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
A Public Private Partnership

IMI Research funding for Academia, SMEs, patients organisations, Regulatory Authorities, etc.

* Research performed by EFPIA member companies = in kind contribution

IMI Research Projects

€1 billion

Innovative Medicines Initiative

EFPIA

European Federation of Pharmaceutical Industries and Associations

€1 billion

European Union

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

Regulators

Patient Groups

DATA

= best approach

Advancing science and treatment of Alzheimer's Disease
Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development
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

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
Lack of markers to demonstrate effective dosing
Lack of markers to determine clinical efficacy

Need to detect the winners earlier

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PharmaCog: focus on innovation, translation and harmonisation

- Develop laboratory based models and clinical models that mimic 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.

**Experimental Models**

- Blood analysis
- Cognitive testing

**Clinical Models**

- Brain scans
- Brain talk (EEG)

Core biomarker set

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PharmaCog Partners

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
What we bring to the project

**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

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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

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Tools to improve decision making in drug development

Dr Alexandra Auffret
PharmaCog: focus on innovation, translation and harmonisation

- 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

Experimental Models

Clinical Models

Blood analysis

Cognitive testing

Core biomarker set

Brain talk (EEG)

Brain scans

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

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The PharmaCog approach

- How can we develop these models?

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

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

Healthy Volunteers
Clinical models

Induce reversible cognitive impairments

Experimental models

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

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WP1: challenge models of transient cognitive impairment in healthy volunteers

Define and harmonize three parallel clinical challenges:

- Sleep Deprivation
- Transcranial Magnetic Stimulation (rTMS)

Harmonised evaluations:

- Blood analysis
- Cognitive testing
- Brain scans
- Brain talk (EEG)

- 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

**Harmonized evaluations across species**

- Sleep Deprivation
- Transcranial Magnetic Stimulation (rTMS)
  - Blood analysis
  - Brain talk (EEG)

**Questions**
- 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

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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 innovation, translation and harmonisation

- Develop laboratory-based models and clinical models that mimic 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.

Experimental Models

- Cognitive testing
- Blood analysis

Clinical Models

- Brain scans
- Brain talk (EEG)
- Core biomarker set

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Drug development in AD

- \(\downarrow\) Aβ production
- \(\downarrow\) Aβ aggregation
- \(\uparrow\) Aβ clearance (immunotherapy)
- \(\downarrow\) Tau aggregation/phosphorylation
- Cholinergic drugs
- Others

Mangialasche et al., 2010
Poor predictive validity of pre-clinical testing

Compounds for AD and cognition disorders discontinued in phase III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Country tested</th>
<th>Reason discontinued?</th>
<th>No. preclinical efficacy pub’s.</th>
<th>Control for bias</th>
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<tbody>
<tr>
<td>Adafenoate (WON 150)</td>
<td>l-lactate dehydrogenase stimulants</td>
<td>Spain</td>
<td>Unknown</td>
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<td>None</td>
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<td>Ensacluln (Anseclun KA 672)</td>
<td>Undefined</td>
<td>Germany</td>
<td>Potential side effects</td>
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<td>None</td>
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<td>Eptastigmine (Heptyllphysostigmine,</td>
<td>Acetylcholinesterase inhibitor</td>
<td>Italy, United Kingdom, USA</td>
<td>Aplastic anemia</td>
<td>7/8</td>
<td>None</td>
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<td>Heptylsigmin, L 693487, MF 201)</td>
<td></td>
<td>Japan</td>
<td>Lack of efficacy</td>
<td>12</td>
<td>None</td>
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<td>Ipidaecine (Amiirin, Amiridine, NIK 247,</td>
<td>Acetylcholinesterase inhibitors;</td>
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<td>Severe hepatotoxicity</td>
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<tr>
<td>Senita)</td>
<td>Potassium channel antagonists</td>
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<td>Lazabemide (RO 196327, Pakio, Tempium)</td>
<td>Antioxidants; Monoamine oxidase B inhibitors</td>
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<td>Linopirdine (Aviva, DUP 996, Linopirine)</td>
<td>Acetylcholine release stimulants</td>
<td>Canada and USA</td>
<td>Lack of efficacy</td>
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<td>Milameline (CI 979, Mirameline, PD 129409,</td>
<td>Muscarinic receptor agonists</td>
<td>European Union and USA</td>
<td>Toxicity</td>
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<td>RU 35926, Vivad)</td>
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<td>ORG 27664</td>
<td>Adenylate cyclase stimulants</td>
<td>USA</td>
<td>Lack of efficacy</td>
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<td>Surltozole (MDL 26479)</td>
<td>Benzodiazepine receptor inverse agonists</td>
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<td>Business decision</td>
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<td>None</td>
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<td>Xanomeline (LY 246708, NNC 110232, Memcor)</td>
<td>Muscarinic M1 and M4 receptor agonists</td>
<td>USA</td>
<td>Adverse effects</td>
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<td>None</td>
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<td>Zanapezil (TAK 147)</td>
<td>Acetylcholinesterase inhibitors</td>
<td>Japan</td>
<td>Lack of efficacy</td>
<td>3</td>
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</tr>
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</table>

The reasons for failure are not always clear

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Poor predictive validity – bias issue

Lindner, Pharmacol & Therap, 2007

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There is a need to improve our pre-clinical and clinical models. Use translatable endpoints to allow pharmacology to be tracked to the clinic and back translate from the clinic.

- Pre-clinical model
- Elderly/healthy volunteers
- AD patients

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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

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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

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WP3 Development of pharmacodynamic biomarkers: clinical approach

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

Healthy Volunteers

Blood analysis

Cognitive testing

Placebo v’s 15d Donepezil

Alzheimer Patients

Brain scans

Brain talk (EEG)

Identify the ‘fingerprint’ which is most predictive

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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

Pre-clinical model
Elderly/healthy volunteers
AD patients

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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

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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

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The PharmaCog approach

Blood analysis + Cognitive testing + Brain talk (EEG) + Brain scans

Cross platform analysis

Cognitive testing + ??? + ??? = Sensitivity

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PharmaCog: focus on innovation, translation and harmonisation

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

Cognitive testing
Blood analysis
Brain talk (EEG)
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)
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Enhancing the predictive capacity of preclinical models

Preclinical models used to progress assets currently under clinical testing

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

Outcome of clinical trials

Outcome of MCI study

Blood analysis

EEG

Blood flow

Brain scans

Glucose use

EEG

Blood flow

Outcome of MCI study

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

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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

AD Neuroimaging Initiative
- characterisation of disease progression using a standard group of tests

Coalition against major diseases uses existing data from clinical trials to determine mathematical models suitable to predict disease progression

PharmaCog
- Focus on translation of drug response from laboratory to patients

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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

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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.

Advancing science and treatment of Alzheimer's Disease
Acknowledgements
To the PharmaCog Team

- David Bartres-Faz, University of Barcelona
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- Peter Schoenknecht, Universitätsklinikum Leipzig
- Maria-Trinidad Herrero Ezquerro, Universidad de Murcia
- Philipp Spitzer, Universität Duisburg-Essen
- Severine Pitel, Qualissima
- Pascal Beurdeley, Exonhit
- John de Barry, Innovative Health Diagnostics
- Nathalie Compagnone, Innovative Concept in Drug Development
- Hans-Göran Hårdemark, AstraZeneca AB
- Bernd Sommer, Boehringer-Ingelheim International
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- Esther Schenker, Institut de Recherche Servier;
- Dirk Beher, Merck Serono S.A.
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- Jan Egebjerg, H. Lundbeck A/S
- Yves Lamberty, UCB
- David Wille, GlaxoSmithKline R&D Ltd
- Oscar della-Pasqua, GlaxoSmithKline R&D Ltd
- Pierre Payoux, Institut National de la Santé et de la Recherche Médicale
- Marina Bentivoglio, University of Verona
- Philippe Verwaerde, Alzprotect

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innovative Medicines Initiative