Pathobiological Targets in AD Trials: Where We Have Been and Where We're Headed

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Alzheimer’s Disease (AD)

• Major & growing unmet need
  – Most common cause of dementia
  – 12-17% life time risk
  – Greatest risk factor is age followed by ApoE status
  – 3rd most costly disease
• Current treatments inadequate
  – Modest symptomatic effects
Pathophysiology of Alzheimer’s Disease

- Loss of **neuronal connectivity** due to synaptic degeneration and neuronal death thought to cause cognitive dysfunction.

- **Prolonged increased cellular activity** in plastic brain regions may put neurons at risk.

- Tau and Aβ pathologies may be **independent but synergistic** processes.

- **Vascular disease & inflammation** contribute to rate of disease progression.

Alzheimer’s Association, 2013
The Amyloid Hypothesis

Soluble Aβ42 oligomers are hypothesized to cause:

- Neuronal dysfunction
- Cognitive deficits
- Tau dysfunction
- Neurodegeneration

APP mutations

Presenilin mutations

ApoE 4 allele
Aβ formed by β-secretase & γ-secretase: Aβ42 oligomers linked to AD by human genetics
Aβ-Directed Therapeutic Mechanisms

Aβ synthesis Inhibitors (BACE, γ-secretase)

γ-secretase modulators (Aβ42 to Aβ38)

Antibodies
Vaccines
Aggregation Inhibitors

Amyloid plaque

β-Secretase
γ-Secretase

Antibodies Vaccines
Aggregation Inhibitors
Recent/Ongoing Late-Stage Clinical Studies

Aβ Hypothesis

- **Gamma Secretase Inhibitors**
  - Semagacestat produced cognitive worsening
  - Avagacestat produced no evidence of cognitive or functional benefit in PDAD and signs of cognitive worsening at higher doses in Mild-Moderate AD

- **Immunotherapy**
  - Solanezumab
    - Two phase 3 trials failed primary endpoints. Third trial (EXPEDITION-3) ongoing
    - Pooled results in mild AD showed significant cog benefit at 80 weeks and trend for functional benefit at 80 weeks – no changes in moderate.
  - Bapineuzemab
    - PhIII failed – no change in cognition, functional endpoints.
  - Pre-symptomatic clinical trials with biomarker and cognitive endpoints are ongoing
    - API and DIAN trials – dominant AD mutations
    - A4 trial – amyloid PET (+), stratified by ApoE status
Treating Alzheimer’s Disease - 3 Key Questions

• When do we need to begin treatment?
  – Ideally, as early as practical
  – Earliest pathology begins 20 years or more before clinical diagnosis
  – Correlation of preclinical biomarkers with disease progression
  – Tau pathology precede Aβ, but detection in CSF is earlier for Aβ
  – CSF Aβ42, Tau, pTau181

• What degree of Aβ lowering is required for efficacy?
  – Human genetic (FAD and protective mutations) and clearance (sporadic AD CSF Aβ) evidence suggests a sustained >25% reduction in Aβ may reduce risk

• What is the relationship between these parameters?
  – Does earlier intervention allow for a smaller magnitude of effect?
Status of the Amyloid Hypothesis

• The amyloid hypothesis is still well-supported by human genetics and preclinical data

• Recent clinical trials have employed therapeutics that have not lowered CSF Aβ by more than 20%

• As a result, the amyloid hypothesis has yet to be tested in AD patients in a manner that allows confirmation or refutation

• GSMs and BACE inhibitors comprise the next generation of promising anti-Aβ therapies
BACE inhibitors reduce CSF Ab in HV’s

- CSF Aβ peptides were lowered >90% in once-daily oral, single, and multiple dose healthy volunteer studies without dose limiting side effects being observed

MK-8931 Multiple Dose Phase I Study

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<td>6</td>
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<td>Dose B</td>
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CSF Aβ1-40 % of Baseline

Day -1, 0 hours (lumbar puncture) → Day 14 Dose (final dose)

CSF = Cerebral spinal fluid
Merck data on file 2011

Public disclosure, Nov 2011; March 2012
Current status of BACE inhibitor efforts

• **MK-8931, Merck, PhIII**
  – PhII/III study (EPOCH) in mild to moderate AD patients was expanded in Dec 2013 following an interim safety analysis in 200 patients on therapy for three months
  – Program to be expanded with a additional trial in prodromal AD

• **AZD3293 (Astra Zeneca) and E2609 (Easai) are at an earlier stage of development**

• **LY2886721 (Lilly, PhII, liver function abnormalities) and RG7129 (Roche, PhI, unspecified) have been terminated from development**
γ-Secretase modulators increase processivity thereby decreasing Aβ42 and increasing Aβ37/38

- Opposite to presenilin mutations that decrease processivity and increase Aβ42
- *Gamma secretase has many other substrates*
- *GSMs do not disrupt Notch signaling*
- Numerous early stage programs are noted
Tau binds and stabilizes microtubules

Brunden, NatRev, 2009
Potential Targets for Tau-Associated Neurodegeneration

1. Microtubule Stabilizers
   *Epothilone D (BMS)*

2. Tau hyperphosphorylation
   Kinase inhibitors (*NYPTA – Noscira*)

3. ↑ Clearance
   Autophagy enhancers

4. Aggregation inhibitors
   *Rember (TauRx)*

5. Immunotherapy
   (blocks tau propagation?)

Adapted from M Hutton, Lilly
Current status of Tau-directed therapies

- Davunetide, Allon, PhII AD
  - neurotrophic, microtubule stabilizing properties reported
  - small peptide delivered intra-nasal
- BMS-241027, BMS, PhI
  - microtubule stabilizing agent
- TRx0237, TauRx, PhIII
  - Proprietary formulation of methylene blue
  - Tau aggregation inhibitor
- Tau immunotherapy – increasing momentum
Emerging/Ongoing Targets for Disease-Modifying Therapy

• Intercellular translocation of copper and zinc
  – PBT2 (Prana, PhII)

• Cholesterol lowering
  – Simvastatin – effect on AD related biomarkers in CSF

• Autophagy-lysosomal clearance modulation

• ApoE4 conversion
  – Gladstone Inst.
The role of symptomatic treatment?

- Rapid improvement in cognitive function
- Maintained in the presence of disease modifying agent
- Distinct symptomatic mechanisms may be additive or synergize
Risks and Issues with Symptomatic Therapies

- Placebo effect or lack of cognitive decline in control group
- Control group likely to be treated with a symptomatic agent
- Lack of predictive validity of cognitive models
- Dose selection may be less complex vs. DM therapy
  - pro-cognitive effects in HVs, patients in PhII
  - MRI
  - more tenable target engagement biomarkers (GPCRs, PDEs, etc.)
Active Symptomatic Therapy Approaches

- RG1577 (Roche) monoamine oxidase-B inhibitor
- PF-05212377/SAM-760 (PFE) - 5HT6 antagonist; AD with psychiatric symptoms
- LuAE58054 (Lundbeck) – 5HT6 antagonist
- ABT-126 (Abbott) - nicotinic a7 receptor agonist
- SAR110894 (Sanofi) - H3 antagonist
- TC-1734 (AZ & Targacept - α4β2 nicotinic receptor activator)
- EVP-6124 (EnVivo) - nicotinic α7 receptor agonist

All are in trials in mild to moderate AD
HDAC2 isoform role in cognition

10 years of literature from multiple labs supports HDAC2 isoforms’ role in cognition

- HDAC-2 expression correlates with neurodegeneration in CK-p25 and 5xFAD mice
  - Reduced acetylation of histones
  - Reduced expression of synaptic plasticity genes
  - Significant neuronal loss, atrophy and learning and memory deficits
- HDAC-2 expression is significantly increased across all AD-related Braak stages
- HDAC-2 (but not HDAC-1) overexpressing (OE) mice exhibit decreased levels of histone acetylation, reduced synaptic plasticity and significant learning and memory deficits; HDAC-2 knockout mice exhibit the converse phenotype.
HDAC-2 relates to impaired memory formation

HDAC2 negatively regulates memory formation and synaptic plasticity *Nature*. 2009 May 7;483(7243):53-60

- HDAC2, but not HDAC1 overexpressing mice exhibit impaired memory formation

WT mice that are overexpressers of HDAC2 exhibit reduced performance in associative memory test and greater escape latency in Morris Water Maze; WT overexpressers of HDAC1 exhibit no significant deficit relative to control population
Reducing HDAC2 levels alleviates memory deficits

HDAC2 expression is significantly increased in the hippocampal CA-1 neurons of CK-p25 mice, and these animals exhibit deficits relative to WT mice in multiple learning and memory models. HDAC2 knockdown with shRNA reverses these cognitive deficits.
**HDAC2i MOA vs Other**

**Symptomatic Approaches**

**HDAC2 inhibition:**
- Reverse the epigenetic blockade or silencing of gene expression critical to synaptic plasticity and function

**Symptomatic therapies in development for AD:**
- Target the modulation of specific neurotransmitters
  - Lu AE58054 (5HT6 antag - PhIII)
    - Improvements in ADAScog in combo with Aricept
    - Stimulates release of Ach and glutamate
  - EVP-6124 (alpha7 nicotinic ag – PhIII)
    - Sensitizes alpha7 receptor to effect of Ach
    - Stimulates release of dopamine and glutamate
Recap of Key Points

• Recent clinical failures of γ-secretase inhibitors and amyloid immunotherapies – has the amyloid hypothesis been adequately tested?

• Ongoing validation of preclinical AD biomarkers sustains continued interest in testing the amyloid hypothesis.
  – Amyloid immunotherapies in prevention studies
  – γ-secretase modulators
  – BACE inhibitors

• Tau directed approaches, particularly immunotherapies, are gaining momentum.

• There are a substantial number of symptomatic therapy approaches under pursuit. Some have reached late stages of development.