TACONIC
Models For Life.

v-Ha-ras (TG.AC) OncoMouse™ Microinjected Mice

Taconic's v-Ha-ras (TG.AC) OncoMouse microinjected model, carrying a v-Ha-ras transgene, provides a powerful *in vivo* laboratory model for:

- Defining the biological effects of putative tumor promoters or complete carcinogens in the skin;
- Conducting early stage carcinogenicity screening;
- Studying molecular mechanisms of carcinogens associated with chemical activation of the transgene;
- Identifying potential chemotherapeutic and chemopreventive agents.

Retrospective Evaluation of NTP Chemicals for Activity in v-Ha-ras(TG.AC) Microinjected Mice[3]

[Data presented in this chart is excerpted from the original article. For the complete chart refer to Table 3, *Environmental Health Perspectives,* Vol. 103, No. 10 (October 1995)]

			NTP bioassay				TG.AC skin paint			
			Rat[c]		Mouse[c]			Average	%	
Chemical	SAL[a]	Route[b]	M	F	M	F	TTFP[e]	papillomas per mouse[f]	Mice with papillomas[f]	Activity
Benzene	–	G	+	+	+	+	5	7.4	77	+
Benzethomium chloride	–	SP	–	–	–	–	8	0.55	22	–
o-Benzyl-*p*-cholorphenol	–	G	–	E(K)	+(K)	–				
		SP	ND	ND	+[g]	+[g]	7	3.0	80	+
2-Chloroethanol	+	SP	–	–	–[g]	–[g]	10	0.10	11	–
p-Cresidine	+	F	+(UB)	+(UB)	+(UB)	+(UB)	6	5.0	58	+
Ethyl acrylate	–	G	+(S)	+(S)	+(S)	+(S)	15	0.6	50	–
Mirex	–	F	+(L,AG)	+(L,HS)	ND	ND	7	12	70	+
Phenol	–	W	–	–	–	–	7	0.20	0.16	–

ND not done.
[a] SAL: *Salmonella* mutagenicity results provided by E. Zeiger, National Toxicology Program.
[b] Route of administration of test chemical. G, oral gavage; SP, skin paint; F, feed; W, drinking water.
[c] F344 rats and $B_6C_3F_1$ mice except as noted. Tumor sites in parenthes: K, kidney, UB, urinary bladder; S, stomach; L, liver; AG, adrenal gland; HS, hematopoietic system. E, equivocal results.
[e] TTFP, time (weeks) to first observation of a skin papilloma in any mouse of that dose group.
[f] At 20 weeks.
[g] CD-1 mice.

Scientific Profile of v-Ha-ras (TG.AC) Microinjected Mice

The TG.AC hemizygous mouse model is maintained on an FVB/NTac inbred back-ground. It carries on one allele a v-Ha-ras transgene with point mutations in codons 12 and 59 that is fused to a mouse ζ-globin promoter.[1] With properties of genetically initiated skin, the TG.AC model is sensitive to TPA (12-0-tetradecanoyl-phorbol-13-acetate) – a well described promoter of skin papillomas – in the two-stage mouse skin tumorigenesis model.[2] TG.AC mice show nearly zero incidence of spontaneous dorsal skin papilloma in untreated animals, and untreated skin appears normal.

The spontaneous tumor profile in TG.AC mice includes a low incidence of odontogenic neoplasms, lymphomas and mammary gland adenoacanthomas that increase with aging.[2]

Short Term Carcinogenicity Screening

By reducing the latency period for the detection of putative carcinogens, the toxicologist can realize cost savings by reducing the number of animals required while shortening the time needed to screen for carcinogens in drug development.

In skin paint studies using the TG.AC model, total

doses of 25-30 µg of TPA administered in 3-10 applications induces an average of 11-15 papillomas per mouse, starting as early as 5 weeks after treatment. Reports from other studies indicate a rapid dose-related papilloma formation response to different tumor promoters representing a range of potencies.[2] Many chemically induced papillomas have subsequent conversion to malignancy.

In addition, this model is under development at NIEHS and the NTP as part of a strategy to develop alternatives to the two-year bioassay for identification of genotoxic and non-genotoxic carcinogens. The evaluation includes the utility of the TG.AC mouse to discriminate a high proportion of carcinogens and non-carcinogens. A basis for this strategic evaluation is the high correlation that exists between retrospective TG.AC skin paint studies and NTP bioassay results in correctly identifying carcinogens and non-carcinogens. Other prospective TG.AC studies are underway at the NTP, the FDA and in the industry.[4]

Responder/Non-Responder Genotype

Successful TG.AC carcinogenicity studies at the NTP instigated efforts to broaden the evaluation of the sensitivity and specificity of the TG.AC mouse papilloma response to potential human carcinogens. The initial efforts resulted in a heterogeneous response to high doses of TPA that were thought to be related to a variability in the response of hemizygous but not homozygous TG.AC mice.[5] Further investigation in the laboratory of Dr. Frank Sistare at the FDA revealed that there is a difference in the transgene of TG.AC mice between Responder and Non-Responder mice.

These studies included the construction of a probe and design of a Southern Blot assay to genotypically differentiate between Responder and Non-Responder TG.AC mice. A positive correlation exists between a Responder genotype and a Responder phenotype (i.e. skin papilloma response to tumor promoters).[6]

Subsequent investigation showed that there is no significant difference between homozygote Responder and hemizygote Responder TG.AC mice to TPA induced papilloma induction.

Origins of the TG.AC Mouse

The TG.AC mice were created using FVB donor embryos. In 1988, Taconic received hemizygous males directly from Dr. Leder's laboratory on behalf of the NIEHS. These were mated to inbred FVB females prior to cesarean derivation in December 1988. Transgenic mice were subsequently mated to FVB's for approximately three generations prior to intercrossing hemizygous mice. In March 1998, the laboratory of Dr. Frank Sistare at the FDA identified the Responder genotype that correlates with TPA-induced tumor formation. This Responder genotype is detected by Southern Blot using a zeta-globin probe. TG.AC hemizygous Responder mice are produced by crossing proven homozygous Responder TG.AC mice with FVB mice.

Quality Assurance Standards for TG.AC

Taconic employs a rigorous quality assurance program to insure that the TG.AC mice are hemizygous for the Responder genotype. This program includes the use of the Southern Blot procedure designed by Dr. Frank Sistare[6] and a TPA skin painting protocol to test for phenotypic (papilloma induction) response. This quality assurance program has been reviewed by the FDA, the NTP and industry Toxicology scientists and determined as an acceptable standard for regulatory studies.

Ready For Your Experiments

Taconic's TG.AC Microinjected Models are produced in Isolator Barrier Unit (IBU™) facilities under MPF™ conditions and shipped in Taconic Transit Cages (TTC™) with an up-to-date health report. Barrier housing conditions are recommended, but not required, for maintenance of each line.

Related Mouse 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
- **TSG-p53 knockout mouse (models P53N4, P53N5 and P53N12)** is deficient in the *p53* tumor suppressor gene and useful for short term carcinogenicity studies

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Rev. 3/08

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v-Ha-ras (TG.AC) OncoMouse™ Microinjected Mice

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