TACONIC

APPSWE Microinjected Mouse Model

Mice that overexpress an Alzheimer's-associated isoform of the human amyloid precursor protein provide a model for human Alzheimer's disease and an experimental tool for a diversity of cellular mechanisms.

Applications for the APPSWE Microinjected Mouse Model

APPSWE Microinjected Mice express a mutated form of the human gene for amyloid precursor protein (APP) known as the Swedish mutation (APP_{SWE}). The gene encodes a double amino acid substitution and is associated with a heritable susceptibility to Alzheimer's Disease (AD). Resulting phenotypic manifestations in APPSWE Microinjected Mice include progressive accumulation of beta amyloid (Aβ) in the brain, analogous to classic "senile plaques" of human AD, and correlated cognitive deficits.

While not every aspect of the mouse phenotype mimics that of human AD (neuronal loss and neurofibrillary tangles are not evident in the mice), both the differences and similarities offer a means to probe mechanisms of AD pathophysiology. This model also is appropriate for investigations of a variety of specific intracellular processing pathways.

Applications include:

- Characterizing temporal dynamics in plaque morphology and biochemistry
- Assessing the relative importance of soluble and insoluble Aβ in disease progression
- Correlating Aβ deposition and plaque characteristics with cognitive function
- Refining models of APPSWE processing, including gene regulation and intracellular control of APPSWE-cleaving enzymes (e.g., α-, β-, and γ-secretases)
- Evaluating the relationship between amyloid deposition, tau protein phosphorylation, and formation of neurofibrillary tangles (the latter are absent in APPSWE Microinjected Mice)
- Clarifying potential roles of cholesterol and apolipoprotein E (ApoE) in amyloid deposition
- Probing the importance of metals (e.g., zinc) in plaque formation and growth
- Establishing the role of inflammatory processes, including cytokine mediation by microglial cells and astrocytes, in plaque deposition, growth, and maintenance
- Evaluating the relative roles and responses of neurons, microglia, and astrocytes in Aβ deposition
- Correlating plaque-associated neuronal dystrophy with changes in neurotransmitter profiles
- Characterizing sex-related aspects of AD pathophysiology
- Identifying potential biochemical screening and diagnostic tools for Aβ, such as levels in plasma
- Modeling human cerebral amyloid angiopathy (vascular amyloid build-up leading to stroke)
- Investigating prion protein disease mechanisms, in which abnormal protein polymerization can seed additional polymerization

Features of APPSWE Microinjected Mice

- Available on two genetic backgrounds: Model 001349 is a on a mixed B6;SJL background, and model 002789 is on an inbred 129S6 background. Pink eyed animals, associated with certain coat colors, and the *Pde6b*^{rd1} retinal degeneration mutation can cause light sensitivity and/or blindness in some animals. This may impact the results of behavioral testing. The mixed genetic background of model 001349 can result in pink eyed animals or homozygosity for the *Pde6b*^{rd1} retinal degeneration mutation. The 129S6 background of model 002789 does not carry the *Pde6b*^{rd1} retinal degeneration mutation, and this strain has pigmented eyes.
- Overexpression of human amyloid precursor protein in several regions of the brain

- Early and progressive accumulation of beta amyloid and development of plaques
- Behavioral deficits that correlate with degree of amyloid deposition
- Neuritic dystrophy and altered synaptic efficacy of plaque-associated neurons
- No evidence of neuronal loss
- Absence of tau protein tangles
- Expression of inflammatory mediators by plaque-associated microglial cells and astrocytes
- Sex differences in some aspects of physiology and behavior
- Age-correlated elevation in brain levels of apoE and cholesterol
- Deposition of amyloid in cerebral blood vessel walls

Beta Amyloid in APPSWE Mouse Brains

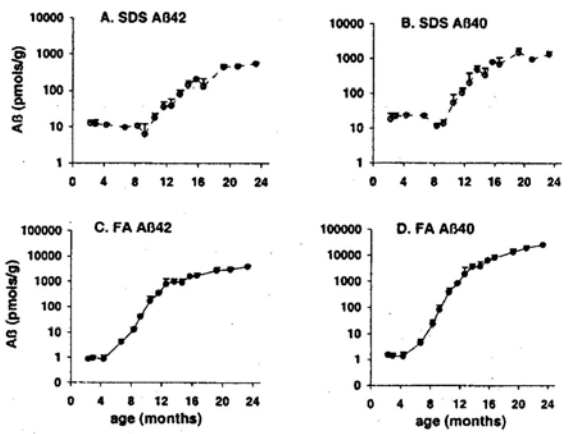

Figure 1. Increasing quantities of beta amyloid peptides (Aβ40, Aβ42) in whole brains from APPSWE Microinjected mice of increasing ages, using two extraction methods (**A,B**: 2% SDS; **C,D**: 70% formic acid). Note that the *y* axes are logarithmic. From Kawarabayashi, T., et al.[8]

Scientific Profile of APPSWE Micro-injected Mice

APPSWE Microinjected Mice show age-dependent cognitive deficits. Numerous studies have documented spatial, learning, and memory impairments in the transgenic mice, beginning as early as age 3 months. Tests have included the Morris water maze, Y-maze T-maze, and circular platform.[1,2,3,4,5,6,7] In the Morris water maze test, transgenic mice as young as 6 months of age exhibit memory loss, just when detergent-insoluble Aβ aggregates begin to appear.[8,7] And while accumulation of insoluble Aβ in the brain (diffusely or in plaques) correlates with degree of memory loss, it may serve only as a marker for excessive formation of Aβ. Instead, smaller Aβ aggregates that are still soluble have been implicated as the disrupters of neuronal function.[1,7] Importantly, soluble Aβ can be neutralized pharmacologically: treatment of APPSWE Microinjected Mice with BAM-10 (a mouse anti-Aβ antibody) restored spatial learning and memory as measured in the Morris water maze.[5] In fact, this treatment led to a full reversal of memory loss. (The antibody is believed to attach to soluble Aβ and prevent its interference with normal activity of neurons.)[5]

APPSWE Mice Display Learning Deficits

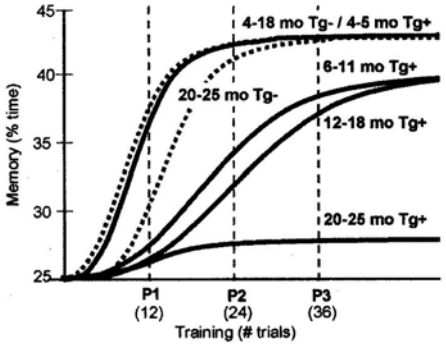

Figure 2. Learning curves of APPSWE Microinjected mice (Tg+) illustrate impaired spatial reference memory (determined by the Morris water maze) compared to a group of control mice (4-25 mo. Tg-). Three probe trials (P1, P2, P3) were conducted after 12, 24, and 36 training trails, respectively. The curve slopes indicate a significant slowing of learning and the curve plateaus indicate a marked lowering (impairment) of the maximum memory ability as the animals age. Tg- mice at 20-25 mo. are impaired compared to 4-18 mo. Tg- mice. From Westerman, M.A.., et al.[7]

Brains of APPSWE Microinjected Mice show early and progressive development of amyloid plaques. Histologically distinct plaques first appear in transgenic mice at 7-8 months of age and are most abundant in cortex, subiculum, and presubiculum.[3] Plaque burden (total cross-sectional area in representative brain slices) and diffuse deposits of Aβ increase rapidly at about 10-21 months of age.[8] Some plaques develop a dense core as do human plaques, though the amyloid peptides contained within them are in some regards distinct: the mouse amyloid appears to lack cross-linked dimers of Aβ,

is soluble in SDS/EDTA, and contains more carboxyterminal fragments and fewer N-terminally-degraded peptides.[9] As in humans, plaques are surrounded by activated microglial cells and reactive astrocytes, both of which are non-neuronal cells suspected of playing some role in progression of the disease.[10,11,12,13] Microglia in particular, which are monocyte-like CNS cells, are postulated to mediate a plaque-associated inflammatory response, or possibly directly contribute to plaque maintenance and growth by Aβ deposition.[13] These histological features correlate temporally with memory and learning deficits (see following).[3,2]

Neuronal manifestations of transgene expression include neuritic dystrophy and altered synaptic efficacy. Neurons that are adjacent to plaques exhibit diminished density of dendrites and substantial morphological alterations like those seen in neurons within or adjacent to human plaques.[14] Dystrophic neurites surrounding plaques contain nitric oxide synthase, a proposed mediator of inflammation and marker of oxidative stress.[15] Abnormalities in synaptic properties are evident. For example, long-term potentiation of neurons in the CA1 and dentate gyrus regions of the hippocampus has been reported to be markedly impaired in older transgenic mice (15-17 months) but not young ones (2-8 months).[2] This was correlated with Aβ accumulation in those brain regions and cognitive decline (e.g., significant failure rates on the forced-choice alternation task in the T-maze behavioral test). Other investigators, however, have found no long-term potentiation deficit, but instead, impaired synaptic transmission.[16]

Neuronal loss is not a feature of the APPSWE Microinjected Mouse brain. APPSWE Microinjected Mice lack a hallmark feature of human AD: death of neurons. Aged transgenic mice have a significant plaque burden and cognitive impairment, but without histological evidence of neuronal loss in the hippocampus, nor of altered neuronal mRNA expression.[2,12] These findings emphasize the importance of altered neuronal function in response to Aβ build-up, rather than cell death, as a likely cause of symptoms.

Cells associated with amyloid plaques express inflammatory chemicals that are expressed in human AD. APPSWE Microinjected Mice may help elucidate the complex interactions among mediators of inflammation, and establish by what means antiinflammatory agents (e.g., ibuprofen, curcumin) elicit the AD-protective effect they confer on humans and mice.[17,18,19,20] For example, IL-1β and TNFα were detected immunohistologically in microglial cells,[10] IL-6 was abundant in astrocytes,[21,10] and IL-6 mRNA levels were elevated in the hippocampus and cortex.[22] Localization of other cytokines such as TGF-β and IL-10 in astrocytes or microglia of mouse brain implicates both pro- and anti-inflammatory mediators in plaque-associated inflammatory dynamics.[21] In addition, neurons adjacent to mouse plaques express neuronal nitric oxide synthase but not the inducible form, suggesting a role in the inflammatory response, the details of which have yet to be clarified.[23]

The formation in brain tissue of tau protein tangles is not a feature of APPSWE Microinjected Mice, as it is of classical AD. Nevertheless, the intracellular fibrillar protein α-synuclein is abundant within plaque neurites of the transgenic mice.[24] Intraneuronal accumulations of α-synuclein characterizes a variant of AD, known as Lewy body variant (as well as Parkinson's disease), in which tau tangles are minimal or lacking.[24]

Sex differences exist in some aspects of transgenic mouse physiology and behavior. Both male and female transgenic mice accumulate plaques with age, but plaque burden in the female brain is greater.[25] This difference first appears at about 12 months of age, and by 15-19 months, plaque burden is nearly three times higher in females. A variety of behavioral tests conducted by one laboratory revealed sex-biased impairments in spatial and memory tasks.[4] These observations indicate that transgenic mice can be a tool for identifying sex-associated physiological correlates of AD, for which human females are at higher risk.

The utility of APPSWE Microinjected Mice as a tool for investigating disease mechanisms in human AD is underscored by additional biochemical similarities. For example, astrocytes surrounding amyloid plaques of transgenic mice express elevated levels of cystatin C.[26] Cystatin C, which is a potent protease inhibitor and neurogenic cofactor essential for neurogenesis, is co-deposited with amyloid[27] in some cases of human AD, and genetic polymorphism in cystatin C is linked to late

onset sporadic AD.[28,29] Also, human AD patients have a deficiency in ethanolamine plasmalogen (a major component of neuronal cell membranes), as do APPSWE Microinjected Mice.[30]

APPSWE Microinjected Mice offer insight into intracellular regulatory pathways of plaque genesis. Many investigators are using APPSWE Microinjected Mice to investigate the complex array of intracellular chemicals that may influence plaque formation and maintenance. Activation and increased expression of a number of phosphokinase C isoforms have been detected in plaque-associated neurons and astrocytes of transgenic mice.[31] Some of these isoforms are known to participate in APPSWE processing, neuronal growth and survival, and possibly in astrocyte cytokine expression. Histochemical analysis has identified reactive zinc in transgenic mouse plaques, offering evidence that, as in human AD brains, chelatable metals may be related to plaque genesis.[32] Interestingly, profuse plaques have been triggered in young transgenic mice by inoculation with brain extracts from human AD patients (and containing insoluble Aβ),[33] reminiscent of the mechanism by which prion proteins instigate fibrillar protein aggregation.

Brain levels of apoE and cholesterol are elevated dramatically with age in APPSWE Microinjected transgenic mice. Mice as young as two months of age show greater apoE concentrations in cerebral cortex than do control mice, with amounts ranging from about 45% to 60% greater at 2 and 14 months, respectively.[34] Immunohistochemical studies localize apoE to astrocytes surrounding plaques, and within plaques.[35] Elevated levels of cholesterol in mature plaques also have been reported.[36] Both of these findings parallel evidence in humans that aopE and cholesterol are risk factors for AD.

The APPSWE Microinjected Mouse has proven to be a viable model in which to assess vaccination protocols, with promising results. Transgenic mice immunized with human Aβ(1-42)[37] or with a nontoxic Aβ homologue[38] had dramatically reduced Aβ(1-42) and Aβ(1-40) in brain tissue, as well as significantly lower plaque load, compared to non-immunized transgenic mice. Deficits in learning and memory also were minimized.[39] Vaccination is less effective in mice in which a significant plaque load already is established.[37]

APPSWE Microinjected Mice also provide a model for developing Alzheimer's screening and preventative treatments, which cannot be easily assessed in humans. Examples include copper-zinc chelation[40] and inhibition of phosphatidyl-inositol kinase[41] (both treatments reduced Aβ accumulation by about half). Studies indicating oxidative stress and damage in mouse brain tissue suggest the value of antioxidant therapy to reduce or prevent amyloid accumulation.[41,43,44] Pre-AD screening and diagnostic methods under study include an Aβ-specific radioligand for brain imaging[45] and plasma profiles of soluble Aβ, which decline as plaques enlarge.[34,8]

Vascular amyloid deposition in transgenic mice mimics that seen in human cerebral amyloid angiopathy. A leading cause of stroke in humans is the accumulation of Aβ peptides in blood vessels surrounding the brain (which frequently co-occurs with AD). APPSWE Microinjected Mice show a similar amyloid build-up in cerebral vessels, with concomitant impairment in function of vascular smooth muscle, compromised response to vasodilators, and cell death.[46] The mice provide an opportunity to clarify the mechanisms by which amyloid damages brain vasculature.

Origin of the Model

The APPSWE Microinjected Mouse was developed by Karen Hsiao Ashe at the Department of Neurology and Neuroscience, University of Minnesota.[3] A construct was created that carried the Swedish mutation form of the human APPSWE gene, which produces a 695-amino acid APPSWE protein with two substitutions ($Lys^{670} \rightarrow$ Asn and $Met^{671} \rightarrow$ Leu). (The Kunitz-like proteinase inhibitor domain is not present in this APPSWE isoform.) The construct was inserted into a hamster prion protein cosmid vector in which the reading frame was replaced with the variant APPSWE open reading frame.

The transgene originally was developed in FVB/N mice, but they were poor breeders and died prematurely.[47] Therefore, the vector was introduced by microinjection into C57BL/6N X SJL/N F2 single-cell embryos, producing transgenic founders. Taconic's colony was established by transfer of embryos resulting from breeding a hemizygous transgenic male to a C57BL/6NTac female. The

resultant male progeny were bred to SJL/JcrNTac females. The model 001349 colony is now maintained by breeding hemizygous transgenic male mice with female B6SJLF1/Tac mice.

To generate model 002789, mice from Founder Line 2576 were backcrossed sixteen generations (N16) to 129S6. Taconic received stock in September 2003. The mice were derived by embryo transfer and are maintained by backcrossing hemizygous male mice with 129S6/SvEvTac female mice.

Ready for Your Experiments

Taconic's APPSWE Microinjected Mice are maintained in Isolator Barrier Unit (IBU™) facilities. Mice are shipped in Taconic Transport Cages (TTC™) and come with an up-to-date health report documenting their Murine Pathogen Free (MPF™) health status. Barrier housing conditions are recommended for maintenance of APPSWE Microinjected Mice.

Considerations for Use in Experiments

Mortality is a phenotype of Taconic APPSWE Microinjected mice, particularly for males. For the 001349-T animals this can occur at young or old ages. Young animals (less than 8 weeks of age) can suffer from sudden death syndrome; therefore, Taconic highly recommends ordering animals to be shipped at 10 to 12 weeks of age. At older ages (greater than 12 weeks) 001349-T and 002789-T mice suffer from premature death. For long-term studies it is not uncommon to see attrition rates of 20%; therefore, when determining study cohort sizes it is always best to order additional animals.

Homozygous males (001349 or 002789) are highly aggressive and fight. For shipping, Taconic packs TTCs carrying heterozygous males at a reduced density. This can increase the total number of TTCs required to ship your order of mice. Taconic highly recommends housing males one per cage. If this is not possible, males should be housed in small groups consisting of animals that have been housed together since weaning.

Related Mouse Models from Taconic

Taconic provides a diversity of inbred, custom hybrid, and transgenic (microinjected and knockout) mouse models for a wide range of research topics. Call or fax for information about these additional models, including these models relevant to neurological function:

- **APPSWE-Tau Double Microinjected Mouse (models 002469 and 003273) –** carries two human transgenes: the APP transgene coding for the 695-amino acid isoform of human Alzheimer ß-amyloid (Aß) precursor protein, and the human P301L mutation of the *MAPT* (microtubule-associated protein tau) gene which encodes for the TAU protein.
- **APOE2 Targeted Replacement Mouse (model 001547) –** expressing the human apoE2 protein instead of murine apoE, with several abnormalities of lipid physiology, including elevated serum levels, altered lipoprotein profiles, and early development of atherosclerosis, all of which parallel features of human type III lipoproteinemia.
- **APOE3 Targeted Replacement Mouse (model 001548) –** expressing the human apoE3 protein instead of murine apoE, with normal serum cholesterol and triglyceride levels, but certain abnormalities of lipid physiology, including delayed clearance of lipoprotein particles (VLDL) and propensity to develop atherosclerosis on a high-fat diet.
- **APOE4 Targeted Replacement Mouse (model 001549) –** expressing the human apoE4 protein instead of murine apoE, with normal serum cholesterol and triglyceride levels but certain abnormalities of lipid physiology that are similar to those of ApoE3 Targeted Replacement Mice; impairment in clearance of lipoprotein particles (VLDL) and development of atherosclerosis on a high-fat diet are more pronounced**.**
- **Mdr1a Targeted Mutation Mouse (model MDR1A)** – carrying a disrupted *Abcb1a* gene and exhibiting a functional deficiency in the blood brain barrier; useful studies of drug transport, neurotoxicology, chemotherapy, multi-drug resistance and oral bioavailability of therapeutic drugs.
- **Mdr1a/b Targeted Mutation Mouse (model 001487)** – carrying a double knockout of *Abcb1a* and *Abcb1b* genes and exhibiting a functional deficiency in the blood brain barrier; useful studies of drug transport, neurotoxicology, chemotherapy,

multi-drug resistance and oral bioavailability of therapeutic drugs.

- **Mdr1a/b-Bcrp Targeted Mutation Mouse (model 003998) –** carries disruptions of three genes; *Abcb1a*,*Abcb1b*, and *Abcg2*, that incode for three drug-extruding transporters.
- **Tau Microinjected Mouse (models 001638 and 002508) –** carries the transgene for the human P301L mutation of the microtubule associated tau gene *(MAPT).* The model develops behavioral and motor disturbances related to development of neurofibrillary tangles (NFT) and can be used to study Alzheimer's disease, Pick disease and other neurological syndromes associated with NFT.

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Additional Publication List
APPSWE Microinjected Mice

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