



Thermo Scientific ToxInsight
Drug Induced Liver Injury (DILI) Cartridge

- Predictive
- Cell-based
- Multi-parameter
- High-throughput

A New Standard

for Assessing Liver Toxicity Risk

Thermo
SCIENTIFIC

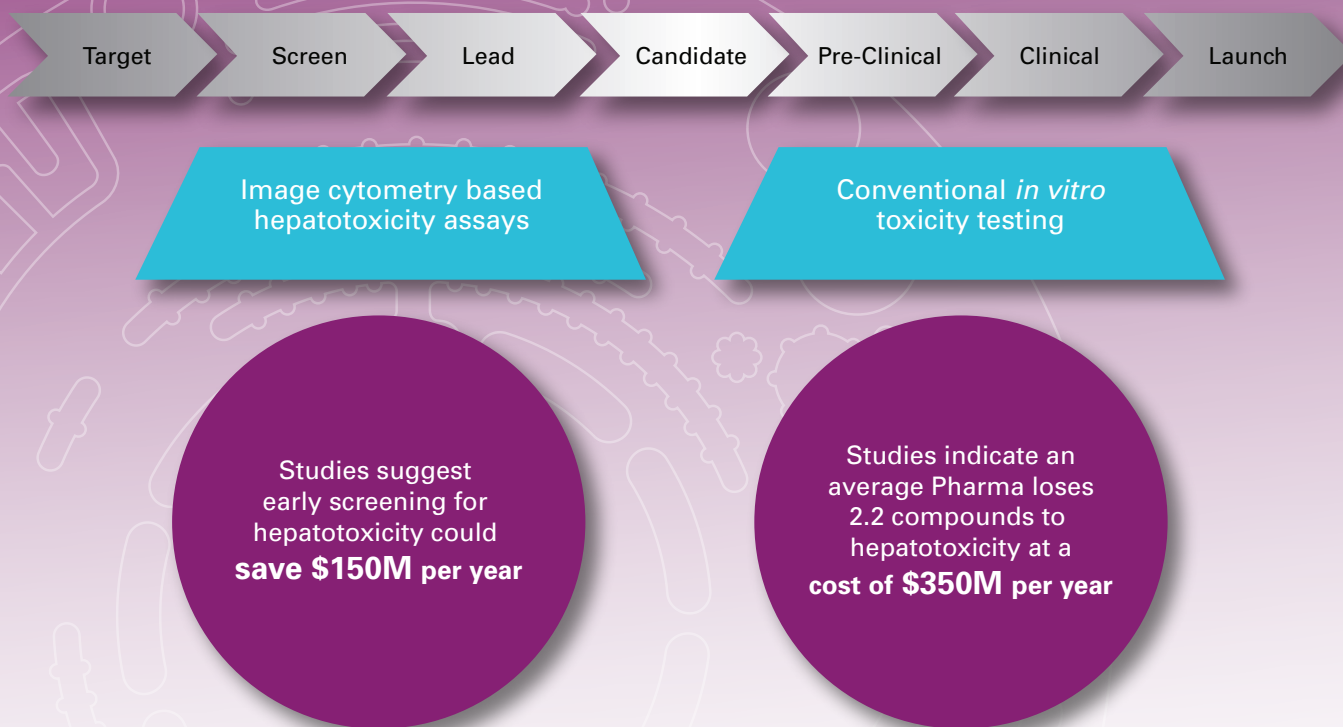
The Attrition Rate Issue – a \$350M Problem

The number of new drugs approved for use has been in sharp decline for the last decade, despite large investments in pharmaceutical R&D. While there are a variety of reasons behind this attrition rate, lack of efficacy and undesirable toxicity are two major reasons for this productivity gap.

- Drug-induced liver injury (DILI) is the leading reason for post-market drug withdrawal.
- Failure of drugs in the late part of the drug discovery process costs the pharma industry billions of dollars per year.
- Research has shown that adopting image cytometry assays, early in the drug discovery process, could save up to \$150M per year per company.

Fail Early, Fail Fast, Fail Smart

ADOPTION OF EARLY STAGE IMAGE CYTOMETRY ASSAYS IMPACTS ATTRITION RATE

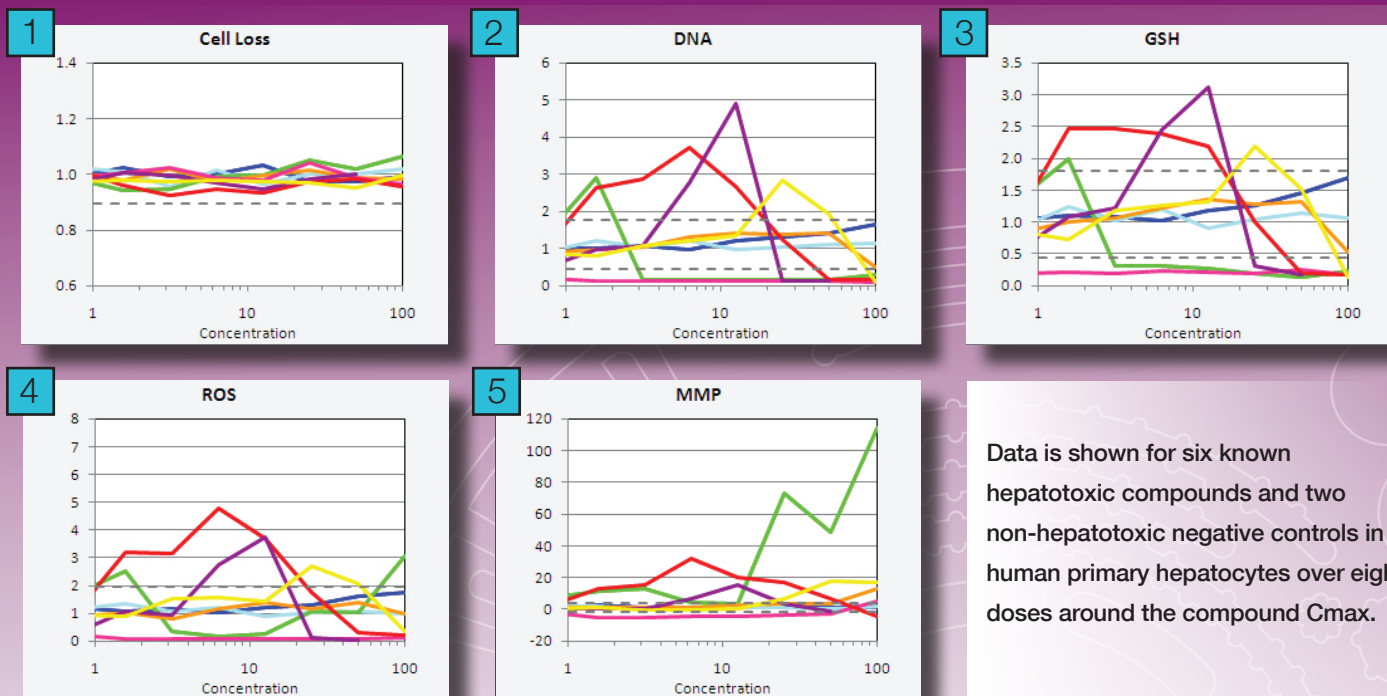


Power of Animal Testing Without the Animals

The Thermo Scientific ToxInsight DILI Cartridge for the ToxInsight™ IVT Platform offers a new multi-parameter cell-based assay to determine the risk of liver injury by chemicals being tested for new drugs or for consumer products safety assessment.

- Measures five intracellular toxicity “biomarkers.”
- Predictive of the risk of liver injury in man.
- High throughput.
- Uses sophisticated image cytometry to measure single cells in response to a chemical perturbation.

A New Standard



The ToxInsight DILI Assay Cartridge measures the following biomarkers in single cells

1. Cell loss
2. Nuclear DNA
3. Reduced glutathione level (GSH)
4. Intracellular reactive oxygen species (ROS)
5. Mitochondrial membrane potential (MMP)

Based on published research, these measures have been shown to be good indicators of organ toxicity and when combined together to be predictive of liver injury based on a study generated using 300 chemicals¹

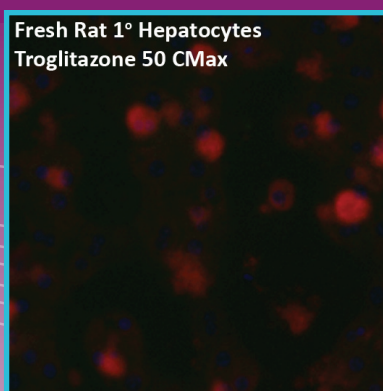
¹Xu *et al.*, Cellular imaging predictions of clinical drug-induced liver injury, Toxicological Sciences, 2008, 105(1):p. 97-105

Extensively Validated in Relevant Cell Types

The ToxInsight DILI Assay was extensively validated in an internal study using a range of four cell types of hepatic origin representing both rodent and human models and a 16 compound truth set. For each cell type, quantitative plots of the dose responses of each of the 16 compounds were generated for each of the biomarkers. Biomarkers were then combined using proprietary statistical algorithms to give a prediction of the liver toxicity risk. The predictions from the assay were compared to the known toxicity of that compound. The results demonstrated:

- The ToxInsight DILI Assay provides a powerful multi-parameter phenotypic profile of organ toxicity.
- For every cell line and all truth set compounds, the ToxInsight DILI Assay showed concordance with published data on known toxicity, dose and toxicity mechanism.¹
- Combining the individual measurements together allowed greater sensitivity and specificity than the individual measurements alone.

Extensively Validated



The ToxInsight DILI Assay is able to determine the difference in toxicity between structurally similar Rosiglitazone (non-hepatotoxic) and Troglitazone (known hepatotoxic). Images show same primary hepatocytes treated with 50Cmax of the compounds.

Table shows sensitivity data for the 16 compound truth set in four different liver cell lines and clearly demonstrates that combining parameters outperforms the singleplex measures.

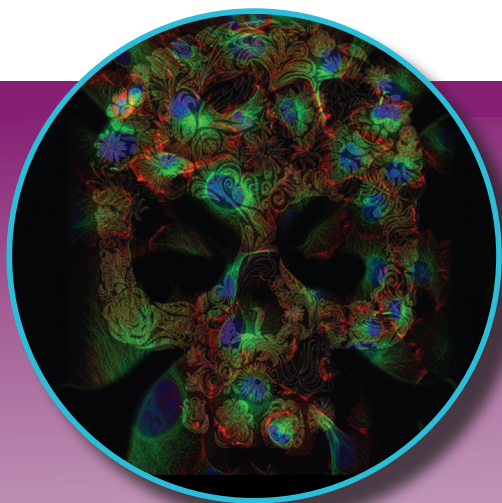
Hepatic Cell Type	Single Parameter Assay Targets					Multiparametric DILI Assay
	Cell Loss	DNA	GSH	ROS	MMP	
Fresh Rat 1° Hepatocytes	58%	92%	92%	75%	100%	100%
Commercial Rat 1° Hepatocytes	92%	100%	92%	75%	67%	100%
Human Hepatocytes	18%	100%	100%	9%	100%	100%
HepG2cells	67%	100%	92%	58%	83%	100%

Innovative Analytics Provide Predictive Power

To provide a predictive ranking of liver toxicity risk using the ToxInsight DILI Assay, the individual toxicity biomarkers (cell loss, DNA content, GSH, ROS and MMP) are combined, using a proprietary patent-pending statistical method, to create a single quantitative 'toxicity index.'

- Use of a single index allows compounds to be compared while fully utilizing the multi-parametric nature of the assay and allowing the contribution of each measurement to be preserved.
- The two multiparametric indices EDI and AI are calculated by comparing the effects of the potential toxic compound in multidimensional space to the negative control, enabling compounds to be ranked on strength of response.
- An Excel® add-in automatically computes all data for the tested compounds, creating a risk profile in minutes.

Predictive Power



ToxInsight DILI Assay Cartridge Excel Analytic Template allows tested compounds to be ranked based on their toxicity risk. The template computes two multiparametric indices based on the individual cell-based measurements of toxicity. Knowledge of toxicity mechanism can be used to repurpose or modify compounds for use in therapy and optimize the therapeutic index.

Sample Compounds	Cell Loss	DNA	GSH	ROS	MMP	#Pos	Result	Rank
Troglitazone	+	+	+	-	+	4	Caution	1
Mefenamic Acid	+	+	+	-	+	4	Caution	2
Phenylbutazone	+	+	+	+	-	4	Caution	3
Gemfibrozil	+	+	+	+	+	5	Caution	4
Tetracycline	+	+	+	+	+	5	Caution	5
Cyproheptadine	+	+	+	+	+	5	Caution	6
Novobiocin	+	+	+	+	+	5	Caution	7
Ticlopidine	+	+	+	+	+	5	Caution	8
Trazodone	+	+	+	-	+	4	Caution	9
Dantrolene	+	+	+	+	-	4	Caution	10
FCCP	-	+	-	+	-	4	Caution	11
Nalidixic Acid	-	-	-	+	-	2	Caution	12
Aspirin	-	-	-	-	-	0		
Fluoxetine	-	-	-	-	-	0		
Melatonin	-	-	-	-	-	0		
Rosiglitazone	-	-	-	-	-	0		

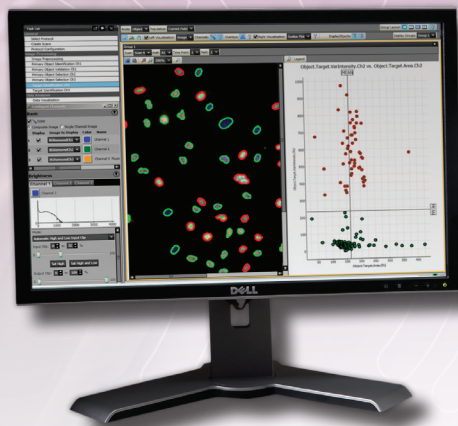
Trust Your *In Vitro* Toxicity Testing to the Leader in Image Cytometry

The ToxInsight DILI Cartridge is designed to run on the Thermo Scientific ToxInsight IVT Platform. This platform offers a predictive, image cytometry approach to determining the toxicity risk of a compound through the measurement of multiple toxicity biomarkers in individual cells.

- The automated, bench-top, easy-to-use platform enables a researcher to benefit from physiologically relevant toxicity assays early in the drug discovery process, rather than traditional late-stage histopathology or animal studies.
- The ToxInsight IVT Platform is designed to both profile compounds for their toxicity risk and then determine the mechanism of action of any toxicity detected, enabling researchers to rapidly understand the therapeutic index of a compound series.
- Compared to traditional biochemical assays (such as cell count, LDH, MTT, etc.) the ToxInsight IVT Platform makes multiple measurements on each cell, generating a phenotype rather than a single measurement.

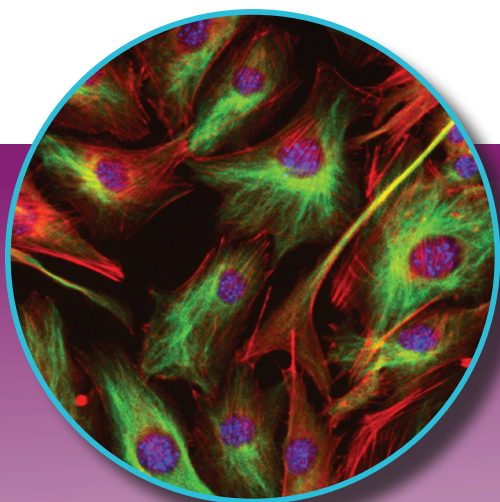
www.thermoscientific.com/toxinsight

The ToxInsight IVT Platform offers intuitive software, ready-made reagent cartridges and easy-to-interpret data analysis tools. The detailed image cytometry data, acquired by multichannel fluorescent imaging of cells *in vitro*, allows analysis on a cell-by-cell basis, to give immediate phenotypic results that cannot be obtained by traditional biochemical assays.



Flexible Configurations for Your In Vitro Toxicity Testing Needs

Ordering information and related products are below. For contact information, please see the back cover of this brochure.



Ordering Information

ToxInsight IVT Platform Products	Description
ToxInsight DILI Assay Cartridge	The ToxInsight Drug-induced Liver Injury Assay Cartridge is for identifying compound hepatotoxicity by simultaneous detection of multiplexed targets, including cell loss, nuclear DNA, reduced glutathione level, intracellular reactive oxygen species and mitochondrial membrane potential. Cartridge includes Hoechst [®] nuclear dye, mBCL for DILI, ROS dye for DILI, Mito dye for DILI and instruction booklet. Cartridge will assay approximately 1000 wells.
ToxInsight IVT Platform	Image cytometry platform for determining <i>in vitro</i> toxicity (IVT) endpoints. Fully automated reader, four-color solid state light engine (DAPI, FITC, TRITC, Cy [®] 5), bench-top footprint [36" (L) x 25" (W) x 20" (H)], 10x (0.3NA) objective, 12-bit high-resolution camera, integrated barcode reader. Accepts SBS standard microplates. Robot-compatible. ToxInsight System Software, image analysis tools and Excel [®] Analytic Template. Instrument PC with monitor. One year warranty.

Thermo Scientific ToxInsight Drug Induced Liver Injury (DILI) Cartridge

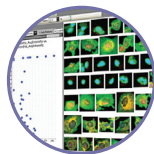


The ToxInsight IVT Platform is part of a complete portfolio of innovative products and solutions for traditional cell biology through to larger scale cellomic studies. Check out our full range of products at our interactive **"World of Cell Biology"** at www.thermoscientific.com/cellomics



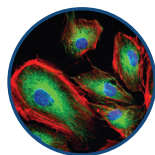
GROW

- Stem cells
- Media & supplements
- Serum
- Speciality growth surfaces



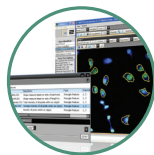
ANALYZE

- Image cytometry instruments
- Single-cell analysis
- Image analysis software
- Higher content cell assays



DETECT

- Fluorescent dyes & labels
- Immunofluorescence kits
- Antibodies
- GFP reporter cell lines



DISCOVER

- Data management
- Bioinformatics & data mining
- Screening & profiling services



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