PharmaCog

Advancing science and treatment of Alzheimer's Disease

Pharmacog: Tackling bottlenecks in AD drug discovery

Dr. Mike O'Neill, Eli Lilly & Co. Ltd,
Dr. Alexandra Auffret, University of Marseille
Jean George, Alzheimer's Europe

IMI Official Satellite Symposium of the AD/PD 2011 Conference, Barcelona, Spain, 2011

efpia

imi
Innovative Medicines Initiative

A Public Private Partnership

* Research performed by EFPIA member companies

= *in kind* contribution

IMI Research funding for

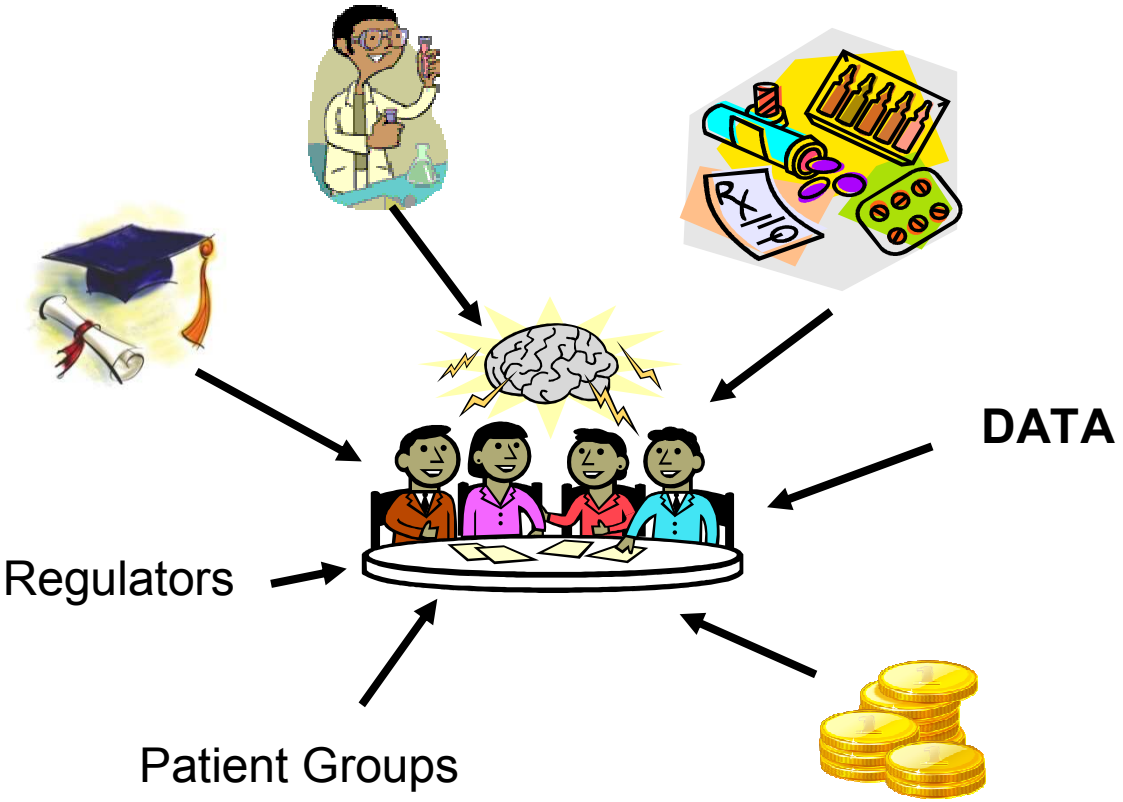
Academia, SMEs, patients organisations, Regulatory Authorities, etc.

IMI Research Projects

IMI objectives

- Making the pharmaceutical R&D process faster and more effective, rather than directly delivering new drugs
- Accelerating the development of safer and more effective medicines for patients in Europe
- Improving the environment for pharmaceutical R&D in Europe
- Boosting the biopharmaceutical sector, Industry and Academic interactions in Europe

IMI: driving cultural change



= best approach

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Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development

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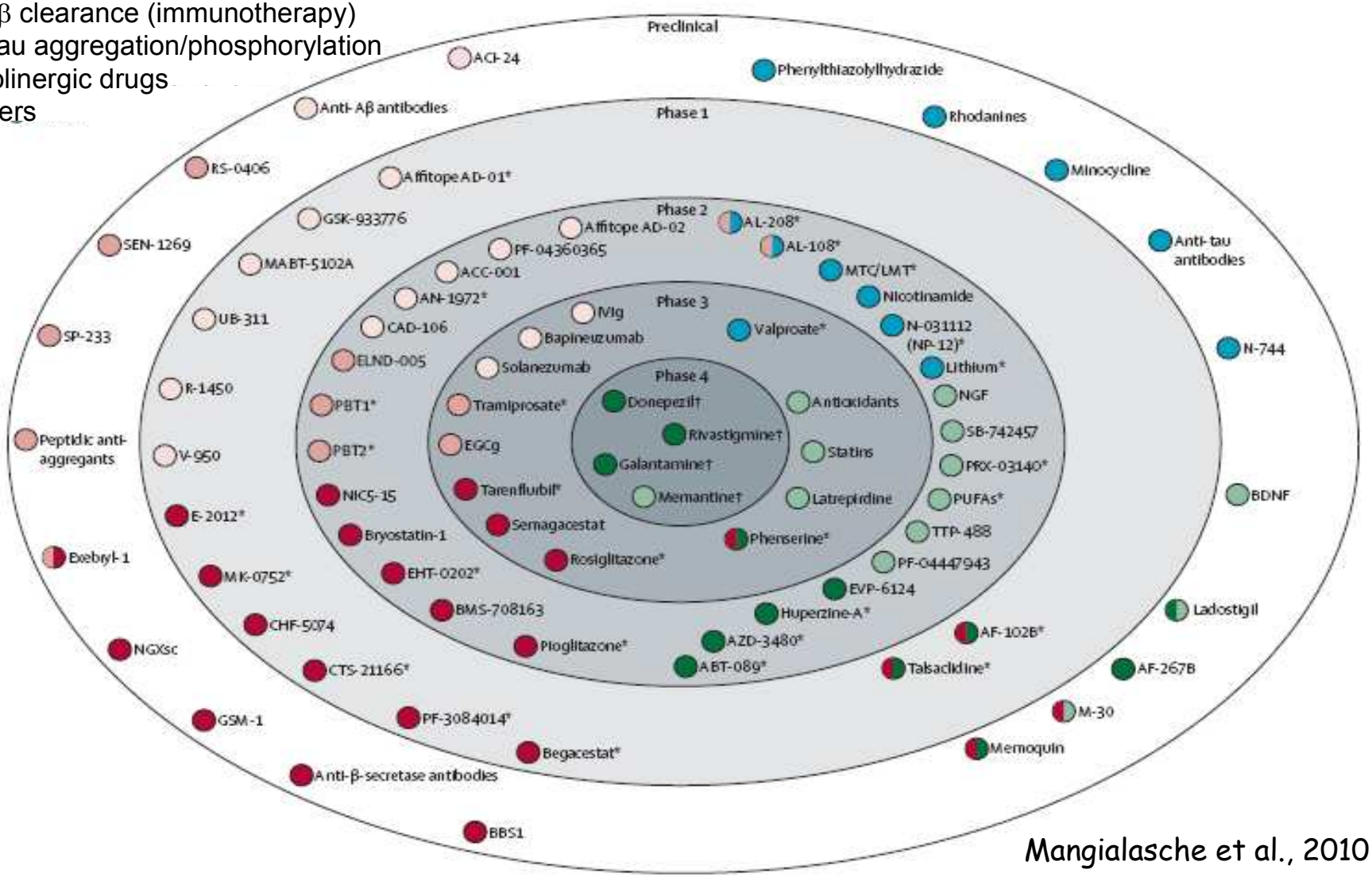
Project Coordinators

- Dr Elaine A Irving, GlaxoSmithKline R&D, new coordinator, Dr Ceri Davies
- Prof Olivier Blin, University of Marseille

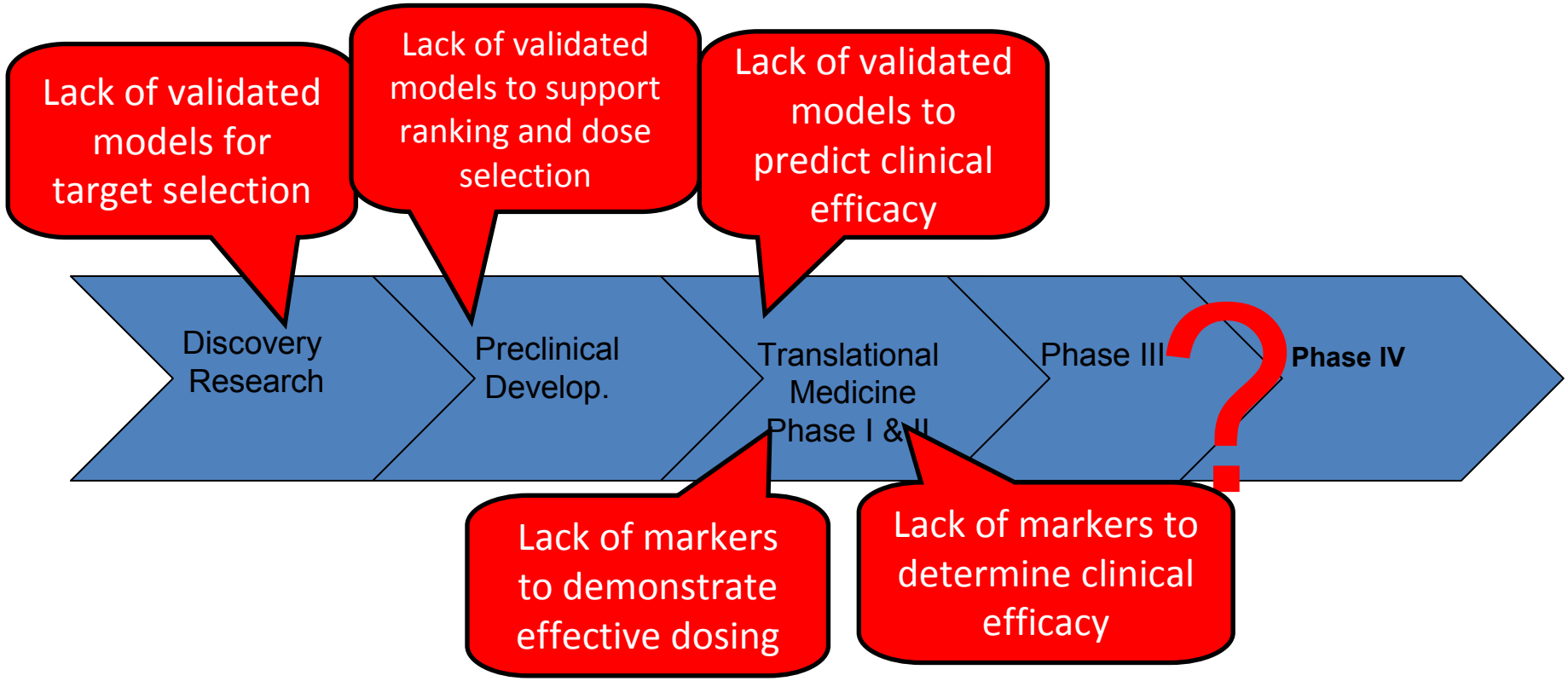
A large number of new approaches for AD are under development

- ↓Aβ production
- ↓Aβ aggregation
- ↑Aβ clearance (immunotherapy)
- ↓Tau aggregation/phosphorylation
- Cholinergic drugs
- Others



Mangialasche et al., 2010

The challenges facing drug discovery in Alzheimer's Disease



Need to detect the winners earlier

Advancing science and treatment of Alzheimer's Disease

PharmaCog : focus on innnovation, translation and harmonisation

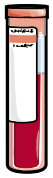
Experimental Models ⟷ Clinical Models

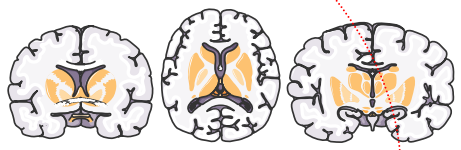
Develop laboratory based models and clinical models that mimics aspects of the disease and help to predict treatment efficacy

Develop markers using these models to predict effective dose ranges and prioritise new medicines

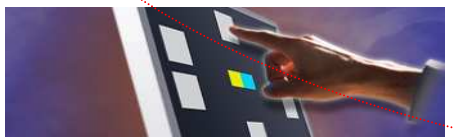
Develop Alzheimer's markers sensitive to the disease progression and drug treatment

Blood analysis



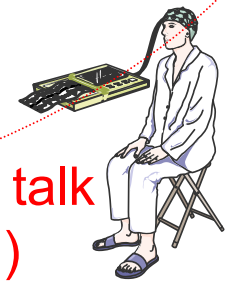


Brain scans



Cognitive testing

Core biomarker set



Brain talk (EEG)

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PharmaCog Partners

Public

Regulators:
EMA

Patient Group:
Alzheimer Europe

Academic Institutions:
University of Marseille (Co-coordinator), France
University of Barcelona, Spain
University of Lille, France
University of Leipzig, Germany
University of Murcia, Spain
University of Duisburg-Essen, Germany
CNRS, France
INSERM, France
University of Verona, Italy
IRCCS FBF, Brescia, Italy
University of Foggia, italy
Mario Negri Institute, Milan, Italy

Small and Medium Enterprises (SMEs):
Qualissima
AlzProtect
ExonHit
Innovative Health Diagnostics
Innovative Concepts in Drug Design

Private

GSK (Co-coordinator)
Astra Zeneca
Boehringer Ingelheim
Eli Lilly
Novartis Pharma
Servier
UCB Pharma
Merck Serono
Janssen Pharmaceuticals
Roche
Lundbeck

Advancing science and treatment of Alzheimer's Disease

Innovative Medicines Initiative

What we bring to the project

PharmaCog

Public

EMA

- Advise on regulatory matters
- Information on clinical trials in AD

Alzheimer Europe

- Communication of project results
- Lead the work on ethical issues

Academic Institutions:

- Expertise of world leading disease scientists
- Technology experts
- Novel models and biomarkers
- European Alzheimer's Disease Neuroimaging Initiative leader

SMEs

- new innovative biomarkers
- Expertise in clinical trial authorization procedures

Private

EFPIA Partners

- Experts in Alzheimer's Disease Drug Discovery
- Archived data from experimental and clinical studies using standard agents
- Quantitative pharmacology expertise
- Experience of multi-centre studies and protocol harmonization

PharmaCog Budget and Timing

Financing:

- IMI funding: €9.6 million
- EFPIA contribution: €10.2 million
- Other contributions: €7.9 million
- Total project cost: €27.7 million

Timing:

- Starting date: 1st January 2010
- Duration: 5 years

Tools to improve decision making in drug development

Dr Alexandra Auffret

PharmaCog : focus on innovation, translation and harmonisation

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Core biomarker set

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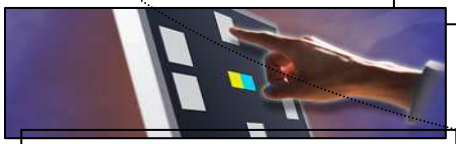
Brain scans



Cognitive testing

Brain talk (EEG)

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Development of cognitive impairment models

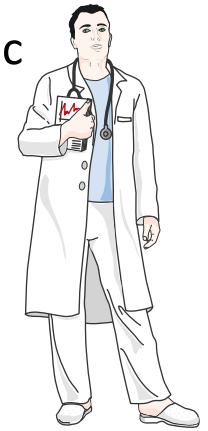
Early hints of efficacy

- Models are used to ‘rank’ potential new drugs and predict the dose required

- The drug Discovery challenge: **improve the predictive capacity of the models**

  - Scientists and clinicians need validated translatable models that mimic Alzheimer’s disease

Experimental Models ⟷ Clinical Models

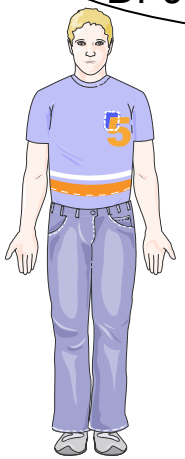


  - Help drug developers to determine the best medicines and the right dose

The PharmaCog approach

- How can we develop these models?

WorkPackage 1
PI : Dr David Bartres-Faz (Barcelona)
Dr Joëlle Micallef (Marseille)



Healthy Volunteers Clinical models

Induce reversible cognitive impairments

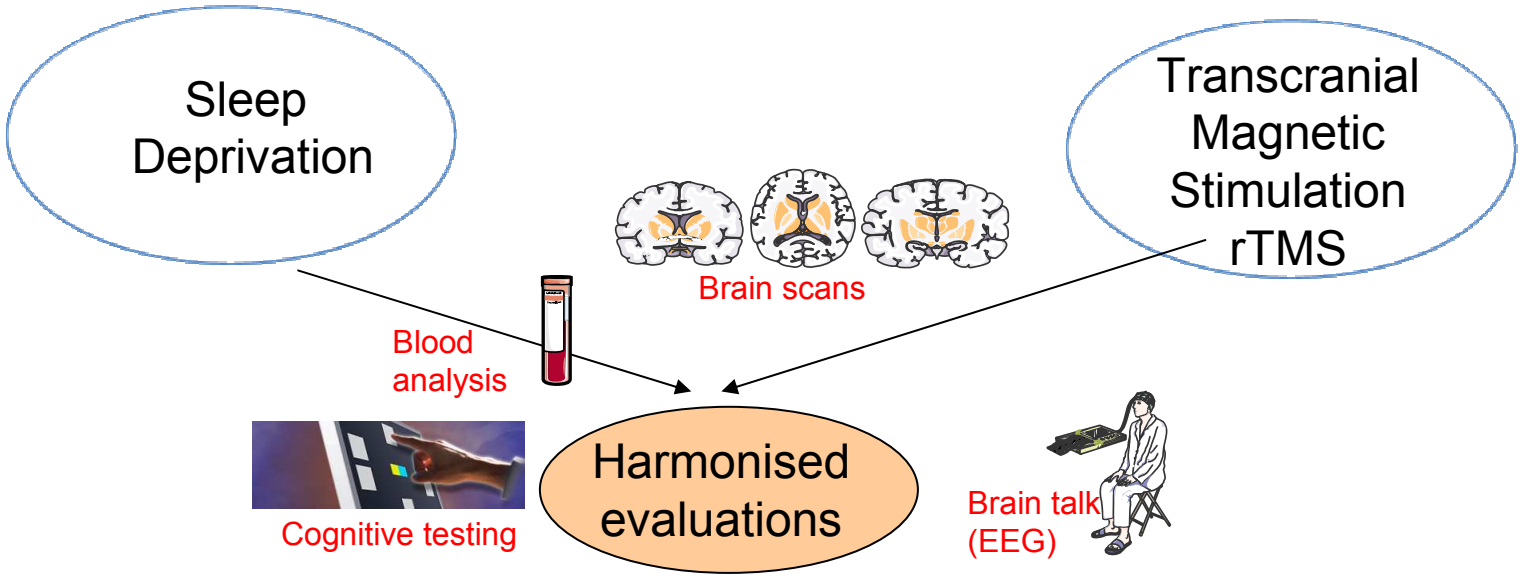
WorkPackage 2
PI : Dr Fabienne Aujard(CNRS)
Dr Yves Lamberty (UCB)

Experimental models

Test the sensitivity to change of the outcomes under Alzheimer's treatment (gold-standards) administration

WP1: challenge models of transient cognitive impairment in healthy volunteers

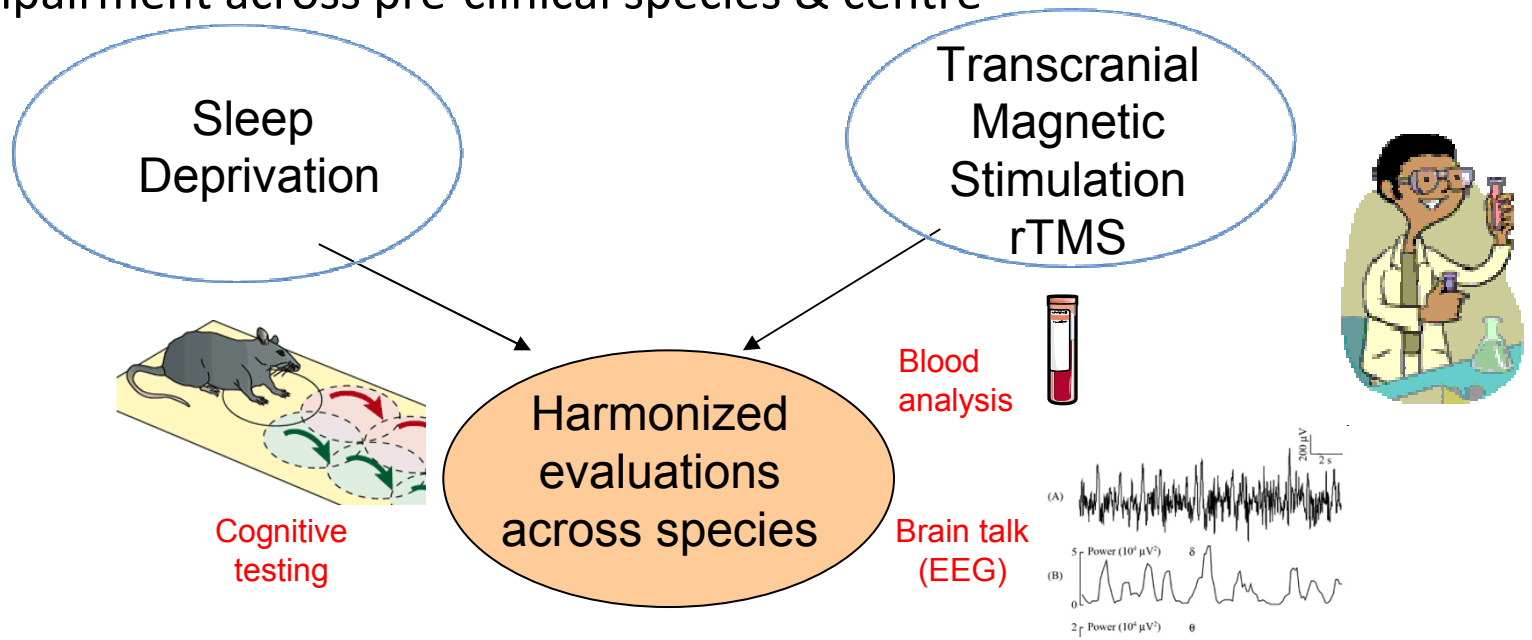
Define and harmonize three parallel clinical challenges:



- **intensity of the induced cognitive deficit?**
- **time course of the induced cognitive deficit?**
- **sensitivity to change of the outcomes under Alzheimer's disease treatment administration?**

WP2: pre-clinical challenge models of transient cognitive impairment

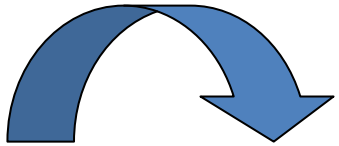
- Define & harmonize preclinical challenge models (sleep deprivation, hypoxia & rTMS "equivalent") of transient cognitive impairment across pre-clinical species & centre



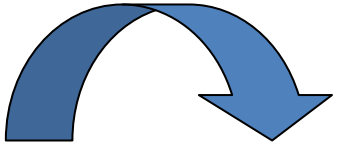
• intensity of the induced cognitive deficit?
• time course of the induced cognitive deficit?
• sensitivity to change of the outcomes under Alzheimer's disease treatment administration?

General Workplans

Literature review and analysis of archived data from studies using Alzheimer's disease treatment administration (gold-standard)



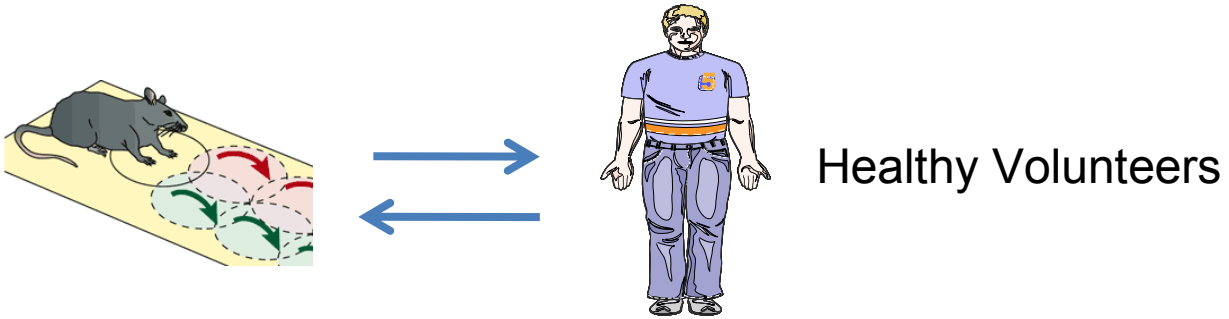
Design and harmonization of the 3 challenges and validation under treatment administration



Selection of the best challenges regarding the predictive capacity

Relationships between effects in pre-clinical species and in healthy volunteers

- Back-translate **data generated** into parallel pre-clinical studies (WP2) in order to identify those challenge clinical models paradigms (WP1) with translational capacity



- Test the reproducibility and sensitivity of novel biomarkers that can be used for pharmacokinetics and pharmacodynamics studies

- Establish mathematical models describing the relationship between drug exposure and biomarker response and the relationship between pre-clinical and clinical studies

Partners

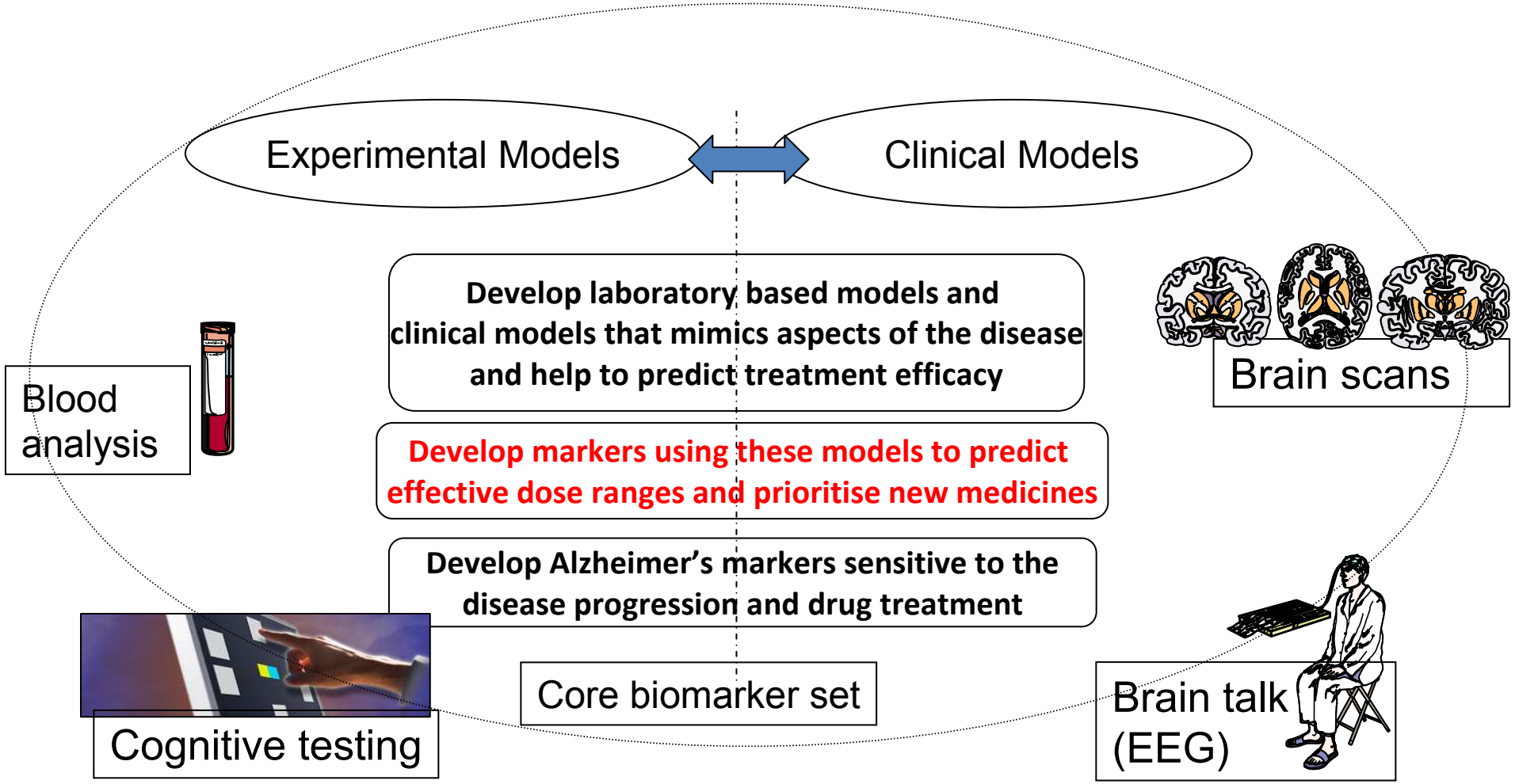
WP1 Leads: *Dr Bartrès-Faz (IDIBAPS, Barcelona)*
Dr Joëlle Micallef (University of Marseille)
WP1 Partners: *UnivMed France, IDIBAPS Spain, Lille Univ France, INSERM France, Foggia Univ. Italy*
Qualissima
Merck Serono, Roche

WP2 Leads:
Academic Lead: Dr Fabienne Aujard (CNRS, France)
Industry Lead: Dr Yves Lamberty (UCB)

WP2 Partners:
University of Lille, France; University of Murcia, Spain; CNRS, France; University of Verona, Italy; University of Foggia, Italy; Mario Negri Institute, Italy
GSK; Servier; UCB; Lilly; J&J

Identification of central pharmacodynamic markers

PharmaCog : focus on innnovation, translation and harmonisation



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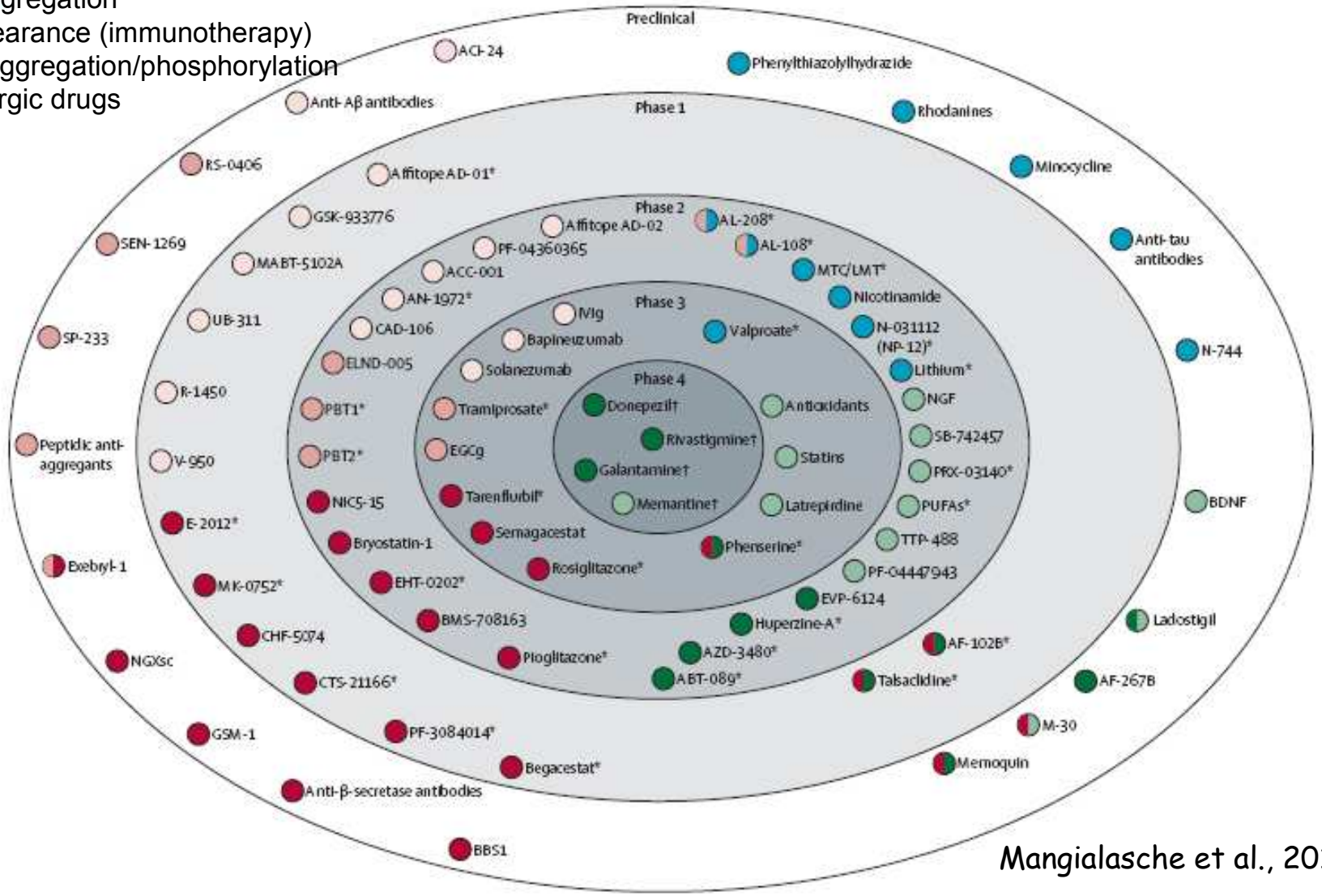
Drug development in AD

- ↓Aβ production
- ↓Aβ aggregation
- ↑Aβ clearance (immunotherapy)
- ↓Tau aggregation/phosphorylation
- Cholinergic drugs
- Others



Adv

Mangialasche et al., 2010

Poor predictive validity of pre-clinical testing

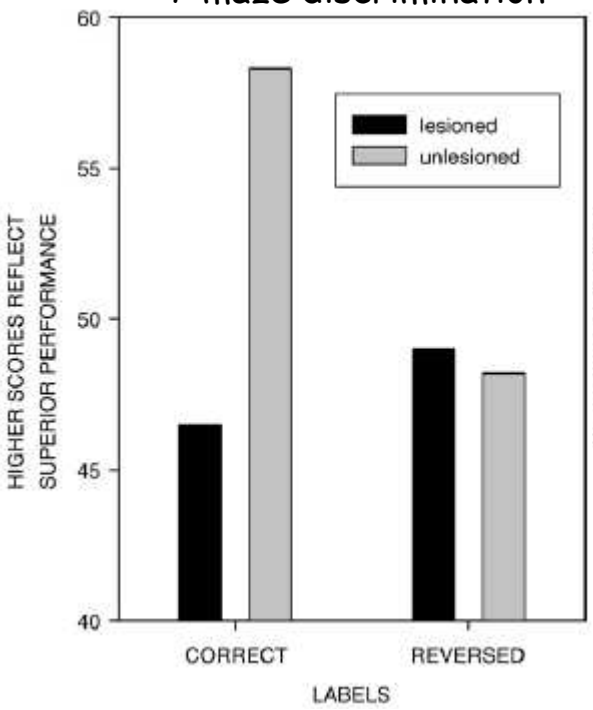
Compounds for AD and cognition disorders discontinued in phase III

Drug	Mechanism of action	Country tested	Reason discontinued?	No. preclinical efficacy pub's.	Control for bias
Adafenoxate (WON 150)	L-lactate dehydrogenase stimulants	Spain	Unknown	7	None
Ensaculin (Anseculin KA 672)	Undefined	Germany	Potential side effects	2	None
Eptastigmine (Heptylphysostigmine, Heptylstigmin, L 693487, MF 201)	Acetylcholinesterase inhibitor	Italy, United Kingdom, USA	Aplastic anemia	7/8	None
Ipidacrine (Amiridin, Amiridine, NIK 247, Senita)	Acetylcholinesterase inhibitors; Potassium channel antagonists	Japan	Lack of efficacy	12	None
Lazabemide (RO 196327, Pakio, Tempium)	Antioxidants; Monoamine oxidase B inhibitors	Europe and Japan	Severe hepatotoxicity	0	N/A
Linopirdine (Aviva, DUP 996, Linopirine)	Acetylcholine release stimulants	Canada and USA	Lack of efficacy	8/10	None
Milameline (CI 979, Mirameline, PD 129409, RU 35926, Vivad)	Muscarinic receptor agonists	European Union and USA	Toxicity	3	None
ORG 2766[a]	Adenylate cyclase stimulants	USA	Lack of efficacy	4	None
Suritozole (MDL 26479)	Benzodiazepine receptor inverse agonists	United Kingdom	Business decision	4	None
Xanomeline (LY 246708, NNC 110232, Memcor)	Muscarinic M1 and M4 receptor agonists	USA	Adverse effects	2	None
Zanapezil (TAK 147)	Acetylcholinesterase inhibitors	Japan	Lack of efficacy	3	None

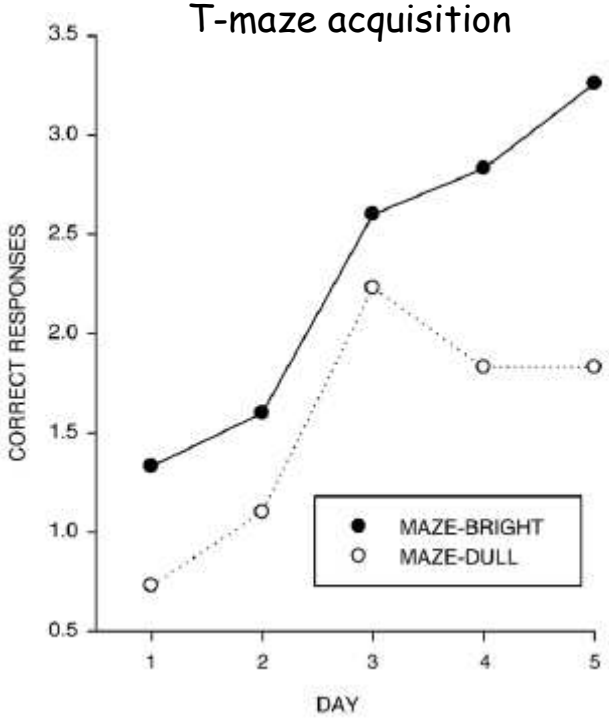
The reasons for failure are not always clear

Poor predictive validity – bias issue

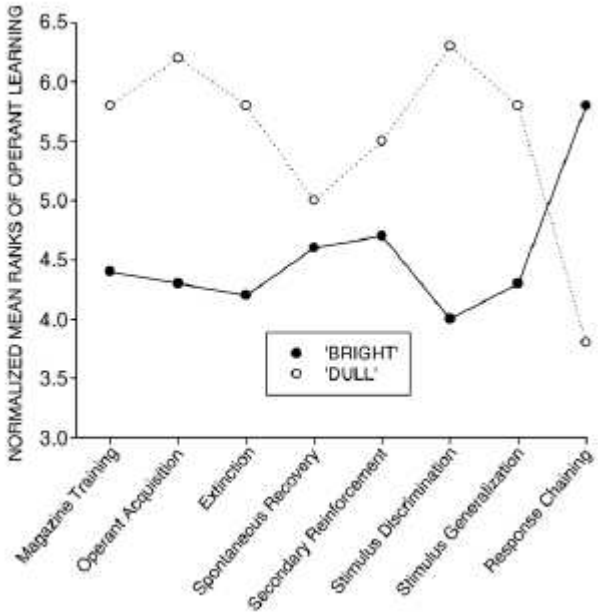
T-maze discrimination



T-maze acquisition

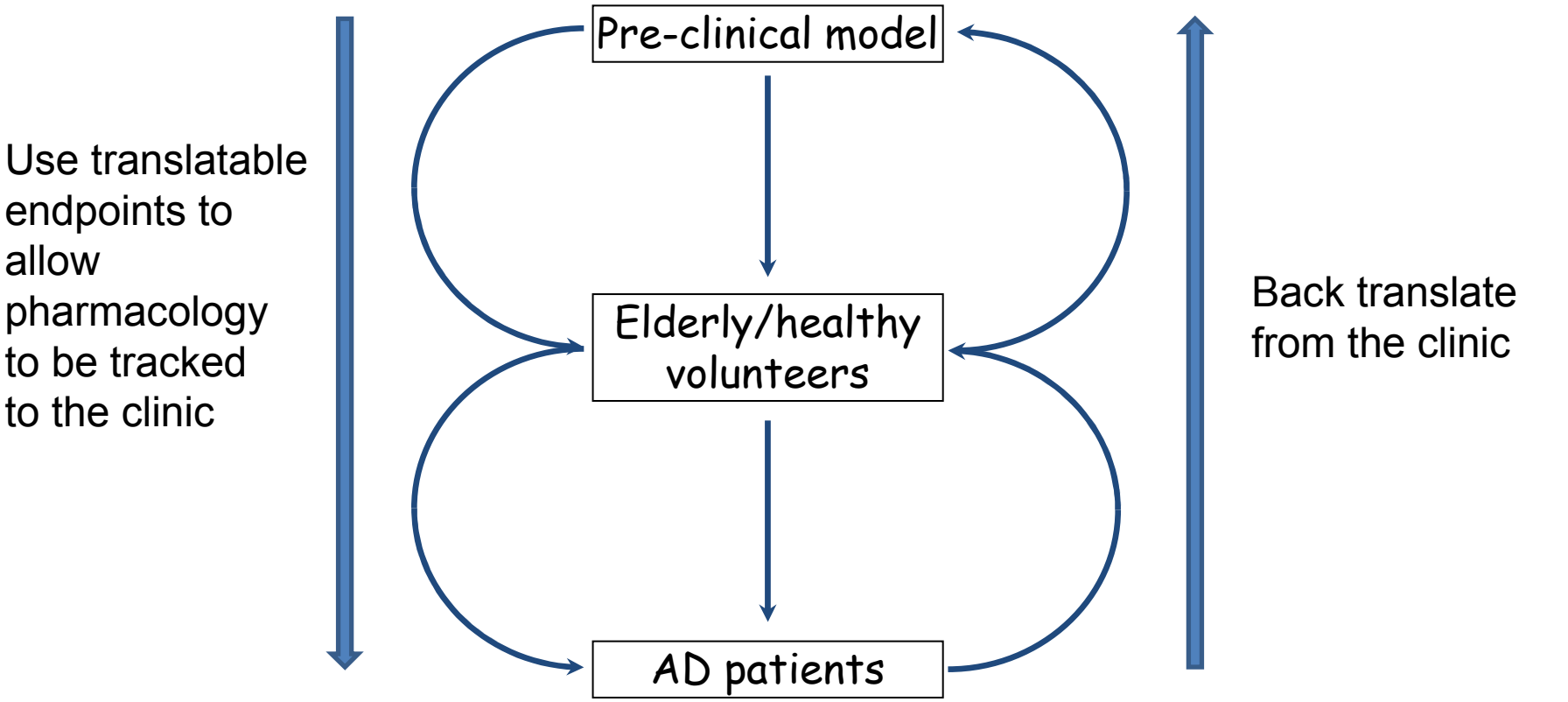


Operant learning



Lindner, Pharmacol & Therap, 2007

There is a need to improve our of pre-clinical and clinical models



WP4 Improving translation: focus on pharmacology

Dr Esther Schenker (Servier) and Dr John Atack (J&J)

Biomarker battery:

regional cerebral blood flow (rCBF)
glucose utilization
electroencephalogram (EEG)
functional Magnetic Resonance Imaging (fMRI)
cognitive tests using brain circuits at risk

and that are easily translatable to the clinic

First steps:

1-Harmonization of measurements across sites
2-Biomarker battery and approved treatments for AD
3-Sensitivity of the biomarker battery
4-Touch screen technology

Development of Touch screen technology in rodents: translatable across species

e.g. paired associate learning (PAL)

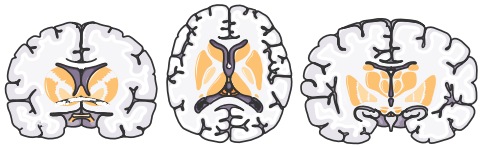
CANTAB battery - humans

Non-verbal tests sensitive to pharmacological agents

WP3 Development of pharmacodynamic biomarkers : clinical approach

To be conducted in France : Prof Regis Bordet (Lille) and Pierre Payoux (Toulouse, INSERM)

Brain scans



Blood analysis

Healthy Volunteers

Placebo v's 15d Donepezil

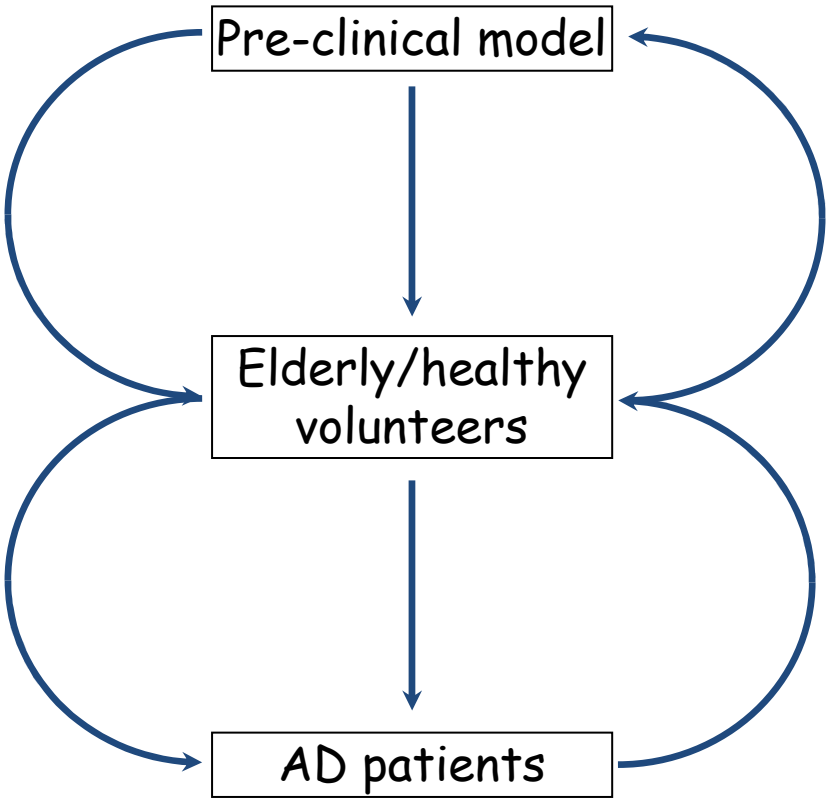
Cognitive testing

Alzheimer Patients

Brain talk (EEG)

Identify the 'fingerprint' which is most predictive

The impact of PharmaCog : Improve translational understanding of pre-clinical and clinical models



Identify pharmacodynamic markers for:

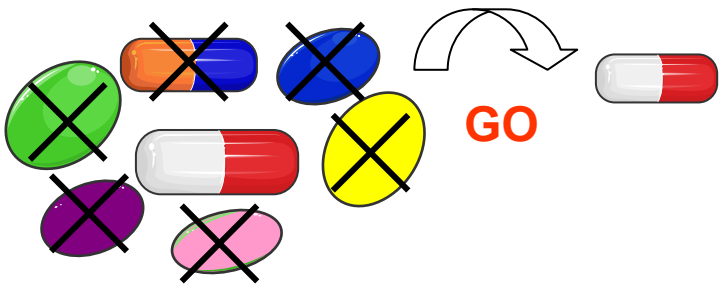
- drug activity
- disease state

to increase the predictability in new drug trials

The impact on the drug discovery process

- Provide robust and well-characterized experimental and clinical models that mimic the disease
- Innovative treatments of Alzheimer's disease efficacy will be assessed on models with proven translational validation
- The translation between experimental and clinical validated models would greatly enhance the predictability of the effect of the drug in phase II and III clinical trials

Sorting the good from the Bad



PharmaCog

Advancing science and treatment of Alzheimer's Disease

Towards designing better clinical studies

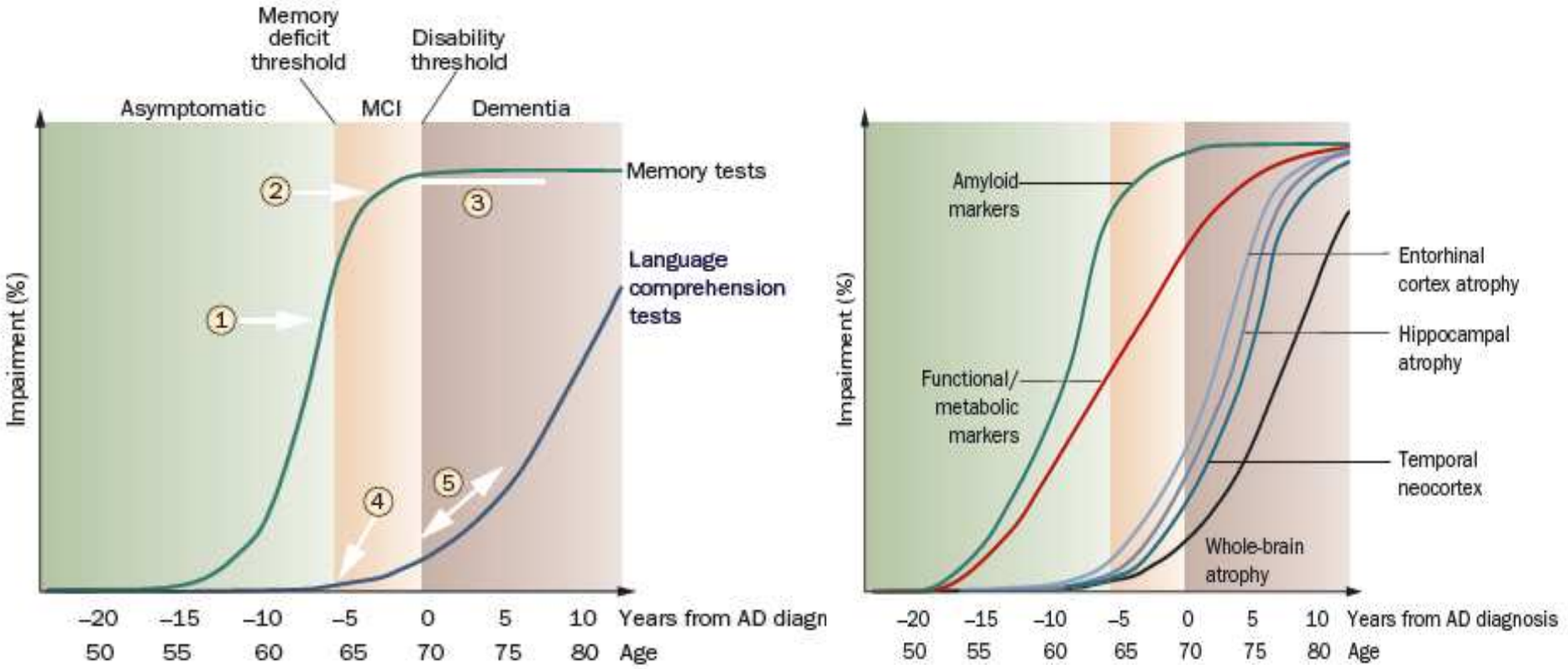
Dr Mike O'Neill

The Challenges

- Symptomatic relief versus altering disease
- No effective treatments currently available for slowing disease
- Long trials with large numbers of patients are required to detect clinical benefit

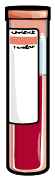
Alzheimer's Disease (AD) diagnosis

State of the art



Frisoni et al., 2010

The PharmaCog approach



Blood analysis

+

Cognitive testing

+

Brain talk (EEG)

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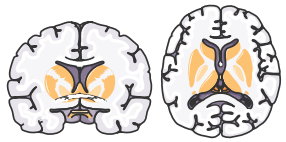


Brain scans

Cross platform analysis

Cognitive testing

+ ??? + ??? = Sensitivity

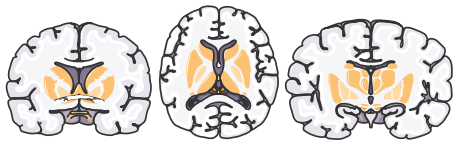
PharmaCog : focus on innovation, translation and harmonisation

Blood analysis

Brain talk (EEG)

Cognitive testing

3 year follow up of 150 MCI patients Italy, France, Germany,Spain



Brain scans

Harmonize collection of a new biomarker matrix and qualify multiple centres across Europe

Biomarker matrix in which change over time in MCI patients is most closely related to atrophy development and clinical deterioration/conversion to AD

Biomarker matrix at baseline in MCI patients that is most closely related to atrophy development and/or clinical deterioration/conversion to AD

Work package leaders : Prof Giovanni Frisoni (Brescia) & Dr Hans-Goran Hardemark (AZ)

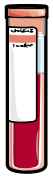
Advancing science and treatment of Alzheimer's Disease

Innovative Medicines Initiative

Enhancing the predictive capacity of preclinical models

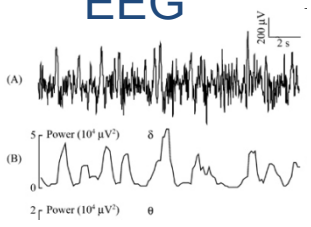
PharmaCog

Blood analysis

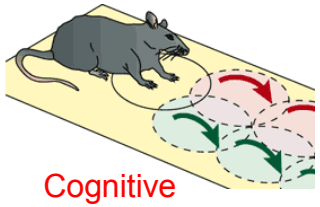


Blood flow

EEG

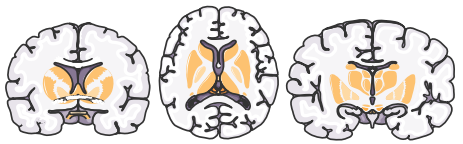


Glucose use



Cognitive testing

Preclinical models used to progress assets currently under clinical testing



Brain scans

Outcome of clinical trials

Outcome of MCI study

Models describing –
1.relationship between disease progression and marker
2.Relationship between pre-clinical models and AD
3.Better understanding of the predictive capacity

WPLs :
Dr Michael O'Neill (Lilly)
Dr Philippe Verwaerde (AlzProtect)

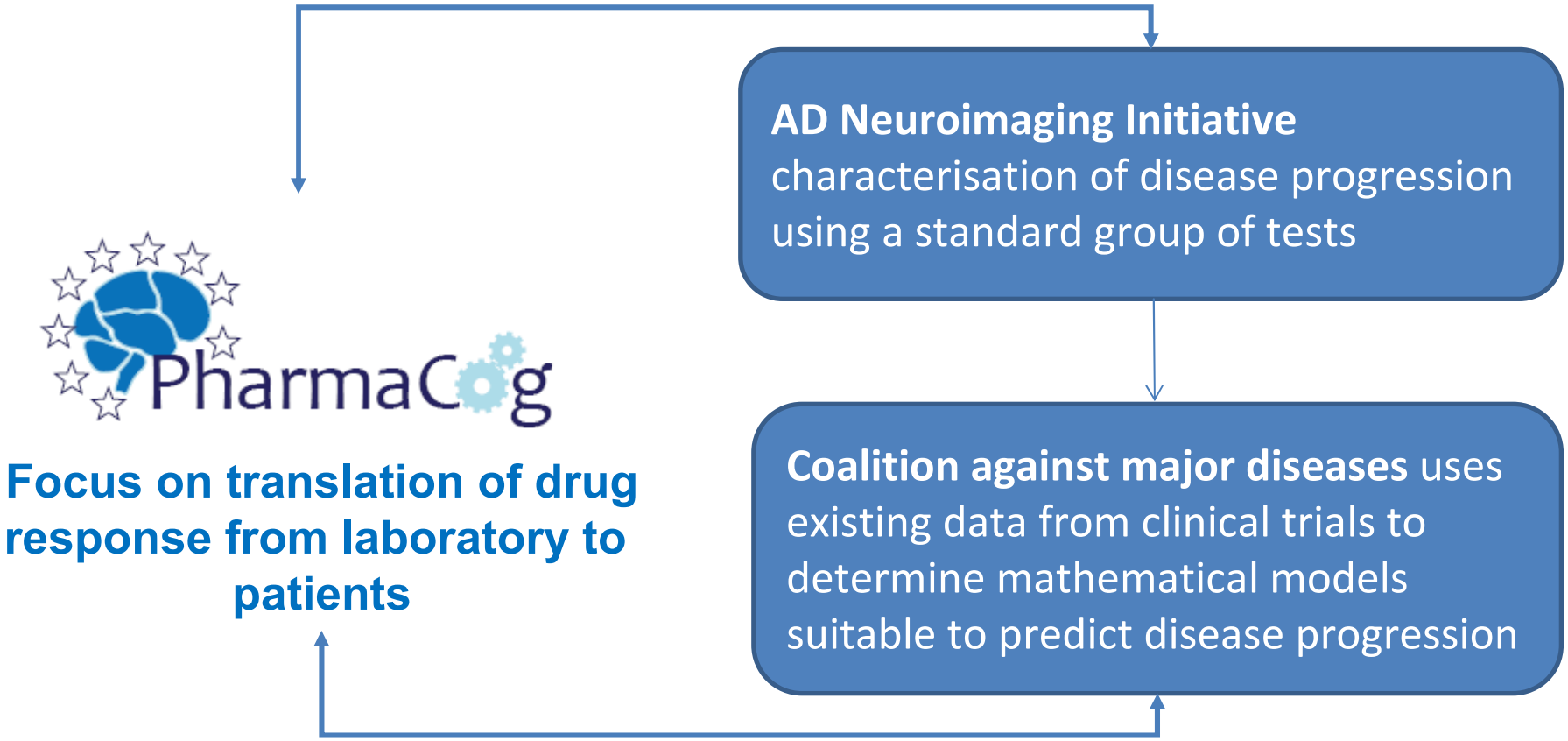
Advancing science and treatment of Alzheimer's Disease

imi
Innovative Medicines Initiative

Outcomes will improve clinical study design

- Better understanding of how pre-clinical models translate to patients
  - Increase ability to rank potential new medicines and select appropriate doses
- Identified a ‘fingerprint’ of markers that reflect disease severity
  - Endpoints potentially sensitive to drug intervention therefore reducing trial size and duration
- Identified a ‘fingerprint’ of markers that predict rate of disease progression from the earliest stages
- Mathematical models to describe relationship of disease progression pre-clinically and clinically

Complementarities with other major Alzheimer's Disease Research Initiatives



The impact of PharmaCog activities

Robust and well-characterized experimental / clinical models to predict drug efficacy

A translational battery of markers qualified for use to support drug dose prediction and clinical efficacy

The ability to model changes in biomarkers to predict clinical efficacy

An Alzheimer's biomarker battery to better predict the disease progression and support new medicine development

PharmaCog : focus on innovation, translation and harmonisation

All studies conducted are designed to improve our ability to identify successful new medicines as early as possible while stopping progression of those destined to fail

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Innovative Medicines Initiative