Prediction and Faster Assessment of Functional Properties of New Drug Candidates for Alzheimer’s Disease in Early Clinical Development:

The IMI PharmaCog project

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There is an urgent requirement for tools that provide objective measures to enable:

- **Stratification** of patient populations (diagnosis)
- **Classification of disease severity** (surrogate endpoint)
- **Prediction** of treatment outcome (risk factor)
- **Drug response** (pharmacodynamics)
Brain Atrophy in AD precedes Cognitive Impairment by years

Unsuccessful Alzheimer’s Drugs in Development 1998-2011

101 drugs failed

PhRMA 2012 RESEARCHING ALZHEIMER’S MEDICINES: SETBACKS AND STEPPING STONES
Why have there been so many Failures in Late Stage Trials for AD?

- Lack of robust pre-clinical data to support clinical study
- Lack of harmonisation of protocols and common data sets at both pre-clinical and clinical levels
- Drugs are usually tested in a heterogeneous population - enrichment of patients may be required to demonstrate proof of mechanism
- Disease modifying therapies tested too late in the course of the disease
- Failure to identify endpoints relevant and accepted for the intended claim or that are sensitive to the full breadth of AD. Lack of clarity on how biomarkers translate into clinical benefit?
The challenges that are impeding the progress of drug discovery in AD

- Lack of validated **models** for target selection
- Lack of validated **models** to support ranking and dose selection
- Lack of validated **models** to predict clinical efficacy
- Currently long trials with large numbers of patients are required to detect clinical benefit

- More extensive target validation required due to lack of precedented mechanisms
- Lack of **markers** to demonstrate effective dosing
- Lack of **markers** to determine clinical efficacy

Discovery Research → Preclinical Develop. → Translational Medicine Phase I & II → Phase III → Phase IV

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Public Private Partnerships are essential to addressing the high hurdles of AD Drug Discovery

Partnership between:
- Academia
- Industry
- SMEs
- Patient Groups
- Regulators

Start date: 1/1/2010
Duration: 5 years
Partners: 38
Total cost: €27.7M
What the PharmaCog partners contribute

**EMA**
- Advice on regulatory matters
- Information on clinical trials in AD

**Alzheimer Europe**
- Communication of project results
- Access to patients

**Academic Institutions:**
- Expertise of world leading disease scientists
- Technology experts
- Novel models and biomarkers
- European Alzheimer's Disease Neuroimaging Initiative (ADNI) leader

**Public**
- Motivation
- Dedication

**Private**
- **EFPIA Partners**
  - Experts in Alzheimer’s Disease Drug Discovery
  - Archived data from experimental & clinical studies using standard agents
  - Quantitative pharmacology expertise
  - Experience of multi centre studies and protocol harmonization
  - Statistics & Bioinformatics

**SMEs**
- New innovative biomarkers
- Expertise in clinical trial authorisation procedures
PharmaCog Project: Objectives

To develop and validate the models required to increase the effectiveness of the drug discovery process in Alzheimer’s disease:

- Develop and validate (i) pre-clinical models with greater predictive value of the drug effect in the clinic and (ii) clinical models that provide an ‘early hint’ of efficacy
- Develop and validate translatable pharmacodynamic markers to support dose selection in humans
- Identify and validate markers of disease progression and patient stratification
- Gain industry and regulatory acceptance of endpoints, PK/PD models and markers of efficacy

Develop pan European network of experts in technologies fully translatable from animal to human, experts in translational medicine, drug discovery and mathematical modelling
Accelerate Translational Medicine Using a Multidimensional MATRIX

Matrix Development Strategy

Challenge

Phase Ia/Ib

GO/NOGO

Phase II

Therapeutic

Electrophysiology
Psychophysiology
Imaging
Biology

Cellular
Animal
HV
Selected Patient

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Focus on Innovation, Translation and Harmonisation

Block 1
(How to model AD cognitive deficits?)

WP1: Clinical rTMS
     Sleep Dep
     Hypoxia

WP2: Pre-Clinical
     Electrical stim
     Sleep Dep
     Hypoxia

Block 2
(How to get the best treatment and dose?)

WP3: Clinical
     HVT
     AD

WP4: Pre-Clinical
     Rat
     Lemurs
     APP Tg

Block 3
(Determine effect of disease progression and drug treatment on biomarker matrix)

WP5: Clinical
     MCI
     HVT

WP6: Pre-Clinical
     PDAPP
     TASTPM
     Triple Tgs
     Lemurs

Specific models/endpoints

WP7
PK/PD modelling

WP8
Statistics

WP7, WP8
Core biomarker set: EEG, Vigilance, P300, MRI, cognition

Harmonised protocols procedures

Centralised and standardised data analysis

Pharma-Cog Standards applied to all studies

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WP5: Development of Disease Markers in Humans

- **Blood analysis**
- **Brain talk (EEG)**
- **Brain scans**

- **Cognitive testing**

- **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**

2 year follow up of 150 MCI patients
Italy, France, Germany, Spain, Greece, The Netherlands

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Innovation through:

• the design closely mirroring a clinical trial with CSF markers for enrichment

• the parallel design of biomarker discovery/validation in humans and animal models, eg. testing of resting state EEG and auditory "oddball" ERPs as electrophysiological markers and assessment of cognitive functions by touch screen technology (e.g. CANTAB) that can be back translated to preclinical research

• the strong emphasis on novel peripheral biomarkers as a result of the participation of a number of SME biotechs

The relationship of PharmaCog with the NA-ADNI focuses on:

• the use in WP5 of data acquisition procedures (MR imaging, neuropsychology, clinical data, biosample collection) closely harmonized to ADNI

• a close relationship of WP5 leader, Professor Giovanni Frisoni with NA-ADNI core leaders enabling regular exchange on progress and methodological developments
Cognitive impairments linked to sleep deprivation established in 3 different species (rat, octodons, lemurs) and reversal using gold standard symptomatic drugs demonstrated in octodons and lemurs

Significant progress in developing and harmonising a unified cognition touchscreen protocol

Intensive harmonisation of EEG protocols across pre-clinical species and profiling of AChE-I and memantine using EEG vigilance state biomarkers in the rat and mouse

Longitudinal characterisation of 3 AD Tg mice using imaging, cognition, EEG, electrophysiological and a biological marker battery (including novel markers from SMEs)

Optimisation of 4 clinical study designs, for which protocols have been finalised, endpoints agreed, procedures harmonised and enrolment started across all sites:
- Sleep deprivation now including positive control as challenge model (WP1)
- Transcranial Magnetic Stimulation (TMS) pilot study as challenge model (WP1)
- 15-day donepezil treatment on biomarkers of AD in HV (WP3)
- Biomarkers sensitive to disease progression in patients with MCI (WP5)
The Impact of PharmaCog Activities: Improving Clinical Study Design

Robust and well-characterised experimental/clinical models to predict drug efficacy:
- screening and ranking of new molecules

A translational battery of markers qualified for use to:
- support dose selection, patient selection and protocol stratification criteria

A model-based approach using:
- changes in biomarkers to predict clinical efficacy

An Alzheimer’s disease biomarker battery:
- to better predict disease progression as well as discriminate disease-modifying from symptomatic treatment effects

Blood analysis

Experimental Models

Clinical Models

PK/PD

Brain scans

Cognitive testing

Brain talk (EEG)
The Wider Impact of PharmaCog

- Driving changes in internal practices and protocols in AD research BASED ON AN IMPROVEMENT OF BACK-TRANSLATION FROM CLINICAL TO PRECLINICAL RESEARCH
- Building an AD network between EFPIA, academia and biotech to foster future collaboration, access technological expertise, share data and to establish ‘harmonised’ clinical centres for drug studies
- Raising issues in AD translational research to budget holders, eg. EU Parliament
- Delivery of a unique database on the effect of AD drugs on a matrix of biomarkers IN HARMONISED PRECLINICAL AND CLINICAL STUDIES
- Enabling early interactions with regulators (FDA/EMA) on standardised and harmonised AD biomarkers
Acknowledgements:

- David Bartres-Faz, University of Barcelona
- Fabien Pifferi, CNRS
- Regis Bordet, University of Lille
- Xavier Langlois, Janssen
- Giovanni Frisoni, IRCCS Fatebenefratelli
- Sophie Dix, Eli Lilly & Co. Ltd
- Gianluigi Forloni, Mario Negri Istituto di Ricerche Farmacologiche
- Claudio Bablioni, University of the Studies of Foggia
- Alex Teligadas, Alzheimer Europe
- Peter Schoenknecht, Universitätsklinikum Leipzig
- Maria-Trinidad Herrero Ezquerro, Universidad de Murcia
- Philipp Spitzer, Universitat Duisburg-Essen
- Severine Pitel, Qualissima
- Maria Isaac, EMA

- Pascal Beurdeley, Exonhit
- Jean de Barry, Innovative Health Diagnostics
- Nathalie Compagnone, Innovative Concept in Drug Development
- Bernd Sommer, Boehringer Ingelheim Pharma GmbH & Co KG
- Cristina Lopez Lopez, Novartis Pharma AG
- Esther Schenker, Institut de Recherche Servier
- Heike Hering, Merck Serono S.A.
- Emilio Merlo-Pich, F. Hoffmann-La Roche
- Jan Egebjerg, H. Lundbeck A/S
- Yves Lamberty, UCB
- Jill Richardson, Oscar della-Pasqua, Lesley Stubbs, David Wille, GlaxoSmithKline R&D Ltd
- Pierre Payoux, Institut National de la Santé et de la Recherche Médicale
- Marina Bentivoglio, University of Verona
- Philippe Verwaerde, Alzprotect
- Lee Dawson, Eisai

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