

Alzheimer's Disease

Epidemiology and genetics

Dementia is generally defined as “a state of serious emotional and intellectual deterioration” and affects memory, language, visuospatial skills, cognition and personality. Its prevalence increases markedly after 75 years of age; making it a disease of older persons (Lockhart and Lestage, 2003). Alzheimer disease (AD), a progressive neurodegenerative disease, is one of the most prominent forms of dementia and accounts for 70% of all cases. The prevalence of AD has been estimated to double every 5 years after the age of 65 and rises to 47% in people over 85 years of age (Hebert and Brayne, 1995). Factors such as geographical localization and cross-cultural differences may also account for the incidence of AD in the general population (2.1 % Japan, 5.2 % Europe and 10% USA, (Brookmeyer and Zeger, 1996).

Aging is the most important risk factor for AD and age-associated forms of dementia, account for 90% of the cases. The early-onset familial forms of Alzheimer's disease (FAD), is linked to mutations in three genes; the presenilin-1 gene (PS1), the presenilin-2 gene (PS2) and mutation in the amyloid precursor protein (APP) gene (Citron et al., 1996). Furthermore, individuals carrying a trisomy of chromosome 21 (Down syndrome) are predicted to develop AD (Wolvetang et al., 2003).

Other risk factors implicated in AD are, apolipoprotein E (ApoE), a carrier of cholesterol in the blood. It also binds amyloid beta (A β) and is involved in the aggregation (Poirier, 2005; Evans et al., 2004) and export of A β from the brain (Tanzi et al., 2004). Also, factors such as blood pressure, insulin resistance, hypercholesterolemia and cerebrovascular disease have been reported to increase the risk for developing late-onset AD (Joshi and Morley, 2006).

The diminishing brain

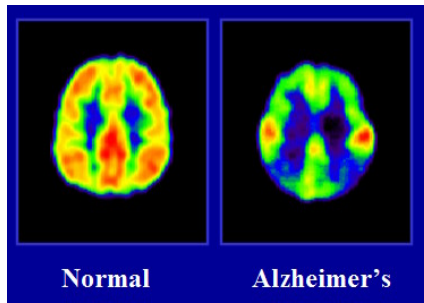


Fig 1. PET scan images. The red-orange coloration indicates metabolism of glucose-normal vs. AD brain. The sugar glucose powers the brain, and a progressively diminishing capacity to make use of glucose contributes to the devastation of mind and personality which is Alzheimer's disease. Images by courtesy of Gary Small, M.D., UCLA Medical Center

Neuropathology

Alzheimer's disease (AD), is a progressive, degenerative form of dementia, and was described for the first time a century ago by Alois Alzheimers (Alzheimer A, 1906). The identification of **amyloid plaques** and **neurofibrillary tangles** defined the neuropathological hallmarks of the disease. The molecular studies identifying **A β peptides** as the major components of plaques, together with the study of inherited forms of disease resulted in the discovery of the causative gene defects. A β 1-40 and 1-42 peptides are the dominant forms derived from proteolytic processing of APP, a transmembrane protein with a single membrane-spanning domain (TM). A β 1-42 peptide is denoted as the more amyloidogenic form due to the extra isoleucine (I) and alanine (A) hydrophobic residues at the C-terminus (Yoshiike et al., 2003).

Another feature of AD is the presence of intracellular neurofibrillary tangles (NFT). Electron microscopy investigations have shown that NFTs contain paired helical filaments (PHF) of **tau** (Kirschner et al., 1986; Mucke et al., 2000). Physiologically tau is a highly soluble microtubule-associated protein (MAP) that promotes microtubule assembly. The hyperphosphorylation of tau, protein aggregation and intracellular accumulation into paired helical filaments (PHFs) has been shown in AD and evidence show that the density of NFTs correlates well with the clinical development of the disease (Arriagada et al., 1992; Braak and Braak, 1991).

Therapeutic interventions in AD

Although efforts in elucidating the pathways involved in the development of AD and its treatment are well under way, there is, up-to-date, no cure for AD. However,

several therapeutic approaches have been pursued and can be divided into symptomatic and disease modifying therapies.

Symptomatic therapies

Today's symptomatic therapies are concentrated in treatment of atrophy of the cholinergic system and decreased synthesis of acetylcholine in AD. However these therapeutic treatments have shown only limited clinical efficacy (Table 1).

Drug	Disease stage
<i>Cholinesterase inhibitors</i>	
Donepezil	Mild to moderate AD
Galantamine	Mild to moderate AD
Rivastigmine	Mild to moderate AD
Tacrine	Mild to moderate AD
<i>NMDA receptor antagonist</i>	
Memantine	Moderate to severe AD

Table 1. Drugs approved by the Food and Drug administration (FDA) for the treatment of AD.

Disease modifying therapies

As the benefits of current therapies are small, the need for more efficacious drugs has lead to new compounds being tested and brought into clinical trials. The therapies receiving most attention will be briefly described, and a selection of other treatment therapies has been compiled in Table 2.

To date, much emphasis has been placed on strategies that reduce the pathogenicity of A β peptides due to their crucial role in AD. *Decreasing A β production* by inhibiting the activity of β and γ -secretase and upregulation of α -secretase activity is being explored as potential therapeutic targets (Golde and Younkin, 2001; Postina et al., 2004). Also, efforts aiming at reducing *A β aggregation* (cuiquinol, curcumiin) are currently in phase II and III clinical trials (Cherny et al., 2001; Ringman and Cummings, 2006; Ringman et al., 2005). *Enhancing A β clearance* by enhancing A β degrading enzymes activity are also being explored (Eckman and Eckman, 2005; Saido and Iwata, 2006; Saito et al., 2003; Iwata et al., 2001; Tucker et al., 2002). *A β immunotherapy*: Promoting A β clearance by immunotherapy is another promising

approach. Active and passive immunization showed reduced amyloid deposits and cognitive and behaviour improvements with no adverse events (Morgan and Gitter, 2004; Janus and Westaway, 2001; Dodart et al., 2003) and has proceeded to Phase II trials.

<i>Treatment Strategies</i>		
<i>Phase III</i>	<i>Phase II</i>	<i>Phase I</i>
A β aggregation inhibitors	γ -secretase inhibitors	Active immunisation
Antioxidants	Glucogen synthase kinase inhibitors	NGF gene therapy
γ -secretase modulators	Muscarinic receptor agonist	
NGF mimics	Nicotinic receptor modulators	
PPAR γ agonist	GABA _B antagonist	
HMG-CoA reductase inhibitors	Cholesterol lowering drugs	
Anti-Inflammatory	Phosphodiesterase inhibitors	
Anti-agitation therapy	AMPA receptor agonist	
Estrogen	Passive immunisation	

Table 2. Selected treatments in clinical trials for AD (Modified from Roberson and Mucke 2006 and www.alzforum.org).

Targeting Tau: Therapies against *tau production* are based very much on the evidence from tau mice models developed for FTDP-17, suggests it is a beneficial strategy (Goedert et al., 1998). Altering *tau aggregation* has been debated and a small clinical trial is currently ongoing (Khlistunova et al., 2006; Pickhardt et al., 2005). Prevention of *tau hyperphosphorylation* by inhibition of kinases involved in the phosphorylation of PFH sites (Jope et al., 2006; Woodgett, 2003) are ongoing activities although the involvement of these kinases in numerous cellular events pose a potential risk.

Other AD alternative therapeutic approaches are being investigated for the treatment of AD (Table 2) including those against oxidative stress, (antioxidants; vitamin E and C, coenzyme Q), anti-inflammatory drugs (NSAIDs, ibuprofen), cholesterol lowering agents (lovastatin, parastatin) and metal chelators (clioquinol) (Doraiswamy and

Finefrock, 2004; Wettstein and Spiegel, 1984; McGeer and McGeer, 2007; Sparks et al., 2006).

Biomarkers

The search for biomarkers is important for screening of populations before the display of clinical symptoms, diagnosis of early disease, for monitoring the effect of disease modifying treatments and also distinguishing the false diagnosis of AD (Boss, 2000). A set of guidelines regarding biomarkers for AD have been proposed from a working group assembled by the Alzheimer's Association and the National Institute of Aging (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and, 1998). The biomarkers should reflect a basic pathogenic feature of AD and need to have sensitivity and specificity of no less than 80%. Tau and A β have been measured in cerebrospinal fluid (CSF) and peripheral fluids (blood and urine). Other biomarkers that reflect some of the processes and changes in AD have been suggested. Candidates, such as oxidative stress, inflammation as well as astrocyte activation are likely to discriminate between AD and controls. The combination of all these biomarker tests can also be used (Blasko et al., 2006).

REFERENCES

- Alzheimer A (1906): Ueber einen eigenartigen, schweren Erkrankungsprozess der Hirnrinde [*On a peculiar, severe disease process of the cerebral cortex*]. *Neurologisches Centralblatt* 25, 1134 [no abstract].
- Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT (1992): Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 42:631-639.
- Blasko I, Lederer W, Oberbauer H, Walch T, Kemmler G, Hinterhuber H, Marksteiner J, Humpel C (2006): Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. *Dement Geriatr Cogn Disord* 21:9-15.
- Boss MA (2000): Diagnostic approaches to Alzheimer's disease. *Biochim Biophys Acta* 1502:188-200.
- Braak H, Braak E (1991): Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 82:239-259.
- Brandt R, Hundelt M, Shahani N (2005): Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochim Biophys Acta* 1739:331-354.
- Brookmeyer R, Zeger S (1996): Statistical issues in prevention and therapeutic trials of Alzheimer disease. *Alzheimer Dis Assoc Disord.* 1996 Fall;10 Suppl 1:27-30
- Cherny RA, Atwood CS, Xilinas ME, Gray DN, Jones WD, McLean CA, Barnham KJ, Volitakis I, Fraser FW, Kim Y, Huang X, Goldstein LE, Moir RD, Lim JT, Beyreuther K, Zheng H, Tanzi RE, Masters CL, Bush AI (2001): Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron* 30:665-676.
- Citron M, Diehl TS, Gordon G, Biere AL, Seubert P, Selkoe DJ. (1996): Evidence that the 42- and 40-amino acid forms of amyloid beta protein are generated from the beta-amyloid precursor protein by different protease activities. *Proc Natl Acad Sci U S A.* 1996 Nov 12;93(23):13170-5.
- Dodart JC, Bales KR, Paul SM (2003): Immunotherapy for Alzheimer's disease: will vaccination work? *Trends Mol Med* 9:85-87.
- Doraiswamy PM, Finebrock AE (2004): Metals in our minds: therapeutic implications for neurodegenerative disorders. *Lancet Neurol* 3:431-434.
- Eckman EA, Eckman CB (2005): Abeta-degrading enzymes: modulators of Alzheimer's disease pathogenesis and targets for therapeutic intervention. *Biochem Soc Trans* 33:1101-1105.
- Evans RM, Hui S, Perkins A, Lahiri DK, Poirier J, Farlow MR. (2004): Cholesterol and APOE genotype interact to influence Alzheimer disease progression. *Neurology.* 2004 May 25;62(10):1869-71.
- Goedert M, Crowther RA, Spillantini MG (1998): Tau mutations cause frontotemporal dementias. *Neuron* 21:955-958.

- Golde TE, Younkin SG (2001): Presenilins as therapeutic targets for the treatment of Alzheimer's disease 21. *Trends Mol Med* 7:264-269.
- Hebert R, Brayne C (1995): Epidemiology of vascular dementia. *Neuroepidemiology*. 1995;14(5):240-57.
- Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, Gerard C, Hama E, Lee HJ, Saido TC (2001): Metabolic regulation of brain Abeta by neprilysin. *Science* 292:1550-1552.
- Janus C, Westaway D (2001): Transgenic mouse models of Alzheimer's disease. *Physiol Behav* 73:873-886.
- Jope RS, Yuskaitis CJ, Beurel E (2006): Glycogen Synthase Kinase-3 (GSK3): Inflammation, Diseases, and Therapeutics. *Neurochem Res*.
- Joshi S, Morley JE. (2006): Cognitive impairment. *Med Clin North Am*. 2006 Sep;90(5):769-87. Review.
- Khlistunova I, Biernat J, Wang Y, Pickhardt M, von BM, Gazova Z, Mandelkow E, Mandelkow EM (2006): Inducible expression of Tau repeat domain in cell models of tauopathy: aggregation is toxic to cells but can be reversed by inhibitor drugs. *J Biol Chem* 281:1205-1214.
- Kirschner DA, Abraham C, Selkoe DJ (1986): X-ray diffraction from intraneuronal paired helical filaments and extraneuronal amyloid fibers in Alzheimer disease indicates cross-beta conformation. *Proc Natl Acad Sci U S A* 83:503-507.
- Lockhart BP, Lestage PJ (2003): Cognition enhancing or neuroprotective compounds for the treatment of cognitive disorders: why? when? which? *Exp Gerontol* 38:119-128.
- McGeer PL, McGeer EG (2007): NSAIDs and Alzheimer disease: Epidemiological, animal model and clinical studies. *Neurobiol Aging* 28:639-647.
- Morgan D, Gitter BD (2004): Evidence supporting a role for anti-Abeta antibodies in the treatment of Alzheimer's disease. *Neurobiol Aging* 25:605-608.
- Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K, McConlogue L (2000): High-level neuronal expression of abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *J Neurosci* 20:4050-4058.
- Pickhardt M, Gazova Z, von BM, Khlistunova I, Wang Y, Hascher A, Mandelkow EM, Biernat J, Mandelkow E (2005): Anthraquinones inhibit tau aggregation and dissolve Alzheimer's paired helical filaments in vitro and in cells. *J Biol Chem* 280:3628-3635.
- Poirier J (2005) Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease. *Neurobiol Aging*. 2005 Mar;26(3):355-61.
- Postina R, Schroeder A, Dewachter I, Bohl J, Schmitt U, Kojro E, Prinzen C, Endres K, Hiemke C, Blessing M, Flamez P, Dequenne A, Godaux E, van LF, Fahrenholz F (2004): A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. *J Clin Invest* 113:1456-1464.
- Ringman JM, Cummings JL (2006): Current and emerging pharmacological treatment options for dementia. *Behav Neurol* 17:5-16.

- Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL (2005): A potential role of the curry spice curcumin in Alzheimer's disease. *Curr Alzheimer Res* 2:131-136.
- Saido TC, Iwata N (2006): Metabolism of amyloid beta peptide and pathogenesis of Alzheimer's disease. Towards presymptomatic diagnosis, prevention and therapy. *Neurosci Res* 54:235-253.
- Sparks DL, Sabbagh M, Connor D, Soares H, Lopez J, Stankovic G, Johnson-Traver S, Ziolkowski C, Browne P (2006): Statin therapy in Alzheimer's disease. *Acta Neurol Scand Suppl* 185:78-86.
- Tanzi RE, Moir RD, Wagner SL. (2004): Clearance of Alzheimer's Aβ peptide: the many roads to perdition. *Neuron*. 2004 Sep 2;43(5):605-8.
- The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and NIA/AAWG (1998): Consensus Report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease". *Neurobiol Aging*. 1998 Mar-Apr;19(2):109-16.
- Tucker HM, Kihiko-Ehmann M, Estus S (2002): Urokinase-type plasminogen activator inhibits amyloid-beta neurotoxicity and fibrillogenesis via plasminogen. *J Neurosci Res* 70:249-255.
- Wettstein A, Spiegel R (1984) Clinical trials with the cholinergic drug RS 86 in Alzheimer's disease (AD) and senile dementia of the Alzheimer type (SDAT) 4. *Psychopharmacology (Berl)* 84:572-573.
- Wolvetang EW, Bradfield OM, Tymms M, Zavarsek S, Hatzistavrou T, Kola I, Hertzog PJ. (2003): The chromosome 21 transcription factor ETS2 transactivates the beta-APP promoter: implications for Down syndrome. *Biochim Biophys Acta*. 2003 Jul 28;1628(2):105-10.
- Woodgett JR (2003): Physiological roles of glycogen synthase kinase-3: potential as a therapeutic target for diabetes and other disorders. *Curr Drug Targets Immune Endocr Metabol Disord* 3:281-290.
- Yoshiike Y, Chui DH, Akagi T, Tanaka N, Takashima A (2003): Specific compositions of amyloid-beta peptides as the determinant of toxic beta-aggregation 3. *J Biol Chem* 278:23648-23655.

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