Qualyst Transporter Solutions
In Vitro Hepatic Models

C-DILI™ Assay

Predict Cholestatic Liver Injury

The C-DILI™ Assay is a novel *in vitro* method to evaluate a compound's potential for cholestatic drug-induced liver injury (DILI).

The C-DILI Assay has demonstrated high *in vitro – in vivo* correlation with compounds known to have a risk for cholestatic hepatotoxicity. It is an effective tool for assessing the risk of cholestatic DILI and providing data useful in lead selection and managing toxicity risk.

At high concentrations, bile acids can cause liver toxicity by signaling apoptotic pathways as well as disrupting membranes. The liver tightly controls bile acid concentrations through multiple regulatory mechanisms including basolateral efflux, biliary efflux, synthesis, and metabolism. However if control mechanisms are disrupted, bile acid concentrations can reach a "tipping point" resulting in hepatotoxicity. The C-DILI Assay combines all of these human-relevant processes in one simple threshold readout, providing a unique clinically-predictive assessment of cholestasis risk.

Our Process

Transporter Certified™ Hepatocytes are cultured in sandwich-culture to re-establish physiologically-relevant uptake, metabolism, regulation and efflux function. The hepatocytes form a matrix with bile pockets and demonstrate transporter function, including BSEP, OSTs, and MRP3/4.

After the culture has been established, Qualyst's proprietary QualGro™ Sensitization Media is added to the wells, along with the test compound, and incubated for 24 hours. Cholestatic hepatotoxicity is evaluated by measuring lactate dehydrogenase (LDH) concentration versus controls in a standard plate-reader assay.

The LDH response of the test article is compared to drugs with known clinical cholestatic effects. Comparison with negative controls (e.g. cyclosporine) and positive controls (e.g. troglitazone) allow compounds to be bucketed for their clinical cholestatic hepatotoxicity potential. In addition, an incubation without the QualGro Sensitization Media can be performed in parallel to assess hepatotoxicity directly from the compound.

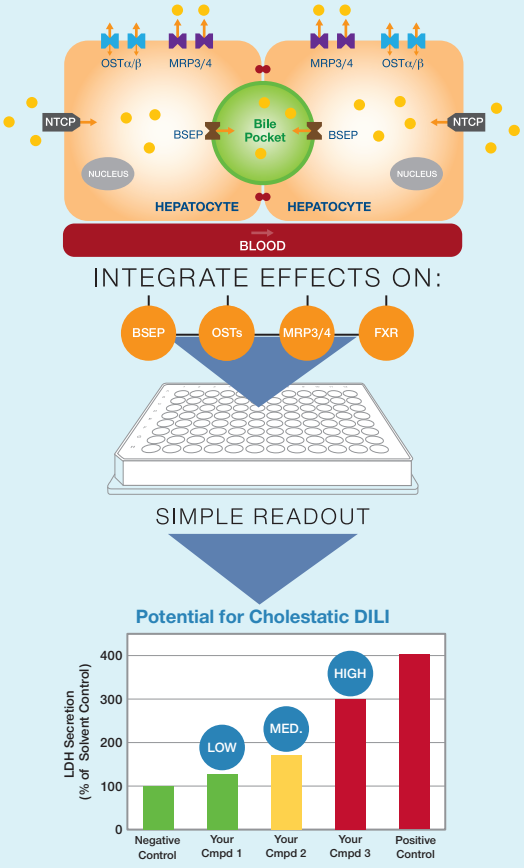
Study Report

The C-DILI Assay report is an easy-to-read assessment of LDH secretion as a % of solvent control, and compared to negative and positive control standards. Test articles are coded as green, orange, or red, for low, medium or high risk of cholestatic DILI potential.

A BREAKTHROUGH ASSAY

In vivo models are inadequate because rats and dogs have different bile acid constituents and metabolism than humans, with different transporter regulation.

The C-DILI Assay is specially constructed to use a simple LDH readout that is specific to compounds that inhibit bile acid transport and antagonize FXR. An LDH readout provides a threshold value, and is analogous to clinical tests for liver toxicity.



Programs to Meet Your Needs

We offer three levels of the C-DILI Assay, each designed to provide actionable data that will inform decision-making:

- **Threshold Assessment:** Evaluate cholestatic hepatotoxicity potential
- **Contrast Assessment:** Evaluate cholestatic hepatotoxicity and cytotoxicity potential
- **Mechanistic Assessment:** Evaluate cholestatic hepatotoxicity and cytotoxicity potential and characterize the mechanisms of toxicity (BSEP inhibition, basolateral efflux and FXR antagonism)

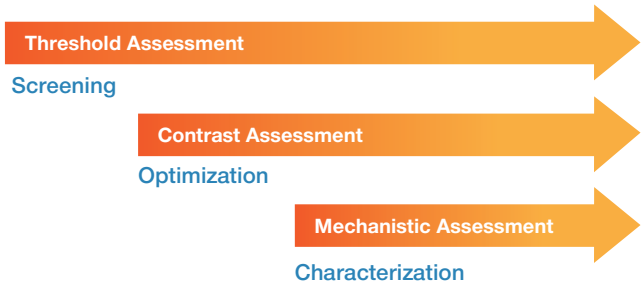
Accelerate Decision-Making

Either as a stand-alone program or implemented with other studies the C-DILI Assay is designed to complement your R&D process. From early stage screening through optimization and characterization the C-DILI Assay informs your SAR, lead selection, and toxicity assessment programs. An added advantage is that the same system, and even the same cells, can be used for more in depth studies later in your characterization work. The data are all connected and consistent so there is no need to translate data from different model systems.

Quality

The C-DILI Assay is conducted in Qualyst's research laboratory in Research Triangle Park and is overseen by research scientists with extensive experience in *in vitro* models.

	Assessment Program		
	Threshold	Contrast	Mechanistic
Test Article Concentrations	1	3	5
Replications	3	3	3
Solubility Assessment	✓	✓	✓
Cholestasis Prediction (Low, Medium, High)	✓	✓	✓
Cytotoxicity Prediction (Low, Medium, High)		✓	✓
Assess BSEP Inhibition			✓
Assess Basolateral Efflux			✓
Assess FXR Antagonism			✓



TRANSPORTER CERTIFIED™ HEPATOCYTES

Transporter Certified is an industry standard that ensures hepatocytes have physiologic transporter function, metabolic competence and appropriate regulatory pathway functionality, under culture conditions Qualyst has defined. In sandwich culture, the intracellular concentrations in Transporter Certified hepatocytes reflect physiologic conditions because the hepatocytes express functioning uptake and efflux transporters and develop bile pockets similar to bile canaliculi.

Collaborate with Us

To discuss collaboration contact us:

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