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ASIP Centennial Review

Alzheimer's Disease 2012

The Great Amyloid Gamble

Vincent T. Marchesi

From the Department of Pathology and the Boyer Center for Molecular Medicine, Yale University, New Haven, Connecticut

Alzheimer's disease threatens to become the scourge of the 21st century. Hundreds of millions of aging people throughout the world are at risk, but it is clear that the disease encompasses more than just the natural aging process. Deposits of amyloid β peptides in the brains of demented individuals are a defining feature of the disease, yet two decades of intensive investigation, focusing on reducing or removing amyloid deposits, have failed to produce any meaningful therapeutic interventions. Some researchers question whether amyloid is the appropriate target. Others maintain that early, presymptomatic intervention would be a more informative test, and propose large-scale clinical trials in patients who are believed to be in the earliest, and potentially reversible, stages of the disease. This review explores the wisdom of that approach. ***(Am J Pathol 2012, 180: 1762–1767; DOI: 10.1016/j.ajpath.2012.03.004)***

The past 25 years have seen truly impressive gains in our understanding of Alzheimer's dementia,[1,2] yet effective treatments and prevention strategies are still distant goals. Newly developed brain scanning methods, including functional positron emission tomography (PET) scans and structural magnetic resonance imaging (MRI), have pointed to toxic forms of amyloid β (Aβ) peptides as the precipitating cause of brain dysfunction and eventual neuronal cell death, results that appear to confirm the primacy of the amyloid hypothesis. However, pursuing amyloid as the most relevant therapeutic target has led to disappointing results, most recently the failure of the high-profile gamma secretase inhibitor semagacestat to have any measurable success. Some question whether the failure of anti-amyloid treatments is telling us that amyloid is not the most relevant target. Others suggest that treating patients with advanced disease is not a valid test of any anti-amyloid agent. These conclusions have led to multiple nationwide, multidisciplinary efforts to focus on patients with mild cognitive impairment (MCI), the earliest detectable stage of Alzheimer's dementia. Brain damage in these individuals is clearly less advanced and therefore potentially more treatable. This effort, led by the Alzheimer's Disease Neuroimaging Initiative (ADNI) and other consortia, is designed to examine whether the amyloid hypothesis is indeed the surest path to the development of new therapies.[3] This Review explores the science behind this approach, some of which has been published within the pages of *The American Journal of Pathology*, and concludes that this thrust, which will require mega-millions of dollars and countless hours of investigator and patient time, must be considered a gamble, justified by the preliminary findings that support it, but a gamble nevertheless because of so many unknowns that still stalk the Alzheimer's crusade.

Background to the Amyloid Hypothesis

Alzheimer's dementia is one of the most destructive and feared human maladies that affects aging members of every population in the world. First recognized a hundred years ago on the basis of amorphous deposits of unknown material in the brains of affected persons, we now know that these deposits are composed in part of small peptide fragments that are generated by proteolytic cleavage of a large *trans*-membrane protein that resides in the brain and other tissues. The functions of both the parent protein (called APP) and the cleaved peptides (referred to as Aβ 40 and 42) are unknown, but there is little doubt that both play critical roles in the workings of the human brain. Moreover, a large body of evidence is consistent with the view that the Aβ peptides not only make up the bulk of the plaques that Alzheimer de-

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Address reprint requests to Vincent T. Marchesi, M.D., Ph.D., Yale University School of Medicine, Boyer Center for Molecular Medicine, 295 Congress Ave, PO Box 9812, New Haven, CT 06536. E-mail: vincent.marchesi@yale.edu.

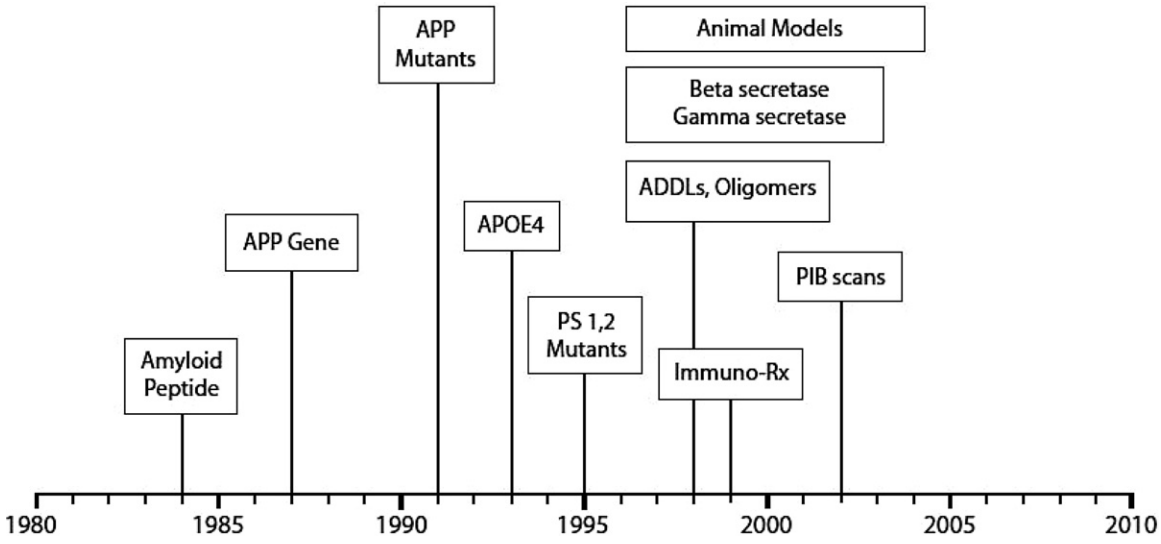

Figure 1. Aβ landmark discoveries. The timeline illustrates when key discoveries in our understanding of Aβ were made, such as discovery of the *APP* gene and its mutants, as well as apolipoprotein E4 allele (*APOE4*), presenilin (*PS1* and *PS2*) mutants, and Aβ oligomeric ligands (ADDLs). The advent of animal models and other techniques such as Pittsburgh compound B (PIB) scans also dramatically improved the study of Alzheimer's disease.

scribed in 1907,[4] but they are also the primary cause of Alzheimer's dementia, making them the prime target for therapeutic intervention. The large body of experimental data and clinical observations that support these views is popularly known as the Amyloid Hypothesis.

It's always difficult, in science, to decide who did what and when first, but George Glenner, a longstanding member of ASIP and Chief of Experimental Pathology at the National Institute of Arthritis and Metabolic Diseases of the NIH in the mid-60's, probably provided the first clue as to the chemical nature of the plaques that Alois Alzheimer described in 1907. Glenner extracted a small peptide from the blood vessels of brains from persons with Alzheimer's, and his analysis of this finding in 1984 led other workers in the field to identify what might be called the "Alzheimer's protein." More about this protein and the peptide that was derived from it will be described later; but the question that readers may be asking is, Why did it take 77 years to make this discovery? Many reasons come to mind.

First, it should be realized that enough people had to live beyond early middle life for the disease to develop to the stage at which it became clinically evident as the major health problem that we now recognize. Moreover, the association of the disease with advancing age encouraged physicians to assume that it was part of the natural aging process. We now know this was an understandable but incorrect assumption: Alzheimer's dementia is indeed a disease that accompanies human aging, but it is not an inevitable consequence of it.[5] Multiple pathological processes occur as we age, and these explain why human dementia and advanced age are so tightly coupled.

Another obstacle to the study of AD was our limited knowledge of the human brain. Encased as it is in a sturdy bony vault, it seemed inaccessible to the tools scientists used to study other human tissues. Biopsies were (and still largely are) not feasible, which meant that the tissues of the brain could only be examined by pathologists after death. This led to the widespread view (still shared by many physicians) that a definitive diagnosis of AD could be made only by autopsy. Autopsy studies are rightly considered the gold standard for determining cause of death and the extent of a disease process, but they have their limitations. For one thing, they only tell what was going on at the time of death, and although they reveal much about the end stage of a complex process such as AD, one can only guess as to what may have happened during the lifetime of the patient. In the case of AD, this limitation is glaring, because we now know that AD probably begins—in some form still to be revealed—years before symptoms appear.

What propelled the AD field forward was the development of recombinant DNA technology. Building on the findings of Glenner, it was possible to identify the larger protein from which the peptide was derived, and this led to a watershed of discoveries. These are highlighted in Figure 1. Several points need emphasizing. Once the amyloid peptide was positively identified, the gene for the amyloid precursor protein (*APP*) was relatively quickly (for that era) deduced, opening the floodgates to a torrent of discoveries. Within a little more than a decade, almost everything that we know about the role of amyloid in AD was revealed. Mutant forms of APP and the gamma secretases showed that defective genes could indeed contribute to disease, but their rarity meant that, for most AD patients (95%) who lacked these defective genes, other causes had to be determined. The *APOE4* allele of apolipoprotein E was found to predict earlier-onset forms of sporadic AD, but this finding was reported two decades ago, and we still have no clear idea how these protein variants contribute to disease. Recombinant DNA technology allowed investigators to develop animal models that appeared to mirror the human form of AD; but such animals usually generated far more amyloid in their brains than most humans ever have, leading many to

question whether they are faithful examples of human AD that can be used to test new forms of therapy.

In 1999 it was discovered that antibodies to the amyloid peptide could be used to flush out amyloid from the brains of genetically engineered mice.[6] This was an extraordinarily important discovery that has led to a multitude of clinical trials that are now in progress. Another pivotal advance was the introduction of amyloid-binding dyes that were able to detect amyloid in living persons. Pittsburgh compound B (PIB) scans, first described in 2002, provided the ability to monitor the progression of amyloid deposits in individuals who have not yet reached full-blown dementia.

Collectively, this huge body of both experimental and clinical information supports the idea that Aβ peptides contribute significantly to the pathogenesis of Alzheimer's disease and its accompanying dementia. That stated, it is still a mystery how the two are causally related. Among the many unknowns are when Alzheimer's disease first starts, and even how it starts. Nor do we have any idea what the triggering elements are. Two features of the disease are generally agreed on: AD probably starts years before clinical symptoms are evident; and, because it takes so long to develop into clinical disease, it must be a very slow disease process, or, more likely, several different processes that act in concert. These two features—its early undetected onset and the long pathogenic course—have made it difficult to reproduce the disease in experimental animals. This accounts in part for so much uncertainty about this disease despite the vast research effort that has already been expended. This great uncertainty has fueled efforts to find ways to identify persons carrying AD-specific biomarkers who might be in the early stages of the disease, long before symptoms appear, and hopefully before significant, possibly irreversible damage has occurred.

The Search for Biomarkers

Biomarkers are objectively measured ways to detect a disease process or the predisposition to disease in a living person. An elevated white blood cell count signals infection, and high serum cholesterol correlates with the predisposition to atherosclerosis. The practice of clinical medicine would grind to a halt without these essential diagnostic tools. Unfortunately, there is no simple, reliable, and reproducible blood test for any aspect of Alzheimer's dementia. Many attempts to develop one have been made, but none has succeeded.

Although attempts to measure Aβ levels in the blood have so far not proved useful, measurements of cerebrospinal fluid (CSF) have produced an unexpected surprise. Levels of Aβ 42 are lower in AD patients than in matched controls; and when they are correlated with positive PIB, a stain for brain amyloid, patients with MCI can be identified. By correlating imaging studies with CSF analysis, it is therefore possible for the first time to identify MCI patients by objective measurement alone. This represented a great advance, as it offered the possibility of evaluating new therapies using objective measurements alone. Jack and colleagues[7] further proposed that by correlating five different biomarkers, including three by imaging (PET-amyloid, FDG-PET, and structural MRI) and two by CSF analysis (Aβ 42 and P-tau), it might be possible to predict the stage of disease in any given patient. This analysis predicts that biomarkers of Aβ deposition become abnormal first, long before neurodegeneration and clinical symptoms appear. In contrast, FDG-PET, CSF Tau, and MRI-detectable atrophy become abnormal in the MCI stage, when symptoms of the disease are already evident. These findings and others like them have led to important policy decisions within the AD investigator community.

Should Reduction of Amyloid Deposits in Brains of Individuals Suffering from MCI Be a High-Priority Goal?

There is a widespread consensus among AD investigators who have participated in the ADNI program that therapies that reduce Aβ accumulations by decreasing production, by increasing turnover, or by antibody removal should be tested first in MCI patients in an attempt to arrest the progression of MCI to advanced dementia. This is based on the following assumptions: i) biomarkers and brain scans can be used to identify MCI patients and to follow their progression to frank dementia; ii) MCI patients will usually progress to clinical dementia over the course of several years; and iii) amyloid-related peptides accumulate in the brain during the MCI stage and are presumed to be pathogenic.

It makes sense to continue to support the expansion of the ADNI program by adding to these studies the testing of new therapies, realizing that existing animal models that focus on amyloid overload have not proved to be reliable ways to test new therapies. Although many recent attempts to treat patients by reducing amyloid levels in the dementia stage of the disease have not succeeded, one assumes that there is a better chance of preserving existing neuronal functions in MCI patients than in those with advanced dementia. An added advantage is the ability to monitor treatment efficacy with objective tests.

Remaining Unknowns

While supporting this program, it is useful to acknowledge the imposing number of questions regarding the pathogenesis of AD that, if they remain unanswered, will continue to constrain our ability to design and test the most appropriate therapies and to formulate rational guidelines for prevention.

1. When, where, and how do the earliest lesions that lead to MCI develop?
2. How do Aβ peptides, in whatever form, damage neurons?
3. What is the physiological function of Aβ peptides?
4. How do neurofibrillary tangles contribute to disease?

5. How does oxidative damage contribute to disease onset?
6. Is inflammation a factor?
7. Does blood vessel damage contribute to amyloid dysregulation?
8. What are the most effective preventive measures?

It is hardly surprising that we have yet to identify the earliest lesions that eventually lead to neuronal degeneration and clinical dementia. As is the case when studying other chronic diseases, looking solely at the late stages of a disease may be misleading, and this is particularly true if we lack suitable animal models. All of the existing murine models that are routinely studied as AD proxies rely on overproduction of amyloid Aβ peptides. Since significant amounts of amyloid accumulate late in the human disease, it seems likely that other processes, such as oxidative damage and/or inflammatory reactions, may precede amyloid dysregulation, as many AD investigators have previously suggested (see references in Marchesi[8]). We must also consider the possibility that large-scale amyloid accumulations are a late event in human AD, triggered by as-yet-unknown processes. In this case, anti-amyloid therapies may not be effective ways to treat MCI.

Another perplexing aspect of the AD field is the surprising lack of any consensus as to what form of Aβ peptides are toxic to neurons in the living brain. Part of the problem is the quixotic nature of the Aβ peptides themselves. Are they critically involved in synaptic activity and neurotransmission, as recent studies suggest,[9] or are they nuisance degradation products prone to clump together and clog up the interstitial spaces? Since elevated levels of Aβ production are found only in patients with rare mutations, reduced clearance of Aβ rather than overproduction is considered the most likely cause of amyloid accumulation in advanced disease and is the basis for a vigorous effort to reduce their level in the brain. Precisely why they accumulate is still unclear; but reducing them, by whatever means, is the stated goal, even though we must also consider the possibility that lowering the level of a normally functioning peptide by blocking its synthesis, or by immune-mediated clearance, might, in the end, impair normal neuronal functions and would therefore be an undesirable side effect. Ideally, targeting the toxic form of Aβ makes the most sense, but this still remains an elusive goal. Much has been made of the tendency of Aβ peptides to aggregate at high concentrations *in vitro*. Oligomeric forms of widely varying sizes have been identified as putative toxic forms; but their mode of action remains unknown, and they are technically demanding to study. At this point they do not seem like promising therapeutic targets.

Neurofibrillary tangles are as omnipresent in AD brains as amyloid plaques, and many have suggested that their presence correlates more faithfully with dementia than the plaques themselves. How and why they develop, and how they contribute to the pathogenic cascade, is just as mysterious as amyloid's contribution to neurotoxicity. This is not to deny their importance, but only to stress the difficulty that we have in evaluating their effects without a suitable animal model.

How does oxidative damage contribute to AD? There is abundant, indeed overwhelming, evidence that reactive oxygen and reactive nitrogen species have the ability to modify every molecular species in the human brain, and are especially prominent in AD brains. Oxidative changes in membrane lipids are widely recognized; however, less attention has been focused on oxidized nucleic acids, which is surprising, as modified DNA and RNA have the potential to generate mutant proteins that could play a pathogenic role.[10] Inflammatory reactions and damaged small blood vessels were once thought to play major pathogenic roles in early AD, but their significance has been eclipsed by the overwhelming logic of the amyloid cascade. The inability of anti-inflammatory agents to modify advanced disease also diminished enthusiasm for an inflammatory mechanism. However, now that we have discovered that anti-amyloid agents are also unable to modify advanced disease, we may have to reconsider anti-inflammatory approaches as therapies for the preclinical stage. Again, the lack of suitable animal models that reflect inflammatory and vascular damage of the brain hampers our ability to test potential anti-oxidative damage and anti-inflammatory agents.

Conclusions

It is a good idea and sound public policy to focus on treating individuals who suffer from MCI. Such individuals can be identified with reliable biomarkers, their progression to frank dementia is predictable, and their response to therapy can be evaluated by objective measurements. However, we must be ready for some surprises. Although amyloid is likely to contribute to advanced disease, its pathogenic potential may rely on as-yet-unidentified factors that could compromise agents or treatments that act on amyloid alone. Moreover, although amyloid deposits are a prominent feature of both MCI and advanced dementia, other pathogenic processes may act in the early stages of the disease, and they may progress to neuronal injury despite the reduction or absence of amyloid. Arresting disease progression is a desirable goal worth pursuing at all costs—but the gold standard will be prevention. This will require answers to the questions stated above.

Postscript: AJP's *Contributions to Our Understanding of AD Pathology*

It is fitting to commemorate ASIP's centennial with a discussion of the present state of Alzheimer's research, as it is generally acknowledged that the modern era of AD research was launched by George Glenner. Glenner's first study of murine amyloidosis was published in *The American Journal of Pathology* in 1972.[11]

Many important contributions to AD research have been published in *AJP* beginning in 1964 with the first ultrastructural analysis of Alzheimer's presenile dementia,[12] followed in 1973 by the finding that Alzheimer's

dementia and Down's syndrome dementia were related.[13] Glenner's findings led to the discovery of the gene for the amyloid precursor protein (*APP*), and this unleashed a cascade of discoveries including the link between brain amyloid, blood vessel amyloid, and dementia[14] and the discovery that Alzheimer's neurofibrillary tangles were associated with the microtubule-associated protein tau.[15] In 1990 it was claimed that diffuse amyloid plaques were not necessarily related to synaptic loss and the accompanying dementia,[16] a prophetic suggestion that was ultimately confirmed in later years.

The 1990s saw a range of significant publications in AJP that included a description of a hereditary form of cerebral angiopathy,[17] an analysis of paired helical tau filaments,[18] the link between apolipoprotein E4 and senile plaques in aged rhesus monkeys,[19] and the finding that the cell cycle regulators P16 and CDK4 might be expressed in AD brains [20]. Three AJP publications that foresaw changes in the way that present-day investigators view the AD problem were the analysis of interstitial fluid drainage pathways as a way to explain Aβ accumulations in AD brains [21], the connection between brain trauma and amyloid–induced neuron death,[22] and the potential role of the complement system in the pathogenesis of AD[23] that has led to an awakened interest in inflammation as a pathogenic mechanism.

The last decade has seen a dramatic increase in publications exploring blood vessels as potential pathogenic targets that lead to dementia. Germ line mutations in APP were found to develop cerebral amyloid angiopathy,[24] mutants of APP that generated vasculotropic Aβ peptides and induce vascular degeneration and euroinflamation[25]; the finding that dense-core amyloid plaques in mutant mice were centered on blood vessel walls[26]; and the idea that brain endothelial cells synthesize neurotoxic thrombin in AD brains [27]. This past year has seen two reports that focus on inflammation as a primary pathogenic cause: one stresses infection in transgenic mice,[28] and the other reports that neurovascular defects and inflammation precede the toxic effects of τ-mediated neurodegeneration.[29]

References

1. Selkoe DJ: Resolving controversies on the path to Alzheimer's therapeutics. Nat Med 2011, 17:1060–1065
2. Karran E, Mercken M, De Strooper B: The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nature Rev Drug Discov 2011, 10:698–712
3. Sperling RA Jack CR, Jr., Aisen PS: Alzheimer's disease testing: the right target and right drug at the right stage. Sci Transl Med. 2011, 30:111–133
4. Stelzmann RA, Schnitzlein HN, Murtagh FR: An English translation of Alzheimer's 1907 paper, "Über eine Eigenartige erkankung der Hirnrinde".Clin Anat 1995 1995, 8:429–431
5. Nelson PT, Head E, Schmitt FA, Davis PR, Neltner JH, Jicha GA, Abner EL, Smith CD, Van Eldik LJ, Kryscio RJ, Scheff SW: Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. Acta Neuropathol 2011, 121:571–587
6. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandevert C, Walker S, Wogulis M, Yednock T, Games D, Seubert P: Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 1999, 400:173–177
7. Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner ME, Petersen RC, Trojanowski JQ: Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010, 9:119
8. Marchesi VT: Alzheimer's dementia begins as a disease of small blood vessels, damaged by oxidative-induced inflammation and dysregulated amyloid metabolism: implications for early detection and therapy. FASEB J 2011, 25:5–13
9. Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S, Holtzman DM: Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron 2005, 48:913–922
10. Lovell MA, Markesbery WR: Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. Nucleic Acids Res 2007, 35:7497–7504
11. Page DL, Glenner GG: Social interaction and wounding in the genesis of "spontaneous" murine amyloidosis. Am J Pathol 1972, 67:555–570
12. Terry RD, Gonatas NK, Weiss, M.: Ultrastructural studies in Alzheimer's presenile dementia. Am J Pathol 1964, 44:269–297
13. Burger PC, Vogel FS: The development of the pathologic changes of Alzheimer's disease and senile dementia in patients with Down's syndrome. Am J Pathol 1973;73:457–476
14. Coria F, Castano EM, Frangione B: Brain amyloid in normal aging and cerebral amyloid angiopathy is antigenically related to Alzheimer's disease beta-protein. Am J Pathol 1987, 129:422–428
15. Yen S.-H, Dickson DW, Crowe A, Butler M, Shelanski ML: Alzheimer's neurofibrillary tangles contain unique epitopes and epitopes in common with the heat-stable microtubule associated proteins tau and MAP2. Am J Pathol 1987, 126:81–91
16. Masliah E, Terry RD, Mallory M, Alford M, Hansen L: Diffuse plaques do not accentuate synapse loss in Alzheimer disease. Am J Pathol 1990, 137:1293–1297
17. Rozemuller AJM, Roos RAC, Bots GTAM, Kamphorst W., Eikelenboom P, Van Nostrand WE: Distribution of β/A4 and amyloid precursor protein in hereditary cerebral hemorrhage with amyloidosis-Dutch type and Alzheimer's disease. Am J Pathol 1993, 142:1449–1457
18. Trojanowski JQ, Lee VM-Y. Paired helical filament tau in Alzheimer's disease: the kinase connection. Am J Pathol 1994, 144:449–453
19. Poduri A, Gearing M, Rebeck GW, Mirra SS, Tigges J, Hyman BT: Apolipoprotein E4 and beta amyloid in senile plaques and cerebral blood vessels of aged rhesus monkeys Am J Pathol 1994, 144:1183–1187
20. McShea A, Harris PLR, Webster KR, Wahl AF, Smith MA: Abnormal expression of the cell cycle regulators p16 and cdk4 in Alzheimer's disease. Am J Pathol 1997, 150:1933–1939
21. Weller RO, Massey A, Newman TA, Hutchings M, Kuo YM, Roher AE: Cerebral amyloid angiopathy: amyloid β accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. Am J Pathol 1998, 153:725–733
22. Smith DH, Nakamura M, McIntosh TK, Wang J, Rodriguez A, Chen XH, Raghupathi R, Saatman KE, Clemens J, Schmidt ML, Lee VM, Trojanowski JQ: Brain trauma induces massive hippocampal neuron death linked to a surge in β-amyloid levels in mice overexpressing mutant amyloid precursor protein. Am J Pathol 1998, 153:1005–1010
23. Yasojima K, Schwab C, McGeer EG, McGeer PL: Upregulated production and activation of the complement system in Alzheimer disease brain. Am J Pathol 1999, 154:927–936
24. Van Dorpe J, Smeijers L, Dewachter I: Prominent cerebral amyloid angiopathy in transgenic mice overexpressing the London mutant of human APP in neurons. Am J Pathol 2000, 157:1283–1298
25. Miao J, Xu F, Davis J, Otte-Holler I, Verbeek MM, Van Nostrand WE: Cerebral microvascular amyloid-β protein deposition induces vascular degeneration and neuroinflammation in transgenic mice expressing human vasculotropic mutant amyloid-β precursor protein. Am J Pathol 2005, 167:505–515
26. Kumar-Singh S, Pirici D, McGowan E, Serneels S, Ceuterick C, Hardy J, Duff K, Dickson D, Van Broeckhoven C: Dense-core plaques in

Tg2576 and PSAPP mouse models of Alzheimer's disease are centered on vessel walls. Am J Pathol 2005, 167:527–543
27. Yin X, Wright J, Wall T, Grammas P: Brain endothelial cells synthesize neurotoxic thrombin in Alzheimer's disease. Am J Pathol 2010, 176: 1600–1606
28. Sy M, Kitazawa M, Medeiros R, Whitman L, Cheng D, Lane TE, Laferla FM: Inflammation induced by infection potentiates tau pathological features in transgenic mice. Am J Pathol 2011, 178: 2811–2822
29. Jaworski T, Lechat B, Demedts D, Gielis L, Devijver H, Borghgraef P, Duimel H, Verheyen F, Kugler S, Van Leuven F: Dendritic degeneration, neurovascular defects, and inflammation precede neuronal loss in a mouse model for tau-mediated neurodegeneration. Am J Pathol 2011, 179:2001–2015