BioReliance

Toxicology Services

Transgenic Carcinogenicity Testing with Tg.rasH2

The use of animal models to determine the carcinogenic potential of pharmaceuticals is a required part of evaluating the overall safety of many new drug products. Advances in our understanding of the mechanisms of carcinogenesis combined with the ability to create transgenic animals have given toxicologists new tools with which to test materials for potential carcinogenic activity.

Validation

Beginning in 1991 BioReliance was awarded several studies to evaluate mouse transgenic models by the United States National Toxicology Program (NTP). Dozens of studies were performed initially with the p53+/- and TG.AC models.

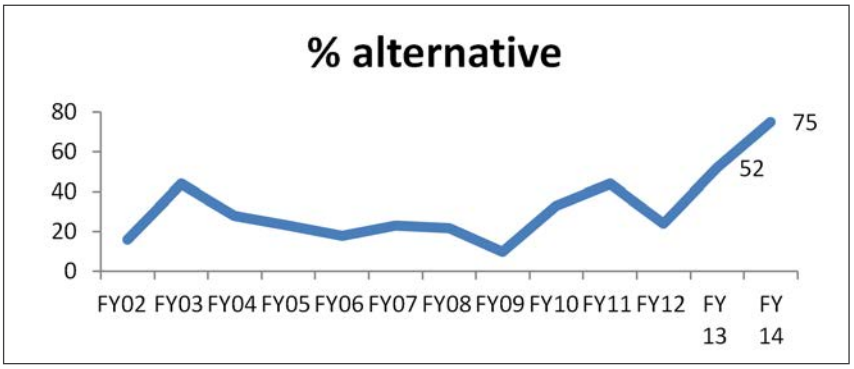
Later in the 1990's the Tg.rasH2 model was introduced by the Central Institute for Experimental Animals (CIEA) and National Institute of Health Sciences of Japan. Prior to the acceptance of all three models with the ICH S1B guideline, comparisons were made under an ILSI/HESI study in which 54 laboratories evaluated 21 chemicals.

This study concluded:

- Tg.rasH2 model has greater sensitivity to human carcinogens than non-transgenic animals.
- Tg.rasH2 model is not susceptible to rodent carcinogens (exception is peroxisome proliferators).
- Tg.rasH2 is well-suited for both non-genotoxic and genotoxic carcinogens.

Growing Acceptance

Transgenic alternative to 2-year carcinogenicity models have increasingly grown in acceptance and (according to the FDA) in 2013 more than 50% of mouse carcinogenicity studies performed were transgenic. In fact in 2014 75% of mouse studies were performed in transgenics, the overwhelming majority being TgRasH2.



Approved

- ICH S1B "Testing for Carcinogenicity of Pharmaceuticals" approved in 1997

Accepted

- More than 75% of mouse carcinogenicity studies are transgenic

Effective alternatives to 2-year studies

- Shorter timeline
- Less expensive
- Reduced animal use
- More predictive, less false positives

Awarded

BioReliance received the ACT President's Award in 2013 for "The Best Paper in International Journal of Toxicology", entitled, "Reduction in the Number of Animals and the Evaluation Period for the Positive Control Group in Tg.rasH2 Short-Term Carcinogenicity Studies"

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Advantages of Transgenic Mice

	Traditional Mouse Study	Transgenic Mouse Study
Dose selection	3 months	1 month
In-life	24 months	6 months
Cost	$1.5 – 2 million+	$850,000+
Animal number	400	250+
Test article requirements	high	less
Spontaneous tumors	high	low
Lethal degenerative changes	high	low
Body weight changes	high	low
Mortality	Moderate	low
Mechanistic information	Little	some

Historical Control Database

In January 2013, BioReliance published the largest historical control database of the most commonly used transgenic mouse model, Tg.rasH2. Today the number of animals in our historical database has exceeded 1,000 males and 1,000 females for a total of >2,200 mice. In total we have examined over 8,000 mice and over a half million tissues in these animals, making our experience with this model unparalleled. This historical control data allows us to analyze the studies with greater confidence and - more importantly - it assures that the conclusions we draw are based on solid scientific reasoning supported by our data, experience and in-depth knowledge of the model.

Incidence of all tumor bearing animals (irrespective of type)

	Tg rasH2	B6C3F1	CD1
MALE	22.2%	87.1%	78.0%
FEMALE	23.46%	75.5%	78.0%

References

Paranjpe, M.G; Elbekai, R.H.; Shah, S.A.; Hickman, M., Wenk, M.L. and Zahalka, E.A. (2013). Historical control data of spontaneous tumors in transgenic CByB6F1-Tg(HRAS)2Jic (Tg.rasH2) mice. Inter J Toxicol 32(1): 48-57.

Paranjpe, M., Denton, M., Shah, S.A., and Elbekai, R.H. (2013). Incidence of spontaneous non-neoplastic lesions in transgenic CBYB6F1-Tg(HRAS)2Jic MICE. Toxicol Pathol. 41, 1137–1145.

Shah, S. A., Paranjpe, M. G., Atkins, P. I., and Zahalka, E. A. (2012). Reduction in the number of animals and the evaluation period for the positive control group in Tg.rasH2 short-term carcinogenicity studies. Int J Toxicol 31, 423–29.

Paranjpe MG, Denton MD, Vidmar TJ, Elbekai RH. (2015). Regulatory Forum Opinion Piece. RETROSPECTIVE EVALUATION OF DOSES IN THE 26 WEEK Tg.rasH2 MICE CARCINOGENICITY STUDIES: RECOMMENDATION TO ELIMINATE HIGH DOSES AT MAXIMUM TOLERATED DOSE (MTD) IN FUTURE STUDIES. Toxicol Pathol 43: 611-620.

Paranjpe MG, Denton MD, Elbekai RH. (2014). The 26-Week Tg.Rash2 Mice Carcinogenicity Studies: Microscopic Examination of Only Select Tissues in Low- and Mid-dose Groups. Toxicol Pathol. 42, 1153-1157

Paranjpe MG, Denton MD, Vidmar TJ, Elbekai RH. (2014).Relationship of Body Weight Parameters with the Incidence of Common Spontaneous Tumors in Tg.rasH2 Mice. Toxicol Pathol. 42, 1143-1152

Paranjpe MG, Denton MD, Vidmar TJ, Elbekai RH. (2014).Trend Analysis of Bodyweight Parameters, Mortality and Incidence of Spontaneous Tumors in Tg.rasH2 Mice. Inter J Toxicol . 33:475-481

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