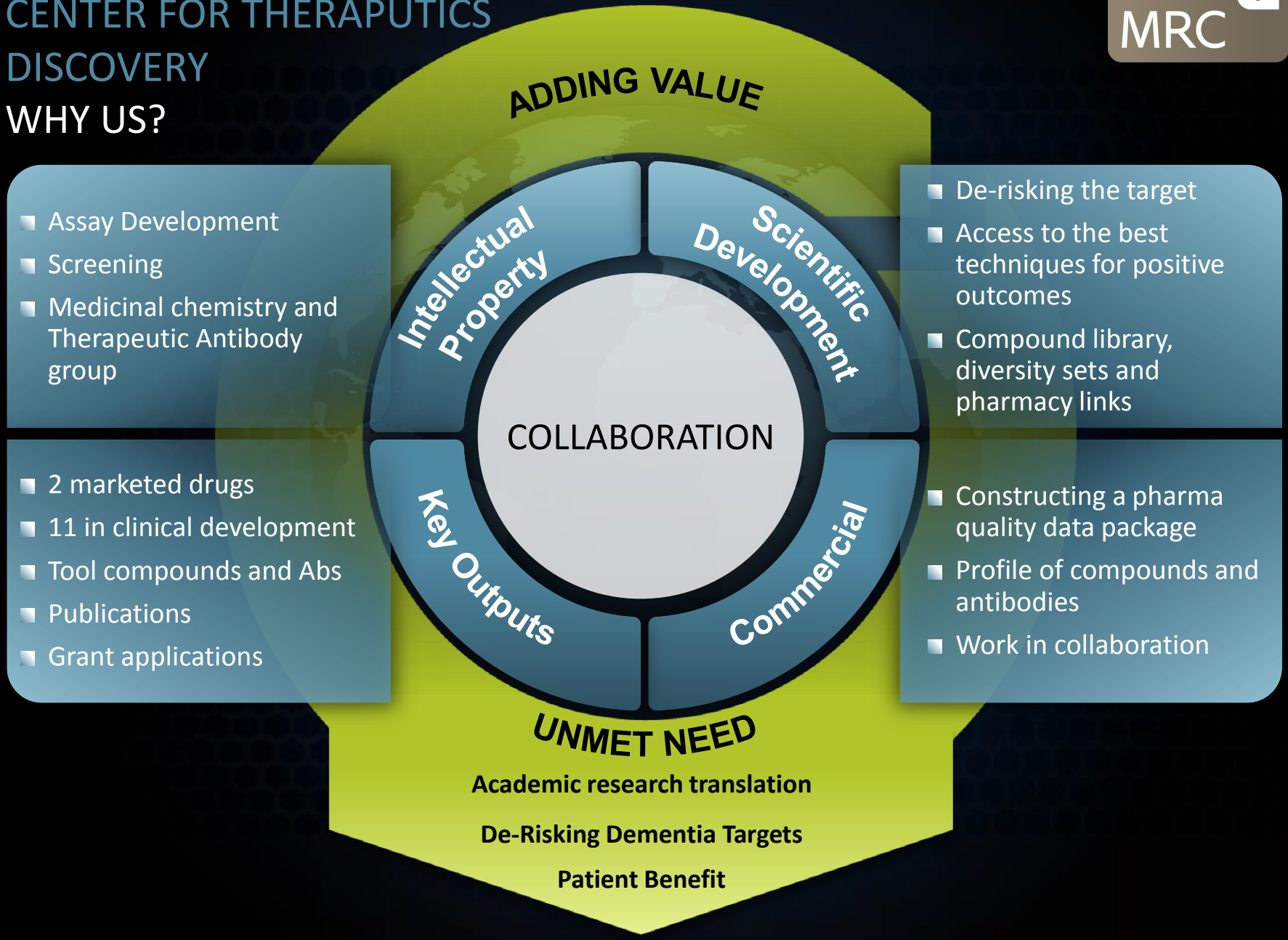
54 Publications and 42 podium talks

ACADEMIC AND NON PROFIT
Institutions

PHARMACEUTICAL BIOTECHNOLOGY
Markets

# CENTER FOR THERAPUTICS DISCOVERY

## WHY US?




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

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

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

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

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Eisai

Lilly

MRC

# 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

# 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?

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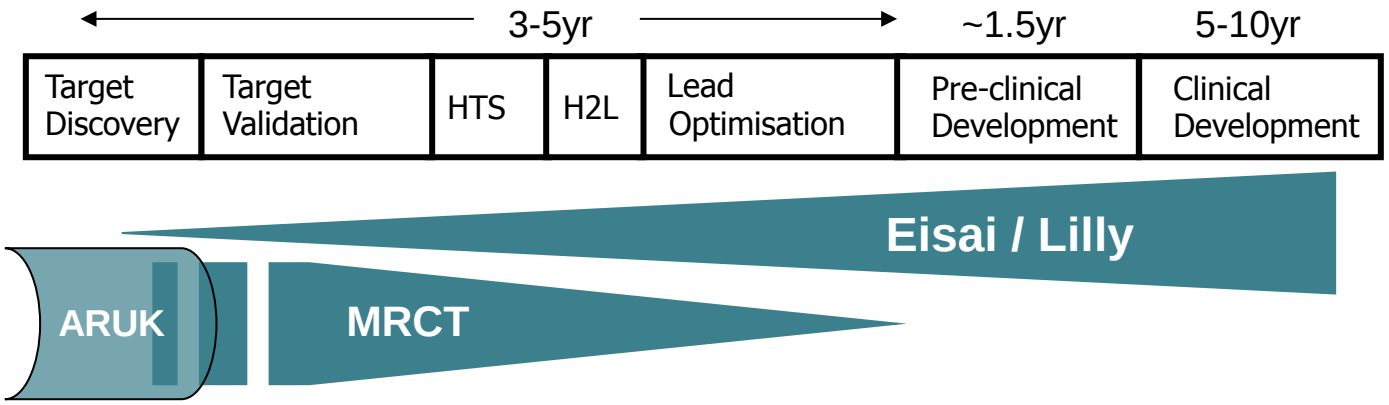
# Resources for Target Validation

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

# 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

# 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

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Eisai

Lilly

MRC

# 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!

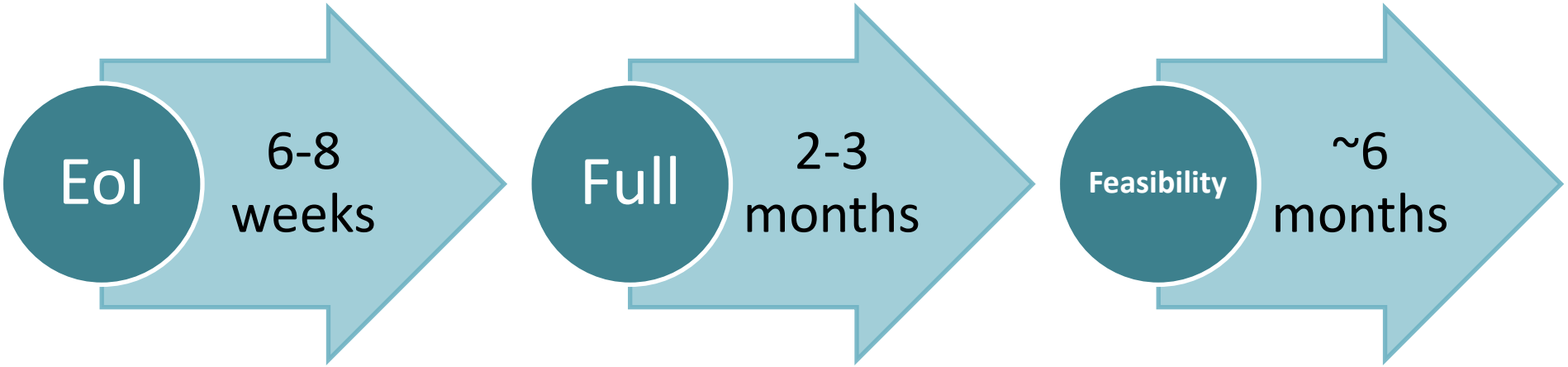
- Contact us to discuss outline of project, suitability, and how we might help

- info@dementiaconsortium.org
- 0207 391 2826

**dementiaconsortium.org**

DEMENTIA Consortium

# Application Process



# 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

# 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…)

# 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

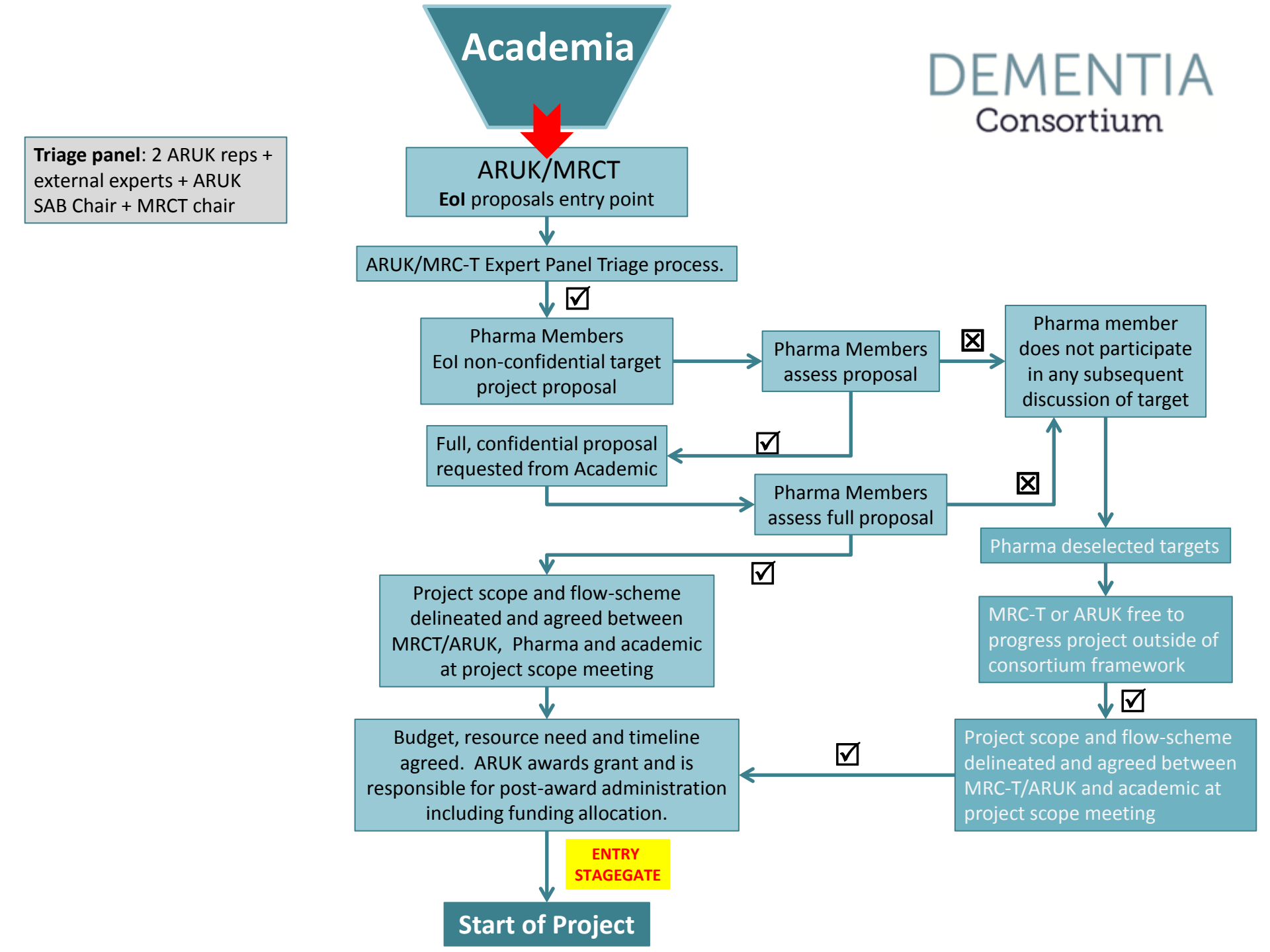
# Intellectual property

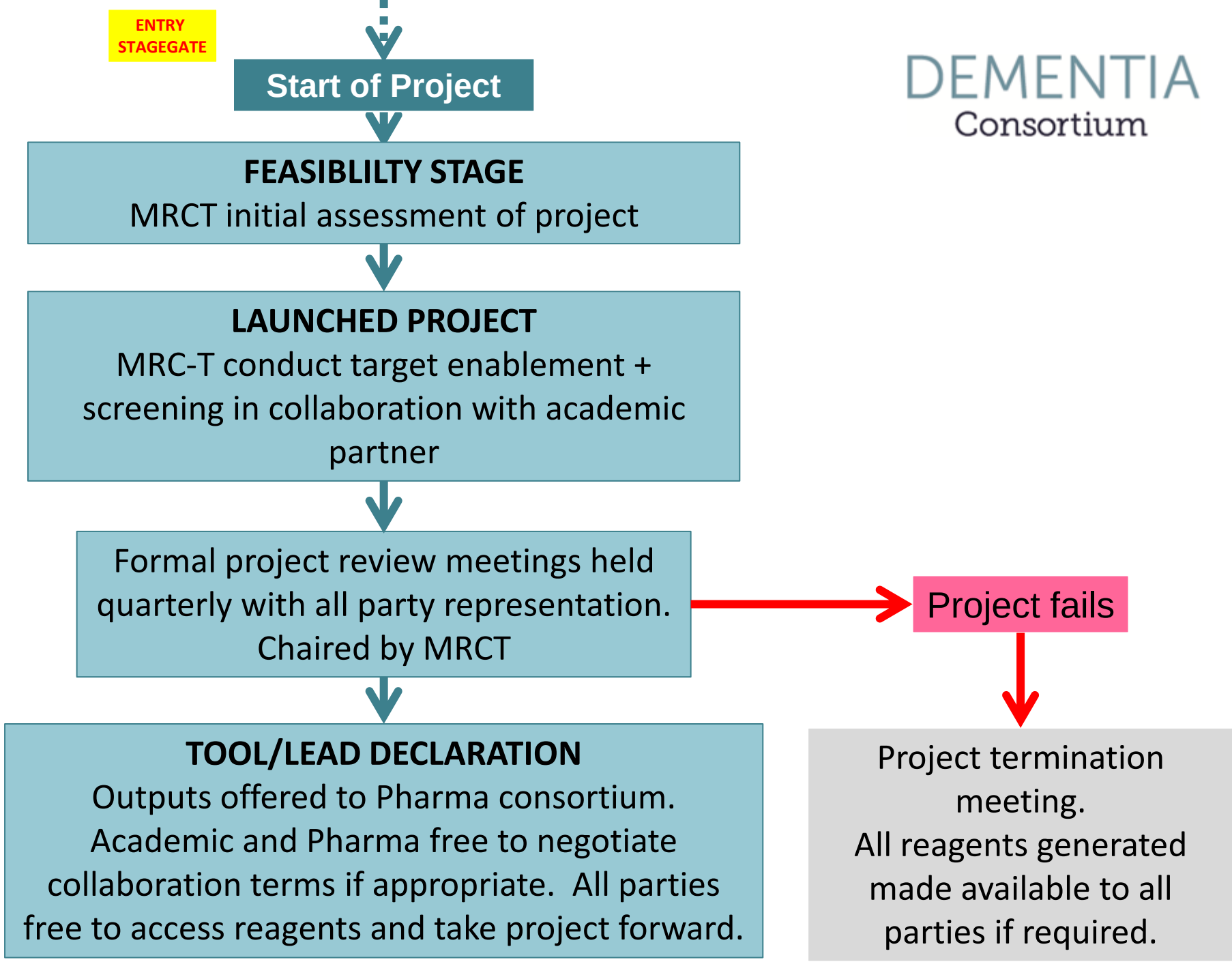
- Foreground IP jointly owned
- MRCT take on patent costs
  - Potential to take on background IP too
- IP made exclusively available to Consortium for further development

- 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


Academia
DEMENTIA
Consortium
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 EoI non-confidential target project proposal
Pharma Members assess proposal
Pharma member does not participate in any subsequent discussion of target
Full, confidential proposal requested from Academic
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
MRC-T or ARUK free to progress project outside of consortium framework
Budget, resource need and timeline agreed. ARUK awards grant and is responsible for post-award administration including funding allocation.
Project scope and flow-scheme delineated and agreed between MRC-T/ARUK and academic at project scope meeting
ENTRY STAGEGATE
Start of Project


ENTRY STAGEGATE
Start of Project
DEMENTIA Consortium
FEASIBLILTY STAGE
MRCT initial assessment of project
LAUNCHED PROJECT
MRC-T conduct target enablement + screening in collaboration with academic partner
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

# 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**

**0207 391 2826**