Current research approaches in Alzheimer disease

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AD Neuropathology

- Senile plaques
  - Extracellular
  - Amyloid β-peptide (Aβ)

- Neurofibrillary tangles
  - Intracellular
  - PHFs
  - Hyperphosphorylated tau

- Neuronal and Synaptic loss
- Inflammatory response

*Bogdanovic & Winblad, Huddinge Brain Bank, 2006*
Risk factors in Alzheimer disease

Healthy brain  ?  Alzheimer brain

Non-modifiable factors
- High age
- Dementia within the family
- ApoE4 risk gene
- Gene mutations

Modifiable factors

Protective factors
- Physical / mental / social activity
- Education
- Antihypertensive drugs
- Lipid lowering drugs
- Anti-oxidants(?)
- Omega-3(?)
- Anti-inflam drugs(?)

Risk factors
- Stroke
- Hypertonia
- Cholesterolemia
- Adipositas
- Diabetes
- Inactivity
- Smoking
- Head trauma

- October 1, 2010
Four key domains of everyday competence

- Cognitive abilities
  - Memory
  - Thinking
  - Orientation

- Communication

- Social behavior

- Basic everyday activities

Bengt Winblad
Good Care - Conclusion

- Nice, friendly environment
- Proper competence
- Diagnostic and prognostic thinking
- Staff continuity, presence and generosity
- Knowledgeable and engaged Unit Leaders
- Meeting basic needs – give relief
- Plausible staffing and flexible routines
- Humanistic philosophy
The evolution of treatments for Alzheimer’s disease

**Aricept® (donepezil)**
- **1997**
- Patch formulation introduced in 2007

**Exelon® (rivastigmine)**
- **1998**

**Reminyl® (galantamine)**
- **2000**

**Ebixa® (memantine)**
- **2002**
- Once-daily formulation introduced in 2008

**New disease-modifying treatments?**
- **>2010**

In most parts of the world (not in Europe) Aricept/donepezil is nowadays also approved for moderate to severe AD.
Summary of studies with rivastigmine patch

- Same effect as capsules, but less side effects
- Applied 1 time/day
- Visible proof that the patient has taken the medication
- Very positive attitudes of caregivers
Patients receiving ChEIs had a significant delay to nursing home placement; this effect was significantly augmented with the addition of memantine.

Memantine reduced the risk of nursing home placement by a factor of 3.4, relative to the group taking ChEIs alone.
Targets for future treatment

- **Aß pathology**
  - Reduce Aß production
  - Increase Aß degradation
  - Reduce Aß aggregation

- **Tau pathology**
  - Reduce Tau phosphorylation
  - Reduce Tau aggregation

- **Lipid dysfunction**
  - Modulate cholesterol metabolism

- **Inflammation**

- **Other (neuroprotective strategies)**
Dimebonstudie, Lancet 2008

**ADAS-cog**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 26</th>
<th>Week 39</th>
<th>Week 52</th>
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<tbody>
<tr>
<td>Dimebon</td>
<td>89</td>
<td>82</td>
<td>77</td>
<td>63</td>
<td>61</td>
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<tr>
<td>Placebo</td>
<td>94</td>
<td>84</td>
<td>76</td>
<td>63</td>
<td>59</td>
</tr>
</tbody>
</table>

**Mean change from baseline (SE)**

- Dimebon: 2.0, 4.0, 5.9, 6.9
- Placebo: 4.0, 5.9, 6.9, 6.9

**LOCF**

- Dimebon: p < 0.0001
- Placebo: p < 0.0001

*Clinical Improvement*

*Clinical Deterioration*

*p = 0.0077*
Dimebon’s mode of action(?)

Ankarcrorna et al, JAD in press
Anti-amyloid immunotherapy

1. Aβ42

2. Active immunisation
   - Aβ fragments
   - Conjugate

3. Passive immunisation
   - Human mAβ

AN 1792
Bapineuzumab (passive)

- **Overall assessment**
  - Results support further evaluation of bapineuzumab in Phase III trials
  - Bapineuzumab generally safe but dose-related vaso-oedema more frequent in carriers
  - Pre-specified efficacy analysis not significant in the total population

- **In Post Hoc analyses**
  - Trends in cognitive endpoints ADAS-cog and NTB in the total population
  - Evidence of significant efficacy in non-carriers (clinical and MRI)
  - Potential efficacy signals over a range of doses, without a clear dose response
CAD106 (active)

- Study designed to assess safety, tolerability and immune response to CAD106

- In this first-in-man study in elderly AD patients, CAD106 50 and 150 ug were shown
  - to induce Aβ-specific IgG antibodies in the majority of the elderly AD patients
  - level of Aβ-specific IgG antibodies doubled upon dose increase
  - antibody response short-lasting ➔ positive feature for safety
  - to be well tolerated

- No meningoencephalitis, vasogenic oedema or hemorrhages were observed

- Results of this study support further development of CAD106
Immunization; some pros and cons

Passive immunization

- **Advantages**
  - Easier to disrupt if side effects
  - Good balance between clearance of amyloid and induction of autoimmunity
  - More target-specific?
  - Elderly less prone to produce ab

- **Disadvantages**
  - Life-long injections, mostly i-v
  - Costly
  - Enough conc in brain?
  - Congiophil Amyloid Angiopathy
  - Vasogenic oedema

Active immunization

- **Advantages**
  - Fewer visits
  - Less costly
  - Constant antibody concentration(?)

- **Disadvantages**
  - Difficult to reduce antibody concentration if side effects
  - Local skin reactions
Tau as a target

INHIBITION OF TAU KINASES

<table>
<thead>
<tr>
<th>Kinase Inhibition</th>
<th>Inhibitor</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>PI3K inhibition</td>
<td>Wortmannin Tg2576</td>
<td>Haugabook, 2001 FASEB J.</td>
</tr>
<tr>
<td>GSK3/β inhibition</td>
<td>Lithium</td>
<td>PDAPP Su, 2003 Biochemistry</td>
</tr>
<tr>
<td>GSK3/β inhibition</td>
<td>Valproic acid</td>
<td>PDAPP Su, 2003 Biochemistry</td>
</tr>
<tr>
<td>GSK3/β inhibition</td>
<td>New drugs</td>
<td>Phase II Mucke 2006 Science</td>
</tr>
<tr>
<td>Cdk5 inhibition</td>
<td>Roscovitine, new drugs</td>
<td>Phase II</td>
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</table>

Potential redundancy between kinases is a big problem

ACTIVATION OF TAU PHOSPHATASES

<table>
<thead>
<tr>
<th>Phosphatase</th>
<th>Inhibitor</th>
<th>Reference</th>
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<tbody>
<tr>
<td>PP2A</td>
<td>Iqbal</td>
<td>2004 Curr Drug Targ.</td>
</tr>
<tr>
<td>Memantine</td>
<td>Li</td>
<td>2004 FEBS lett.</td>
</tr>
<tr>
<td>Memantine</td>
<td>Lannfelt</td>
<td>2007, Dement Geriatr Cogn Disord.</td>
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</table>

INHIBITION OF TAU AGGREGATION

Screening of molecules (Anthraquinones, Pickhart, 2006 JBC) (Epothilone, rTg4510 mice, Andofer ICAD 2008 Rember (Phase II) methyl thioninium chloride (MTC) ICAD 2008

POTENTIAL ANTI-TAU AGGREGATION VACCINE?

Using a P-Tau peptide PS1-tau mice Asuni, 2007 J Neurosc
Cell biodelivery of NGF to the cholinergic basal forebrain of AD patients

- Phase 1b, open label, 12 m study
- A total of 6 Pts with bilat implants
- Two cohorts
  - 3 patients with 1 implant bilat
  - 3 patients with 2 implants bilat
- Primary objective
  - Safety and tolerability
- Secondary objective
  - Efficacy, disease modifying effects

Pl: Maria Eriksdotter-Jönhagen, Karolinska Univ Hospital
On-going trials in AD

Mangialasche, Winblad et al, Lancet Neurol 2010
Conclusion

- AD is a multifactorial disease

- There is a need for **DISEASE MODIFYING DRUGS**
  → With different modes of action and perhaps also individualized regimens

- In parallel, there is a need for **EARLY DIAGNOSTIC TOOLS / BIOMARKERS**
The Swedish Brain Power biomarker initiative –

**Sensitivity 83%     Specificity 88%**

**STARD cut-off established in the AD group applied in the MCI group (n= 750)**

MCI-AD vs. controls

MCI-AD vs. stable MCI + MCI-other

Mattsson N, et al, JAMA 2009

Bengt Winblad
Amyloid imaging in MCI converter and non-converter

Forsberg et al Neurobiology of Aging 2007
Summary

- Prevention!
  - Better knowledge on risk and protective factors

- Treatment directed towards disease mechanisms

- Optimal combination of prevention, drug treatment and adequate care

- Translation
  - Reducing the gap between what we know from research and what we do in the clinic!
6th IPECAD
International Pharmaco-Economic Conference on Alzheimer Disease

London, February 3-4, 2011

Organisers: Anders Wimo, Linus Jönsson, Bengt Winblad,
Howard Fillit, Anders Gustavsson, Gunilla Johansson