PharmaCog – Alzheimer’s Disease

Esther Schenker
Institut de Recherches Servier
France
The issue

People with dementia

- 70% of global societal costs of dementia: USA and Western Europe
- 46% of people with dementia live in high income countries

Current lifetime risk of AD dementia in a 65-year old: 10.5% (Sperling et al., 2011)

Total costs

<table>
<thead>
<tr>
<th>Region</th>
<th>Billions US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>210.12</td>
</tr>
<tr>
<td>Central Europe</td>
<td>14.19</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>14.33</td>
</tr>
</tbody>
</table>

Wimo et al. 2013
The issue – 2

- Cognitive impairment
- Disability
- Behavioral & physiological symptoms
- Depression
- Presence of pain
- Physical illness

Early therapeutic intervention can improve:

Cognitive function
Depression, etc. ...

... and delay institutionalization

**Acetylcholinesterase inhibitors (AChE-I)**

- Donepezil (Aricept®)
- Galantamine (Reminyl®)
- Rivastigmine (Exelon®)

**NMDA receptor antagonist**

- Memantine (Ebixa®)
Key research challenges

**Diagnosis**

AD Progression

- **CSF Aβ42**
- **Amyloid imaging**
- **CSF Tau**
- **FDG PET**
- **MRI Hipp volume**
- **Cognitive performance**
- **Function ADL**

Aisen et al., 2010
The need for a PPP

- Building an AD network between EFPIA, academia and biotech to foster future collaboration, access technological expertise and to establish 'harmonised' clinical centres for drug studies
- Enabling early interactions with regulators (FDA/EMA) on AD biomarkers
- Raising issues in AD translational research to budget holders, e.g. EU Parliament
- Delivery of a unique database on the effect of AD drugs on a matrix of biomarker
Headline achievements

Novel Disease Markers in Development by SMEs

**AlzProtect**
Platelets: APP metabolites namely 55 kD and 25 kD fragments determined by Western blots

**Exonhit (now Diaxonhit)**
Lymphocytes: about 150 RNA transcripts including transcripts related to Abeta pathway, to inflammatory pathway and to immune mechanism determined by microarray

**Innovative Health Diagnostics (IHD)**
Red blood cells: binding of Abeta1-42 on cellular membrane and change in PKC conformation in red blood cells, determined by specific fluorescent probes

**Innovative Concept in Drug Development (ICDD)**
Red blood cells: panel of inflammatory markers
Headline achievements

- Touchscreen technology in mice: cross-validation study to assess reliability of the touchscreens - visual discrimination task
- Validation for testing pharmacological agents: in transgenic mice

1) Visual discrimination & cognitive flexibility
2) Visuo-spatial associative learning
3) Sustained attention

CANTAB battery - humans
Non-verbal tests sensitive to pharmacological agents
Pathological cortical neural synchronization in PDAPP and TASTPM mice

- Normalized EEG power density - wake active minus passive behavioral state
- The grand average of the EEG power density for all frequency bands of interest is reported for WT vs. PDAPP mice and WT vs. TASTPM mice
Structural MRI in 3 transgenic mouse strains, e.g. TASTPM (APP/PS1)
What next?

- Longitudinal studies in transgenic mice using novel disease modifiers
- Testing the biomarker battery with novel symptomatic treatments
- Backtranslate from clinical ongoing studies
- Modelisation of efficacious dose using PK/PD analyses in rodents and humans
Remaining challenges

Treatment, symptomatic & disease modifying
Better, earlier diagnosis
Better understanding of the disease
Thank you

- 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, Universitätshäklinikum Leipzig
- Maria-Trinidad Herrero Ezquerro, Universidad de Murcia
- Philipp Spitzer, Universität 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, 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