BioReliance®
Toxicology Services

Genetic Toxicology Programs for Early Discovery and Lead Assessment

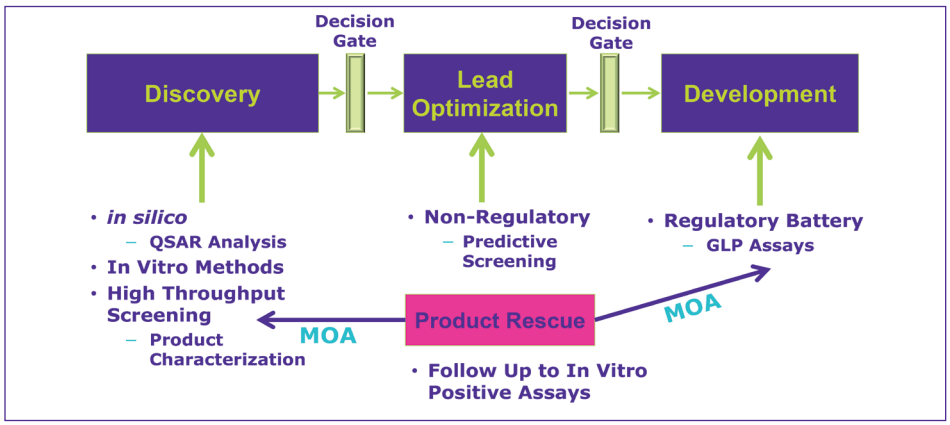
Strategies for Screening and Early Assessment

Identifying potential genotoxicity issues with candidate compounds is an essential part of the product development process. GLP assays will eventually be required for regulatory approval, however, a number of screening assays and programs can be employed early in the process, providing mechanistic information, predicting the potential outcomes of GLP assays and ultimately saving you time, cost, and valuable test material (these assays are run with 5-100 mg of test substance vs. the gram quantities required in GLP assays). The output of these tests will help you prioritize which compounds to continue in development, and which should be discontinued.

Discovery Methods

- In silico modeling (QSAR - Quantitative Structure-Activity Relationship)
- HTP Screening (High-throughput)
- Predictive Screening

Product Development Process Flow



Benefits:

- Accelerated turnaround time
- Minimal expense
- Small sample requirements

QSAR - Quantitative Structure-Activity Relationship

QSAR is a computer-based approach using models to explore the chemical and molecular structure of chemicals. These mathematical models summarize the relationship between chemical structures and biological activity, and then predict the activity of the chemical. There are two primary computational methods employed: knowledge-based and statistical-based. The combination of these analyses and a literature search will identify whether the potential for mutagenicity, genotoxicity, or carcinogenicity exists in candidate compounds. QSAR is a valuable tool to identify potential hazards and mitigate risk at the lead selection stage. QSAR has also become a regulatory requirement in the assessment of mutagenic impurities in pharmaceuticals (ICH M7).

Uses of QSAR in Genetic Toxicology:

- Chemical Assessment (REACH, EPA/TSCA)
  - Read-Across
  - Risk/Hazard Assessment
  - Classification
  - Prioritization
- Lead Candidate Selection for Pharmaceuticals
- Hazard Assessment of Agricultural Chemicals
- ICH M7 Pharmaceutical Impurity Assessment

MilliporeSigma

BioReliance Toxicology Services

Selecting the Appropriate Screening Assay

Identification of the appropriate assay or group of assays is critical to the success of a screening program. There are many screening assays available to investigate the different mechanisms of DNA damage, with each having different strengths and weaknesses. Some of the assays use the same cells and endpoints that are used in the core GLP regulatory assays that will eventually be run on the final drug or chemical (Predictive Screening Assays), while other assays use different cells, endpoints or biomarkers of DNA damage to discover MOA/Mode of Action (HTP Screening Assays). When designing a screening program, many factors need to be considered, including: what the purpose of the testing is (e.g. prediction of GLP assays or investigation of mechanism), how the data will be used, the quantity of test article available, as well as the cost and timeline. Our scientists are available to work with you to design and implement the most appropriate screening approach to meet your needs. We have decades of experience with almost every category of drugs and chemicals.

High-throughput (HTP) Screening Assays

HTP Screening assays require the least amount of test article and the least time to complete of all the Genetic Toxicology screening options. They can also be performed on numerous compounds at the same time.

Features and Advantages of HTP Screening Assays:

- Multi-well liquid format (microtiter plates)
- Low Test Article requirements
- Numerous compounds can be tested at one time
- Automated for speed, easy handling and evaluation

CAN MultiFlow™ Assay

This assay uses TK6 cells and multiple biomarkers in a 96-well format to screen for Clastogens, Aneugens and Non-Genotoxicants (Modes of Action/MOA) using Flow Cytometry. Insight into this MOA allows the interpretation of risk and the prioritization or elimination of leads accordingly.

Ames II™ Assay

This assay is a second generation bacterial reverse mutation assay modified into a 96-well format. Potential Mutagenicity is identified through the detection of frameshift mutations and base-pair substitutions utilizing various bacterial strains.

Predictive Screening Assays

Ames Screening Assays

A number of miniaturized screening versions of the Ames assay are available. These screening Ames assays predict the standard Ames assay (OECD 471). A variety of different assay designs exist using various strains and exposure methods, with test article requirements ranging from 5 to 120 milligrams per assay.

In Vitro Mammalian Cell Mutation Screening Assay

The screening version of the mouse lymphoma assay predicts the standard assay, OECD 490. This assay measures forward mutations due to mutagenic or clastogenic mechanisms. Elimination of pretoxicity testing, single cultures and widely spaced doses are used.

In Vitro Mammalian Cell Cytogenetic Screening Assays

Screening versions of Micronucleus and Chromosome Aberration assays are available to assess the clastogenic potential of test articles, predicting the standard assays OECD 473 and 487. Assay versions with various cell types are available including human peripheral blood lymphocytes (HPBL), human TK6 cells (both offer the advantage of normal human p53 function) and CHO cells.

In Vivo Cytogenetic Screening Assays

The screening version of the in vivo micronucleus assay predicts the standard assay, OECD 474. This assay is available with scoring by microscopy and flow cytometry. The screening version targets the highest possible dose, eliminates dose-range finding, and can be customized to meet client needs.

To place an order or receive technical assistance

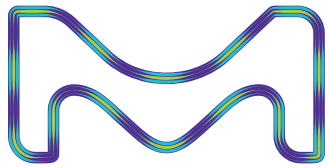
Phone +1 301 738 1000
Toll Free +1 800 553 5372

Email toxicology@bioreliance.com

See specific assays at:

bioreliance.com

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.



Lit. No. SMR F-1580417
07/2017