TACONIC

Neuroscience Portfolio

A DIVERSE PORTFOLIO OF RODENT MODELS AND SERVICES FOR NEUROSCIENCE RESEARCH

Taconic Biosciences Neuroscience Portfolio

From neuro-developmental disorders to neurodegeneration, Taconic's Neuroscience Portfolio provides relevant solutions for pre-clinical research.

A major challenge in neuroscience research and drug discovery is the lack of easy access to relevant animal models for use in screening drug candidates.

Taconic's Neuroscience Portfolio provides scientists with easy access to models and services for the study of neuroscience and neurodegenerative diseases. Many of these models are available exclusively from Taconic with rights to use. Together with scientific support from PhD scientists, extensive phenotyping data, and Taconic's customized breeding and aging services, we help you accelerate your neuroscience research efforts.

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PORTFOLIO OVERVIEW

MODELS AND SERVICES COVERED IN THE NEUROSCIENCE PORTFOLIO

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ALZHEIMER'S DISEASE MODELS

Amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) combined with deficits in learning and memory are hallmarks of Alzheimer's disease. Understanding how plaques and tangles are formed and discovering effective therapeutics that prevent these neurodegenerative processes are important factors for winning the battle against Alzheimer's disease.

Taconic offers a variety of transgenic rodent models that develop plaques and tangles and can be used for screening of novel drug candidates for treating Alzheimer's and other neurodegenerative diseases.

FAMILIAL ALZHEIMER'S DISEASE MODELS

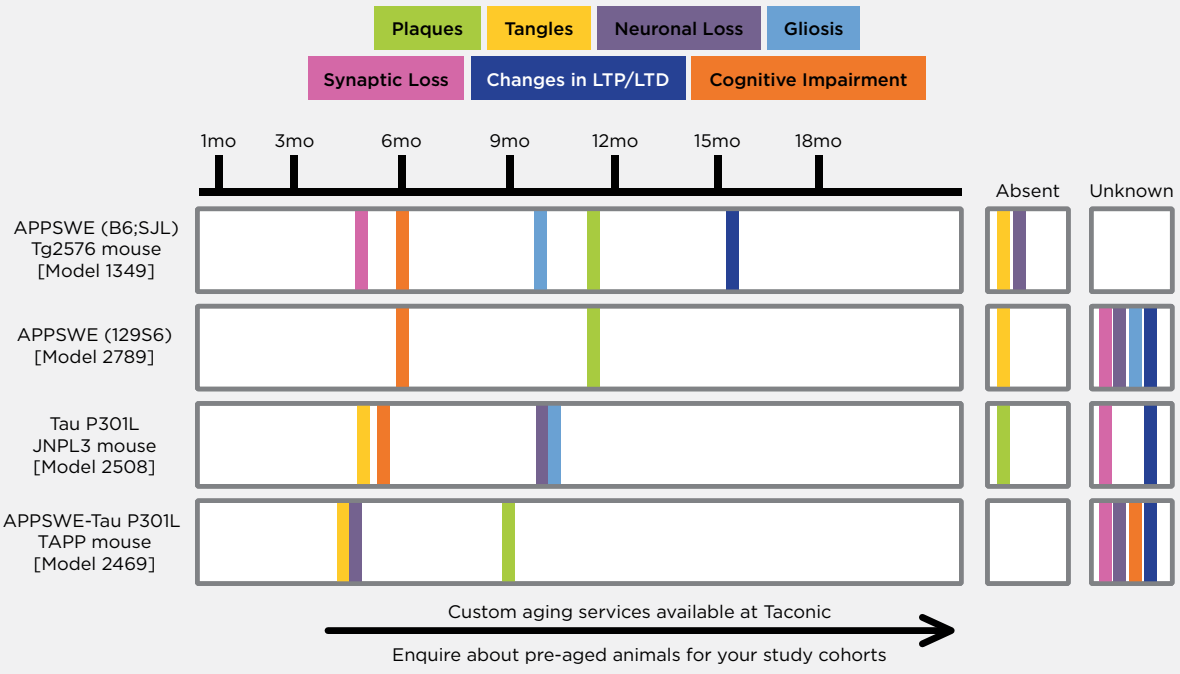
- APPSWE (Tg2576)
- TAU P301L (JNPL3)
- APPSWE-TAU P301L (TAPP)

SPORADIC ALZHEIMER'S DISEASE MODELS

- HUMANIZED APOE 2/3/4

Timeline of neuropathology of popular Alzheimer's mouse models available from Taconic

Graphic adapted from 'Research Models Visualization" at www.alzforum.org



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MODELS OF FAMILIAL ALZHEIMER'S DISEASE

APPSWE (Tg2576)

SWEDISH MUTATIONS K670N AND M671L
RANDOM TRANSGENIC (B6;SJL MIXED BACKGROUND)

- Also known as the Tg2576 mouse, one of the most widely used models of Alzheimer's disease pathology.
- Carries a transgene coding for the 695-amino acid isoform of human amyloid β precursor protein (APP) carrying the Swedish mutations (K670N, M671L).
- Expresses high concentrations of the mutant Aβ protein, develops significant amyloid plaques, and displays memory deficits.
- Useful for the study of APP expression, amyloid plaque formation, neuronal decline, and memory loss associated with Alzheimer's.
- Carries the *Pde6b*^{rd1} retinal degeneration mutation observed in many inbred strains of mice.

MODEL NUMBER **1349**

MODEL NUMBER **1349-RD1**
(Screened for *Pde6b*^{rd1} mutation)

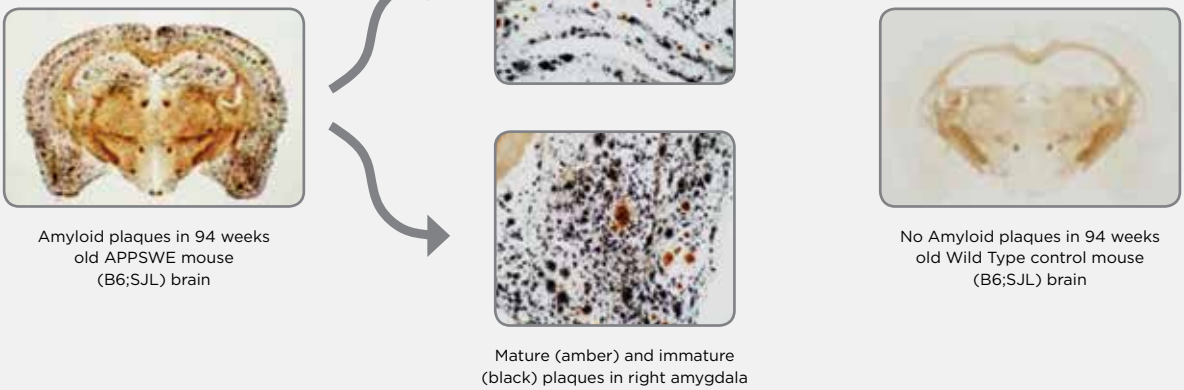
NOMENCLATURE

B6;SJL-Tg(APPSWE)2576Kha

This may impact the results of behavioral testing.**

** Pink eyed animals, associated with certain coat colors, and the *Pde6b*^{rd1} retinal degeneration mutation found in several inbred strains of mice can cause light sensitivity and/or blindness in some animals. This may impact the results of behavioral testing. Upon request, Taconic can screen for eye color, coat color, and/or rd1 homozygosity for an additional fee.

AMYLOID PLAQUE DEVELOPMENT IN APPSWE MOUSE BRAIN



APPSWE

SWEDISH MUTATIONS K670N AND M671L
RANDOM TRANSGENIC (129S6 BACKGROUND)

NOMENCLATURE

129S6.Cg-Tg(APPSWE)2576Kha N20+?

- Carries the same mutation as Tg2576 mouse, but on a different genetic background.
- Carries a transgene coding for the 695-amino acid isoform of human Alzheimer β-amyloid precursor protein (APP) carrying the Swedish mutations (K670N, M671L).
- Expresses high concentrations of the mutant Aβ protein, develops significant amyloid plaques, and displays memory deficits correlating with the development of amyloid plaques.
- This background does not carry the *Pde6*^{brd1} retinal degeneration mutation, but as with all 129 substrains does carry a mutated *Disc1* gene.

MODEL NUMBER **2789**

TAU P301L (JNPL3 mouse)

P301L MUTATION IN HUMAN TAU
RANDOM TRANSGENIC (C57BL/6, DBA/2,
SW MIXED BACKGROUND)

NOMENCLATURE

STOCK Tg(Prnp-MAPT*P301L)JNPL3Hlmc

- Also known as the JNPL3 mouse.
- Carries the transgene for the human P301L mutation of the microtubule associated protein tau gene (MAPT).
- Aggregates of filaments of TAU result in neurofibrillary tangles which are associated with Alzheimer's disease, Pick disease, and other neurological syndromes.
- Develops behavioral and motor disturbances related to development of neurofibrillary tangless.
- Sex differences in transgene expression have been observed with females expressing higher levels of protein than males.
- Carries the *Pde6b*^{rd1} retinal degeneration mutation observed in many inbred strains of mice. This may impact the results of behavioral testing.**

** Pink eyed animals, associated with certain coat colors, and the *Pde6b*^{rd1} retinal degeneration mutation found in several inbred strains of mice can cause light sensitivity and/or blindness in some animals. This may impact the results of behavioral testing. Upon request, Taconic can screen for eye color, coat color, and/or rd1 homozygosity for an additional fee.

MODEL NUMBER **2508**
(Homozygous transgenic)

MODEL NUMBER **1638**
(Hemizygous and wild type)

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APPSWE-TAU P301L (TAPP mouse)

SWEDISH MUTATIONS K670N, M671L IN HUMAN APP AND P301L MUTATION IN HUMAN TAU
RANDOM TRANSGENIC (C57BL/6, DBA/2, SJL, SW MIXED BACKGROUND)

NOMENCLATURE

STOCK Tg(APPSWE)2576Kha
Tg(Prnp-MAPT*P301L)JNPL3Hlmc

- Carries the transgene coding for the 695-amino acid isoform of human amyloid β precursor protein (APP) in addition to the transgene for the human P301L mutation of the microtubule-associated protein tau gene (MAPT).
- Amyloid plaque distribution, number, morphology, and density is similar between APPSWE-TAU and APPSWE mice.
- Motor disturbances and morphology of neurofibrillary tangles are comparable between APPSWE-TAU and TAU P301L mice.
- Useful for studies that focus on formation of β-amyloid plaques and neurofibrillary tangles, and for developing novel therapeutics for the prevention and treatment of Alzheimer's disease.
- Carries the *Pde6b*^{rd1} retinal degeneration mutation observed in many inbred strains of mice. This may impact the results of behavioral testing.**

** Pink eyed animals, associated with certain coat colors, and the *Pde6b*^{rd1} retinal degeneration mutation found in several inbred strains of mice can cause light sensitivity and/or blindness in some animals. This may impact the results of behavioral testing. Upon request, Taconic can screen for eye color, coat color, and/or rd1 homozygosity for an additional fee.

MODEL NUMBER **2469**

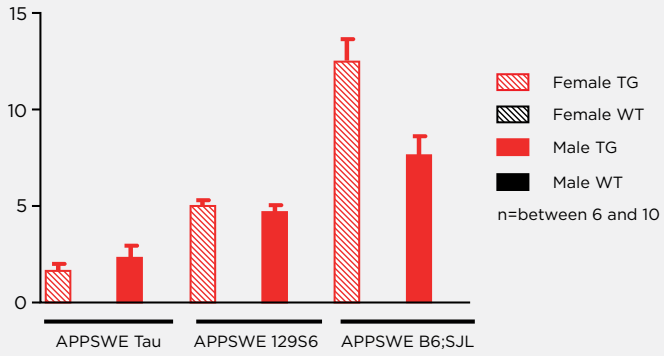
MODEL NUMBER **3723**
(Wild Type control)

MODEL NUMBER **2469-RD1**
(Screened for *Pde6b*^{rd1} mutation)

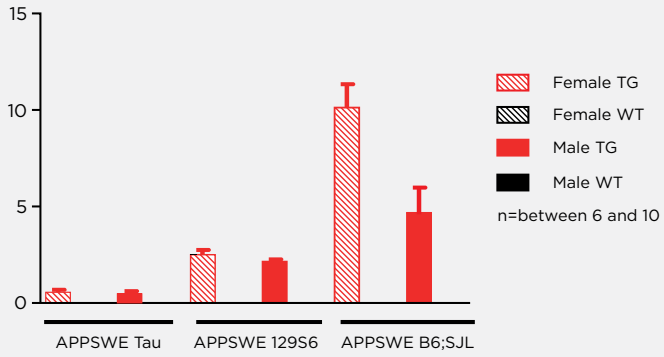
MODEL NUMBER **3723-RD1**
(Screened for *Pde6b*^{rd1} mutation)

PATHOGENIC Aβ IN ALZHEIMER'S MOUSE MODELS

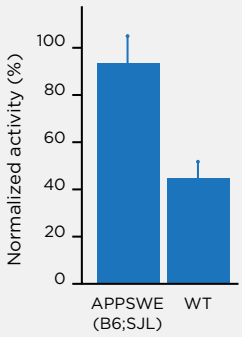
$A\beta_{40}$ at 28–29 Weeks



$A\beta_{42}$ at 28–29 Weeks



LEARNING DEFICITS IN APPSWE MICE



Impaired trace fear conditioning in 54 weeks old APPSWE mice

MODELS OF SPORADIC ALZHEIMER'S DISEASE

HUMANIZED APOLIPOPROTEIN E (ApoE) BASED NEURODEGENERATION MODELS

ApoE and Neurodegeneration Quick Facts

ApoE is a plasma protein involved in cholesterol transport, with three human isoforms: E2, E3, and E4. In addition to genotype-phenotype associations with cardiovascular disease, isoforms of apoE have also been implicated as risk factors for sporadic forms of late-onset Alzheimer's disease.

- In the brain, apoE is synthesized primarily by astrocytes and microglia. It is then lipidated by the ABCA1 transporter to form lipoprotein particles. Once formed, lipidated apoE binds to soluble Aβ and facilitates Aβ uptake via cell surface receptors.
- The association between specific apoE isoform expression and human neurodegenerative disorders has focused on the role of apoE isoforms in lipoprotein receptor-dependent synaptic modulation.
- Among the three isoforms, apoE4 appears to drive amyloid pathology by inhibiting brain clearance of Aβ peptides, and by promoting Aβ aggregation.
- Targeting apoE and apoE receptor pathways may offer novel therapeutic strategies to combat neurodegenerative diseases.

Taconic provides three humanized apoE mouse models that are useful for studying the role of human APOE polymorphism in neurodegenerative disorders.

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APOE2

HUMANIZED KNOCK IN (C57BL/6 BACKGROUND)

NOMENCLATURE

B6.129P2-*Apoe*$^{tm1(APOE*2)Mae}$ N9

- Homozygous for a human APOE2 gene targeted replacement of the endogenous mouse *Apoe* gene.
- Expresses human apoliprotein E2 isoform under the control of the murine *Apoe* regulatory sequences.
- E2 is the least common isoform in the human population.
- In humans, the E2 allele decreases the risk and delays onset of Alzheimer's disease, but increases the risk of type III hyperlipoproteinemia.
- These mice develop spontaneous atherogenesis, which is exacerbated by a high fat diet.

MODEL NUMBER **1547**

APOE3

HUMANIZED KNOCK IN (C57BL/6 BACKGROUND)

NOMENCLATURE

B6.129P2-*Apoe*$^{tm2(APOE*3)Mae}$ N8

- Homozygous for a human APOE3 gene targeted replacement of the endogenous mouse *Apoe* gene.
- Expresses human apoliprotein E3 isoform under the control of the murine *Apoe* regulatory sequences.
- E3 is the most common isoform, expressed by almost 80% of the human population.
- On a normal diet these mice have normal plasma cholesterol and triglyceride levels, but relative quantities of plasma lipoprotein particles are altered, and clearance of vLDL particles is delayed.
- On a high-fat diet, these mice develop abnormal serum lipid profiles and atherosclerotic plaques.
- On a high-fat diet, these mice exhibit an increased risk of atherosclerosis and hypercholesterolemia relative to wild type mice.

MODEL NUMBER **1548**

APOE4

HUMANIZED KNOCK IN (C57BL/6 BACKGROUND)

NOMENCLATURE

B6.129P2-*Apoe*$^{tm3(APOE*4)Mae}$ N8

- Homozygous for a human APOE4 gene targeted replacement of the endogenous mouse *Apoe* gene.
- Expresses human apoliprotein E4 isoform under the control of the murine *Apoe* regulatory sequences.
- E4 occurs in approximately 14% of the human population and has been implicated as a risk factor for developing Alzheimer's disease.
- On a normal diet, these mice have normal plasma cholesterol and triglyceride levels, but relative quantities of plasma lipoprotein particles are altered, and clearance of vLDL particles is delayed.
- On a high-fat diet, these mice exhibit an increased risk of atherosclerosis relative to wild type, and APOE3 targeted replacement mice.

MODEL NUMBER **1549**

NEUROPSYCHIATRIC DISORDER MODELS

Copy Number Variation Models

Copy number variations (CNVs) are a type of genetic structural variation involving deletions or duplications of specific and relatively large (>1 kb) regions of DNA. Geneticists now recognize that CNVs and other rare structural variants contribute toward the genetic basis of common diseases and disorders, including autism and schizophrenia.

Taconic offers three neuropsychiatric disorder CNV models that develop distinct neurological and behavioral phenotypes. These CNV models can be used for screening of novel drug candidates for treating schizophrenia, autism spectrum disorders, epilepsy and other neuropsychiatric disorders.

HUMAN 15q13.3 DELETION ([Df(h15q13)/+] mouse)

CONSTITUTIVE KNOCK OUT (GENOMIC DELETION)
C57BL/6 BACKGROUND

NOMENCLATURE

C57BL/6-*Chrna7*$^{tm2087(5'loxP)Arte}$Mtmr15$^{tm2128(3'loxP)Arte}$

- Carries a genomic deletion of a region of mouse chromosome 7 that corresponds to human chromosome region 15q13.3.
- In humans, hemizygous deletion of chromosome 15q13.3 confers high risk of schizophrenia, autism, and epilepsy.
- Useful as a model of schizophrenia-like pathology and studying the underlying biology of schizophrenia, epilepsy, and other neural circuit defects associated with 15q13.3 deletion in humans.
- Schizophrenia related phenotype: EEG characterization revealed auditory processing deficits similar to those observed in schizophrenia. They have impaired long-term spatial reference memory and decreased performance in the novel object recognition task.
- Epilepsy related phenotype: Human 15q13.3 deletion mice show changes in neuronal excitability in acute seizure assays, with increased propensity to develop myoclonic and absence-line seizures; decreased propensity for clonic and tonic seizures.

MODEL NUMBER **10962**

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HUMAN 22q11.2 DELETION ([Df(h22q11)/+] mouse)

CONSTITUTIVE KNOCK OUT (GENOMIC DELETION)
C57BL/6 BACKGROUND

NOMENCLATURE

C57BL/6-Dgcr2$^{(5'loxP)}$Hira$^{tm2129-(3'loxP)Arte}$

- Carries a genomic deletion of a region of mouse chromosome 16 that corresponds to human chromosome region 22q11.2.
- In humans, hemizygous deletion of chromosome 22q11.2 confers high risk of neurodevelopmental disorders, including autism and schizophrenia, with up to 41% of deletion carriers experiencing psychotic symptoms.
- Df(h22q11)/+] mice have reduced prepulse inhibition (PPI) and increased acoustic startle response (ASR).
- Increased 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the pre-frontal cortex.
- Increased NMDA-receptor antagonist-induced locomotion: show increased activity in response to PCP- and ketamine-induced locomotor activity in postpubertal mice.
- Useful as a model of schizophrenia-like pathology and for studying the underlying biology of schizophrenia and other psychiatric disorders related to 22q11.2 deletion in humans.

MODEL NUMBER **11026**

HUMAN 1q21.1 DELETION ([Df(h1q21)/+] mouse)

CONSTITUTIVE KNOCK OUT (GENOMIC DELETION)
C57BL/6 BACKGROUND

NOMENCLATURE

C57BL/6-Gpr89$^{tm2086(5'loxP)Arte}$Prkab2$^{tm2127(3'loxP)}$

- Carries a genomic deletion of a region of mouse chromosome 3 that corresponds to human chromosome region 1q21.1.
- In humans, hemizygous deletion of chromosome 1q21.1 confers high risk of schizophrenia and may also increase risk of ADHD and autism spectrum disorders.
- Useful as a model of schizophrenia-like pathology and for studying the underlying biology of schizophrenia and other psychiatric disorders related to 1q21.1 deletion in humans.

MODEL NUMBER **11025**

TABLE SUMMARIZING PHENOTYPE DATA FOR 15Q13.3

DOMAIN	ASSAY	PHENOTYPE	COMMENT
Basal	Body weight	↑	
Aggression	Stress-induced aggression	↑	Corticosterone response to restraint stress unaltered
Light/Dark Cycle	Diurnal activity	↓ (dark phase)	
Seizures	MEST	↓ (dark phase)	
	PTZ seizures	↓ (Clonic, tonic), Up (myoclonic jerks, single spikes, absence-like)	Behavioral and EEG level.
	Nicotine seizures	↓	15 mg/kg (nicotine tartrate = 5.2 mg/kg nicotine)
Sensorimotor Processing	Acoustic startle response	↓	
Positive Symptoms	Basal motility	↓	Decreased activity during exploration
Cognition	Morris watermaze	↓ (24h retrieval)	4 days acquisition, probe test on day 5
EEG	AEP amplitude	↓ (PC,FC)	
	Baseline gamma power	↑	Measured during active state (animal moving)
	Evoked gamma power	↓	
	Peak theta frequency	↓	Active state

Adapted from https://www.ncbi.nlm.nih.gov/pubmed/24090792

AMYOTROPHIC LATERAL SCLEROSIS (ALS) MODEL

The hallmarks of Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, are muscle weakness, reduced motor function, and paralysis. Understanding how motor neurons are targeted for degeneration and discovering effective therapeutics that prevent motor neuron degeneration are important factors for winning the battle against ALS.

Taconic offers a humanized animal model sponsored by the ALS Association. This model allows investigators to screen novel compounds for efficacy against the various pathologies associated with ALS.

SOD1 RAT

SOD1 G93A MUTATION
RANDOM TRANSGENIC (SPRAGUE DAWLEY® BACKGROUND)

NOMENCLATURE

NTac:SD-Tg(SOD1G93A)L26H

- Carries the transgene encoding the human *SOD1* gene with the G93A mutation.
- Hemizygous rats express SOD1G93A in the spinal cord approximately 8-fold above endogenous levels, and develop motor neuron disease with abnormal gait and hind limb paralysis.
- SOD1G93A is also expressed across many brain regions as well as peripheral tissues.
- By end stage, mutant SOD1 levels accumulate approximately 16-fold over endogenous levels, representing an additional 2-fold increase in SOD1G93A compared with levels in young, presymptomatic rats (6 weeks old).
- Rapid decline of SOD1G93A rats coincides with substantial loss of spinal cord motor neurons as well as marked increases in gliosis and degeneration of muscle integrity and function.

MODEL NUMBER **2148**

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PARKINSON'S DISEASE RESEARCH MODELS

Rat Tools For Parkinson's Research
Quick Facts

- Loss of nigrostriatal dopamine neurons and reduced motor abilities are hallmarks of Parkinson's disease.
- Mutations in the *LRRK2* and alpha synuclein (*SNCA*) genes are associated with familial Parkinson's disease and are known to affect the nigrostriatal pathway.
- The rat as an experimental organism can offer some unique strengths compared to mice:
  - Rats can perform more sophisticated behavioral tasks.
  - Rats are better suited for electrophysiological multichannel recordings.
  - Nigrostriatal circuit of the rat is more sensitive to insults compared to that of mice.

Alpha Synuclein (*SNCA*) mutations (A53T, A30P, E46K) and gene duplication or triplication can lead to Parkinson's disease.

LRRK2 G2019S is the most prevalent mutation found in familial and sporadic Parkinson's disease.

6-OHDA insult to brain dopamine neurons mimic pathologies associated with Parkinson's disease.

THE MICHAEL J. FOX FOUNDATION SPONSORED RAT TOOLS FOR PARKINSON'S RESEARCH

TACONIC OFFERS SEVERAL TRANSGENIC RATS, SPONSORED BY THE MICHAEL J. FOX FOUNDATION, THAT CAN BE USED AS TOOLS TO DEVELOP THERAPIES AGAINST PARKINSON'S DISEASE.

HUMAN ALPHA SYNUCLEIN RAT

NOMENCLATURE

Tac:SD-Tg(SNCA*WT)446Cjli

EXPRESSES HUMAN *SNCA*
RANDOM TRANSGENIC (SD BACKGROUND)

- Carries the wild type human alpha synuclein gene (*SNCA*).

MODEL NUMBER **10680**

HUMAN ALPHA SYNUCLEIN A53T RAT

NOMENCLATURE

NTac:SD-Tg(SNCA*A53T)268Cjli

EXPRESSES A53T ON HUMAN *SNCA* GENE
RANDOM TRANSGENIC (SD BACKGROUND)

- Carries the A53T mutation on the human alpha synuclein gene (*SNCA*).
- Neuronal loss and Lewy bodies in the substantia nigra and locus ceruleus are associated with the A53T alpha-synuclein mutation.

MODEL NUMBER **10678**

HUMAN ALPHA SYNUCLEIN E46K RAT

NOMENCLATURE

NTac:SD-Tg(SNCA*E46K)70Cjli

EXPRESSES E46K ON HUMAN *SNCA* GENE
RANDOM TRANSGENIC (SD BACKGROUND)

- Carries the E46K mutation on the human alpha synuclein gene (*SNCA*).
- Atrophy of the substantia nigra and build-up of Lewy bodies are associated with the E46K alpha synuclein mutation.

MODEL NUMBER **10679**

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HUMAN LRRK2 G2019S RAT

EXPRESSES G2019S ON HUMAN *LRRK2* GENE
RANDOM TRANSGENIC (SD BACKGROUND)

NOMENCLATURE

NTac:SD-Tg(LRRK2*G2019S)571Cjli

- Carries the G2019S mutation on the human *LRRK2* gene.
- Non-specific deterioration of the substantia nigra and absence of Lewy bodies is associated with the G2019S mutation.

MODEL NUMBER **10681**

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hTH-GFP RAT

GFP EXPRESSION UNDER HUMAN
TYROSINE HYDROXYLASE PROMOTER
RANDOM TRANSGENIC (SD BACKGROUND)

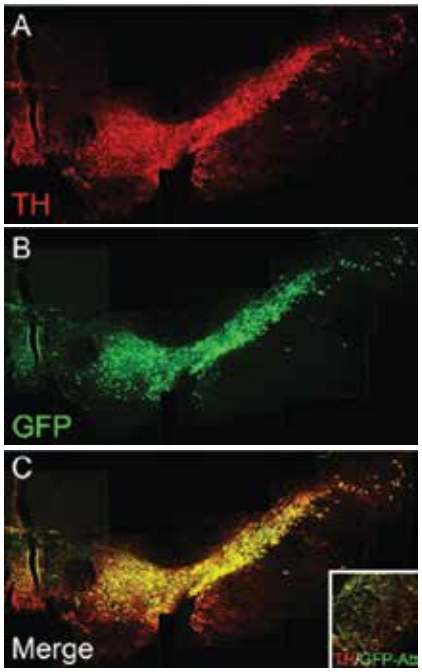
NOMENCLATURE

NTac:SD-Tg(TH-EGFP)7Xen
NTac:SD-Tg(TH-EGFP)24Xen

- Carries an EGFP transgene driven by the human Tyrosine Hydroxylase (hTH) promoter.
- Robust and specific EGFP expression observed in dopaminergic neurons of various brain structures including the substantia nigra, ventral tegmental area, striatum, olfactory bulb, and hypothalamus. Minimal ectopic expression observed in other regions of the brain.
- Dopamine neurons are susceptible to damage/loss in Parkinson's disease and therefore this rat can be used as a tool to study damage/loss of dopamine neurons, e.g., after MPTP or 6-OHDA treatment.
- Useful for *in vivo* anatomical visualization and micro-dissection of rat midbrain structures and axonal projections. High EGFP expression permits fluorescence imaging of brain slices. Also useful for FACS purification and *in vitro* culture of dopamine neurons for studies of disease pathogenesis in culture.
- This rat is also practical for study of early embryonic development of dopamine neurons, since EGFP is more easily detected than TH immunostaining at early developmental stages.
- X-linked and autosomal hTH-GFP transgenic rat models available.

MODEL NUMBER **12108**

MODEL NUMBER **12141**
(X-linked hTH-GFP transgene)



GFP expression overlaps with TH expression in the midbrain.

SURGICALLY INDUCED MODEL OF PARKINSON'S DISEASE

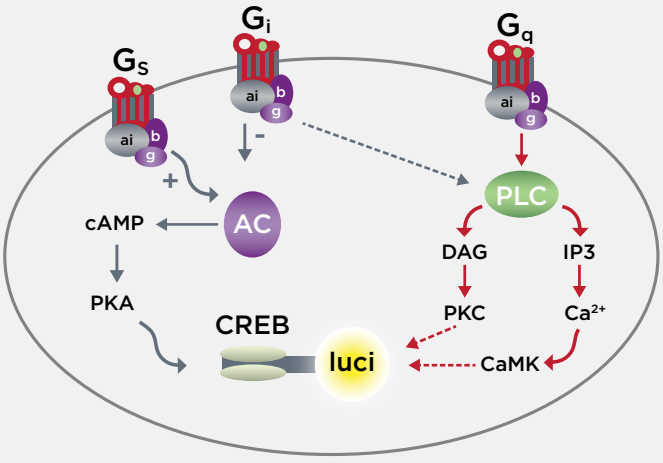
Unilateral 6-Hydroxydopamine Lesion of the Nigrostriatal Pathway

- Animal models with unilaterally destroyed central dopamine neurons are important tools in the study of neurodegenerative disease processes associated with Parkinson's disease.
- The neurotoxin 6-hydroxydopamine (6-OHDA) is administered into certain brain areas. This results in a selective destruction of catecholamine (adrenaline, noradrenaline, and dopamine) neurotransmitter neurons.
- The unilateral destruction of dopamine neurons results in a chemical imbalance of dopamine content across the brain hemispheres.
- As a result of this chemical imbalance or asymmetry, administration of certain dopamine agonists, such as apomorphine, causes stimulation of intact dopamine neurons in the unaffected brain hemisphere.
- This asymmetric stimulation is behaviorally manifested by locomotion in the direction of the unaffected hemisphere (i.e., the animal runs in circles).
- The quantification of circling behavior can be used to access the efficacy of therapeutic agents which may be used in the treatment of Parkinson's disease.

CRE-LUC GPCR REPORTER MOUSE PLATFORM

AN *IN VITRO/IN VIVO* LUCIFERASE REPORTER PLATFORM FOR PROFILING OF LEADS IN GPCR DRUG DEVELOPMENT

- A panel of luciferase reporter mice are available that allow monitoring of GPCR pathway activation (via the two main GPCR classes, G_s and G_i) in various tissues, and help better profile leads in GPCR drug development.
- The CRE-Luc GPCR reporter mouse platform enables investigators to rapidly conduct *in vivo* PK/PD profiling of compounds with quantitative data to compare pharmacological action.
- The central nervous system CRE-Luc reporter is specifically expressed in the brain and spinal cord, and can be leveraged in a variety of assays including *in vitro* (primary neuronal cultures), *in vivo* (whole animal), and *ex vivo* (brain slices).

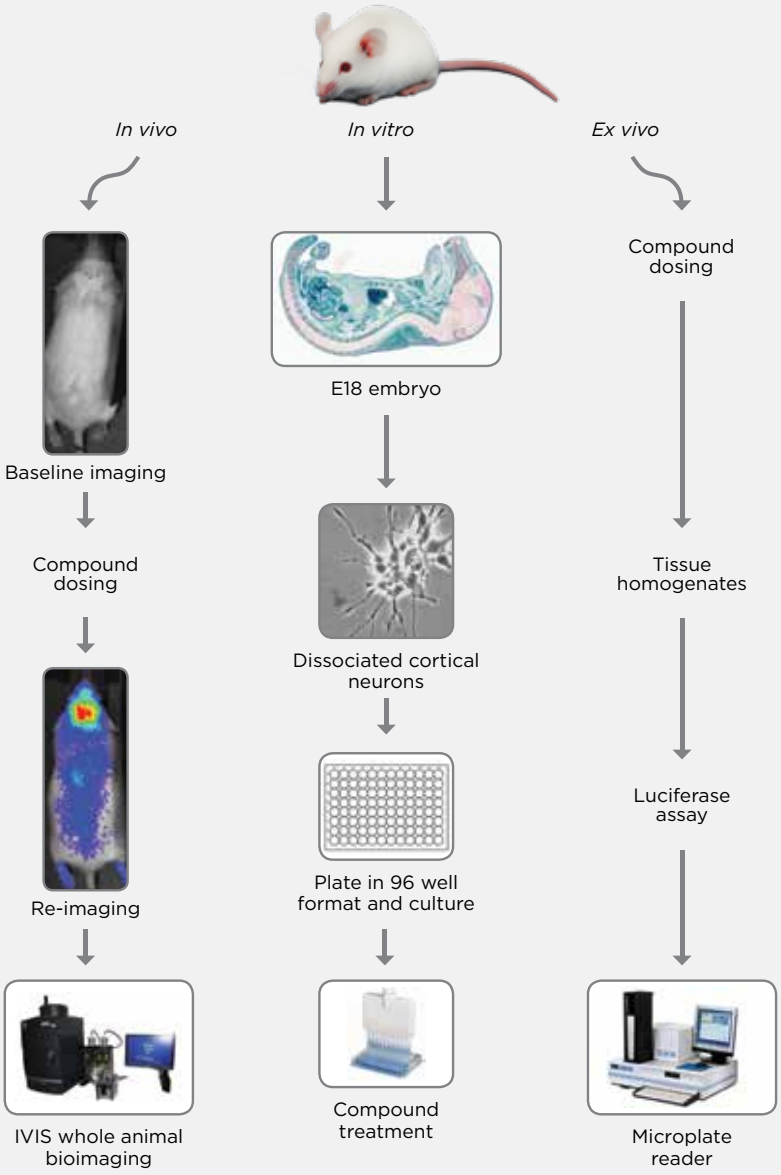


HOW THE CRE-LUC GPCR REPORTER PLATFORM WORKS

- CRE-Luc transgenic models contain a luciferase reporter under the control of a synthetic promoter CRE, which supports real-time bioimaging of GPCR ligand activity in whole animals, tissues, or primary cells.
- GPCR signaling, via the cAMP pathway, can be detected from the target GPCR in its native cellular environment with the full complement of associated receptors and membrane constituents.
- The platform accelerates the transition from high throughput screening (HTS) to *in vivo* profiling of GPCR small molecule leads, in addition to helping define the mode of action of GPCR drugs.

For more information on the CRE-Luc reporter platform, visit: taconic.com/cre-luc

CRE-LUC MOUSE PLATFORM USED IN DIFFERENT ASSAY SYSTEMS



KEY STRENGTHS OF THE PLATFORM

- Helps accelerate the difficult transition from *in vitro* to *in vivo* assays in GPCR pharmaceutical programs.
- Multiple assay formats can enhance lead optimization and progression.
- Supports monitoring of any GPCR signaling through the camp pathway in a native environment where the critical membrane interfaces are interacting with the targeted GPCR.

MODEL NUMBER	REPORTER EXPRESSION
11515	Pancreas
11516	Intestine, liver, pancreas, lungs
11517	Kidney, liver
11518	Spleen, kidney, liver
11519	Brain, lungs
11520	Brain, spinal cord
11521	Kidney, brain, pancreas, lungs

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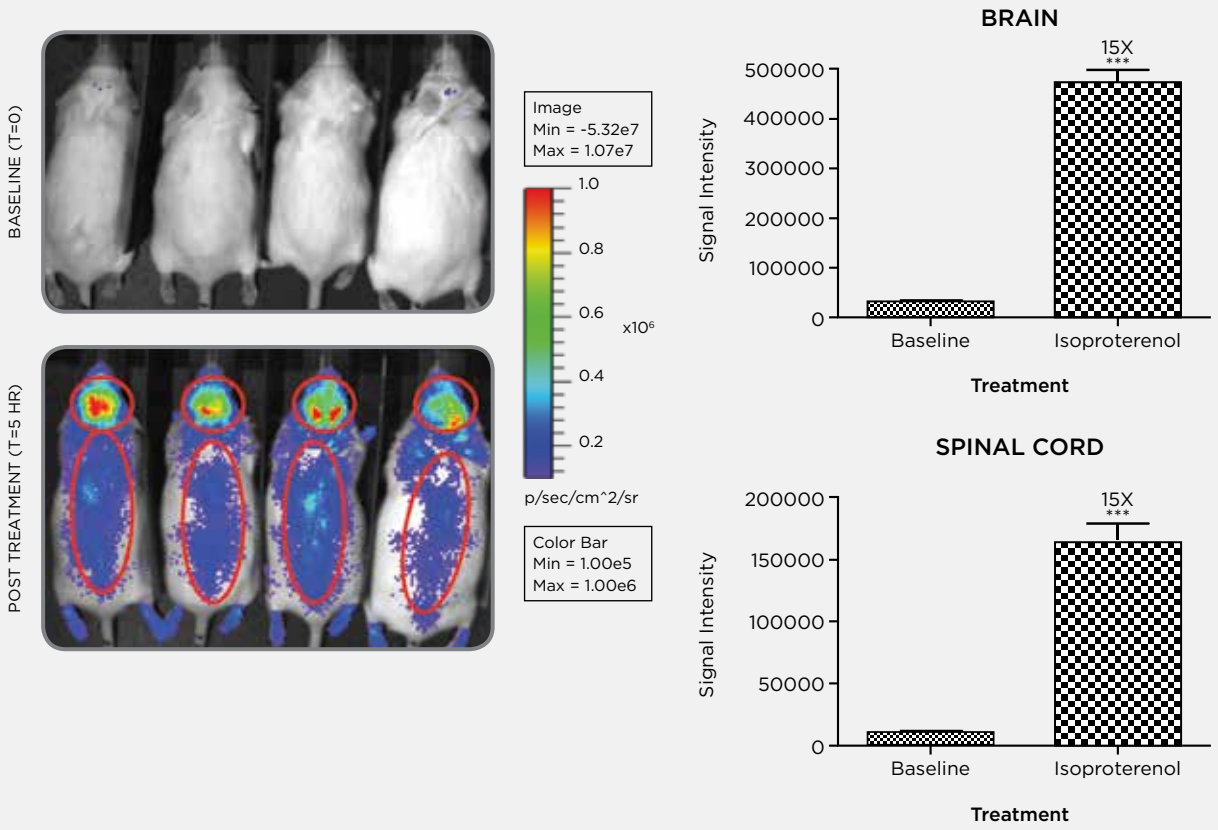
APPLICATIONS IN STUDIES OF GPCR SIGNALING IN THE CNS

APPLICATIONS IN STUDIES OF GPCR SIGNALING IN THE CNS

Whole Animal Imaging



Treatment of mice (Model #11520) with Isoproterenol (β-adrenergic receptor agonist) shows CNS response

EXAMPLE WORKFLOW WITH THE CRE-LUC REPORTER PLATFORM

The CRE-Luc lines can serve as a source of primary cells with the GPCR reporter in its native environment. Therefore *in vitro* studies can be first performed followed by *in vivo* studies.

IN VITRO STUDIES (PRIMARY CELLS)

Primary cell cultures derived from CRE-Luc models can be used to confirm ligand activation. For example, CRE-Luc cultures support GPCR receptor specificity assays, like the use of RNAi or ligand competition assays. These assays are an important validation step since it is possible that any receptor (or combination of receptors) can be activated by a single ligand.

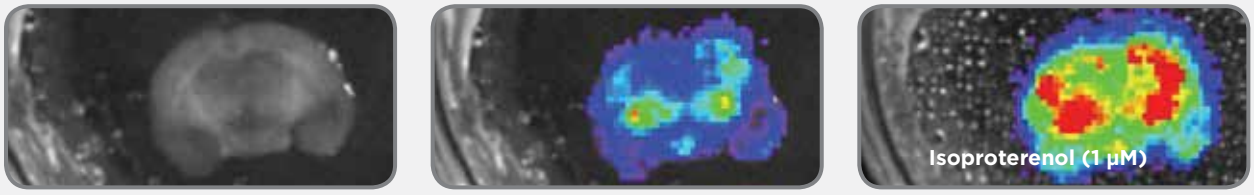
Once ligand activation has been profiled in primary cells, more complex tissue profiles can be assayed for luciferase enzyme levels either *ex vivo* or using tissue homogenates. Although tissue homogenate analyses can be time consuming, it is especially valuable when combined with dosing in whole animals, as it allows investigators to generate tissue-specific, and quantitative ligand activation profiles.

IN VIVO STUDIES (WHOLE ANIMAL)

Once the activation profiles have been established using primary cells, ligand profiles can be probed in whole animals using bioimaging techniques, while also incorporating dose-response and time-course assays. Data analysis can occur in the same day as the imaging session which allows unknown endpoints or results in the assay to be defined as the study progresses. This feature impacts flexibility in the animal study and can save significant time in avoiding repetitive studies to capture overlooked data.

The whole animal bioimaging assay can quantitatively define the site and magnitude of ligand activation, and can support a quantitative comparison of similar compounds which can be useful for selecting optimal lead structures, and SAR.

BRAIN SLICE IMAGING (MODEL #11520)



Brain Slice | Baseline Luciferase | Iso-induced Luciferase

Imaging of compound induced changes in luciferase levels by a β-adrenergic receptor agonist

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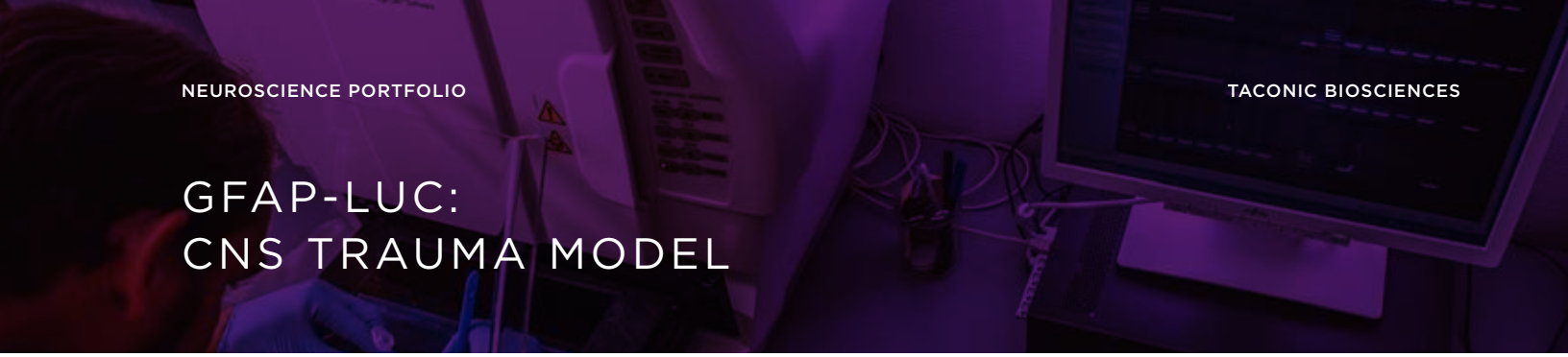

GFAP-LUC: CNS TRAUMA MODEL

CNS TRAUMA AND GFAP
Quick Facts

- Glial fibrillary acidic protein (GFAP) is an intermediate filament protein found in the cytoskeleton of astroglia. GFAP may serve as a traumatic brain injury and central nervous system cell damage reporter.
- Physical trauma, chemical treatment, and bacterial infections resulting in cellular damages in the CNS or changes in pressure within the cerebral spinal fluid are most likely to regulate Gfap expression.
- The Gfap-luc mouse provides an easy to use tool to study CNS damage.

Gfap-luc MOUSE

EXPRESSES LUCIFERASE UNDER GFAP PROMOTER
RANDOM TRANSGENIC (FVB BACKGROUND)

NOMENCLATURE

FVB/N-Tg(Gfap-luc)53Xen

- The Gfap-luc model carries a luciferase reporter gene under the control of the GFAP promoter.
- The reporter is inducible following injury to the CNS and the model is useful for studying changes in the health of the CNS that result in Gfap gene regulation.
- Useful for studying brain trauma, CNS regeneration, astrocyte regeneration, meningitis, physical trauma, chemical insult, and glial scarring.
- Animals have albino coat color making them suitable for whole body imaging.

MODEL NUMBER **10501**

EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

EAE
Quick Facts

- Experimental Autoimmune Encephalomyelitis (EAE) is an animal model of brain inflammation.
- It is widely studied as an animal model of the human CNS demyelinating diseases, including multiple sclerosis (MS) and acute disseminated encephalomyelitis.
- EAE is also the prototype for T cell-mediated autoimmune disease in general.
- EAE can be induced in rodents, for example by administering antigens such as spinal cord homogenate (SCH) or purified myelin, such as myelin basic protein (MBP).

Gfap-luc B6 albino

EXPRESSES LUCIFERASE UNDER GFAP PROMOTER
RANDOM TRANSGENIC (FVB BACKGROUND)

- Gfap-luc in B6 albino x FVB F1 mouse is susceptible to Experimental Autoimmune Encephalomyelitis (EAE).
- This mouse can be used for studying brain inflammation, and CNS demyelination disorders such as MS.
- Animals have albino coat color making them suitable for whole body imaging.

INQUIRE FOR AVAILABILITY

Black 6

INBRED MOUSE

- Superior performance in MOG/CFA-induced EAE studies.
- Available at multiple health standards; MPF recommended for EAE studies.

NOMENCLATURE

C57BL/6NTac

MODEL NUMBER **B6**

SJL

INBRED MOUSE

- Can be used to model relapsing-remitting MS via PLP139-151/CFA-induced EAE.

NOMENCLATURE

SJL/JCrNTac

MODEL NUMBER **SJL**

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BEHAVIORAL MODELS

Long Evans

OUTBRED RAT

- Commonly used for behavior and other neurological studies.

MODEL NUMBER **LONGEV**

NOMENCLATURE

SimTac:LE

Sprague Dawley®

OUTBRED RAT

- Commonly used for behavior and other neurological studies.
- Suitable for chemoconvulsant-induced epilepsy studies.

MODEL NUMBER **SD**

NOMENCLATURE

NTac:SD

Swiss Webster

OUTBRED MOUSE

- Commonly used for behavior and other neurological studies.

MODEL NUMBER **SW**

NOMENCLATURE

Tac:SW

129S6

INBRED MOUSE

- Carries a spontaneous mutation of the *Disc1* gene, which may be relevant to studies of schizophrenia and other psychiatric disorders.

MODEL NUMBER **129SVE**

NOMENCLATURE

129S6/SvEvTac

ADDICTION MODELS

Sprague Dawley®

OUTBRED RAT

- Commonly used for behavior and other neurological studies.
- Suitable for chemoconvulsant-induced epilepsy studies.

MODEL NUMBER **SD**

NOMENCLATURE

NTac:SD

Black 6

INBRED MOUSE

- Commonly used for addiction studies.

MODEL NUMBER **B6**

NOMENCLATURE

C57BL/6NTac

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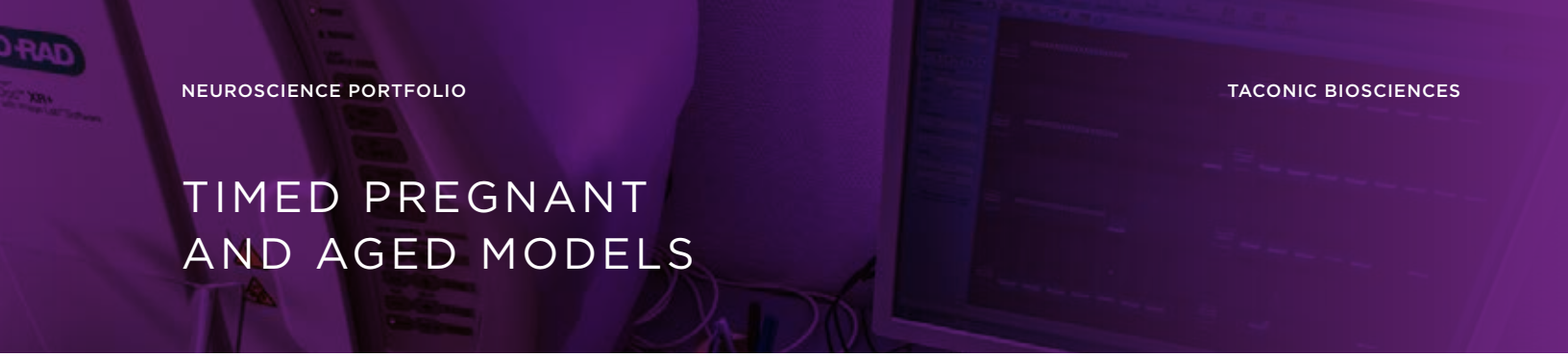

TIMED PREGNANT AND AGED MODELS

Timed Pregnant Animals

Timed mating produces embryos and fetuses of a defined gestational age. This is useful both for developmental studies as well as for derivation of primary neuronal cultures.

Taconic offers timed pregnant females of the following strains and stocks useful for neuroscience research:

- Sprague Dawley®
- Swiss Webster
- Black 6

Aged Models

Readily available aged animal models accelerate your aging research. Taconic offers off-the-shelf inventory of virgin Black 6 males at up to 52 weeks of age. For many strains and stocks, retired breeders are available in small quantities. Retired breeders vary in age, but are typically between 6–9 months. While availability of retired breeders is limited, quantities are often sufficient to perform pilot studies or obtain proof of concept results to justify further experiments with aged virgin animals.

STUDY READY SERVICES FOR NEUROSCIENCE RESEARCH

To effectively evaluate drug efficacy or disease progression when using *in vivo* models, it is critical to have the ability to perform manipulations and conduct biological sampling.

Taconic provides a wide array of services that can be performed on our rodent models to help you accelerate your discovery pipeline. These services include custom aging, administration of specialized diets, microdialysis implants, brain cannulations, and murine biospecimen collection services. Below is a description of each service.

Pde6b^{rd1} Retinal Degeneration Genotyping Assay

Animals homozygous for the *Pde6b*^{rd1} allele become blind by weaning. The presence of this allele may be very important in mice used for behavioral testing. This assay may be used to screen out *Pde6b*^{rd1} homozygotes prior to behavioral work.

To learn more about the rd1 mutation and order our screening service please contact: **info@taconic.com**.

MODEL NUMBER **GENO_RD1_PCR**

Nnt Mutation Testing

Nnt (nicotinamide nucleotide transhydrogenase) is a gene present in humans, mice, and bacteria. The enzyme encoded by the *Nnt* gene plays an important role in cellular metabolism, and also helps in the detoxification of cells under conditions of stress.

When a mutation of the *Nnt* gene occurs, like in models with B6/J strain background, this often results in abnormal glucose metabolism under conditions of stress. This property makes *Nnt* important in research that spans across a variety of biological systems such as neurodegenerative diseases, diabetes, cancer, aging, and cardiomyopathy.

Taconic provides an *Nnt* mutation screening service that can help ensure your transgenics are free of the *Nnt* mutation.

To learn more about the *Nnt* mutation and order our screening service please contact: **info@taconic.com**.

MODEL NUMBER **GENO-NNT-TEST**

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Telemetry

- Subcutaneous or intraperitoneal placement of transmitters.
- Allows for continuous monitoring of neurological data (EEG, EMG, temperature, and activity) in fully awake and freely moving laboratory animals.
- Taconic staff have been trained by Data Sciences International™.

Brain Cannulations

- Nominally intrusive surgery for placement of cannulas into the brain.
- Cannulas enable researchers to inject substances directly into the brain.
- Cannulation options include: Intracerebroventricular and third ventricle.
- Custom coordinate brain cannulations available upon request.
- Brain cannulations can be performed in both rats and mice.

Microdialysis Implants

- Minimally invasive *in vivo* sampling technique for extracellular tissue fluid allowing for the continuous measurement of small particles such as neurotransmitters.
- General applications include: drug metabolism and pharmacokinetics, behavioral studies, psychological research, neurological and neurochemical studies, addiction and chemical dependency.
- A microdialysis guide cannula is implanted in targeted areas of the brain such as hippocampus, prefrontal and striatal portions of the brain. Custom brain coordinates available upon request.
- Cannula can be placed both in rats and mice.

Aging and Specialized Diets

- Rodent models of neurodegeneration often need to be aged in order for the pathological phenotype to develop. Taconic offers a wide range of customized aging services including resources to allow for natural aging.
- Animals are housed in our Isolated Barrier Units.
- Animals can be maintained on specialized diets (e.g., high-fat diet to induce atherosclerotic plaques).
- Taconic's PhD scientists discuss with clients the aging and diet conditions, and advise in selecting cohort sizes to help offset the mortality rate inherent in aged neurodegeneration models.

Murine Biospecimens

- Brain and other biospecimens (e.g., brain sections, eye, embryo) can serve as important components to any research project, including comparative evaluations.
- Superior quality organs (e.g., brain, heart, lungs), fluids (e.g., CNS fluid, whole blood, plasma), tissue (e.g., skin, muscle), and embryo products can be harvested from all Taconic animal models.
- Biospecimens are available fresh harvest, frozen, or flash frozen using dry ice and in *RNAlater*.

Rodent Identification

Taconic Biosciences offers dependable and humane solutions for animal identification, keeping your research moving further, faster. With many options for identification including ear tags, tattoos, and microchips, Taconic offers the solution your studies need.

Knock Out Repository and The GEM Collection

The Knock Out Repository provides unparalleled access to over 4000 fully-licensed, healthy knockout mouse models. These knock-out mice are highly valuable research tools that rapidly accelerate the drug discovery and development processes.

Visit **taconic.com/ko** to search for the knock-out model that you need.

The GEM Collection (for access by non-profit organizations only). The GEM Collection contains several hundred proprietary mouse lines which include conditional (cKO) and constitutive (KO) Knock Out mice, transgenic (Tg) over-expressing lines, conditional (cTTG) and constitutive targeted transgenesis (TTG) lines.

Scientific Support

Have questions related to your animal research? Taconic's experts can help you with model selection, study design, optimal use of various disease models, diet questions, and more!

Consult with Taconic's PhD neuroscientists to help get your research off on the right track. Contact us to set up your consultation.

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Take Your Research Further

GEMs DESIGN

Taconic Biosciences GEMs Design empowers our clients to develop research models specifically suited to the unique needs of their discovery and development studies or therapeutic programs.

- Gene Inactivation
- Gene Mutation or Replacement
- CRISPR Gene Editing
- Transgene Expression
- miRNA Expression
- Cohort Production Packages

PRECISION RESEARCH MODELS

Research organizations demand precision tools that better reflect human physiology. Taconic Biosciences leads the field delivering innovative solutions to meet these continually evolving needs. Our core competencies include the delivery of complex strategies that both integrate human genetic sequences and engraft human cells and tissues into custom mouse and rat models.

- Human Gene Replacement
- Human Cell and Tissue Engraftment

GEMs MANAGEMENT

Taconic's fully integrated GEMs Management brings innovative models from design to study-ready cohorts with unprecedented speed and transparency.

- Embryology
- Rapid Colony Expansion
- Contract Breeding
- Surgical Services
- Tissue Collection
- Genotyping and Molecular Analysis
- Microbiome and Germ-Free Research Models and Services

CHOOSE TACONIC

For more than 60 years, Taconic has anticipated the needs of the scientific community to deliver models and services that meet the diverse needs of biomedical and biopharmaceutical researchers.

Today that forward thinking and commitment to working collaboratively has resulted in a client-centric environment infused with a knowledge bank that allows you to select the optimum model for your study based on informed insight into the generation of genetically engineered mouse and rat models.

YOUR COLLABORATIVE PARTNER

As a full-service biosciences company, Taconic can help you acquire, test, develop, breed, cryopreserve, prepare, and distribute highly relevant research lines worldwide. Whether you require custom genetically engineered, cell or tissue engrafted models or traditional models, Taconic's scientists will partner with you to rapidly and efficiently deliver the highest quality models.

TALK TO A SCIENTIST

Our scientific teams are happy to meet and talk with you about the most efficient way to achieve your study goals. Working in partnership with clients the world over, our scientific teams offer expert advice that can help you speed up your research and reduce your overall costs.

TALK TO A REPRESENTATIVE

For general information, you can talk to a member of our customer service team. Our customer service team is here to help you make the right decisions and get the models you need fast. Contact us at **info@taconic.com**

VISIT TACONIC.COM

For more information on the entire Taconic portfolio of products and services designed to help further your research, visit **taconic.com**

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