Clinical Candidates for the Treatment of Alzheimer's Disease

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Disclosures

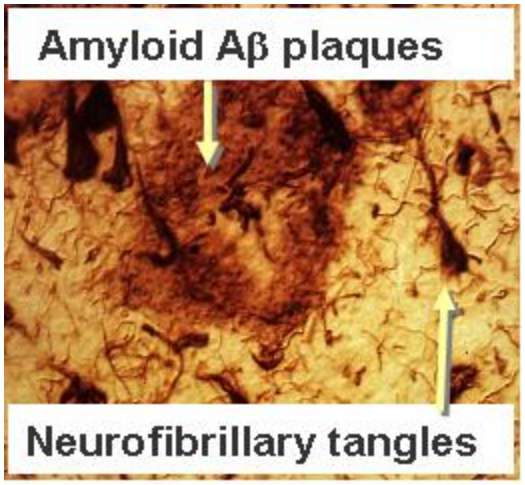
- 50% Time Contractee to NIH
- Consulting to Industry
  - Lilly
  - Amgen
  - Takeda,
  - Taisho
  - Praxis
- Stockholder in Merck (has a BACE candidate)

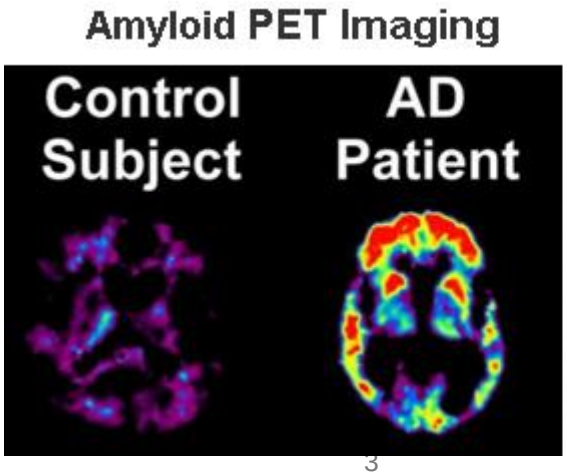
Alzheimer's Disease: a Well-Defined Neuropathology

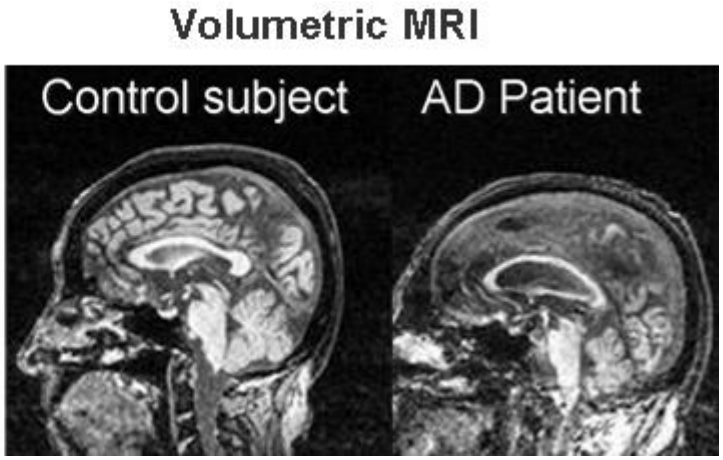
Figure 3: **Auguste D**
Photograph dated November, 1902.

- Progressive deficits in cognition (especially memory) activities of daily living (ADL) and behavior
- Neuropathology:
  - Extracellular amyloid plaques
    - Main constituent aggregated Aβ peptides
  - Intracellular neurofibrillary tangles
    - Main constituent aggregated hyper-phosphorylated tau
  - Dystrophic neurites
  - Neuroinflammation

Synaptic loss, nerve cell loss, decreased neuronal metabolism, brain atrophy







Epidemiology and Implications for Treatment*

- 40M worldwide projected to double q20yrs through 2050
- >50% Lifetime Risk if APOE4 homozygote, 20-30% if E4/E3 heterozygote vs 11-14% independent of genotype
- European (and US) cohort studies show 20% ***decline*** in age specific incidence comparing 2000 to 1990 data raising possibility of better control of risk factors
- "Treatable" risk factors include: Cardiovascular and "Increasing evidence suggests that many other lifestyle related factors, including diabetes, obesity, physical and mental inactivity, depression, smoking, low educational attainment and diet…"

*Scheltens P[1], Blennow K[2] et al. **Alzheimer's disease.** Lancet. 2016 Feb 23. pii: S0140-6736(15)01124-1. doi: 10.1016/S0140-6736(15)01124-1. [Epub ahead of print]

Stages of AD and Implications for Treatment

The Progression of Alzheimer's Disease

There is a pre-dementia form of AD (analogy to schizophrenia prodrome?) that can be identified by cognitive deficits and biomarker profiles. Early intervention may ameliorate pathology leading to dementia.

Current AD diagnosis is based upon clinical symptoms (DSM-IV, NINCDS-ADRDA) often requiring specialist confirmation. Diagnosis is based upon confirmation of dementia of the Alzheimer's disease type.

Best Prevention Opportunity?

Prevention of Dementia In Patients with Cognitive Complaint. *Focus for Today*

Treatment of Dementia

Genes Associated with AD Relevant to Rx

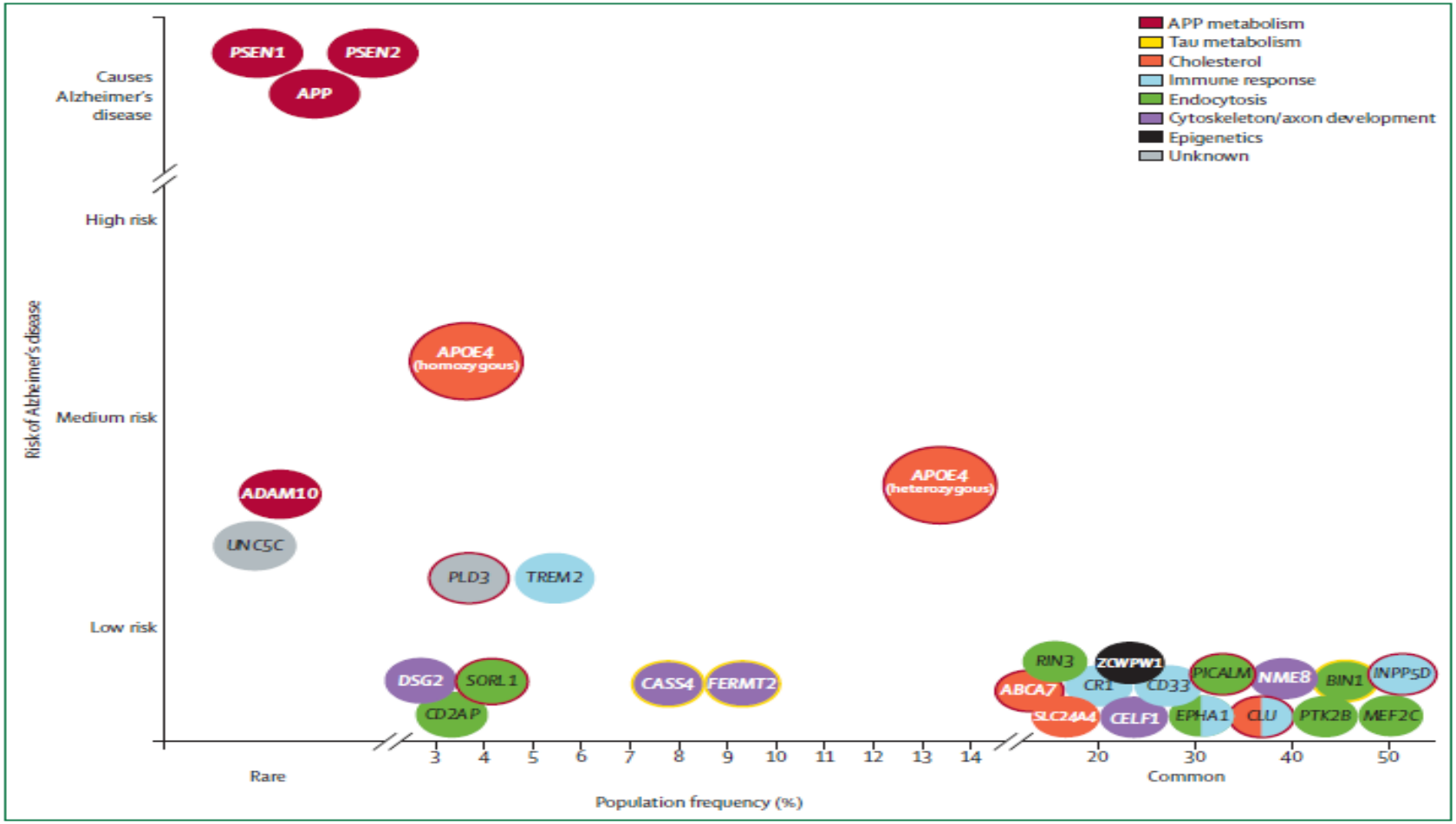
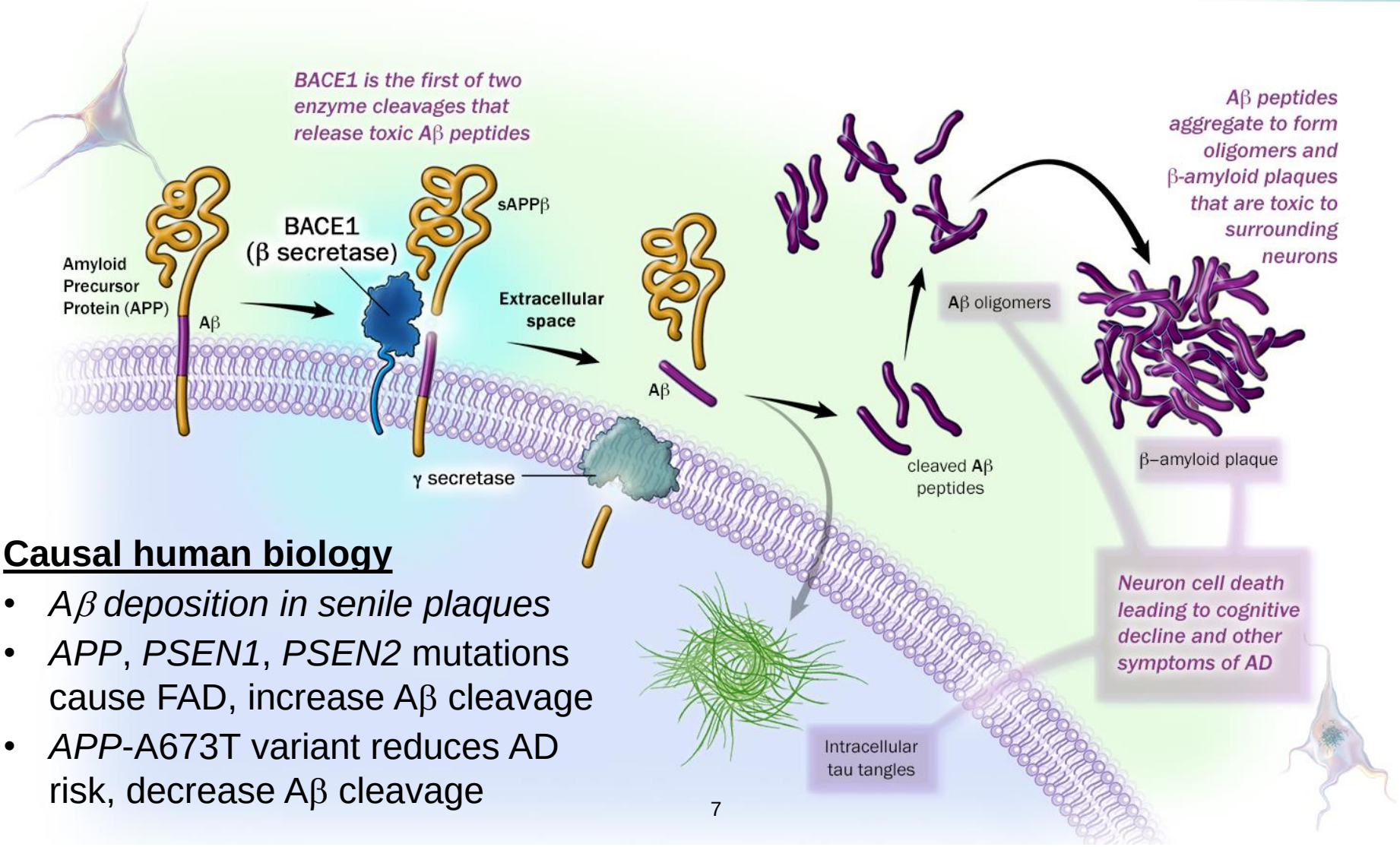


Figure: **Schematic overview of genes linked to Alzheimer's disease**
The colours in the key show the pathways in which these genes are implicated. Genes that are known to affect APP metabolism are circled in red, whereas those that affect the tau pathway are circled in yellow. The interior colours provide further information on what functions the genes have. When there are two colours, the gene might have functional roles in two different biological pathways. Many of the genes have been related to APP processing or trafficking (red or red border), suggesting the central importance of APP metabolism in Alzheimer's disease. The figure was adapted with permission from Karch et al, 2015.[39]

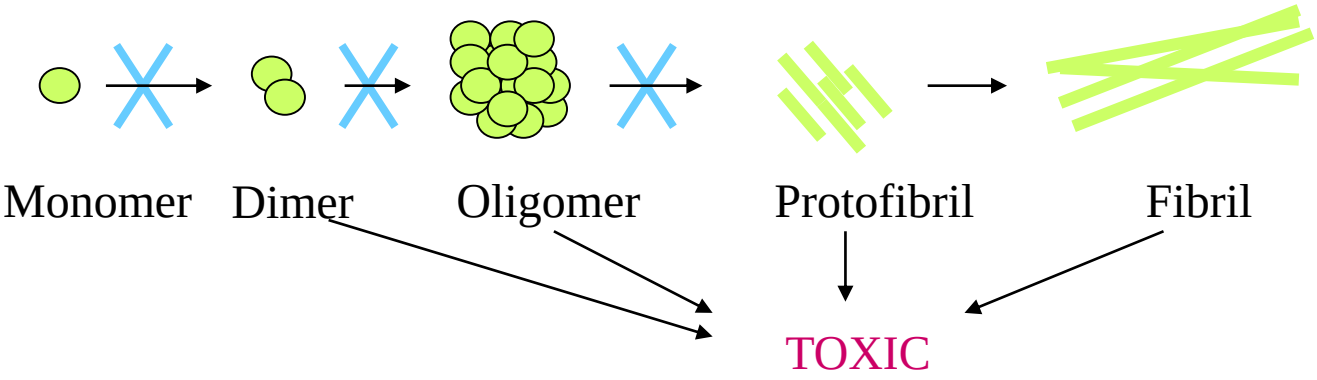
Amyloid hypothesis and Alzheimer's disease: *the role of the APP gene and BACE1 in disease initiation*



Causal human biology

- *Aβ deposition in senile plaques*
- *APP*, *PSEN1*, *PSEN2* mutations cause FAD, increase Aβ cleavage
- *APP*-A673T variant reduces AD risk, decrease Aβ cleavage

Amyloid Aggregation Pathway

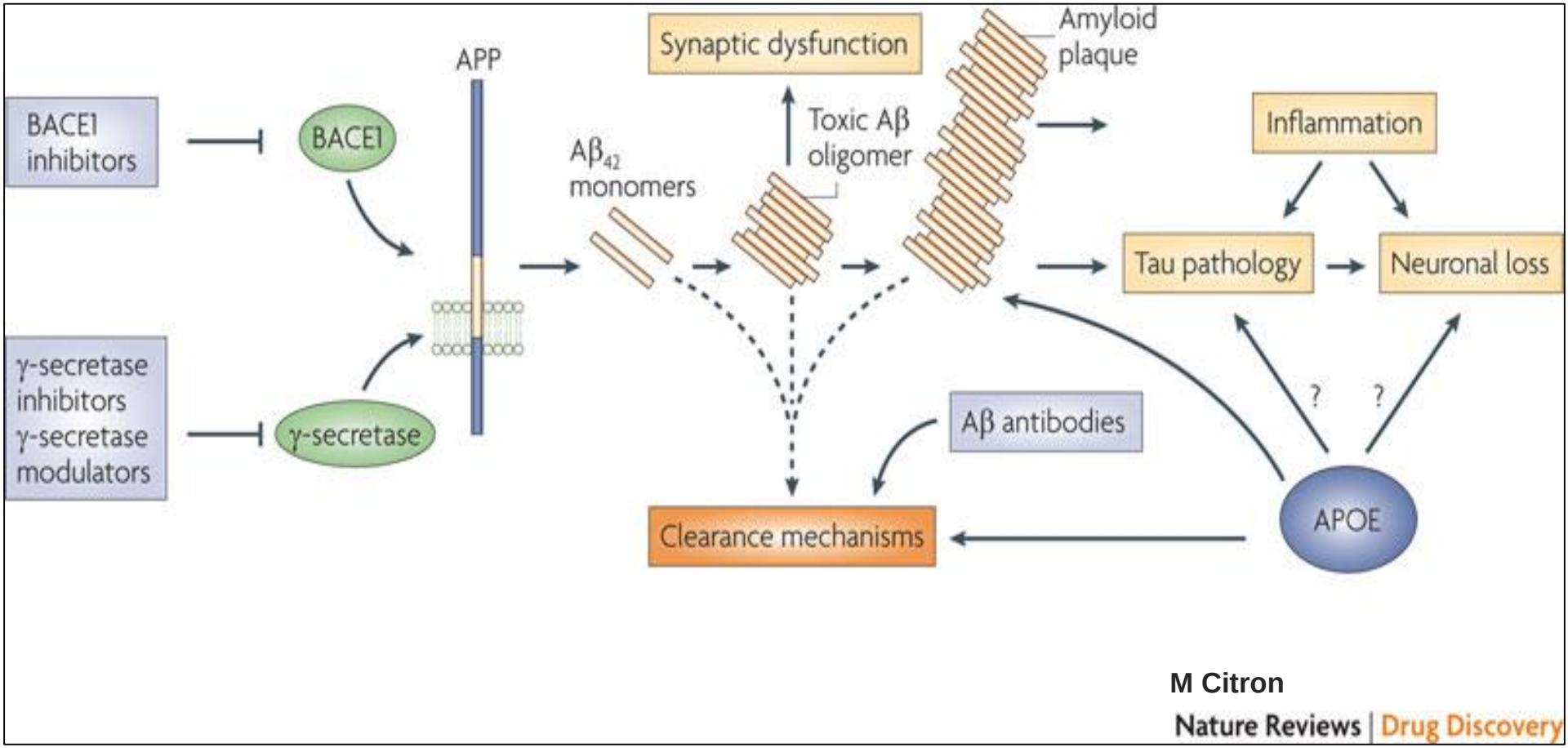


Role of Soluble Amyloid in AD

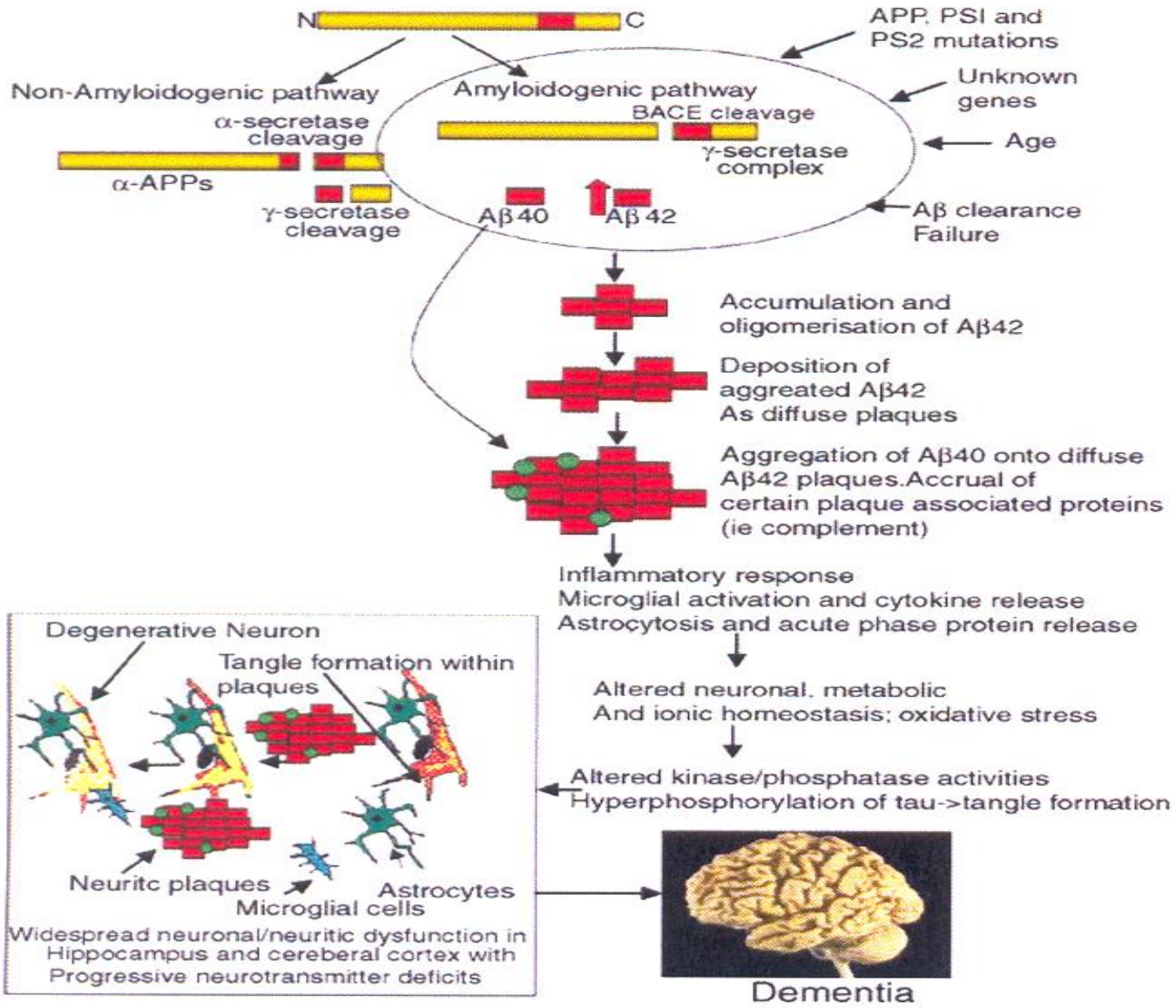
- Soluble amyloid levels correlate with cognitive decline and synaptic loss in AD brains
- Oligomeric amyloid interacts with RAGE, ABAD and α-7-nicotinic receptor leading to decreased cerebral blood flow, cellular toxicity, and disruption of cognitive behavior
- Cognitive improvements in Aβ vaccinated APP-transgenic mice prior to plaque reduction suggest that soluble amyloid may contribute to cognitive decline in this model

Alzheimer's Disease Target Selection

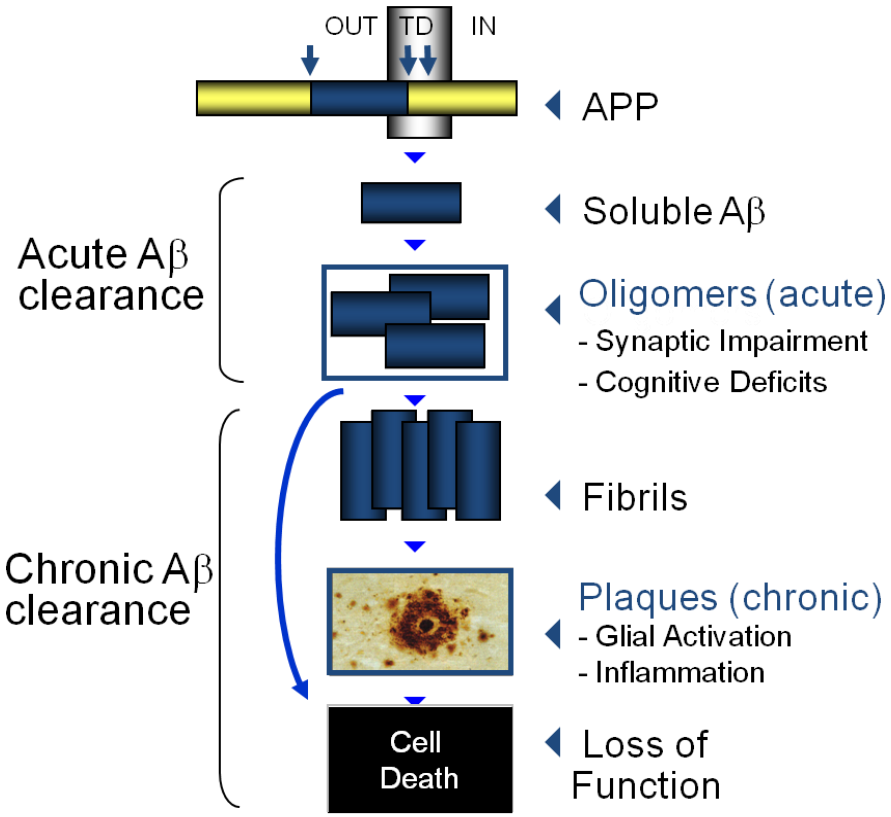
Myriad of Potential Therapeutic Targets



Transgenic Animal Models Developed to Produce Amyloid Deposition With a Variety of Associated Anatomical, Biochemical and Functional Changes



Rationale for Aβ Immunotherapy



- Effective in Animal Models
- 0.1 % of Abs cross BBB
- Abs target multiple Aβ species
- Clearance of Aβ may:
  - reduce pathology
  - Improve cognition
- Multiple proposed mechanisms for Aβ clearance
  - Microglia mediated
  - Peripheral sink
  - Direct resolution

Slow Progress of All Target Development – 2010 Status

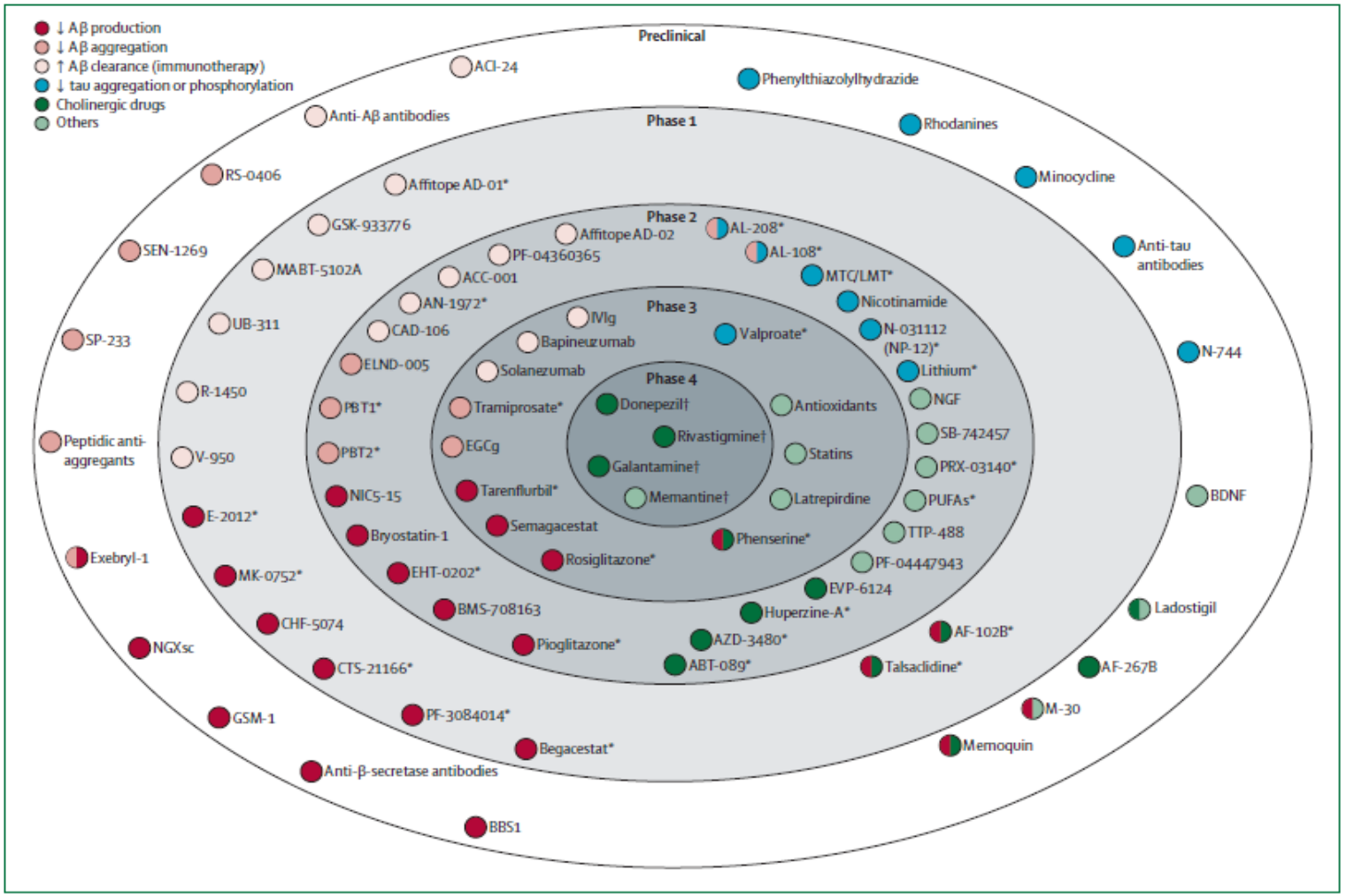
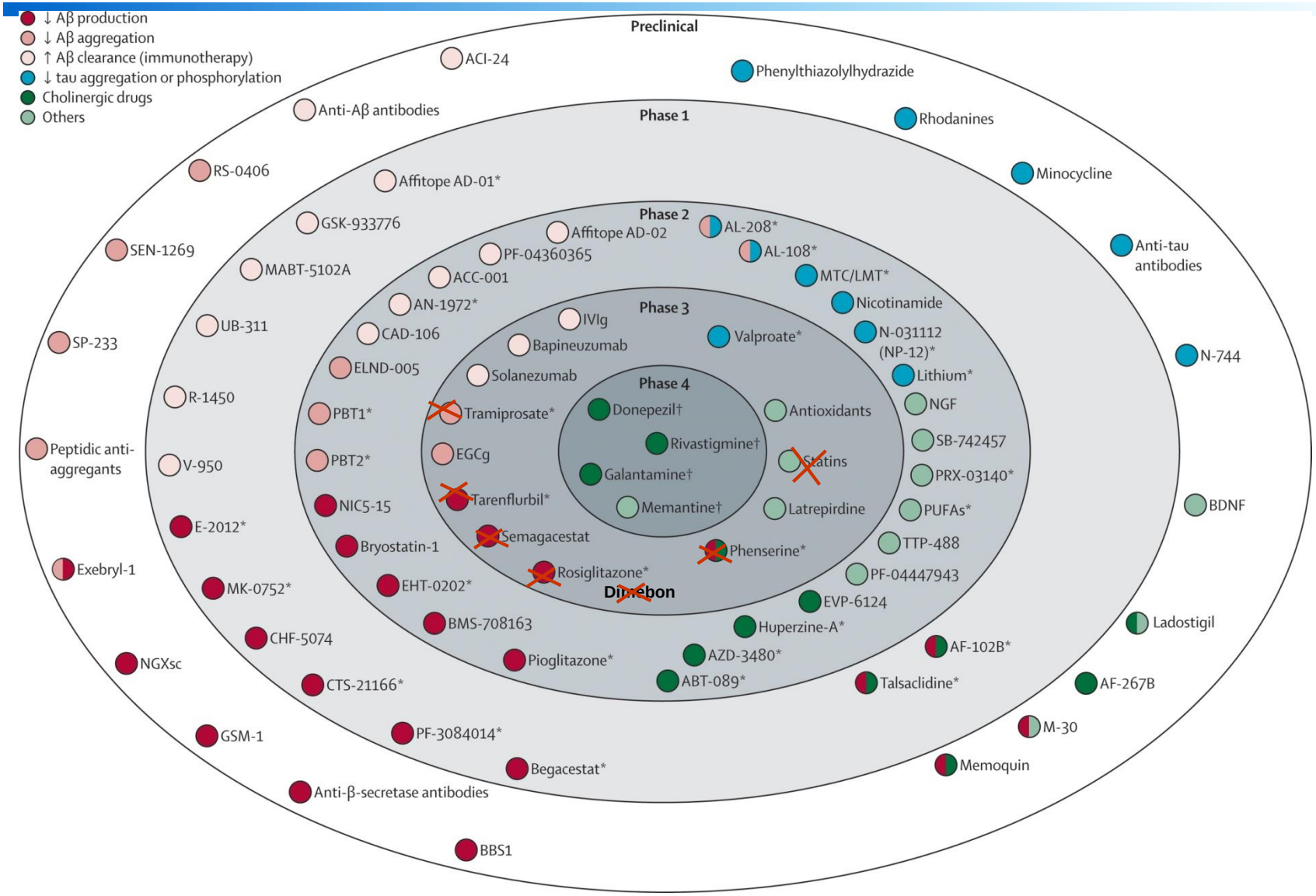


Figure: **Drug development in Alzheimer's disease**

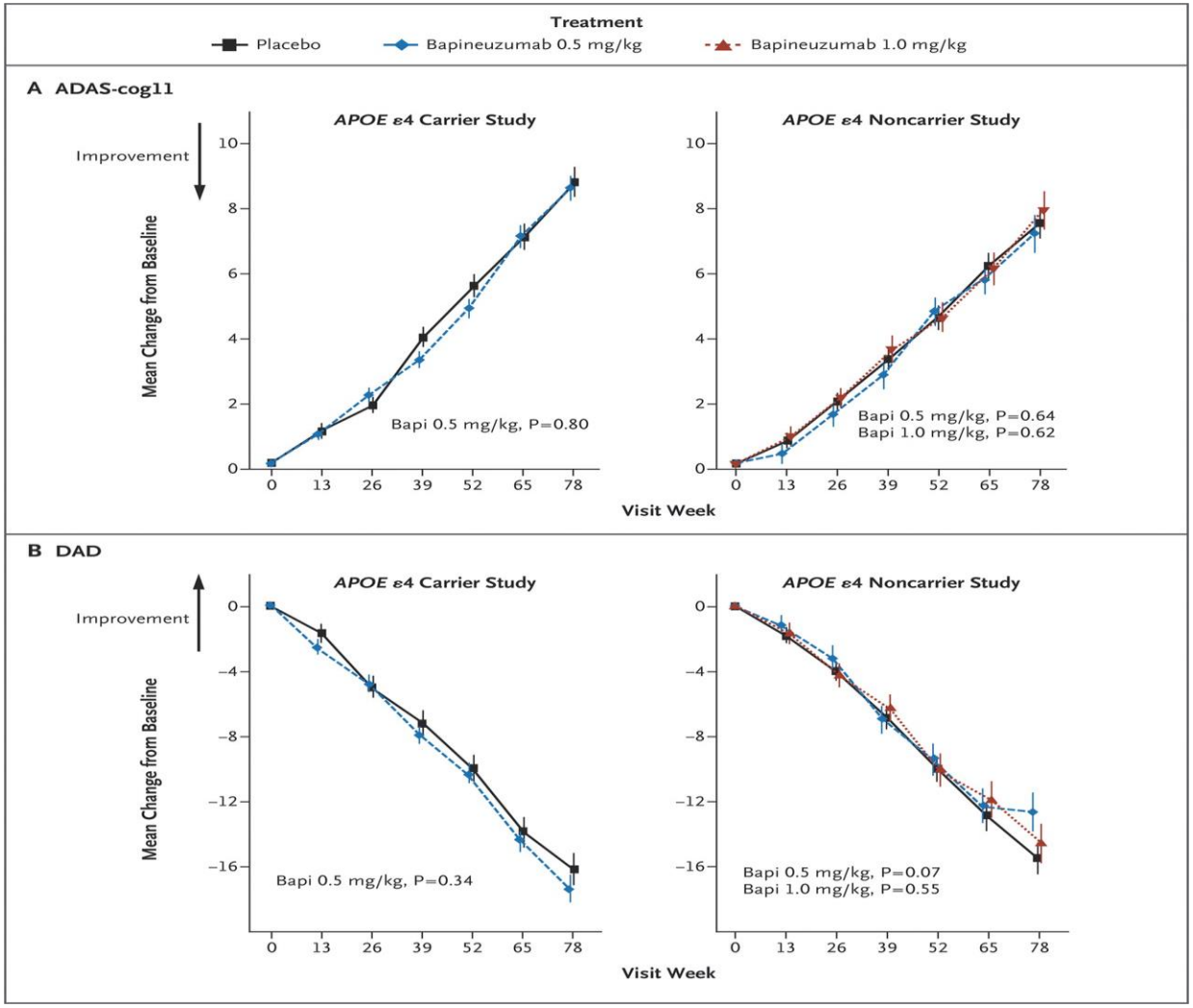
Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies in vitro and animal models). Aβ=amyloid β. BBS1=anti-β-site antibodies. BDNF=brain-derived neurotrophic factor. EGCg=epigallocatechin-3-gallate. IVIg=intravenous immunoglobulin. LMT=leuco-methylthioninium. MTC=methylthioninium chloride. NGF=nerve growth factor. NGXsc=NGX series compounds. PUFAs=polyunsaturated fatty acids. GSM=γ-secretase modulator. RCT=randomised controlled trial. *RCTs in Alzheimer's disease not ongoing. †Drugs approved for the treatment of Alzheimer's disease.

Mangialasche et al. Lancet Neurol 2010

Current Clinical Trial Experience in AD
High Failure Rate



Bapineuzumab Phase 3 Results* (> 300/arm)



Salloway S, Sperling R et al. **Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease.** N Engl J Med. 2014 Jan 23;370(4):322-33

A NEW CURE FOR ALZHEIMER‘S DISEASE - TREATMENT SUCCESS IN MICE AND RATS! –

Lessons Learned

- Preclinical models of limited utility in predicting clinical efficacy and *can encourage costly failed studies*
- Demonstration of clinical benefit requires lengthy trials focused on categorical outcomes - true for any "developmental" disorder
- Lack of sensitive methods to detect disease progression = large clinical studies during early development (high front-end costs)
- AD patients often manifest additional neurodegenerative diseases = need to reduce patient heterogeneity
- AD pathology precedes emergence of dementia.
- Thus, critical need for ***biomarkers*** to:
  - Inform dose selection
  - Stratify patients
  - Predict clinical outcomes

Types of Biomarkers with Potential to Assist AD Trials

- Amyloid aggregation related: Abeta and oligomers
- Neurofibrillary tangle related: phospho-Tau
- Neuroinflammatory: cytokines (in CSF??)
- Risk factor related: APOE
- Neural tissue loss – Structural MRI
- Decreased neuronal function – FDG-PET, fMRI?

But Too much for Any Single Entity to Generate

Therefore ADNI 1(2004) and now 3(1016)

- The Alzheimer's disease neuroimaging initiative (ADNI) - a longitudinal natural history study.
- ADNI was designed to standardize AD clinical trial methodology involving imaging and biofluid biomarkers at over 57 sites in the US and Canada.
- Long-term goal is to qualify methods for early detection and disease progression.
- $67M study funded through private-public partnerships

Naturalistic study of AD progression

- **200 NORMAL 3 yrs**
- **400 amnestic MCI 3 yrs**
- **200 AD 2 yrs**
- **Visits every 6 months**
- **57 sites**
- **Clinical, blood, LP-CSF collected**
- **Cognitive Tests**
- **1.5T MRI**

Some also have

- **3.0T MRI (25%)**
- **FDG-PET (50%)**
- **PiB-PET (approx 100)**

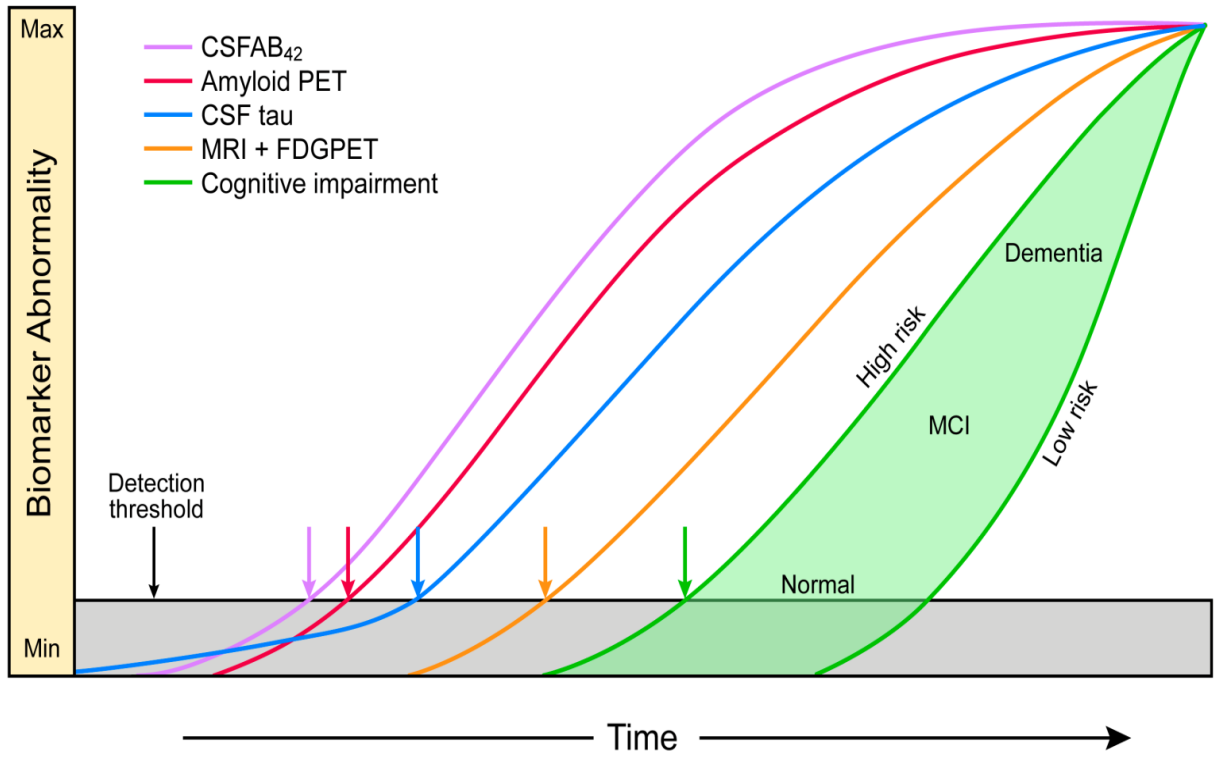
ADNI Public-Private Partnership Structure

A Model of Biomarker Informed Development of Alzheimer's Emerging from ADNI

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

Lancet Neurol 2013



Treatment Questions Addressed with Biomarkers

- Which analytes inform best as to drug action and in which compartment?
- ***Which measures for characterizing patients are most appropriate for selecting or stratifying by treatment mechanism? – Now applied to Trials***
- Which measures are best used to follow disease progression (if any) independent of treatment mechanism

Conclusions

- Increasing knowledge on and tools for exploring pathophysiology of Alzheimer's
- Prevailing "amyloid hypothesis" being tested with BACE inhibitors and MABs
- Risk factors, including genetic, inform animal models to expand portfolio of therapeutic targets
- Biomarkers play increasing role in setting doses for trials, selecting patients and relating preclinical to clinical studies