Alzheimer Review Series

J. Cell. Mol. Med. Vol 13, No 6, 2009 pp. 1034-1042

Guest Editor: B. O. Popescu

The rat as an animal model of Alzheimer's disease

Eirikur Benedikz [a, †, *], Ewa Kloskowska [a, †], Bengt Winblad [b]

[a] *Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Neurodegeneration, Novum, Stockholm, Sweden*

[b] *Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, KI-Alzheimer's Disease Research Center, Novum, Stockholm, Sweden*

Received: March 17, 2009; Accepted: April 29, 2009

Abstract

As a disease model, the laboratory rat has contributed enormously to neuroscience research over the years. It has also been a popular animal model for Alzheimer's disease but its popularity has diminished during the last decade, as techniques for genetic manipulation in rats have lagged behind that of mice. In recent years, the rat has been making a comeback as an Alzheimer's disease model and the appearance of increasing numbers of transgenic rats will be a welcome and valuable complement to the existing mouse models. This review summarizes the contributions and current status of the rat as an animal model of Alzheimer's disease.

Keywords: Alzheimer's disease • rat • transgenic • amyloid • cholinergic

Introduction

Alzheimer's disease (AD) is characterized by a progressive cognitive decline, where memory of recent facts, spatial orientation, attention and executive functions are ones of the first affected. This is followed by speech and behavioural problems, which affect everyday life [1]. The pathological changes in the brain, which define the disease, are abundant extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs), accompanied by synaptic and neuronal loss, and brain inflammation [2–5]. The amyloid plaques are composed mainly of aggregated amyloid-β peptide (Aβ) [6, 7], which is derived by proteolytic cleavage from the amyloid precursor protein (APP) [8]. The Aβ peptide can consist of 39–43 amino acid residues, but the two major forms are Aβ40 accounting for ~90% of all Aβ released from cells and the longer Aβ42 accounting for only ~10%. Aβ42 is more hydrophobic and more prone to aggregation than Aβ40 [9], and is the predominant form found in the amyloid plaques of AD [10]. The NFTs consist of an aggregated form of hyperphosphorylated microtubule-associated protein, tau [11].

Although the cause of AD still is the subject of considerable debate, the so-called amyloid cascade hypothesis remains the best-defined and most studied conceptual framework for the disease [12]. This hypothesis is based upon the pathological characteristics and the genetics of the disease [13, 14]. To date, about 200 mutations causative of a hereditary early onset form of AD (familial AD; FAD) have been discovered within the genes encoding APP, presenilin 1 (PS1) and presenilin 2 (http://www.molgen.ua.ac.be/ADMutations). The presenilins are involved in the processing of APP and mutations in all three proteins result in altered production

[†]These authors contributed equally.
*Correspondence to: Eirikur BENEDIKZ, Ph.D.,
Karolinska Institutet, Department of Neurobiology,
Care Sciences and Society, Division of Neurodegeneration,
Norum, pl. 5, 141 86 Stockholm, Sweden.
Tel.: +46 8 58 58 38 92
Fax: +46 8 58 58 38 80
E-mail: eirikur.benedikz@ki.se

doi:10.1111/j.1582-4934.2009.00781.x

of Aβ. Although details of the amyloid cascade hypothesis have evolved since it was first proposed, its core principle remains essentially unaltered in that the Aβ peptides are the root cause of AD. It is therefore not surprising that many anti-amyloid and other neuroprotective therapeutic approaches are currently under investigation [15].

Animal models offer valuable tools for evaluating new therapeutic strategies for treatment of human diseases, as well as for studying the pathological mechanisms involved in the disease processes. Due to the lack of complete understanding of the aetiology of AD, all the available models have limitations, which have to be carefully considered when using them. There are no natural models of AD, so most of the research is performed using models simulating the disease phenotypes by active manipulation of the animals, or more recently using transgenic animal models. Numerous animal species have been used to model different aspects of AD. Initially, the rat was a favoured species, but during the last decade the increasing knowledge of advanced genetic techniques developed in the mouse, in addition to the discovery of gene mutations causative of familial forms of AD allowed for the generation of a growing number of transgenic mouse models. A fairly complete list of transgenic mouse models relevant for AD is continuously updated on the Alzheimer Research Forum homepage (http://www.alzforum.org/res/com/tra/default.asp). But in recent years, the rat has been making a comeback as an AD model. There are several reasons for this, *e.g.* sequencing of the rat genome, recent developments in technologies to manipulate the rat genome and poor predictive power of mouse models for drug efficacy in human beings.

The laboratory rat

The rat was the first mammalian species domesticated for scientific research over 180 years ago [16]. Since then, it has been one of the most extensively studied model organism, particularly in cardiovascular, cancer, toxicology, behavioural, neurodegeneration and aging research [17]. Selective breeding has resulted in the generation of over 200 inbred rat strains modelling different aspects of human diseases [18]. The rat's contribution to human health cannot be overestimated [16] and it has been the organism of choice for most physiological and behavioural research for decades. Behavioural scientists favour the rat because it is an intelligent and quick learner, whereas physiologists take advantage of the fact that physiological processes are similar in rats and human beings. Furthermore, rats are large enough for convenient physiological measurements [19]. Geneticists on the other hand prefer the mouse, which is smaller and easier to manipulate genetically [20]. Since the mouse has proven easier to manipulate genetically than the rat, it has become the most prevailing mammalian model organism in the transgenic research field. But, what mice provide genetically, they often lack in terms of physiological insights, with researchers often extrapolating from rat data [21]. One of the critical features of an animal model of AD is the ability to analyse memory and cognition in behavioural tests. The differences between the behaviour of rats and mice are far greater than many people realize, although most tasks can be performed by both species [22]. Compared to the rat, the mouse exhibits a simpler behavioural repertoire and much less flexibility in dealing with novel situations. Therefore, the mouse poses a problem for neurobehavioral research as it is a species functioning at a low level of complexity, relative to the rat [23]. Recently, rats have been shown to be able to make adaptive decisions about future behaviour contingent on currently available knowledge. This ability, to reflect on one's own mental processes is termed metacognition and, has previously been thought to be unique to primates [24, 25]. In neuroscience research the rat offers good technological possibilities for neurosurgical/stereotaxic manipulations, neuroimaging, histopathology, electrophysiological recordings or serial sampling of cerebrospinal fluid. In the case of hypertension, atherosclerosis, HIV pathology, Huntington's disease or modelling activation of the complement system, rat models have been shown to represent the human pathology more accurately than analogous mouse models [26–30].

Some of the contributions the rat has made to the field of AD research are summarized below and the recently available transgenic rats are discussed.

Rat models of cholinergic-dysfunction

Early discoveries dating from the 1960s showing deleterious effects of drugs that block cholinergic activity like atropine and scopolamine on memory in rats, and parallel evidence for cholinergic dysfunction in AD subsequently led to the formulation of the 'cholinergic hypothesis of geriatric memory dysfunction' [31, 32]. Since then different approaches to induce cholinergic lesions in rats have been used to study the role of the cholinergic system in cognitive function [33, 34]. The most commonly used neurotoxins included excitatory amino acid neurotransmitters such as glutamate and its analogues (ibotenate, N-methyl-d-aspartate [NMDA], kainate, quisqualate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]), the AF64A toxin specific to cholinergic neurons, or muscarinic receptor antagonists scopolamine and atropine [35]. In 1990, a chronic rat model with a continuous intracerebroventricular infusion of quinolinic acid was developed to simulate the slow evolution of neurodegenerative diseases, including AD [36, 37]. Continuous infusion of quinolinic acid at low doses into the lateral ventricle causes a reduction of the hippocampal and cortical choline acetyltransferase activities in rats. Since some of the earliest affected neurons in the AD brain are cholinergic neurons of the basal forebrain [38, 39] the generation of the immunotoxin 192IgG-saporin, that specifically targets the rat p75 low affinity neurotrophin receptor expressing cholinergic cells of the nucleus basalis of Meynert (or rats equivalent nucleus basalis magnocellularis) and medial septum, allowed for a more

adequate modelling of the disease [40, 41]. Similarly, a selective destruction of nerve growth factor (NGF) dependent cholinergic neurons of the septum was achieved by a direct intraseptal infusion of anti-NGF antibodies [42]. The memory deficits obtained in all these models were similar to those seen in AD, supporting the notion that functional cholinergic pathways are important for memory and cognition and paving the way for cholinergic-based therapies for AD. After initial unsuccessful trials with acetylcholine precursors choline and lecithin, acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) became commonly used drugs for symptomatic treatment of the disease [32, 43].

Aβ-based models of AD

The discovery that Aβ is the main constituent of the characteristic amyloid plaques in the brains of AD patients [6, 7] and is toxic to neurons [44, 45] led to *in vivo* studies on the effects of Aβ in the brain. The acute neurodegenerative effect of Aβ and amyloid cores from the brains of AD patients was demonstrated *in vivo* already in 1991, when these substances were injected into the brain of two different rat models [46, 47]. In both cases, a significant induction of abnormal tau phosphorylation was observed in the immediate vicinity of the Aβ immunoreactive sites. In the following years, several laboratories reported contradictory results from acute injections or continuous infusions of Aβ directly into the rat brain. Whereas many groups demonstrated neurotoxicity, AD-like astrogliosis, tau hyperphosphorylation [48–53] and/or memory decline in the experimental models [51, 53–57], others showed no significant effect of the peptides [58–60]. Likewise, contradictory results were obtained in similar experiments performed on rhesus monkeys [61, 62]. Much of the variance in the results obtained depended on the nature of the peptide (fibrillized or soluble Aβ) or solvent used, concentration of the solution and manner of introduction (single injections or continuous infusions over different periods of time into rat ventricles, hippocampus or septum), age of the treated animals (young *versus* old) and time frame when the effects were assessed (immediate or long-term effects). More models demonstrating a deteriorating effect of Aβ *in vivo* followed in the 2000s, proving that this is still a viable approach for modelling different aspects of AD pathology. These models have, for example, been used for testing the protective effects of ginkgo biloba extracts, docosahexaenoic acid (DHA), ginseng, estradiols, green tea, synthetic cognitive enhancers or antioxidants [63–70] and the deteriorating effects of chronic stress [71] on memory in Aβ injected/infused rats. In 2007, Takata *et al.* [72] showed that exogenous microglia, transplanted into the brains of rats microinjected with Aβ, participate in Aβ clearance.

Recently, a variation on the Aβ infusion model was reported [73]. In this model, Aβ was combined with inducers of oxidative stress to induce neuronal cell death, amyloid deposits, gliosis and memory impairment following a 4 week intracerebroventricular infusion. Oxidative stress was induced using the pro-oxidative cation Fe^{2+} and the glutathione synthesis inhibitor buthionine sulfoximine (BSO). This model is now available through a commercial vendor.

Transgenic rats

The first transgenic models of AD, harbouring human APP with FAD-causative mutations, appeared over ten years ago [74, 75]. These models were generated in mouse but simultaneously, unsuccessful attempts were made to develop AD transgenic rats [76, 77]. Today, many transgenic mouse lines show the presence of amyloid deposits that progress with age. Synaptic and neuronal loss differs considerably between the different lines and behavioural testing has also exposed varying degrees of deficits in reference and working memory tasks [78, 79]. A common feature of these models is the absence of NFTs; only mice expressing mutated human tau develop tangle pathology. Although no tau mutations have been reported in AD patients, they do cause other dementia disorders like fronto-temporal dementia associated with chromosome 17 (FTDP-17), proving that tau dysfunction can cause memory deterioration. Data from these models have allowed for a better understanding of the biophysical and pathological properties of tau polymers in dementia [80, 81]. All in all, the transgenic mouse models have contributed extensively to our understanding of AD pathogenesis and to investigations of possible therapeutic strategies.

Multiple genetically manipulated mouse lines have been generated in the past years: not only transgenic but also knockout, knockin and conditional mutant strains (in which genes can be conveniently switched off and on). Until recently, this has not been possible in rats, due to the impossibility of isolating rat embryonic stem cells, which have been normally used for genetic manipulations [19]. The increasing evolution of transgenic, targeted mutagenesis and cloning techniques has however paved the way for the generation of genetically manipulated rat lines [82, 83]. Whereas the first transgenic rat appeared already in 1990, transgenic rat models of human neurodegenerative diseases started appearing only in the 2000s, and the first rat knockout animal was reported in 2003 [30, 84–87]. During the last few years, several single- and multi-transgenic rat models of AD have emerged (Table 1). Being available for a much shorter time, the transgenic AD rat models are not yet as well characterized as many of the mouse lines with respect to the pathology and memory deterioration, but they do offer a promising new era for AD pharmacological research. Below is a brief review of the APP transgenic rat models that have been published to date.

The TgAPPswe rat

The first APP transgenic rat to be published was the TgAPPswe rat by Ruiz-Opazo *et al.* in 2004 [88]. These Fisher-344 rats over-expressed a minigene cDNA construct with human APP containing the Swedish AD mutation (K670N; M671L) driven by the

Table 1 Alzheimer's disease transgenic rat models

Rat AD models	Background strain	Transgene(s)	Promoter(s)	Extracellular Aβ pathology	Behavioural impairment	References
TgAPPswe	Fischer-344	APPswe	PDGF	No	Attenuated memory decline	[88]
UKUR25	Wistar	APP751 swe/ind hPS1 Finn	PDGF	No	16 months (mild impairment)	[91, 92]
Tg6590	Sprague-Dawley	APPswe	Ubiquitin-C	Yes after 15 months	9 months	[93, 94]
Tg478/Tg116	Sprague-Dawley	APP695 swe APP swe/ind	Rat synapsin I PDGFβ	Yes after 18 months	Nr	[97]
Tg478/Tg1116/Tg11587	Sprague-Dawley	APP695 swe APP swe/ind hPS1 Finn	Rat synapsin I PDGFβ rat synapsin I	Yes after 9 months	7 months	[97, 99]
APP21 and APP31	Fisher-344	APP695 swe/ind	Ubiquitin-C	Nr	Nr	[101]
#318 line	SHR	hTau truncated	Mouse Thy-1	No (tau pathology)	Yes	[102, 104]

APPswe, APP with the 'Swedish' K670N/M671L mutation; APPind, V717F 'Indiana' mutation; PS1 Finn, PS1 with the M146L Finnish mutation; hTau truncated, human tau truncated at amino acid positions 151–391; PDGF, platelet-derived growth factor; PrP, prion promoter; Thy1, Thymocyte differentiation antigen 1 promoter; P-tau, phosphorylated tau immunoreactivity; SHR, spontaneously hypertensive rat; Nr, not reported.

platelet-derived growth factor (PDGF) promoter. The increase in APP expression was low, only 56.8% at the mRNA level. The Aβ levels in the brain were increased by 21% for Aβ42 and 6% for Aβ40 at the age of 12 months. No AD-related pathology was found in these animals up to an age of 18 months. Surprisingly, the TgAPPswe rats performed significantly better in the Morris water maze than the age-matched controls at 6 and 12 months of age. Although the TgAPPswe rats are not a model of AD, the findings certainly raise questions concerning the physiological role for APP and its derivatives in learning and memory functions.

The UKUR25 rat

The same year as the TgAPPswe rat was reported, a series of papers on double-transgenic Wistar rat line UKUR25 were published [89–92]. The UKUR25 rats express human APP containing the Swedish and Indiana (V717F) mutations, and mutated PS1 (M146L). Both constructs were driven by the PDGF promoter. The main pathological feature in the brain of these animals, visible after 6 months of age, was the accumulation of Aβ intracellularly in neurons of the hippocampus and cortex. The levels of Aβ in the brain has however not been reported. No extracellular amyloid was seen in these animals up to 24 months of age. Behaviour analysis of 7- and 16-month-old UKUR25 rats revealed mild impairment in acquisition learning in 16-month-old male rats. Following acquisition learning the platform was moved and the rats were meant to learn the new location. There was no significant difference between the trangenics and controls in this task. At the age of 9 months, there was an increase in active phospho-ERK2 in the UKUR25 rat brain, which was accompanied by increased levels of tau phosphorylation at S396 and S404 ERK2 sites (recognized by the PHF-1 antibody). The lack of any extracellular pathology together with the mild behavioural phenotype may limit the use of this transgenic rat in AD research.

The Tg6590 rat

In 2007, Folkesson *et al.* [93] published on a transgenic rat line Tg6590 that expresses human APP with the Swedish mutation driven by the ubiquitin promoter. The Tg6590 rat line shows mainly neuronal expression of the human APP protein, with the highest levels found in the cortex, hippocampus and cerebellum. These rats developed mild extracellular Aβ immunoreactivity but no compact mature amyloid deposits. The level Aβ42 and Aβ40 are increased to a similar extent as would be expected due to the mutation used [94]. The levels of both Aβ species are increased 65% in hippocampus and 40% in cortex of 11-month-old animals. The Tg6590 rats display learning and memory deficits in the Morris water maze at the age of 9 months and altered spontaneous behaviour measured in open-field [94]. As in several APP mouse models, these behavioural changes are seen prior to the appearance of any amyloid depositions. Similar to the UKUR25 line, there is an apparent increase in phosphorylated tau at the PHF-1 site in the Tg6590 rat brain, but the increase does not reach statistical significance. Cultured primary hippocampal neurons from this line show complex alterations of calcium homeostasis, that could potentially play a role in the learning and memory impairments seen in these animals [95, 96]. Although the Tg6590

line needs to be further characterized in terms of onset and progression of behavioural phenotypes, it represents a promising model for advanced behavioural studies.

The triple transgenic rat

Towards the end of 2007, Flood *et al.* [97] published a paper on new lines of transgenic rats that were developed at Cephalon, Inc. and were first described in an abstract in 2003 [98]. In this paper, two lines of Sprague-Dawley rats with transgenes expressing human APP were crossed. The Tg478 line expresses human APP with the Swedish mutation driven by the rat synapsin promoter. The Tg1116 line expresses a human APP minigene containing the Swedish mutation and Indiana familial AD mutations. The resulting double homozygous rats produce sufficient levels of Aβ for amyloid deposition to occur by the age of 17–18 months. This was reduced to 7 months of age by crossing in a third transgenic rat line carrying a human PS-1 transgene with the familial AD mutation M146V (Tg11587). The triple homozygous transgenic rat, Tg478/Tg1116/Tg11587, has also been called the PSAPP Tg rat [99]. The amyloid deposits in this model are similar to that seen in some mouse models and the compact amyloid deposits found are associated with activated microglia, reactive astrocytes and phosphorylated tau immunoreactivity [99]. These triple transgenic animals showed deficits in the Morris water maze tasks from the age of 7 months, but in both the open field and elevated plus maze behavioural tests, the triple transgenics did not differ from controls [99]. This is the first transgenic rat to develop extensive amyloid deposits, but gross overexpression of multiple transgenes puts an excessive burden on the organism and this rat line has been shown to be prone to premature death due to health problems like chronic kidney disease, hypertension and immunosuppression [100].

The APP21 and APP31 transgenic rats

Last year, two additional APP transgenic rat lines were reported [101]. These lines were generated by lentiviral vector infection of Fischer 344 zygotes. The resulting transgenic rat lines, APP21 and APP31, express a human APP double mutant construct containing the Swedish and Indiana AD mutations driven by the ubiquitin-C promoter. The APP transgene is reported to be expressed in the brain, in neuronal but not glial cells. No pathological or behavioural studies have been published yet.

The AD-tau rat

Similarly to the mouse AD models, the APP or APP/PS1 transgenic rats do not show NFTs. The only rodent model with tau pathology specifically relevant for AD is the transgenic rat developed by Novak's group [102]. In contrast to the many mouse tau models, which harbour tau mutations characteristic of other dementia diseases than AD, this transgenic rat expresses a truncated form of the human tau protein (truncated at amino acid positions 151–391), which is found in the brains of sporadic AD patients. Interestingly, the truncated tau induces neurofibrillary aggregation and decreases the lifespan of the animals without causing any measurable neuronal loss in the hippocampus or brain stem [102, 103]. This lack of neuronal loss might be explained by the inadequately long lifespan of the animal. These transgenic rats show altered spatial navigation in Morris water maze while spontaneous locomotor activity and anxiety in open field is not affected. However, beam-walking test indicates development of progressive sensorimotor disturbances related to the animal's age [104]. To our knowledge, the interesting cross between these tau transgenic rats and an APP transgenic rat has not yet been done.

Transgenic rats – summary

In general, the APP transgenic rat lines show lower expression levels of the APP transgene than mouse AD models and in most cases only mild or no Aβ deposition in the brain, which might indicate that APP processing is under more stringent control in the rat as compared to mouse, and possibly that Aβ clearance is more efficient. In order to obtain extensive extracellular amyloid deposits in a rat model, introduction of two mutant APP constructs and one mutated PS1 was needed [97]. As in mice, amyloid deposition seems not to be a prerequisite for memory impairment in the transgenic rats. Both the UKUR25, double transgenic APP/PS1 [91] and the single APP transgenic Tg6590 rat [93] lines, show learning and memory impairment in the absence of gross amyloid pathology (Table 1). Even the triple transgenic rat mentioned above shows impairments in memory before the appearance of amyloid plaques [99]. These results are in line with the growing notion that Aβ oligomers might be the villain in the disease process; also soluble Aβ correlates better with memory deterioration in AD than its aggregated forms [105].

Virally induced models of AD

The independence of Aβ deposition and Aβ-related memory deficits has been examined in two novel AD rat models in which virus mediated gene transfer was used to induce expression of APP with the Swedish mutation or Aβ fragments, selectively in the hippocampus of adult rats. Gong *et al.* [106] demonstrated that Swedish mutated APP transfected rats, displaying Aβ42 immunoreactivity in the vicinity to the injection sites but no plaques nor signs of neurotoxicity up to 15 months post-transfection, had impaired memory retention in the probe phase of Morris water maze task. In the other virally induced rat model, cDNAs encoding a fusion between human Aβ40 or Aβ42 and the BRI protein, which is involved in amyloid deposition in British and Danish

familial dementia, were introduced into hippocampus of adult animals [107]. Only the BRI-Aβ42 infused animals showed diffuse plaque-like structures in the hippocampus 3 months post-infusion, but displayed no impairment in the open-field or water maze tests. On the other hand, animals infused with both BRI-Aβ42 and BRI-Aβ40 showed mild behaviour alterations but exhibited no extracellular Aβ depositions supporting data showing that Aβ deposition is not needed for behavioural impairments in rodent models.

Concluding remarks

The rat is one of the most commonly used experimental animal species in biomedical research and because of its relevance to human physiology, the rat may provide highly predictable models for research and the pharmaceutical industry [108]. The availability of new genetic research tools in rats provides considerable advances in the areas where rats are extensively used. In AD research, the rat has for decades been a very important model, for instance in studies on cholinergic dysfunction and memory impairment which played a crucial role in the development of the cholinesterase inhibitor drugs that are currently in use. The attractiveness of the rat as an experimental animal model has been increased further by the availability of the rat genome data and technologies allowing genetic manipulation in rats. In recent years, a number of transgenic rats as models for AD have been reported and new models are under development. We believe that in the coming years, transgenic rats will be a welcome and valuable complement to the available mouse models in AD research.

References

1. **Almkvist O.** Neuropsychological features of early Alzheimer's disease: preclinical and clinical stages. *Acta Neurol Scand Suppl.* 1996; 165: 63–71.
2. **Ball MJ.** Neuronal loss, neurofibrillary tangles and granulovacuolar degeneration in the hippocampus with ageing and dementia. A quantitative study. *Acta Neuropathol.* 1977; 37: 111–8.
3. **Braak H, Braak E.** Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* 1991; 82: 239–59.
4. **Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ.** Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. *Neurology.* 2007; 68: 1501–8.
5. **Schultzberg M, Lindberg C, Aronsson AF, Hjorth E, Spulber SD, Oprica M.** Inflammation in the nervous system-physiological and pathophysiological aspects. *Physiol Behav.* 2007; 92: 121–8.
6. **Glenner GG, Wong CW.** Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun.* 1984; 120: 885–90.
7. **Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K.** Amyloid plaque protein in Alzheimer's disease and Down's syndrome. *Proc Natl Acad Sci USA.* 1985; 82: 4245–9.
8. **Kang J, Lemaire H-G, Unterbeck A, Salbaum JM, Masters CL, Grzeschik KH, Multhaup G, Beyreuther K, Müller-Hill B.** The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature.* 1987; 325: 733–6.
9. **Verdile G, Fuller S, Atwood CS, Laws SM, Gandy SE, Martins RN.** The role of beta amyloid in Alzheimer's disease: still a cause of everything or the only one who got caught? *Pharmacol Res.* 2004; 50: 397–409.
10. **Lippa CF, Nee LE, Mori H, St. George-Hyslop P.** Abeta-42 deposition precedes other changes in PS-1 Alzheimer's disease. *Lancet.* 1998; 352: 1117–8.
11. **Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM.** Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. *J Biol Chem.* 1986; 261: 6084–9.
12. **Pimplikar SW.** Reassessing the amyloid cascade hypothesis of Alzheimer's disease. *Int J Biochem Cell Biol.* 2009; 41: 1261–8.
13. **Hardy JA, Higgins GA.** Alzheimer's disease: the amyloid cascade hypothesis. *Science.* 1992; 256: 184–5.
14. **Hardy J.** Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. *J Alzheimers Dis.* 2006; 9: 151–3.
15. **Salloway S, Mintzer J, Weiner MF, Cummings JL.** Disease-modifying therapies in Alzheimer's disease. *Alzheimers Dement.* 2008; 4: 65–79.
16. **Gibbs RA, Weinstock GM, Metzker ML, Muzny DM, Sodergren EJ, Scherer S, Scott G, Steffen D, Worley KC, Burch PE, Okwuonu G, Hines S, Lewis L, DeRamo C, Delgado O, Dugan-Rocha S, Miner G, Morgan M, Hawes A, Gill R, Celera, Holt RA, Adams MD, Amanatides PG, Baden-Tillson H, Barnstead M, Chin S, Evans CA, Ferriera S, Fosler C, Glodek A, Gu Z, Jennings D, Kraft CL, Nguyen T, Pfannkoch CM, Sitter C, Sutton GG, Venter JC, Woodage T, Smith D, Lee HM, Gustafson E, Cahill P, Kana A, Doucette-Stamm L, Weinstock K, Fechtel K, Weiss RB, Dunn DM, Green ED, Blakesley RW, Bouffard GG, De Jong PJ, Osoegawa K, Zhu B, Marra M, Schein J, Bosdet I, Fjell C, Jones S, Krzywinski M, Mathewson C, Siddiqui A, Wye N, McPherson J, Zhao S, Fraser CM, Shetty J, Shatsman S, Geer K, Chen Y, Abramzon S, Nierman WC, Havlak PH, Chen R, Durbin KJ, Egan A, Ren Y, Song XZ, Li B, Liu Y, Qin X, Cawley S, Worley KC, Cooney AJ, D'Souza LM, Martin K, Wu JQ, Gonzalez-Garay ML, Jackson AR, Kalafus KJ, McLeod MP, Milosavljevic A, Virk D, Volkov A, Wheeler DA, Zhang Z, Bailey JA, Eichler EE, Tuzun E, Birney E, Mongin E, Ureta-Vidal A, Woodwark C, Zdobnov E, Bork P, Suyama M, Torrents D, Alexandersson M, Trask BJ, Young JM, Huang H, Wang H, Xing H, Daniels S, Gietzen D, Schmidt J, Stevens K, Vitt U, Wingrove J, Camara F, Mar Albà M, Abril JF, Guigo R, Smit A, Dubchak I, Rubin EM, Couronne O, Poliakov A, Hübner N, Ganten D, Goesele C, Hummel O, Kreitler T, Lee YA, Monti J, Schulz H, Zimdahl H, Himmelbauer H, Lehrach H, Jacob HJ, Bromberg S, Gullings-Handley J, Jensen-Seaman MI, Kwitek AE, Lazar J, Pasko D, Tonellato PJ, Twigger S, Ponting CP, Duarte JM, Rice S, Goodstadt L, Beatson SA, Emes RD, Winter EE, Webber C, Brandt P, Nyakatura G, Adetobi M, Chiaromonte F, Elnitski L, Eswara P, Hardison RC, Hou M, Kolbe D, Makova K, Miller W,**

Nekrutenko A, Riemer C, Schwartz S, Taylor J, Yang S, Zhang Y, Lindpaintner K, Andrews TD, Caccamo M, Clamp M, Clarke L, Curwen V, Durbin R, Eyras E, Searle SM, Cooper GM, Batzoglou S, Brudno M, Sidow A, Stone EA, Venter JC, Payseur BA, Bourque G, López-Otín C, Puente XS, Chakrabarti K, Chatterji S, Dewey C, Pachter L, Bray N, Yap VB, Caspi A, Tesler G, Pevzner PA, Haussler D, Roskin KM, Baertsch R, Clawson H, Furey TS, Hinrichs AS, Karolchik D, Kent WJ, Rosenbloom KR, Trumbower H, Weirauch M, Cooper DN, Stenson PD, Ma B, Brent M, Arumugam M, Shteynberg D, Copley RR, Taylor MS, Riethman H, Mudunuri U, Peterson J, Guyer M, Felsenfeld A, Old S, Mockrin S, Collins F; Rat Genome Sequencing Project Consortium. Genome sequence of the Brown Norway rat yields insights into mammalian evolution. *Nature.* 2004; 428: 493–521.

17. **Gill TJ 3rd, Smith GJ, Wissler RW, Kunz HW.** The rat as an experimental animal. *Science.* 1989; 245: 269–76.
18. **Hedrich HJ.** History, strains and models. In: Krinke GJ, editor. The laboratory rat. New York: Academic Press; 2005. pp. 3–16.
19. **Abbott A.** Laboratory animals: the Renaissance rat. *Nature.* 2004; 428; 464–6.
20. **Lindblad-Toh K.** Genome sequencing: three's company. *Nature.* 2004; 428: 475–6.
21. **Petit-Zeman S.** Rat genome sequence reignites preclinical model debate. *Nat Rev Drug Discov.* 2004; 3: 287–8.
22. **Deacon RM.** Housing, husbandry and handling of rodents for behavioral experiments. *Nat Protoc.* 2006; 1: 936–46.
23. **Whishaw IQ, Metz GA, Kolb B, Pellis SM.** Accelerated nervous system development contributes to behavioral efficiency in the laboratory mouse: a behavioral review and theoretical proposal. *Dev Psychobiol.* 2001; 39: 151–70.
24. **Foote AL, Crystal JD.** Metacognition in the rat. *Curr Biol.* 2007; 17: 551–5.
25. **Kepecs A, Uchida N, Zariwala HA, Mainen ZF.** Neural correlates, computation and behavioural impact of decision confidence. *Nature.* 2008; 455: 227–31.
26. **Loeffler DA.** Using animal models to determine the significance of complement activation in Alzheimer's disease. *Neuroinflammation.* 2004; 1: 18.
27. **Mullins JJ, Peters J, Ganten D.** Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene. *Nature.* 1990; 344: 541–4.
28. **Herrera VL, Makrides SC, Xie HX, Adari H, Krauss RM, Ryan US, Ruiz-Opazo N.** Spontaneous combined hyperlipidemia, coronary heart disease and decreased survival in Dahl salt-sensitive hypertensive rats transgenic for human cholesteryl ester transfer protein. *Nat Med.* 1999; 5: 1383–9.
29. **Reid W, Sadowska M, Denaro F, Rao S, Foulke J Jr, Hayes N, Jones O, Doodnauth D, Davis H, Sill A, O'Driscoll P, Huso D, Fouts T, Lewis G, Hill M, Kamin-Lewis R, Wei C, Ray P, Gallo RC, Reitz M, Bryant J.** An HIV-1 transgenic rat that develops HIV-related pathology and immunologic dysfunction. *Proc Natl Acad Sci USA.* 2001; 98: 9271–6.
30. **von Hörsten S, Schmitt I, Nguyen HP, Holzmann C, Schmidt T, Walther T, Bader M, Pabst R, Kobbe P, Krotova J, Stiller D, Kask A, Vaarmann A, Rathke-Hartlieb S, Schulz JB, Grasshoff U, Bauer I, Vieira-Saecker AM, Paul M, Jones L, Lindenberg KS, Landwehrmeyer B, Bauer A, Li XJ, Riess O.** Transgenic rat model of Huntington's disease. *Hum Mol Genet.* 2003; 12: 617–24.
31. **Bartus RT, Dean RL 3rd, Beer B, Lippa AS.** The cholinergic hypothesis of geriatric memory dysfunction. *Science.* 1982; 217: 408–14.
32. **Bartus RT, Dean RL, Pontecorvo MJ, Flicker C.** The cholinergic hypothesis: a historical overview, current perspective, and future directions. *Ann N Y Acad Sci.* 1985; 444: 332–58.
33. **Muir JL, Page KJ, Sirinathsinghji DJ, Robbins TW, Everitt BJ.** Excitotoxic lesions of basal forebrain cholinergic neurons: effects on learning, memory and attention. *Behav Brain Res.* 1993; 57: 123–1.
34. **Wrenn CC, Wiley RG.** The behavioral functions of the cholinergic basal forebrain: lessons from 192 IgG-saporin. *Int J Dev Neurosci.* 1998; 16: 595–602.
35. **McDonald MP, Overmier JB.** Present imperfect: a critical review of animal models of the mnemonic impairments in Alzheimer's disease. *Neurosci Biobehav Rev.* 1998; 22: 99–120.
36. **Yamada K, Fuji K, Nabeshima T, Kameyama T.** Neurotoxicity induced by continuous infusion of quinolinic acid into the lateral ventricle in rats. *Neurosci Lett.* 1990; 118: 128–31.
37. **Yamada K, Nabeshima T, Kameyama T.** Impairment of active avoidance response in rats with continuous infusion of quinolinic acid into the lateral ventricle. *J Pharmacobiodyn.* 1991; 14: 351–5.
38. **Davies P, Maloney AJ.** Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet.* 1976; 2: 1403.
39. **Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, Delon MR.** Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science.* 1982; 215: 1237–9.
40. **Wiley RG, Oeltmann TN, Lappi DA.** Immunolesioning: selective destruction of neurons using immunotoxin to rat NGF receptor. *Brain Res.* 1991; 562: 149–53.
41. **Book AA, Wiley RG, Schweitzer JB.** Specificity of 192 IgG-saporin for NGF receptor-positive cholinergic basal forebrain neurons in the rat. *Brain Res.* 1992; 590: 350–5.
42. **Nitta A, Murase K, Furukawa Y, Hayashi K, Hasegawa T, Nabeshima T.** Memory impairment and neural dysfunction after continuous infusion of anti-nerve growth factor antibody into the septum in adult rats. *Neuroscience.* 1993; 57: 495–9.
43. **Ibach B, Haen E.** Acetylcholinesterase inhibition in Alzheimer's Disease. *Curr Pharm Des.* 2004; 10: 231–51.
44. **Yankner BA, Dawes LR, Fisher S, Villa-Komaroff L, Oster-Granite ML, Neve RL.** Neurotoxicity of a fragment of the amyloid precursor associated with Alzheimer's disease. *Science.* 1989; 245: 417–20.
45. **Pike CJ, Walencewicz AJ, Glabe CG, Cotman CW.** *In vitro* aging of beta-amyloid protein causes peptide aggregation and neurotoxicity. *Brain Res.* 1991; 563: 311–4.
46. **Kowall NW, Beal MF, Busciglio J, Duffy LK, Yankner BA.** An *in vivo* model for the neurodegenerative effects of beta amyloid and protection by substance P. *Proc Natl Acad Sci USA.* 1991; 88: 7247–51.
47. **Frautschy SA, Baird A, Cole GM.** Effects of injected Alzheimer beta-amyloid cores in rat brain. *Proc Natl Acad Sci USA.* 1991; 88: 8362–6.
48. **Nitta A, Itoh A, Hasegawa T, Nabeshima T.** β-Amyloid protein-induced Alzheimer's disease animal model. *Neurosci Lett.* 1994; 170: 63–6.
49. **Giovannelli L, Casamenti F, Scali C, Bartolini L, Pepeu G.** Differential effects of amyloid peptides beta-(1–40) and beta-(25–35) injections into the rat nucleus basalis. *Neuroscience.* 1995; 66: 781–92.
50. **Sigurdsson EM, Lee JM, Dong XW, Hejna MJ, Lorens SA.** Bilateral injections of amyloid-beta 25–35 into the amygdala of young Fischer rats: behavioral, neurochemical, and time dependent histopathological effects. *Neurobiol Aging.* 1997; 18: 591–608.

51. **Harkany T, O'Mahony S, Kelly JP, Soós K, Törõ I, Penke B, Luiten PG, Nyakas C, Gulya K, Leonard BE.** Beta-amyloid (Phe(SO3H)24)25–35 in rat nucleus basalis induces behavioral dysfunctions, impairs learning and memory and disrupts cortical cholinergic innervation. *Behav Brain Res.* 1998; 90: 133–45.
52. **Weldon DT, Rogers SD, Ghilardi JR, Finke MP, Cleary JP, O'Hare E, Esler WP, Maggio JE, Mantyh PW.** Fibrillar beta-amyloid induces microglial phagocytosis, expression of inducible nitric oxide synthase, and loss of a select population of neurons in the rat CNS *in vivo*. *J Neurosci.* 1998; 18: 2161–73.
53. **Nakamura S, Murayama N, Noshita T, Annoura H, Ohno T.** Progressive brain dysfunction following intracerebroventricular infusion of beta(1–42)-amyloid peptide. *Brain Res.* 2001; 912: 128–36.
54. **McDonald MP, Dahl EE, Overmier JB, Mantyh P, Cleary J.** Effects of an exogenous beta-amyloid peptide on retention for spatial learning. *Behav Neural Biol.* 1994; 62: 60–7.
55. **Chen SY, Wright JW, Barnes CD.** The neurochemical and behavioral effects of beta-amyloid peptide(25–35). *Brain Res.* 1996; 720: 54–60.
56. **Sweeney WA, Luedtke J, McDonald MP, Overmier JB.** Intrahippocampal injections of exogenous beta-amyloid induce postdelay errors in an eight-arm radial maze. *Neurobiol Learn Mem.* 1997; 68: 97–101.
57. **Oka J, Suzuki E, Goto N, Kameyama T.** Endogenous GLP-1 modulates hippocampal activity in beta-amyloid protein-treated rats. *Neuroreport.* 1999; 10: 2961–4.
58. **Games D, Khan KM, Soriano FG, Keim PS, Davis DL, Bryant K, Lieberburg I.** Lack of Alzheimer pathology after beta-amyloid protein injections in rat brain. *Neurobiol Aging.* 1992; 13: 569–76.
59. **Clemens JA, Stephenson DT.** Implants containing beta-amyloid protein are not neurotoxic to young and old rat brain. *Neurobiol Aging.* 1992; 13: 581–6.
60. **Winkler J, Connor DJ, Frautschy SA, Behl C, Waite JJ, Cole GM, Thal LJ.** Lack of long-term effects after beta-amyloid protein injections in rat brain. *Neurobiol Aging.* 1994; 15: 601–7.
61. **Geula C, Wu CK, Saroff D, Lorenzo A, Yuan M, Yankner BA.** Aging renders the brain vulnerable to amyloid beta-protein neurotoxicity. *Nat Med.* 1998; 4: 827–31.
62. **Podlisny MB, Stephenson DT, Frosch MP, Lieberburg I, Clemens JA, Selkoe DJ.** Synthetic amyloid beta-protein fails to produce specific neurotoxicity in monkey cerebral cortex. *Neurobiol Aging.* 1992; 13: 561–7.
63. **Tang F, Nag S, Shiu SY, Pang SF.** The effects of melatonin and Ginkgo biloba extract on memory loss and choline acetyltransferase activities in the brain of rats infused intracerebroventricularly with beta-amyloid 1–40. *Life Sci.* 2002; 71: 2625–31.
64. **Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H, Fujii Y, Ishibashi Y, Oka J, Shido O.** Docosahexaenoic acid provides protection from impairment of learning ability in Alzheimer's disease model rats. *J Neurochem.* 2002; 81: 1084–91.
65. **Wang LC, Wang B, Ng SY, Lee TF.** Effects of ginseng saponins on beta-amyloid-induced amnesia in rats. *J Ethnopharmacol.* 2006; 103: 103–8.
66. **Hruska Z, Dohanich GP.** The effects of chronic estradiol treatment on working memory deficits induced by combined infusion of beta-amyloid (1–42) and ibotenic acid. *Horm Behav.* 2007; 52: 297–306.
67. **Haque AM, Hashimoto M, Katakura M, Hara Y, Shido O.** Green tea catechins prevent cognitive deficits caused by Abeta1–40 in rats. *J Nutr Biochem.* 2008; 19: 619–26.
68. **Yamaguchi Y, Miyashita H, Tsunekawa H, Mouri A, Kim HC, Saito K, Matsuno T, Kawashima S, Nabeshima T.** Effects of a novel cognitive enhancer, spiro[imidazo-[1,2-a]pyridine-3,2-indan]-2(3H)-one (ZSET1446), on learning impairments induced by amyloid-beta1–40 in the rat. *J Pharmacol Exp Ther.* 2006; 317: 1079–87.
69. **Nguyen PT, Kimura T, Ho SA, Tran AH, Ono T, Nishijo H.** Ameliorative effects of a neuroprotective agent, T-817MA, on place learning deficits induced by continuous infusion of amyloid-beta peptide (1–40) in rats. *Hippocampus.* 2007; 17: 443–55.
70. **Yamada K, Tanaka T, Han D, Senzaki K, Kameyama T, Nabeshima T.** Protective effects of idebenone and alpha-tocopherol on beta-amyloid-(1–42)-induced learning and memory deficits in rats: implication of oxidative stress in beta-amyloid-induced neurotoxicity *in vivo*. *Eur J Neurosci.* 1999; 11: 83–90.
71. **Srivareerat M, Tran TT, Alzoubi KH, Alkadhi KA.** Chronic psychosocial stress exacerbates impairment of cognition and long-term potentiation in beta-amyloid rat model of Alzheimer's disease. *Biol Psychiatry.* 2008; (doi:10.1016/j.biopsych.2008.08.021).
72. **Takata K, Kitamura Y, Yanagisawa D, Morikawa S, Morita M, Inubushi T, Tsuchiya D, Chishiro S, Saeki M, Taniguchi T, Shimohama S, Tooyama I.** Microglial transplantation increases amyloid-beta clearance in Alzheimer model rats. *FEBS Lett.* 2007; 581: 475–8.
73. **Lecanu L, Greeson J, Papadopoulos V.** Beta-amyloid and oxidative stress jointly induce neuronal death, amyloid deposits, gliosis, and memory impairment in the rat brain. *Pharmacology.* 2006; 76: 19–33.
74. **Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, Clemens J, Donaldson T, Gillespie F, Guido T, Hagopian S, Johnson-Wood K, Khan K, Lee M, Leibowitz P, Lieberburg I, Little S, Masliah E, McConlogue L, Montoya-Zavala M, Mucke L, Paganini L, Penniman E, Power M, Schenk D, Seubert P, Snyder B, Soriano F, Tan H, Vitale J, Wadsworth S, Wolozin B, Zhao J.** Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. *Nature.* 1995; 373: 523–7.
75. **Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G.** Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. *Science.* 1996; 274: 99–102.
76. **Marshall VJ, Hsiao KK, Chapman PF.** The production of a rat model of Alzheimer's disease. *Soc Neurosci Abstr.* 1999; 25: 741.16.
77. **Falinska AM, Marshall VJ, Chapman PF.** The effects of highcholesterol diet on behavior and synaptic physiology in APP transgenic rats. *Soc Neurosci Abstr.* 2002; 28: 191.2.
78. **Sankaranarayanan, S.** Genetically modified mice models for Alzheimer's disease. *Curr Top Med Chem.* 2006; 6: 609–27.
79. **Spires TL, Hyman, BT.** Transgenic models of Alzheimer's disease: learning from animals. *NeuroRx.* 2005; 2: 423–37.
80. **Brandt R, Hundelt M, Shahani N.** Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochim Biophys Acta.* 2005; 1739: 331–54.
81. **García-Sierra F, Mondragón-Rodríguez S, Basurto-Islas G.** Truncation of tau protein and its pathological significance in Alzheimer's disease. *J Alz Dis.* 2008; 14: 401–9.
82. **Tesson L, Cozzi J, Ménoret S, Rémy S, Usal C, Fraichard A, Anegon I.** Transgenic modifications of the rat genome. *Transgenic Res.* 2005; 14: 531–46.

83. **Zhou Q, Renard JP, Le Friec G, Brochard V, Beaujean N, Cherifi Y, Fraichard A, Cozzi J.** Generation of fertile cloned rats by regulating oocyte activation. *Science.* 2003; 302: 1179.
84. **Mullins JJ, Ganten D.** Transgenic animals: new approaches to hypertension research. *J Hypertens Suppl.* 1990; 8: S35–37.
85. **Nagai M, Aoki M, Miyoshi I, Kato M, Pasinelli P, Kasai N, Brown RH Jr, Itoyama Y.** Rats expressing human cytosolic copper-zinc superoxide dismutase transgenes with amyotrophic lateral sclerosis: associated mutations develop motor neuron disease. *J Neurosci.* 2001; 21: 9246–54.
86. **Howland DS, Liu J, She Y, Goad B, Maragakis NJ, Kim B, Erickson J, Kulik J, DeVito L, Psaltis G, DeGennaro LJ, Cleveland DW, Rothstein JD.** Focal loss of the glutamate transporter EAAT2 in a transgenic rat model of SOD1 mutant-mediated amyotrophic lateral sclerosis (ALS). *Proc Natl Acad Sci USA.* 2002; 99: 1604–9.
87. **Zan Y, Haag JD, Chen KS, Shepel LA, Wigington D, Wang YR, Hu R, Lopez-Guajardo CC, Brose HL, Porter KI, Leonard RA, Hitt AA, Schommer SL, Elegbede AF, Gould MN.** Production of knockout rats using ENU mutagenesis and a yeast-based screening assay. *Nat Biotechnol.* 2003; 21: 645–51.
88. **Ruiz-Opazo N, Kosik KS, Lopez LV, Bagamasbad P, Ponce LR, Herrera VL.** Attenuated hippocampus-dependent learning and memory decline in transgenic TgAPPswe Fischer-344 rats. *Mol Med.* 2004; 10: 36–44.
89. **Vercauteren FG, Clerens S, Roy L, Hamel N, Arckens L, Vandesande F, Alhonen L, Janne J, Szyf M, Cuello AC.** Early dysregulation of hippocampal proteins in transgenic rats with Alzheimer's disease-linked mutations in amyloid precursor protein and presenilin 1. *Brain Res Mol Brain Res.* 2004; 132: 241–59.
90. **Lopez EM, Bell KF, Ribeiro-da-Silva A, Cuello AC.** Early changes in neurones of the hippocampus and neocortex in transgenic rats expressing intracellular human Aβ. *J Alzheimers Dis.* 2004; 6: 421–31.
91. **Echeverria V, Ducatenzeiler A, Dowd E, Janne J, Grant SM, Szyf M, Wandosell F, Avila J, Grimm H, Dunnett SB, Hartmann T, Alhonen L, Cuello AC.** Altered mitogen-activated protein kinase signalling, tau hyperphosphorylation and mild spatial learning dysfunction in transgenic rats expressing β-amyloid peptide intracellularly in hippocampal and cortical neurons. *Neuroscience.* 2004; 129: 583–92.
92. **Echeverria V, Ducatenzeiler A, Alhonen L, Janne J, Grant SM, Wandosell F, Muro A, Baralle F, Li H, Duff K, Szyf M, Cuello AC.** Rat transgenic models with a phenotype of intracellular Aβ accumulation in hippocampus and cortex. *J Alz Dis.* 2004; 6: 209–19.
93. **Folkesson R, Malkiewicz K, Kloskowska E, Nilsson T, Popova E, Bogdanovic N, Ganten U, Ganten D, Bader M, Winblad B, Benedikz E.** A transgenic rat expressing human APP with the Swedish Alzheimer's disease mutation. *Biochem Biophys Res Commun.* 2007; 358: 777–82.
94. **Kloskowska E, Pham TM, Nilsson T, Zhu S, Öberg J, Codita A, Pedersen LØ, Pedersen JT, Malkiewicz K, Winblad B, Folkesson R, Benedikz E.** Cognitive impairment in the Tg6590 transgenic rat model of Alzheimer's disease. *J Cell Mol Med.* 2009; in press.
95. **Kloskowska E, Malkiewicz K, Winblad B, Benedikz E, Bruton JD.** APPswe mutation increases the frequency of spontaneous Ca2+-oscillations in rat hippocampal neurons. *Neurosci Lett.* 2008; 436: 250–4.
96. **Kloskowska E, Bruton JD, Winblad B, Benedikz E.** The APP670/671 mutation alters calcium signaling and response to hyperosmotic stress in rat primary hippocampal neurons. *Neurosci Lett.* 2008; 444: 275–9.
97. **Flood DG, Lin YG, Lang DM, Trusko SP, Hirsch JD, Savage MJ, Scott RW, Howland DS.** A transgenic rat model of Alzheimer's disease with extracellular Abeta deposition. *Neurobiol Aging.* 2007; doi:10.1016/j.neurobiolaging.2007.10.006.
98. **Flood DG, Howland DS, Lin Y-G, Ciallella JR, Trusko SP, Scott RW, Savage MS.** Aβ deposition in a transgenic rat model of Alzheimer's disease. Washington, DC: Society for Neuroscience; 2003.
99. **Liu L, Orozco IJ, Planel E, Wen Y, Bretteville A, Krishnamurthy P, Wang L, Herman M, Figueroa H, Yu WH, Arancio O, Duff K.** A transgenic rat that develops Alzheimer's disease-like amyloid pathology, deficits in synaptic plasticity and cognitive impairment. *Neurobiol Dis.* 2008; 31: 46–57.
100. **Zahorsky-Reeves J, Lawson G, Chu DK, Schimmel A, Ezell PC, Dang M, Couto M.** Maintaining longevity in a triple transgenic rat model of Alzheimer's disease. *J Am Assoc Lab Anim Sci.* 2007; 46: 124.
101. **Agca C. Fritz JJ, Walker LC, Levey AI, Chan AW, Lah JJ, Agca Y.** Development of transgenic rats producing human β-amyloid precursor protein as a model for Alzheimer's disease: transgene and endogenous APP genes are regulated tissue-specifically. *BMC Neurosci.* 2008; 9: 28.
102. **Zilka N, Filipcik P, Koson P, Fialova L, Skrabana R, Zilkova M, Rolkova G, Kontsekova E, Novak M.** Truncated tau from sporadic Alzheimer's disease suffices to drive neurofibrillary degeneration *in vivo. FEBS Lett.* 2006; 580: 3582–8.
103. **Koson P, Zilka N, Kovac A, Kovacech B, Korenova M, Filipcik P, Novak M.** Truncated tau expression levels determine life span of a rat model of tauopathy without causing neuronal loss or correlating with terminal neurofibrillary tangle load. *Eur J Neurosci.* 2008; 28: 239–46.
104. **Hrnkova M, Zilka N, Minichova Z, Koson P, Novak M.** Neurodegeneration caused by expression of human truncated tau leads to progressive neurobehavioural impairment in transgenic rats. *Brain Res.* 2007; 1130: 206–13.
105. **Walsh DM, Selkoe DJ.** Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron.* 2004; 44: 181–93.
106. **Gong Y, Meyer EM, Meyers CA, Klein RL, King MA, Hughes JA.** Memory-related deficits following selective hippocampal expression of Swedish mutation amyloid precursor protein in the rat. *Exp Neurol.* 2006; 200: 371–7.
107. **Lawlor PA, Bland RJ, Das P, Price RW, Holloway V, Smithson L, Dicker BL, During MJ, Young D, Golde TE.** Novel rat Alzheimer's disease models based on AAV-mediated gene transfer to selectively increase hippocampal Aβ levels. *Mol Neurodegener.* 2007; 2: 11 (doi:10.1186/17501326-211).
108. **Cozzi J, Fraichard A, Thiam K.** Use of genetically modified rat models for translational medicine. *Drug Discov Today.* 2008; 13: 488–94.