Animal models of Cerebral Amyloid Angiopathy

L. Jäkel[1], W.E. Van Nostrand[2], J.A.R. Nicoll[3], D. Werring[4], M.M. Verbeek[1]

Affiliations

[1] Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Departments of Neurology and Laboratory Medicine, Radboud Alzheimer Centre, Nijmegen, The Netherlands

[2] Stony Brook University, Department of Neurosurgery, Stony Brook, NY, USA

[3] Clinical Neurosciences, Clinical & Experimental Sciences, University of Southampton, Southampton, UK

[4] UCL Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK

Corresponding author:

Correspondence to: Dr. Marcel M. Verbeek, Department of Neurology, 830 TML, Radboud University Nijmegen Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 243615192; Fax: +31 312 436 68754; Email: marcel.verbeek@radboudumc.nl; www.neurochemistry.nl

Keywords

- Cerebral amyloid angiopathy
- Animal models
- Amyloid-β
- Transgenic mice

Abbreviations

Aβ = amyloid β

AD = Alzheimer's disease

ApoE = apolipoprotein E

APP = amyloid precursor protein

AQP4 = aquaporin 4

BACE1 = beta-secretase 1

BCAS = bilateral common carotid artery stenosis

CAA = cerebral amyloid angiopathy

CSF = cerebrospinal fluid

HCHWA-D = hereditary cerebral hemorrhage with amyloidosis - Dutch type

HHcy = hyperhomocysteinemia

ISF = interstitial fluid

L-NAME = Nω-Nitro-l-arginine methyl ester hydrochloride

M_1R = muscarinic receptor 1

MRA = magnetic resonance angiography

MRI = magnetic resonance imaging

NOS2 = nitric oxide synthase 2

PDGF = platelet-derived growth factor

PET = positron emission tomography

PrP = prion protein

SRA = scavenger receptor A

STZ = streptozotocin

TAC = transverse aortic constriction

Abstract

Cerebral amyloid angiopathy (CAA), due to vascular amyloid β (Aβ) deposition, is a risk factor for intracerebral hemorrhage and dementia. CAA can occur in sporadic or rare hereditary forms, and is almost invariably associated with Alzheimer's disease (AD). Experimental (animal) models are of great interest in studying mechanisms and potential treatments for CAA. Naturally occurring animal models of CAA exist, including cats, dogs and non-human primates, which can be used for longitudinal studies. However, due to ethical considerations and low throughput of these models, other animal models are more favourable for research. In the past two decades, a variety of transgenic mouse models expressing the human Aβ precursor protein (APP) has been developed. Many of these mouse models develop CAA in addition to senile plaques, whereas some of these models were generated specifically to study CAA. In addition, other animal models make use of a second stimulus, such as hypoperfusion or hyperhomocysteinemia, to accelerate CAA. In this manuscript, we provide a comprehensive review of existing animal models for CAA, which can aid in understanding the pathophysiology of CAA and explore the response to potential therapies.

1. Introduction

1.1 Cerebral amyloid angiopathy (CAA)

Cerebral amyloid angiopathy (CAA) results from accumulation of amyloidogenic proteins in cerebral arteries, arterioles and capillaries (fig. 1). The most prevalent form of CAA involves the accumulation of the amyloid β protein (Aβ) (2, 3). CAA often occurs sporadically, being observed in 30% of non-demented elderly individuals and in >80% of all patients with Alzheimer's disease (AD) (4, 5). CAA can also occur as a rare, monogenetic hereditary disorder, that results from mutations within the Aβ sequence of the human Aβ precursor protein (APP) and also mutations in the presenilin-1 and presenilin-2 genes, involved in cleavage of APP to produce Aβ (6, 7). Hereditary CAA is characterized by an earlier age of onset, a more severe clinical course and reduced life expectancy, compared to sporadic CAA (8). For example, patients with hereditary cerebral hemorrhage with amyloidosis - Dutch type (HCHWA-D), caused by the E693Q mutation in the APP gene, suffer from hemorrhagic strokes, infarcts and vascular dementia (9). Life expectancy is severely reduced; the first stroke occurs between the ages of 40 and 65 years and is often fatal. Surviving patients suffer from recurrent strokes (10, 11). Patients with hereditary CAA present with a relatively pure form of this condition where Aβ deposition is primarily found in the vasculature. Therefore, animal models expressing APP with similar mutations may serve as suitable CAA models. Several other mutations in the APP gene have been identified, such as the Swedish and London mutations (Fig. 1) (8, 12). Most of these genes are associated with familial AD, but also increase the risk of developing AD-associated CAA. Animal models harbouring such mutations may therefore serve as models for AD-related CAA.

1.2 Morphology and topography of human CAA

Two forms of CAA, based on the location of Aβ deposition, can be distinguished: CAA type 1 and type 2 (13). In the more common CAA type 2, Aβ is restricted to vessel walls of cortical and meningeal arteries and arterioles (fig.1 B & C), without Aβ deposition in capillaries. Because Aβ is confined within the vessel wall in CAA type 2, this type is not typically associated with brain parenchymal neuroinflammation, but, rather, promotes smooth muscle cell death and hemorrhages. By contrast, in CAA type 1, Aβ is also deposited in the cortical capillaries (fig.1 A), and may penetrate into the surrounding brain parenchyma ("dyshoric angiopathy" (2, 13)), which induces a neuroinflammatory response. CAA type 1 is associated with the apolipoprotein E (*APOE*) ε4 allele, which is also a risk factor for AD, whereas CAA type 2 is associated with the *APOE* ε2 allele (13).

Aβ deposition often starts in the tunica adventitia and the abluminal part of the tunica media, and surrounds the smooth muscle cells (14). As the CAA progresses, all layers of the vessel wall become affected and a loss of smooth muscle cells becomes apparent, whereas endothelial cells are usually preserved (2).

CAA is mainly composed of $A\beta_{40}$, and contains to a lesser extent the slightly longer $A\beta_{42}$. This is in contrast to parenchymal plaques, of which $A\beta_{42}$ is the main constituent (15-17). In addition, other Aβ isoforms are observed in CAA, such as C-terminal (15, 18) or N-terminal truncated Aβ isoforms (19) and pyro-glutamate modified Aβ isoforms (20). The brain region most frequently and severely affected by Aβ deposition is the occipital lobe, followed by frontal, parietal and temporal lobes; the cerebellum may also be involved, but the white matter, basal ganglia and brainstem are only rarely affected (2, 21, 22). Leptomeningeal vessels are more frequently affected than cortical vessels. It is thus assumed that leptomeningeal vessels are affected earlier, while cortical vessels become involved in later stages of CAA (2). Veins are generally less frequently affected than arteries (2, 23).

1.3 Aims of this review

Definite CAA can only be diagnosed by post-mortem neuropathological evaluation (24). A diagnosis of probable CAA during life is established using clinical data, neuroimaging markers including cerebral microbleeds on T2*-weighted magnetic resonance imaging (MRI) and, if available, histopathological findings (24, 25). However, pre-mortem brain biopsies are rarely available, and current neuroimaging-based diagnostic criteria have high specificity but limited sensitivity. MRI detection *in vivo* of cortical superficial siderosis (26) or white matter perivascular spaces (27) has promise to increase diagnostic sensitivity. Likewise, functional MRI to detect impaired vascular reactivity due to smooth muscle cell damage can provide information on the downstream functional effects of CAA (28). Positron emission tomography (PET) imaging with amyloid ligands shows promise but cannot yet reliably discriminate between CAA and cortical amyloid plaques (27, 29). In addition, longitudinal human CAA research on the disease from early stages is difficult; when CAA is detected through the incidence of cerebral microbleeds or stroke resulting from a large lobar hemorrhage, the disease is already at a late stage.

Because of these limitations of in vivo imaging methods, animal models are needed to better understand the pathophysiology and time course of CAA, to establish new and early diagnostic tools and to trial new potential therapies for efficacy and side effects. This review therefore aims to provide a comprehensive overview of the animal models available for CAA research. We discuss naturally occurring models of CAA, such as non-human primates, cats and dogs. We then consider transgenic mouse models that develop significant CAA, as well as other models that use a trigger to induce CAA in animals. Since

CAA based on the deposition of Aβ is the most prevalent form of this condition, this review does not include forms of CAA based on other amyloidogenic proteins (e.g. Cystatin C or A-Bri (30, 31)).

A comprehensive search for original research articles concerning CAA animal models was performed in PubMed and EMBASE. The search consisted of two components, 'cerebral amyloid angiopathy' and 'model', combined with the Syrcle animal filter (32, 33) to restrict the search to animal research (see Table 1 for the complete search strategy). Only studies written in the English language were eligible for inclusion, and reviews, book chapters and conference abstracts were excluded. No date restrictions were applied. Papers were excluded when they did not concern animal research, when they concerned non-CAA related animal models, or when they cited the use of a previously described model without adding new information. The reference lists of the selected articles and relevant reviews were screened for additional potentially relevant articles.

2. Naturally occurring models

2.1 (Non-human) Primates

Compared to human amyloid pathology, $A\beta_{40}$ seems to be a more prominent component of parenchymal plaques in non-human primates (orangutans, chimpanzees and rhesus monkeys), whereas both $A\beta_{40}$ and $A\beta_{42}$ are found in CAA in these animals (34, 35). In addition to the non-human primate models described below, CAA is also detected in meningeal and cortical capillaries and arterioles of chimpanzees (*Pan troglodytes*). These Aβ-containing vessels are also immunopositive for apoE (36). Although one case report does not report any CAA in an aged (44-year-old) gorilla (*Gorilla gorilla*) (37), a more recent case report describes the discovery of Aβ in small blood vessels (38).

2.1.1 Baboon

The presence of CAA has also been reported in aged (26 and 30 years old) baboon monkeys (*Papio hamadryas*) (39). In a study that included 6 baboons above the age of 20 years, the cerebrovascular immunoreactivity of $A\beta_{40}$ and $A\beta_{42}$ was studied. All animals displayed arteriolar and capillary CAA, with a slightly predominant $A\beta_{42}$ immunoreactivity (40).

2.1.2 Cynomolgus monkeys

Cynomolgus monkeys (*Macaca fascicularis*) have both senile plaques and CAA (41, 42). In a study with 64 cynomolgus monkeys between 2 and 35 years old, CAA was found in 10 out of 16 animals older than 22 years. CAA was observed frequently in capillaries, and in addition, CAA was found in parenchymal

arterioles, but less frequently in meningeal arterioles (43). In animals younger than 21 years, no CAA was seen (43). A more recent study of cynomolgus monkeys older than 20 years found that, in contrast to human CAA, Aβ appears predominantly in small veins and capillaries (44). In this study, the frontal and temporal lobes were most commonly affected, followed by the occipital and parietal lobes and the hippocampus (44). Immunohistochemistry with $A\beta_{40}$- and $A\beta_{42/43}$-specific antibodies has revealed that cortical capillaries are predominantly stained by the $A\beta_{42/43}$-specific antibody, whereas parenchymal and meningeal arterioles are more intensely stained by the $A\beta_{40}$-specific antibody (45), which is in concordance with human CAA. CAA-affected cortical blood vessels are also detected by anti-apoE staining, indicating the presence of apoE in these Aβ deposits (41).

2.1.3 Grey mouse lemur

Several studies have reported the presence of CAA in cerebral blood vessels of microcebus monkeys (*Microcebus murinus,* or grey mouse lemur*)* (46, 47)*.* In a study of 8 aged (> 8 years old) microcebus monkeys, all animals had CAA, whereas only 4 had parenchymal plaques. The CAA was found in leptomeningeal and cortical arteries and arterioles, infiltrating the tunica media. In addition, CAA was identified in capillaries (48).

2.1.4 Rhesus monkeys

A study of 81 rhesus monkeys (*Macaca mulatta*) showed that these animals develop CAA from the age of 20 years, with a prevalence of 8.3% in 20- to 25-year-old monkeys, increasing to 37.5% in 33- to 39-year-old monkeys (49). CAA is usually less common than the development of amyloid plaques in this species (50). Large cortical and meningeal arterioles are most commonly affected, with some minor involvement of capillaries and venules. In contrast to humans, CAA is rarely found in the occipital lobe and more abundantly in the frontal and temporal lobes (50). Aβ-containing vessels are also immunopositive for apoE, indicating the presence of this protein (51).

2.1.5 Squirrel monkeys

In squirrel monkeys (*Saimiri sciureus*), in contrast to rhesus monkeys, CAA, rather than senile plaques, is the predominant form of Aβ deposition in (50, 52, 53). In a study of 9 squirrel monkeys ranging from 8 to 27 years of age, all aged (>22 years old) animals had Aβ in association with meningeal and cortical arterioles and capillaries (52). In contrast to humans, in which the occipital lobe is the brain region most severely and frequently affected, CAA development in squirrel monkeys is greatest in the rostral cortex while the occipital lobe is relatively spared (54). In addition, unlike human CAA in which larger arteries are

most commonly affected, CAA in squirrel monkeys is characterized by abundant Aβ in the capillaries (55). $A\beta_{40}$ is deposited predominantly in the arterioles, whereas $A\beta_{42}$ is found mainly in cortical capillaries (56), which is similar to human CAA (57). Aged squirrel monkeys have decreased Aβ clearance at the BBB, which is thought to cause or contribute to the development of CAA (56).

2.1.6 Vervet monkey

In a study of 3 aged (15, 22 and 30 years) vervet monkeys (*Chlorocebus pygerythrus*), Aβ was found in leptomeningeal and cortical blood vessels but not in plaques. These vessels were predominantly positive for $A\beta_{40}$, but also $A\beta_{42}$ was detected (58). As in humans, the occipital cortex is most severely affected by Aβ (58). A case report of a 29-year-old vervet monkey reports the presence of apoE in CAA (59).

2.2 Cats

A study from 1995 showed that aged (> 15 years old) cats have extensive Aβ deposits, some of which are vessel-associated. These vascular deposits had weak staining for both $A\beta_{40}$ and $A\beta_{42}$ (60). Another study found Aβ-positive vessels (arterioles and capillaries) only in the oldest (20 years) of 7 studied cats (61). These vessels were identified with Congo Red staining or an anti-$A\beta_{40}$ antibody, indicating the presence of $A\beta_{40}$ in these vessels. However, in another study, immunohistochemistry with $A\beta_{40}$- and $A\beta_{42}$-specific antibodies detected only $A\beta_{42}$-containing vascular deposits, especially in the white matter of the prefrontal cortex (62). In a study from 2005, Aβ expression in the brain of Siamese and Domestic Shorthair cats (7.5- to 21-years-old) was examined by immunohistochemistry (63). Coronal brain slices were stained with Congo red or Aβ-specific antibodies. In addition to senile plaques, CAA was detected in meningeal and cerebral vessels and around cerebral capillaries. Siamese cats were more prone to develop CAA than Domestic Shorthair cats. Vascular deposition generally started around 12 years of age and gradually increased with age. Vascular amyloid was more prominently stained by an $A\beta_{42}$-specific antibody than by an $A\beta_{40}$ or pan-Aβ antibody, indicating that in contrast to human CAA, $A\beta_{42}$ is the most prominent constituent of feline CAA (63).

2.3. Dogs

CAA in the brains of aged dogs was first observed in 1956 (64). These results have been confirmed many times in the 1990s, when much attention went towards the characterization of canine CAA (65-70). CAA is detected in a broad range of breeds (65, 71-73). In an extensive study of 90 dogs aged 0-19 years, CAA was detected in 28 dogs in an age-dependent manner. CAA was first detected in 9-year old dogs with an incidence increasing to 100% in 15-year old dogs, often accompanied by cerebral hemorrhages (67). With

immunohistochemistry and immunoelectron microscopy, it was discovered that amyloid deposits occur in leptomeningeal and cortical arteries and capillaries of most aged dogs (10-22 years) (74). These results are confirmed by a study of 30 mongrels, of which all animals older than 13.2 years had CAA (75). Thus CAA incidence and severity in dogs appear to increase with age (75, 76).

Another study of dogs aged 10 to 17 years showed that meningeal vessels of the dorsal cerebrum, and to a lesser degree the cerebellum, are first affected. In advanced stages, penetrating cortical vessels and meningeal arteries of other brain regions (except the ventral area) are affected (77). In general, the frontal, parietal and entorhinal cortices seem to be most commonly affected (74, 78). In addition to CAA, senile plaques are also found in the canine cortex (67, 77). Although parenchymal plaques mainly consist of $A\beta_{42}$, canine vascular Aβ consists mainly of $A\beta_{40}$ (72, 79), which is similar to humans. Also, pyro-glutamate modified Aβ isoforms are found in canine CAA (78, 80). Amyloid accumulation is first found in the tunica media of large vessels, leading to degeneration of smooth muscle cells (71, 74, 75). As not all Aβ-positive vessels are detected by Thioflavin S, vascular deposits may contain non-fibrillar Aβ (75). In addition, other constituents such as apoE, cathepsin D, cystatin C and α-1-antichymotrypsin are found (81).

In summary, several naturally occurring animal models of CAA exist (table 2). Cats only exhibit limited vascular Aβ compared to parenchymal deposits, which, in combination with the late age of CAA onset, makes them an unfavourable model. Overall, canine CAA seems most comparable to the human form, and the similar exposure to human diet and living environments add to their suitability as a CAA model. However, the late age of onset is again a major draw-back of this model. Non-human primates are also a physiological relevant model for human CAA, because of their close homology to humans and spontaneous occurrence of CAA. However, the late age of CAA onset (table 2), ethical considerations and high costs impede the use of primates for large studies. An exception may be microcebus monkeys; their relatively short live span (< 18 years) and the predominant development of CAA over parenchymal plaques make this animal an attractive model to study CAA (82).

3. Mouse models

3.1 Transgenic mouse models

3.1.1 APPDutch mice

APPDutch mice are generated by overexpression (± 5-fold) of the E693Q-mutated human APP_{751} under control of the neuron-specific Thy1 promotor element. These mice develop vascular amyloid deposits at approximately 22-25 months of age, first in leptomeningeal vessels, followed by cortical vessels, with an earlier onset for female mice (83). In contrast to the majority of transgenic CAA mouse models, in which CAA develops secondary to AD-related plaque pathology, APPDutch mice were primarily designed to study CAA. CAA $A\beta_{40}$ immunoreactivity is stronger compared to $A\beta_{42}$, and the $A\beta_{D40}$:$A\beta_{D42}$ ratio is 4 times higher compared to the $A\beta_{40}$:$A\beta_{42}$ ratio in APPwt mice (expressing human wild-type APP under control of the same promotor) (83). Vascular deposition of $A\beta_{D40}$ is accompanied by irregular thickening of the basement membrane and deposition of amyloid fibrils in the basement membrane (predominantly at the adventitial side), which results in severe loss of smooth muscle cells while the endothelial cell layer remains intact. Hemorrhages occur in aged mice (29 months old) (83). No dense plaques are found and diffuse parenchymal plaques are rarely detected, whereas in APPwt mice, amyloid is mainly targeted towards the parenchyma. This indicates that the E693Q amino acid substitution is sufficient to target Aβ towards the vessel walls. In the close vicinity of amyloid-laden vessels, perivascular microglial reactions are detected, and astrocytes are activated in affected neocortical areas (83).

Mice overexpressing human BACE1 (Beta-secretase 1, an enzyme involved in Aβ production) produce excessive amounts of Aβ by increased cleaving at the β-site of APP (84). Crossbreeding of APPDutch mice with BACE1 transgenic mice leads to a moderately accelerated formation of CAA compared to the APPDutch mice, i.e. they develop CAA at 22 months of age, mainly in the thalamus. In addition, some parenchymal deposition of Aβ in cortex and subiculum is observed. Like in APPDutch mice, the predominant Aβ species in APPDutch/BACE1 double transgenic mice is $A\beta_{D40}$ (85).

Taken together, the development of CAA in the absence of parenchymal plaques makes APPDutch mice an attractive model of hereditary human CAA, but a significant drawback of this model is the late age of onset.

3.1.2 Tg-SwDI

Another transgenic mouse model that was primarily designed to study CAA, is the Tg-SwDI mouse model. These mice express human APP_{770} containing the Swedish, Dutch and Iowa (D694N) mutations under control of the mouse Thy1 promoter, with expression levels lower (<50%) than those of endogenous mouse APP (86). In the cortex, Aβ is primarily deposited as plaques, although they are mainly of diffuse form and not stained by Thioflavin S (86, 87). Notably, microvascular Aβ deposition is observed, predominantly in the thalamus and subiculum (86, 87). Already at 3 months of age, amyloid levels in the thalamic and subicular microvasculature are higher compared with the rest of the forebrain (86). CAA is

first observed at 3 months of age (86, 87) and at 12 months of age, $A\beta_{40}$ and $A\beta_{42}$ levels in thalamic/subicular brain microvessels are 12- and 14-fold higher than those in whole forebrain tissue homogenates (86). At 12 months of age, 50% of the microvasculature is affected (86), increasing to 85-90% at the age of 24 months (87). In contrast to the subiculum and thalamus, the vessels in the fronto-temporal cortex are only minimally affected by CAA (87). Although some arterioles are affected, the amyloid pathology is most prominent in the capillaries, which is less frequently observed in sporadic human CAA. Microhemorrhages are seen incidentally, but they are not a prominent feature of Tg-SwDI mice (86). With ELISA, higher levels of $A\beta_{40}$ compared to $A\beta_{42}$ have been measured in isolated cerebral microvessels (87).

At 3 months of age, Tg-SwDI mice exhibit impaired spatial learning and memory, which coincides with the development of subicular microvascular amyloid and increased numbers of reactive astrocytes and activated microglia (88).

The accumulation of Aβ in vessels is accompanied by a loss of smooth muscle cells and apoptosis of vascular cells (87). Microvessel densities are reduced as a result of CAA in the subicular and thalamic regions (87). Laser-Doppler flowmetry in Tg-SwDI mice showed that these mice have reduced cerebral blood flow responses to different stimulants when compared with wild-type mice (89).

In a study comparing Tg-SwDI to Tg-Sw mice (the same mice, but lacking the Dutch and Iowa mutations), Aβ was measured in plasma over time. In Tg-Sw mice, that do not develop Aβ deposits in the parenchyma or vasculature up to 2 years of age, stable amounts of Aβ were measured from 3 to 24 months of age. In contrast, no Aβ was measured in plasma of Tg-SwDI mice at any time point up to 2 years of age. These findings indicate that Tg-SwDI mice have diminished clearance of Aβ across the vasculature into the circulation (90). These results are supported by increased brain retention times of intracerebrally injected Dutch/Iowa mutant Aβ, compared to injected wild-type Aβ (86).

Tg-SwDI mice have increased numbers of reactive astrocytes and activated microglia associated with amyloid-laden microvessels (87), with numbers being the highest in the thalamus and subiculum. In addition, levels of the inflammatory cytokines IL-6 and IL-1β are elevated in Tg-SwDI mice. These findings indicate that CAA in the microvasculature is associated with neuroinflammation (87). Furthermore, the complement components C1q, C3 and C4 are strongly expressed in the microvasculature of the thalamus, hippocampus and subiculum of Tg-SwDI mice (91).

ApoE is strongly associated with amyloid deposits in the microvasculature (92). Tg-SwDI mice bred onto a human *APOE* ε2/ε2, ε3/ε3 or ε4/ε4 background display a shift of fibrillar amyloid from the microvasculature to the parenchyma (93, 94). When Tg-SwDI mice are bred onto an apoE knock-out background, fibrillar cerebral microvascular Aβ deposition is reduced (95). Interestingly, this is not due to

changed levels of total Aβ or increased levels of soluble Aβ. Tg-SwDI/apoE$^{+/+}$ mice have increased numbers of reactive astrocytes and activated microglia and elevated IL-6 levels compared to Tg-SwDI/apoE$^{-/-}$ mice (95). Similarly, blocking the Aβ-apoE interaction results in a reduction of amyloid burden, microhemorrhages, inflammation, and a reduction of cognitive impairments (96).

Cholinergic pathways seem to be involved in AD pathology (97). For instance, alterations of the muscarinic receptor 1 (M_1R) influence AD pathology, and M_1R agonists have been proposed as AD therapy (98). Crossbreeding Tg-SwDI with $M_1R^{-/-}$ mice leads to an extensive acceleration of vascular Aβ deposition, presumably by altering APP processing in favour of the amyloidogenic pathway (99).

In summary, Tg-SwDI mice develop early-onset CAA, predominantly in capillaries, whereas larger vessels are relatively spared. Parenchymal deposits occur, but they are not of fibrillar nature. This model exhibits CAA-associated cognitive impairment and displays a robust neuroinflammatory response. Taken together, Tg-SwDI mice provide a unique and valuable model to study CAA type 1.

3.1.3 APP/London mice

APP/London (APP/Ld) mice overexpress (2- to 3-fold) the London mutant (V717I) of the human APP_{695} gene, under control of the neuron specific mouse Thy-1 gene promoter (100). Histological analysis has revealed that, in addition to plaques, APP/Ld mice develop substantial CAA after 15 to 24 months (10-50 affected vessels per coronal brain section) (101), first in leptomeningeal vessels, later followed by cortical, thalamic and hippocampal vessels (101). CAA deposition increases with age, and vascular accumulation occurs somewhat later than the first plaque appearances. Arteries are more frequently affected than veins. Although capillaries are only rarely affected, some capillaries have CAA deposits with amyloid extending into the neuropil (101).

In concordance with human CAA, there is a pattern of concentric ring accumulations in severely affected vessels, whereas less affected vessels show focal accumulations (101). Amyloid in the leptomeningeal arterioles accounts for 70% of total vascular amyloid load, versus 30% in cortical vessels (101). In 20- to 24-month-old mice, neither hemorrhages nor alterations in cerebral blood flow are detected, despite the presence of aneurysms (101, 102). Electron microscopy shows that, similar to human CAA, amyloid deposition starts in the abluminal part of the tunica media and spreads towards the internal elastic lamina, interrupting the smooth muscle layer. In addition, $Aβ_{40}$ levels are significantly higher in leptomeningeal blood vessels compared to plaques (101).

APP/LdxPS1/Mut mice have an additional incorporation of the PS1-A246E mutation (that selectively increases levels of $Aβ_{42}$), which results in a significant increase in both plaque and vascular amyloid severity, and the development of plaques and CAA already at the age of 6-9 months (103).

Compared to APPDutch mice, APP/London mice develop CAA at an earlier age. The CAA pathology of APP/London mice resembles human CAA, and as a result, APP/London mice have been used as a valid model for CAA. A limitation of this model is the absence of intracerebral hemorrhages due to CAA.

3.1.4 APP23

APP23 mice overexpress (7-fold) human APP_{751} with the Swedish double mutation (K670N/M671L) under control of the neuron-specific mouse Thy-1 gene promoter (104-106). In addition to plaques, which start to deposit at 6 months of age, these mice develop CAA in leptomeningeal, cortical and hippocampal vessels in an age-dependent matter, with an onset around 9 to 12 months of age (104, 106, 107). Thalamic vessels are affected as well (104, 108). The thalamus is an important site of CAA in APP23 mice, in contrast to human CAA (108, 109). CAA formation occurs predominantly in arterioles and capillaries (104). Immunohistochemistry and electron microscopy have shown that in some cortical and thalamic vessels (mostly capillaries), amyloid penetrates into the neuropil, resulting in the activation of microglia (104). Similar to human CAA, arteries are more frequently affected than veins, and amyloid fibrils are most commonly found in association with the abluminal side of the vessel wall (104).

When total vascular amyloid load in isolated vascular trees of 22-month-old APP23 mice is analyzed with Thioflavin S staining, a very heavy amyloid load in arteries and arterioles of APP23 mice is seen, compared to a relatively moderate amyloid load in Tg2576 mice, a commonly used AD mouse model (107). Immunostaining with $A\beta_{40}$- and $A\beta_{42}$-specific antibodies has revealed a predominance of $A\beta_{40}$ (108).

Confocal microscopy with double-labelling for Aβ and smooth muscle cell actin has shown loss of smooth muscle cells in the tunica media of CAA-affected vessels in 19- and 27-month old mice. As a consequence, vessels walls are weakening, leading to aneurysm-like vasodilatation (108), which results in cerebral microhemorrhages in older APP23 animals (104, 108). The first microhemorrhages occur at 16 months of age, with numbers increasing with age (110, 111). Two-thirds of the bleeds are detected in the cortex and one third in the thalamus (110). The latter is in contrast to human CAA in which bleeds are predominantly cortical.

CAA in APP23 mice is directly related to alterations in cerebral circulation. CAA causes microvascular alterations that can be detected by magnetic resonance angiography (MRA) or MRI (109, 112, 113). In 25-month-old mice, but not in 7.5-month old mice, hemodynamic responses to $GABA_A$ are compromised (114). Cerebral blood flow is decreased in 16-month-old APP23 mice, and continues to decrease with age. This loss of perfusion is correlated to amyloid-burden detected by PET-MRI with [11C]Pittsburgh compound B (111).

APP23 mice develop significant age-related CAA with an onset at 9-12 months, in association with neuroinflammation and hemorrhages. A difference to human CAA is the strong involvement of the thalamus. As in APP23 mice capillaries are frequently affected by CAA, these mice may serve as a suitable model for CAA type 1.

3.1.5 ArcAβ mice

ArcAβ mice overexpress (6-fold) human APP_{695} containing the Arctic (E693G) and Swedish mutations under control of the prion protein (PrP) promotor (115). In these mice, $Aβ_{40}$ is the predominant peptide, but also $Aβ_{38}$ and $Aβ_{42}$ are found (115). Between 9 and 15 months of age, ArcAβ mice develop dense-core plaques and CAA in an age-dependent manner, in addition to intracellular Aβ deposits (115). As a result, vascular reactivity in response to a vasodilatory stimulus is decreased (116). In old mice (16- to 22-months-old), the smooth muscle layer of amyloid-affected vessels is disrupted (117). Cerebral microbleeds are found in 18-month old ArcAβ mice, in contrast to wild-type controls (118).

Similar to humans, in ArcAβ mice CAA is predominantly found in smaller vessels (119), mostly in cortical areas while the thalamus is almost completely spared (119). ArcAβ mice display age-dependent changes of the cerebral vasculature, such as a reduction of functional intracortical microvessel density, whereas larger vessels are spared (119). Already at 6 months of age, astrogliosis is observed around blood vessels, with severity increasing with age (117). Connections between astrocytic endfeet and vessel walls are disrupted, leading to disturbed neurovascular coupling. At 9 to 13 months of age, ArcAβ mice have decreased expression of the glucose transporter GLUT1 at the BBB, which results in impaired blood-to-brain glucose transport (117).

The ArcAβ model has mainly been characterized by means of neuroimaging methods. However, severe CAA development, accompanied by neuroinflammation, hemorrhages and reduced cerebrovascular functioning, indicate the suitability of ArcAβ mice as CAA model.

3.1.6 PDAPP mice

PDAPP mice overexpress (18-fold) human APP_{770} with the V717F Indiana mutation under control of the platelet-derived growth factor (PDGF)-β (120). Aβ deposition in vessels starts around 7 to 10 months of age, and increases with age, but to a substantially lesser degree compared to Tg2576 mice (121, 122). PDAPP mice develop microhemorrhages in association with CAA (121). In vivo multi-photon imaging after Thioflavin S injection shows that 15- to 21-month-old PDAPP mice develop CAA especially in the proximity of vessel branches (123). The leptomeninges seem to be the predominant site for vascular Aβ deposition

in PDAPP mice (124, 125). Like in other transgenic mice models for CAA, the $A\beta_{40}$:$A\beta_{42}$ ratio in PDAPP mice is increased in the cerebral vasculature compared to the whole brain (121, 125).

Although many reports only mention minimal CAA development in PDAPP mice, several studies have used the PDAPP model to study CAA. Because of the similarity of CAA and plaque distribution and morphology compared to AD patients, this model might be of interest to study AD-related CAA.

3.1.7 Tg2576 mice

Tg2576 mice (synonym APPSwe) overexpress (± 5.5-fold) the human APP_{695} gene with the Swedish double mutation, under control of the hamster PrP promoter (126). This model is one of the most widely studied transgenic mouse models for AD. In addition to parenchymal Aβ deposition, vascular Aβ deposition starts to develop at 7 to 10 months of age (121, 122, 127), in both leptomeningeal and cortical blood vessels (128). Microhemorrhages occur in association with amyloid-containing vessels, with numbers and size of hemorrhages increasing with age (121, 129). At 21 to 22 months of age, Tg2576 mice have developed a substantial number of microbleeds, all in close proximity to amyloid-affected vessels (130). Electrophoresis and ELISA analyses of the amyloid composition of isolated cortical vessels from Tg2576 mice have shown an elevated $A\beta_{40}$:$A\beta_{42}$ ratio, compared to parenchymal lysates (121), which is in concordance with human CAA.

Multiphoton microscopy of co-staining of Thioflavin S and Phalloidin (which stains actin filaments and can be used to visualize vascular SMCs) in intact brains of 16-months-old Tg2576 mice has revealed that larger vessels are earliest and most severely affected. Complete amyloid rings are formed around these vessels, whereas smaller vessels have less amyloid. Only arterioles are affected while venules are spared (131). Another study with whole brain multiphoton imaging has revealed a pattern of leptomeningeal CAA progression in Tg2576 mice. Around 10 months of age, amyloid accumulates first in the large arteries of the anterior region of the brain. At 16 and 23 months, CAA has progressed to other regions of the brain, while the circle of Willis remains amyloid-free (122). The same group has demonstrated that CAA progression occurs primarily through propagation of existing vascular deposits, rather than the initiation of new deposits (132), as was revealed by real-time multiphoton microscopy of vascular amyloid over the course of several weeks.

Multiphoton imaging can also be used to study the architecture of SMCs in Tg2576 mice. While at 6 months of age SMCs look normal, in 14- and 24-month-old transgenic mice, Thioflavin S positive vessels are accompanied by a disrupted SMC layer. In 24-month-old mice, SMCs are lost in areas of severe amyloid deposition (131). These effects of amyloid deposition on SMC architecture have been confirmed later by a similar study (133). As a result of impaired SMC architecture, Tg2576 mice with CAA have a dose- and

age-dependent impairment of vasomotor function (131, 133, 134). Interestingly, already in 6-month-old mice, that not yet have CAA deposition, vasomotor function is decreased, most likely due to elevated soluble Aβ levels (133). MRA provides an alternative tool to detect blood flow alterations in Tg2576 mice. MRA of 18-month-old Tg2576 mice followed by histological analysis of amyloid in the brain indicates that CAA may indeed have a causal role on blood flow alterations (135). Assessing the cerebrovascular distribution of dextran after injection into the hippocampus provides insight into perivascular drainage efficacy. Compared to wild-type mice, Tg2576 mice have disrupted perivascular drainage of dextran (127).

Tg2576/apoE$^{-/-}$ mice however, have no CAA deposits, indicating that apoE influences vascular deposition of Aβ in this model (121, 128). In addition, these Tg2576/apoE$^{-/-}$ mice have a substantially reduced number of microhemorrhages (121). When the human *APOE* ε4 gene is knocked-in in Tg2576 mice, onset of CAA development is delayed. However, these mice display a shift in Aβ deposition; Aβ is found almost exclusively in the vasculature with only very few plaques. This might be due to the elevated $A\beta_{40}$:$A\beta_{42}$ ratio caused by *APOE* ε4 knock-in (136).

S100B is a proinflammatory molecule, and when this molecule is overexpressed in Tg2576 mice, both parenchymal plaque and CAA development are increased. In addition, neuroinflammation is increased, as microgliosis and astrocytosis are augmented and levels of cytokines are elevated (137).

In summary, Tg2576 mice develop CAA and plaques. However, CAA is a less prominent feature in Tg2576 compared to APP23 mice and might therefore be less favourable as model for sporadic CAA. It might be better suited as research model for AD with associated CAA pathology.

3.1.8 TgCRND8

TgCRND8 mice express the Swedish double mutation and the Indiana mutation of human APP_{695} under the control of the Syrian hamster PrP gene promotor, resulting in ± 5-fold higher expression of APP (138). In addition to diffuse and dense core plaques, that start to develop at 3 months of age, CAA has been detected in these mice by Thioflavin S staining already at 5.5 months of age (138). Another study has detected Aβ-positive blood vessels already at 4 months of age (139). Multiphoton microscopy of intact brains, after staining with Thioflavin S, shows that TgCRND8 mice have severe Aβ deposition in leptomeningeal vessels at 11 months of age (122). The temporal development of CAA in this model has been evaluated by Thioflavin S staining of tissue sections of early-stage CAA (2-3 months), mid-stage CAA (4-6 months) and late-stage CAA (7-12 months) mice. Already at 4 months of age, numerous amyloid-positive blood vessels are detected, and the extent of vascular deposition increases with age (140). The pattern of leptomeningeal and cortical vascular Aβ deposition is similar to human CAA (139, 141). In TgCRND8 mice, CAA affects microvessels and arterioles (142), but not venules (140). Analysis of Aβ isoform

distribution by ELISA has revealed that $A\beta_{42}$ levels in CAA are comparable to the amounts in the cortex, whereas there is significantly more $A\beta_{40}$ in vessels relative to cortex (140), which is in concordance with human CAA. Aβ deposition is accompanied by an in increase in tortuosity of penetrating arterials and narrowing of the arteriolar lumen, both indications of microvascular impairment (140). Interestingly, although Thioflavin S staining detects amyloid deposition in penetration cortical arterioles, and not in penetrating cortical venules, loss of mural cells (pericytes and smooth muscle cells) has only been detected in the latter (143).

TgCRND8 mice develop CAA already a few months after birth, with a pattern similar to human CAA. However, one should keep in mind that there is extensive plaque development as well, and that the Aβ pathology is therefore of mixed nature.

3.2 Other APP transgenic mouse models

In addition to the previously described widely used models for CAA, some models exist that are less known or less well characterized for CAA, but nonetheless develop CAA and should therefore be mentioned. APP/PS1 mice (APP_{swe}/$PSEN_{1de9}$, expressing human APP containing the Swedish mutation and presenilin-1 with exon 9 deletion), a well-characterized model for AD with extensive plaque development, also has Aβ accumulation in the vasculature, predominantly in the leptomeninges (144). CAA development starts around 6 months of age, with an age-dependent increase, but overall CAA development is significantly less pronounced compared to Tg2576 mice (145). This may be explained by the production of high levels of $A\beta_{42}$ in this model, whereas levels of the vasculotropic $A\beta_{40}$ are relatively low (145). Female APP/PS1 mice develop more severe CAA and subsequent microhemorrhages and neuroinflammation, compared to male mice (146). Experimental induction of stroke, by occlusion of the middle cerebral artery, seems to increase vascular Aβ burden, as well as plaque development (147). Another APP/PS model, the APP_{SweLon}/$PS1_{M146L}$ mouse model, starts to develop CAA containing predominantly the $A\beta_{40}$ isoform, in addition to plaques, already at the age of 18 weeks, with severity increasing with age (148). A third APP/PS model, APP_{Swe}/ $PS1_{M146V}$ (named ARTE10) also develops CAA as well as plaques (149).

Although many studies describe only minimal development of CAA in 5xFAD mice (expressing human APP_{695} with the Swedish, London and Florida (I716V) mutations, as well as the M146L and L286V mutations in human PS1 under control of the mouse Thy1 promoter (150)), some CAA can be detected as early as 3 months of age using multi-photon imaging. CAA is observed in larger cortical and leptomeningeal vessels, with severity increasing with age. Virtually no CAA is detected in the microvasculature (151). A high-fat diet seems to exacerbate cerebrovascular Aβ pathology (152).

APP DSL knock-in mice express human APP with the Dutch, Swedish and London mutations. Crossing these mice with PS1 M146V mice results in offspring that develops robust CAA and parenchymal plaques, starting around 10 to 12 months of age. Around 18 months of age, microhemorrhages occur in these mice, and the introduction of transverse aortic constriction (TAC) exacerbates the development of CAA (153).

E22ΔAβ mice express human APP_{695} with the Swedish mutation and the Osaka mutation (deletion of amino acid 693). These mice do not develop parenchymal plaques, but show development of vascular amyloid deposits at old age (24 months) in cortical and especially leptomeningeal arteries. $A\beta_{40}$ is the predominant isoform in these vascular deposits. E22ΔAβ mice display cognitive impairment (154).

Tg-ArcSwe mice express human APP with the Swedish and the Arctic mutations under control of the murine Thy-1 promotor element (155). These mice develop both parenchymal plaques and CAA (156, 157). CAA is detected in 8-month-old mice (156), and at 15 months of age, abundant CAA can be seen in capillaries, arterioles and arteries (157).

Lastly, BRI-Aβ transgenic mice express $A\beta_{40}$ of $A\beta_{42}$ fused with the BRI protein that is involved in British or Danish dementia. BRI-$A\beta_{42}$ mice develop parenchymal and vascular plaques, whereas BRI-$A\beta_{40}$ mice do not (158).

3.3 Alternative mouse models

3.3.1 Hypoperfusion and hypertension

Hypoperfusion is frequently observed in AD patients and may reinforce Aβ pathology. From that rationale, the induction of hypoperfusion in CAA models may accelerate and exacerbate CAA pathology (159-161). A method frequently used to induce chronic hypoperfusion is bilateral common carotid artery stenosis (BCAS); by causing constriction of these arteries, supply of blood to the brain is reduced. A study that used microcoils to induce BCAS in Tg-SwDI mice shows that as a result, cerebral blood flow is reduced by 26% and leptomeningeal Aβ accumulation is increased (162). Another study used ameroid constrictors that gradually narrow the carotid arteries. This may mimic chronic cerebral hypoperfusion more accurately, as perfusion decreased gradually. Using this BCAS technique in APP23 mice results in an increase of CAA in small cortical and leptomeningeal vessels (163). Another method to induce cerebral hypoperfusion is the constriction of the transverse aorta (TAC), which results in a decrease of cerebral blood flow to the (left side of) the brain. In the APP-DSL model, TAC reduces cerebral blood flow and results in an exacerbation of CAA pathology (153, 164)

Another risk factor for the development of vascular dementia is hypertension. Induction of hypertension by administration of angiotensin II results in an exacerbation of CAA in APP-DSL mice (164). Similarly, the administration of angiotensin II to APPS1 mice increases cerebral vascular amyloid deposition with 30 to 40% (165). Nω-Nitro-l-arginine methyl ester hydrochloride (L-NAME) also induces hypertension, and when administrated to Tg-SwDI mice, it accelerates microvascular, but not parenchymal Aβ accumulation with coinciding microglia activation and BBB leakage (166). Tg2576 mice display increased occurrence of intracerebral hemorrhages after administration of L-NAME (167).

3.3.2 Hyperhomocysteinemia

Homocysteine is an amino acid that is involved in methylation and transsulfuration. Hyperhomocysteinemia (HHcy) is a risk factor for cerebrovascular diseases (168). In mice, HHcy can be induced by a deficiency in the vitamins B6, B12 and folate, while supplementing with methionine. When HHcy is induced in APP/PS1 mice, after six months a shift of Aβ deposition from the parenchyma to the vasculature is observed (169). Furthermore, an increase of microhemorrhages is observed in both APP/PS1 and WT mice with induced HHcy (169).

3xTg mice express the Swedish mutant APP, mutant PS1 and mutant tau and develop parenchymal plaques, but not CAA. In these mice, 7 months after induction of HHcy, CAA is observed without the occurrence of microhemorrhages (170). It is hypothesized that the development of CAA is caused by reduced levels of apoE due to HHcy (170). HHcy in TgCRND8 mice increases CAA in large vessels and capillaries, both 2 and 5 months after induction, in addition to increases in parenchymal plaque load (171).

3.3.2 NOS2 deficiency

Nitric oxide synthase 2 (NOS2) plays a role in vascular functioning and is involved in Aβ production (172). Partial deficiency of endothelial NOS results in an increase of CAA in 18-month-old mice, both in the leptomeninges and the cortex. Mild CAA can already be detected in 8-month-old $eNOS^{+/-}$ mice, whereas $eNOS^{+/+}$ mice show no evidence of CAA (173). $eNOS^{+/-}$ mice also display an increase in SMC degeneration and cerebral microhemorrhages (173).

Knocking out NOS2 in Tg2576 mice increases CAA levels 2- to 5-fold in 52-week-old mice (174). Interestingly, no differences in CAA are observed when comparing Tg-SwDI/$NOS2^{-/-}$ with Tg-SwDI mice (174). However, Tg-SwDI/$NOS2^{-/-}$ have a more severe capillary CAA-pathology, including perivascular activated microglia and perivascular phosphorylated-tau, and highly resemble human CAA type 1 (175).

Hypoperfusion, hypertension, hyperhomocysteinemia and NOS deficiency all play a role in vascular dysfunction, and exacerbate the development of CAA. Hypoperfusion and hyperhomocysteinemia seem to shift Aβ deposition from the parenchyma towards the vasculature. The above-mentioned models may be useful tools in increasing the suitability of models that normally develop only moderate levels of vascular Aβ, or develop CAA at a late age. However, it is likely that these vascular risk factors have undesirable side effects besides CAA development.

4. Other models

4.1 Rats

Although mice are the predominant species used to study and induce CAA, some literature exists on how CAA might be induced in rats to obtain useful CAA models. Treatment with streptozotocin (STZ) can cause insulin resistance, which, given the role of insulin in AD, is hypothesized to lead to Aβ pathology. Rats indeed start to develop CAA three months after STZ treatment (176). Follow-up research shows an age-dependent increase of CAA 6 and 9 months after STZ treatment. CAA is found in cortical and meningeal arteries and arterioles, and is especially pronounced in the thalamus, hypothalamus and hippocampus (177). This is deviant from human CAA, in which vascular Aβ deposits are only sparsely found in these brain regions.

Another rat model is the F344-AD model that overexpresses two human genes: APP with the Swedish mutation and exon 9 mutant human presenilin-1 (PS1ΔE9). These rats develop both plaques and CAA in an age-dependent manner. CAA is detected in the cerebral cortex, but also in the cerebellum and hippocampus, areas that are less frequently affected in human CAA patients (178).

TgAPP21 rats overexpress human APP with the Swedish double mutation and the Indiana mutation (179). This model expresses high levels of $A\beta_{40}$ and does not develop plaques and only minimal vascular Aβ pathology. However, induction of hydrocephalus by administration of Kaolin accelerates vascular Aβ pathology, probably through reduced clearance of $A\beta_{40}$ (180). Another way to induce Aβ pathology in TgAPP21 rats is the injection of AD brain extracts, which results in the development of plaques and CAA within nine months (181).

4.2 Rabbits

Rabbits do not develop Aβ pathology naturally. However, in a study with 6 rabbits, immunization with thyroglobulin resulted in robust vascular Aβ pathology in 3 out of 6 animals. Although parenchymal

plaques were occasionally detected, CAA was the predominant form of Aβ deposition. In two rabbits, small hemorrhages were observed (182).

Cholinergic pathways may play a role in AD pathology, and based on this hypothesis, Aβ pathology was investigated in a rabbit model with cholinergic deafferentation. In these rabbits, Aβ can be found at the basal lamina of the vasculature, both in larger arteries and capillaries (183). It is hypothesized that the cholinergic deafferentation leads to increased release of Aβ by neurons, and subsequent diffusion to and accumulation at the vasculature (183).

5. Experimental models to study the mechanisms of CAA formation

The perivascular drainage pathway comprises the removal of solutes with interstitial fluid (ISF) from the parenchyma by intramural perivascular drainage along the basement membranes of capillaries and arteries. Intracerebral injections of soluble tracers into mice brain have shown that ISF solutes enter the perivascular pathway, move along the basement membrane to leptomeningeal arteries and end up in cervical lymph nodes (184, 185). It is proposed that this drainage is driven by pulsations of the blood vessel walls (186, 187). In the ageing mouse brain, perivascular drainage is impaired (127). Also, the presence of CAA impairs perivascular drainage (127). For reviews, see (185, 187-189).

The concept of paravascular fluid circulation was first described in 1985 (190), and more recently, this process has been renamed as glymphatic flow. The glymphatic system describes the exchange of solutes between cerebrospinal fluid (CSF) and ISF, and elimination via paravenous pathways. One of the first characterizations of the glymphatic system was achieved by two-photon microscopy in mice. Using fluorescent tracers, it was shown that CSF enters the parenchyma via paravascular spaces around penetrating arteries, and that ISF is cleared through paravenous drainage pathways (191). Labelled $A\beta_{40}$ injected into the striatum was shown to be cleared along the glymphatic pathway (191). Aged mice have reduced clearance of Aβ along paravascular pathways compared to young mice (192). Aquaporin 4 (AQP4) is a water channel that is expressed at astrocytic endfeet around the brain vasculature. AQP4 knockout mice have a reduced CSF influx to the parenchyma and a reduced clearance of $A\beta_{40}$, indicating that AQP4 facilitates transport of CSF into the parenchyma (191). It is believed that the accumulation of Aβ in the vasculature might be caused by impairment of the glymphatic system, and in turn, that accumulation of Aβ might further impair the glymphatic mechanisms (193). For reviews, see (193, 194).

6. Modelling responses to therapy targeting Aβ

The amyloid cascade hypothesis, putting accumulation of Aβ at a key point in the pathophysiology of AD, has led to exploration of Aβ-targeted therapies for the treatment of AD. Clearance of amyloid plaques

from the cortex by anti-Aβ immunotherapeutic approaches leads to an apparent increase in severity of CAA in humans (195). The side effects associated with Aβ immunotherapy which have hampered most clinical trials seem likely to be due largely to these changes in CAA (196, 197). Because of the limitations in our ability to study these factors directly in human tissue, experimental models are very important in attempting to understand these therapy-related side effects, in addition to the potential to treat CAA itself by such approaches (83, 124, 198).

7. Conclusions

Sporadic CAA poses a significant risk for stroke and dementia, yet there is no treatment and it can still be difficult to diagnose in humans *in vivo* without a sample of brain tissue, particularly in those at the earlier stages of the disease. Animal models are thus critical to the improvement of our understanding of CAA and the development of new diagnostic and therapeutic tools. CAA occurs naturally in a variety of animals, including non-human primates, cats and dogs. In the early years of CAA research, these models significantly contributed to our knowledge of the pathology of CAA. The spontaneous development of CAA makes these models attractive, as they resemble sporadic CAA in elderly humans. However, their longevity and the relatively late age of CAA onset, high costs, limited access and ethical considerations restrict their wider use in CAA research.

More recently, transgenic mouse models have emerged. These models vary in the degree of CAA and the degree of co-occurrence of parenchymal plaques, but provide us with some key understandings of CAA: 1) vascular Aβ is mainly of neuronal origin (since in most animals the expression of the transgene is driven by a neuronal promoter), 2) CAA seems due to impaired clearance of Aβ by perivascular drainage, and 3) the $A\beta_{40}$:$A\beta_{42}$ ratio largely determines whether Aβ accumulates in the brain parenchyma or vessel walls. Their short life span, low expense and the possibilities of genetic manipulations contribute to the attractiveness of mice models. However, there are substantial anatomical and physiological differences between mice and humans, including immune responses which seem to play a pivotal role in CAA. Extrapolation of results from transgenic mice to humans should therefore be done with care.

Animal models often display only certain aspects of CAA pathology; for instance, CAA is present, but in other brain regions or blood vessel types than in humans, or there is strong evidence of CAA, but without the occurrence of cognitive decline or microbleeds. Therefore, there is an urgent need for more complete models of CAA. However, despite their incompleteness, transgenic mice will remain important tools that will help us to further decipher the pathogenesis of CAA and develop effective therapies. In addition to Aβ transgenic mice models, some other animal models of CAA exist, such as $NOS2^{-/-}$ models, that will further improve our understanding of CAA pathophysiology.

As no single model for CAA is complete or perfectly resembles human CAA, it is necessary to consider the differences between animal models when selecting a model to address a specific research question. For example, for the study of type 1 CAA in a relatively short time frame, the Tg-SwDI mouse model seems to a useful model, whereas to study CAA type 2, the APP/Ld or APPDutch models seem to be suitable (see table 2). With this review, we have provided an overview of animal models that are available for CAA research (table. 2), and their resemblances and differences compared to human CAA.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

This work was supported by grants to MMV from Alzheimer Nederland (no. 14502) and the CAVIA project which has been made possible by ZonMW (no 733050202). The CAVIA project is part of 'Memorabel', the research and innovation programme for dementia, as part of the Dutch national 'Deltaplan for Dementia': zonmw.nl/dementiaresearch". The CAVIA project is a consortium of Radboudumc, LUMC, Erasmus MC, VUmc, ADX Neurosciences, Philips Healthcare, Stony Brook University and Massachusetts General Hospital.

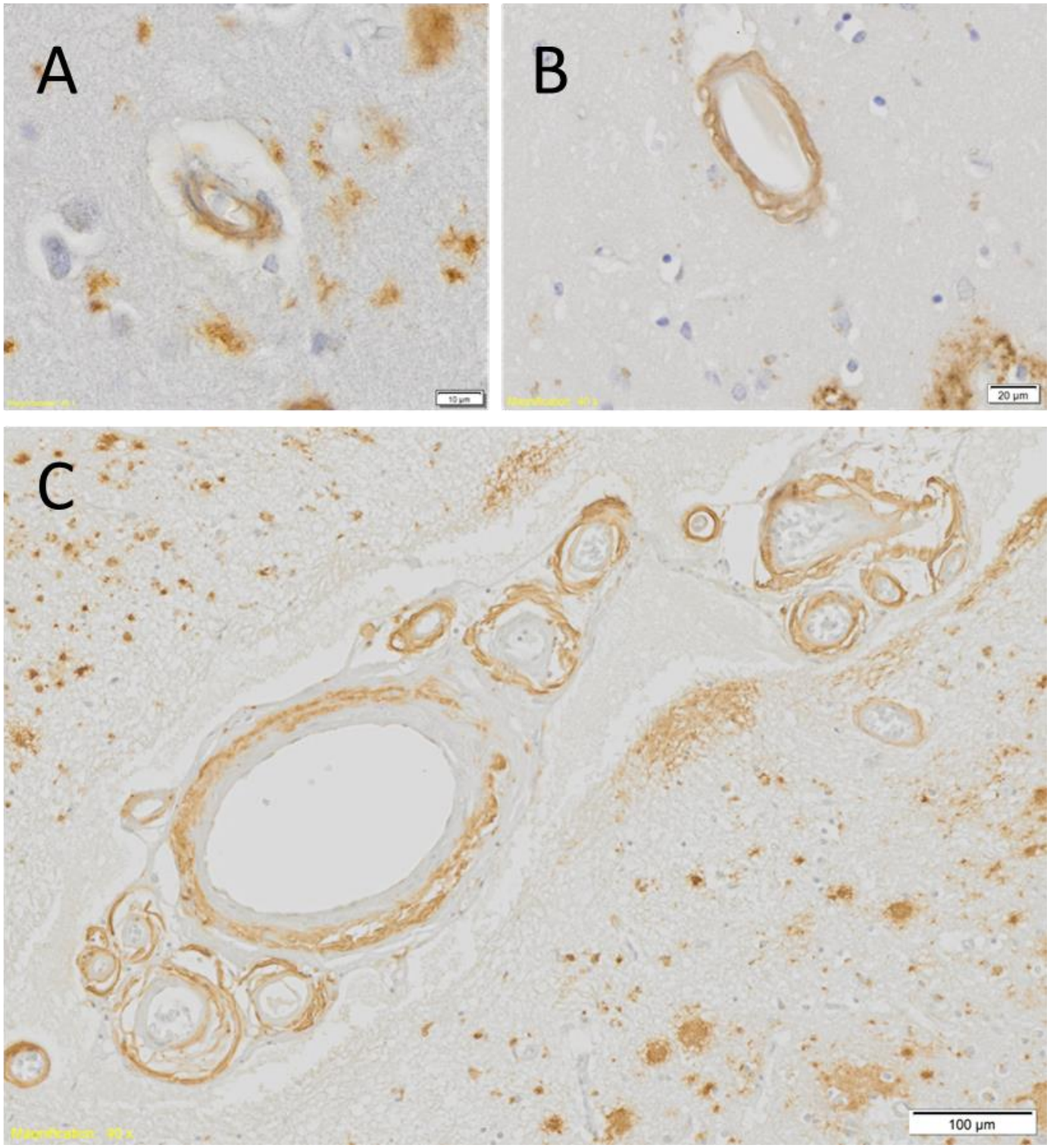

Figure 1. Anti-Aβ immunohistochemistry of A) capillary, B) cortical arteriolar and C) leptomeningeal CAA.

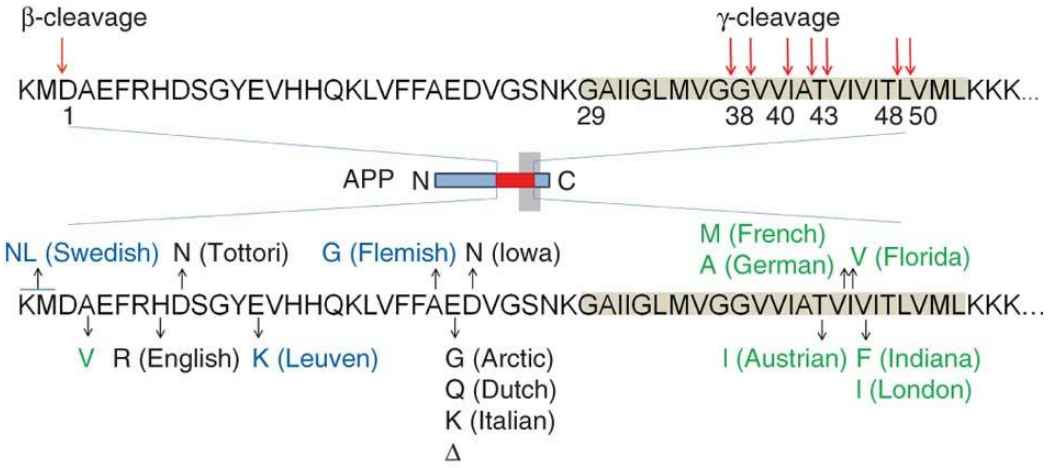

Figure 2. Mutations in the Aβ region of the APP gene. Mutations indicated in blue increase Aβ production, mutations indicated in black alter biophysical characteristics and mutations indicated in green affect both production and biophysical characteristics. Reproduced with permission from (1).

Database	Search strategy
PubMed	(“Cerebral Amyloid Angiopathy"[Mesh] OR CAA[tiab]OR congophilic angiopathy[tiab] OR congophilic angiopathies[tiab] OR cerebral amyloid angiopathy[tiab] OR cerebral amyloid angiopathies[tiab] OR vascular amyloid[tiab] OR vascular amyloidosis[tiab] OR cerebral vascular amyloid[tiab] OR cerebral vascular amyloidosis[tiab] OR vascular amyloid pathology[tiab] OR vascular amyloid pathologies[tiab] OR vascular amyloid-beta pathology[tiab] OR vascular amyloid-beta pathologies [tiab] OR cerebral hemorrhage with amyloid[tiab] OR cerebral hemorrhages with amyloid[tiab]) AND (Model*[tiab]) AND Syrcle animal filter [33]
EMBASE	(Vascular amyloidosis/ OR CAA.ti,ab,kw.OR congophilic angiopathy.ti,ab,kw. OR congophilic angiopathies.ti,ab,kw. OR cerebral amyloid angiopathy.ti,ab,kw. OR cerebral amyloid angiopathies.ti,ab,kw. OR vascular amyloid.ti,ab,kw. OR vascular amyloidosis.ti,ab,kw. OR cerebral vascular amyloid.ti,ab,kw. OR cerebral vascular amyloidosis.ti,ab,kw. OR vascular amyloid pathology.ti,ab,kw. OR vascular amyloid pathologies.ti,ab,kw. OR vascular amyloid-beta pathology.ti,ab,kw. OR vascular amyloid-beta pathologies.ti,ab,kw. OR cerebral hemorrhage with amyloid.ti,ab,kw. OR cerebral hemorrhages with amyloid.ti,ab,kw.) AND (Model*.ti,ab,kw.) AND Syrcle animal filter [32]

Exclusion criteria	Reviews, book chapters, conference abstracts Not in English Non-animal research, clinical studies Non-disease related animal models Articles citing the use of previously described model that does not contain new information.

Table 1. PubMed and EMBASE search strategies.

	Model	Age of onset	Predominant Aβ-species CAA	Presence of plaques	CAA type resemblance	Brain regions affected
Primates	Baboons	± 26 years	$A\beta_{42} > A\beta_{40}$	Yes	Type 1	
	Cynomongus	± 22 years	Arterioles: $A\beta_{40}$ Capillaries: $A\beta_{42}$	Yes	Type 1	Frontal & temporal lobe, followed by occipital & parietal lobes an hippocampus
	Microcebus	± 8 years		CAA > plaques	Type 1	
	Rhesus	± 20 years		Plaques > CAA	Type 2	Frontal & Temporal. Occipital lobe rarely affected
	Squirrel	± 22 years	Arterioles: $A\beta_{40}$ Capillaries: $A\beta_{42}$	CAA > plaques	Type 1	Rostral > Caudal
	Vervet	± 15 years	$A\beta_{40} > A\beta_{42}$	No		Occipital
Cats		15-20 years	$A\beta_{42} > A\beta_{40}$	Plaques > CAA	Type 1	White matter
Dogs		9-13 years	$A\beta_{40}$	Yes	Type 1	Frontal , parietal & entorhinal cortex
Transgenic mice	APPDutch	22 months	$A\beta_{40}$	No	Type 2	Cortex
	Tg-SwDI	6 months	$A\beta_{40} > A\beta_{42}$	CAA > plaques (diffuse)	Type 1	Thalamus, subiculum
	APP/Ld	15-24 months	$A\beta_{40}$	Yes	Type 2	Cortex
	APP23	9-12 months	$A\beta_{40} > A\beta_{42}$	Yes	Type 1	Cortex, hippocampus, thalamus
	ArcAβ	9-15 months	$A\beta_{40} > A\beta_{42}$	Yes	Type 1	Cortex
	PDAPP	15-21 months	$A\beta_{40} > A\beta_{42}$	Plaques > CAA		
	Tg2576 / APPSwe	7-10 months	$A\beta_{40} > A\beta_{42}$	Yes	Type 2	Anterior > Posterior
	TgCRND8	4 months	$A\beta_{40} > A\beta_{42}$	Yes	Type 1	Cortex

Table 2. Characteristics of CAA animal models.

References

1. Benilova I, Karran E, De Strooper B. The toxic A[beta] oligomer and Alzheimer's disease: an emperor in need of clothes. Nat Neurosci. 2012;15(3):349-57.
2. Attems J. Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. Acta Neuropathol. 2005;110(4):345-59.
3. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. Lancet Neurol. 2003;2(2):89-98.
4. Esiri MM, Wilcock GK. Cerebral amyloid angiopathy in dementia and old age. J Neurol Neurosurg Psychiatry. 1986;49(11):1221-6.
5. Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol. 2011;69(2):320-7.
6. Dermaut B, Kumar-Singh S, De Jonghe C, Cruts M, Lofgren A, Lubke U, et al. Cerebral amyloid angiopathy is a pathogenic lesion in Alzheimer's disease due to a novel presenilin 1 mutation. Brain. 2001;124(Pt 12):2383-92.
7. Nochlin D, Bird TD, Nemens EJ, Ball MJ, Sumi SM. Amyloid angiopathy in a Volga German family with Alzheimer's disease and a presenilin-2 mutation (N141I). Ann Neurol. 1998;43(1):131-5.
8. Biffi A, Greenberg SM. Cerebral Amyloid Angiopathy: A Systematic Review. J Clin Neurol. 2011;7(1):1-9.
9. Kamp JA, Moursel LG, Haan J, Terwindt GM, Lesnik Oberstein SA, van Duinen SG, et al. Amyloid beta in hereditary cerebral hemorrhage with amyloidosis-Dutch type. Rev Neurosci. 2014;25(5):641-51.
10. Wattendorff AR, Bots GT, Went LN, Endtz LJ. Familial cerebral amyloid angiopathy presenting as recurrent cerebral haemorrhage. J Neurol Sci. 1982;55(2):121-35.
11. Wattendorff AR, Frangione B, Luyendijk W, Bots GT. Hereditary cerebral haemorrhage with amyloidosis, Dutch type (HCHWA-D): clinicopathological studies. J Neurol Neurosurg Psychiatry. 1995;58(6):699-705.
12. Grabowski TJ, Cho HS, Vonsattel JP, Rebeck GW, Greenberg SM. Novel amyloid precursor protein mutation in an Iowa family with dementia and severe cerebral amyloid angiopathy. Ann Neurol. 2001;49(6):697-705.
13. Thal DR, Ghebremedhin E, Rub U, Yamaguchi H, Del Tredici K, Braak H. Two types of sporadic cerebral amyloid angiopathy. J Neuropathol Exp Neurol. 2002;61(3):282-93.
14. Vinters HV. Cerebral amyloid angiopathy. A critical review. Stroke. 1987;18(2):311-24.
15. Castano EM, Prelli F, Soto C, Beavis R, Matsubara E, Shoji M, et al. The length of amyloid-beta in hereditary cerebral hemorrhage with amyloidosis, Dutch type. Implications for the role of amyloid-beta 1-42 in Alzheimer's disease. J Biol Chem. 1996;271(50):32185-91.
16. Suzuki N, Iwatsubo T, Odaka A, Ishibashi Y, Kitada C, Ihara Y. High tissue content of soluble beta 1-40 is linked to cerebral amyloid angiopathy. Am J Pathol. 1994;145(2):452-60.
17. 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;13(1):45-53.
18. Reinert J, Martens H, Huettenrauch M, Kolbow T, Lannfelt L, Ingelsson M, et al. Abeta38 in the brains of patients with sporadic and familial Alzheimer's disease and transgenic mouse models. J Alzheimers Dis. 2014;39(4):871-81.
19. Tekirian TL, Saido TC, Markesbery WR, Russell MJ, Wekstein DR, Patel E, et al. N-terminal heterogeneity of parenchymal and cerebrovascular Abeta deposits. J Neuropathol Exp Neurol. 1998;57(1):76-94.
20. Harigaya Y, Saido TC, Eckman CB, Prada CM, Shoji M, Younkin SG. Amyloid beta protein starting pyroglutamate at position 3 is a major component of the amyloid deposits in the Alzheimer's disease brain. Biochem Biophys Res Commun. 2000;276(2):422-7.

21. Vinters HV, Gilbert JJ. Cerebral amyloid angiopathy: incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. Stroke. 1983;14(6):924-8.
22. Attems J, Jellinger KA, Lintner F. Alzheimer's disease pathology influences severity and topographical distribution of cerebral amyloid angiopathy. Acta Neuropathol. 2005;110(3):222-31.
23. Revesz T, Holton JL, Lashley T, Plant G, Rostagno A, Ghiso J, et al. Sporadic and familial cerebral amyloid angiopathies. Brain Pathol. 2002;12(3):343-57.
24. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology. 2001;56(4):537-9.
25. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy(CME). Neurology. 2010;74(17):1346-50.
26. Charidimou A, Linn J, Vernooij MW, Opherk C, Akoudad S, Baron JC, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. Brain. 2015;138(Pt 8):2126-39.
27. Charidimou A, Jaunmuktane Z, Baron J-C, Burnell M, Varlet P, Peeters A, et al. White matter perivascular spaces: An MRI marker in pathology-proven cerebral amyloid angiopathy? Neurology. 2014;82(1):57-62.
28. Dumas A, Dierksen GA, Gurol ME, Halpin A, Martinez-Ramirez S, Schwab K, et al. Functional MRI Detection of Vascular Reactivity in Cerebral Amyloid Angiopathy. Ann Neurol. 2012;72(1):76-81.
29. Farid K, Charidimou A, Baron J-C. Amyloid positron emission tomography in sporadic cerebral amyloid angiopathy: A systematic critical update. NeuroImage : Clinical. 2017;15:247-63.
30. Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, et al. Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. Acta Neuropathol. 2009;118(1):115-30.
31. Ghiso J, Frangione B. Cerebral amyloidosis, amyloid angiopathy, and their relationship to stroke and dementia. J Alzheimers Dis. 2001;3(1):65-73.
32. de Vries RB, Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Updated version of the Embase search filter for animal studies. Lab Anim. 2014;48(1):88.
33. Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. Lab Anim. 2010;44(3):170-5.
34. Gearing M, Tigges J, Mori H, Mirra SS. A beta40 is a major form of beta-amyloid in nonhuman primates. Neurobiol Aging. 1996;17(6):903-8.
35. Gearing M, Tigges J, Mori H, Mirra SS. beta-Amyloid (A beta) deposition in the brains of aged orangutans. Neurobiol Aging. 1997;18(2):139-46.
36. Gearing M, Rebeck GW, Hyman BT, Tigges J, Mirra SS. Neuropathology and apolipoprotein E profile of aged chimpanzees: implications for Alzheimer disease. Proc Natl Acad Sci U S A. 1994;91(20):9382-6.
37. Kimura N, Nakamura S, Goto N, Narushima E, Hara I, Shichiri S, et al. Senile plaques in an aged western lowland gorilla. Exp Anim. 2001;50(1):77-81.
38. Marquez M, Serafin A, Fernandez-Bellon H, Serrat S, Ferrer-Admetlla A, Bertranpetit J, et al. Neuropathologic findings in an aged albino gorilla. Vet Pathol. 2008;45(4):531-7.
39. Schultz C, Dehghani F, Hubbard GB, Thal DR, Struckhoff G, Braak E, et al. Filamentous tau pathology in nerve cells, astrocytes, and oligodendrocytes of aged baboons. J Neuropathol Exp Neurol. 2000;59(1):39-52.
40. Ndung'u M, Hartig W, Wegner F, Mwenda JM, Low RW, Akinyemi RO, et al. Cerebral amyloid beta(42) deposits and microvascular pathology in ageing baboons. Neuropathol Appl Neurobiol. 2012;38(5):487-99.

41. Nakamura S, Kiatipattanasakul W, Nakayama H, Ono F, Sakakibara I, Yoshikawa Y, et al. Immunohistochemical characteristics of the constituents of senile plaques and amyloid angiopathy in aged cynomolgus monkeys. J Med Primatol. 1996;25(4):294-300.
42. Kodama R, Yang X, Saski Y, Iwashige S, Tanigawa Y, Yoshikawa T, et al. Age-Related Lesions in the Cerebrum in Middle-Aged Female Cynomolgus Monkeys. Toxicol Pathol. 2010;38(2):303-11.
43. Nakamura S, Nakayama H, Goto N, Ono F, Sakakibara I, Yoshikawa Y. Histopathological studies of senile plaques and cerebral amyloidosis in cynomolgus monkeys. J Med Primatol. 1998;27(5):244-52.
44. Darusman HS, Sajuthi D, Schapiro SJ, Gjedde A, Kalliokoski O, Kristianingrum YP, et al. Amyloid beta 1-42 and phoshorylated tau threonin 231 in brains of aged cynomolgus monkeys (Macaca fascicularis). Front Aging Neurosci. 2014;6(313):1-7.
45. Nakamura S, Tamaoka A, Sawamura N, Shoji S, Nakayama H, Ono F, et al. Carboxyl end-specific monoclonal antibodies to amyloid beta protein (A beta) subtypes (A beta 40 and A beta 42(43)) differentiate A beta in senile plaques and amyloid angiopathy in brains of aged cynomolgus monkeys. Neurosci Lett. 1995;201(2):151-4.
46. Silhol S, Calenda A, Jallageas V, Mestre-Frances N, Bellis M, Bons N. β-Amyloid Protein Precursor inMicrocebus murinus:Genotyping and Brain Localization. Neurobiol Dis. 1996;3(3):169-82.
47. Bons N, Mestre N, Petter A. Senile plaques and neurofibrillary changes in the brain of an aged lemurian primate, Microcebus murinus. Neurobiol Aging. 1992;13(1):99-105.
48. Bons N, Mestre N, Ritchie K, Petter A, Podlisny M, Selkoe D. Identification of amyloid beta protein in the brain of the small, short- lived Lemurian primate Microcebus murinus. Neurobiol Aging. 1994;15(2):215-20.
49. Uno H, Alsum PB, Dong S, Richardson R, Zimbric ML, Thieme CS, et al. Cerebral amyloid angiopathy and plaques, and visceral amyloidosis in aged macaques. Neurobiol Aging. 1996;17(2):275-81.
50. Walker LC. Animal models of cerebral beta-amyloid angiopathy. Brain Res Rev. 1997;25(1):70-84.
51. Poduri A, Gearing M, Rebeck GW, Mirra SS, Tigges J, Hyman BT. Apolipoprotein E4 and beta amyloid in senile plaques and cerebral blood vessels of aged rhesus monkeys. Am J Pathol. 1994;144(6):1183-7.
52. Walker LC, Masters C, Beyreuther K, Price DL. Amyloid in the brains of aged squirrel monkeys. Acta Neuropathol. 1990;80(4):381-7.
53. Chambers JK, Kuribayashi H, Ikeda S, Une Y. Distribution of neprilysin and deposit patterns of Abeta subtypes in the brains of aged squirrel monkeys (Saimiri sciureus). Amyloid. 2010;17(2):75-82.
54. Elfenbein HA, Rosen RF, Stephens SL, Switzer RC, Smith Y, Pare J, et al. Cerebral beta-amyloid angiopathy in aged squirrel monkeys. Histol Histopathol. 2007;22(1-3):155-67.
55. Rosen RF, Tomidokoro Y, Farberg AS, Dooyema J, Ciliax B, Preuss TM, et al. Comparative pathobiology of beta-amyloid and the unique susceptibility of humans to Alzheimer's disease. Neurobiol Aging. 2016;44:185-96.
56. Bading JR, Yamada S, Mackic JB, Kirkman L, Miller C, Calero M, et al. Brain clearance of Alzheimer's amyloid-beta40 in the squirrel monkey: A SPECT study in a primate model of cerebral amyloid angiopathy. J Drug Target. 2002;10(4):359-68.
57. Attems J, Lintner F, Jellinger KA. Amyloid beta peptide 1-42 highly correlates with capillary cerebral amyloid angiopathy and Alzheimer disease pathology. Acta Neuropathol. 2004;107(4):283-91.
58. Lemere CA, Beierschmitt A, Iglesias M, Spooner ET, Bloom JK, Leverone JF, et al. Alzheimer's disease abeta vaccine reduces central nervous system abeta levels in a non-human primate, the Caribbean vervet. Am J Pathol. 2004;165(1):283-97.
59. Nakamura S, Okabayashi S, Ageyama N, Koie H, Sankai T, Ono F, et al. Transthyretin amyloidosis and two other aging-related amyloidoses in an aged vervet monkey. Vet Pathol. 2008;45(1):67-72.
60. Cummings BJ, Satou T, Head E, Milgram NW, Cole GM, Savage MJ, et al. Diffuse plaques contain C-terminal A beta 42 and not A beta 40: evidence from cats and dogs. Neurobiol Aging. 1996;17(4):653-9.

61. Nakamura S, Nakayama H, Kiatipattanasakul W, Uetsuka K, Uchida K, Goto N. Senile plaques in very aged cats. Acta Neuropathol. 1996;91(4):437-9.
62. Head E, Moffat K, Das P, Sarsoza F, Poon WW, Landsberg G, et al. Beta-amyloid deposition and tau phosphorylation in clinically characterized aged cats. Neurobiol Aging. 2005;26(5):749-63.
63. Brellou G, Vlemmas I, Lekkas S, Papaioannou N. Immunohistochemical investigation of amyloid beta-protein (Abeta) in the brain of aged cats. Histol Histopathol. 2005;20(3):725-31.
64. Von Braunmuhl A. [Congophile angiopathy and senile plaques in aged dogs]. Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr. 1956;194(4):396-414.
65. Giaccone G, Verga L, Finazzi M, Pollo B, Tagliavini F, Frangione B, et al. Cerebral preamyloid deposits and congophilic angiopathy in aged dogs. Neurosci Lett. 1990;114(2):178-83.
66. Uchida K, Miyauchi Y, Nakayama H, Goto N. Amyloid angiopathy with cerebral hemorrhage and senile plaque in aged dogs. Nihon Juigaku Zasshi. 1990;52(3):605-11.
67. Uchida K, Nakayama H, Goto N. Pathological studies on cerebral amyloid angiopathy, senile plaques and amyloid deposition in visceral organs in aged dogs. J Vet Med Sci. 1991;53(6):1037-42.
68. Uchida K, Tani Y, Uetsuka K, Nakayama H, Goto N. Immunohistochemical studies on canine cerebral amyloid angiopathy and senile plaques. J Vet Med Sci. 1992;54(4):659-67.
69. Uchida K, Nakayama H, Tateyama S, Goto N. Immunohistochemical analysis of constituents of senile plaques and cerebro-vascular amyloid in aged dogs. J Vet Med Sci. 1992;54(5):1023-9.
70. Uchida K, Okuda R, Yamaguchi R, Tateyama S, Nakayama H, Goto N. Double-labeling immunohistochemical studies on canine senile plaques and cerebral amyloid angiopathy. J Vet Med Sci. 1993;55(4):637-42.
71. Borras D, Ferrer I, Pumarola M. Age-related changes in the brain of the dog. Vet Pathol. 1999;36(3):202-11.
72. Colle MA, Hauw JJ, Crespeau F, Uchihara T, Akiyama H, Checler F, et al. Vascular and parenchymal Abeta deposition in the aging dog: correlation with behavior. Neurobiol Aging. 2000;21(5):695-704.
73. Cummings BJ, Su JH, Cotman CW, White R, Russell MJ. Beta-amyloid accumulation in aged canine brain: a model of early plaque formation in Alzheimer's disease. Neurobiol Aging. 1993;14(6):547-60.
74. Ishihara T, Gondo T, Takahashi M, Uchino F, Ikeda S, Allsop D, et al. Immunohistochemical and immunoelectron microscopical characterization of cerebrovascular and senile plaque amyloid in aged dogs' brains. Brain Res. 1991;548(1-2):196-205.
75. Wegiel J, Wisniewski HM, Dziewiatkowski J, Tarnawski M, Nowakowski J, Dziewiatkowska A, et al. The origin of amyloid in cerebral vessels of aged dogs. Brain Res. 1995;705(1–2):225-34.
76. Yoshino T, Uchida K, Tateyama S, Yamaguchi R, Nakayama H, Goto N. A retrospective study of canine senile plaques and cerebral amyloid angiopathy. Vet Pathol. 1996;33(2):230-4.
77. Shimada A, Kuwamura M, Awakura T, Umemura T, Takada K, Ohama E, et al. Topographic relationship between senile plaques and cerebrovascular amyloidosis in the brain of aged dogs. J Vet Med Sci. 1992;54(1):137-44.
78. Schmidt F, Boltze J, Jager C, Hofmann S, Willems N, Seeger J, et al. Detection and Quantification of beta-Amyloid, Pyroglutamyl Abeta, and Tau in Aged Canines. J Neuropathol Exp Neurol. 2015;74(9):912-23.
79. Wisniewski T, Lalowski M, Bobik M, Russell M, Strosznajder J, Frangione B. Amyloid beta 1-42 deposits do not lead to Alzheimer's neuritic plaques in aged dogs. Biochem J. 1996;313(Pt 2):575-80.
80. Schutt T, Helboe L, Pedersen LO, Waldemar G, Berendt M, Pedersen JT. Dogs with Cognitive Dysfunction as a Spontaneous Model for Early Alzheimer's Disease: A Translational Study of Neuropathological and Inflammatory Markers. J Alzheimers Dis. 2016;52(2):433-49.
81. Uchida K, Kuroki K, Yoshino T, Yamaguchi R, Tateyama S. Immunohistochemical study of constituents other than beta-protein in canine senile plaques and cerebral amyloid angiopathy. Acta Neuropathol. 1997;93(3):277-84.

82. Heuer E, Rosen RF, Cintron A, Walker LC. Nonhuman primate models of alzheimer-like cerebral proteopathy. Curr Pharm Des. 2012;18(8):1159-69.
83. Herzig MC, Winkler DT, Burgermeister P, Pfeifer M, Kohler E, Schmidt SD, et al. Abeta is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis. Nat Neurosci. 2004;7(9):954-60.
84. Bodendorf U, Danner S, Fischer F, Stefani M, Sturchler-Pierrat C, Wiederhold KH, et al. Expression of human beta-secretase in the mouse brain increases the steady-state level of beta-amyloid. J Neurochem. 2002;80(5):799-806.
85. Herzig MC, Paganetti P, Staufenbiel M, Jucker M. BACE1 and mutated presenilin-1 differently modulate Abeta40 and Abeta42 levels and cerebral amyloidosis in APPDutch transgenic mice. Neurodegener Dis. 2007;4(2-3):127-35.
86. Davis J, Xu F, Deane R, Romanov G, Previti ML, Zeigler K, et al. Early-onset and robust cerebral microvascular accumulation of amyloid beta-protein in transgenic mice expressing low levels of a vasculotropic Dutch/Iowa mutant form of amyloid beta-protein precursor. J Biol Chem. 2004;279(19):20296-306.
87. Miao J, Xu F, Davis J, Otte-Holler I, Verbeek MM, Van Nostrand WE. Cerebral microvascular amyloid beta protein deposition induces vascular degeneration and neuroinflammation in transgenic mice expressing human vasculotropic mutant amyloid beta precursor protein. Am J Pathol. 2005;167(2):505-15.
88. Xu F, Grande AM, Robinson JK, Previti ML, Vasek M, Davis J, et al. Early-onset subicular microvascular amyloid and neuroinflammation correlate with behavioral deficits in vasculotropic mutant amyloid beta-protein precursor transgenic mice. Neuroscience. 2007;146(1):98-107.
89. Park L, Koizumi K, El Jamal S, Zhou P, Previti ML, Van Nostrand WE, et al. Age-dependent neurovascular dysfunction and damage in a mouse model of cerebral amyloid angiopathy. Stroke. 2014;45(6):1815-21.
90. Davis J, Xu F, Miao J, Previti ML, Romanov G, Ziegler K, et al. Deficient cerebral clearance of vasculotropic mutant Dutch/Iowa Double A beta in human A betaPP transgenic mice. Neurobiol Aging. 2006;27(7):946-54.
91. Fan R, DeFilippis K, Van Nostrand WE. Induction of complement proteins in a mouse model for cerebral microvascular Abeta deposition. J Neuroinflammation. 2007;4 (22).
92. Van Vickle GD, Esh CL, Daugs ID, Kokjohn TA, Kalback WM, Patton RL, et al. Tg-SwDI transgenic mice exhibit novel alterations in AbetaPP processing, Abeta degradation, and resilient amyloid angiopathy. Am J Pathol. 2008;173(2):483-93.
93. Xu F, Vitek MP, Colton CA, Previti ML, Gharkholonarehe N, Davis J, et al. Human Apolipoprotein E Redistributes Fibrillar Amyloid Deposition in Tg-SwDI Mice. J Neurosci. 2008;28(20):5312-20.
94. Xu F, Vitek MP, Colton CA, Previti ML, Davis J, Van Nostrand WE. Human apolipoprotein E2 promotes parenchymal amyloid deposition and neuronal loss in vasculotropic mutant amyloid-beta protein Tg-SwDI mice. J Alzheimers Dis. 2012;31(2):359-69.
95. Miao J, Vitek MP, Xu F, Previti ML, Davis J, Van Nostrand WE. Reducing cerebral microvascular amyloid-beta protein deposition diminishes regional neuroinflammation in vasculotropic mutant amyloid precursor protein transgenic mice. J Neurosci. 2005;25(27):6271-7.
96. Yang J, Ji Y, Mehta P, Bates KA, Sun Y, Wisniewski T. Blocking the apolipoprotein E/amyloid-beta interaction reduces fibrillar vascular amyloid deposition and cerebral microhemorrhages in TgSwDI mice. J Alzheimers Dis. 2011;24(2):269-85.
97. Kihara T, Shimohama S. Alzheimer's disease and acetylcholine receptors. Acta Neurobiol Exp (Wars). 2004;64(1):99-105.
98. Fisher A. Cholinergic treatments with emphasis on m1 muscarinic agonists as potential disease-modifying agents for Alzheimer's disease. Neurotherapeutics. 2008;5(3):433-42.

99. Medeiros R, Kitazawa M, Caccamo A, Baglietto-Vargas D, Estrada-Hernandez T, Cribbs DH, et al. Loss of muscarinic M<inf>1</inf> receptor exacerbates Alzheimer's disease-like pathology and cognitive decline. Am J Pathol. 2011;179(2):980-91.
100. Moechars D, Dewachter I, Lorent K, Reverse D, Baekelandt V, Naidu A, et al. Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. J Biol Chem. 1999;274(10):6483-92.
101. Van Dorpe J, Smeijers L, Dewachter I, Nuyens D, Spittaels K, Van den Haute C, et al. Prominent cerebral amyloid angiopathy in transgenic mice overexpressing the London mutant of human APP in neurons. Am J Pathology. 2000;157(4):1283-98.
102. Van Dooren T, Dewachter I, Borghgraef P, van Leuven F. Transgenic mouse models for APP processing and Alzheimer's disease: early and late defects. Subcell Biochem. 2005;38:45-63.
103. Dewachter I, Van Dorpe J, Spittaels K, Tesseur I, Van Den Haute C, Moechars D, et al. Modeling Alzheimer's disease in transgenic mice: Effect of age and of Presenilin1 on amyloid biochemistry and pathology in APP/London mice. Exp Gerontol. 2000;35(6-7):831-41.
104. Calhoun ME, Burgermeister P, Phinney AL, Stalder M, Tolnay M, Wiederhold KH, et al. Neuronal overexpression of mutant amyloid precursor protein results in prominent deposition of cerebrovascular amyloid. Proc Natl Acad Sci U S A. 1999;96(24):14088-93.
105. Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, et al. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. Proc Natl Acad Sci U S A. 1997;94(24):13287-92.
106. Sturchler-Pierrat C, Staufenbiel M. Pathogenic mechanisms of Alzheimer's disease analyzed in the APP23 transgenic mouse model. Ann N Y Acad Sci. 2000;920:134-9.
107. Kuo YM, Beach TG, Sue LI, Scott S, Layne KJ, Kokjohn TA, et al. The evolution of Abeta peptide burden in the APP23 transgenic mice: Implications for Abeta deposition in Alzheimer disease. Mol Med. 2001;7(9):609-18.
108. Winkler DT, Bondolfi L, Herzig MC, Jann L, Calhoun ME, Wiederhold KH, et al. Spontaneous hemorrhagic stroke in a mouse model of cerebral amyloid angiopathy. J Neurosci. 2001;21(5):1619-27.
109. Thal DR, Capetillo-Zarate E, Larionov S, Staufenbiel M, Zurbruegg S, Beckmann N. Capillary cerebral amyloid angiopathy is associated with vessel occlusion and cerebral blood flow disturbances. Neurobiol Aging. 2009;30(12):1936-48.
110. Reuter B, Venus A, Heiler P, Schad L, Ebert A, Hennerici MG, et al. Development of cerebral microbleeds in the APP23-transgenic mouse model of cerebral amyloid angiopathy-a 9.4 tesla MRI study. Front Aging Neurosci. 2016;8 (170).
111. Maier FC, Wehrl HF, Schmid AM, Mannheim JG, Wiehr S, Lerdkrai C, et al. Longitudinal PET-MRI reveals beta-amyloid deposition and rCBF dynamics and connects vascular amyloidosis to quantitative loss of perfusion. Nat Med. 2014;10.
112. Beckmann N, Gerard C, Abramowski D, Cannet C, Staufenbiel M. Noninvasive magnetic resonance imaging detection of cerebral amyloid angiopathy-related microvascular alterations using superparamagnetic iron oxide particles in APP transgenic mouse models of Alzheimer's disease: Application to passive Abeta immunotherapy. J Neurosci. 2011;31(3):1023-31.
113. Beckmann N, Schuler A, Mueggler T, Meyer EP, Wiederhold KH, Staufenbiel M, et al. Age-dependent cerebrovascular abnormalities and blood flow disturbances in APP23 mice modeling Alzheimer's disease. J Neurosci. 2003;23(24):8453-9.
114. Mueggler T, Sturchler-Pierrat C, Baumann D, Rausch M, Staufenbiel M, Rudin M. Compromised hemodynamic response in amyloid precursor protein transgenic mice. J Neurosci. 2002;22(16):7218-24.
115. Knobloch M, Konietzko U, Krebs DC, Nitsch RM. Intracellular Abeta and cognitive deficits precede beta-amyloid deposition in transgenic arcAbeta mice. Neurobiol Aging. 2007;28(9):1297-306.

116. Princz-Kranz FL, Mueggler T, Knobloch M, Nitsch RM, Rudin M. Vascular response to acetazolamide decreases as a function of age in the arcAbeta mouse model of cerebral amyloidosis. Neurobiol Dis. 2010;40(1):284-92.
117. Merlini M, Meyer EP, Ulmann-Schuler A, Nitsch RM. Vascular beta-amyloid and early astrocyte alterations impair cerebrovascular function and cerebral metabolism in transgenic arcAbeta mice. Acta Neuropathol. 2011;122(3):293-311.
118. Klohs J, Deistung A, Schweser F, Grandjean J, Dominietto M, Waschkies C, et al. Detection of cerebral microbleeds with quantitative susceptibility mapping in the ArcAbeta mouse model of cerebral amyloidosis. J Cereb Blood Flow Metab. 2011;31(12):2282-92.
119. Klohs J, Baltes C, Princz-Kranz F, Ratering D, Nitsch RM, Knuesel I, et al. Contrast-enhanced magnetic resonance microangiography reveals remodeling of the cerebral microvasculature in transgenic ArcAbeta mice. J Neurosci. 2012;32(5):1705-13.
120. Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. Nature. 1995;373(6514):523-7.
121. Fryer JD, Taylor JW, DeMattos RB, Bales KR, Paul SM, Parsadanian M, et al. Apolipoprotein E markedly facilitates age-dependent cerebral amyloid angiopathy and spontaneous hemorrhage in amyloid precursor protein transgenic mice. J Neurosci. 2003;23(21):7889-96.
122. Domnitz SB, Robbins EM, Hoang AW, Garcia-Alloza M, Hyman BT, Rebeck GW, et al. Progression of cerebral amyloid angiopathy in transgenic mouse models of Alzheimer disease. J Neuropathol Exp Neurol. 2005;64(7):588-94.
123. Kimchi EY, Kajdasz S, Bacskai BJ, Hyman BT. Analysis of cerebral amyloid angiopathy in a transgenic mouse model of Alzheimer disease using in vivo multiphoton microscopy. J Neuropathol Exp Neurol. 2001;60(3):274-9.
124. Schroeter S, Khan K, Barbour R, Doan M, Chen M, Guido T, et al. Immunotherapy reduces vascular amyloid-beta in PDAPP mice. J Neurosci. 2008;28(27):6787-93.
125. Racke MM, Boone LI, Hepburn DL, Parsadainian M, Bryan MT, Ness DK, et al. 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;25(3):629-36.
126. Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, et al. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science. 1996;274(5284):99-102.
127. Hawkes CA, Hartig W, Kacza J, Schliebs R, Weller RO, Nicoll JA, et al. Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Acta Neuropathol. 2011;121(4):431-43.
128. Holtzman DM, Fagan AM, Mackey B, Tenkova T, Sartorius L, Paul SM, et al. Apolipoprotein E facilitates neuritic and cerebrovascular plaque formation in an Alzheimer's disease model. Ann Neurol. 2000;47(6):739-47.
129. Fisher M, Vasilevko V, Passos GF, Ventura C, Quiring D, Cribbs DH. Therapeutic modulation of cerebral microhemorrhage in a mouse model of cerebral amyloid angiopathy. Stroke. 2011;42(11):3300-3.
130. Lo P, Crouzet C, Vasilevko V, Choi B. Visualization of microbleeds with optical histology in mouse model of cerebral amyloid angiopathy. Microvasc Res. 2016;105:109-13.
131. Christie R, Yamada M, Moskowitz M, Hyman B. Structural and functional disruption of vascular smooth muscle cells in a transgenic mouse model of amyloid angiopathy. Am J Pathol. 2001;158(3):1065-71.
132. Robbins EM, Betensky RA, Domnitz SB, Purcell SM, Garcia-Alloza M, Greenberg C, et al. Kinetics of cerebral amyloid angiopathy progression in a transgenic mouse model of Alzheimer disease. J Neurosci. 2006;26(2):365-71.

133. Han BH, Zhou ML, Abousaleh F, Brendza RP, Dietrich HH, Koenigsknecht-Talboo J, et al. Cerebrovascular dysfunction in amyloid precursor protein transgenic mice: contribution of soluble and insoluble amyloid-beta peptide, partial restoration via gamma-secretase inhibition. J Neurosci. 2008;28(50):13542-50.
134. Shin HK, Jones PB, Garcia-Alloza M, Borrelli L, Greenberg SM, Bacskai BJ, et al. Age-dependent cerebrovascular dysfunction in a transgenic mouse model of cerebral amyloid angiopathy. Brain. 2007;130(Pt 9):2310-9.
135. Kara F, Dongen ES, Schliebs R, Buchem MA, Groot HJ, Alia A. Monitoring blood flow alterations in the Tg2576 mouse model of Alzheimer's disease by in vivo magnetic resonance angiography at 17.6 T. Neuroimage. 2012;60(2):958-66.
136. Fryer JD, Simmons K, Parsadanian M, Bales KR, Paul SM, Sullivan PM, et al. Human apolipoprotein E4 alters the amyloid-beta 40:42 ratio and promotes the formation of cerebral amyloid angiopathy in an amyloid precursor protein transgenic model. J Neurosci. 2005;25(11):2803-10.
137. Mori T, Koyama N, Arendash GW, Horikoshi-Sakuraba Y, Tan J, Town T. Overexpression of human S100B exacerbates cerebral amyloidosis and gliosis in the Tg2576 mouse model of Alzheimer's disease. Glia. 2010;58(3):300-14.
138. Chishti MA, Yang DS, Janus C, Phinney AL, Horne P, Pearson J, et al. Early-onset amyloid deposition and cognitive deficits in transgenic mice expressing a double mutant form of amyloid precursor protein 695. J Biol Chem. 2001;276(24):21562-70.
139. Hawkes CA, McLaurin J. Selective targeting of perivascular macrophages for clearance of beta-amyloid in cerebral amyloid angiopathy. Proc Natl Acad Sci U S A. 2009;106(4):1261-6.
140. Dorr A, Sahota B, Chinta LV, Brown ME, Lai AY, Ma K, et al. Amyloid-beta-dependent compromise of microvascular structure and function in a model of Alzheimer's disease. Brain. 2012;135(10):3039-50.
141. Thomason LAM, Stefanovic B, McLaurin J. Cerebrovascular contributions to Alzheimer's disease pathophysiology and potential therapeutic interventions in mouse models. Eur J Neurosci. 2013;37(12):1994-2004.
142. Religa P, Cao R, Religa D, Xue Y, Bogdanovic N, Westaway D, et al. VEGF significantly restores impaired memory behavior in Alzheimer's mice by improvement of vascular survival. Sci Rep. 2013;3:2053.
143. Lai AY, Dorr A, Thomason LAM, Koletar MM, Sled JG, Stefanovic B, et al. Venular degeneration leads to vascular dysfunction in a transgenic model of Alzheimer's disease. Brain. 2015;138(4):1046-58.
144. Van Groen T, Kiliaan AJ, Kadish I. Deposition of mouse amyloid β in human APP/PS1 double and single AD model transgenic mice. Neurobiol Dis. 2006;23(3):653-62.
145. Garcia-Alloza M, Robbins EM, Zhang-Nunes SX, Purcell SM, Betensky RA, Raju S, et al. Characterization of amyloid deposition in the APPswe/PS1dE9 mouse model of Alzheimer disease. Neurobiol Dis. 2006;24(3):516-24.
146. Jiao SS, Bu XL, Liu YH, Zhu C, Wang QH, Shen LL, et al. Sex Dimorphism Profile of Alzheimer's Disease-Type Pathologies in an APP/PS1 Mouse Model. Neurotox Res. 2016;29(2):256-66.
147. Garcia-Alloza M, Gregory J, Kuchibhotla KV, Fine S, Wei Y, Ayata C, et al. Cerebrovascular lesions induce transient beta-amyloid deposition. Brain. 2011;134(12):3694-704.
148. El Tannir El Tayara N, Delatour B, Volk A, Dhenain M. Detection of vascular alterations by in vivo magnetic resonance angiography and histology in APP/PS1 mouse model of Alzheimer's disease. Magn Reson Mater Phy. 2010;23(1):53-64.
149. Willuweit A, Velden J, Godemann R, Manook A, Jetzek F, Tintrup H, et al. Early-onset and robust amyloid pathology in a new homozygous mouse model of Alzheimer's disease. PLoS One. 2009;4 (11)(e7931).
150. Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J Neurosci. 2006;26(40):10129-40.

151. Giannoni P, Arango-Lievano M, Neves ID, Rousset MC, Baranger K, Rivera S, et al. Cerebrovascular pathology during the progression of experimental Alzheimer's disease. Neurobiol Dis. 2016;88:107-17.
152. Lin B, Hasegawa Y, Takane K, Koibuchi N, Cao C, Kim-Mitsuyama S. High-fat-diet intake enhances cerebral amyloid angiopathy and cognitive impairment in a mouse model of alzheimer's disease, independently of metabolic disorders. J Am Heart Assoc. 2016;5 (6) (e003154).
153. Li H, Guo Q, Inoue T, Polito VA, Tabuchi K, Hammer RE, et al. Vascular and parenchymal amyloid pathology in an Alzheimer disease knock-in mouse model: interplay with cerebral blood flow. Mol Neurodegener. 2014;9:28.
154. Kulic L, McAfoose J, Welt T, Tackenberg C, Spani C, Wirth F, et al. Early accumulation of intracellular fibrillar oligomers and late congophilic amyloid angiopathy in mice expressing the Osaka intra-Abeta APP mutation. Transl Psychiatry. 2012;2 (e183).
155. Lord A, Kalimo H, Eckman C, Zhang XQ, Lannfelt L, Nilsson LN. The Arctic Alzheimer mutation facilitates early intraneuronal Abeta aggregation and senile plaque formation in transgenic mice. Neurobiol Aging. 2006;27(1):67-77.
156. Yang J, Lunde LK, Nuntagij P, Oguchi T, Camassa LMA, Nilsson LNG, et al. Loss of astrocyte polarization in the Tg-ArcSwe mouse model of Alzheimer's disease. J Alzheimers Dis. 2011;27(4):711-22.
157. Merlini M, Shi Y, Keller S, Savarese G, Akhmedov A, Derungs R, et al. Reduced nitric oxide bioavailability mediates cerebroarterial dysfunction independent of cerebral amyloid angiopathy in a mouse model of Alzheimer's disease. Am J Physiol Heart Circ Physiol. 2017;312(2):H232-H8.
158. McGowan E, Pickford F, Kim J, Onstead L, Eriksen J, Yu C, et al. Abeta42 is essential for parenchymal and vascular amyloid deposition in mice. Neuron. 2005;47(2):191-9.
159. De Jong GI, De Vos RA, Steur EN, Luiten PG. Cerebrovascular hypoperfusion: a risk factor for Alzheimer's disease? Animal model and postmortem human studies. Ann N Y Acad Sci. 1997;826:56-74.
160. De la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol. 2004;3(3):184-90.
161. Mazza M, Marano G, Traversi G, Bria P, Mazza S. Primary cerebral blood flow deficiency and Alzheimer's disease: shadows and lights. J Alzheimers Dis. 2011;23(3):375-89.
162. Okamoto Y, Yamamoto T, Kalaria RN, Senzaki H, Maki T, Hase Y, et al. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. Acta Neuropathol. 2012;123(3):381-94.
163. Zhai Y, Yamashita T, Nakano Y, Sun Z, Shang J, Feng T, et al. Chronic Cerebral Hypoperfusion Accelerates Alzheimer's Disease Pathology with Cerebrovascular Remodeling in a Novel Mouse Model. J Alzheimers Dis. 2016;53(3):893-905.
164. Gentile MT, Poulet R, Di Pardo A, Cifelli G, Maffei A, Vecchione C, et al. Beta-amyloid deposition in brain is enhanced in mouse models of arterial hypertension. Neurobiol Aging. 2009;30(2):222-8.
165. Cifuentes D, Poittevin M, Dere E, Broqueres-You D, Bonnin P, Benessiano J, et al. Hypertension accelerates the progression of Alzheimer-like pathology in a mouse model of the disease. Hypertension. 2015;65(1):218-24.
166. Kruyer A, Soplop N, Strickland S, Norris EH. Chronic Hypertension Leads to Neurodegeneration in the TgSwDI Mouse Model of Alzheimer's Disease. Hypertension. 2015;66(1):175-82.
167. Passos GF, Kilday K, Gillen DL, Cribbs DH, Vasilevko V. Experimental hypertension increases spontaneous intracerebral hemorrhages in a mouse model of cerebral amyloidosis. J Cereb Blood Flow Metab. 2016;36(2):399-404.
168. Abraham JM, Cho L. The homocysteine hypothesis: still relevant to the prevention and treatment of cardiovascular disease? Cleve Clin J Med. 2010;77(12):911-8.
169. Sudduth TL, Weekman EM, Brothers HM, Braun K, Wilcock DM. beta-amyloid deposition is shifted to the vasculature and memory impairment is exacerbated when hyperhomocysteinemia is induced in APP/PS1 transgenic mice. Alzheimers Res Ther. 2014;6 (3)(32).

170. Li JG, Pratico D. High levels of homocysteine results in cerebral amyloid angiopathy in mice. J Alzheimers Dis. 2015;43(1):29-35.
171. Chung YC, Kruyer A, Yao Y, Feierman E, Richards A, Strickland S, et al. Hyperhomocysteinemia exacerbates Alzheimer's disease pathology by way of the beta-amyloid fibrinogen interaction. J Thromb Haemost. 2016;14(7):1442-52.
172. Austin SA, Santhanam AV, Hinton DJ, Choi DS, Katusic ZS. Endothelial nitric oxide deficiency promotes Alzheimer's disease pathology. J Neurochem. 2013;127(5):691-700.
173. Tan XL, Xue YQ, Ma T, Wang X, Li JJ, Lan L, et al. Partial eNOS deficiency causes spontaneous thrombotic cerebral infarction, amyloid angiopathy and cognitive impairment. Mol Neurodegener. 2015;24.
174. Wilcock DM, Vitek MP, Colton CA. Vascular amyloid alters astrocytic water and potassium channels in mouse models and humans with Alzheimer's disease. Neuroscience. 2009;159(3):1055-69.
175. Van Nostrand WE, Xu F, Rozemuller AJ, Colton CA. Enhanced capillary amyloid angiopathy-associated pathology in Tg-SwDI mice with deleted nitric oxide synthase 2. Stroke. 2010;41(10 Suppl):S135-8.
176. Salkovic-Petrisic M, Tribl F, Schmidt M, Hoyer S, Riederer P. Alzheimer-like changes in protein kinase B and glycogen synthase kinase-3 in rat frontal cortex and hippocampus after damage to the insulin signalling pathway. J Neurochem. 2006;96(4):1005-15.
177. Salkovic-Petrisic M, Osmanovic-Barilar J, Bruckner MK, Hoyer S, Arendt T, Riederer P. Cerebral amyloid angiopathy in streptozotocin rat model of sporadic Alzheimer's disease: A long-term follow up study. J Neural Transm. 2011;118(5):765-72.
178. Cohen RM, Rezai-Zadeh K, Weitz TM, Rentsendorj A, Gate D, Spivak I, et al. A transgenic Alzheimer rat with plaques, tau pathology, behavioral impairment, oligomeric abeta, and frank neuronal loss. J Neurosci. 2013;33(15):6245-56.
179. Agca C, Fritz JJ, Walker LC, Levey AI, Chan AW, Lah JJ, et al. Development of transgenic rats producing human beta-amyloid precursor protein as a model for Alzheimer's disease: transgene and endogenous APP genes are regulated tissue-specifically. BMC Neurosci. 2008;9:28.
180. Silverberg GD, Miller MC, Pascale CL, Caralopoulos IN, Agca Y, Agca C, et al. Kaolin-induced chronic hydrocephalus accelerates amyloid deposition and vascular disease in transgenic rats expressing high levels of human APP. Fluids Barriers CNS. 2015;12 (1)(2).
181. Rosen RF, Fritz JJ, Dooyema J, Cintron AF, Hamaguchi T, Lah JJ, et al. Exogenous seeding of cerebral beta-amyloid deposition in betaAPP-transgenic rats. J Neurochem. 2012;120(5):660-6.
182. Premachandra BN, Naidu RG, Williams IK, Blumenthal HT. Cerebral vascular amyloid deposition in rabbits with induced thyroglobulin immunity. Neurosci Lett. 1995;188(1):65-9.
183. Beach TG, Potter PE, Kuo YM, Emmerling MR, Durham RA, Webster SD, et al. Cholinergic deafferentation of the rabbit cortex: A new animal model of Abeta deposition. Neurosci Lett. 2000;283(1):9-12.
184. Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JA, Perry VH, et al. Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathol Appl Neurobiol. 2008;34(2):131-44.
185. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, et al. Clearance systems in the brain—implications for Alzheimer disease. Nat Rev Neurol. 2015;11(8):457-70.
186. Schley D, Carare-Nnadi R, Please CP, Perry VH, Weller RO. Mechanisms to explain the reverse perivascular transport of solutes out of the brain. J Theor Biol. 2006;238(4):962-74.
187. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol. 2008;18(2):253-66.

188. Bakker EN, Bacskai BJ, Arbel-Ornath M, Aldea R, Bedussi B, Morris AW, et al. Lymphatic Clearance of the Brain: Perivascular, Paravascular and Significance for Neurodegenerative Diseases. Cell Mol Neurobiol. 2016;36(2):181-94.
189. Morris AW, Carare RO, Schreiber S, Hawkes CA. The Cerebrovascular Basement Membrane: Role in the Clearance of beta-amyloid and Cerebral Amyloid Angiopathy. Front Aging Neurosci. 2014;6:251.
190. Rennels ML, Gregory TF, Blaumanis OR, Fujimoto K, Grady PA. Evidence for a 'paravascular' fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Brain Res. 1985;326(1):47-63.
191. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med. 2012;4(147):147ra11.
192. Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, et al. Impairment of paravascular clearance pathways in the aging brain. Ann Neurol. 2014;76(6):845-61.
193. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. Neurochem Res. 2015;40(12):2583-99.
194. Iliff JJ, Nedergaard M. Is there a cerebral lymphatic system? Stroke. 2013;44(6 Suppl 1):S93-5.
195. Boche D, Zotova E, Weller RO, Love S, Neal JW, Pickering RM, et al. Consequence of Abeta immunization on the vasculature of human Alzheimer's disease brain. Brain. 2008;131(Pt 12):3299-310.
196. Boche D, Denham N, Holmes C, Nicoll JA. Neuropathology after active Abeta42 immunotherapy: implications for Alzheimer's disease pathogenesis. Acta Neuropathol. 2010;120(3):369-84.
197. Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology. 2003;61(1):46-54.
198. Bales KR, O'Neill SM, Pozdnyakov N, Pan F, Caouette D, Pi Y, et al. Passive immunotherapy targeting amyloid-beta reduces cerebral amyloid angiopathy and improves vascular reactivity. Brain. 2016;139(Pt 2):563-77.