CARCINOGENICITY TESTING

Regulatory Requirements

Evaluation of tumorigenic potential is a key regulatory requirement for novel therapeutics or chemicals to which humans will receive chronic exposure. Carcinogenicity studies may also be required if (a) an agent is a member of (or metabolized to) a chemical class with known carcinogenicity; (b) positive or equivocal evidence of mutagenicity has been seen in genetic toxicology studies; and/or (c) preneoplastic lesions were induced or other evidence suggesting possible carcinogenicity was identified in subchronic toxicology bioassays. Carcinogenicity studies are most often conducted prior to application for marketing approval of a new therapeutic.

2-Year Rodent Bioassays

The two-year rodent bioassay is generally considered to be the "gold standard" for experimental assessment of carcinogenicity.[1] These studies involve exposure of large (≥50 per sex) groups of rats or mice to a drug or chemical for two years, followed by a complete necropsy and comprehensive microscopic evaluation of tissues by a board-certified veterinary pathologist. Historical databases are available at IITRI for several rodent strains.

6-Month Bioassays in Genetically Engineered Mice

The IITRI team has worked extensively with genetically engineered mouse models for carcinogenicity testing, including the p53+/– (p53 knockout) mouse and several models expressing or overexpressing ras oncogenes.

The FDA and other regulatory agencies commonly accept data from a 6-month carcinogenicity study in the rasH2 mouse in lieu of data from a 2-year carcinogenicity study in mice. Carrying both the human homolog of the Hras oncogene and the murine Ha-ras oncogene, rasH2 mice are highly sensitive to tumor induction and offer a model suitable for accelerated evaluation of carcinogenicity.

At study termination, tissues from 6-month carcinogenicity studies in rasH2 mice are also evaluated by a board-certified veterinary pathologist; an extensive historical control database is available.

6-Month vs 2-Year Studies

Advantages of replacing a two-year mouse carcinogenicity study with a six-month carcinogenicity study in rasH2 mice include:

- Accelerated study completion
- Reduced animal utilization (25 versus ≥50/sex/group)
- Substantially reduced study cost

Experienced, Stable IITRI Team

The experience of scientific and technical staff is a critical factor for the effective and accurate performance of *in vivo* bioassays. IITRI offers an exceptionally stable scientific team: the average tenure of our toxicologists and toxicology technicians exceeds 15 years. We can ensure that a coherent, experienced team performs your study from start to finish.

IITRI Expertise in Carcinogenesis

IITRI has performed carcinogenicity studies in rodent models for over 40 years. We have been a major preclinical contractor to the National Cancer Institute for decades, and our scientists are known as leaders in carcinogenicity evaluation and in studies of mechanisms of carcinogenesis and the modulation of cancer induction by hormones, pharmaceuticals, and food components. In addition to numerous unpublished studies performed for commercial sponsors, studies performed by IITRI scientists have resulted in over 200 published papers and book chapters in the fields of carcinogenesis, cancer chemoprevention, and cancer chemotherapy

In 2015, we completed the largest single agent carcinogenicity studies (~3000 animals) ever performed for the National Toxicology Program.[2]

Routes of Administration

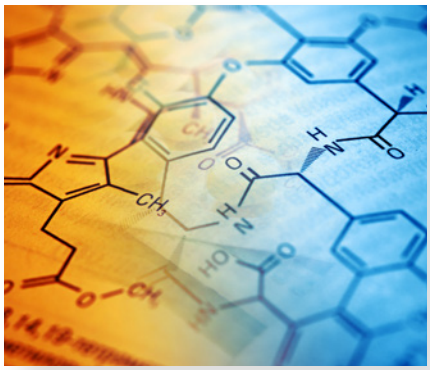
IITRI scientists and technicians are experienced in conducting single dose, subchronic, and chronic bioassays using the following routes of exposure:

- Oral (gavage, diet, drinking water)
- Inhalation (nose only, whole body)
- Dermal
- Injection (subcutaneous)
- Implantation (subcutaneous)

1 McCormick DL, 2016. Preclinical Evaluation of Carcinogenicity Using Standard-Bred and Genetically Engineered Rodent Models. In: Faqi, A.S. (ed), *A Comprehensive Guide to Toxicology in Nonclinical Drug Development*, 2nd Edition, Elsevier.

2 McCormick DL, 2017. Two-year oncogenicity evaluations of cell phone radiofrequency radiation in Sprague-Dawley rats and B6C3F1 mice. *Proc. Eurotox.*, 2017.

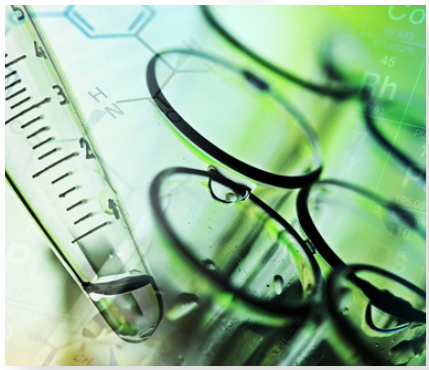
Core Services



ANALYTICAL/ BIOANALYTICAL

Our team of analytical scientists has extensive experience in the development, transfer and optimization of bioanalytical methods from your laboratory to ours.

- Dose formulation analysis
- Method development, method validation
- Quantitation in complex tissues
- Toxicokinetic analysis and modeling
- Immunogenicity testing (ADA, neutralization assays)
- Assessment of biomarkers
- Cell-mediated immune response assays



TOXICOLOGY

We have one of the most experienced toxicology teams in the industry with each technician having over 10 years experience in preclinical toxicology.

- Repeat-dose toxicology studies
  - All relevant routes of administration including inhalation
  - Rodents, non-rodents (canine, mini-pig), non-human primates
- Immunotoxicology
- Clinical pathology
- Histopathology

SAFETY PHARMACOLOGY

We offer the core battery of safety pharmacology tests. These can be performed as stand-alone studies or integrated into repeat-dose studies.

- Central nervous system
  - FOB
  - Expanded neurotoxicity
- Cardiovascular
  - Telemetry
  - hERG assay
- Respiratory
  - Plethysmography

GENETIC TOXICOLOGY

Flexible programs are available to meet your specific needs, from complete GLP test battery to non-GLP assays and individual test options.

- Ames assay
- Structural chromosomal aberration assay
- Rat micronucleus assay
- Mouse micronucleus assay
- Mouse lymphoma assay

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