CellCiphr® Toxicity Profiling Services

Increase the value of your pipeline

CELLUMEN

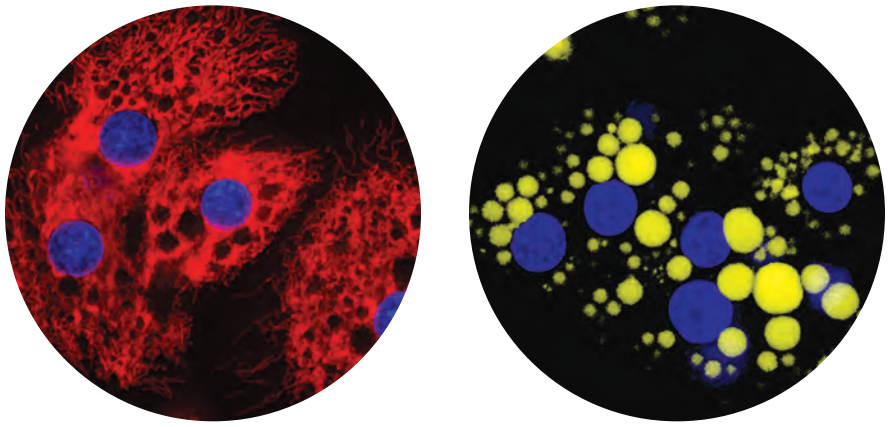
Predictive Science Applied to Drug Discovery

Discovery Toxicology Solutions through Cellular Systems Biology (CSB™)

Cellumen's solution for today is focused on decreasing the drug attrition rate due to toxicity. CellCiphr® CSB™ Toxicity Profiling used from late in primary screening to early in preclinical phases can reliably identify toxic compounds before entering expensive pre-clinical testing. CellCiphr® CSB™ Toxicity Profiling used in the prioritization of lead series will enrich the pipeline with compounds with less risk of attrition due to toxicity.

Cellumen's vision for the future is that the majority of animal testing can one day be replaced by CSB™ Toxicity Profiling panels comprised of comprehensive sets of appropriate target-organ systems, multiple, integrated objective measurements of relevant cellular systems responses to toxic challenge, and advanced informatics to identify toxicophores and to accurately predict human toxic liabilities.

Cellumen's CSB™ solutions drive Discovery Toxicology by providing the most accurate predictions of drug efficacy and safety.



Human Primary Hepatocytes

Discovery Toxicology Solutions

CellCiphr® Toxicity Profiling areas of possible application

Achieve Quantifiable Cost Savings

CellCiphr® CSB™ Toxicity Profiling assigns a Safety Risk Index to compounds that reliably predicts potential rodent or human toxicity. The CellCiphr Classifier is designed to identify CSB profiles that are associated with significant toxic liability while avoiding any false toxic classifications.

Cellumen projects that CellCiphr Toxicity Profiling used to filter out toxic compounds at the start of the hit-to-lead phase can save over $91M in direct costs. Alternatively, using CellCiphr to selectively advance compounds with reduced risk of attrition due to toxicity can increase the value of the typical clinical pipeline by $35M.

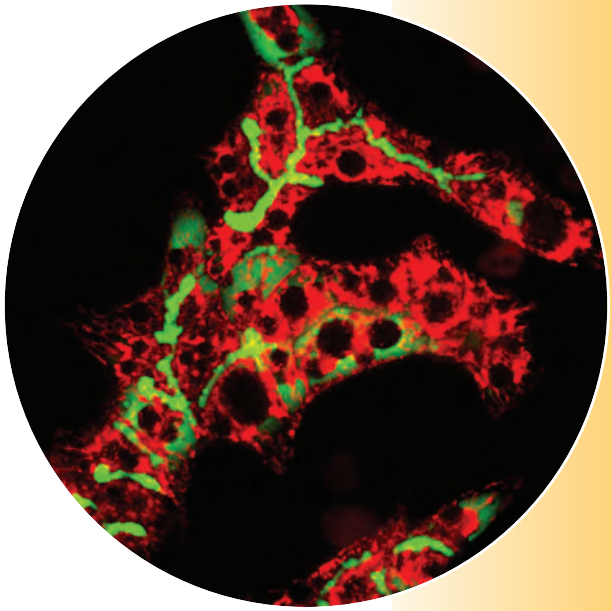
Cost Savings Model

	Start of Phase		
5 Therapeutic Programs	Hit-to-Lead	Lead Opt.	Preclinical
Compounds Entering Each Phase	450	90	30
Estimated Toxic Compounds	100	20	5
Toxic Compounds Identified Upfront by CellCiphr®	40	8	3
Cost Savings			
Development Cost Per Compound	$ 1,000,000	$ 4,000,000	$ 9,300,000
CellCiphr® Cost Savings	$91,500,000	$56,000,000	$25,700,000

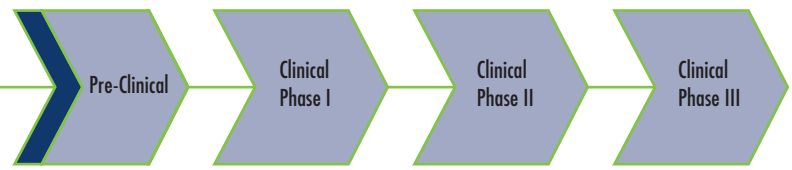
Clinical Pipeline Value Increase

	Start of Phase		
5 Therapeutic Programs	Hit-to-Lead	Lead Opt.	Preclinical
Compounds Entering Each Phase	450	90	30
Estimated Toxic Compounds	100	20	5
Toxic Compounds Identified Upfront by CellCiphr®	40	8	3
Margin Acceleration			
CellCiphr® Value	$35,800,000	$19,300,000	$ 7,400,000

Contact us for more details or to schedule a presentation on the financial value proposition.



Rat Hepatobiliary



The CSB™ Advantage

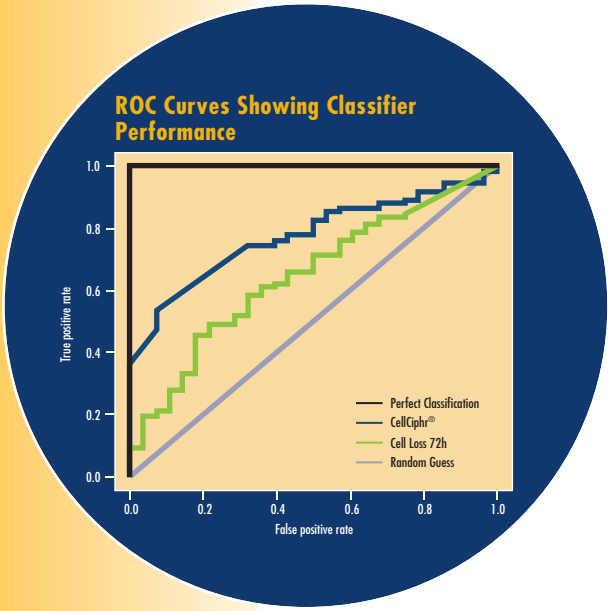
CellCiphr® CSB™ Toxicity Profiling uses a combination of primary cells, stem cell-derived cells and cell lines, biomarkers and proprietary classification algorithms to quantify cellular system responses to toxic challenges. All of the measurements are made simultaneously in the same population of cells enabling the identification of subtle, complex responses to toxins: the so-called emergent properties of the cellular system. CSB™ is the only toxicity screening approach that provides precise spatial, temporal and contextual information on the interrelationships among the activities of toxic indicators coupled to advanced classifier software.

CellCiphr® CSB™ Toxicity Profiling provides many advantages over *in vitro* toxicity testing:

- Acquire detailed profiles that integrate the systems response to toxicity with changes in time and dose
- Distinguish early, late and chronic responses to toxicity
- Determine cause and effect through dose- and time-dependent measures of critical cell functions
- Identify sub-lethal effects on cell health and function

Classifier Benefits/Strategy

For each CSB™ Toxicity Panel, Cellumen profiles a growing set of reference compounds for which safety data are available. The profiles from these compounds are used to create a proprietary classification algorithm that produces a rank order of risk of failure in safety studies (Safety Risk Index). The present generation classifier is designed to identify profiles that are always associated with toxic liability while avoiding any false toxic classifications. Therefore, the classification as High Risk provides a very reliable prediction of failure due to toxicity.



The CellCiphr® classifier accurately predicts toxic liability while avoiding false positives.

CellCiphr® CSB™ Toxicity Profiling Services

CSB™ Profiling

Cellumen currently offers two distinct CellCiphr® CSB™ Toxicity Panels. The HepG2 Panel and the Rodent Primary Hepatocyte Panel can identify both general and liver-specific toxicity.

HepG2 Panel 1
Cell Features
Cell Loss
Cell Cycle Arrest
Nuclear Size
Oxidative Stress
Stress Kinase Activation
DNA Damage Response
Mitochondrial Function I
Mitochondrial Function II
Mitosis Marker
Cytoskeletal Disruption

Rodent Primary Hepatocyte Panel 2
Cell Features
Cell Loss
DNA Condensation
Nuclear Size
Apoptosis
Steatosis
Phospholipidosis
Mitochondrial Function
DNA Damage Response

Panels include 10 point dose response curves at early, late and chronic exposures.

CSB™ Panels in Development (Multiple Species and Systems)

- Human Hepatocyte (primary and stem-cell derived) Panel
- Human Cardiomyocyte Panel
- Human Neuronal Panel
- Human Kidney Panel
- Rodent Hepatobiliary Panel
- Rodent Cardiomyocyte Panel
- Rodent Neuronal Panel
- Rodent Kidney Panel

Collaborative Development Services

CSB™ Panels and Classifiers

Partnering with Cellumen to develop custom CSB™ Toxicity Profiles will accelerate your internal efforts to develop more comprehensive screens to predict toxicity in multiple species and systems.

Collaborative development services may include:

- *Target organ systems:* liver, brain, heart, kidney, GI, immune cells, primary cells, stem cells, cell lines, or engineered tissue
- *CSB™ Toxicity Panels and/or toxicity pathway biomarkers:* Fixed End-Point, Live Cell Kinetic assays or both
- *Advanced Classifiers:* Informatics to develop predictive models of human toxicity

Conventional Cell Health Analysis (High Content Assays)

Cellumen also provides conventional assays using only 2–4 parameters, e.g., Genotoxicity, Neurite Outgrowth and Inflammation, when less detailed toxicity profiles are required. These conventional assays can also be profiled with our CSB™ panels as a collaborative service.

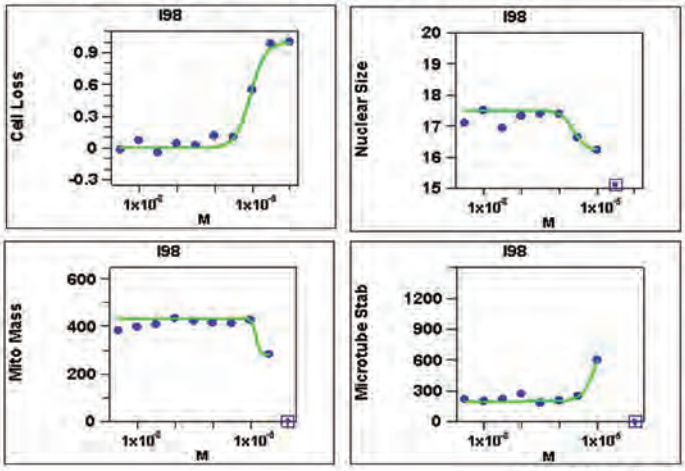
Deliverables

CellCiphr® Report Excerpt

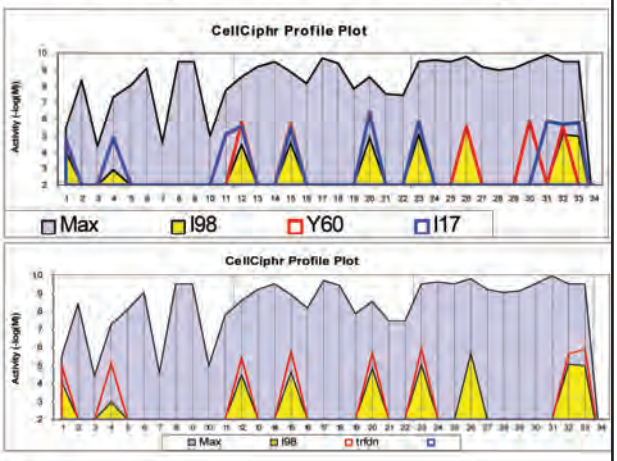
CellCiphr® Toxicity Report CSB™ HepG2 Panel 1	Compound I98 Measurable Effects	AC_{50} (M) 1 hr	 24 hr	 72 hr
Maximum Tolerated Dose	>70% Cell Loss	46.0E-6		13.0E-6
Earliest Toxic Indicator	Cell Loss		85.5E-6	
Most Sensitive Toxic Indicator	Nuclear Size			2.3E-6
General Indicator(s) of Toxicity	Cell Loss	28.5E-6	85.5E-6	8.9E-6
	Nuclear Size	20.8E-6	1.1E-3	2.3E-6
Mechanistic Indicators of Toxicity	Cell Cycle Arrest			
	Mitotic Arrest			8.8E-6
	Microtubule Stability			10.0E-6
	DNA Damage Response			
	Oxidative Stress Activity			
	Stress Kinase Activity			
	Mitochondrial Potential			
	Mitochondrial Mass	13.8E-6		
CellCiphr® Classification	Rank Order 66	Safety Risk Index		Low Risk

CellCiphr® Correlation	Compound			Correlation Coefficient		
Similarity with Compounds in Set	Y60	I17	X69	0.82	0.75	0.69
Similarity with CellCiphr® ToxProfile™ DB	CE 826			0.88		

Dose-Response for General, Early & Sensitive Indicators



CellCiphr® ToxProfile™ Similarity Plots



CellCiphr® Toxicity Report

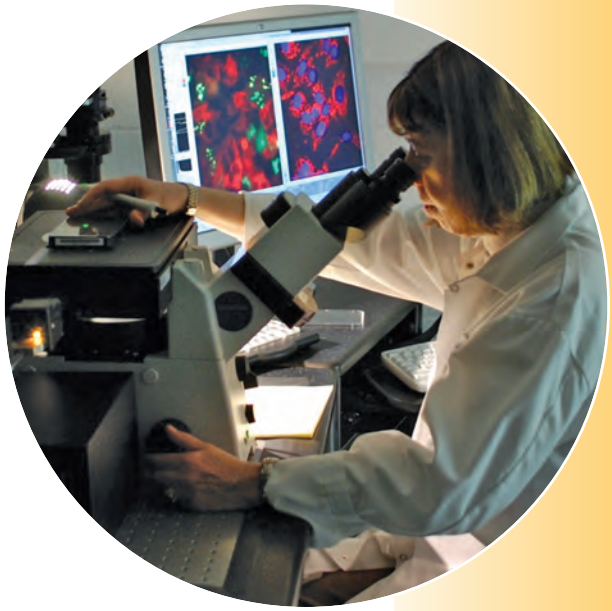
Customers receive a CellCiphr® Toxicity Report for each compound summarizing:

- CellCiphr® Safety Risk Index
- Maximum Tolerated Dose
- Earliest Toxic Indicator
- Most Sensitive Toxic Indicator
- General Indicators of Toxicity
- Mechanistic Indicators of Toxicity
- CellCiphr® Correlation Analysis, including other compounds in the project, compounds in the reference database, and CellCiphr® ToxProfile™ Similarity Plots

The standard CellCiphr® data package is delivered electronically in a 3 page Excel file for each compound. It also includes: AC50 values, 10 point dose-response curves (up to 100uM) for all indicators at each exposure, and curve fit parameters including, min, max and slope. All customer data is treated as proprietary and maintained in a secure environment.

Optional Data Reports Can Include:

- Table of AC50 values for customer cluster and correlation analysis
- Table of correlation values for customer compounds and CellCiphr® CSB™ Profile Library compounds
- A clustered heat map showing similarities and differences between the CellCiphr® ToxProfiles™ of compounds within a set
- All well level data supplied as a series of tables in a TAB delimited file for in-house curve fitting
- All measurement data and images (additional cost depending on customer format requirements)



Cellumen is dedicated to an evolving CSB™ Toxicity Profiling platform including 3D cultures and engineered tissue models.

QA/QC Process

Rigorous Assay Validation

- Full plate variability assessment utilizing NIH HTS guidelines
- Z'> 0.25 for each feature

Complete Quality Control

- Intra plate: Negative controls ≤20% CV
- Inter-day: Positive control AC50 ≤0.5 log from Historical Mean

CELLUMEN

Predictive Science Applied to Drug Discovery

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