Is the current landscape of medical research in Alzheimer’s disease delivering? What needs to change?

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But delaying AOO by 5 years, AD prevalence would be reduced by ~ 50%
Prevalence of Dementia (DEM), Alzheimer's disease (AD) and other forms of dementia (OD) in China in 1990, 2000 and 2010 by 5-year age groups.

Chen et al, Lancet Neurol, 2013
> 75% of LOAD patients > 75 years of age
Medicare Spending on Alzheimer’s Disease (in billions)

The challenging process of discovering and developing new drugs

Gene to Target → Target to Lead → Lead to Candidate → Candidate selection to FTIM → FTIM to PoC → PoC to Phase III → Phase III → File & Launch

Success rate: 10% 30% 50%

~ 1,000,000,000 USD

~ 12 years

- R&D attrition & Costs are reflected in pharma pricing policy in recently marketed targeted medicines, mainly in oncology
- Unsustainable for DEM/AD....
Pharma R&D Productivity vs Costs
AD is a “complex” disease of late-life

- Common, affecting many millions of people
- Chronic, slowly progressive
- Etiology and physiopathology are neither linear nor additive multifactorial “like a ballet choreographed interactively over time” involving genetic, gene expression, epigenetic and a multitude of environmental factors
- Nosological boundaries? Heterogeneity? One or more pathways or pathway clusters?
# Limb- Girdle Muscular Dystrophy

From one to >25 diseases in a decade of genetics studies

1. **Proteins of the extracellular matrix**
   - laminin a2 (MDC1A)
   - Collagen 6A1, A2, A3 (UCMD)
   - Integrin a7 (ITGA7)

2. **Transsarcolemmal proteins**
   - dystrophin (DMD-BMD)
   - a, b, g, d sarcoglycans (LGMD2C-2D-2E-2F)
   - caveolin (LGMD1C)
   - dysferlin (LGMD2B)

3. **Sarcomeric proteins**
   - myotilin (LGMD1A)
   - dysferlin (LGMD2G)
   - titin (LGMD2H)

4. **Nuclear proteins**
   - emerin (XL-EDMD)
   - lamin A/C (AD-EDMD/LGMD1B)
   - PAB2 (OFMD)

5. **Proteins with enzymatic activity**
   - calpain (LGMD2A)
   - fukutin (FCMD)
   - fukutin-related protein (MDC1C/ LGMD2I)
   - POMGnT1 (MEB)

6. **Cytoskeletal proteins**
   - plectin (MD+ epid.bull)
Preclinical Alzheimer’s Disease

- Age prevalence of Aβ deposition as detected at postmortem in cognitively unimpaired subjects (green triangles).

- Age prevalence of AD in the general population (red diamonds).

- Prevalence of high PiB binding in HC from the AIBL cohort (blue dots).

Rowe et al. 2012
When to intervene?

Jack et al, Lancet Neurol 2010
The “black box” of disease progression in Alzheimer’s disease

- Onset of pathology
- Asymptomatic phase?
  - Risk prediction
- Onset of symptoms (MCI - AD diagnosis)
- 5-10 years Clinical phase
- 100% Cognitive performance
- Tau/amyloid accumulation & brain atrophy

Cognos, 2001

Imperial College
London
What have we learned from Prospective Cohorts on Risk and Protective Factors for AD, in last decade

**Risk Factors for AD**
- Age > 65 years, risk doubles / 5 years
- Genes: APoE4/ TOMM40 (ISV-6) + 21 gns
- Diabetes increases risk 54%
- Mid-life Obesity increases risk 59%
- Vascular disease and HTA
- Metabolic Syndrome
- Head Trauma
- Depression
- Chronic Stress?

**Protective factors for AD**
- Genes: APoE2
- Lifetime & Environment (early, mid-life, late-life)
  - Education
  - Socioeconomic status
  - Mediterranean Diet
  - Physical activity
  - Social Networking
Education, Vascular Risk and leisure activities vs APoE4

Fig. 1. Kaplan–Meier survival estimates from baseline to dementia occurrence by APOE ε4 in combination with education, vascular risk factors, and leisure activities (adjusted for age and sex). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

from Ferrari et al, 2012
An Active Lifestyle Postpones Dementia Onset by a Year and a half in Very Old Adults

*Paillard-Borg S et al, 2012*

- From Kungsholmen project: In 1375 community dementia–free dwellers (mean age 81.2), over a 9 year period, there were 388 dementia cases.

- 17 months difference in AOO of dementia between active and inactive groups, independent of education, medical condition(s), functional status and APoE
Is dementia incidence declining? Trends in dementia since 1990 in the Rotterdam study

*Schrijvers et al, 2012*

<table>
<thead>
<tr>
<th>Age stratum, y</th>
<th>Total</th>
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<td>Incidence rate 1990</td>
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<td>Incidence rate 2000</td>
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<td>IRR (95% CI)</td>
<td>0.75 (0.56-1.02)</td>
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<td>Incidence rate 2000</td>
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<td>IRR (95% CI)</td>
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<td>0.84 (0.56-1.26)</td>
<td>0.98 (0.51-1.90)</td>
<td>0.77 (0.45-1.29)</td>
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</table>
Trends in age-specific incidence rates of AD in Rochester, Minnesota

Rocca et al, 2011
The emerging *human disease* based model in pharmaceutical R&D

**Prospective cohorts**
- Clinical Data
- Genetics-Bioinformatics
- Neuroimaging
- Plasma Biomarkers

**Risk factors**
- Natural History
- Disease Nosology

**DISEASE UNDERSTANDING**
- New Indications + Targets
- Biomarkers

**Pathway Analysis**
- Biomarker Discovery
- Neuroimaging

**Linkage/Association**
- Sequencing/Epigenetics
- Omics Platforms

**Susceptibility alleles**
- Rare variants
- Telomere length/methylation

**FTIH**
- Ph II to PoC

**PoC to commit to Phase III**
- Phase III
- File and launch
- Life cycle management

**Disease selection**
- Gene function to target

**Target to Lead**
- Lead to Candidate
- Pre-clinical

**Lead to Candidate**
- Pre-clinical
The new *human disease & patient driven* Model of R&D

- Needed Now!
- The first Step: Support studies to better understand the disease, its boundaries, heterogeneity and its markers and progression
- Long-term funding and coordination of well designed prospective longitudinal cohorts and “big data” studies, around the globe
- Requires new models of Public, Academic and Private (Industry, SMEs, CROs) Partnerships
- Innovation in legal (IP, data protection/access), in funding and in organizational/ data management issues
- *Disruptive Innovation* in *human* based academic research and R&D
- Data sharing = Cost sharing = Benefits sharing
European Cohort Consortium
(1,500,000 participants in EU)

European Prospective Investigation into Cancer (EPIC): 500,000 participants since 1992