

# TSG-p53<sup>®</sup> Targeted Mutation Mice from Taconic

## *In vivo* System for Drug Discovery and Toxicology

**MUTATIONS IN THE p53 GENE ARE THE MOST FREQUENTLY OBSERVED GENETIC LESION IN HUMAN CANCERS.<sup>1</sup>**

Taconic TSG-p53 Targeted Mutation Mice, deficient in one or both of the genes, provide powerful *in vivo* laboratory models for:

- Studying the loss of p53 tumor suppressor function;
- Screening chemopreventive and chemotherapeutic agents;
- Early-stage carcinogenicity screening.

### Develop Chemopreventive and Chemotherapeutic Agents

Homozygous TSG-p53 Targeted Mutation Mice can be used to study genetic or epigenetic events that occur in conjunction with the loss of p53 function to produce malignant neoplasms. Chemopreventive agents and chemotherapeutics can be tested *in vivo* to reverse the impact of loss of function of tumor suppressor proteins.

Although Taconic TSG-p53 Targeted Mutation Mice are otherwise developmentally normal, a wide variety of tumor types is observed in about half of the homozygous mice by 4.5 months of age. By 10 months of age, all of the homozygous TSG-p53 mice had died or developed tumors.<sup>2,3</sup>

SEX	GENOTYPE	AGE (in weeks)	HISTOLOGIC TYPE	ANATOMIC SITE
M	m/m	8	gonadoblastoma	testis
			malignant lymphoma	thymus
F	m/m	9	malignant lymphoma	generalized
M	m/m	14	malignant lymphoma	generalized
F	m/m	14	malignant lymphoma	generalized
F	m/m	15	malignant lymphoma	generalized
M	m/m	15	hemangiosarcoma	subcutis
F	m/m	15	malignant lymphoma	generalized
			hemangioma	heart
F	m/m	15	mammary adenocarcinoma	mammary gland
M	m/m	16	osteosarcoma	pelvis
M	m/m	16	malignant lymphoma	generalized
			hemangiosarcoma	subcutis
			hemangioma	muscle
M	m/m	17	malignant lymphoma	thymus
M	m/m	17	malignant lymphoma	generalized
			hemangiosarcoma	heart/perirenal fat
M	m/m	18	undifferentiated sarcoma	subcutis
M	m/m	18	hemangiosarcoma	subcutis/liver
F	m/m	18	malignant lymphoma	thymus
M	m/m	19	malignant lymphoma	generalized
M	m/m	21	malignant lymphoma	thymus
M	m/m	21	malignant lymphoma	thymus
M	m/m	22	malignant lymphoma	generalized
			alveolar/bronchiolar adenoma	lung
M	m/m	22	malignant lymphoma	thymus
M	m/m	24	undifferentiated sarcoma	vertebra
			hemangiosarcoma	subcutis
M	m/m	24	hemangiosarcoma	subcutis/muscle
			malignant lymphoma	generalized
M	m/m	24	hemangiosarcoma	subcutis
			malignant lymphoma	generalized
M	m/m	24	malignant Schwannoma	salivary gland
			malignant lymphoma	generalized
			hemangioma	subcutis
M	m/+	24	embryonal carcinoma	testis
M	m/m	25	undifferentiated sarcoma	lumbar muscle
M	m/+	37	malignant lymphoma	generalized

*Tumors observed in TSG-p53 deficient mice.<sup>2</sup> A broad spectrum of tumors, marked by a high degree of malignancy, is seen in TSG-p53 deficient mice. Early onset of tumors is seen only in homozygous mice.*

*m/m: Homozygous for p53 gene inactivation.*

*m/+ : Heterozygous for p53 gene inactivation.*

## TSG-p53® Targeted Mutation Mice

Model Number	Nomenclature	Gene(s) of Interest	Genotype	Background Strain
P53N4-M	B6;129- <i>Trp53</i> <sup>tm1Brd</sup> N4	<i>Trp53</i>	Homozygote	incipient congenic C57BL/6
P53N5-T	B6.129- <i>Trp53</i> <sup>tm1Brd</sup> N5	<i>Trp53</i>	Heterozygote	partial congenic C57BL/6
P53N5-W	B6.129- <i>Trp53</i> <sup>tm1Brd</sup> N5	<i>Trp53</i>	Wild-Type for P53N5-T	partial congenic C57BL/6
P53N12-M	B6.129- <i>Trp53</i> <sup>tm1Brd</sup> N12	<i>Trp53</i>	Homozygote	full congenic C57BL/6
P53N12-T	B6.129- <i>Trp53</i> <sup>tm1Brd</sup> N12	<i>Trp53</i>	Heterozygote	full congenic C57BL/6

### Short Term Carcinogenicity Screening

By reducing the latency period for the detection of carcinogens, the toxicologist can realize cost savings in animal care and the number of animals required while reducing the time required to screen for carcinogens in drug development.

Heterozygous Taconic TSG-p53 Targeted Mutation Mice have a low incidence of spontaneous tumors (about 2% of animals at nine months of age) but a shorter latency period upon induction, compared to non-transgenic mice.<sup>3</sup>

A recently published study demonstrated that the rate of induction of hemangiosarcomas by DMN was significantly faster in heterozygous mice than in wild types.<sup>3</sup> Another study involved heterozygous TSG-p53 Targeted Mutation Mice as a potential skin carcinogenesis model.

With a DMBA-initiator/TPA promoter-protocol, the papilloma to carcinoma progression rate was observed to be faster in heterozygous mice than in wild type mice.<sup>4</sup>

The FDA and other regulatory agencies have recognized the use of the P53N5-T model in 26 week short term carcinogenicity assays as an alternative to the 2 year rodent bioassay.

### Scientific Profile of the TSG-p53 Targeted Mutation Mouse

Taconic TSG-p53 Targeted Mutation Mice were generated in 129-derived embryonic stem cells (AB1) and have been backcrossed onto a C57BL/6 background. The homozygous offspring may develop tumors as early as ten weeks and have an average life span of five months. The heterozygous animals have a far lower incidence of spontaneous tumors with a greater survival rate.<sup>2</sup>

### Origins of the Model

Developed by Donehower and Bradley at the Baylor College of Medicine. Received at Taconic in November 1991 at two backcrosses (N2) onto C57BL/6 from the 129/Sv x C57BL/6 chimera. Bred to N3 prior to cesarean derivation in December 1991 and to N4 immediately after derivation.

**N4 and N5 colonies:** The N4 homozygous colony is maintained by mating of N4 homozygous males with N4 heterozygous females. The N5 heterozygous colony is maintained at N5 through mating of N4 male homozygotes with C57Bl/6NTac female mice. The Wild Type control colony is maintained at N5 through mating of N4 wild types with C57BL/6NTac mice.

**N12 colonies:** The N12 colonies were bred at Taconic, beginning in 1995, by backcrossing the N4 heterozygote to N12 with C57BL/6NTac. The line was embryo transfer derived in 1998. Heterozygous and homozygous mice are maintained at N12 by mating of homozygous male mice with heterozygous female mice.

### Ready for Your Experiments

Taconic TSG-p53 mice are shipped in Taconic Transport Cages (TTC™) and come with an up-to-date health report. They are easy to handle and maintain. Clean conditions are recommended for the homozygous TSG-p53 mice.

### Related Mouse Models from Taconic

Taconic provides a number of mouse models relevant to carcinogenicity studies. Call or fax to inquire about the following additional models:

- **K6-ODC Microinjected Mouse (models 000993 and 003000)** expresses high levels of the enzyme ornithine decarboxylase in skin and other tissues

- **rasH2 Microinjected Mouse (model 001178)** carries the human *c-HRAS* gene and is susceptible to malignant tumor induction
- **Stat1 Targeted Mutation Mouse (model 2045)** carries a homozygous disruption of the *Stat1* gene and may have applications in determining the role of a variety of cytokines in immune responses and in evaluating the role of STAT1 protein in mediating interferon-dependent responses and tumorigenesis
- **v-Ha-ras (TG.AC) Microinjected Mouse (model TGAC)** carries a mutated *v-Ha-ras* gene fused to a fetal zeta globin promoter and is useful in rapidly identifying environmental carcinogens

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