BioReliance

Toxicology Services

Genetic Toxicology Screening Assays

Rationale and Strategies for In Vitro Screening Assays

Early identification of potential genotoxic issues with candidate compounds is an essential part of a product development process. BioReliance offers a variety of rapid, low-cost genetic toxicology assays that can be performed with milligram quantities of test article. These non-GLP assays are utilized early in the development process for various reasons, including: lead optimization, prediction of the results of GLP regulatory-compliant assays and to investigate mechanism of action and relative potency.

Selection of Assays

Selection of the appropriate assay or group of assays is critical to the success of a screening program. Many screening assays are available to investigate different mechanisms of DNA damage, each with different strengths and weaknesses. Some assays use the same cells and endpoints as used in core GLP regulatory assays that eventually will be run on the final drug or chemical. Other assays use different cells, endpoints or biomarkers of DNA damage. When designing a screening program, various factors need to considered, including: what the purpose of the testing is (e.g. prediction of GLP assays or investigation of mechanism of action), how the data will be used, the quantity of test article available, cost and timeline.

BioReliance scientists are available to work with you to design the most appropriate screening approach to meet your needs. With our scientists, you gain the advantage of decades of experience from globally recognized experts who have worked with most every category of drugs and chemicals.

Bacterial Reverse Mutation (Ames) Screening Assays

The Ames Assay measures a chemical's ability to induce reverse mutations in different bacterial/***e.coli*** strains. The predictivity of a positive result in the Ames Assay for rodent carcinogenicity is very high and as a result an Ames screening assay is often a key part of a genetic toxicology screening program.

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.

Ames II Screening Assay

BioReliance offers the Ames II assay, using modified Ames bacterial strains, 384 well plates for mutant selection, and the ability for automation, while keeping test article requirements at 6 milligrams or less.

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. Assay versions with various cell types are available including human peripheral blood lymphocytes, human TK6 (both offer the advantage of normal human p53 function) and CHO cells.

In Vitro Micronucleus Screening Assay

With the recent adoption of the ICH S2 guideline, the in vitro micronucleus assay has been added to the core battery of acceptable cytogenetic assays. The screening version of this assay predicts the standard in vitro micronucleus assay described in the new OECD guideline 487. This assay can be scored either microscopically or using Flow Cytometry. The flow method in CHO cells provides information on clastogenic and aneugenic mechanisms of action.

In Vitro Chromosome Aberration Assays

The screening in vitro chromosome aberration assay uses the same cells and endpoints as used in regulatory GLP assays. Screening designs eliminate pretoxicity tests and summarize damage.

Genetic Toxicology Assessment in a Fraction of the Time, Money and Compound

Some advantages of BioReliance's high throughput screening assays are:

- Minimal amount of sample
- Accelerated turnaround time
- Lower expense

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In Vitro Mammalian Cell Mutation Screening Assays

Screening Mouse Lymphoma Mutation Assay

The screening version of the mouse lymphoma assay predicts the standard assay, OECD 476. This assay measures forward mutations due to mutagenic or clastogenic mechanisms. Elimination of pretoxicity testing, single cultures and widely spaced doses are used.

DNA Damage and Transformation Assays

Other in vitro screening assays are available to evaluate different genetic toxicology endpoints or to meet specific testing objectives. Some assays such as the Comet or GreenScreen assay measure DNA damage that is "upstream" of the endpoints of mutation and cytogenetic damage measured in regulatory GLP assays, while other assays such as the Bhas-42 assay and SHE Cell Transformation assay evaluate a test article's ability to transform a "normal" cell into a "transformed" cancerous cell.

In Vitro Comet Assay

This assay measures DNA strand breakage. This assay can be performed in a 24 or 96-well plate format using a wide variety of cells or may be multiplexed into other assays.

GreenScreen HC

Genotoxicity is determined using the GreenScreen Human Cell (HC) Assay. This assay measures upregulation of the GADD45α DNA damage gene through production of Green Fluorescent Protein. The assay is performed in a 24 or 96-well plate format.

Bhas-42 Initiator and Promoter Cell Transformation Assay

This assay measures induction of cell transformation from initiated cells to transformed foci. The assay can be run using either a 6 well or 96 well plate format. Study design permits investigation of both initiation and promotional capabilities of test materials.

Syrian Hamster Embryo (SHE) Cell Transformation Assay

This assay measures induction of morphological transformation of primary SHE cells.

Cytotoxicity Assays and BioMarkers of DNA Damage

Intracellular biomarkers of DNA damage and cytotoxicity can be multiplexed into other screening assays using the Meso Scale Discovery platform. Families of biomarkers that can be analyzed include apoptosis, MAP kinases and cytokines. In addition, a variety of cytotoxicity assays including Agar Diffusion, Agar Overlay, Direct Contact, Filter Diffusion, MEM Elution, Neutral Red Uptake (NRU) are available.

Overview of BioReliance Screening Assays

The table below lists out the types of assays and their classifications. BioReliance's globally recognized scientists are available to work with you to design the most appropriate screening approach to meet your needs. For questions, please consult a BioReliance Technical Representative.

Assay		Protocol #	GLP Equivalent	OECD Equivalent	Endpoints Detected	TA (mg)		TAT (weeks)	
						Screen	Standard	Screen	Standard
Bacterial Mutation	Abbreviated Standard	501	Standard Ames	471	Frameshift and base pair substitution reverse mutations	90	900	3	7
	Ames Spot Test	512				120		3	
	Kado Microsuspension	501030				30		3	
	6-Well Mini-Ames	501007/501008				20+		3	
	24-Well Micro Ames	501009/501010				5+		3	
	Ames II	850	Ames	N/A		6		3	
In Vitro Mammalian Cell Gene Mutation	Abbreviated Mouse Lymphoma	702007	Mouse Lymphoma	476	Mutations at Tk locus caused by point mutations or large-scale damage, and aneugen detection	400	3500	5	10
Cytogenetics	In Vitro Chromosome Aberration	336/346	In Vitro Chromosome Aberration	473	Structural and Numerical Chromosome Changes	150+	1500	4	10
	In Vitro Micronucleus	349/369	In Vitro Micronucleus	487	Structural and Numerical Chromosome Changes	50+	1500	4	10
	In Vitro Micronucleus by Flow Cytometry	369Flow				50	1500	4	10
	In Vivo Micronucleus	121	In Vivo Micronucleus	474	Structural and Numerical Chromosome Changes	2500	7000	4	10
	In Vivo Micronucleus by Flow Cytometry	121Flow				2500	7000	4	10
DNA Damage and Repair	In Vitro Comet	400	N/A	N/A	DNA strand breaks	50	N/A	4	N/A
	GreenScreen HC	801	N/A	N/A	DNA damage processing	10	N/A	3	N/A
Morphological Transformation	Bhas-42 Initiator and Promoter Cell Transformation	320	Cell Transformation Assays	N/A	Transformation initiating and promoting capability of a test article/substance	100	5000	8	12
	Syrian Hamster Embryo (SHE) Cell Transformation	308/309/310/311				500	7000	8	12

Genetic Damage
Mutation
Structural and Numerical Chromosome Changes
DNA Damage

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