Expression of the human P301L mutant protein in the Tau Microinjected Mouse leads to development of neurofibrillary tangles and associated motor and behavioral abnormalities.

Applications for the Tau Microinjected Mouse

Aggregates of filaments of the microtubule-associated protein tau result in neurofibrillary tangles (NFT) that are associated with a number of human neurological syndromes. Because the Tau Microinjected Model develops NFT along with other neurological lesions, there are a number of potential research applications, including:

• Defining the role of tau protein mutations and NFT in neurodegenerative diseases, including Alzheimer disease, Pick disease, progressive supranuclear palsy, and corticobasal degeneration

• Examining the relationship between development of NFT and other neurodegenerative processes

• Further definition of the pathogenesis of neurodegenerative diseases with NFT

• Evaluation of potential therapies for NFT-related diseases

Table 1. Samples scored on H&E stained brain sections for relative comparison of NFT numbers in various locations of the brain. Data provided by D.W. Dickson, Mayo Clinic, Jacksonville, FL, from Tau Microinjected Mice prior to receipt by Taconic. Data represents samples from studies using both homozygous and hemizygous Tau mice performed at the Mayo Clinic.

Features of the Tau Microinjected Mouse

• Model 002508-M is homozygous for microinjection of P301L mutant human Tau. Model 001638-T is hemizygous for microinjection of P301L mutant human Tau. Model 001638-W animals are wild type controls (no transgene) produced as littermates to the 001638-T hemizygotes. 001638-W are ideal controls for 001638-T and approximate controls for 002508-M (homozygotes are produced in a separate colony, and no wild type littermates are produced). 001638-W mice are more appropriate controls than B6D2F1 mice in most experiments.

• Largely neuronal transgene expression pattern with strongest signals in cerebellum and hippocampus

• Fibrillary gliosis in spinal cords of affected mice

• Reduction of ~48% of motor neuron counts in spinal cord (See Figure 1)
Filamentous aggregates in perikarya and proximal dendrites of brainstem and spinal cord neurons with NFT

- Small groups of atrophic, angulated fibers in skeletal muscle, consistent with neurogenic atrophy
- The hemizygous Tau Transgenic Mouse offered by Taconic expresses the human tau protein at levels roughly equivalent to endogenous mouse tau levels (human tau is 50% of total tau)

**Scientific Profile of the Tau Microinjected Mouse**

The Tau Microinjected Mouse carries the human P301L mutation of the microtubule associated protein tau (Mapt) gene. Frontotemporal dementia and parkinsonism linked to chromosome 17 (FDTP-17) have been correlated to mutations in the Mapt gene encoding tau protein. This relationship demonstrates that dysfunctions in tau protein are sufficient to initiate neurodegeneration. The most common Mapt mutation is referred to as P301L, a missense mutation of Pro\(^{301}\)→Leu. In order to evaluate the effects of the P301L mutation, scientists at the Mayo Clinic in Jacksonville, Florida developed the Tau Microinjected Mouse Model.

**Age of Phenotypic Onset**

The initial publication for this model reported research performed with F1 animals that were 75% SW and 25% DBA/2-C57BL/6. Animals arriving at Taconic from the originator’s lab were from a later generation. Those mice were mated to SW and B6D2F1 for embryo transfer rederivation. After derivation, offspring from both backgrounds were combined to create the hemizygous source colony. Taconic takes hemizygous males and mates them with B6D2F1 females in a production colony to produce 001638-T and 001638-W animals. For line 002508-M, hemizygotes were bred together in order to generate a homozygous colony. The 002508-M homozygotes are produced through a rotational mating setup of homozygote x homozygote.

Results have been published on both homozygous and hemizygous transgenic animals, and some of the following information was obtained from homozygous animals. Phenotypic expression of the tau-related lesions in homozygous and hemizygous animals differs only in the age of onset, with ultimate severity of lesions being the same. In the initial publication, behavioral and pathological lesions were observed as early as 4.5 months of age in homozygous mice, and by around 6.5 months of age for the hemizygous Tau mice.

Motor and behavioral disturbances were observed in ~90% of transgenic mice by 10 months of age. For animals produced in Taconic’s colonies, age of onset may vary. More recently published reports indicate that age of phenotypic onset is later, starting around 10 months in females and later (12-14) months in males. Abundant hyperphosphorylated tau has been observed in the brains of mice from Taconic’s colonies at 10-18 months of age. Taconic recommends that animals be observed for initiation of motor deficits before conducting certain experiments. Lack of escape extension is often the first sign of phenotypic onset. A pilot study may be necessary for new users of the Tau model to determine the best time points at which to perform specific experiments.

NFT have been associated with development of a number of human degenerative diseases. Onset of symptoms of Alzheimer disease, Pick disease, progressive supranuclear palsy and corticobasal degeneration has been connected to formation of insoluble deposits of the microtubule associated protein tau, referred to as neurofibrillary tangles (NFT). The Tau Microinjected Mouse develops NFT in association with the onset of neurological and behavioral deficits, thus providing a link between the NFT pathology and the neuronal loss.

**Progressive deterioration of motor function is observed in the Tau Microinjected Mouse.** The Tau Microinjected Mouse hemizygotes and homozygotes...
show a loss of escape extension during tail elevation and spontaneous back paw clenching while standing. Phenotypic expression of the Tau transgene is similar between the hemizygous and homozygous mice, and differs only in the age of onset. Both homozygous and hemizygous microinjected mice have a delayed righting response which progresses to an inability to right. Ambulatory capabilities may be lost within two weeks of the onset of signs. Other evidence of motor function deficits include weakening of the blink reflex and decreased grooming and vocalization. Ultimately the transgenic animals become moribund. 

**Extensive neuronal pathology and NFT formation is associated with the loss of motor function.** Fibrillary gliosis is seen in the anterior horns, along with axonal degeneration in the anterior roots and axonal spheroids of the spinal cord. Figure 1 shows a comparison of neuronal counts in the spinal cords of control and Tau Microinjected Mice. Extensive axonal and myelin degeneration is also seen in peripheral nerves. Immunostaining for tau protein has identified the presence of NFT in the diencephalon, brainstem, cerebellar nuclei and spinal cord. The relative concentration of NFT in the brains of the Tau Microinjected Mouse is shown in Table 1. 

The development of NFT and neuronal loss and the distribution of lesions in the Tau Microinjected Mouse are similar to FTDP-17 and other human tauopathies. By demonstrating a link between neurofibrillary pathology and neuronal loss, the Tau Microinjected Mouse facilitates investigation of tau-induced neurodegeneration. The Tau Microinjected Mouse can also be used to examine the relationship of neurofibrillary degeneration to other neurological lesions, and the model serves to evaluate therapeutic modalities.

**Origin of the Model**

The Tau Microinjected Model was developed by Hutton, et al., at Mayo Clinic in Jacksonville, Florida. Transgenic constructs containing the P301L mutation of the microtubule associated tau gene and mouse prion promoter were microinjected into fertilized eggs of hybrid C57BL/6 x DBA2 x SW mice. Founder JNPL3 transgenic mice were mated to B6D2F1 hybrids. Received at Taconic in December, 2000, the mice were mated to SW and to B6D2F1 hybrids and embryo transfer derived. After derivation, offspring from both backgrounds were combined to create the hemizygous source colony. Taconic takes hemizygous males and mates them with B6D2F1 females in a production colony to produce 001638-T and 001638-W animals. For line 002508-M, hemizygotes were bred together to generate homozygotes. The 002508-M homozygotes are produced through a rotational mating setup of homozygote x homozygote.

**Ready for Your Experiments**

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

**Related Mouse Models from Taconic**

- **APPSWE Microinjected Mouse (models 001349 and 002789)** - carrying the APPSWE (2576) transgene coding for the 695-amino acid isoform of human Alzheimer β-amyloid precursor protein derived from a Swedish family with early-onset Alzheimer’s disease; useful for study of the development and treatment of Alzheimer’s disease
- **Mdr1a Targeted Mutation Mouse (model MDR1A)** – carrying a disrupted Abcb1a gene, a multi-drug resistance-associated transport protein, conferring a deficiency in the blood-brain barrier; useful in neurotoxicology and in studies of drug design, cellular transport and testing
- **Mdr1a/b Targeted Mutation Mouse (model 001487)** – carrying disruptions of two genes, Abcb1a and Abcb1b and lacking cellular transport mechanisms by their two multi-drug resistance-associated protein products, conferring a deficiency in the blood-brain barrier; useful in neurotoxicology and in studies of drug design, cellular transport and testing
- **Mdr1a/b-Bcrp Targeted Mutation Mouse (model 003998)** carries disruptions of three genes; Abcb1a,Abcb1b, and Abcg2, that encode for three drug-extruding transporters.

Please Note: e-mail transmission of this document may result in the loss of formatting or symbols, i.e., Greek letters or symbols for trademark, degrees, etc.
References Cited:


© Copyright 2008, Taconic Biosciences, Inc. RG290495

Every Taconic Transgenic Model™ carries a label license granting you a license under Taconic’s in-licensed patent right(s) to use the model in your research. TTM™s are produced and distributed under rights to patents that Taconic has licensed from various institutions, including exclusive distribution rights to Positive Negative Selection and Isogenic DNA gene targeting technologies. Taconic is the only commercial breeder that can supply transgenic models with these licenses for use in your research.

Conditions of Use for Taconic Transgenic Models™

TACONIC TRANSGENIC MODELS™ ("MODELS") are produced and distributed under rights to patents and intellectual property licensed from various institutions. Taconic grants to each purchaser a right under Taconic's rights in such licensed patents and intellectual property to use the purchased MODEL in consideration of purchasers’ acknowledgement of and agreement to the Terms and Conditions of Sale and the following terms of use:

- Title to these MODELS and biological materials derived from them remains WITH TACONIC Biosciences, INC.
- The MODELS will be used for research purposes only.
- The MODELS will not be bred except to obtain embryos or fetuses required for research purposes unless the purchaser maintains a Research Crossbreeding Agreement with TACONIC Biosciences, INC.
- The MODELS and biological materials derived from them will not be distributed to third parties or used for commercial purposes.

Patents applicable to Taconic Transgenic Models are posted on Taconic’s website at www.taconic.com

For more information or to place an order contact:

TACONIC
Suite 304, 1 Discovery Drive
Rensselaer, NY 12144
Toll Free: 1-888-TACONIC
Phone: 518-537-6208
Fax: 518-537-7287
e-mail: custserv@taconic.com
Internet: http://www.taconic.com

in Europe: Taconic Europe
Bomholtvej 10 P.O. Box 39
DK 8680 Ry DENMARK
Phone: +45 70 23 04 05
e-mail: TaconicEurope@taconic.com
Internet: http://www.taconic.com

in Japan: Immuno-Biological Laboratories, Co., Ltd.
5-1 Aramachi, Takasaki-Shi
Gunma 370-0831 JAPAN
Phone: +81 273-10-8040
Fax: +81 273-10-8045
e-mail: do-ibl@ibl-japan.co.jp
Internet: http://www.ibl-japan.co.jp

© Copyright 2008, Taconic Biosciences, Inc. RG290495

Every Taconic Transgenic Model™ carries a label license granting you a license under Taconic's in-licensed patent right(s) to use the model in your research. TTM™s are produced and distributed under rights to patents that Taconic has licensed from various institutions, including exclusive distribution rights to Positive Negative Selection and Isogenic DNA gene targeting technologies. Taconic is the only commercial breeder that can supply transgenic models with these licenses for use in your research.

© Copyright 2008, Taconic Biosciences, Inc. RG290495

Every Taconic Transgenic Model™ carries a label license granting you a license under Taconic’s in-licensed patent right(s) to use the model in your research. TTM™s are produced and distributed under rights to patents that Taconic has licensed from various institutions, including exclusive distribution rights to Positive Negative Selection and Isogenic DNA gene targeting technologies. Taconic is the only commercial breeder that can supply transgenic models with these licenses for use in your research.


