Clinical Candidates for the Treatment of Alzheimer’s Disease

William Z Potter, M.D., PhD
Sr Advisor, NIMH
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

• 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…”

Stages of AD and Implications for Treatment

The Progression of Alzheimer’s Disease

Presymptomatic (Biomarkers?)

Pre-Dementia (Subtle Cognitive Signs & Biomarkers)

Dementia Current Dx and Rx

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

Treatment of Dementia

In Patients with Cognitive Complaint. Focus for Today
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, 2015.¹⁹
Amyloid hypothesis and Alzheimer’s disease: the role of the APP gene and BACE1 in disease initiation

Causal human biology

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

BACE1 inhibitors
γ-secretase inhibitors
γ-secretase modulators

APP

BACE1

Aβ_{42} monomers

Toxic Aβ oligomer

Amyloid plaque

Synaptic dysfunction

Inflammation

Tau pathology

Neuronal loss

APOE

Clearance mechanisms

Aβ antibodies

M Citron

Nature Reviews | Drug Discovery
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 property (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, PUFA=polysaturated fatty acids, GSM=y-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)

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

Don't worry I suffered from Alzheimer's disease and they cured me!
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

Private/Philanthropic + Public

National Institute on Aging

U.S. National Institutes of Health

ADNI Executive Steering Committee
PET Core: Berkeley, Mayo: Jack Jagust
MRI Core: Mayo: Jack
Clinical Core: UCSD: Aisen, Mayo: Peterson
Administrative Core: UCSF
Biomarkers Core: UPenn: Trojanowski/Shaw

PI Mike Weiner

Publications Core: BostonU: Green
Informatics Core: UCLA: Toga
Pathology Core: WashU: Morris

Bioinformatics Core: UCD: Beckett

57 Clinical Sites: ADNI PIs and Cores

3/24/2016
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

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