

Review

Open Access

Preventing β -amyloid fibrillization and deposition: β -sheet breakers and pathological chaperone inhibitors

Thomas Wisniewski*^{1,2,3} and Martin Sadowski^{1,2,4}

Address: ¹Department of Neurology, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA, ²Department of Pathology, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA, ³Department of Psychiatry, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA and ⁴Department of Pharmacology, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA

Email: Thomas Wisniewski* - Thomas.wisniewski@nyumc.org; Martin Sadowski - martin.sadowski@nyumc.org

* Corresponding author

from 8th International Conference on Alzheimer's Disease Drug Discovery
New York, NY, USA. 15–16 October 2007

Published: 3 December 2008

BMC Neuroscience 2008, 9(Suppl 2):S5 doi:10.1186/1471-2202-9-S2-S5

This article is available from: <http://www.biomedcentral.com/1471-2202/9/S2/S5>

© 2008 Wisniewski and Sadowski; licensee BioMed Central Ltd.

This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Central to the pathogenesis of Alzheimer's disease (AD) is the conversion of normal, soluble β -amyloid (sA β) to oligomeric, fibrillar A β . This process of conformational conversion can be influenced by interactions with other proteins that can stabilize the disease-associated state; these proteins have been termed 'pathological chaperones'. In a number of AD models, intervention that block soluble A β aggregation, including β -sheet breakers, and compounds that block interactions with pathological chaperones, have been shown to be highly effective. When combined with early pathology detection, these therapeutic strategies hold great promise as effective and relatively toxicity free methods of preventing AD related pathology.

Introduction

Formation of β -amyloid (A β) fibrils and deposition of A β in the brain parenchyma, or in the brain's vessels, occurs in the setting of increased A β peptide concentrations [1,2]. Initially, conditions do not favor aggregation of fibrils, but once a critical nucleus has been formed, conditions change to favor aggregation in an exponential manner. Any available monomer becomes instantly entrapped in an aggregate or fibril. Several compounds – for example, Congo red [3], anthracycline [4], rifampicin [5], anionic sulphonates [6], and melatonin [7] – can interact with A β and prevent its aggregation into oligomers and fibrils *in vitro*, reducing toxicity. These oligomeric structures have been associated with the greatest toxicity [8].

Several A β homologous peptides have been identified that have amino acid substitutions using residues such as proline and can bind to A β oligomers and fibril structures, leading to disruption of the β -sheet conformation [9-12]. These peptides have been termed β -sheet breakers. An advantage of such compounds, in comparison to other putative therapeutic approaches for AD, such as vaccination, is that they specifically target the abnormal conformation of A β and will not disrupt any possible normal function of the soluble A β peptide. Several modifications have been used to extend the serum half-life and increase the blood-brain barrier (BBB) permeability of these β -sheet breakers. Permanne *et al.* [13], using a BBB permeable pentapeptide (iA β 5), were able to demonstrate a

reduction of A β load in AD Tg mice compared to an age-matched control group. Of interest, a similar concept of β -sheet breakers appears to be applicable to other protein conformational disorders caused by prions [14].

Pathological chaperone inhibitors

A β homologous peptides can spontaneously aggregate and form fibrils *in vitro*; however, *in vivo* this process appears more dependant on A β pathological chaperones. This group of proteins actively promotes conformational transformation by increasing the β -sheet content of these disease-specific proteins, stabilizing their abnormal structure [15-17]. Examples in Alzheimer's disease (AD) include apolipoprotein E (apoE), especially its E4 isoform [16,18], α 1-antichymotrypsin [19], and C1q complement factor [20,21]. In their presence, the formation of A β fibrils in a solution of soluble A β monomers becomes much more efficient [16,19]. These 'pathological chaperone' proteins have been found histologically and biochemically in association with fibrillar A β deposits [15,22-24], but not in preamyloid aggregates, which are not associated with neuronal toxicity [25-27]. Inheritance of the apoE4 isoform has been identified as the major genetic risk factor for sporadic, late-onset AD [28] and correlates with an earlier age of onset and greater A β deposition in an allele-dose-dependent manner [28,29]. On the other hand, epidemiological data suggest that inheritance of the E2 allele has a protective effect. *In vitro* all apoE isoforms can propagate the β -sheet content of A β peptides promoting fibril formation [16,23], with apoE4 being the most efficient [16]. The critical dependence of A β deposition in plaques on the presence of apoE has also been confirmed in AD Tg amyloid precursor protein (APP)^{V717F}/apoE^{-/-} mice, which have a delayed onset of A β deposition, a reduced A β load, and no fibrillar A β deposits compared with APP^{V717F}/apoE^{+/+} Tg mice. APP^{V717F}/apoE^{+/-} mice demonstrate an intermediate level of pathology [30-33]. Neutralization of the chaperoning effect of apoE would therefore potentially have a mitigating effect on A β accumulation. ApoE binds hydrophobically to amino acids 12-28 of A β , forming SDS-insoluble complexes [34-36]. Ma *et al.* [37] have demonstrated that a synthetic peptide homologous to this sequence of A β can be used as a competitive inhibitor of the binding of full length A β to apoE, resulting in reduced fibril formation *in vitro* and increased survival of cultured neurons. Several modifications to A β 12-28, including the replacement of a valine for proline at position 18 (A β 12-28P), made this peptide non-toxic, non-fibrillogenic, and prevented any potential for co-deposition on existing A β plaques. Further modifications included protection of its amino and carboxyl termini, and using D-amino acids resulted in an extended serum half-life (62 \pm 18 minutes, mean \pm standard deviation). These modifications did not limit its ability to block the apoE-A β interaction (K_i = 11.37 nM) [38,39].

Although A β 12-28P had a limited serum half-life, it was able to cross the BBB, exerting a therapeutically prolonged effect. Treatment of APP^{K670N/M671L}/PS1^{M146L}, and APP^{K670N/M671L} AD Tg mice with A β 12-28P resulted in a significant reduction of A β deposition in brain parenchyma and in brain vessels [39]. Furthermore, treatment with A β 12-28P prevented memory decline in single APP Tg mice. Measurement of A β levels in the brain homogenate revealed a significant reduction in the absolute A β level while the concentrations of the soluble A β fraction and A β oligomers remained stable during treatment [39]. This observation is important in light of a concern regarding the blocking of the apoE-A β interaction and that this form of therapeutic interference could destabilize fibrillar A β assemblies, and impair apoE-mediated A β clearance, potentially increasing brain levels of soluble A β , thus favoring the formation of toxic oligomers [8,40]. During treatment with A β 12-28P, no signs of toxicity, including systemic amyloidosis or disturbance of vascular integrity leading to cerebral hemorrhages (as observed with some vaccination approaches [39]), were noted. The treatment outcome with A β 12-28P could not be attributed to an immunization effect since there were no significant changes in the serum titer of anti-A β antibodies before and after the treatment of AD Tg animals. Thus, interference with the apoE-A β interaction *in vivo* appears to have a net effect of increasing A β clearance and reducing the absolute A β level in the brain, producing a cognitive benefit. Further development of ligands inhibiting the apoE-A β interaction, potentially making them suitable for clinical application, should be aggressively pursued.

Of interest, Pepys and co-workers [41] have developed a ligand that chelates serum amyloid-P component. Serum amyloid-P component, along with apoE, binds to amyloid fibrils *in vivo* in amyloid-A primary systemic amyloidosis, and inhibits the normal degradative process of amyloid-A [42]. Both disease model animals and affected humans treated with this compound in phase I/II clinical trials demonstrated reduced amyloid-A deposition [41].

A similar treatment concept is being developed based on inhibiting the interaction between glycosaminoglycans and A β fibrils [6]. Neurochem Inc. is conducting clinical trials to determine the efficacy of 3-amino-1-propanesulfonic acid (3APS), a synthetic sulphated glycosaminoglycan mimetic designed to compete with naturally occurring glycosaminoglycans in their binding to A β to prevent its deposition <http://www.neurochem.com/ResearchActivities.htm>. The efficacy of this compound is being tested for AD and cerebral amyloid angiopathy under two different brand names, Alzhemed[™] and Cerebril[™], respectively. The phase II clinical trial of Alzhemed[™] (tramiprosate) demonstrated a good safety profile, with the most frequently reported adverse events being nausea and vomiting, the

occurrence of which appeared to be dose related. This multi-centre, double-blind, placebo-controlled study recruited 58 patients who received either tramiprosate (100 mg, 200 mg or 300 mg daily) or placebo. Results of this trial indicated that tramiprosate reduced the A β 1–42 concentration in the cerebrospinal fluid and stabilized cognitive decline (monitored using the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scales) compared with the control group [43]. Unfortunately, the North American phase III clinical trial of tramiprosate, which finished in late 2007, did not provide clear enough benefit in a large population. The clinical data gathered by this trial are being subjected to secondary statistical analysis. Currently, the prospect of FDA approval for tramiprosate remains unclear.

Another class of compounds characterized by inherent anti-A β aggregation properties *in vivo* comprises the cyclohexanehexol (inositol) stereoisomers. These compounds are naturally occurring sugars characterized by good gastrointestinal absorption, making them attractive candidates for clinical development. When administered orally to AD Tg mice, the cyclohexanehexol stereoisomers scyllo-cyclohexanehexol and epi-cyclohexanehexol reduced several disease features, including impaired cognition, altered synaptic physiology, and cerebral A β deposition [44]. Clinical trials of scyllo-cyclohexanehexol are currently entering a multi-center phase II trial under the name ELND005.

The US phase II clinical trial of NC-758 (Cerebril™) for the prevention of hemorrhagic stroke due to cerebral amyloid angiopathy has recently finished. This multi-center, randomized, double-blind and parallel-designed study was conducted at five centers, enrolled 24 cerebral amyloid angiopathy (CAA) patients, and found no safety concerns related to the use of NC-758. Neurochem Inc. has also recently successfully finished a phase II/III clinical trial of 1,3-propanedisulfonate (Fibrillex™), a compound designed to treat amyloidosis A, which is associated with a number of systemic, chronic inflammatory diseases, including rheumatoid arthritis and Crohn's disease. Its mechanism of action is analogous to that of tramiprosate. Based on the results of this trial the company has filed for market approval.

Necessity for early diagnosis and treatment

For maximal benefit, it is likely that all of the interventions discussed above will need to be initiated at the earliest stages of AD pathology [45]. From AD models, therapeutic strategies to prevent and remove amyloid deposition using methods such as vaccination are very effective at preventing cognitive deficits when initiated at the time deposition first starts. However, when the same treat-

ment is administered after deposits are well-established there are no cognitive benefits [46]. In AD patients it is estimated that mild cognitive impairment slowly develops over 10–30 years prior to the presentation of pathology [47,48]. In the active vaccination study, which targeted early clinical stage AD, patients showed a very modest cognitive benefit [49,50] despite the fact that autopsies on four study participants indicated that the vaccine had produced a significant reduction in amyloid plaques [51]. Positron emission tomography (PET) imaging of amyloid binding ligands can detect amyloid deposition at early stages [52] and similar methods are being developed for amyloid detection by magnetic resonance imaging (MRI) [53]. These methods will be critical in identifying patients who are at risk of developing clinical AD and who might benefit from preventing A β aggregation and deposition therapies.

Conclusion

Numerous therapeutic interventions are currently being developed for AD. It is likely that, in the future, multimodal therapies will be tailored to individual patients based on their genotype, immune status, and pathological stage of their disease. However, β -sheet breakers and pathological chaperone inhibitors are likely to be among the most effective and safest strategies.

List of abbreviations used

A β : β -amyloid; AD: Alzheimer's disease; apoE: apolipoprotein E; APP: amyloid precursor protein; BBB: blood-brain barrier; CAA: cerebral amyloid angiopathy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Both authors carried out a literature review. TW wrote the draft, which was modified and corrected by MS.

Acknowledgements

This manuscript was supported by NIH grants AG15408, AG24847 and AG31221.

This article has been published as part of *BMC Neuroscience* Volume 9 Supplement 2: 2008 Proceedings of the 8th International Conference on Alzheimer's Disease Drug Discovery The full contents of the supplement are available online at <http://www.biomedcentral.com/1471-2202/9?issue=S2>.

References

1. Barrow CJ, Yasuda A, Kenny PT, Zagorski MG: **Solution conformations and aggregational properties of synthetic amyloid beta-peptides of Alzheimer's disease. Analysis of circular dichroism spectra.** *J Mol Biol* 1992, **225**:1075-1093.
2. Wisniewski T, Ghiso J, Frangione B: **Biology of A β amyloid in Alzheimer's disease.** *Neurobiol Dis* 1997, **4**:313-328.
3. Lorenzo A, Yankner BA: **Beta-amyloid neurotoxicity requires fibril formation and is inhibited by congo red.** *Proc Natl Acad Sci USA* 1994, **91**:12243-12247.

4. Merlini G, Ascari E, Amboldi N, Bellotti V, Arbustini E, Perfetti V, Ferrarini M, Zorzoli I, Marinone MG, Garini P: **Interaction of the anthracycline 4'-iodo-4'-deoxydoxorubicin with amyloid fibrils: inhibition of amyloidogenesis.** *Proc Natl Acad Sci USA* 1995, **92**:2959-2963.
5. Tomiyama T, Shoji A, Kataoka K, Suwa Y, Asano S, Kaneko H, Endo N: **Inhibition of amyloid β protein aggregation and neurotoxicity by rifampicin – Its possible function as a hydroxyl radical scavenger.** *J Biol Chem* 1996, **271**:6839-6844.
6. Kisilevsky R, Lemieux LJ, Fraser PE, Kong X, Hultin PG, Szarek WA: **Arresting amyloidosis in vivo using small-molecule anionic sulphates or sulphates: implications for Alzheimer's disease.** *Nat Med* 1995, **1**:143-148.
7. Pappolla M, Bozner P, Soto C, Shao H, Robakis NK, Zagorski M, Frangione B, Ghiso J: **Inhibition of Alzheimer beta-fibrillogenesis by melatonin.** *J Biol Chem* 1998, **273**:7185-7188.
8. Walsh DM, Selkoe DJ: **Abeta oligomers – a decade of discovery.** *J Neurochem* 2007, **101**:1172-1184.
9. Hilbich C, Kisters-Woike B, Reed J, Masters CL, Beyreuther K: **Substitutions of hydrophobic amino acids reduce the amyloidogenicity of Alzheimer's disease β A4 peptides.** *J Mol Biol* 1992, **228**:1-14.
10. Soto C, Kindy MS, Baumann M, Frangione B: **Inhibition of Alzheimer's amyloidosis by peptides that prevent β -sheet conformation.** *Biochem Biophys Res Commun* 1996, **226**:672-680.
11. Soto C, Sigurdsson EM, Morelli L, Kumar A, Castaño EM, Frangione B: **β -sheet breaker peptides inhibit fibrillogenesis in a rat brain model of amyloidosis: implications for Alzheimer's therapy.** *Nat Med* 1998, **4**:822-826.
12. Sigurdsson EM, Permann B, Soto C, Wisniewski T, Frangione B: **In vivo reversal of amyloid β lesions in rat brain.** *J Neuropath Exp Neurol* 2000, **59**:11-17.
13. Permann B, Adessi C, Saborio GP, Fraga S, Frossard MJ, Van Dorpe J, Dewachter I, Banks WA, Van Leuven F, Soto C: **Reduction of amyloid load and cerebral damage in a transgenic mouse model of Alzheimer's disease by treatment with a β -sheet breaker peptide.** *FASEB J* 2002, **16**:860-862.
14. Soto C, Kacsak RJ, Saborio GP, Aucouturier P, Wisniewski T, Prelli F, Kacsak R, Mendez E, Harris DA, Ironside J, Tagliavini F, Carp RI, Frangione B: **Reversion of prion protein conformational changes by synthetic β -sheet breaker peptides.** *Lancet* 2000, **355**:192-197.
15. Wisniewski T, Frangione B: **Apolipoprotein E: a pathological chaperone protein in patients with cerebral and systemic amyloid.** *Neurosci Lett* 1992, **135**:235-238.
16. Wisniewski T, Castaño EM, Golabek AA, Vogel T, Frangione B: **Acceleration of Alzheimer's fibril formation by apolipoprotein E in vitro.** *Am J Pathol* 1994, **145**:1030-1035.
17. Sadowski M, Wisniewski T: **Disease modifying approaches for Alzheimer's pathology.** *Curr Pharmaceutical Design* 2007, **13**:1943-1954.
18. Sanan DA, Weisgraber KH, Russell SJ, Mahley RW, Huang D, Saunders A, Schmechel D, Wisniewski T, Frangione B, Roses AD, Strittmatter WJ: **Apolipoprotein E associates with beta amyloid peptide of Alzheimer's disease to form novel monofibrils. Isoform apoE4 associates more efficiently than apoE3.** *J Clin Invest* 1994, **94**:860-869.
19. Ma J, Yee A, Brewer HB Jr, Das S, Potter H: **Amyloid-associated proteins alpha I-antichymotrypsin and apolipoprotein E promote assembly of Alzheimer beta-protein into filaments.** *Nature* 1994, **372**:92-94.
20. Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH: **The Alzheimer's A beta-peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration.** *Proc Natl Acad Sci USA* 2002, **99**:11830-11835.
21. Boyett KW, DiCarlo G, Jantzen PT, Jackson J, O'Leary C, Wilcock D, Morgan D, Gordon MN: **Increased fibrillar beta-amyloid in response to human C1q injections into hippocampus and cortex of APP+PS1 transgenic mice.** *Neurochem Res* 2003, **28**:83-93.
22. Wisniewski T, Lalowski M, Golabek AA, Vogel T, Frangione B: **Is Alzheimer's disease an apolipoprotein E amyloidosis?** *Lancet* 1995, **345**:956-958.
23. Golabek AA, Soto C, Vogel T, Wisniewski T: **The interaction between apolipoprotein E and Alzheimer's amyloid β -peptide is dependent on β -peptide conformation.** *J Biol Chem* 1996, **271**:10602-10606.
24. Permann B, Perez C, Soto C, Frangione B, Wisniewski T: **Detection of apolipoprotein E dimeric soluble amyloid β complexes in Alzheimer's disease brain supernatants.** *Biochem Biophys Res Commun* 1997, **240**:715-720.
25. Wisniewski HM, Sadowski M, Jakubowska-Sadowska K, Tarnawski M, Wegiel J: **Diffuse, lake-like amyloid-beta deposits in the paraventricular layer of the presubiculum in Alzheimer disease.** *J Neuropathol Exp Neurol* 1998, **57**:674-683.
26. Kida E, Golabek AA, Wisniewski T, Wisniewski KE: **Regional differences in apolipoprotein E immunoreactivity in diffuse plaques in Alzheimer's disease brain.** *Neurosci Lett* 1994, **167**:73-76.
27. Gallo G, Wisniewski T, Choi-Miura NH, Ghiso J, Frangione B: **Potential role of apolipoprotein-E in fibrillogenesis.** *Am J Pathol* 1994, **145**:526-530.
28. Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D, Roses AD: **Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease.** *Proc Natl Acad Sci USA* 1993, **90**:9649-9653.
29. Rebeck GW, Reiter JS, Strickland DK, Hyman BT: **Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions.** *Neuron* 1993, **11**:575-580.
30. Bales KR, Verina T, Dodel RC, Du YS, Altstiel L, Bender M, Hyslop P, Johnstone EM, Little SP, Cummins DJ, Piccardo P, Ghetti B, Paul SM: **Lack of apolipoprotein E dramatically reduces amyloid β -peptide deposition.** *Nat Genet* 1997, **17**:263-264.
31. Bales KR, Verina T, Cummins DJ, Du Y, Dodel RC, Saura J, Fishman CE, DeLong CA, Piccardo P, Petegnief V, Ghetti B, Paul SM: **Apolipoprotein E is essential for amyloid deposition in the APPV717F transgenic mouse model of Alzheimer's disease.** *Proc Natl Acad Sci USA* 1999, **96**:15233-15238.
32. Holtzman DM, Bales KR, Wu S, Bhat P, Parsadanian M, Fagan AM, Chang LK, Sun Y, Paul SM: **Expression of human apolipoprotein E reduces amyloid-beta deposition in a mouse model of Alzheimer's disease.** *J Clin Invest* 1999, **103**:R15-R21.
33. Holtzman DM, Bales KR, Tenkova T, Fagan AM, Parsadanian M, Sartorius LJ, Mackey B, Olney J, McKeel D, Wozniak D, Paul SM: **Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease.** *Proc Natl Acad Sci USA* 2000, **97**:2892-2897.
34. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Englund J, Salvesen GS, Roses AD: **Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease.** *Proc Natl Acad Sci USA* 1993, **90**:1977-1981.
35. Wisniewski T, Golabek AA, Matsubara E, Ghiso J, Frangione B: **Apolipoprotein E: binding to soluble Alzheimer's beta-amyloid.** *Biochem Biophys Res Commun* 1993, **192**:359-365.
36. Naslund J, Thyberg J, Tjernberg LO, Wernstedt C, Karlstrom AR, Bogdanovic N, Gandy SE, Lannfelt L, Terenius L, Nordstedt C: **Characterization of stable complexes involving apolipoprotein E and the amyloid beta peptide in Alzheimer's disease brain.** *Neuron* 1995, **15**:219-228.
37. Ma J, Brewer BH, Potter H, Brewer HB Jr: **Alzheimer A β neurotoxicity: promotion by antichymotrypsin, apoE4; inhibition by A β -related peptides.** *Neurobiol Aging* 1996, **17**:773-780.
38. Sadowski M, Pankiewicz J, Scholtzova H, Ripellino JA, Li Y, Schmidt SD, Mathews P, Fryer JD, Holtzman DM, Sigurdsson EM, Wisniewski T: **Blocking the apolipoprotein E/ β -amyloid interaction reduces β -amyloid toxicity and decreases β -amyloid load in transgenic mice.** *Am J Pathol* 2004, **165**:937-948.
39. Sadowski M, Pankiewicz J, Scholtzova H, Mehta P, Prelli F, Quartermain D, Wisniewski T: **Blocking the apolipoproteinE/Amyloid β interaction reduces the parenchymal and vascular amyloid- β deposition and prevents memory deficit in AD transgenic mice.** *Proc Natl Acad Sci USA* 2006, **103**:18787-18792.
40. Kirkitadze MD, Bitan G, Teplow DB: **Paradigm shifts in Alzheimer's disease and other neurodegenerative disorders: the emerging role of oligomeric assemblies.** *J Neurosci Res* 2002, **69**:567-577.
41. Pepys MB, Herbert J, Hutchinson WL, Tennent GA, Lachmann HJ, Gallimore JR, Lovat LB, Bartfai T, Alanine A, Hertel C, Hoffmann T, Jakob-Roetne R, Norcross RD, Kemp JA, Yamamura K, Suzuki M,

- Taylor GW, Murray S, Thompson D, Purvis A, Kolstoe S, Wood SP, Hawkins PN: **Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis.** *Nature* 2002, **417**:254-259.
42. Gillmore JD, Hawkins PN, Pepys MB: **Amyloidosis: a review of recent diagnostic and therapeutic developments.** *Br J Haematol* 1997, **99**:245-256.
 43. Aisen PS, Mehran M, Poole R, Lavoie E, Gervais F, Laurin J, Brainin R, Garceau L: **Clinical data on Alzhemed after 12 months of treatment in patients with mild to moderate Alzheimer's disease.** *Neurobiol Aging* 2004, **25**:20.
 44. McLaurin J, Kierstead ME, Brown ME, Hawkes CA, Lambermon MH, Phinney AL, Darabie AA, Cousins JE, French JE, Lan MF, Chen F, Wong SS, Mount HT, Fraser PE, Westaway D, St George-Hyslop P: **Cyclohexanehexol inhibitors of Abeta aggregation prevent and reverse Alzheimer phenotype in a mouse model.** *Nat Med* 2006, **12**:801-808.
 45. DeKosky S: **Early intervention is key to successful management of Alzheimer disease.** *Alzheimer Dis Assoc Disord* 2003, **17**(Suppl 4):S99-104.
 46. Asuni A, Boutajangout A, Scholtzova H, Knudsen E, Li Y, Quartermain D, Frangione B, Wisniewski T, Sigurdsson EM: **A β derivative vaccination in alum adjuvant prevents amyloid deposition and does not cause brain microhemorrhages in Alzheimer's model mice.** *Eur J Neurosci* 2006, **24**:2530-2542.
 47. Mondadori CR, Buchmann A, Mustovic H, Schmidt CF, Boesiger P, Nitsch RM, Hock C, Streffer J, Henke K: **Enhanced brain activity may precede the diagnosis of Alzheimer's disease by 30 years.** *Brain* 2006, **129**:2908-2922.
 48. Schmitt FA, Davis DG, Wekstein DR, Smith CD, Ashford JW, Markesbery WR: **"Preclinical" AD revisited: neuropathology of cognitively normal older adults.** *Neurology* 2000, **55**:370-376.
 49. Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Boada Rovira M, Forette F, Orgogozo JM: **Clinical effects of A β immunization (AN1792) in patients with AD in an interrupted trial.** *Neurology* 2005, **64**:1553-1562.
 50. Hock C, Konietzko U, Straffer JR, Tracy J, Signorell A, Muller-Tillmanns B, Lemke U, Henke K, Moritz E, Garcia E, Axel Wollmar M, Umbricht D, de Quervain DJF, Hofmann M, Maddalena A, Papassotiropoulos A, Nitsch RM: **Antibodies against β -amyloid slow cognitive decline in Alzheimer's disease.** *Neuron* 2003, **38**:547-554.
 51. Wisniewski T, Sigurdsson EM: **Therapeutic approaches for prion and Alzheimer's diseases.** *FEBS J* 2007, **274**:3784-3798.
 52. Klunk WE, Price JC, Mathis CA, Tsopelas ND, Lopresti BJ, Ziolko SK, Bi W, Hoge JA, Cohen AD, Ikonomic MD, Saxton JA, Snitz BE, Pollen DA, Moonis M, Lippa CF, Swearer JM, Johnson KA, Rentz DM, Fischman AJ, Aizenstein HJ, DeKosky ST: **Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees.** *J Neurosci* 2007, **27**:6174-6184.
 53. Sigurdsson E, Wadghiri YZ, Mosconi L, Blind JA, Knudsen E, Asuni A, Tsui WH, Sadowski M, Turnbull D, de Leon M, Wisniewski T: **A non-toxic ligand for voxel-based MRI analysis of plaques in AD transgenic mice.** *Neurobiol Aging* 2008, **29**:836-847.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

