Mechanisms underlying the initiation of cerebral beta-amyloidosis and neurofibrillary tau pathology: New insights from transgenic mice

Inauguraldissertation
Zur
Erlangung der Würde eines Doktors der Philosophie
Vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
Der Universität Basel

Von

Tristan Bolmont
Aus Frankreich

Basel, 2006

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

First I would like to specially acknowledge my supervisor Prof. Dr. Mathias Jucker for giving me the opportunity to carry out my PhD thesis in his lab and for his scientific excellence.

I am grateful to Prof. Michael Mihatsch for hosting my work at the Institute of Pathology. I would also like to express special thanks to Prof. Dr. Markus Rüegg and Dr. Matthias Staufenbiel for their participation in my dissertation.

Thanks are also due to Prof. Markus Tolnay and Prof. Alphonse Probst for their scientific help and precious psychological support. Sincere thanks to the members of their team for technical support, particularly Sabine Ipsen, Claudia Mistl and Edith Hui Bon Hoa.

I'm especially grateful to Dr. Michael Calhoun for being a great group leader, for lots of scientific inputs and earth-shaking discussions on cats placed in sealed boxes.

Especially I would like to thank all my colleagues, former and present, of the Jucker Lab at the Institute for Pathology in Basel and the Hertie Institute for Clinical Brain Research in Tübingen: Martin Herzig, Melanie Meyer-Luehmann, Florence Clavaguera, Sonia Boncristiano, Stefan Käser, Janaky Coomaraswamy, Michelle Pfeifer, Ane Stadler, Esther Kohler, Irene Neudorfer, Claudia Schäfer, Rebecca Radde, Bettina Braun, Daniel Eicke, Yvonne Eisele, Luca Bondolfi, Ana Fulgencio, Bernadette Graus, Ellen Kilger, Dennis Lindau, Jörg Odenthal, Lars Stoltze, Florent Haiss, Simone Eberle, Zhenyu Gao, Stefan Grathwohl, Isolde Guhl, Frederique Oddos, Nadine Kuohn, Roman Beck, Christin Hünefeld, Gabi Kagels, Roswitha Kemmner, Amrita Kythiala, Christina Nordhammer, Uli Pfeiffer, Tobias Rasse, Daniela Rosenkranz, Julia Salih, Christian Thetard and Nicolas Catz.

I would also like to express my love and gratitude to my parents Dominique and Marie-Claire Bolmont for their "incommensurable" support and patience. Without them, none of this would have been achievable.

SUMMARY

Numerous neurodegenerative disorders result from the aggregation of proteins that misfold and accumulate as fibrillar amyloid deposits in selectively vulnerable regions of the central nervous system. Alzheimer's disease (AD) is one of these protein conformational diseases and the leading cause of dementia in the Western world. Postmortem, it is characterized by two major neuropathological features: extracellular deposition of Abeta (Aβ) peptide and intracellular aggregates of neurofibrillary lesions made of hyperphosphorylated tau protein. The observation that early-onset familial forms of AD are caused by mutations in three genes (the amyloid precursor protein (APP), presenilin-1 (PS1), and presenilin-2 (PS2)), all of which increase the production of Aβ, led to the so-called amyloid cascade hypothesis. This hypothesis proposed that the aggregation of polymerized forms of Aβ in soluble multimeric and/or insoluble senile plaque deposits in the brain is an early and critical event that triggers a cascade of pathological events leading to hyperphosphorylation and somatodendritic segregation of tau, formation of neurofibrillary lesions, neuroinflammation, neurodegeneration and, finally, dementia.

The generation of transgenic (tg) mice that exhibit cerebral Aβ-amyloidosis through expression of mutated human APP gene has provided new opportunities to explore pathogenic mechanisms and treatments of AD. The studies presented below were done in part using the well-established APP23 tg mouse model that carries human KM670/671NL mutated APP under the control of a neuron specific Thy-1 promoter and develops amyloid deposits progressively with age. We also generated and made use of a novel tg model, the APPPS1 mouse. This model coexpresses KM670/671NL mutated APP and L166P mutated PS1 that lead to accelerated cerebral amyloidosis concomitantly with additional AD-like pathologies such as local neuron loss, hyperphosphorylated tau-positive neuritic structures, dystrophic synaptic boutons and robust cortical gliosis. Because of the early onset of amyloid pathology, APPPS1 mice are well suited for studying the mechanism and impact of cerebral amyloidosis and to test therapeutic amyloid-targeting strategies.

The aggregation of Aβ protein is an established pathogenic mechanism in Alzheimer's disease, however little is known about the initiation of this process *in vivo*. The first set of experiments were therefore performed to characterize the induction of cerebral Aβ-

amyloidosis *in vivo*, and to clarify which factors are involved in the seeding process. We show that aggregation of Aβ can be exogenously induced in a time- and concentration-dependent manner by injecting Aβ-containing brain extracts from humans with Alzheimer's disease or APP23 tg mice into the brains of young APP23 tg host mice. By injecting extracts from APPPS1 tg mice into APP23 hosts and vice versa, our results suggest that characteristics of both the brain extract and the host are important in governing the phenotype of the induced amyloid. Intriguingly, intracerebral injections of synthetic fibrillar Aβ preparations as well as cell culture-derived Aβ in concentrations similar to brain extract levels were not able to seed Aβ aggregation *in vivo*. And yet the seeding requires an aggregated form of Aβ, because formic acid denaturation and Aβ-immunodepletion abolished the Aβ-inducing activity of the extract. Last but not least, we show that β-amyloid-induction is halted by Aβ-immunization of the host, demonstrating that the earliest stages of cerebral Aβ-amyloidosis deposition are amenable to therapeutic intervention.

AD presents morphologically with abundant neurofibrillary lesions, but the events that initiate tau pathogenesis *in vivo* remain unclear. Thus, the second series of experiments were performed to characterize the induction of tau pathology *in vivo*, as well as to identify potential tau-inducing candidates. We show that intracerebral injection of Aβ-containing brain extract from human with AD or β-amyloid-laden APP23 mouse induces neurofibrillary pathology in transgenic mice expressing human tau with the P301L mutation. Importance of soluble Aβ species for exogenous induction of tau pathogenesis was demonstrated by intracerebral injection of human brain extract with low Aβ level. Notably, intracerebral injection of brain extract from aged tangle-bearing P301L transgenic mouse induced only limited deposition of tau in brains. Our results show that neurofibrillary pathology is exogenously induced by extracts from Aβ-containing brains, and provide further support for the hypothesis that Aβ is a causative pathogenic factor of AD.

It has long been recognized that microglial cells react to β-amyloid deposition as to other brain injuries, but various aspects of their reactive kinetics and ability to phagocytose amyloid *in vivo* remain hypothetical, despite their potential as therapeutic target. To resolve these controversies, we have designed in a third series of experiments a set of robust

analysis tools centered around intracranial multiphoton imaging to characterize the time-course and extend of microglia's response to amyloid deposition in tg mice. By following individual plaques and microglia over time in the living brain, we have shown that plaque formation was accompanied by microglial process extension and subsequent migration to the site of injury where individual microglia then exhibited signs of uptake of the Aß peptide. Furthermore, by infusing fluorescent Aß-antibody into the brain parenchyma we demonstrated that the interaction of microglia with plaques can be stimulated, leading to further internalization of Aß and at least partial clearance of existing dense deposits. Together, these results demonstrate an ongoing dynamic homeostasis between plaques and microglia that is amenable to therapeutic intervention.

In summary, the experiments described herein have increased our understanding of the mechanisms underlying the initiation of cerebral Aβ-amyloidosis and neurofibrillary pathology *in vivo*. We have shown that cerebral Aβ-amyloidosis can be induced by exogenous, Aβ-rich brain extract, and that intrinsic properties of the Aβ in the extract as well as of the host are crucial for the induction of Aβ accumulation in brain. We also demonstrated that neurofibrillary pathology can be induced *in vivo* by intracerebral infusion of Aβ-rich brain extract into a susceptible transgenic host, and that soluble Aβ species are potent effectors of tau pathology in the brain. Moreover, our observations that interaction of microglial cells with amyloid plaques can be stimulated, such that these cells are induced to clear existing Aβ deposits, provide the mechanistic clues necessary for development of additional therapeutic targets for amyloid clearance.

1.INTRODUCTION

1.1.Protein misfolding and amyloid formation in degenerative disorders

Proteins are involved in virtually every biological process in a living system. They are synthesized on ribosomes as linear chains of amino acids in a specific order from information encoded within the cellular DNA. In order to perform their biological function these chains of amino acids must fold into the native three-dimensional structures that are characteristic of the individual proteins. How and whether a protein folds is influenced primarily by its amino acid sequence and the cellular environment surrounding the amino acid chain (Anfinsen, 1973; Jackson, 1998; Baldwin and Rose, 1999; Horwich, 1999). Mutations, abnormal physiological concentrations, coupled with prolonged time and certain biochemical conditions are thought to destabilize the native three-dimensional state, or divert soluble proteins from their normal folding pathway, often leading to their aggregation into stable insoluble amyloid deposits. Numerous degenerative diseases arise due to the build up of insoluble misfolded protein deposits (Kelly, 1996; Dobson, 1999; Rochet and Lansbury, 2000; Hetz and Soto, 2003). These proteopathies include neurological disorders such as bovine spongiform encephalopathy and its human equivalent Creutzfeld-Jakob disease, and also Alzheimer's disease, Parkinson's disease, Huntington's disease, in addition to diverse systemic amyloidosis (Carrell and Lomas, 1997; Prusiner, 1998; Rochet and Lansbury, 2000; Walker and Levine, 2000; Selkoe, 2003) (Table 1).

No sequence or structural similarities are apparent between any of the proteins that display the ability to form amyloids. Despite these differences, the fibrils formed by different polypeptides share a number of structural characteristics (Serpell et al., 1997; Sunde et al., 1997; Dobson, 2003). For example, X-ray fiber diffraction studies indicate that the peptide backbone of the fibers adopts a cross β-structure (Sunde and Blake, 1997; Blake and Serpell, 1996; Guijarro et al., 1998; Chiti et al, 1999). In this structure, the individual β-strands are oriented perpendicular to the long axis of the fiber, while the hydrogen bonds are oriented parallel with the long axis of the fiber (Blake et al, 1996; Wetzel, 2002). Amyloid fibers are also resistant to proteolysis, and display characteristic apple-green birefringence when stained with the histological dye Congo red and seen under polarized light (Sunde et al., 1997). There are also striking similarities in the aggregation behavior of many misfolded proteins, even if their propensity to aggregate can vary markedly between different sequences (Chiti et al., 2003). Amyloid fibrils are thought to form through self-assembly of protein monomers via a nucleation dependent pathway initiated in partially

	Disease	*Protein Involved*
Organ-limited extra cellular amyloidoses	Alzheimer's disease	Amyloid β-peptide
	Spongiform encephalopathies	Prion protein
	Hereditary cerebral hemorrhage with amyloidosis	Amyloid β-peptide or cystatin C
	Type II diabetes	Amylin (Islet amyloid polypeptide)
	Medullary carcinoma of the thyroid	Procalcitonin
	Atrial amyloidosis	Atrial natriuretic factor
Systemic extra cellular amyloidoses	Primary systemic amyloidosis	Intact Ig light chains or fragments
	Secondary systemic amyloidosis	Fragments of serum amyloid A protein
	Familial Mediterranean fever	Fragments of serum amyloid A protein
	Familial amyloidotic polyneuropathy1	Mutant transthyretin and fragments
	Senile systemic amyloidosis	Wild-type transthyretin and fragments
	Familial amyloidotic polyneuropathy II	Fragments of apolipoprotein A-1
	Haemodialysis-related amyloidosis	2-Microglobulin
	Finnish hereditary amyloidosis	Fragments of mutant gelsolin
	Lysozyme amyloidosis	Full-length mutant lysozyme
	Insulin-related amyloid	Full-length insulin
	Fibrinogen α-chain amyloidosis	Fibrinogen α-chain variants
Intracellular amyloidoses	Alzheimer's disease	Amyloid β-peptide, Tau
	Frontotemporal dementia with parkinsonism	Tau
	Parkinson's disease; dementia with Lewy bodies	α-Synuclein
	Creutzfeldt-Jakob disease	Prion protein
	Polyglutamine expansion diseases	Long glutamine stretches within certain proteins
	Amyotrophic lateral sclerosis	Superoxide dismutase

Table 1. List of diseases resulting from amyloid formation (adapted from Selkoe, 2003)

denatured states of amyloidogenic proteins (Jarret et al., 1993; Jarrett and Lansbury, 1993; Harper and Lansbury, 1997; Kelly, 1998; Kayed et al., 1999; Scherzinger et al., 1999; Wood et al., 1999; Maioli et al., 2000; Yao et al., 2003; Dobson, 2004). However, even though the formation of fibrils via a nucleation-dependent pathway seems to be generic, most of the studies to date have been done *in vitro* and may not mimic the situation in human diseases (Wetzel, 2002; Buxbaum, 2003). The nucleation-dependent polymerisation mechanism is similar to the highly ordered process of protein crystallization (Harper et al., 1997). This mechanism dictates that aggregation is dependent on protein concentration and time, and consists of an initial nucleation (or lag) phase followed by an elongation (or growth) phase and a steady state phase in which the protein aggregates and monomer are at equilibrium (Harper and Lansbury, 1997). In a typical nucleation-dependent polymerization, oligomerization is not observed until the monomer concentration exceeds a certain level known as the critical concentration. During the lag phase protein associates in a supersaturated solution to form ordered soluble oligomeric nuclei, but no detectable fibers

are formed. Addition of preformed protein nuclei during the lag time results in immediate polymerization, a process known as seeding (Harper et al., 1997). Once the oligomeric nuclei are formed, the aggregates grow rapidly (elongation phase) until a thermodynamic equilibrium between the aggregate and monomer is reached (Harper et al., 1997; Walsh et al., 1997).

Alzheimer's disease is a member of the amyloid disease group, wherein two major kinds of protein aggregates are key contributors to the pathogenesis (Hardy et al., 1998; Hardy and Selkoe, 2002). Extracellular aggregates known as neuritic plaques have their major constituent the Aβ peptide, which is derived from proteolytic processing of the amyloid precursor protein (APP). The Aβ-containing aggregates have β-sheet structure and Congo red and thioflavin-T reactivity characteristic of amyloid (Serpell and Smith, 2000). The aggregation process that converts soluble Aβ into amyloid fibrils *in vitro* is thought to be a nucleation-dependent process (Harper and Landsbury, 1997). In AD, there are also intracellular aggregates of the microtubule-associated protein tau, called neurofibrillary lesions. The molecular structure of tau filaments has been controversial but there is consensus now that tau fibrils in AD fit the amyloidosis definition (Berriman et al., 2003). Kinetics datas support the view that tau fiber may also form via a nucleation-dependent mechanism, tau oligomerization and nucleation events being the rate-limiting step in filament formation (Friedhoff et al., 1998; King et al., 1999). Nevertheless, the major caveat remains that we have yet to learn how these aggregational events begin *in vivo* and how their development lead to the progressive behavioral and cognitive demise that characterizes the human disease.

1.2.Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes. The symptoms of the disease as a distinct entity were fist identified by Emil Kraepelin, and the characteristic neuropathology first observed by Alois Alzheimer, a German psychiatrist, in 1906.

1.2.1. Clinical symptoms and diagnosis

Alzheimer's original patient (Alzheimer, 1907) exemplified several cardinal features of the disorder that we still observe in most patients nowadays. One of the first noticeable symptoms is short-term memory loss, which usually manifests as minor forgetfulness that becomes more pronounced with illness progression, with relative preservation of older memories (Morris et al., 1989; Petersen et al., 1999). It is difficult to distinguish these earliest disease-related cognitive changes of AD from those associated with normal aging (Small, 2001; Collie et al., 2001; Morris et al., 2001). As the disorder progresses, cognitive impairment extends to the domains of language, skilled movements, recognition, and executive functions (Morris et al., 1989; Morris, 1996). As subjects continue to lose ground cognitively, slowing of motor functions such as gait and coordination often lead to a picture resembling extrapyramidal motor disorders (Selkoe, 2001). In the final stages, patients become immobile and die of respiratory difficulties such as pneumonia (Fotstl and Kurz, 1999). Average duration of the disease is approximately 7-10 years, although cases are known where reaching the final stage occurs within 4-5 years, or up to 15-20 years (Fotstl and Kurz, 1999).

Although definitive diagnosis requires a postmortem neuropathological examination, neurologists and neuropsychologists have now developed clinical criteria that often lead to ~90% accuracy in diagnosing AD. To make the diagnosis of AD and to exclude other causes of dementia, clinicians rely on histories from patients and informants; physical, neurological, and psychiatric examinations; neuropsychological testing; laboratory assessments; and a variety of other diagnostic tests including neuroimaging (Clark and Karlawish, 2003). Biochemical changes that reflect the presence of disease-related pathology also have the potential to serve as diagnostic biomarkers of Alzheimer disease (Growdon, 1999). To date, the most extensively studied biochemical markers are the cerebrospinal fluid proteins tau and β-amyloid (Andreasen et al., 2001; Knopman, 2001). Both are particularly relevant to the pathology of Alzheimer disease and thus may provide diagnostically useful information.

1.2.2. Neuropathological phenotype

The classical pathophysiology of AD includes extensive neuronal degeneration and synapse loss resulting in marked atrophy of brain regions critical for learning and memory (Fig. 1, A), together with an inflammatory response to the deposition of senile plaques and neurofibrillary lesions (Fig. 1, B and C, respectively) (Terry et al., 1991; West et al., 1994; Gomez-Isla et al., 1996, Selkoe, 2001). The interaction between amyloid plaques, neurofibrillary tangles, their constituent molecules and the neuronal and synaptic losses that characterize the disease has been the subject of speculations for many years and still remains an unresolved issue.

1.2.2.1. β-amyloid plaques and the Aβ centric theory of Alzheimer's

Neuritic or senile plaques are one of the histopathological hallmarks of AD. Senile plaques are extracellular deposits primarily composed of β-amyloid (Aβ) protein that are surrounded by dystrophic axons as well as the processes of astrocytes and microglia (Arai et al., 1990, 1992; Schmidt et al., 1991; Masliah et al., 1992; Trojanowski et al., 1993; Dickson, 1997; Selkoe, 1999, 2001; Masters et al., 2006). In addition and at least to some

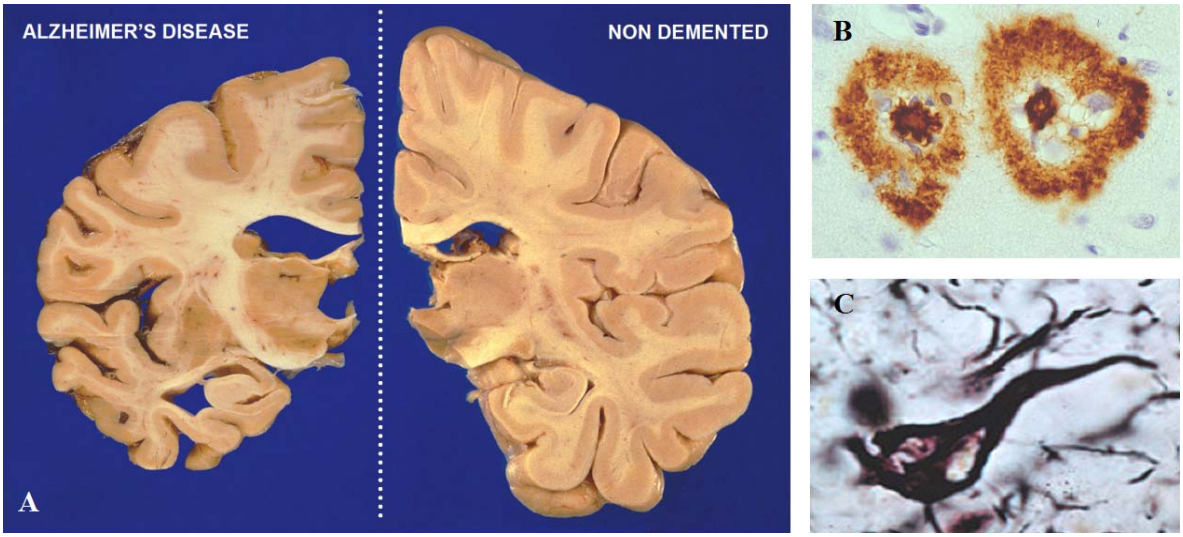

Figure 1. The neuropathological hallmarks of AD. Characteristic pathophysiological changes include loss of neurons, neuronal processes and synapses in the cerebral cortex and certain subcortical regions. These changes are associated with gross atrophy of the affected regions and enlargement of the lateral ventricules (A). Histological stainings of senile plaques (B) and neurofibrillary tangles (C) in an AD brain.

degree, Aβ deposits are also apparent within the walls of leptomeningeal and cerebral vessels (Selkoe et al., 1987; Vinters, 1987; Yamada et al., 1987; Martin et al., 1991; Jellinger, 2002). The evolution of Aβ deposits in the brain follows a distinct sequence in which the regions are hierarchically involved (Thal et al., 2002). The first phase is the neocortical phase 1, followed by the allocortical phase 2. In phase 3, the diencephalic nuclei, the striatum and the cholinergic nuclei of the basal forebrain develop Aβ deposits, and in phase 4 several brainstem nuclei become additionally involved. Finally, phase 5 is characterized by cerebellar Aβ deposition.

The principal constituent of plaques is Aβ (Glenner and Wong, 1984; Masters et al., 1985; Selkoe et al., 1986), a 4 kDA protein fragment of 39-43 amino acids which is formed after sequential cleavage of the amyloid precursor protein (APP) by the β- and γ-secretases (see section 1.2.3.) (Cappai and White, 1999; Selkoe, 2001). Much of the fibrillar Aβ found in the neuritic plaques is the species ending at amino acid 42 (Aβ42), the slightly longer, less soluble form that is particularly prone to aggregation (Jarrett et al., 1993b; Harper et al., 1997c). However, the Aβ species ending at amino acid 40 (Aβ40), which is normally more abundantly produced by cells than Aβ42, is usually colocalized with Aβ42 in the plaque (Iwatsubo et al., 1994). Within amyloid deposits and immediately surrounding them, neurites are marked by ultrastructual abnormalities that include enlarged lysosomes, numerous mitochondria, and paired helical filaments (PHFs) (Arai et al., 1990; Schmidt et al., 1991; Masliah et al., 1992; Trojanowski et al., 1993; Dickson, 1997; Selkoe, 2001). Senile plaques are also surrounded by reactive astrocytes displaying abundant glial filaments, and are also intimely associated with microglia expressing surface antigens associated with activation, such as CD45 and HLA-DR (Itagaki et al., 1989; McGeer and McGeer, 1995; Rogers et al., 1996). Microglia represent the macrophage-derived cells in the nervous system that are capable of responding rapidly to various types of insults (Nimmerjahn et al., 2005; Davalos et al., 2005). Thus, these cells represent reasonable candidates for early cellular respondents of β-amyloid deposition. Nevertheless, microglia and astrocytes are also involved in the overproduction and release of various inflammatory mediators, leading to profound inflammatory disturbance in limbic and association cortices observed in AD (Abraham et al. 1988; Griffin et al., 1989; Rogers et al., 1992; Itagaki et al., 1994).

Many of the plaques found in limbic and association cortices but also thalamus, caudate, putamen, and cerebellum, show relatively light, amorphous Aβ immunoreactivity that occurs without a compacted fibrillar center (Yamaguchi et al., 1988; Joachim et al., 1989). These lesions that are referred to as "diffuse" plaques, contain mainly Aβ42 species with little or no Aβ40 (Gowing et al., 1994; Iwatsubo et al., 1994, 1995; Lemere et al., 1996) and lack neuritic dystrophy, glial changes and PHFs (Selkoe, 1991; Dickson, 1997; Selkoe, 2001). In contrast to the Aβ deposited in compact senile plaques, diffuse deposits are not detected with Congo red or other dyes, such as Thioflavin S, that bind amyloid. Moreover, they are also observed in normal ageing individuals, but the density is lower than in AD patients (Perry et al., 1978). It has been suggested that diffuse plaques may represent precursors to the classical neuritic plaques (Tagliavini et al., 1988; Yamaguchi et al., 1988; Iwatsubo et al., 1996; Lemere et al., 1996; Masters et al., 2006). This hypothesis is best illustrated by studies of Down's syndrome. Here, patients have little or no Aβ deposition in the first decade of life, but by around 12 years, one begins to see diffuse plaques containing Aβ42 (not Aβ40), and more and more Down's subjects develop such plaques during the second and third decade of life (Lemere et al, 1996). Then, after the age of 30 years, one begins to see amyloid fibril formation in plaques and there is associated microgliosis, astrocytosis and some neuritic dystrophy. These neuritic plaques become then more prevalent over the next 2 decades of life. A model for the deposition of Aβ in amyloid plaques consistent with the view that diffuse plaques represent immature precursors to the plaques with surrounding cytopathology is illustrated in the Figure 2.

It has been more than 15 years since it was first proposed that the neurodegeneration in Alzheimer's disease (AD) may be caused by deposition of Aβ peptide in plaques (the amyloid cascade hypothesis) (Hardy and Allsop, 1991). According to this hypothesis, accumulation of Aβ fibrils in the brain is the primary influence driving AD pathogenesis. The rest of the disease process, including formation of neurofibrillary lesions containing tau protein, microgliosis, synaptic dysfunction and neuronal loss is proposed to result from an imbalance between Aβ production and Aβ clearance. The pathogenic role of β-amyloid deposition in AD is underscored by the evidence that each of the disease-causing mutations in familial AD results in enhanced production of amyloidogenic Aβ peptides (Hardy and Selkoe, 2002). Although the large Aβ aggregates present in plaques were initially regarded as the culprits responsible for neurodegeneration, the distribution and density of both

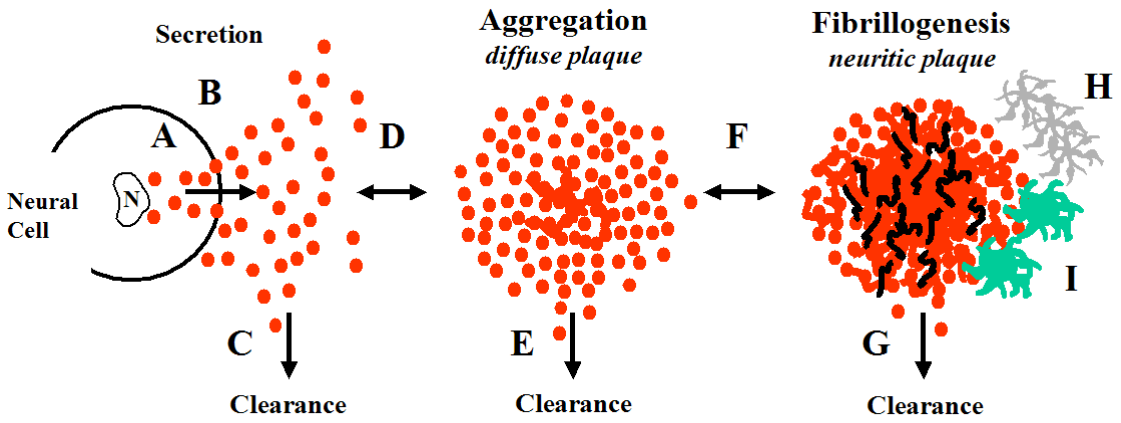

Figure 2. Hypothetical mechanism for the deposition of Aβ in amyloid plaques. Soluble Aβ peptides (depicted by the ref filled circles) are produced in neurons (N=nucleus of a cell) and secreted (A) into the extracellular space (B) from whence they are cleared in the brains of normal young individuals (C). With advancing age, soluble Aβ aggregates into diffuse plaques (closely packed filled circles to the right of the D). Some aggregated soluble Aβ also may be cleared from these plaques (E). In AD, soluble Aβ in diffuse plaques may be induced to form fibrillar Aβ aggregates that lead to the formation of mature senile plaques (to the right of the F) which accumulate many additional components including more soluble Aβ, PHFs (curvilinear black profiles), in addition to microglial cells (I) and reactive astrocytes (H). Nonfibrillar or soluble Aβ might be cleared from senile plaques (G), but the continued presence of factors that induce the fibrillogenesis and insolubility of soluble Aβ would favour the persistence of amyloid in the AD brain.

diffuse and senile plaques at the light microscopic level have not been consistently shown to correlate well with the degree of cognitive impairment that the patient experienced in life (Terry, 1991; Berg et al., 1998; Hardy et al., 1998; McLean et al., 1999; Wang et al., 1999). Moreover, abundant cortical Aβ deposits may also be found in cognitively intact ederly subjects (Dickson et al., 1991; Arriagada et al., 1992). The best correlation with the degree of dementia occurs with soluble levels of Aβ, measured biochemically (Lue et al., 1999; Mc Lean et al., 1999; Wang et al., 1999; Naslund et al., 2000). In accordance with these observations, several lines of evidence have recently converged to demonstrate that soluble oligomeric assemblies of Aβ, but not insoluble amyloid fibrils, may be responsible for the loss of neurons and synaptic dysfunction observed in AD (Klein et al., 2001; Kirkitadze et al., 2002; Selkoe, 2002). Importantly, such oligomeric forms of Aβ have been shown to be neurotoxic both *in vitro* and *in vivo* (Oda et al., 1995; Walsh et al., 1997; Lambert et al., 1998; Hartley et al., 1999; Walsh et al., 1999; Nilsberth et al., 2001, Walsh et al., 2002) and to inhibit long-term potentiation (Walsh et al., 2002). These evidence supports a revision of the amyloid cascade hypothesis such that Aβ assembly into neurotoxic oligomers, and not into amyloid fibrils, is the seminal event in AD pathogenesis (Klein et al., 2001, 2004;

Kirkitadze et al., 2002; Walsh et al., 2002b). It might well be that fibrillar amyloid acts as a reservoir for the soluble oligomers, or represent the sequestered pool of soluble and now precipitated Aβ, therefore fulfilling a protective function, or just the end stage of the Aβ cascade (Masters et al., 2006).

1.2.2.2. Neurofibrillary lesions

The second histopathological hallmark of AD is the neurofibrillary lesions (NFLs). NFLs are intracellular filamentous deposits largely composed of microtubule-associated protein tau in a hyperphosphorylated and abnormally phosphorylated state (Brion et al., 1985; Grundke-Iqbal et al., 1986; Nukina and Ihara, 1986; Wood et al., 1986; Kosik et al., 1988; Goedert, 1993; Lee, 1995; Morishima-Kawashima et al., 1995). There are three main types of NFLs according to their localizations in nerve cells: (i) neurofibrillary tangles (NFTs) in the cell body and apical dendrites of neurons, (ii) neuropil threads (NTs) in distal dendrites and (iii) dystrophic neurites associated with neuritic plaques (Tolnay and Probst, 1999). Ultrastructurally, NFLs contain bundles of abnormal fibers that consist of pairs of ~10nm filaments wound into helices (paired helical filaments or PHFs) as a major fibrous component and straight, 10- to 15-nm filaments (or SFs) as a minor component (Selkoe, 2001). Most of these filaments are highly insoluble and resistant to detergent such as sodium dodecyl sulfate (Selkoe et al., 1982). Tau proteins are the major, if not the sole, building block of PHFs in the major NFLs of the AD brain. However, immunohistochemical studies have demonstrated that PHFs also contain neurofilament proteins (Anderton et al., 1982; Perry et al., 1985; Sternberger et al., 1985; Miller et al., 1986), actin (Vogelsang et al., 1988), ubiquitin (Mori et al., 1987; Perry et al., 1987), MAP2 (Yen et al., 1987) and Aβ protein (Kidd et al., 1985; Masters et al., 1985). Although very poorly documented, the appearance and development of NFLs is associated with an inflammatory response, indicated by a progressive microglial and astrocytic reaction to tau deposition (Perlmutter et al., 1992; Sheng et al., 1997).

The manner in which neurofibrillary pathology spreads to various brain areas during the course of AD is not random but follows a stereotyped pattern which has been used to define six neuropathological stages, the Braak stages (Braak and Braak, 1991). On the basis of cross-sectional analysis of unselected cases coming to post-mortem, Braak and Braak have

reported that neurofibrillary tangles are first observed in the transentorhinal and entorhinal cortex (stages I and II or transentorhinal stages). A more extensive involvement of the entorhinal cortex and the formation of NFTs in sector CA1 (Cornu Ammonis 1) of the hippocampus correspond to stages III and IV or to limbic stages. Pathology then spreads into sectors CA2, 3 and 4 of the hippocampus, the subiculum, and into isocortical areas, particularly the temporal and parietal cortices (Stage V). The final stage VI is characterized by more extensive spread in neocortical areas, with relative sparing of primary motor and sensory areas. There is a close correlation between the burden of NFTs and the degree of dementia in AD, at least in some cortical and subcortical regions (Bondareff et al., 1989; Arriagada et al., 1992; Holzer et al., 1994; Bierer et al., 1995). At Braak stages I and II, patients are cognitively unimpaired whereas subjects with limbic stages III and IV usually present with mild cognitive impairment. Subjects with stages V and VI are severely demented and meet the neuropathological tau criteria for the diagnosis of AD.

Morphologically, three main subtypes of NFTs can be distinguished, corresponding to different evolutionary stages of this lesion (Tolnay and Probst, 1999). The earliest stage, also termed pretangle stage, is characterized by the accumulation of hyperphosphorylated tau protein in the somatodendritic domain of affected neurons without formation of PHFs and SFs (Bancher et al., 1989; Braak et al., 1994). Therefore pretangle neurons are only detectable with anti-tau antibodies in contrast to the later stage of classical NFT formation wherein tau aggregates are identified with silver staining techniques such as Bielschowsky and Gallyas stains. The third stage of NFT formation corresponds to extracellular NFTs or "ghost" tangles (Tolnay and Probst, 1999; Bancher et al., 1989). It has been proposed that the release of NFTs from dying neurons could result in interactions between aggregated tau and the soluble Aβ normally secreted by neurons or other brain cells (Seubert et al., 1992; Shoji et al., 1992; Wertkin et al., 1993Trojanowski et al., 1993; Trojanowski and Lee, 1994). Thus, the chronic but progressive degeneration of neurons in the AD brain may release NFTs into the extracellular space, which then are able to recruit or immobilize soluble Aβ into deposits. These same neuronal debris also may play a role in inducing aggregated Aβ to undergo fibrillogenesis and the formation of neuritic amyloid plaques (Shin et al., 1993, 1994). These data intersect well with the work of Braak and Braak (1991) who stated that initial NFTs predate morphologically detectable amyloid plaques. However, as Hardy and Selkoe (2002) point out, the postmortem cases used to establish the Braak stage I neuropathology criteria were non-demented older individuals, in whom it is

impossible to conclude that they would all have developed AD if they had survived longer. Second, the Braak analysis cannot exclude a toxic effect of any soluble oligomeric forms of Aβ that have not yet reached the stage of microscopically visible amyloid plaques. Moreover, in patients with the rare presenilin 1 mutations or individuals with Down's syndrome who died prematurely from other diseases, the presence of Aβ (either as diffuse deposits or typical plaques) precedes the appearance of neurofibrillary tangles (Lemere et al., 1996; Lippa et al., 1998).

PHFs resembling those of AD have been assembled from recombinant tau *in vitro*. This process is usually very slow (days or weeks), corresponding to the highly soluble nature of tau. Several principles have emerged from these *in vitro* studies over the past few years; the repeat domain of tau is important for PHF aggregation (Wille et al., 1992; Wilson and Binder, 1995; DeTure et al., 1996); aggregation is strongly enhanced by oxidation (Wille et al., 1992; Schweers et al., 1995) or in the presence of polyanions such as heparin, ribonucleic acids, or acidic peptides (Perez et al., 1996; Goedert el al., 1996; Kampers et al., 1996); mutations of tau found in hereditary frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) favor tau aggregation and PHF formation (Barghorn et al., 2000; Goedert et al., 1999; Gamblin et al., 2000; Hong et al., 1998). The reasons for this may be heterogeneous, depending on the type of mutation but at least in the cases of P301L they can be traced back to an enhanced propensity for β-structure, a feature common to many pathological amyloids (Fraser et al., 1994; Pike et al., 1995; Lansbury, 1997). In AD, PHF formation is not due to mutations in the tau gene but rather to some cellular cascade triggered by Aβ that results in abnormal phosphorylation of tau proteins that causes them to assemble into filaments. This statement intersects well with the observation that Aβ in the vicinity of neurons enhanced tau phosphorylation *in vitro* and *in vivo* (Busciglio et al., 1995; Geula et al., 1998). This is further supported in a recent article showing that double transgenic mice expressing mutant human tau (P301L) and mutant APP developed enhanced neurofibrillary pathology and degeneration in cortical and subcortical brain regions (Lewis et al., 2001). Moreover, recent work has indicated that direct intracranial injection of synthetic Aβ peptide increases tau phosphorylation and NFT formation in transgenic mice expressing the P301L tau mutant (Gotz et al., 2001). Although the molecular mechanism by which the extracellular accumulation of Aβ peptides promotes the intracellular assembly of pathologic tau filaments *in vivo* remains poorly unterstood, a

mechanistic link between the two is emerging. Exposure of primary neurons to Aβ activates the tau kinase GSK3β (glycogen synthase kinase β), increases tau phosphorylation, and leads to cell death (Takashima et al., 1998; Zheng et al., 2002). The tau kinase cdk5 (cyclin-dependent kinase 5) is also activated by Aβ in cultured neurons and in AD (Dhavan and Tsai, 2001). The activity of the cdk5 kinase is regulated by a 35-kDa myristoylated membrane-attached protein, p35 (Zheng et al., 2002b). When p35 undergoes calpain-mediated cleavage to p25, kinase activity is greatly enhanced. The cdk5/p25 complex appears to be delocalized from the plasma membrane, leading to nonphysiologic phosphorylation of tau, its dissociation from microtubules and self-assembly into insoluble filaments (Michealis, 2002).

1.2.3. Epidemiology and genetics of Alzheimer's disease

AD is the most common cause of dementia (Table 2) and affects approximately 7% of people older than 65 and perhaps 40% of people over the age of 80 (McKhann et al., 1984; Evans et al., 1989; Rocca et al., 1991; Ebly et al., 1994; Lautenschlager et al., 1996; Lobo et al., 2000). Because of increased life expectancy and the post-World War II baby boom, the elderly is the fastest growing segment of our society (Olshansky, 1993). More than twelve million people worldwide now suffer from AD, a striking figure that is predicted to almost triple by 2050 (Hebert et al., 2003). Thus, AD is one of society's major public health problems.

The vast majority of AD cases are sporadic and occur late in life with no clearly defined etiology. However, genetic factors are known to be important and, in fact, after age, family history is the second greatest risk factor for AD (Selkoe, 1999). Autosomal dominant mutations in three different genes (amyloid precursor protein, presenilin 1 and presenilin 2) have been identified that account for a small number of cases of familial, early-onset AD (FAD) (Schellenberg, 1995; Kim and Tanzi, 1997). The first genetic mutation associated with FAD was in the APP gene. Suspicion of the involvement of APP in FAD arose since the gene resides on chromosome 21 (Kang et al., 1987) and people with Down's syndrome (who have an extra copy of chromosome 21) develop neuropathological attributes of AD by age 40 (Wisniewski et al., 1985). Genetic linkage studies also suggested the involvement of a locus near the APP gene on chromosome 21 in FAD (Tanzi et al., 1987; Goate et al.,

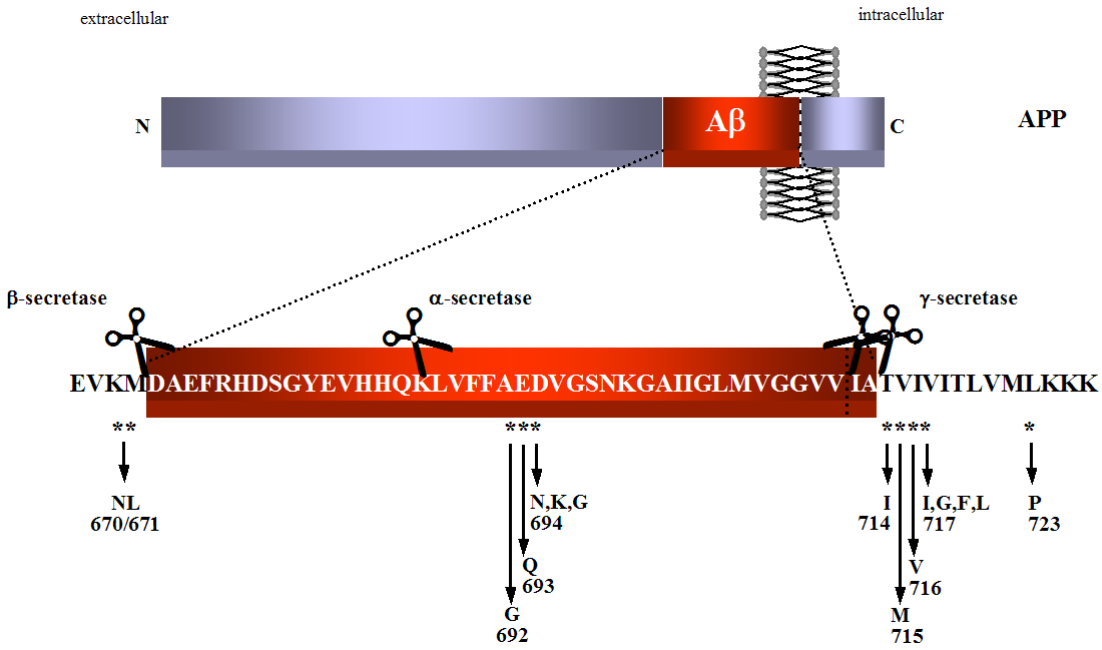

Figure 3. Structure of the β-amyloid precursor protein (APP, in blue), the β-amyloid (Aβ, in red), and missense mutations located within APP. APP is proteolytically cleaved by sequential actions of α-, β-, and γ-secretases (indicated by the scissors). The location of APP mutations associated with early-onset familial AD (FAD) and/or cerebrovascular pathology are marked by asterisks and the amino acid substitutions are indicated.

1989). In 1991 the first genetic linkages of AD were identified as missense mutations in the APP gene located on chromosome 21 (Naruse et al., 1991; Goate et al., 1991). Since then, more than 20 pathological mutations in APP have been identified (Figure 6). Most of these are near the proteolytic cleavage sites involved in Aβ production (Goate et al., 1991; Hendriks et al., 1992; Mullan et al., 1992; Ghiso and Frangione, 2002). Mutations in APP do not account for all cases of FAD. In the mid 1990s, further genetic linkage studies uncovered mutations in presenilin 1 on chromosome 14 (St George-Hyslop et al., 1992; Sherrington et al., 1995) and presenilin 2 on chromosome 1 (Levy-Lahad et al., 1995; Rogaev et al., 1995). Presenilin forms the active site of the γ-secretase complex involved in the production of Aβ (De Strooper, 2003). To date there are more than 120 different mutations identified in the PS1 gene, while only 8 missense mutations have been identified in PS2. FAD mutations in PS1, PS2 and APP result in overproduction of total Aβ and/or lead to an increase of secreted Aβ42, the primary component of β-amyloid plaques in the brain (Tamaoka et al., 1994; Hardy, 1997; Price an Sisodia, 1998; Selkoe, 1999; Haass and DeStrooper, 1999).

In addition to the mutations that have been associated with early-onset FAD, other genetic factors have been identified that increase the risk of developing sporadic AD. These include the ε4 allele of the apolipoprotein E (ApoE) gene (Strittmatter et al., 1993) on chromosome 19 (Olaisen et al., 1982), the proteinase inhibitor α2-macroglobulin gene (Blacker et al., 1998) on chromosome 12 (Pericak-Vance et al., 1997), insulin degrading enzyme gene on chromosome 10 (Vekrellis et al., 2000), low density lipoprotein receptor-related protein (Olson, 1998) or angiotensin converting enzyme (Kehoe et al., 1999).

At present, no mutations in the tau gene have been identified in AD. Nevertheless, several mutations in human tau on chromosome 17 result in a cluster of neurodegenerative diseases, termed FTDP-17, that are characterized by the accumulation of neurofibrillary tangles in affected brain regions (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998). They include missense mutations in coding regions of the tau gene in exons 9, 10, 12 and 13, silent mutations as well as a deletion mutation in exon 10, and intronic mutations located close to the splice-donor site of the intron following exon 10. These pathogenic mutations either reduce the ability of tau to bind to microtubules or alter the splicing of exon 10 resulting in increased 4 repeat tau isoforms (Hutton et al., 1998). To date more than 20 different tau gene mutations have been identified in a large number of FTDP-17 families. The identification of these mutations provided direct evidence that tau dysfunction per se is sufficient to cause neurodegeneration (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998; Clark et al., 1998), presumably due to failure of the self-assembled tau to regulate the microtubule dynamics essential for cell survival (Lee et al., 2001). Notably, the exact form of tau which causes neuronal degeneration is now being re-examined (Duff and Planel, 2005), with data emerging that the soluble aggregated species, akin to soluble Aβ oligomers, might represent the best target.

1.2.4. Origin of Aβ proteins: cell biology of APP

APP is a type-I integral transmembrane glycoprotein that is ubiquistouly expressed, and is encoded by a gene located on chromosome 21 (Masters et al., 1985). Alternative splicing of the APP gene gives rise to at least three transcripts that encode proteins of 695, 751 and 770 amino acids (Hardy, 1997; Selkoe, 1999). The two longer isoforms contain a motif which is homologous to the Kunitz-type of serine protease inhibitors (KPI) (Kitaguchi et al., 1988;

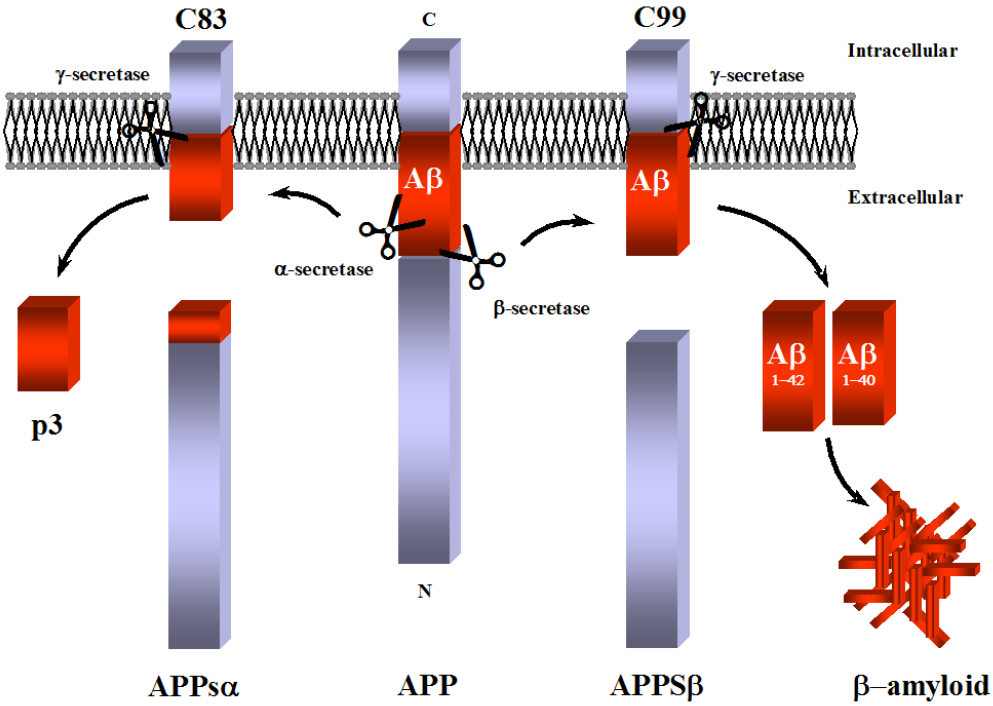

Figure 4. Pathways processing the APP by α-, β- and γ-secretases. Cleavage by α-secretase does not result in Aβ production but in release of soluble APPsα and retention of a 83-residue C-terminal peptide (C83). Cleavage by β-secretase produces soluble APPsβ and a 99-residue C-terminal (C99). Both C83 and C99 are substrates for γ-secretase that yields a 3-kD peptide called p3 from cleavage of C83, and Aβ from cleavage of C99.

Ponte el al., 1988; Tanzi et al., 1988), whereas the shorter form of 695 amino acids lacks this 56-residue Kunitz domain (Golde et al., 1990). All of the APP isoforms contain the 39-43 amino acids long Aβ domain. The shorter form of 695 amino acids is the main isoform expressed in neurons (Golde et al., 1990). At present the physiological function of APP in the brain remains unclear, although it has been proposed to have functions in transmembrane signal transduction (Nishimoto et al., 1993), cell proliferation and adhesion (Saitoh et al., 1989), calcium regulation (Mattson et al., 1993) and neurite outgrowth (Milward et al., 1992).

A characteristic feature of APP is its proteolytic cleavage by the α-, β- and γ-secretases (Figure 4) (Selkoe, 2001). The differential actions of these secretases lead either to the non-amyloidogenic or amyloidogenic pathway. α-secretase cleaves APP within the Aβ region to produce the soluble α-APPs and the 83-residue COOH-terminal fragment C83 (Esch et al., 1990; Sisodia et al., 1990). The α-cleavage pathway is considered as default, non-amyloidogenic pathway. The β-secretase (or BACE for β-site APP-cleaving enzyme)

cleavage corresponds to the alternative, amyloidogenic pathway, that produces a 99-residue COOH-terminal fragment C99 and the soluble β-APPs (Sinha et al., 1999; Vassar, 1999). Both the C83 and C99 fragments remain anchored in the membrane where they are processed by γ-secretase to produce p3 from C83 or Aβ from C99. γ-secretase cleavage is not sequence specific resulting in Aβ peptides of varying length (Selkoe, 2001).

1.2.5. Human tau gene and protein isoforms

Tau proteins belong to the microtubule-associated proteins family (MAP) and are abundant in both central and peripheral nervous system neurons, although reports have suggested that tau can be expressed in other cell types (Weingarten et al., 1975; Schoenfeld and Obar, 1994; Tucker, 1990; LoPresti et al., 1995; Wakabayashi et al., 2006). As part of the cytoskeleton, tau proteins bind to microtubules and function to stabilize microtubules in the polymerized state as well to facilitate the polymerization of tubulin subunits (Drechsel et al., 1992; Cassimeris, 1993; Ludin and Matus, 1993; Goode and Feinstein, 1994). The human tau gene is located on the chromosome 17 (Neve et al., 1986) and contains 16 exons (Figure 5, A) with the major tau protein isoforms being encoded by 11 of them (Andreadis et al., 1992; Buee et al., 2000). Through alternative messenger RNA splicing of exons 2, 3 and 10 (Figure 5, B) a set of six isoforms ranging from 352 to 441 amino-acids are generated in adult human brain (Figure 5, C) (Himmler et al., 1989; Kosik, 1989). Exons 9-13 encode four microtubule-binding motifs which are imperfect repeats of 31 or 32 amino acids in the carboxy terminal half of the tau molecule. The alternative splicing of exon 10 thus generates tau protein isoforms with either three (3R) or four (4R) microtubule-binding repeats. Further, the 6 isoforms differ by alternative splicing of exons 2 and 3 resulting in the absence (0N) or presence of one (1N) or two (2N) 29 amino acid inserts in the amino-terminal half of the tau molecule. Thus, alternative splicing of exons 2, 3 and 10 allows for six combinations: the longest 441-amino acids (4R2N), 410-amino acids (3R2N), 412-amino acids (4R1N), 381-amino acids (3R1N), 393-amino-acids component (4R0N) and the shortest 352-amino acids isoform (3R0N). Each of these isoforms is likely to have particular physiological roles since they are differentially expressed during development (Kosik et al., 1989). Also, the degree of phosphorylation is developmentally regulated. Thus, tau from fetal brain is phosphorylated at more sites than tau from adult brain (Buée et al., 2000).

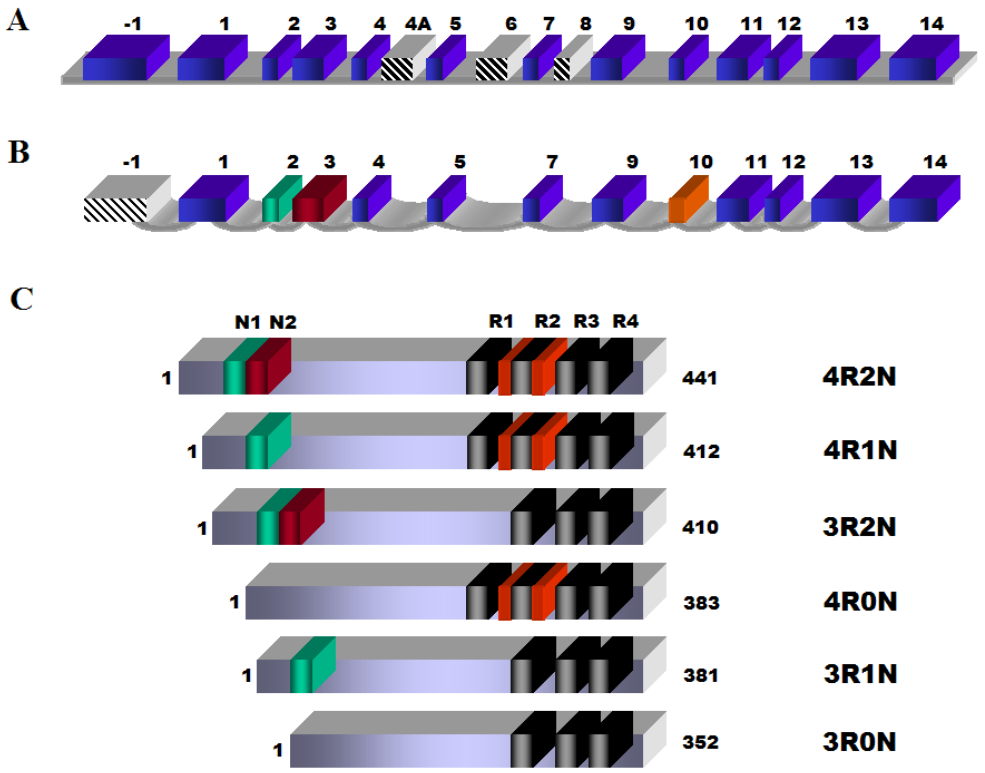

Figure 5. Schematic representation of the human tau gene (A), the tau primary transcript (B) and the six tau isoforms (C). The human tau gene is located on the long arm of the chromosome 17 at position 17q21 and contains 16 exons, with exon –1 is a part of the promoter. (B) The Tau primary transcript contains 13 exons, since exons 4A, 6 and 8 are not transcribed in human. (C) Through alternative messenger RNA splicing of exons 2, 3 and 10 a set of six isoforms ranging from 352 to 441 amino-acids are generated in adult human brain The six tau isoforms differ by the absence or presence of one or two 29 amino acids inserts encoded by exon 2 (green box) and 3 (dark red boxes) in the amino-terminal part, in combination with either three or four repeat-regions (black boxes) in the carboxy-terminal part. The fourth microtubule-binding domain is encoded by exon 10 (orange box).

Tau proteins contain two functional domains (Buée et al., 2000). The amino-terminal part of tau proteins, referred to as projection domain, interacts with cytoskelatal elements to determine spacings between microtubules in axons (Brandt et al., 1995; Hirokawa et al., 1988). The amino-terminal part is also involed in signal transduction pathways by interacting with proteins as phospholipase C-γ (Hwang et al., 1996). The carboxy-terminal part, referred to as microtubules binding domain, regulates the rate of microtubules polymerization (Butner and Kirschner, 1991; Goedert and Jakes, 1990). It is also involved in the binding with functional proteins as protein phosphatase 2A (Sontag et al., 1999) or presenilin-1 (Takashima et al., 1998).

1.2.6. Transgenic mouse models of Alzheimer's disease

The identification and sequencing of APP and PS genes has provided new opportunities to explore pathogenic mechanisms and treatments of AD using genetically engineered mice. Multiple lines of transgenic mice expressing mutated human APP now exist that develop age-dependent cerebral Aβ-amyloidosis concomitantly with additional AD-like pathologies such as memory deficits, gliosis, regional neuronal loss, cerebral amyloid angiopathy and dystrophic neurites (Games et al., 1995; Hsiao et al., 1996; Sturchler-Pierrat et al., 1997; Calhoun et al., 1998; Stalder et al., 1999; Moechars et al., 1999; Bronfman et al., 2000; Kumar-Singh et al., 2000; Van Dorpe et al., 2000; Bondolfi et al., 2002; Kelly et al., 2003). In addition to mice expressing mutations in the APP gene, mouse models bearing PS mutations have been generated (Duff et al., 1996; Citron et al., 1997). Except for increased production of Aβ42/43, no pathological phenotype could be observed. Other models combine the insertion of mutated APP with an insertion of mutated PS1 that lead to accelerated amyloid plaque deposition (Figure 7) (Borchelt et al., 1996, 1997; Holcomb et al., 1998; Lamb et al., 1999; Chishti et al., 2001; Gordon et al., 2002). Several of these Aß depositing mouse models develop hyperphosphorylated tau-positive structures around plaques but all of them consistently fail to show intracellular filamentous deposits of tau protein, which are an essential hallmark of AD. The difference in tau sequence between mouse and humans may explain why despite the progressive and severe Aβ deposition there are no neurofibrillary tangles and very little neuronal loss in these APP models (Hsiao, 1996; Irizarry et al., 1997).

As APP transgenic models failed to develop insoluble tau aggregates, tau transgenic mice have been developed. The first transgenic tau models expressing wild-type human tau were generated before pathogenic tau mutations had been identified (Gotz et al., 1995; Brion et al., 1999; Spittaels et al., 1999; Probst et al., 2000). Overexpressing the 3 or 4 repeat wild-type human tau in these models resulted in hyperphosphorylation of tau and somatodendritic localization; however, none of these transgenic mice developed neurofibrillary tangles. The discovery of mutations in the tau gene in FTDP-17 has provided the basis for the generation of transgenic mouse models that exhibit age-related filamentous tau deposits through expression of mutant human tau protein (Lewis et al., 2000; Gotz et al., 2001; Hutton et al., 2001). Among others models, Lewis and al. (2000) developed transgenic mice expressing the shortest 4 repeat (4R0N) tau with the P301L

mutation under control of the mouse prion promoter. These mice developed motor and behavioural deficits accompanied by age- and gene dose-dependent accumulation of neurofibrillary tangles (Figure 8) in both brain and spinal cord, with associated neurodegeneration and reactive gliosis (Lewis et al., 2000). Using a transgenic line expressing the longest 4 repeat (4R2N) tau with the same mutation under the mouse Thy1.2 promoter, Götz et al. (2001) reported quite similar results. A recent study also showed a correlation between the number of NFT and decline in performance on the Morris water maze in transgenic mice expressing the P301L mutation, indicating a detrimental effect of NFT on memory (Arendash et al., 2004). The FTDP-17-associated mutation P301S has also been used to make mouse models. P301S mutant tau expressed under the mouse Thy1.2 promoter caused tau hyperphosphorylation and formation of tau filaments in affected brain regions. FTDP-17 mutations V337M (Tanemura et al., 2001, 2002) and G272V (Gotz et al., 2001) also were expressed in transgenic mice. Neurofibrillary lesions and associated neurodegeneration were found in neurons of V337M mutant mice (Tanemura et al., 2002), while G272V mutant mice developed prominent oligodendroglial tau filament formation (Götz et al., 2001). None of these tau depositing mouse models developed deposits of amyloid-β protein, suggesting that the neurofibrillary tangles in AD are secondary to Aβ production (Hardy et al., 1998) and probably triggered by Aβ (Rapoport et al., 2002).

In an attempt to obtain mouse models that display the entire neuropathological spectrum of AD, APP transgenic mice were breed with mice expressing the P301L mutant tau. Interestingly double mutant mice exhibited substantially enhanced neurofibrillary tangle pathology in limbic areas as compared to single tau mutant mice. Notably, plaque formation was unaffected by the presence of the tau lesions (Lewis et al., 2001). Thus, amyloid plaques can cause tau tangles, but vice versa tangles do not obligate amyloid plaque formation. Recently, triple-transgenic mice harboring mutated PS1 (M146V), APP (Swedish) and tau (P301L) transgenes have been created that develop extracellular Aβ deposits prior to tangle formation in AD relevant brain regions (Oddo et al., 2003). Moreover, treatment of the amyloid pathology in these triple transgenic mice led to a partial resolution of tau abnormalities (Oddo et al., 2004).

1.2.7. Treating and preventing Alzheimer's disease

At present there is no cure for AD. Present-day therapies focus on treating associated symptoms, such as depression, agitation, sleep disorders, hallucinations, and delusions (Clippingdale et al., 2002). To date, only four medications have been approved for the symptomatic treatment of patients with Alzheimer disease. These are tacrine (Cognex, Warner-Lambert, Morris Plains, New Jersey); donepezil (Aricept, Eisai, Inc., Teaneck, New Jersey, and Pfizer, Inc., New York, New York); rivastigmine (Exelon, Novartis, Basel, Switzerland); and galantamine (Reminyl, Janssen, Titusville, New Jersey). All are cholinesterase inhibitors that are aimed at counterbalancing deficits in the neurotransmitter acetylcholine observed in AD (Emilien et al., 2000). Unfortunately, these drugs induce, at best, a very modest effect on cognitive functions and activities of daily living and do do not stop the progression of AD (Grutzendler and Morris, 2001). If the amyloid cascade hypothesis of AD pathogenesis (Hardy and Allsop, 1991) is correct, the most rational strategy to treat the disease would rather involve retarding, halting or even reversing the process that leads to increased production of Aβ.

With the identification of the α-, β- and γ- secretases, new approaches to treat AD have become possible. Therefore, a promising strategy might be reducing formation of Aβ by inhibiting either β- or γ-secretases and/or enhancing α-secretase activity (Xia, 2003). There are already potent γ-secretase inhibitors tested in a variety of experimental models (Lanz et al., 2004; Wong et al., 2004). Several classes of inhibitors are showing favourable acute pharmacokinetics with rapid lowering of plasma and CSF Aβ levels (Anderson et al., 2005; Barten et al., 2005) but are also revealing unanticipated effects on synaptic function (Dash et al., 2005). New classes of γ-secretase inhibitors continue to be disclosed, as part of the attempt to develop compounds that are devoid of side-effects (Gundersen et al., 2005; Lewis et al., 2005). The major concern is the inhibition of signaling in the Notch pathway, which is important for a variety of cell fate decisions during embryogenesis and also in adult tissues (Milner and Bigas, 1999; Doerfler et al., 2001; Sisodia and St George-Hyslop, 2002; van Es et al., 2005). Compounds that inhibit Aβ formation without affecting Notch cleavage may offer new leads for the design of APP-specific γ-secretase inhibitors. The development of β-secretase inhibitors has been focused on the discovery and design of compounds which target the active site of BACE-1 which is thought to be an ideal

therapeutic target as it catalyses the first step of Aβ production. Furthermore, β-secretase knockout mice are apparently normal showing no obvious anatomical or physiological abnormalities (Luo et al., 2001; Roberds et al., 2001) except for a dramatic reduction in Aβ levels. However, one major challenge for the generation of specific inhibitors is the large active site of this secretase (Hong et al., 2000).

A chronic inflammatory response, exemplified by activated microglia, reactive astrocytes, complement factors, and increased inflammatory cytokine expression, is associated with Aβ deposits in AD brain (Akiyama et al., 2000; Emmerling et al., 2000). Therefore, trials of anti-inflammatories in AD have been conducted, and considerable research efforts undertaken to examine the effects of anti-inflammatories in a variety of experimental models. These include the non-steroidal anti-inflammatory drugs (NSAIDs) (Farias et al., 2005; Morihara et al., 2005), cannabionoids (Ramirez et al., 2005) and glucocorticoids (Boedker et al., 2005). NSAIDs have been suggested to delay the onset and slow the progression of AD by inhibiting the cyclooxygenase, and therefore prostaglandin synthesis, resulting in reduced inflammatory response (Launer, 2003). Besides an anti-inflammatory action, some NSAIDs have also been shown to have direct effects on the cleavage of APP by γ-secretase, an effect that is independent of the drugs' inhibition of cyclooxygenase and other inflammatory mediators (Weggen et al., 2001). Some such drugs reduce cytopathology in APP tg mice (Lim et al, 2001; Jantzen et al., 2002), perhaps by lowering the production of the highly amyloidogenic Aβ (Weggen et al., 2001). However, although epidemiological studies suggest that NSAIDs reduce the risk of developing AD, clinical trials in patients with mild to moderate AD have been negative (Aisen et al., 2003; Launer, 2003).

Epidemiological studies suggest that cholesterol-lowering drugs could provide some degree of protection from AD and therefore could be an attractive treatment strategy (Jick et al., 2000; Fassbender et al., 2001). Conversely, high blood cholesterol levels have been correlated with a higher risk of developing AD (Kivipelto et al., 2001) and high cholesterol diets increase Aβ deposition in transgenic mice and in rabbits (Sparks et al., 1994; Refolo et al., 2000). A molecular explanation might be that high cholesterol favors processing of APP through the amyloidogenic β-secretase pathway *in vitro* and *in vivo* (Simons et al., 1998; Fassbender et al., 2001). Inhibitors of cholesterol synthesis (statins) have been shown to

decrease Aβ production resulting in reduced pathology in APP tg mice (Fassbender et al., 2001; Refolo et al., 2001). However, while some early phase clinical trials with statins have shown encouraging results (Masse et al., 2005), others have not (Höglund et al., 2005).

Passive immunization with antibodies against Aβ (Bard et al., 2000; DeMattos et al., 2001; Wilcok et al., 2003), or active immunization with Aβ (Schenk et al., 1999; Janus et al., 2000) were proven to prevent amyloid deposition in young mice but also cleared plaques and reduced associated glial and neuronal cytopathology in older animals. Moreover, immunization with Aβ was found to protect again or reverse cognitive deficits in mice (Janus et al., 2000; Morgan et al., 2000; Younkin, 2001; Dodart et al., 2002). Based on these results, Elan Corporation moved into clinical trials with the active Aβ-vaccination approach. Toxicological testing in several animal species, and Phase I clinical trials in 104 AD cases suggested that the vaccination with aggregated Aβ42 was safe (Senior, 2002). Therefore, in June 2001, a Phase II trial was begun with 360 early to moderate stage Alzheimer's patients in the United States and Europe. However, the phase IIa clinical trial for an AD vaccine (AN-1792) was suspended in January 2002 when 6% of the patients developed clinical signs of meningoencephalitis, a potentially deadly inflammation of the brain (Munch and Robinson, 2002; Senior, 2002; Nicoll et al., 2003; Orgogozo et al., 2003). The mechanism of this inflammation is unknown, but the appearance of the inflammatory reaction before anti-Aβ antibody production in some patients indicates the involvement of a T-cell-mediated immune response to Aβ (Weiner and Selkoe, 2002). Despite the serious side effects encountered, autopsy evaluation and cognitive assessment of patients involved in the study suggest that immunization might work (Nicoll et al., 2003). The aborted clinical trial with the AN1972 vaccination approach has provided a wealth of clinical information (Gilman et al., 2005; Lee et al., 2005) which will assist further development of strategies designed to avoid the auto-immune adverse events (Lee et al., 2005b; Racke et al., 2005). Chief among these will be avoidance of T-cell-mediated responses (Agadjanyan et al., 2005) and the development of passive immunization protocols (Hartman et al., 2005). Passive immunization clinical trials are currently underway. In the meantime, novel methods of antigen presentation are being tested (Frenkel et al., 2005). Three main possible mechanisms have been suggested to be responsible for Aβ clearance: (i) Aβ antibodies enter the CNS and target aggregated Aβ deposits where they form immune complexes. The Fc-region of the anti-Aβ antibodies

binds to the Fc-receptors on microglia and induces phagocytosis of the Aβ peptide. (Bard et al., 2000); (ii) Aβ antibodies generate a peripheral sink for efflux of Aβ out of CNS compartments, reducing the potential for aggregation and deposition (DeMattos et al., 2001); (iii) Aβ antibodies prevent the fibrillar aggregation of Aβ and/or neutralize Aβ fibers (Solomon et al., 1996; 1997).

Excessive phosphorylation of the tau protein in AD is thought to cause formation of insoluble tau filaments with resulting neurofibrillary tangles, disruption of microtubules, and subsequent neuronal dysfunction (Trojanowski and Lee, 2002). Thus, drugs targeted to preventing neurofibrillary pathology may help slow progression of cell death. Identification of such agents is still in very early stages, but some efforts are focused on agents that might decrease abnormal phosphorylation of tau and/or prevent the loss of microtubule structure. Inhibition of proline-directed kinases has become a major focus for drug development. Of the proline-directed kinases, glycogen synthase kinase β (GSK3β) and cyclin-dependent kinase 5 (cdk5) are the primary targets for drug discovery efforts because of their association with microtubules, their phosphorylation of tau at AD-relevant epitopes, and their involvement in apoptotic cascades in various models (Lau et al., 2002a, b). Their inhibition would be expected to decrease tau pathology in AD. The finding that valproate, a well-established epilepsy and mood-stabilizing medication, inhibits GSK3β (Chen et al., 1999) has led to proposal that this drug might improve symptoms of or slow progression of AD (Loy and Tariot, 2002). Interestingly, lithium, another well-established mood stabilizer, has also been shown to inhibit GSK3β (Alvarez et al., 2002). Another recent neuroprotective approach emerging from microtubule studies is the development of small molecules that stabilize microtubules such as paclitaxel (Taxol). Down regulation of expression of the tau gene (Santacruz et al., 2005) or changing the alternative splicing (Rodriguez-Martin et al., 2005) could also confer some new strategies.

Although many therapeutic agents are in various stages of development for the treatment of AD, the design of clinical trials has been hampered by the difficulty of identifying patients early enough on the disease continuum to test new drugs for effectiveness in slowing the progression of deterioration. Thus, success in pharmacological interventions hinges on developments in both the diagnostic arena and elucidation of the molecular pathogenesis of nerve cell death. Moreover, it is extremely unlikely that a single class of compound or

targeting a single mechanism of action will be sufficient to treat AD. For this complex disease, it is far more likely that a combination of drugs targeting various aspects of the Aβ and/or tau pathways will evolve into some form of rational therapy.

Abraham CR, Selkoe DJ, Potter H. Immunochemical identification of the serine protease inhibitor alpha 1-antichymotrypsin in the brain amyloid deposits of Alzheimer's disease. Cell. 1988 Feb 26;52(4):487-501.

Agadjanyan MG, Ghochikyan A, Petrushina I, Vasilevko V, Movsesyan N, Mkrtichyan M, Saing T, Cribbs DH. Prototype Alzheimer's disease vaccine using the immunodominant B cell epitope from beta-amyloid and promiscuous T cell epitope pan HLA DR-binding peptide. J Immunol. 2005 Feb 1;174(3):1580-6.

Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, Farlow MR, Jin S, Thomas RG, Thal LJ; Alzheimer's Disease Cooperative Study. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA. 2003 Jun 4;289(21):2819-26.

Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mrak R, Mackenzie IR, McGeer PL, O'Banion MK, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strohmeyer R, Tooyoma I, Van Muiswinkel FL, Veerhuis R, Walker D, Webster S, Wegrzyniak B, Wenk G, Wyss-Coray T. Inflammation and Alzheimer's disease. Neurobiol Aging. 2000 May-Jun;21(3):383-421.

Alvarez G, Munoz-Montano JR, Satrustegui J, Avila J, Bogonez E, Diaz-Nido J. Regulation of tau phosphorylation and protection against beta-amyloid-induced neurodegeneration by lithium. Possible implications for Alzheimer's disease. Bipolar Disord. 2002 Jun;4(3):153-65.

Alzheimer A. Ueber eine eigenartige Erkrankung der Hirnrinde. (A characteristic disease of the cerebral cortex). Allgemeine Zeitschrift für Psychiatrie und Psychisch- Gerichtliche Medizin. 1907. 64:146-148.

Anderson JJ, Holtz G, Baskin PP, Turner M, Rowe B, Wang B, Kounnas MZ, Lamb BT, Barten D, Felsenstein K, McDonald I, Srinivasan K, Munoz B, Wagner SL. Reductions in beta-amyloid concentrations in vivo by the gamma-secretase inhibitors BMS-289948 and BMS-299897. Biochem Pharmacol. 2005 Feb 15;69(4):689-98.

Anderton BH, Breinburg D, Downes MJ, Green PJ, Tomlinson BE, Ulrich J, Wood JN, Kahn J. Monoclonal antibodies show that neurofibrillary tangles and neurofilaments share antigenic determinants. Nature. 1982 Jul 1;298(5869):84-6.

Andreadis A, Brown WM, Kosik KS. Structure and novel exons of the human tau gene. Biochemistry. 1992 Nov 3;31(43):10626-33.

Andreasen N, Minthon L, Davidsson P, Vanmechelen E, Vanderstichele H, Winblad B, Blennow K. Evaluation of CSF-tau and CSF-Abeta42 as diagnostic markers for Alzheimer disease in clinical practice. Arch Neurol. 2001 Mar;58(3):373-9.

Anfinsen CB. Principles that govern the folding of protein chains. Science. 1973 Jul 20;181(96):223-30.

Arai H, Lee VM, Otvos L Jr, Greenberg BD, Lowery DE, Sharma SK, Schmidt ML, Trojanowski JQ. Defined neurofilament, tau, and beta-amyloid precursor protein epitopes distinguish Alzheimer from non-Alzheimer senile plaques. Proc Natl Acad Sci U S A. 1990 Mar;87(6):2249-53.

Arbel M, Yacoby I, Solomon B. Inhibition of amyloid precursor protein processing by beta-secretase through site-directed antibodies. Proc Natl Acad Sci U S A. 2005 May 24;102(21):7718-23. Epub 2005 May 13.

Arendash GW, Lewis J, Leighty RE, McGowan E, Cracchiolo JR, Hutton M, Garcia MF. Multi-metric behavioral comparison of APPsw and P301L models for Alzheimer's disease: linkage of poorer cognitive performance to tau pathology in forebrain. Brain Res. 2004 Jun 25;1012(1-2):29-41.

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 1992 Mar;42(3 Pt 1):631-9.

Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. Neurology. 1992 Sep;42(9):1681-8.

Baldwin RL, Rose GD. Is protein folding hierarchic? I. Local structure and peptide folding. Trends Biochem Sci. 1999 Jan;24(1):26-33.

Bancher C, Brunner C, Lassmann H, Budka H, Jellinger K, Wiche G, Seitelberger F, Grundke-Iqbal I, Iqbal K, Wisniewski HM. Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. Brain Res. 1989 Jan 16;477(1-2):90-9.

Bard F, Cannon C, Barbour R, Burke RL, Games D, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Lieberburg I, Motter R, Nguyen M, Soriano F, Vasquez N, Weiss K, Welch B, Seubert P, Schenk D, Yednock T. Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. Nat Med. 2000 Aug;6(8):916-9.

Barghorn S, Zheng-Fischhofer Q, Ackmann M, Biernat J, von Bergen M, Mandelkow EM, Mandelkow E. Structure, microtubule interactions, and paired helical filament aggregation by tau mutants of frontotemporal dementias. Biochemistry. 2000 Sep 26;39(38):11714-21.

Barten DM, Guss VL, Corsa JA, Loo A, Hansel SB, Zheng M, Munoz B, Srinivasan K, Wang B, Robertson BJ, Polson CT, Wang J, Roberts SB, Hendrick JP, Anderson JJ, Loy JK, Denton R, Verdoorn TA, Smith DW, Felsenstein KM. Dynamics of {beta}-amyloid reductions in brain, cerebrospinal fluid, and plasma of {beta}-amyloid precursor protein transgenic mice treated with a {gamma}-secretase inhibitor. J Pharmacol Exp Ther. 2005 Feb;312(2):635-43.

Berg L, McKeel DW Jr, Miller JP, Storandt M, Rubin EH, Morris JC, Baty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol. 1998 Mar;55(3):326-35.

Berriman J, Serpell LC, Oberg KA, Fink AL, Goedert M, Crowther RA. Tau filaments from human brain and from in vitro assembly of recombinant protein show cross-beta structure. Proc Natl Acad Sci U S A. 2003 Jul 22;100(15):9034-8. Epub 2003 Jul 9.

Bierer LM, Hof PR, Purohit DP, Carlin L, Schmeidler J, Davis KL, Perl DP. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. Arch Neurol. 1995 Jan;52(1):81-8.

Blacker D, Wilcox MA, Laird NM, Rodes L, Horvath SM, Go RC, Perry R, Watson B Jr, Bassett SS, McInnis MG, Albert MS, Hyman BT, Tanzi RE. Alpha-2 macroglobulin is genetically associated with Alzheimer disease. Nat Genet. 1998 Aug;19(4):357-60.

Blake C, Serpell L. Synchrotron X-ray studies suggest that the core of the transthyretin amyloid fibril is a continuous beta-sheet helix. Structure. 1996 Aug 15;4(8):989-98.

Blake CC, Serpell LC, Sunde M, Sandgren O, Lundgren E. A molecular model of the amyloid fibril. Ciba Found Symp. 1996;199:6-15

Boedker M, Boetkjaer A, Bazan NG, Cui JG, Zhao Y, Pelaez RP, Lukiw WJ. Budesonide epimer R, LAU-8080 and phenyl butyl nitrone synergistically repress cyclooxygenase-2 induction in [IL-1beta+Abeta42]-stressed human neural cells. Neurosci Lett. 2005 May 20-27;380(1-2):176-80. Epub 2005 Feb 10.

Bondareff W, Mountjoy CQ, Roth M, Hauser DL. Neurofibrillary degeneration and neuronal loss in Alzheimer's disease. Neurobiol Aging. 1989 Nov-Dec;10(6):709-15.

Bondolfi L, Calhoun M, Ermini F, Kuhn HG, Wiederhold KH, Walker L, Staufenbiel M, Jucker M. Amyloid-associated neuron loss and gliogenesis in the neocortex of amyloid precursor protein transgenic mice. J Neurosci. 2002 Jan 15;22(2):515-22.

Borchelt DR, Thinakaran G, Eckman CB, Lee MK, Davenport F, Ratovitsky T, Prada CM, Kim G, Seekins S, Yager D, Slunt HH, Wang R, Seeger M, Levey AI, Gandy SE, Copeland NG, Jenkins NA, Price DL, Younkin

SG, Sisodia SS. Familial Alzheimer's disease-linked presenilin 1 variants elevate Abeta1-42/1-40 ratio in vitro and in vivo. Neuron. 1996 Nov;17(5):1005-13.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl). 1991;82(4):239-59.

Braak E, Braak H, Mandelkow EM. A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. Acta Neuropathol (Berl). 1994;87(6):554-67.

Brandt R, Leger J, Lee G. Interaction of tau with the neural plasma membrane mediated by tau's amino-terminal projection domain. J Cell Biol. 1995 Dec;131(5):1327-40.

Brion JP, Couck AM, Passareiro E, Flament-Durand J. Neurofibrillary tangles of Alzheimer's disease: an immunohistochemical study. J Submicrosc Cytol. 1985 Jan;17(1):89-96.

Brion JP, Tremp G, Octave JN. Transgenic expression of the shortest human tau affects its compartmentalization and its phosphorylation as in the pretangle stage of Alzheimer's disease. Am J Pathol. 1999 Jan;154(1):255-70.

Bronfman FC, Moechars D, Van Leuven F. Acetylcholinesterase-positive fiber deafferentation and cell shrinkage in the septohippocampal pathway of aged amyloid precursor protein london mutant transgenic mice. Neurobiol Dis. 2000 Jun;7(3):152-68.

Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Brain Res Rev. 2000 Aug;33(1):95-130.

Butner KA, Kirschner MW. Tau protein binds to microtubules through a flexible array of distributed weak sites. J Cell Biol. 1991 Nov;115(3):717-30.

Busciglio J, Lorenzo A, Yeh J, Yankner BA. beta-amyloid fibrils induce tau phosphorylation and loss of microtubule binding. Neuron. 1995 Apr;14(4):879-88.

Buxbaum JN. Diseases of protein conformation: what do in vitro experiments tell us about in vivo diseases? Trends Biochem Sci. 2003 Nov;28(11):585-92.

Calhoun ME, Wiederhold KH, Abramowski D, Phinney AL, Probst A, Sturchler-Pierrat C, Staufenbiel M, Sommer B, Jucker M. Neuron loss in APP transgenic mice. Nature. 1998 Oct 22;395(6704):755-6.

Cappai R, White AR. Amyloid beta. Int J Biochem Cell Biol. 1999 Sep;31(9):885-9.

Carrell RW, Lomas DA. Conformational disease. Lancet. 1997 Jul 12;350(9071):134-8.

Cassimeris L.Regulation of microtubule dynamic instability. Cell Motil Cytoskeleton. 1993;26(4):275-81.

Chen G, Huang LD, Jiang YM, Manji HK. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. J Neurochem. 1999 Mar;72(3):1327-30.

Chishti MA, Yang DS, Janus C, Phinney AL, Horne P, Pearson J, Strome R, Zuker N, Loukides J, French J, Turner S, Lozza G, Grilli M, Kunicki S, Morissette C, Paquette J, Gervais F, Bergeron C, Fraser PE, Carlson GA, George-Hyslop PS, Westaway D. Early-onset amyloid deposition and cognitive deficits in transgenic mice expressing a double mutant form of amyloid precursor protein 695. J Biol Chem. 2001 Jun 15;276(24):21562-70.

Chiti F, Webster P, Taddei N, Clark A, Stefani M, Ramponi G, Dobson CM. Designing conditions for in vitro formation of amyloid protofilaments and fibrils. Proc Natl Acad Sci U S A. 1999 Mar 30;96(7):3590-4.

Chiti F, Stefani M, Taddei N, Ramponi G, Dobson CM. Rationalization of the effects of mutations on peptide and protein aggregation rates. Nature. 2003 Aug 14;424(6950):805-8.

Citron M, Westaway D, Xia W, Carlson G, Diehl T, Levesque G, Johnson-Wood K, Lee M, Seubert P, Davis A, Kholodenko D, Motter R, Sherrington R, Perry B, Yao H, Strome R, Lieberburg I, Rommens J, Kim S, Schenk D, Fraser P, St George Hyslop P, Selkoe DJ. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. Nat Med. 1997 Jan;3(1):67-72.

Clark LN, Poorkaj P, Wszolek Z, Geschwind DH, Nasreddine ZS, Miller B, Li D, Payami H, Awert F, Markopoulou K, Andreadis A, D'Souza I, Lee VM, Reed L, Trojanowski JQ, Zhukareva V, Bird T, Schellenberg G, Wilhelmsen KC. Pathogenic implications of mutations in the tau gene in pallido-ponto-nigral degeneration and related neurodegenerative disorders linked to chromosome 17. Proc Natl Acad Sci U S A. 1998 Oct 27;95(22):13103-7.

Clark CM, Karlawish JH. Alzheimer disease: current concepts and emerging diagnostic and therapeutic strategies. Ann Intern Med. 2003 Mar 4;138(5):400-10.

Clippingdale AB, Wade JD, Barrow CJ. The amyloid-beta peptide and its role in Alzheimer's disease. J Pept Sci. 2001 May;7(5):227-49.

Collie A, Maruff P, Shafiq-Antonacci R, Smith M, Hallup M, Schofield PR, Masters CL, Currie J. Memory decline in healthy older people: implications for identifying mild cognitive impairment. Neurology. 2001 Jun 12;56(11):1533-8.

Dash PK, Moore AN, Orsi SA. Blockade of gamma-secretase activity within the hippocampus enhances long-term memory. Biochem Biophys Res Commun. 2005 Dec 16;338(2):777-82. Epub 2005 Oct 11.

Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB. ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci. 2005 Jun;8(6):752-8.

DeMattos RB, Bales KR, Cummins DJ, Dodart JC, Paul SM, Holtzman DM. Peripheral anti-A beta antibody alters CNS and plasma A beta clearance and decreases brain A beta burden in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. 2001 Jul 17;98(15):8850-5. Epub 2001 Jul 3.

De Strooper B. Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex. Neuron. 2003 Apr 10;38(1):9-12.

DeTure MA, Zhang EY, Bubb MR, Purich DL. In vitro polymerization of embryonic MAP-2c and fragments of the MAP-2 microtubule binding region into structures resembling paired helical filaments. J Biol Chem. 1996 Dec 20;271(51):32702-6.

Dickson DW, Crystal HA, Mattiace LA, Masur DM, Blau AD, Davies P, Yen SH, Aronson MK. Identification of normal and pathological aging in prospectively studied nondemented elderly humans. Neurobiol Aging. 1992 Jan-Feb;13(1):179-89.

Dickson DW. The pathogenesis of senile plaques. J Neuropathol Exp Neurol. 1997 Apr;56(4):321-39.

Dobson CM. Protein misfolding, evolution and disease. Trends Biochem Sci. 1999 Sep;24(9):329-32.

Dobson CM. Protein folding and misfolding. Nature. 2003 Dec 18;426(6968):884-90.

Dobson CM. Experimental investigation of protein folding and misfolding. Methods. 2004 Sep;34(1):4-14.

Dodart JC, Bales KR, Gannon KS, Greene SJ, DeMattos RB, Mathis C, DeLong CA, Wu S, Wu X, Holtzman DM, Paul SM. Immunization reverses memory deficits without reducing brain Abeta burden in Alzheimer's disease model. Nat Neurosci. 2002 May;5(5):452-7.

Doerfler P, Shearman MS, Perlmutter RM. Presenilin-dependent gamma-secretase activity modulates thymocyte development. Proc Natl Acad Sci U S A. 2001 Jul 31;98(16):9312-7. Epub 2001 Jul 24.

Drechsel DN, Hyman AA, Cobb MH, Kirschner MW. Modulation of the dynamic instability of tubulin assembly by the microtubule-associated protein tau. Mol Biol Cell. 1992 Oct;3(10):1141-54.

Duff K, Eckman C, Zehr C, Yu X, Prada CM, Perez-tur J, Hutton M, Buee L, Harigaya Y, Yager D, Morgan D, Gordon MN, Holcomb L, Refolo L, Zenk B, Hardy J, Younkin S. Increased amyloid-beta42(43) in brains of mice expressing mutant presenilin 1. Nature. 1996 Oct 24;383(6602):710-3.

Duff K, Planel E. Untangling memory deficits. Nat Med. 2005 Aug;11(8):826-7.

Ebly EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. Neurology. 1994 Sep;44(9):1593-600.

Emilien G, Beyreuther K, Masters CL, Maloteaux JM. Prospects for pharmacological intervention in Alzheimer disease. Arch Neurol. 2000 Apr;57(4):454-9.

Emmerling MR, Watson MD, Raby CA, Spiegel K. The role of complement in Alzheimer's disease pathology. Biochim Biophys Acta. 2000 Jul 26;1502(1):158-71.

Esch FS, Keim PS, Beattie EC, Blacher RW, Culwell AR, Oltersdorf T, McClure D, Ward PJ. Cleavage of amyloid beta peptide during constitutive processing of its precursor. Science. 1990 Jun 1;248(4959):1122-4.

Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH, Taylor JO. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA. 1989 Nov 10;262(18):2551-6.

Farias GG, Godoy JA, Vazquez MC, Adani R, Meshulam H, Avila J, Amitai G, Inestrosa NC. The anti-inflammatory and cholinesterase inhibitor bifunctional compound IBU-PO protects from beta-amyloid neurotoxicity by acting on Wnt signaling components. Neurobiol Dis. 2005 Feb;18(1):176-83.

Fassbender K, Simons M, Bergmann C, Stroick M, Lutjohann D, Keller P, Runz H, Kuhl S, Bertsch T, von Bergmann K, Hennerici M, Beyreuther K, Hartmann T. Simvastatin strongly reduces levels of Alzheimer's disease beta -amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. Proc Natl Acad Sci U S A. 2001 May 8;98(10):5856-61.

Forstl H, Kurz A. Clinical features of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 1999;249(6):288-90.

Fraser PE, McLachlan DR, Surewicz WK, Mizzen CA, Snow AD, Nguyen JT, Kirschner DA. Conformation and fibrillogenesis of Alzheimer A beta peptides with selected substitution of charged residues. J Mol Biol. 1994 Nov 18;244(1):64-73.

Frenkel D, Maron R, Burt DS, Weiner HL. Nasal vaccination with a proteosome-based adjuvant and glatiramer acetate clears beta-amyloid in a mouse model of Alzheimer disease. J Clin Invest. 2005 Sep;115(9):2423-33.

Friedhoff P, von Bergen M, Mandelkow EM, Davies P, Mandelkow E. A nucleated assembly mechanism of Alzheimer paired helical filaments. Proc Natl Acad Sci U S A. 1998 Dec 22;95(26):15712-7.

Gamblin TC, King ME, Dawson H, Vitek MP, Kuret J, Berry RW, Binder LI. In vitro polymerization of tau protein monitored by laser light scattering: method and application to the study of FTDP-17 mutants. Biochemistry. 2000 May 23;39(20):6136-44.

Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, Clemens J, Donaldson T, Gillespie F, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. Nature. 1995 Feb 9;373(6514):523-7.

Geula C, Wu CK, Saroff D, Lorenzo A, Yuan M, Yankner BA. Aging renders the brain vulnerable to amyloid beta-protein neurotoxicity. Nat Med. 1998 Jul;4(7):827-31.

Glenner GG, Wong CW. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. Biochem Biophys Res Commun. 1984 Aug 16;122(3):1131-5.

Ghiso J, Frangione B. Cerebral amyloidosis, amyloid angiopathy, and their relationship to stroke and dementia. J Alzheimers Dis. 2001 Feb;3(1):65-73.

Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo JM; AN1792(QS-21)-201 Study Team. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology. 2005 May 10;64(9):1553-62.

Goate AM, Haynes AR, Owen MJ, Farrall M, James LA, Lai LY, Mullan MJ, Roques P, Rossor MN, Williamson R, et al. Predisposing locus for Alzheimer's disease on chromosome 21. Lancet. 1989 Feb 18;1(8634):352-5.

Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1991 Feb 21;349(6311):704-6.

Goedert M, Jakes R. Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization. EMBO J. 1990 Dec;9(13):4225-30.

Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. Trends Neurosci. 1993 Nov;16(11):460-5.

Goedert M, Jakes R, Spillantini MG, Hasegawa M, Smith MJ, Crowther RA. Assembly of microtubule-associated protein tau into Alzheimer-like filaments induced by sulphated glycosaminoglycans. Nature. 1996 Oct 10;383(6600):550-3.

Goedert M, Jakes R, Crowther RA. Effects of frontotemporal dementia FTDP-17 mutations on heparin-induced assembly of tau filaments. FEBS Lett. 1999 May 7;450(3):306-11.

Gordon MN, Holcomb LA, Jantzen PT, DiCarlo G, Wilcock D, Boyett KW, Connor K, Melachrino J, O'Callaghan JP, Morgan D. Time course of the development of Alzheimer-like pathology in the doubly transgenic PS1+APP mouse. Exp Neurol. 2002 Feb;173(2):183-95.

Golde TE, Estus S, Usiak M, Younkin LH, Younkin SG. Expression of beta amyloid protein precursor mRNAs: recognition of a novel alternatively spliced form and quantitation in Alzheimer's disease using PCR. Neuron. 1990 Feb;4(2):253-67.

Gomez-Isla T, Price JL, McKeel DW Jr, Morris JC, Growdon JH, Hyman BT. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci. 1996 Jul 15;16(14):4491-500.

Goode BL, Feinstein SC. Identification of a novel microtubule binding and assembly domain in the developmentally regulated inter-repeat region of tau. J Cell Biol. 1994 Mar;124(5):769-82.

Gotz J, Probst A, Spillantini MG, Schafer T, Jakes R, Burki K, Goedert M. Somatodendritic localization and hyperphosphorylation of tau protein in transgenic mice expressing the longest human brain tau isoform. EMBO J. 1995 Apr 3;14(7):1304-13.

Gotz J, Chen F, Barmettler R, Nitsch RM. Tau filament formation in transgenic mice expressing P301L tau. J Biol Chem. 2001 Jan 5;276(1):529-34.

Gotz J, Chen F, van Dorpe J, Nitsch RM. Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. Science. 2001 Aug 24;293(5534):1491-5.

Gotz J, Tolnay M, Barmettler R, Chen F, Probst A, Nitsch RM. Oligodendroglial tau filament formation in transgenic mice expressing G272V tau. Eur J Neurosci. 2001 Jun;13(11):2131-40.

Gowing E, Roher AE, Woods AS, Cotter RJ, Chaney M, Little SP, Ball MJ. Chemical characterization of A beta 17-42 peptide, a component of diffuse amyloid deposits of Alzheimer disease. J Biol Chem. 1994 Apr 15;269(15):10987-90.

Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, White CL 3rd, Araoz C. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. Proc Natl Acad Sci U S A. 1989 Oct;86(19):7611-5.

Growdon JH. Biomarkers of Alzheimer disease. Arch Neurol. 1999 Mar;56(3):281-3.

Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci U S A. 1986 Jul;83(13):4913-7.

Grutzendler J, Morris JC. Cholinesterase inhibitors for Alzheimer's disease. Drugs. 2001;61(1):41-52.

Guijarro JI, Sunde M, Jones JA, Campbell ID, Dobson CM. Amyloid fibril formation by an SH3 domain. Proc Natl Acad Sci U S A. 1998 Apr 14;95(8):4224-8.

Gundersen E, Fan K, Haas K, Huryn D, Steven Jacobsen J, Kreft A, Martone R, Mayer S, Sonnenberg-Reines J, Sun SC, Zhou H. Molecular-modeling based design, synthesis, and activity of substituted piperidines as gamma-secretase inhibitors. Bioorg Med Chem Lett. 2005 Apr 1;15(7):1891-4.

Haass C, De Strooper B. The presenilins in Alzheimer's disease--proteolysis holds the key. Science. 1999 Oct 29;286(5441):916-9.

Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci. 1991 Oct;12(10):383-8.

Hardy J. Amyloid, the presenilins and Alzheimer's disease. Trends Neurosci. 1997 Apr;20(4):154-9.

Hardy J, Duff K, Hardy KG, Perez-Tur J, Hutton M. Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau. Nat Neurosci. 1998 Sep;1(5):355-8.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002 Jul 19;297(5580):353-6.

Harper JD, Lansbury PT Jr. Models of amyloid seeding in Alzheimer's disease and scrapie: mechanistic truths and physiological consequences of the time-dependent solubility of amyloid proteins. Annu Rev Biochem. 1997;66:385-407.

Harper JD, Lieber CM, Lansbury PT Jr. Atomic force microscopic imaging of seeded fibril formation and fibril branching by the Alzheimer's disease amyloid-beta protein. Chem Biol. 1997 Dec;4(12):951-9.

Harper JD, Wong SS, Lieber CM, Lansbury PT. Observation of metastable Abeta amyloid protofibrils by atomic force microscopy. Chem Biol. 1997 Feb;4(2):119-25.

Hartley DM, Walsh DM, Ye CP, Diehl T, Vasquez S, Vassilev PM, Teplow DB, Selkoe DJ. Protofibrillar intermediates of amyloid beta-protein induce acute electrophysiological changes and progressive neurotoxicity in cortical neurons. J Neurosci. 1999 Oct 15;19(20):8876-84.

Hartman RE, Izumi Y, Bales KR, Paul SM, Wozniak DF, Holtzman DM. Treatment with an amyloid-beta antibody ameliorates plaque load, learning deficits, and hippocampal long-term potentiation in a mouse model of Alzheimer's disease. J Neurosci. 2005 Jun 29;25(26):6213-20.

Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003 Aug;60(8):1119-22.

Hendriks L, van Duijn CM, Cras P, Cruts M, Van Hul W, van Harskamp F, Warren A, McInnis MG, Antonarakis SE, Martin JJ, et al. Presenile dementia and cerebral haemorrhage linked to a mutation at codon 692 of the beta-amyloid precursor protein gene. Nat Genet. 1992 Jun;1(3):218-21.

Hetz C, Soto C. Protein misfolding and disease: the case of prion disorders. Cell Mol Life Sci. 2003 Jan;60(1):133-43.

Himmler A, Drechsel D, Kirschner MW, Martin DW Jr. Tau consists of a set of proteins with repeated C-terminal microtubule-binding domains and variable N-terminal domains. Mol Cell Biol. 1989 Apr;9(4):1381-8.

Hirokawa N, Shiomura Y, Okabe S. Tau proteins: the molecular structure and mode of binding on microtubules. J Cell Biol. 1988 Oct;107(4):1449-59.

Hoglund K, Syversen S, Lewczuk P, Wallin A, Wiltfang J, Blennow K. Statin treatment and a disease-specific pattern of beta-amyloid peptides in Alzheimer's disease. Exp Brain Res. 2005 Jul;164(2):205-14.

Holcomb L, Gordon MN, McGowan E, Yu X, Benkovic S, Jantzen P, Wright K, Saad I, Mueller R, Morgan D, Sanders S, Zehr C, O'Campo K, Hardy J, Prada CM, Eckman C, Younkin S, Hsiao K, Duff K. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. Nat Med. 1998 Jan;4(1):97-100.

Holzer M, Holzapfel HP, Zedlick D, Bruckner MK, Arendt T. Abnormally phosphorylated tau protein in Alzheimer's disease: heterogeneity of individual regional distribution and relationship to clinical severity. Neuroscience. 1994 Nov;63(2):499-516.

Hong M, Zhukareva V, Vogelsberg-Ragaglia V, Wszolek Z, Reed L, Miller BI, Geschwind DH, Bird TD, McKeel D, Goate A, Morris JC, Wilhelmsen KC, Schellenberg GD, Trojanowski JQ, Lee VM. Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. Science. 1998 Dec 4;282(5395):1914-7.

Hong L, Koelsch G, Lin X, Wu S, Terzyan S, Ghosh AK, Zhang XC, Tang J. Structure of the protease domain of memapsin 2 (beta-secretase) complexed with inhibitor. Science. 2000 Oct 6;290(5489):150-3.

Horwich AL, Weber-Ban EU, Finley D. Chaperone rings in protein folding and degradation. Proc Natl Acad Sci U S A. 1999 Sep 28;96(20):11033-40.

Hsiao K. Transgenic mice expressing Alzheimer amyloid precursor proteins. Exp Gerontol. 1998 Nov-Dec;33(7-8):883-9.

Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science. 1996 Oct 4;274(5284):99-102.

Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, Pickering-Brown S, Chakraverty S, Isaacs A, Grover A, Hackett J, Adamson J, Lincoln S, Dickson D, Davies P, Petersen RC, Stevens M, de Graaff E, Wauters E, van Baren J, Hillebrand M, Joosse M, Kwon JM, Nowotny P, Che LK, Norton J, Morris JC, Reed LA, Trojanowski J, Basun H, Lannfelt L, Neystat M, Fahn S, Dark F, Tannenberg T, Dodd PR, Hayward N,

Kwok JB, Schofield PR, Andreadis A, Snowden J, Craufurd D, Neary D, Owen F, Oostra BA, Hardy J, Goate A, van Swieten J, Mann D, Lynch T, Heutink P. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998 Jun 18;393(6686):702-5.

Hutton M, Lewis J, Dickson D, Yen SH, McGowan E. Analysis of tauopathies with transgenic mice. Trends Mol Med. 2001 Oct;7(10):467-70.

Hwang SC, Jhon DY, Bae YS, Kim JH, Rhee SG. Activation of phospholipase C-gamma by the concerted action of tau proteins and arachidonic acid. J Biol Chem. 1996 Aug 2;271(31):18342-9.

Irizarry MC, Soriano F, McNamara M, Page KJ, Schenk D, Games D, Hyman BT. Abeta deposition is associated with neuropil changes, but not with overt neuronal loss in the human amyloid precursor protein V717F (PDAPP) transgenic mouse. J Neurosci. 1997 Sep 15;17(18):7053-9.

Itagaki S, McGeer PL, Akiyama H, Zhu S, Selkoe D. Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. J Neuroimmunol. 1989 Oct;24(3):173-82.

Itagaki S, Akiyama H, Saito H, McGeer PL. Ultrastructural localization of complement membrane attack complex (MAC)-like immunoreactivity in brains of patients with Alzheimer's disease. Brain Res. 1994 May 9;645(1-2):78-84.

Iwatsubo T, Odaka A, Suzuki N, Mizusawa H, Nukina N, Ihara Y. Visualization of A beta 42(43) and A beta 40 in senile plaques with end-specific A beta monoclonals: evidence that an initially deposited species is A beta 42(43). Neuron. 1994 Jul;13(1):45-53.

Iwatsubo T, Saido TC, Mann DM, Lee VM, Trojanowski JQ. Full-length amyloid-beta (1-42(43)) and amino-terminally modified and truncated amyloid-beta 42(43) deposit in diffuse plaques. amyloid-beta 42(43) deposit in diffuse plaques. Am J Pathol. 1996 Dec;149(6):1823-30.

Jackson SE. How do small single-domain proteins fold? Fold Des. 1998;3(4):R81-91.

Jantzen PT, Connor KE, DiCarlo G, Wenk GL, Wallace JL, Rojiani AM, Coppola D, Morgan D, Gordon MN. Microglial activation and beta -amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. J Neurosci. 2002 Mar 15;22(6):2246-54.

Janus C, Pearson J, McLaurin J, Mathews PM, Jiang Y, Schmidt SD, Chishti MA, Horne P, Heslin D, French J, Mount HT, Nixon RA, Mercken M, Bergeron C, Fraser PE, St George-Hyslop P, Westaway D. A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. Nature. 2000 Dec 21-28;408(6815):979-82.

Jarrett JT, Berger EP, Lansbury PT Jr. The C-terminus of the beta protein is critical in amyloidogenesis. Ann N Y Acad Sci. 1993 Sep 24;695:144-8.

Jarrett JT, Berger EP, Lansbury PT Jr. The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease. Biochemistry. 1993 May 11;32(18):4693-7.

Jarrett JT, Lansbury PT Jr. Seeding "one-dimensional crystallization" of amyloid: a pathogenic mechanism in Alzheimer's disease and scrapie? Cell. 1993 Jun 18;73(6):1055-8.

Jellinger KA. Alzheimer disease and cerebrovascular pathology: an update. J Neural Transm. 2002 May;109(5-6):813-36.

Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet. 2000 Nov 11;356(9242):1627-31.

Joachim CL, Morris JH, Selkoe DJ. Diffuse senile plaques occur commonly in the cerebellum in Alzheimer's disease. Am J Pathol. 1989 Aug;135(2):309-19.

Kampers T, Friedhoff P, Biernat J, Mandelkow EM, Mandelkow E. RNA stimulates aggregation of microtubule-associated protein tau into Alzheimer-like paired helical filaments. FEBS Lett. 1996 Dec 16;399(3):344-9.

Kang J, Lemaire HG, Unterbeck A, Salbaum JM, Masters CL, Grzeschik KH, Multhaup G, Beyreuther K, Muller-Hill B. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature. 1987 Feb 19-25;325(6106):733-6.

Kayed R, Bernhagen J, Greenfield N, Sweimeh K, Brunner H, Voelter W, Kapurniotu A. Conformational transitions of islet amyloid polypeptide (IAPP) in amyloid formation in vitro. J Mol Biol. 1999 Apr 9;287(4):781-96.

Kehoe PG, Russ C, McIlory S, Williams H, Holmans P, Holmes C, Liolitsa D, Vahidassr D, Powell J, McGleenon B, Liddell M, Plomin R, Dynan K, Williams N, Neal J, Cairns NJ, Wilcock G, Passmore P, Lovestone S, Williams J, Owen MJ. Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. Nat Genet. 1999 Jan;21(1):71-2.

Kelly JW. Alternative conformations of amyloidogenic proteins govern their behavior. Curr Opin Struct Biol. 1996 Feb;6(1):11-7.

Kelly JW. The alternative conformations of amyloidogenic proteins and their multi-step assembly pathways. Curr Opin Struct Biol. 1998 Feb;8(1):101-6.

Kelly PH, Bondolfi L, Hunziker D, Schlecht HP, Carver K, Maguire E, Abramowski D, Wiederhold KH, Sturchler-Pierrat C, Jucker M, Bergmann R, Staufenbiel M, Sommer B. Progressive age-related impairment of cognitive behavior in APP23 transgenic mice. Neurobiol Aging. 2003 Mar-Apr;24(2):365-78.

Kidd M, Allsop D, Landon M. Senile plaque amyloid, paired helical filaments, and cerebrovascular amyloid in Alzheimer's disease are all deposits of the same protein. Lancet. 1985 Feb 2;1(8423):278.

Kim TW, Tanzi RE. Presenilins and Alzheimer's disease. Curr Opin Neurobiol. 1997 Oct;7(5):683-8.

King ME, Ahuja V, Binder LI, Kuret J. Ligand-dependent tau filament formation: implications for Alzheimer's disease progression. Biochemistry. 1999 Nov 9;38(45):14851-9.

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 Sep 1;69(5):567-77.

Kitaguchi N, Takahashi Y, Tokushima Y, Shiojiri S, Ito H. Novel precursor of Alzheimer's disease amyloid protein shows protease inhibitory activity. Nature. 1988 Feb 11;331(6156):530-2.

Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001 Jun 16;322(7300):1447-51.

Klein WL, Krafft GA, Finch CE. Targeting small Abeta oligomers: the solution to an Alzheimer's disease conundrum? Trends Neurosci. 2001 Apr;24(4):219-24.

Knopman D. Cerebrospinal fluid beta-amyloid and tau proteins for the diagnosis of Alzheimer disease. Arch Neurol. 2001 Mar;58(3):349-50.

Kosik KS, Orecchio LD, Binder L, Trojanowski JQ, Lee VM, Lee G. Epitopes that span the tau molecule are shared with paired helical filaments. Neuron. 1988 Nov;1(9):817-25.

Kosik KS. The molecular and cellular pathology of Alzheimer neurofibrillary lesions. J Gerontol. 1989 May;44(3):B55-8.

Kosik KS, Orecchio LD, Bakalis S, Neve RL. Developmentally regulated expression of specific tau sequences. Neuron. 1989 Apr;2(4):1389-97.

Kumar-Singh S, Dewachter I, Moechars D, Lubke U, De Jonghe C, Ceuterick C, Checler F, Naidu A, Cordell B, Cras P, Van Broeckhoven C, Van Leuven F. Behavioral disturbances without amyloid deposits in mice overexpressing human amyloid precursor protein with Flemish (A692G) or Dutch (E693Q) mutation. Neurobiol Dis. 2000 Feb;7(1):9-22.

Lamb BT, Bardel KA, Kulnane LS, Anderson JJ, Holtz G, Wagner SL, Sisodia SS, Hoeger EJ. Amyloid production and deposition in mutant amyloid precursor protein and presenilin-1 yeast artificial chromosome transgenic mice. Nat Neurosci. 1999 Aug;2(8):695-7.

Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M, Morgan TE, Rozovsky I, Trommer B, Viola KL, Wals P, Zhang C, Finch CE, Krafft GA, Klein WL. Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. Proc Natl Acad Sci U S A. 1998 May 26;95(11):6448-53.

Lansbury PT Jr. Structural neurology: are seeds at the root of neuronal degeneration? Neuron. 1997 Dec;19(6):1151-4.

Lanz TA, Hosley JD, Adams WJ, Merchant KM. Studies of Abeta pharmacodynamics in the brain, cerebrospinal fluid, and plasma in young (plaque-free) Tg2576 mice using the gamma-secretase inhibitor N2-[(2S)-2-(3,5-difluorophenyl)-2-hydroxyethanoyl]-N1-[(7S)-5-methyl-6-oxo-6,7-dihydro-5H-dibenzo[b,d]azepin-7-yl]-L-alaninamide (LY-411575). J Pharmacol Exp Ther. 2004 Apr;309(1):49-55.

Lau LF, Seymour PA, Sanner MA, Schachter JB. Cdk5 as a drug target for the treatment of Alzheimer's disease. J Mol Neurosci. 2002 Dec;19(3):267-73.

Lau LF, Schachter JB, Seymour PA, Sanner MA. Tau protein phosphorylation as a therapeutic target in Alzheimer's disease. Curr Top Med Chem. 2002 Apr;2(4):395-415.

Launer LJ. Nonsteroidal anti-inflammatory drugs and Alzheimer disease: what's next? JAMA. 2003 Jun 4;289(21):2865-7.

Lautenschlager NT, Cupples LA, Rao VS, Auerbach SA, Becker R, Burke J, Chui H, Duara R, Foley EJ, Glatt SL, Green RC, Jones R, Karlinsky H, Kukull WA, Kurz A, Larson EB, Martelli K, Sadovnick AD, Volicer L, Waring SC, Growdon JH, Farrer LA. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old? Neurology. 1996 Mar;46(3):641-50.

Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annu Rev Neurosci. 2001;24:1121-59.

Lee M, Bard F, Johnson-Wood K, Lee C, Hu K, Griffith SG, Black RS, Schenk D, Seubert P. Abeta42 immunization in Alzheimer's disease generates Abeta N-terminal antibodies. Ann Neurol. 2005 Sep;58(3):430-5.

Lee EB, Leng LZ, Lee VM, Trojanowski JQ. Meningoencephalitis associated with passive immunization of a transgenic murine model of Alzheimer's amyloidosis. FEBS Lett. 2005 May 9;579(12):2564-8.

Lemere CA, Blusztajn JK, Yamaguchi H, Wisniewski T, Saido TC, Selkoe DJ. Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: implications for initial events in amyloid plaque formation. Neurobiol Dis. 1996 Feb;3(1):16-32.

Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science. 1995 Aug 18;269(5226):973-7.

Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul Murphy M, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P, Hutton M. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat Genet. 2000 Aug;25(4):402-5.

Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science. 2001 Aug 24;293(5534):1487-91.

Lewis SJ, Smith AL, Neduvelil JG, Stevenson GI, Lindon MJ, Jones AB, Shearman MS, Beher D, Clarke E, Best JD, Peachey JE, Harrison T, Castro JL. A novel series of potent gamma-secretase inhibitors based on a benzobicyclo[4.2.1]nonane core. Bioorg Med Chem Lett. 2005 Jan 17;15(2):373-8.

Lim GP, Yang F, Chu T, Gahtan E, Ubeda O, Beech W, Overmier JB, Hsiao-Ashec K, Frautschy SA, Cole GM. Ibuprofen effects on Alzheimer pathology and open field activity in APPsw transgenic mice. Neurobiol Aging. 2001 Nov-Dec;22(6):983-91.

Lippa CF, Nee LE, Mori H, St George-Hyslop P. Abeta-42 deposition precedes other changes in PS-1 Alzheimer's disease. Lancet. 1998 Oct 3;352(9134):1117-8.

Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H, Hofman A. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(11 Suppl 5):S4-9.

LoPresti P, Szuchet S, Papasozomenos SC, Zinkowski RP, Binder LI. Functional implications for the microtubule-associated protein tau: localization in oligodendrocytes. Proc Natl Acad Sci U S A. 1995 Oct 24;92(22):10369-73.

Loy R, Tariot PN. Neuroprotective properties of valproate: potential benefit for AD and tauopathies. J Mol Neurosci. 2002 Dec;19(3):303-7.

Ludin B, Matus A. The neuronal cytoskeleton and its role in axonal and dendritic plasticity. Hippocampus. 1993;3 Spec No:61-71.

Lue LF, Kuo YM, Roher AE, Brachova L, Shen Y, Sue L, Beach T, Kurth JH, Rydel RE, Rogers J. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. Am J Pathol. 1999 Sep;155(3):853-62.

Luo Y, Bolon B, Kahn S, Bennett BD, Babu-Khan S, Denis P, Fan W, Kha H, Zhang J, Gong Y, Martin L, Louis JC, Yan Q, Richards WG, Citron M, Vassar R. Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation. Nat Neurosci. 2001 Mar;4(3):231-2.

Maioli E, Torricelli C, Santucci A, Pacini A. Molecular assembly of endogenous and synthetic big atrial natriuretic peptide (ANP) and its amyloidogenic implications. Biochim Biophys Acta. 2000 Jan 3;1500(1):31-40.

Martin LJ, Sisodia SS, Koo EH, Cork LC, Dellovade TL, Weidemann A, Beyreuther K, Masters C, Price DL. Amyloid precursor protein in aged nonhuman primates. Proc Natl Acad Sci U S A. 1991 Feb 15;88(4):1461-5.

Masliah E, Mallory M, Hansen L, Alford M, Albright T, Terry R, Shapiro P, Sundsmo M, Saitoh T. Immunoreactivity of CD45, a protein phosphotyrosine phosphatase, in Alzheimer's disease. Acta Neuropathol (Berl). 1991;83(1):12-20.

Masliah E, Ellisman M, Carragher B, Mallory M, Young S, Hansen L, DeTeresa R, Terry RD. Three-dimensional analysis of the relationship between synaptic pathology and neuropil threads in Alzheimer disease. J Neuropathol Exp Neurol. 1992 Jul;51(4):404-14.

Masse I, Bordet R, Deplanque D, Al Khedr A, Richard F, Libersa C, Pasquier F. Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2005 Dec;76(12):1624-9.

Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc Natl Acad Sci U S A. 1985 Jun;82(12):4245-9.

Masters CL, Cappai R, Barnham KJ, Villemagne VL. Molecular mechanisms for Alzheimer's disease: implications for neuroimaging and therapeutics. J Neurochem. 2006 Jun;97(6):1700-25.

Mattson MP, Cheng B, Culwell AR, Esch FS, Lieberburg I, Rydel RE. Evidence for excitoprotective and intraneuronal calcium-regulating roles for secreted forms of the beta-amyloid precursor protein. Neuron. 1993 Feb;10(2):243-54.

McGeer PL, McGeer EG. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Res Brain Res Rev. 1995 Sep;21(2):195-218.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939-44.

McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, Bush AI, Masters CL. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999 Dec;46(6):860-6.

Michaelis ML. Drugs targeting Alzheimer's disease: some things old and some things new. J Pharmacol Exp Ther. 2003 Mar;304(3):897-904.

Miller CC, Brion JP, Calvert R, Chin TK, Eagles PA, Downes MJ, Flament-Durand J, Haugh M, Kahn J, Probst A. Alzheimer's paired helical filaments share epitopes with neurofilament side arms. EMBO J. 1986 Feb;5(2):269-76.

Milner LA, Bigas A. Notch as a mediator of cell fate determination in hematopoiesis: evidence and speculation. Blood. 1999 Apr 15;93(8):2431-48.

Milward EA, Papadopoulos R, Fuller SJ, Moir RD, Small D, Beyreuther K, Masters CL. The amyloid protein precursor of Alzheimer's disease is a mediator of the effects of nerve growth factor on neurite outgrowth. Neuron. 1992 Jul;9(1):129-37.

Moechars D, Dewachter I, Lorent K, Reverse D, Baekelandt V, Naidu A, Tesseur I, Spittaels K, Haute CV, Checler F, Godaux E, Cordell B, Van Leuven F. Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. J Biol Chem. 1999 Mar 5;274(10):6483-92.

Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, Arendash GW. A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. Nature. 2000 Dec 21-28;408(6815):982-5.

Morihara T, Teter B, Yang F, Lim GP, Boudinot S, Boudinot FD, Frautschy SA, Cole GM. Ibuprofen suppresses interleukin-1beta induction of pro-amyloidogenic alpha1-antichymotrypsin to ameliorate beta-amyloid (Abeta) pathology in Alzheimer's models. Neuropsychopharmacology. 2005 Jun;30(6):1111-20.

Morishima-Kawashima M, Hasegawa M, Takio K, Suzuki M, Yoshida H, Watanabe A, Titani K, Ihara Y. Hyperphosphorylation of tau in PHF. Neurobiol Aging. 1995 May-Jun;16(3):365-71

Mori H, Kondo J, Ihara Y. Ubiquitin is a component of paired helical filaments in Alzheimer's disease. Science. 1987 Mar 27;235(4796):1641-4.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED, Clark C. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989 Sep;39(9):1159-65.

Morris JC. Classification of dementia and Alzheimer's disease. Acta Neurol Scand Suppl. 1996;165:41-50.

Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol. 2001 Mar;58(3):397-405.

Mullan M, Crawford F, Axelman K, Houlden H, Lilius L, Winblad B, Lannfelt L. A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid. Nat Genet. 1992 Aug;1(5):345-7.

Munch G, Robinson SR. Potential neurotoxic inflammatory responses to Abeta vaccination in humans. J Neural Transm. 2002 Jul;109(7-8):1081-7.

Naruse S, Igarashi S, Kobayashi H, Aoki K, Inuzuka T, Kaneko K, Shimizu T, Iihara K, Kojima T, Miyatake T, et al. Mis-sense mutation Val----Ile in exon 17 of amyloid precursor protein gene in Japanese familial Alzheimer's disease. Lancet. 1991 Apr 20;337(8747):978-9.

Naslund J, Haroutunian V, Mohs R, Davis KL, Davies P, Greengard P, Buxbaum JD. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. JAMA. 2000 Mar 22-29;283(12):1571-7.

Neve RL, Harris P, Kosik KS, Kurnit DM, Donlon TA. Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. Brain Res. 1986 Dec;387(3):271-80.

Nicoll JA, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: a case report. Nat Med. 2003 Apr;9(4):448-52.

Nilsberth C, Westlind-Danielsson A, Eckman CB, Condron MM, Axelman K, Forsell C, Stenh C, Luthman J, Teplow DB, Younkin SG, Naslund J, Lannfelt L. The 'Arctic' APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation. Nat Neurosci. 2001 Sep;4(9):887-93.

Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005 May 27;308(5726):1314-8.

Nishimoto I, Okamoto T, Matsuura Y, Takahashi S, Okamoto T, Murayama Y, Ogata E. Alzheimer amyloid protein precursor complexes with brain GTP-binding protein G(o). Nature. 1993 Mar 4;362(6415):75-9.

Nukina N, Ihara Y. One of the antigenic determinants of paired helical filaments is related to tau protein. J Biochem (Tokyo). 1986 May;99(5):1541-4.

Oda T, Wals P, Osterburg HH, Johnson SA, Pasinetti GM, Morgan TE, Rozovsky I, Stine WB, Snyder SW, Holzman TF, et al. Clusterin (apoJ) alters the aggregation of amyloid beta-peptide (A beta 1-42) and forms slowly sedimenting A beta complexes that cause oxidative stress. Exp Neurol. 1995 Nov;136(1):22-31.

Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003 Jul 31;39(3):409-21.

Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM. Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. Neuron. 2004 Aug 5;43(3):321-32.

Olaisen B, Teisberg P, Gedde-Dahl T Jr. The locus for apolipoprotein E (apoE) is linked to the complement component C3 (C3) locus on chromosome 19 in man. Hum Genet. 1982;62(3):233-6.

Olshansky SJ. The human life span: are we reaching the outer limits? Geriatrics. 1993 Mar;48(3):85-8.

Olson RE. Discovery of the lipoproteins, their role in fat transport and their significance as risk factors. J Nutr. 1998 Feb;128(2 Suppl):439S-443S.

Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology. 2003 Jul 8;61(1):46-54.

Perez M, Valpuesta JM, Medina M, Montejo de Garcini E, Avila J. Polymerization of tau into filaments in the presence of heparin: the minimal sequence required for tau-tau interaction. J Neurochem. 1996 Sep;67(3):1183-90.

Pericak-Vance MA, Bass MP, Yamaoka LH, Gaskell PC, Scott WK, Terwedow HA, Menold MM, Conneally PM, Small GW, Vance JM, Saunders AM, Roses AD, Haines JL. Complete genomic screen in late-onset familial Alzheimer disease. Evidence for a new locus on chromosome 12. JAMA. 1997 Oct 15;278(15):1237-41.

Perlmutter LS, Scott SA, Barron E, Chui HC. MHC class II-positive microglia in human brain: association with Alzheimer lesions. J Neurosci Res. 1992 Dec;33(4):549-58.

Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. Br Med J. 1978 Nov 25;2(6150):1457-9.

Perry G, Rizzuto N, Autilio-Gambetti L, Gambetti P. Paired helical filaments from Alzheimer disease patients contain cytoskeletal components. Proc Natl Acad Sci U S A. 1985 Jun;82(11):3916-20.

Perry G, Friedman R, Shaw G, Chau V. Ubiquitin is detected in neurofibrillary tangles and senile plaque neurites of Alzheimer disease brains. Proc Natl Acad Sci U S A. 1987 May;84(9):3033-6.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999 Mar;56(3):303-8.

Pike CJ, Walencewicz-Wasserman AJ, Kosmoski J, Cribbs DH, Glabe CG, Cotman CW. Structure-activity analyses of beta-amyloid peptides: contributions of the beta 25-35 region to aggregation and neurotoxicity. J Neurochem. 1995 Jan;64(1):253-65.

Ponte P, Gonzalez-DeWhitt P, Schilling J, Miller J, Hsu D, Greenberg B, Davis K, Wallace W, Lieberburg I, Fuller F. A new A4 amyloid mRNA contains a domain homologous to serine proteinase inhibitors. Nature. 1988 Feb 11;331(6156):525-7.

Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, Andreadis A, Wiederholt WC, Raskind M, Schellenberg GD. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann Neurol. 1998 Jun;43(6):815-25.

Price DL, Sisodia SS. Mutant genes in familial Alzheimer's disease and transgenic models. Annu Rev Neurosci. 1998;21:479-505.

Probst A, Gotz J, Wiederhold KH, Tolnay M, Mistl C, Jaton AL, Hong M, Ishihara T, Lee VM, Trojanowski JQ, Jakes R, Crowther RA, Spillantini MG, Burki K, Goedert M. Axonopathy and amyotrophy in mice transgenic for human four-repeat tau protein. Acta Neuropathol (Berl). 2000 May;99(5):469-81.

Prusiner SB. Prions. Proc Natl Acad Sci U S A. 1998 Nov 10;95(23):13363-83.

Racke MM, Boone LI, Hepburn DL, Parsadainian M, Bryan MT, Ness DK, Piroozi KS, Jordan WH, Brown DD, Hoffman WP, Holtzman DM, Bales KR, Gitter BD, May PC, Paul SM, DeMattos RB. Exacerbation of cerebral amyloid angiopathy-associated microhemorrhage in amyloid precursor protein transgenic mice by immunotherapy is dependent on antibody recognition of deposited forms of amyloid beta. J Neurosci. 2005 Jan 19;25(3):629-36.

Ramirez BG, Blazquez C, Gomez del Pulgar T, Guzman M, de Ceballos ML. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. J Neurosci. 2005 Feb 23;25(8):1904-13.

Rapoport M, Dawson HN, Binder LI, Vitek MP, Ferreira A. Tau is essential to beta -amyloid-induced neurotoxicity. Proc Natl Acad Sci U S A. 2002 Apr 30;99(9):6364-9.

Refolo LM, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, Tint GS, Sambamurti K, Duff K, Pappolla MA. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiol Dis. 2000 Aug;7(4):321-31.

Roberds SL, Anderson J, Basi G, Bienkowski MJ, Branstetter DG, Chen KS, Freedman SB, Frigon NL, Games D, Hu K, Johnson-Wood K, Kappenman KE, Kawabe TT, Kola I, Kuehn R, Lee M, Liu W, Motter R, Nichols NF, Power M, Robertson DW, Schenk D, Schoor M, Shopp GM, Shuck ME, Sinha S, Svensson KA, Tatsuno G, Tintrup H, Wijsman J, Wright S, McConlogue L. BACE knockout mice are healthy despite lacking the primary beta-secretase activity in brain: implications for Alzheimer's disease therapeutics. Hum Mol Genet. 2001 Jun 1;10(12):1317-24.

Rocca WA, Hofman A, Brayne C, Breteler MM, Clarke M, Copeland JR, Dartigues JF, Engedal K, Hagnell O, Heeren TJ, et al. Frequency and distribution of Alzheimer's disease in Europe: a collaborative study of 1980-1990 prevalence findings. The EURODEM-Prevalence Research Group. Ann Neurol. 1991 Sep;30(3):381-90.

Rochet JC, Lansbury PT Jr. Amyloid fibrillogenesis: themes and variations. Curr Opin Struct Biol. 2000 Feb;10(1):60-8.

Rodriguez-Martin T, Garcia-Blanco MA, Mansfield SG, Grover AC, Hutton M, Yu Q, Zhou J, Anderton BH, Gallo JM. Reprogramming of tau alternative splicing by spliceosome-mediated RNA trans-splicing: implications for tauopathies. Proc Natl Acad Sci U S A. 2005 Oct 25;102(43):15659-64.

Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature. 1995 Aug 31;376(6543):775-8.

Rogers J, Cooper NR, Webster S, Schultz J, McGeer PL, Styren SD, Civin WH, Brachova L, Bradt B, Ward P, et al. Complement activation by beta-amyloid in Alzheimer disease. Proc Natl Acad Sci U S A. 1992 Nov 1;89(21):10016-20.

Rogers J, Webster S, Lue LF, Brachova L, Civin WH, Emmerling M, Shivers B, Walker D, McGeer P. Inflammation and Alzheimer's disease pathogenesis. Neurobiol Aging. 1996 Sep-Oct;17(5):681-6.

Saitoh T, Sundsmo M, Roch JM, Kimura N, Cole G, Schubert D, Oltersdorf T, Schenk DB. Secreted form of amyloid beta protein precursor is involved in the growth regulation of fibroblasts. Cell. 1989 Aug 25;58(4):615-22.

Santacruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, Guimaraes A, DeTure M, Ramsden M, McGowan E, Forster C, Yue M, Orne J, Janus C, Mariash A, Kuskowski M, Hyman B, Hutton M, Ashe KH. Tau suppression in a neurodegenerative mouse model improves memory function. Science. 2005 Jul 15;309(5733):476-81.

Schellenberg GD. Molecular genetics of familial Alzheimer's disease. Arzneimittelforschung. 1995 Mar;45(3A):418-24.

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 Jul 8;400(6740):173-7.

Scherzinger E, Sittler A, Schweiger K, Heiser V, Lurz R, Hasenbank R, Bates GP, Lehrach H, Wanker EE. Self-assembly of polyglutamine-containing huntingtin fragments into amyloid-like fibrils: implications for Huntington's disease pathology. Proc Natl Acad Sci U S A. 1999 Apr 13;96(8):4604-9.

Schmidt ML, Lee VM, Trojanowski JQ. Comparative epitope analysis of neuronal cytoskeletal proteins in Alzheimer's disease senile plaque neurites and neuropil threads. Lab Invest. 1991 Mar;64(3):352-7.

Schoenfeld TA, Obar RA. Diverse distribution and function of fibrous microtubule-associated proteins in the nervous system. Int Rev Cytol. 1994;151:67-137.

Schweers O, Mandelkow EM, Biernat J, Mandelkow E. Oxidation of cysteine-322 in the repeat domain of microtubule-associated protein tau controls the in vitro assembly of paired helical filaments. Proc Natl Acad Sci U S A. 1995 Aug 29;92(18):8463-7.

Selkoe DJ, Ihara Y, Salazar FJ. Alzheimer's disease: insolubility of partially purified paired helical filaments in sodium dodecyl sulfate and urea. Science. 1982 Mar 5;215(4537):1243-5.

Selkoe DJ, Abraham CR, Podlisny MB, Duffy LK. Isolation of low-molecular-weight proteins from amyloid plaque fibers in Alzheimer's disease. J Neurochem. 1986 Jun;46(6):1820-34.

Selkoe DJ, Bell DS, Podlisny MB, Price DL, Cork LC. Conservation of brain amyloid proteins in aged mammals and humans with Alzheimer's disease. Conservation of brain amyloid proteins in aged mammals and humans with Alzheimer's disease. Science. 1987 Feb 20;235(4791):873-7.

Selkoe DJ. Alzheimer's disease. In the beginning... Nature. 1991 Dec 12;354(6353):432-3.

Selkoe DJ. The cell biology of beta-amyloid precursor protein and presenilin in Alzheimer's disease. Trends Cell Biol. 1998 Nov;8(11):447-53.

Selkoe DJ. Translating cell biology into therapeutic advances in Alzheimer's disease. Nature. 1999 Jun 24;399(6738 Suppl):A23-31.

Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev. 2001 Apr;81(2):741-66.

Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. 2002 Oct 25;298(5594):789-91.

Selkoe DJ. Folding proteins in fatal ways. Nature. 2003 Dec 18;426(6968):900-4.

Senior K. Dosing in phase II trial of Alzheimer's vaccine suspended. Lancet Neurol. 2002 May;1(1):3.

Serpell LC, Sunde M, Blake CC. The molecular basis of amyloidosis. Cell Mol Life Sci. 1997 Dec;53(11-12):871-87.

Serpell LC, Smith JM. Direct visualisation of the beta-sheet structure of synthetic Alzheimer's amyloid. J Mol Biol. 2000 May 26;299(1):225-31.

Seubert P, Vigo-Pelfrey C, Esch F, Lee M, Dovey H, Davis D, Sinha S, Schlossmacher M, Whaley J, Swindlehurst C, et al. Isolation and quantification of soluble Alzheimer's beta-peptide from biological fluids. Nature. 1992 Sep 24;359(6393):325-7.

Sheng JG, Mrak RE, Griffin WS. Glial-neuronal interactions in Alzheimer disease: progressive association of IL-1alpha+ microglia and S100beta+ astrocytes with neurofibrillary tangle stages. J Neuropathol Exp Neurol. 1997 Mar;56(3):285-90.

Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995 Jun 29;375(6534):754-60.

Shin RW, Bramblett GT, Lee VM, Trojanowski JQ. Alzheimer disease A68 proteins injected into rat brain induce codeposits of beta-amyloid, ubiquitin, and alpha 1-antichymotrypsin. Proc Natl Acad Sci U S A. 1993 Jul 15;90(14):6825-8.

Shin RW, Lee VM, Trojanowski JQ. Aluminum modifies the properties of Alzheimer's disease PHF tau proteins in vivo and in vitro. J Neurosci. 1994 Nov;14(11 Pt 2):7221-33.

Shoji M, Golde TE, Ghiso J, Cheung TT, Estus S, Shaffer LM, Cai XD, McKay DM, Tintner R, Frangione B, et al. Production of the Alzheimer amyloid beta protein by normal proteolytic processing. Science. 1992 Oct 2;258(5079):126-9.

Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG, Simons K. Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc Natl Acad Sci U S A. 1998 May 26;95(11):6460-4.

Sinha S, Anderson JP, Barbour R, Basi GS, Caccavello R, Davis D, Doan M, Dovey HF, Frigon N, Hong J, Jacobson-Croak K, Jewett N, Keim P, Knops J, Lieberburg I, Power M, Tan H, Tatsuno G, Tung J, Schenk D, Seubert P, Suomensaari SM, Wang S, Walker D, Zhao J, McConlogue L, John V. Purification and cloning of amyloid precursor protein beta-secretase from human brain. Nature. 1999 Dec 2;402(6761):537-40.

Sisodia SS, Koo EH, Beyreuther K, Unterbeck A, Price DL. Evidence that beta-amyloid protein in Alzheimer's disease is not derived by normal processing. Science. 1990 Apr 27;248(4954):492-5.

Sisodia SS, St George-Hyslop PH. gamma-Secretase, Notch, Abeta and Alzheimer's disease: where do the presenilins fit in? Nat Rev Neurosci. 2002 Apr;3(4):281-90.

Small GW. Investigations into geriatric psychiatry challenges: AAGP Senior Investigator Award 2000. Am J Geriatr Psychiatry. 2000 Fall;8(4):276-83.

Solomon B, Koppel R, Hanan E, Katzav T. Monoclonal antibodies inhibit in vitro fibrillar aggregation of the Alzheimer beta-amyloid peptide. Proc Natl Acad Sci U S A. 1996 Jan 9;93(1):452-5.

Solomon B, Koppel R, Frankel D, Hanan-Aharon E. Disaggregation of Alzheimer beta-amyloid by site-directed mAb. Proc Natl Acad Sci U S A. 1997 Apr 15;94(8):4109-12.

Sontag E, Nunbhakdi-Craig V, Lee G, Brandt R, Kamibayashi C, Kuret J, White CL 3rd, Mumby MC, Bloom GS. Molecular interactions among protein phosphatase 2A, tau, and microtubules. Implications for the regulation of tau phosphorylation and the development of tauopathies. J Biol Chem. 1999 Sep 3;274(36):25490-8.

Sparks DL, Scheff SW, Hunsaker JC 3rd, Liu H, Landers T, Gross DR. Induction of Alzheimer-like beta-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. Exp Neurol. 1994 Mar;126(1):88-94.

Spillantini MG, Murrell JR, Goedert M, Farlow M, Klug A, Ghetti B. Mutations in the tau gene (MAPT) in FTDP-17: The family with Multiple System Tauopathy with Presenile Dementia (MSTD). J Alzheimers Dis. 2006 Aug;9(3 Suppl):373-80.

Spittaels K, Van den Haute C, Van Dorpe J, Bruynseels K, Vandezande K, Laenen I, Geerts H, Mercken M, Sciot R, Van Lommel A, Loos R, Van Leuven F. Prominent axonopathy in the brain and spinal cord of transgenic mice overexpressing four-repeat human tau protein. Am J Pathol. 1999 Dec;155(6):2153-65.

Stalder M, Phinney A, Probst A, Sommer B, Staufenbiel M, Jucker M. Association of microglia with amyloid plaques in brains of APP23 transgenic mice. Am J Pathol. 1999 Jun;154(6):1673-84.

Sternberger NH, Sternberger LA, Ulrich J. Aberrant neurofilament phosphorylation in Alzheimer disease. Proc Natl Acad Sci U S A. 1985 Jun;82(12):4274-6.

St George-Hyslop P, Haines J, Rogaev E, Mortilla M, Vaula G, Pericak-Vance M, Foncin JF, Montesi M, Bruni A, Sorbi S, et al. Genetic evidence for a novel familial Alzheimer's disease locus on chromosome 14. Nat Genet. 1992 Dec;2(4):330-4.

Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild 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 U S A. 1993 Mar 1;90(5):1977-81.

Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, Ledermann B, Burki K, Frey P, Paganetti PA, Waridel C, Calhoun ME, Jucker M, Probst A, Staufenbiel M, Sommer B. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. Proc Natl Acad Sci U S A. 1997 Nov 25;94(24):13287-92.

Sunde M, Blake C. The structure of amyloid fibrils by electron microscopy and X-ray diffraction. Adv Protein Chem. 1997;50:123-59.

Sunde M, Serpell LC, Bartlam M, Fraser PE, Pepys MB, Blake CC. Common core structure of amyloid fibrils by synchrotron X-ray diffraction. J Mol Biol. 1997 Oct 31;273(3):729-39.

Tagliavini F, Giaccone G, Frangione B, Bugiani O. Preamyloid deposits in the cerebral cortex of patients with Alzheimer's disease and nondemented individuals. Neurosci Lett. 1988 Nov 11;93(2-3):191-6.

Takashima A, Honda T, Yasutake K, Michel G, Murayama O, Murayama M, Ishiguro K, Yamaguchi H. Activation of tau protein kinase I/glycogen synthase kinase-3beta by amyloid beta peptide (25-35) enhances phosphorylation of tau in hippocampal neurons. Neurosci Res. 1998 Aug;31(4):317-23.s

Takashima A, Murayama M, Murayama O, Kohno T, Honda T, Yasutake K, Nihonmatsu N, Mercken M, Yamaguchi H, Sugihara S, Wolozin B. Presenilin 1 associates with glycogen synthase kinase-3beta and its substrate tau. Proc Natl Acad Sci U S A. 1998 Aug 4;95(16):9637-41.

Tamaoka A, Odaka A, Ishibashi Y, Usami M, Sahara N, Suzuki N, Nukina N, Mizusawa H, Shoji S, Kanazawa I, et al. APP717 missense mutation affects the ratio of amyloid beta protein species (A beta 1-42/43 and a beta 1-40) in familial Alzheimer's disease brain. J Biol Chem. 1994 Dec 30;269(52):32721-4.

Tanemura K, Akagi T, Murayama M, Kikuchi N, Murayama O, Hashikawa T, Yoshiike Y, Park JM, Matsuda K, Nakao S, Sun X, Sato S, Yamaguchi H, Takashima A. Formation of filamentous tau aggregations in transgenic mice expressing V337M human tau. Neurobiol Dis. 2001 Dec;8(6):1036-45.

Tanemura K, Murayama M, Akagi T, Hashikawa T, Tominaga T, Ichikawa M, Yamaguchi H, Takashima A. Neurodegeneration with tau accumulation in a transgenic mouse expressing V337M human tau. J Neurosci. 2002 Jan 1;22(1):133-41.

Tanzi RE, St George-Hyslop PH, Haines JL, Polinsky RJ, Nee L, Foncin JF, Neve RL, McClatchey AI, Conneally PM, Gusella JF. The genetic defect in familial Alzheimer's disease is not tightly linked to the amyloid beta-protein gene. Nature. 1987 Sep 10-16;329(6135):156-7.

Tanzi RE, McClatchey AI, Lamperti ED, Villa-Komaroff L, Gusella JF, Neve RL. Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease. Nature. 1988 Feb 11;331(6156):528-30.

Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002 Jun 25;58(12):1791-800.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991 Oct;30(4):572-80.

Tolnay M, Probst A. REVIEW: tau protein pathology in Alzheimer's disease and related disorders. Neuropathol Appl Neurobiol. 1999 Jun;25(3):171-87.

Trojanowski JQ, Schmidt ML, Shin RW, Bramblett GT, Rao D, Lee VM. Altered tau and neurofilament proteins in neuro-degenerative diseases: diagnostic implications for Alzheimer's disease and Lewy body dementias. Brain Pathol. 1993 Jan;3(1):45-54.

Trojanowski JQ, Lee VM. Paired helical filament tau in Alzheimer's disease. The kinase connection. Am J Pathol. 1994 Mar;144(3):449-53.

Trojanowski JQ, Lee VM. The role of tau in Alzheimer's disease. Med Clin North Am. 2002 May;86(3):615-27.

Tucker RP. The roles of microtubule-associated proteins in brain morphogenesis: a review. Brain Res Brain Res Rev. 1990 May-Aug;15(2):101-20.

Van Dorpe J, Smeijers L, Dewachter I, Nuyens D, Spittaels K, Van Den Haute C, Mercken M, Moechars D, Laenen I, Kuiperi C, Bruynseels K, Tesseur I, Loos R, Vanderstichele H, Checler F, Sciot R, Van Leuven F. Prominent cerebral amyloid angiopathy in transgenic mice overexpressing the london mutant of human APP in neurons. Am J Pathol. 2000 Oct;157(4):1283-98.

van Es JH, van Gijn ME, Riccio O, van den Born M, Vooijs M, Begthel H, Cozijnsen M, Robine S, Winton DJ, Radtke F, Clevers H. Notch/gamma-secretase inhibition turns proliferative cells in intestinal crypts and adenomas into goblet cells. Nature. 2005 Jun 16;435(7044):959-63.

Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, Citron M. Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science. 1999 Oct 22;286(5440):735-41.

Vekrellis K, Ye Z, Qiu WQ, Walsh D, Hartley D, Chesneau V, Rosner MR, Selkoe DJ. Neurons regulate extracellular levels of amyloid beta-protein via proteolysis by insulin-degrading enzyme. J Neurosci. 2000 Mar 1;20(5):1657-65.

Vinters HV. Cerebral amyloid angiopathy. A critical review. Stroke. 1987 Mar-Apr;18(2):311-24.

Vogelsang GD, Zemlan FP, Dean GE. Hyperpurification of paired helical filaments reveals elevations in hydroxyproline content and a core structure related peptide fragment. Prog Clin Biol Res. 1989;317:791-800.

Wakabayashi K, Mori F, Hasegawa M, Kusumi T, Yoshimura I, Takahashi H, Kaneko S. Co-localization of beta-peptide and phosphorylated tau in astrocytes in a patient with corticobasal degeneration. Neuropathology. 2006 Feb;26(1):66-71.

Walker LC, LeVine H. The cerebral proteopathies: neurodegenerative disorders of protein conformation and assembly. Mol Neurobiol. 2000 Feb-Apr;21(1-2):83-95.

Walsh DM, Lomakin A, Benedek GB, Condron MM, Teplow DB. Amyloid beta-protein fibrillogenesis. Detection of a protofibrillar intermediate. J Biol Chem. 1997 Aug 29;272(35):22364-72.

Walsh DM, Hartley DM, Kusumoto Y, Fezoui Y, Condron MM, Lomakin A, Benedek GB, Selkoe DJ, Teplow DB. Amyloid beta-protein fibrillogenesis. Structure and biological activity of protofibrillar intermediates. J Biol Chem. 1999 Sep 3;274(36):25945-52.

Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature. 2002 Apr 4;416(6880):535-9.

Walsh DM, Klyubin I, Fadeeva JV, Rowan MJ, Selkoe DJ. Amyloid-beta oligomers: their production, toxicity and therapeutic inhibition. Biochem Soc Trans. 2002 Aug;30(4):552-7.

Wang J, Dickson DW, Trojanowski JQ, Lee VM. The levels of soluble versus insoluble brain Abeta distinguish Alzheimer's disease from normal and pathologic aging. Exp Neurol. 1999 Aug;158(2):328-37.

Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, Findlay KA, Smith TE, Murphy MP, Bulter T, Kang DE, Marquez-Sterling N, Golde TE, Koo EH. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature. 2001 Nov 8;414(6860):212-6.

Weiner HL, Selkoe DJ. Inflammation and therapeutic vaccination in CNS diseases. Nature. 2002 Dec 19-26;420(6917):879-84.

Weingarten MD, Lockwood AH, Hwo SY, Kirschner MW. A protein factor essential for microtubule assembly. Proc Natl Acad Sci U S A. 1975 May;72(5):1858-62.

Wertkin AM, Turner RS, Pleasure SJ, Golde TE, Younkin SG, Trojanowski JQ, Lee VM. Human neurons derived from a teratocarcinoma cell line express solely the 695-amino acid amyloid precursor protein and produce intracellular beta-amyloid or A4 peptides. Proc Natl Acad Sci U S A. 1993 Oct 15;90(20):9513-7.

West MJ, Kawas CH, Stewart WF, Rudow GL, Troncoso JC. Hippocampal neurons in pre-clinical Alzheimer's disease. Neurobiol Aging. 2004 Oct;25(9):1205-12.

Wetzel R. Ideas of order for amyloid fibril structure. Structure. 2002 Aug;10(8):1031-6.

Wilcock DM, DiCarlo G, Henderson D, Jackson J, Clarke K, Ugen KE, Gordon MN, Morgan D. Intracranially administered anti-Abeta antibodies reduce beta-amyloid deposition by mechanisms both independent of and associated with microglial activation. J Neurosci. 2003 May 1;23(9):3745-51.

Wille H, Drewes G, Biernat J, Mandelkow EM, Mandelkow E. Alzheimer-like paired helical filaments and antiparallel dimers formed from microtubule-associated protein tau in vitro. J Cell Biol. 1992 Aug;118(3):573-84.

Wilson DM, Binder LI. Polymerization of microtubule-associated protein tau under near-physiological conditions. J Biol Chem. 1995 Oct 13;270(41):24306-14.

Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. Ann Neurol. 1985 Mar;17(3):278-82.

Wong GT, Manfra D, Poulet FM, Zhang Q, Josien H, Bara T, Engstrom L, Pinzon-Ortiz M, Fine JS, Lee HJ, Zhang L, Higgins GA, Parker EM. Chronic treatment with the gamma-secretase inhibitor LY-411,575 inhibits beta-amyloid peptide production and alters lymphopoiesis and intestinal cell differentiation. J Biol Chem. 2004 Mar 26;279(13):12876-82.

Wood JG, Mirra SS, Pollock NJ, Binder LI. Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). Proc Natl Acad Sci U S A. 1986 Jun;83(11):4040-3.

Wood SJ, Wypych J, Steavenson S, Louis JC, Citron M, Biere AL. alpha-synuclein fibrillogenesis is nucleation-dependent. Implications for the pathogenesis of Parkinson's disease. J Biol Chem. 1999 Jul 9;274(28):19509-12.

Xia W. Amyloid inhibitors and Alzheimer's disease. Curr Opin Investig Drugs. 2003 Jan;4(1):55-9.

Yamada M, Tsukagoshi H, Otomo E, Hayakawa M. Cerebral amyloid angiopathy in the aged. J Neurol. 1987 Aug;234(6):371-6.

Yamaguchi H, Hirai S, Morimatsu M, Shoji M, Harigaya Y. Diffuse type of senile plaques in the brains of Alzheimer-type dementia. Acta Neuropathol (Berl). 1988;77(2):113-9.

Yao TM, Tomoo K, Ishida T, Hasegawa H, Sasaki M, Taniguchi T. Aggregation analysis of the microtubule binding domain in tau protein by spectroscopic methods. J Biochem (Tokyo). 2003 Jul;134(1):91-9.

Yen SH, 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 Jan;126(1):81-91.

Younkin SG. Amyloid beta vaccination: reduced plaques and improved cognition. Nat Med. 2001 Jan;7(1):18-9.

Zheng WH, Bastianetto S, Mennicken F, Ma W, Kar S. Amyloid beta peptide induces tau phosphorylation and loss of cholinergic neurons in rat primary septal cultures. Neuroscience. 2002;115(1):201-11.

Zheng YL, Li BS, Amin ND, Albers W, Pant HC. A peptide derived from cyclin-dependent kinase activator (p35) specifically inhibits Cdk5 activity and phosphorylation of tau protein in transfected cells. Eur J Biochem. 2002 Sep;269(18):4427-34.

6. CONCLUSION

The objective of this thesis has been to gain new insights into the mechanisms underlying the initiation of cerebral Aβ-amyloidosis and neurofibrillary pathology using transgenic mouse models of AD.

A major finding of our studies is that cerebral Aβ-amyloidosis can be induced by exogenous, Aβ-rich brain extract, and that intrinsic properties of the Aβ in the extract as well as of the host are crucial for the induction of Aβ accumulation in brain. The present results indicate that Aβ plays a crucial role in β-amyloid induction *in vivo*, but the inability of synthetic Aβ to potently stimulate protein deposition suggests that β-amyloid induction is dependent on a conformation of Aβ and/or cofactors that are specific to the brain. The identification of potential conditions and chaperones that are necessary to transform synthetic Aβ into a potent amyloid-inducing agent will be crucial for the understanding of the *in vivo* mechanisms of cerebral Aβ-amyloidosis. Moreover, our findings demonstrate that the nature of the host is important for the exogenous induction of cerebral Aβ-amyloidosis and support the possibility that Aβ can form multiple proteopathic strains reminiscent of prions. Together, this work also adds indirect support to therapeutic efforts targeted at early-stage amyloid formation.

A second important observation is that neurofibrillary pathology, akin to Aβ-amyloidosis, can also be induced *in vivo* by intracerebral infusion of Aβ-rich brain extract into a susceptible transgenic host. The finding that human extract with low Aβ levels had no tau-inducing activity indicates that soluble Aβ species are potent effectors of tau pathology *in vivo* and further supports the hypothesis that a similar interaction occurs in AD. It remains to be determined whether a particular Aβ assembly is responsible for the induction of tau phenotype. Moreover, our results do not exclude the possibility that factors other than Aβ could also induce neurofibrillary pathology in brain, in view of the many tauopathies associated with neurofibrillary lesions in the absence of Aβ pathology. In this regard, the intracerebral infusion of brain extracts from patients affected by frontotemporal dementia or other demented conditions could help to identify such tau-inducing candidates.

In a third set of experiments, we have provided a thorough characterization of the kinetics of the microglial response to amyloid pathogenesis in the living brain via multiphoton microscopy. The observation that plaque-associated microglia remain very motile at the

plaque-glial interface and exhibit signs of uptake of the Aß peptide, provides compelling evidence of a dynamic process of homeostasis. Notably, the interaction of microglia with plaques could be stimulated by intracerebral infusion of Aß antibody, such that these cells adopted a more macrophagic morphology and were induced to clear existing amyloid deposits. Together, our results highlight the dynamic nature of microglia surrounding amyloid plaques and indicate that these cells are capable of Aβ clearance *in vivo*, holding great potential for the fight against AD.

ABBREVIATIONS

Aβ	beta-amyloid
AD	Alzheimer's disease
ApoE	apolipoprotein E
APP	amyloid precursor protein
BACE	β-site of APP cleaving enzyme
CA	Cornu Ammonis
Cdk5	cyclin-dependent kinase 5
CD	cluster of differentiation molecule
CNS	central nervous system
DNA	deoxyribonucleic acid
FAD	familial Alzheimer's disease
FTDP-17	frontotemporal dementia and parkinsonism linked to chromosome 17
GSK3β	glycogen synthase kinase β
HLA-DR	human lymphocyte antigen-classII-DR
KPI	Kunitz-type of serine protease inhibitor
MAP	microtubule-associated protein
NFL(s)	neurofibrillary lesion(s)
NFT(s)	neurofibrillary tangle(s)
NSAIDs	non-steroidal anti-inflammatory drugs
NT(s)	neuropil thread(s)
PHF(s)	paired helical filament(s)
PS1	presenilin-1
PS2	presenilin-2
RNA	ribonucleic acid
SF(s)	straight filament(s)

CURRICULUM VITAE

Personal Data

Name:	Tristan Hugo Wilfried Bolmont
Place and date of birth:	Paris, March 24th, 1978
Citizenship:	French
Email:	Tbolmont@yahoo.fr
Current address:	Neue Weinsteige 47-49
	72181 Stuttgart
	Germany
	Phone: +49 711 888 2205

Business Address

Institute of Pathology
Neuropathology
University of Basel
Schönbeinstrasse 40
4031 Basel
Switzeland
Phone: +41 61 265 3796

Hertie-Institute for Clinical Brain Research (HIH)
Department of Cellular Neurology
University of Tübingen
Ottfried-Müller Strasse 27
72076 Tübingen
Germany
Phone: +49 7071 29 81945

Education

2002 – present	PhD student in the group of Prof. Mathias Jucker Institute of Pathology, University of Basel, Switzerland HIH, University of Tübingen, Germany
2002	**Diploma Thesis, Neuroscience** Louis Pasteur University, Strasbourg, France Minor in: neuroimmunology, neurophysiology
2001	**B.A., Cognitive and Experimental Psychology** Louis Pasteur University, Strasbourg, France Minor in: neurobiology and behavioral pharmacology, neurophysiology
2000	**Licence, Cognitive and Experimental Psychology** Louis Pasteur University, Strasbourg, France Minor in: cognitive neuropsychology, sensorial psychophysiology
1999	**DEUG II, Psychology** Louis Pasteur University, Strasbourg, France
1998	**DEUG I, Psychology** Louis Pasteur University, Strasbourg, France
1995	**Baccalauréat, Sciences** Minor in: mathematics Jeanne d'Arc High School, Mulhouse, France

BIBLIOGRAPHY

Peer Reviewed Journal Papers

Bolmont T, Haiss F, Eicke D, Radde R, Mathis CA, Klunk WE, Kohsaka S, Jucker M, Calhoun ME. Amyloid plaque formation leads to a rapid, ongoing, and modifiable microglial response. 2006. Submitted

Bolmont T, Clavaguera F, Meyer-Luehmann M, Herzig M, Radde R, Lewis L, Hutton M, Staufenbiel M, Tolnay M, Jucker M. Neurofibrillary pathology is induced in vivo by intracerebral infusion of Abeta-containing brain extracts. 2006. Submitted.

Meyer-Luehmann M [*], Coomaraswamy J [*], **Bolmont T** [*], Kaeser S, Schaefer C, Kilger E, Neuenschwander A, Abramowski D, Frey P, Jaton AL, Vigouret JM, Paganetti P, Walsh DM, Mathews PM, Ghiso J, Staufenbiel M, Walker LC, Jucker M. Exogenous Induction of Cerebral beta-Amyloidogenesis is Governed by Agent and Host. Science. 2006, in press.

Radde R, **Bolmont T**, Kaeser SA, Coomaraswamy J, Lindau D, Stoltze L, Calhoun ME, Jaggi F, Wolburg H, Gengler S, Haass C, Ghetti B, Czech C, Holscher C, Mathews PM, Jucker M. Abeta42-driven cerebral amyloidosis in transgenic mice reveals early and robust pathology. EMBO Rep. 2006 Sep;7(9):940-6.

Galani R, Lehmann O, **Bolmont T**, Aloy E, Bertrand F, Lazarus C, Jeltsch H, Cassel JC. Selective immunolesions of CH4 cholinergic neurons do not disrupt spatial memory in rats. Physiol Behav. 2002 May 1;76(1):75-90.

[*] *contributed equally to this work*

Abstracts

Bolmont T, Haiss F, Eicke D, Radde R, Kohsaka S, Jucker M, Calhoun ME. In vivo imaging of the changes in microglia dynamics and morphology in relation to amyloid formation. Alzheimer's & Dementia: The Journal of the Alzheimer's Association July 2006 (Vol. 2, Issue 3 (Supplement), Page S129).

Bolmont T, Clavaguera F, Meyer-Luehmann, M, Herzig M, Lewis J, Hutton M, Staufenbiel M, Jucker M, Tolnay M. Neurofibrillary pathology in mutant tau transgenic mice is triggered by intracerebral infusion of human Alzheimer's disease brain extract. Swiss Society for Neuropathology, St-Moritz, 2005.

Meyer-Luehmann M, Walker LC, Neuenschwander A, Kaeser S, **Bolmont T**, Ghiso J, Frey P, Jaton AL, Vigouret JM, Staufenbiel M, Jucker M. Initiation of amyloid deposition in APP23 transgenic mice. Society for Neuroscience, New Orleans, 2003. Abstract 29, 731.11.

Invited presentations

Bolmont T, Meyer-Luehmann M, Tolnay M, Probst A, Staufenbiel M, Hutton M, Jucker M. Impact of Abeta amyloid formation on the initiation and spread of neurofibrillary pathology. 1st Symposium of the Hertie-Institute for Clinical Brain Research, Tübingen, 2003.