Therapeutic Strategies for Alzheimer’s Disease

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Possible sites of intervention for AD therapeutics according to the amyloid cascade hypothesis

Overproduction, decreased clearance or enhanced aggregation of Aβ42 → Aβ42 oligomerization and deposition into **PLAQUES** in cortex → Microglial and astrocytic activation - **INFLAMMATION**

Subtle effects of Aβ42 oligomers on synapses

Altered kinase / phosphatase activities - **TANGLES** → Progressive synaptic and neuronal injury → Altered neuronal ionic homeostasis & oxidative injury

Widespread neuronal dysfunction and cell death with attendant transmitter deficits → **DEMENTIA**
Therapeutic strategies based on decreasing amyloid burden in the AD brain

Amyloid Precursor Protein (APP) → \( \beta \)-secretase → A\( \beta \)42 monomers → \( \gamma \)-secretase
β-secretase (BACE-1) and γ-secretase inhibitors

**β-secretase (BACE-1)**
- Identified in 1999 as an aspartyl protease
- Long substrate binding site makes it challenging to design small molecule inhibitors that are potent but still small enough to penetrate the blood brain barrier
- No compound has yet made it to the clinic

**γ-secretase**
- Protein complex consisting of 4 different subunits
- Mutations in one of the subunits (Presenilin-1/2) causes aggressive “early onset” familial AD
- γ-secretase also cleaves a number of other substrates, most notably the Notch receptor.
- Inhibition of the Notch signalling pathway can cause side-effects - seen with some non-selective γ-secretase inhibitors
- LY-450139 (a γ-secretase inhibitor) is currently being evaluated in Phase II clinical trials; Flurizan (a γ-secretase modulator) currently in Phase III trials
Drugs that affect cholesterol levels

• Cholesterol levels are known to modulate Aβ production

• Several studies have suggested that raised blood cholesterol can increase the risk of developing Alzheimer’s disease in later life

• Several retrospective epidemiological studies have provided preliminary clinical evidence that the chronic use of statins is associated with a decreased risk of developing dementia

• Controlled clinical trials have so far generated mixed results for statins in AD patients, though most studies have found no or very limited positive effects

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• In the brain, the cholesterol-carrying protein apolipoprotein E (ApoE) also plays a dominant role in clearing brain Aβ peptides

• Individuals carrying the APOE-ε4 gene have an increased likelihood of developing late-onset AD

• Drugs that increase expression of APOE may have beneficial effects in AD
Therapeutic strategies based on decreasing amyloid burden in the AD brain

Amyloid Precursor Protein (APP)

β-secretase

Aβ42 monomers

γ-secretase

Clearance mechanisms

• Immunotherapy
• Enzymes that naturally break down Aβ
Enhancing Aβ clearance - Immunotherapy

• First approach (AN1792) used “active” vaccination of Aβ(1-42) peptide; although initial results looked promising clinical trial was halted in Phase II when 6% of patients developed meningoencephalitis

• In late 2005 Elan/Wyeth began another Phase I clinical trial using ACC-001, a modified Aβ immuno-conjugate

• A potentially safer approach is to use “passive” immunization; Lilly & Wyeth/Elan both have anti-amyloid antibodies in clinical trials at the moment
Possible mechanisms of amyloid clearance by anti-Aβ antibodies

**a** Direct resolution

Amyloid-β fibrils → Amyloid-β-specific antibody

**b** Microglial-cell mediated

Microglial cell

- Phagocytosis

**c** Peripheral sink hypothesis

Blood-brain barrier → Plasma

Weiner and Frenkel (2006), *Nature Reviews Immunology*, 6, 404
Enhancing Aβ clearance - Aβ degrading enzymes

- Several enzymes (Neprilysin, Insulin Degrading Enzyme (IDE), Matrix Metalloproteinases) are involved in the degradation of Aβ, and there is some evidence to suggest that the activity of these enzymes decreases with age.

- Enhancing the activity of one of these enzymes therefore appears to be a promising therapeutic approach.

- It may be possible to develop positive modulators of IDE.
Therapeutic strategies based on decreasing amyloid burden in the AD brain

Amyloid Precursor Protein (APP) → β-secretase → Aβ42 monomers

- Enhance Clearance Mechanisms
- Prevent Aggregation and Deposition of Aβ

γ-secretase → Aβ42 Oligomers & Aggregates

→ Neurotoxicity

• Alzhemed
Preventing Aggregation & Deposition of Aβ peptides

Alzhemed (Neurochem)

• Currently in Phase III trials in both USA and Europe

• Thought to act by reducing the deposition of amyloid in the brain by binding to soluble Aβ peptide and therefore inhibit the inflammatory response associated with amyloid deposition
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- **Progressive synaptic and neuronal injury**
- **Altered neuronal ionic homeostasis & oxidative injury**
- **Altered kinase / phosphatase activities - TANGLES**
- **Widespread neuronal dysfunction and cell death with attendant transmitter deficits**
- **DEMENTIA**
- **• TTP488**
- **• PBT-2**
- **• PPARγ modulators**
- **• Estrogens**
- **• NSAIDs**
Preventing Aβ-mediated inflammation & neurotoxicity – (1)

**TTP488 (Transtech Pharma/Pfizer)**

- Phase II trial of AD patients completed
- RAGE (Receptor for Advanced Glycation Endproducts) antagonist
- RAGE-Aβ interaction may have several adverse consequences:
  - Amplification of glial inflammatory responses
  - Elevation of oxidative stress
  - Increased Aβ influx at the blood brain barrier

**PBT-2 (Prana Biotech)**

- Just starting Phase II clinical trials
- Based on the hypothesis that the interaction between metals and Aβ causes neurotoxicity in Alzheimer's disease; PBT-2 is a copper/zinc binding drug
- This is a follow-up molecule to PBT-1 (clioquinol) – development of this molecule was suspended because the manufacturing process resulted in certain mutagenic impurities that could not be reduced to an acceptable level
Preventing $A_\beta$-mediated inflammation & neurotoxicity – (2)

**PPAR$\gamma$ modulators (Rosiglitazone (Avandia); Pioglitazone (Actos))**

- PPAR$\gamma$ is a nuclear receptor that regulates the transcription of pro-inflammatory molecules
- Recent clinical trials of rosiglitazone showed that the drug improved cognition in a subset of patients, though the effect was small
- It is unclear if the positive effects are related to anti-inflammatory action of molecule or other effects (e.g. insulin sensitization & increase in metabolic efficiency of cells, reduction in amyloid pathology)

**Estrogens & HRT**

- Several epidemiological studies suggest the use of estrogen in postmenopausal women may delay the onset or risk of AD
- However, large clinical trials have failed to show any protective effects of estrogens/HRT on cognitive functioning in elderly (>65 years) women or men

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

- Epidemiological studies have shown that long-term use of a subset of NSAIDs decreases the risk for developing AD
- Several NSAIDs have been tested in clinical trials for AD, though so far none have shown beneficial results except Flurizan
- Mechanism of flurizan is likely unrelated to anti-inflammatory action but rather modulation of $\gamma$-secretase activity
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      - DEMENTIA
Altered neuronal ionic homeostasis

Memantine (Ebixa™, Namenda™)

• Approved for the treatment of moderately severe to severe AD in EU in May 2002 and in US in October 2003.

• Excessive activation of neurons by glutamate at NMDA receptors, with consequent accumulation of intracellular calcium, is thought to initiate a cascade of events that results in neuronal death.

• Memantine modulates activation of NMDA receptors, by altering the “signal to noise” ratio at this receptor.
  • Improves memory
  • Potentially protects neurons from the toxic effects of excess glutamate (but no evidence of disease modification).

MEM-1003 (Memory Pharmaceuticals)

• Neuronal L-type calcium channel modulator; currently in Phase II trials.
Oxidative Injury – Use of antioxidants

• There is some evidence that oxidative stress occurs prior to the onset of symptoms in AD

• Several studies have suggested that increased dietary levels of vitamins E and C (both antioxidants) can protect against the onset of AD in humans, though not all studies agree on this

• Several different antioxidants have been tested in clinical trials on patients that already have AD (Idebenone, *Gingko biloba*)

• Whilst there were some promising early results with Idebenone its development has been discontinued; the study with *Gingko biloba* was negative

• It is likely that for antioxidants to work effectively they will need to be taken in a preventative manner, rather than after the onset of disease
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Kinases that phosphorylate tau as targets for AD

• Hyperphosphorylated tau protein is the principal component of neurofibrillary tangles

• As such, identifying the proteins (kinases) that phosphorylate tau and inhibiting them is perhaps an attractive strategy for an AD therapeutic

• However, over 30 sites are phosphorylated on tau and many different kinases can phosphorylate tau protein on these different sites

• At the moment it is not clear which are the most important sites/kinases that are key to AD progression, nor indeed if phosphorylation of tau is central to disease progression

• As such, pursuing drugs that inhibit phosphorylation of tau is a somewhat risky approach, though most companies are working in this area
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Reversing the neurotransmitter deficits in AD

Cholinesterase Inhibitors

• Neurons that use acetylcholine to signal to each other are lost in the forebrain of AD patients

• Acetyl cholinesterase is an enzyme responsible for “switching off” acetylcholine signalling
  • Inhibitors of this enzyme therefore partially reverse the acetylcholine deficit

• Acetyl cholinesterase inhibitors (AchEIs) are the mainstays for treating AD

• Four AchEIs approved for the treatment of AD: tacrine (Cognex®; rarely used – liver toxicity), donepezil (Aricept®), rivastigmine (Exelon®) & galantamine (Razadyne®/Reminyl™)

• Current NICE guidelines only suggest use of these medications once patients have progressed to moderate AD in the UK

GABA-B Receptor Antagonists (SGS742; Saegis/Novartis)

• A Phase II clinical study for SGS742 in Mild Cognitive Impairment (MCI) showed improvements in computer and paper based learning and memory tests

• A subsequent single study in patients with mild to moderate AD also demonstrated an effect in lesser impaired patients
Summary

• Currently available medications result, at best, in modest cognitive improvement
  • They all provide symptomatic rather than disease-modifying therapy

• Increased understanding of the underlying pathology of AD has led to the amyloid cascade hypothesis & identification of numerous therapeutic targets

• Over the next 5-10 years many molecules that act via a diversity of mechanisms will be tested for efficacy in the clinic

• Many of these newer molecules have disease-modifying potential
  • Potential to significantly improve the standard of care for AD patients

• This will ultimately prove/disprove (or at the very least, modify!) the amyloid cascade hypothesis of AD, upon which many of these treatments are based