CRITICAL PATH INSTITUTE

Innovative Medicines Initiative

# 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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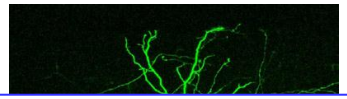
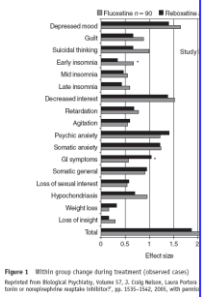
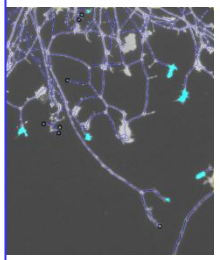
# Challenges of Neuroscience Drug Discovery

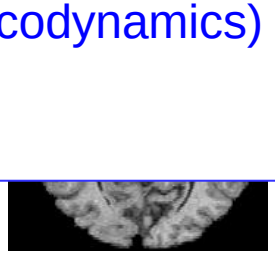




There is an urgent requirement for **tools** that provide **objective measures** to enable:

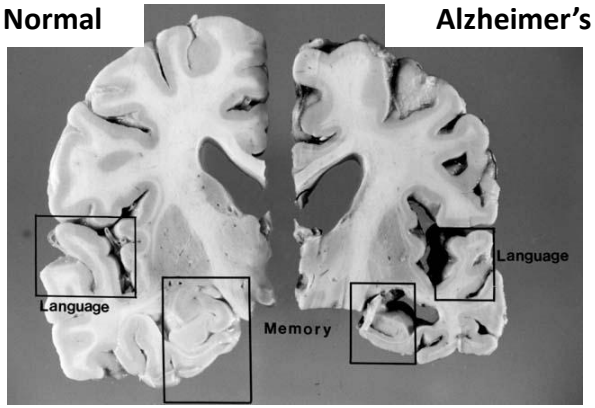
- Stratification of patient populations (diagnosis)
- Classification of disease severity (surrogate endpoint)
- Prediction of treatment outcome (risk factor)
- Drug response (pharmacodynamics)

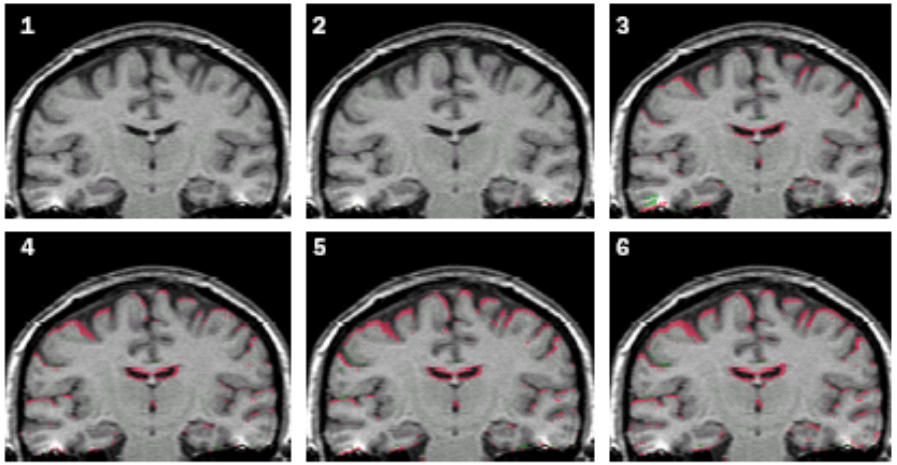


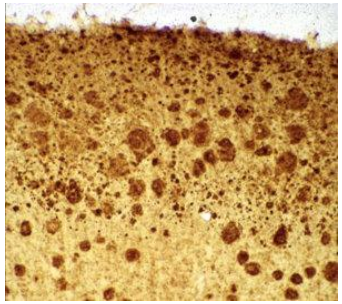



➢ **Tolerance \ Sensitization**

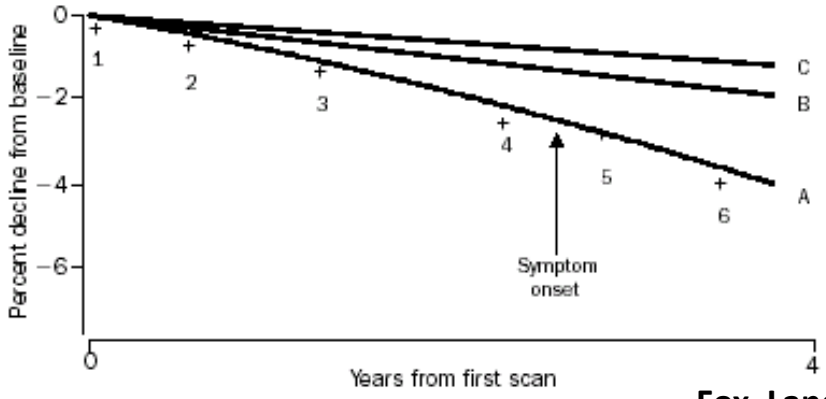
# Brain Atrophy in AD precedes Cognitive Impairment by years



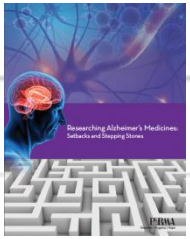
Aβ plaques




Fox, Lancet (2004)

# Unsuccessful Alzheimer's Drugs in Development

## 1998-2011



**101 drugs failed**

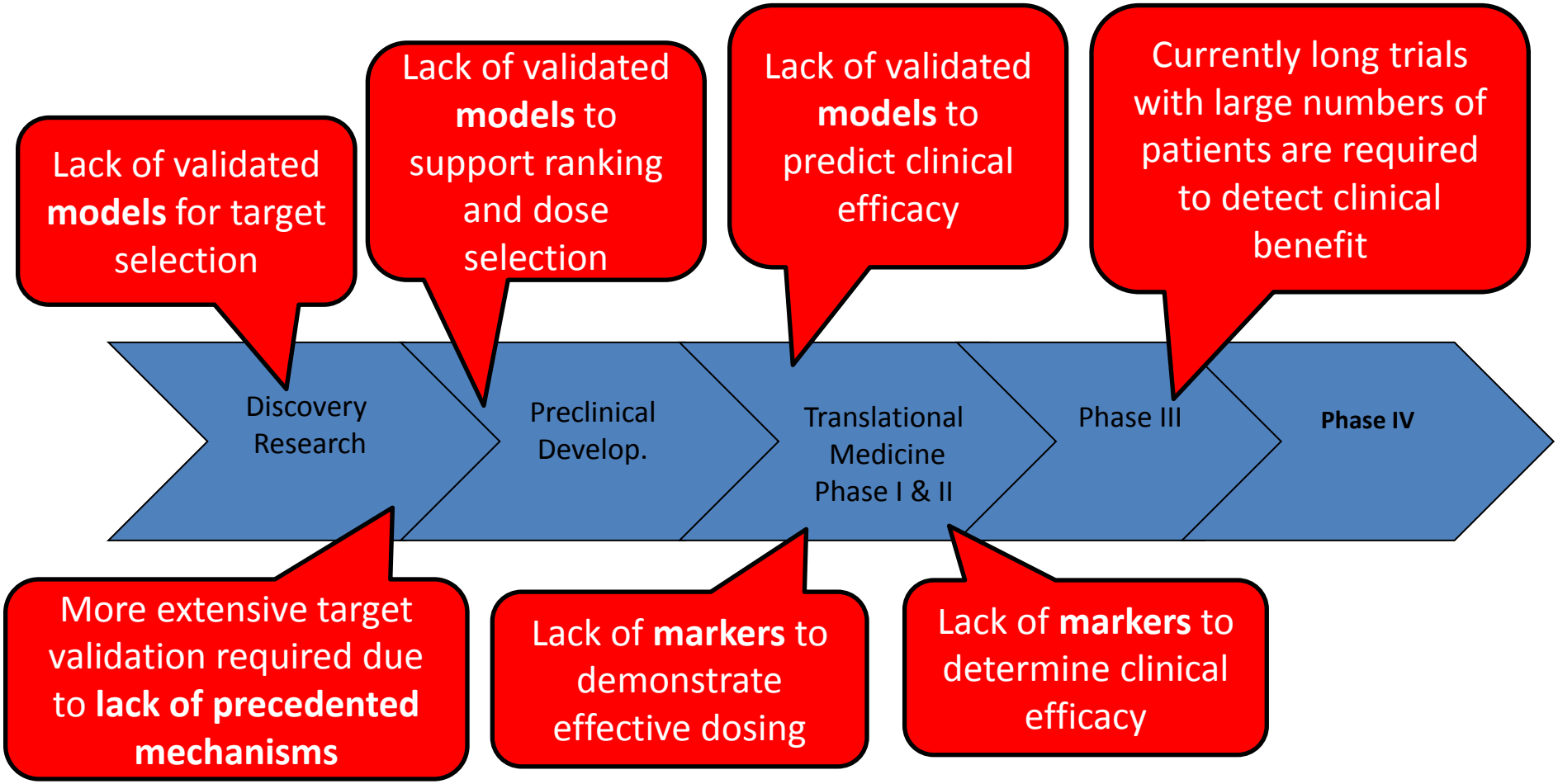



PhRMA 2012 RESEARCHING ALZHEIMER'S MEDICINES: SETBACKS AND STEPPING STONES

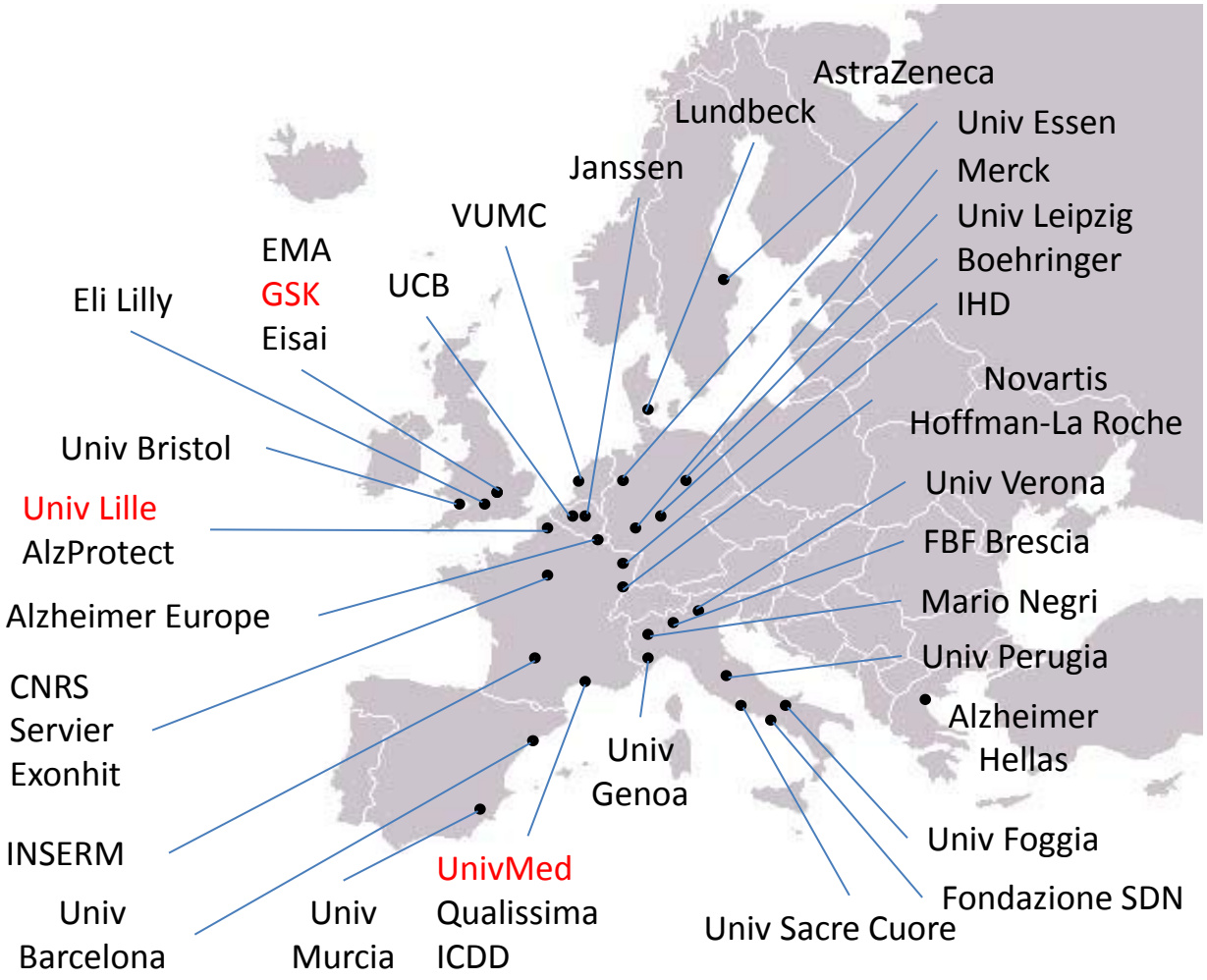
# Why have there been so many Failures in Late Stage Trials for AD?

- 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



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




PharmaCog

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

**Public**

*Motivation*
*Dedication*

**Private**

**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


**SMEs**
- New innovative biomarkers
- Expertise in clinical trial authorisation procedures

**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

# 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

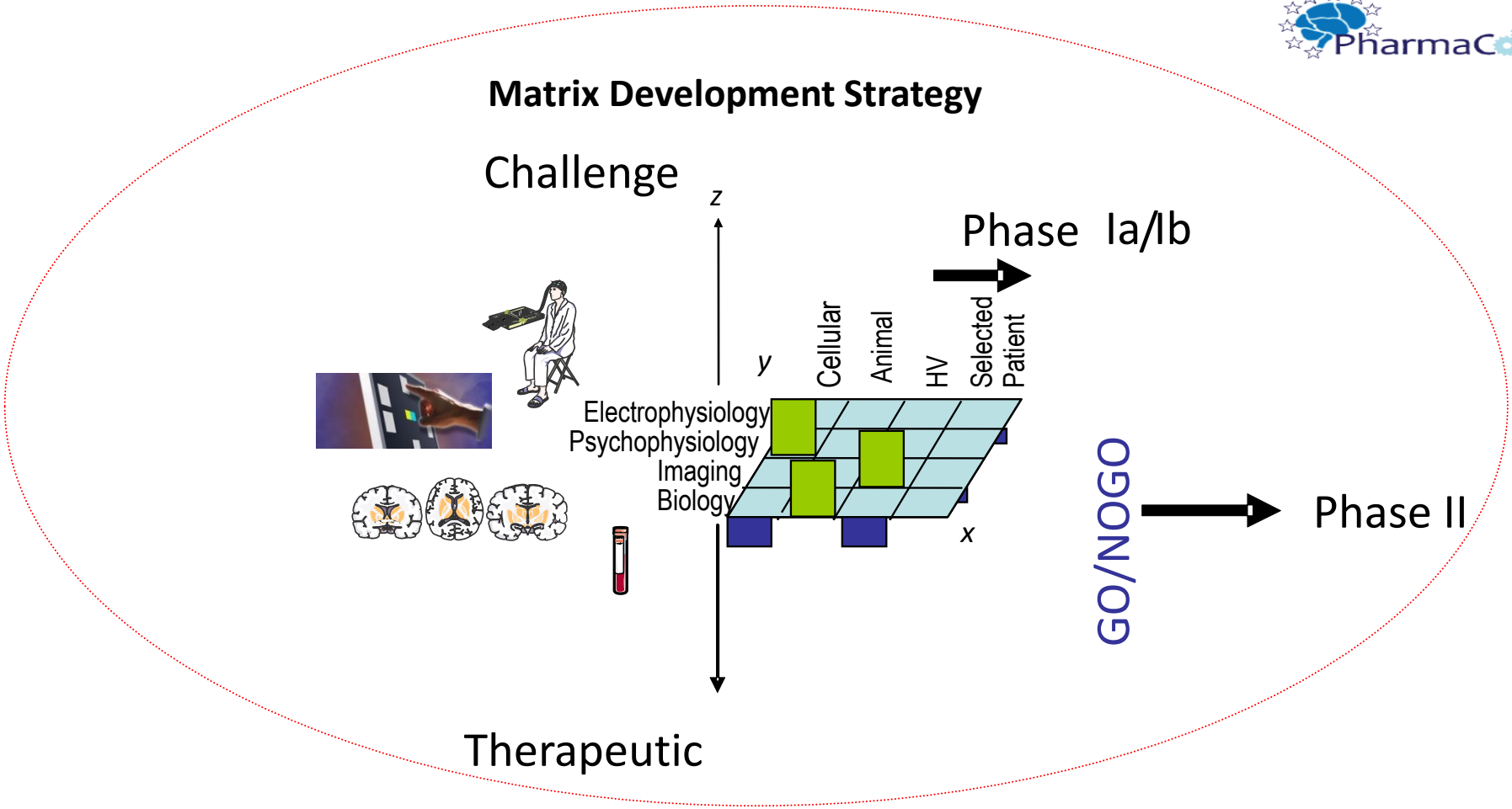
Develop and validate translatable pharmacodynamic markers to support dose selection in humans

Identify and validate markers of disease progression and patient stratification

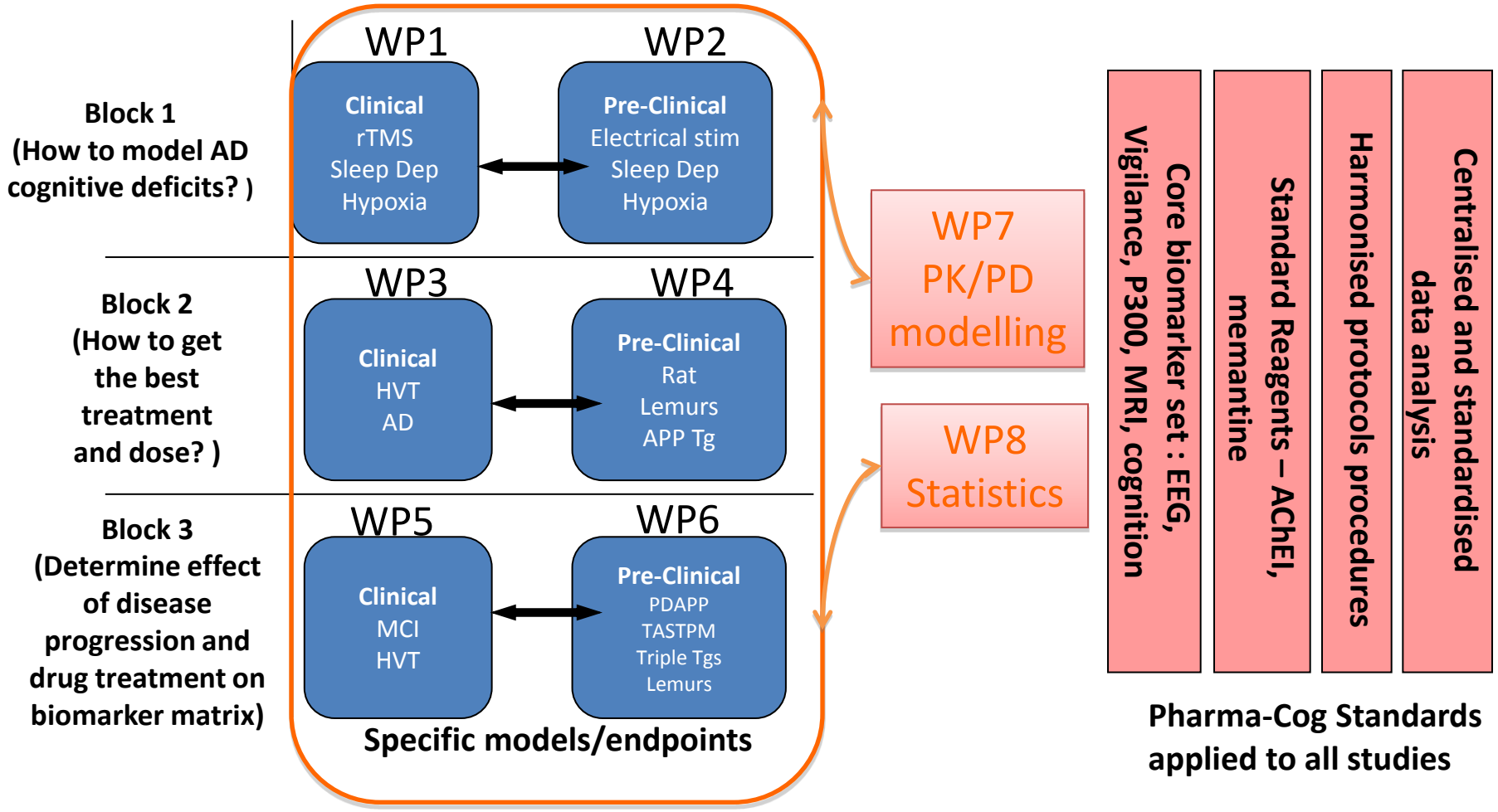
Gain industry and regulatory acceptance of endpoints, PK/PD models and markers of efficacy

Develop pan European network of experts in technologies fully translatable from animal to human, experts in translational medicine, drug discovery and mathematical modelling

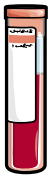
# Accelerate Translational Medicine Using a Multidimensional MATRIX



# Focus on Innovation, Translation and Harmonisation



# WP5 : Development of Disease Markers in Humans

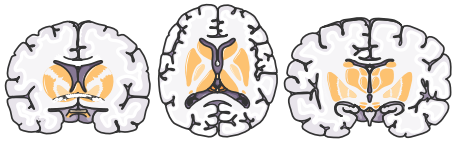


Blood analysis

Brain talk (EEG)

Cognitive testing

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



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

# Relationship of PharmaCog to other AD Initiatives

**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

# Highlights of PharmaCog Progress

- 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

PK/ PD

Experimental Models ⟷ Clinical Models

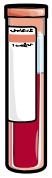
Robust and well-characterised experimental/ clinical models to predict drug efficacy:
screening and ranking of new molecules

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

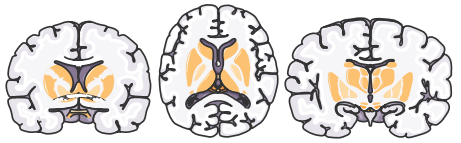
A model-based approach using:
changes in biomarkers to predict clinical efficacy

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

**Blood analysis**



**Cognitive testing**



**Brain scans**

**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

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