Primary Human Hepatocyte Spheroid Model for Predicting Drug-induced Liver Injury

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Agenda

- **Background on Drug-induced Liver Injury (DILI) and 3D liver models**
- **Spheroid culture with primary human hepatocytes (PHHs)**
- **PHH 3D spheroids for liver toxicity screening**
- **Overview of Corning® Gentest℠ Contract Research Services**
- **Q&A**

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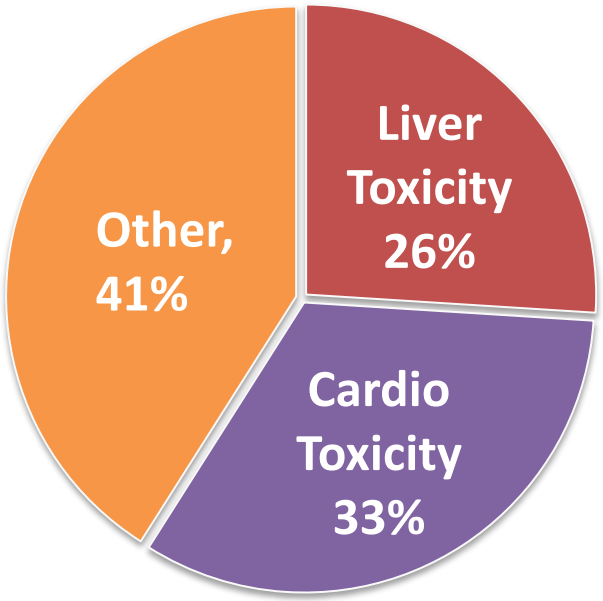
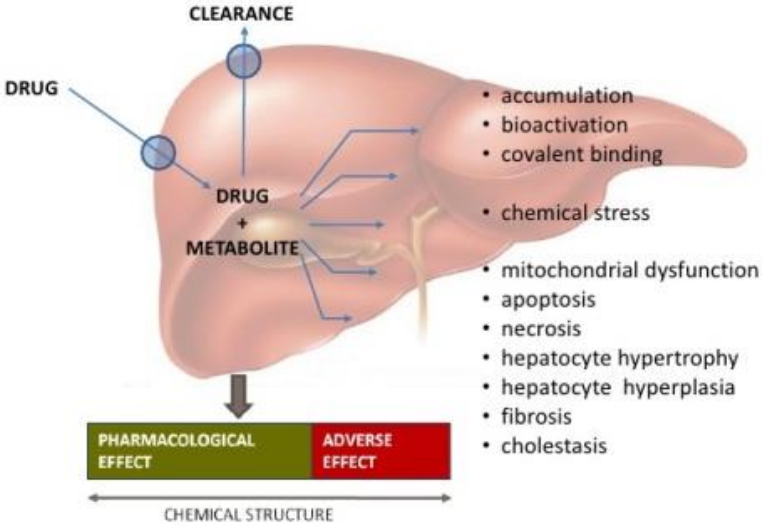
DILI Remains a Leading Cause for Drug Attrition and Clinical Failure

- Among drugs withdrawn due to toxicity, 26% are attributed to DILI

Drugs Withdrawn Due to Toxicity (1990-2010)



Complex mechanisms for DILI



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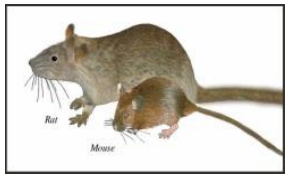
Shift from the Current Animal-based Drug Safety Assessment Paradigm

National Centre for the Replacement Refinement & Reduction of Animals in Research



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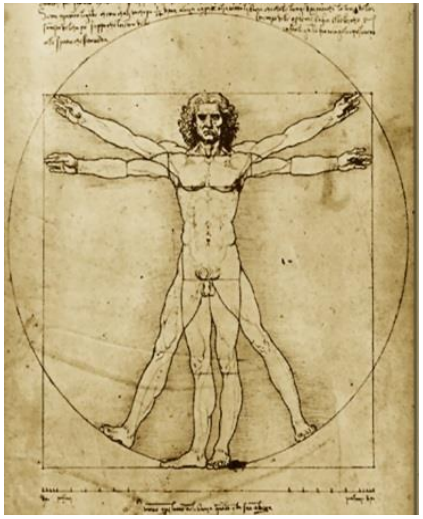

- High failure rate of preclinical drug candidates highlights the critical gap between conventional 2D cell culture systems, animal models, and human.
- More physiologically and more human relevant models needed.

Chen M, et al. Predicting idiosyncratic drug-induced liver injury: some recent advances Expert Rev Gastroenterol Hepatol. 2014 Sep;8(7):721-3.
Olson H, Betton G, Robinson D, et al. Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul Toxicol Pharmacol 2000;32(1):56-67

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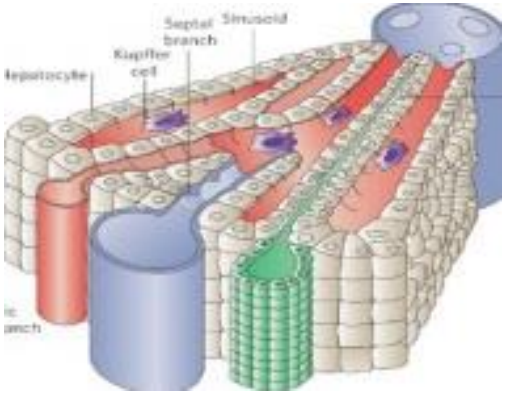
Limitations and Gaps of Current 2D PHH Culture

2D PHH Monolayer

3D Architecture of Liver Tissue



- 2D culture systems have been playing a pivotal role in biomedical research; however, conventional 2D culture systems are too simplistic to reflect the complexity of the liver.
- 3D culture systems have been shown to sustain the cell viability; maintain the *in vivo* like phenotypes, gene, and protein expression of hepatocytes.
- In comparison to other 3D systems, spheroids require fewer cells, are technically easier, and adaptable to high throughput studies.

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3D Cell Culture Platforms

Scaffold-based

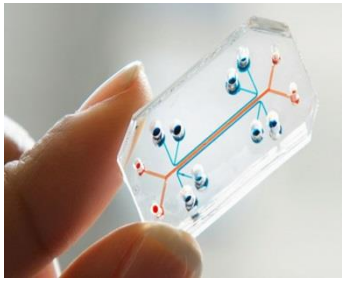
- Hydrogels:
  - ECM (e.g., Corning® Matrigel® matrix); Plant-derived (Alginate) and Synthetic (e.g., PEG)
- Inert matrix:
  - Porous 200 µm thick polystyrene scaffold
  - Methyl cellulose

Scaffold-free Systems

- Low adhesion plates: Corning Ultra-Low Attachment spheroid microplates
- Hanging drop

Combination of 3D and Microfluidic Cell Culture

- Organ-on-a-chip



3D Bioprinting

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- **Spheroid culture with primary human hepatocytes (PHHs)**
- PHH 3D spheroids for liver toxicity screening
- Overview of Corning® Gentest℠ Contract Research Services

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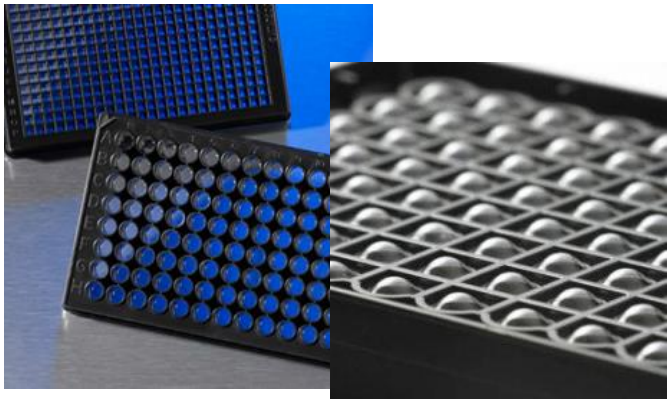
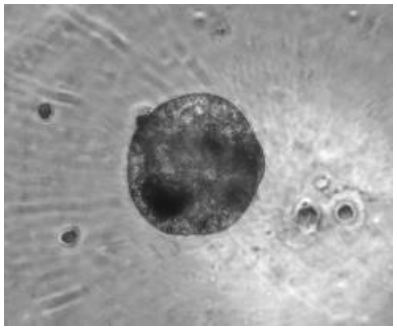
Corning Technologies for Building a 3D Liver Spheroid Model

Corning® Spheroid Microplates



Cryopreserved PHH

3D Liver Spheroid



- Establish PHH spheroid culture protocol
- Develop 3D liver toxicity assay

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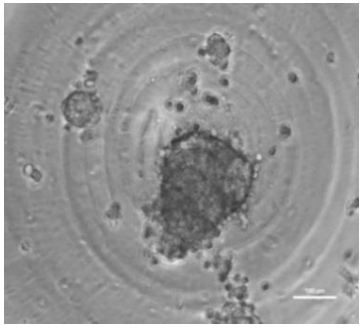
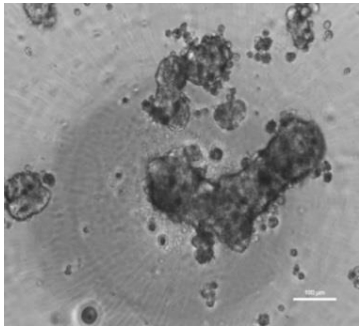
PHH Lot-to-Lot Variations in Spheroid Formation

Day 3 Culture **Williams' E + 10% FBS**

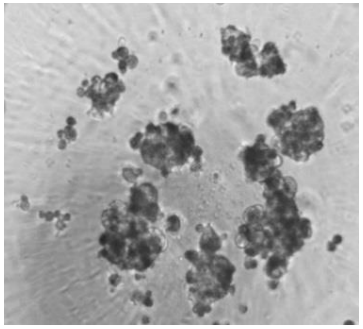
Lot 345



Lot 397



Lot 348A



- Initial test with gravity only.
- FBS (>5%) is needed for spheroid formation; but not for maintaining the culture.
- Spheroid formation time varies among different lots of PHHs.
- Not all PHH lots give rise to spheroids; pre-test for 3D spheroid culture is needed prior to targeted applications.

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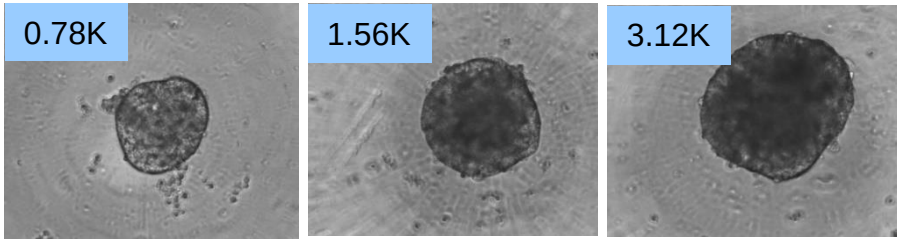
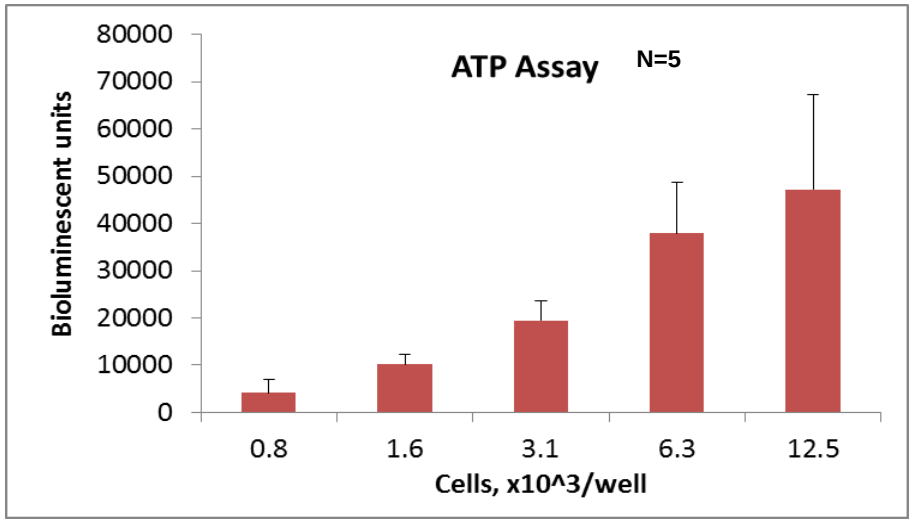
Correlation Between Initial Seeding Density, Spheroid Size, and ATP Levels

Day 7 Spheroid



Spheroid Viability Measurement



- Spheroid morphology and sizes are routinely monitored.
- Bioluminescent ATP assay for viability assessment can be performed on the same Corning spheroid microplates.
- Usually, single spheroids can form with seeding densities <5K cells/well on a 96-well spheroid microplate.

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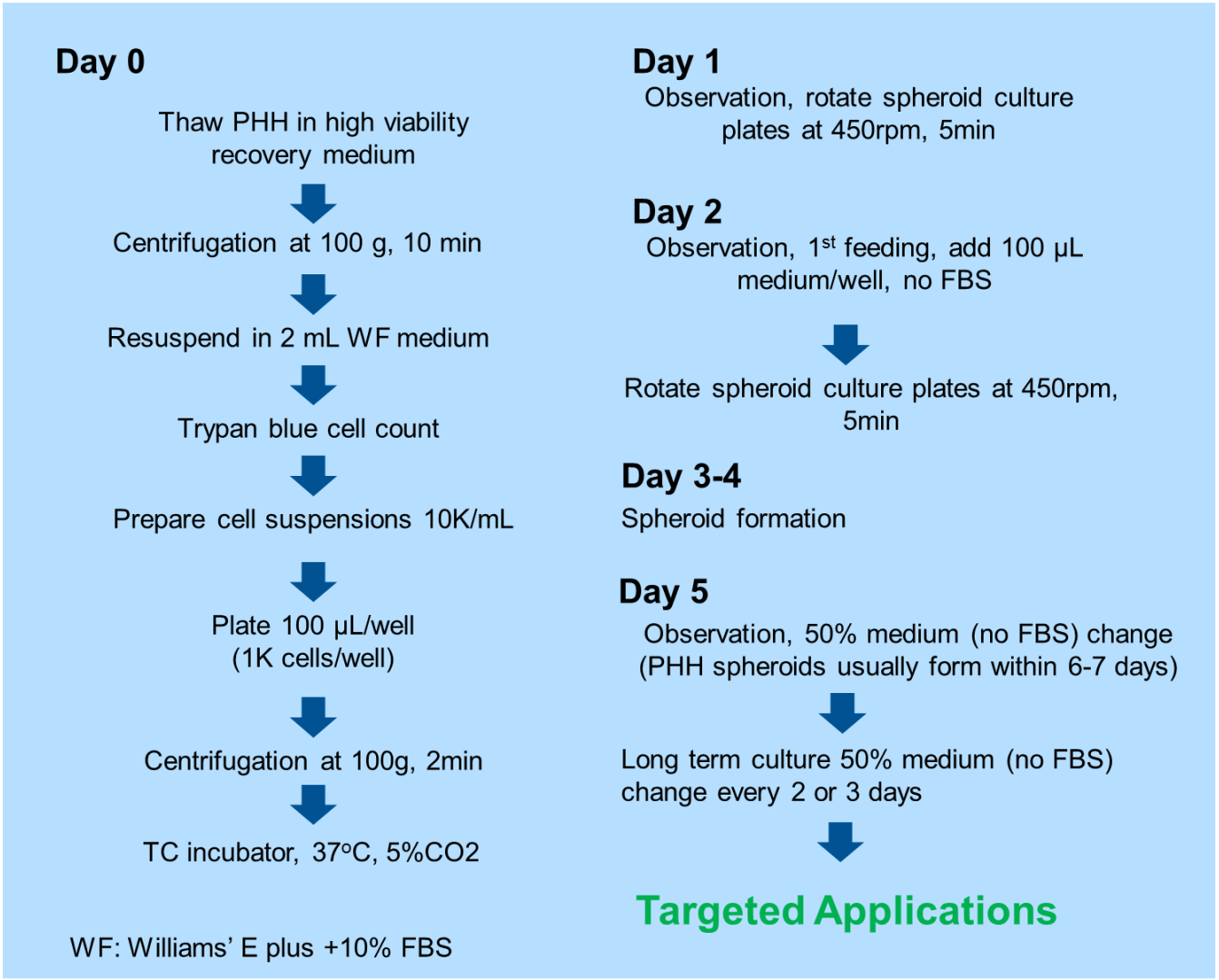
3D PHH Spheroid Culture Using a Corning Ultra-Low Attachment 96-well Spheroid Microplate



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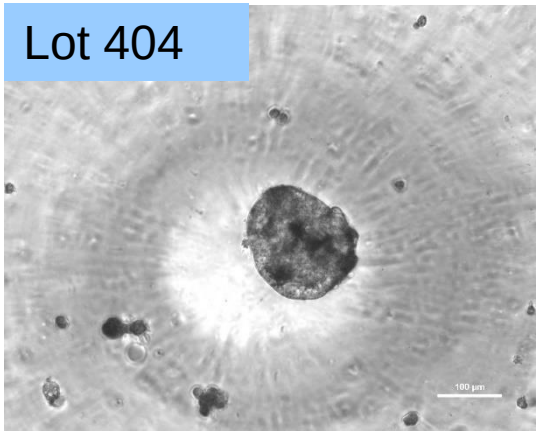
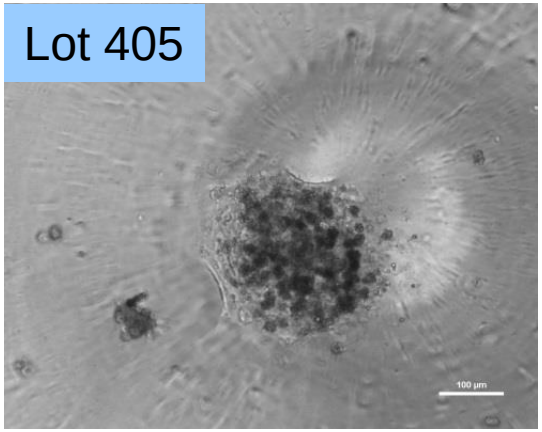
Screening PHH Lots with an In-house Protocol for 3D Spheroid Culture

Day 6 Spheroid Culture

Lot 404



Lot 405



- Not all PHH lots form spheroids.
- Variable spheroid formation time and stability was observed.
- 30 lots of were PHH tested for 3D spheroid culture.

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PHH Lots Tested for 3D Spheroid Culture

Corning Cat. No.	Description	Lots Tested	3D Lots	Ranking	Spheroid Formation	Spheroid Stability
454541	Plateable Transporter-qualified ≥5 million cells	342, 345, 380, 393A, 393B, 396, 399, 404, 405A,	342 345 380 393A 399 404	+++ ++ ++++ +++ ++++ ++++	Day 6-8 Day 4-5 Day 6-8 Day 6-8 Day 4-6 Day 5-6	≥3 weeks ~2 weeks ≥3 weeks ≥3 weeks ≥3 weeks ≥3 weeks
454543	Plateable Metabolism-qualified ≥5 million cells	303, 304, 330, 358, 397, 410, 416	303 304 330 397 410	++++ ++ +++ ++++ ++	Day 6-8 Day 5-6 Day 8-10 Day 5-6 Day 8-10	≥3 weeks ~2 weeks ≥3 weeks ≥3 weeks ~2 weeks
454550	Inducible-qualified 2-5 million cells	299, 338, 348A, 411A, 412	299 338 348A	+++ ++ ++++	Day 8-10 Day 4-5 Day 5-6	≥3 weeks ~2 weeks ≥3 weeks
454551	Inducible-qualified ≥5 million cells	314, 336, 337A, 349, 363, 375, 385, 391, 395	336 349 363 391	+++ +++ +++ ++	Day 6-8 Day 3-4 Day 8-10 Day 5-6	≥3 weeks ~2 weeks ≥2 weeks ~2 weeks
454426	Suspension Assays, Transporter-qualified	370	Spheroid did not form			

Stability: >50% single spheroids (out of 48 wells initially plated) maintained during culture

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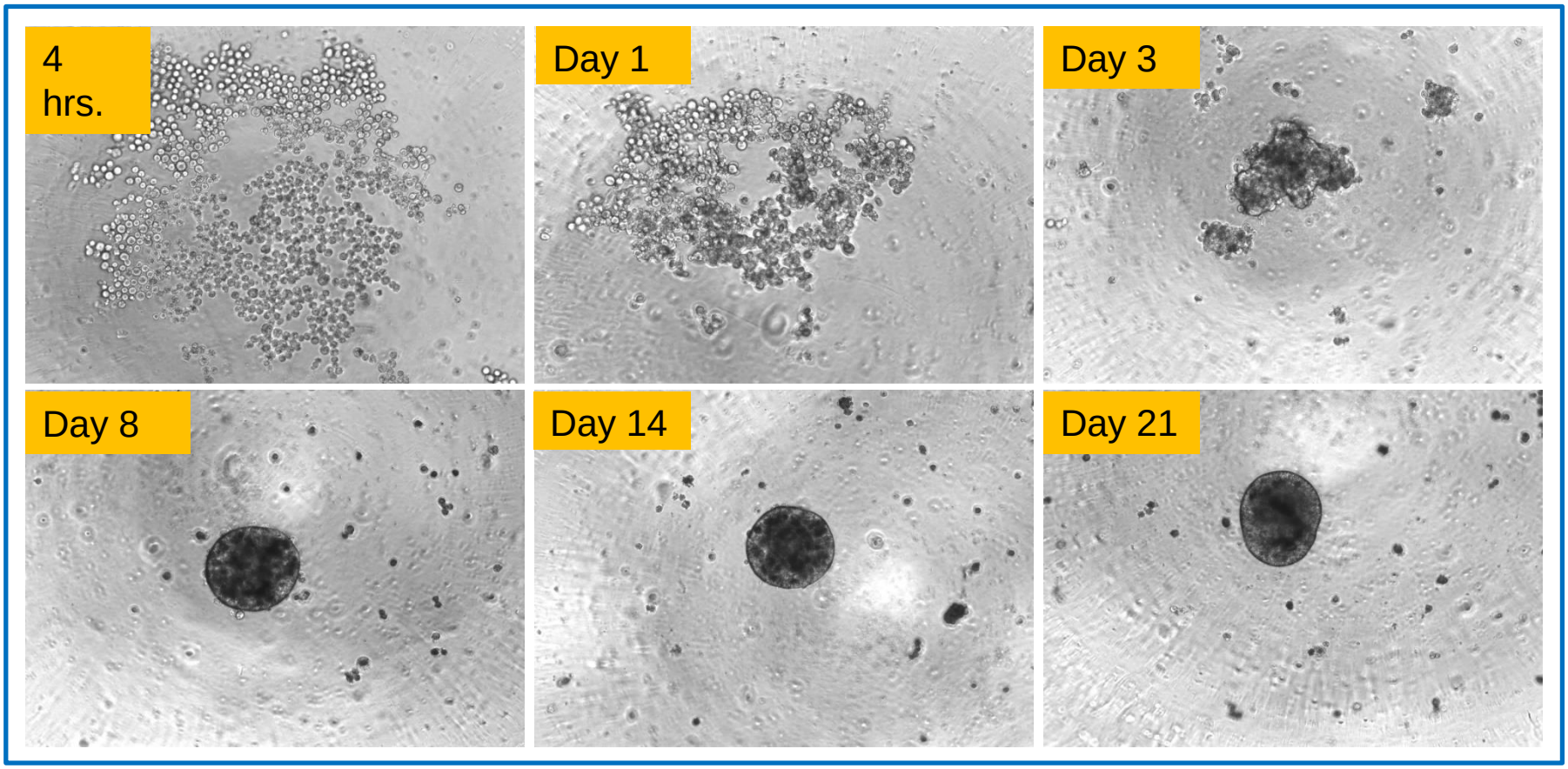
The Size and Morphology of Liver Spheroids Remain Stable During Long Term Culture



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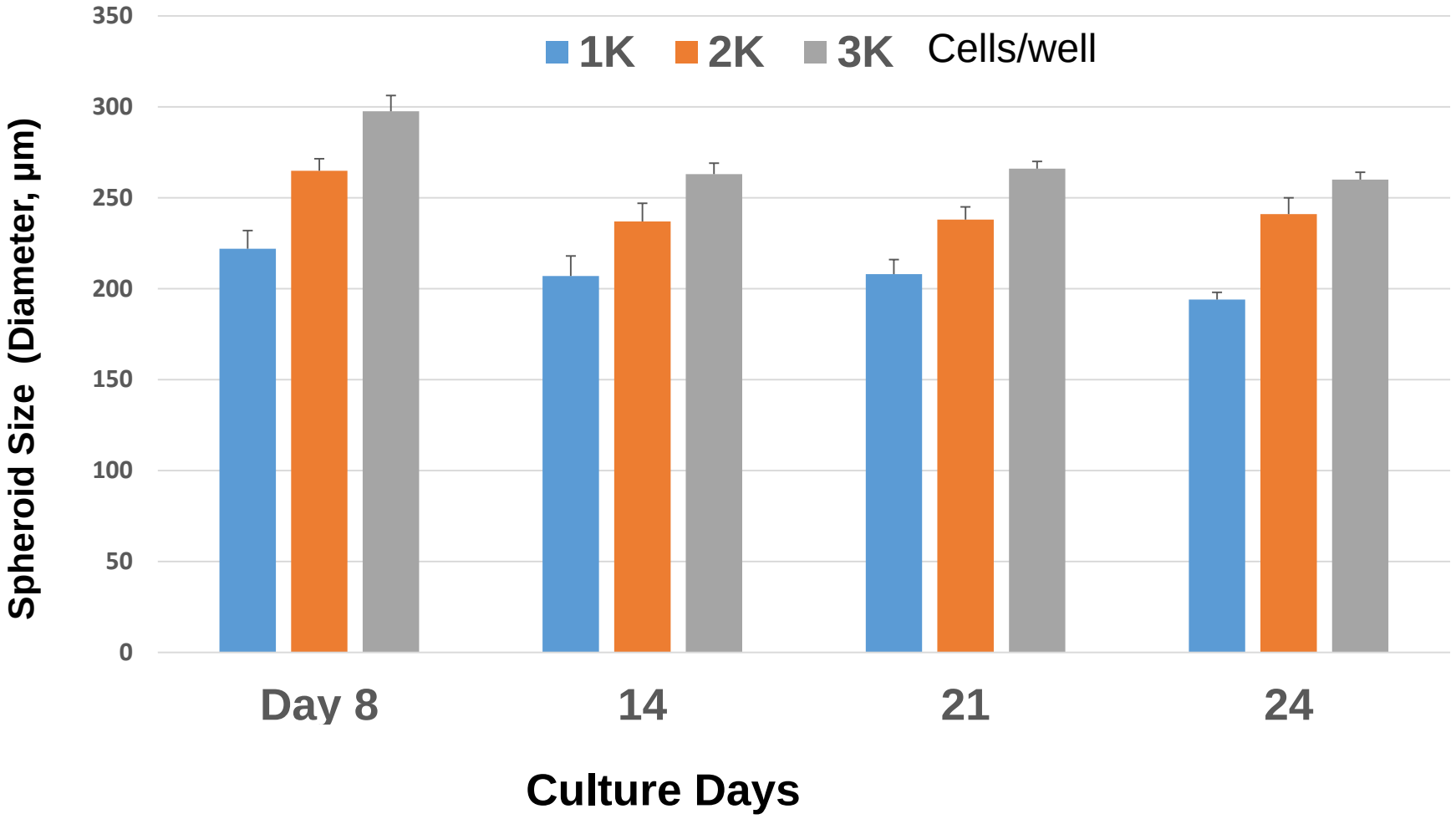
The Size and Morphology of Liver Spheroids Remain Stable During Long Term Culture



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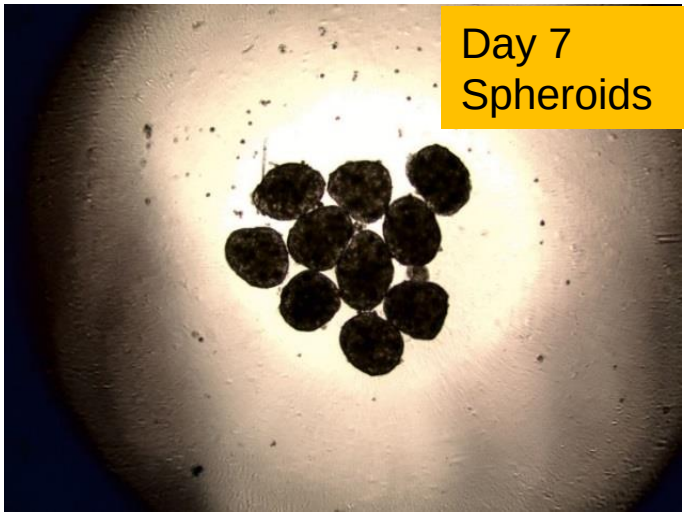
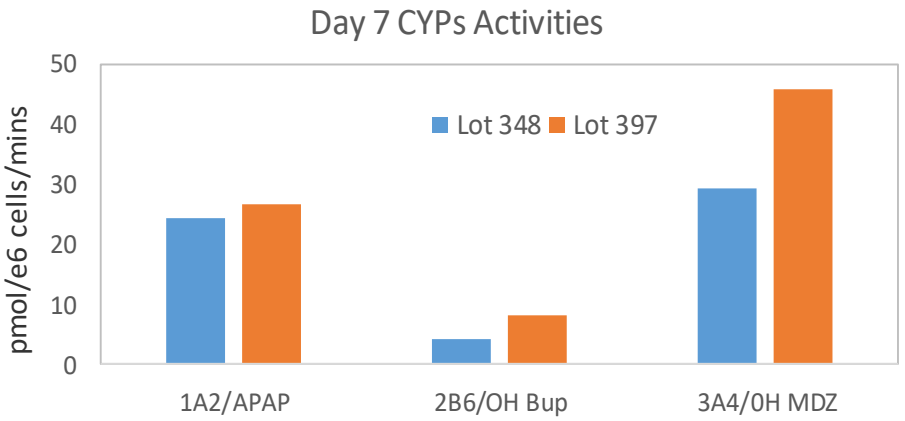
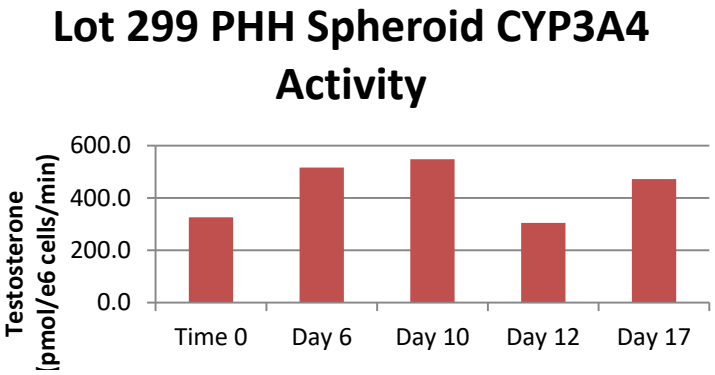
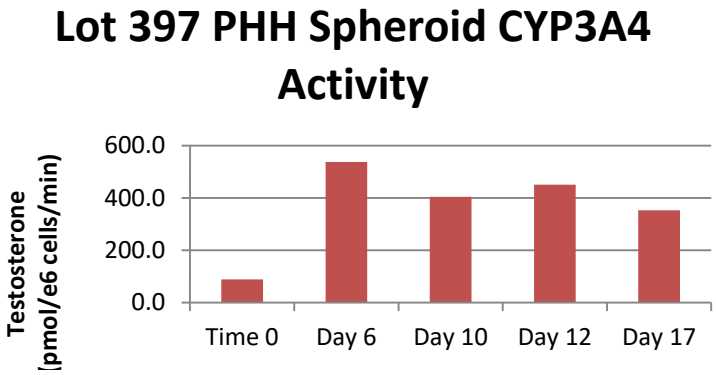
PHH Spheroids Maintain Drug Metabolic Activities



10 spheroids = 10K cells







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Summary of PHH 3D Spheroid Culture

- We have established an in-house protocol for PHH 3D spheroid culture with Corning® spheroid microplates.
- Serum is needed for the formation of liver spheroids but not for maintaining spheroid culture.
- Lot-to-lot variation was observed for spheroid culture.
- Pre-qualified PHH lots for 3D culture.
- Liver spheroids made from pre-qualified PHH lots remain stable over time.

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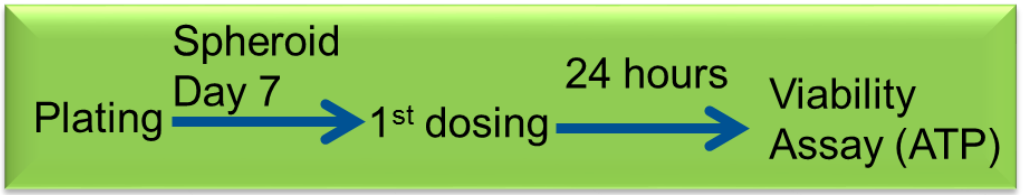
3D Hepatotoxicity Assay Development: Selection of DILI Compounds and Pilot Single Dosing Tests

DILI Severity Category	Compound	C_{max} (μM)
1. Severe	Amiodarone	5.3
	Bosentan	7.4
	Nefazodone	4.3
	Tolcapone	47.6
	Troglitazone	6.4
	Trovafloxacin	5.0
	Valproic Acid	693.4
2. High concern	Diclofenac	10.1
	Rosiglitazone	1
3. Low concern	Acetaminophen	165.4
	Chlorpromazine	0.9
	Pioglitazone	2.95
4: Enzyme elevations	Dexamethasone	0.2
5. No DILI	Flumazenil	1.1

3D spheroid single dosing toxicity assay



- Half medium changes to remove residue FBS
- 2X compound working solutions for dosing
- Bioluminescent ATP measurement to generate dose response curves
- IC_{50} values calculation

Proctor, et al. Utility of spherical human liver microtissues for prediction of clinical drug-induced liver injury Arch Toxicol. 2017 Aug;91(8):2849-2863.

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DILI Response of Spheroids from Individual PHH Lot vs. Pooled Lots

Compound list	DILI Severity Category	IC_{50} µM (In-house) 3D-24 hrs.				
		Lot 348	**Lot 397**	**Lot 404**	**Lot Pool**	**Average 3D-24 hr.**
Amiodarone	1. Severe clinical DILI	356.6	192.5	117.5	250	229
Bosentan	1. Severe clinical DILI	1311	696.8	>625	649.4	886
Nefazodone	1. Severe clinical DILI	29.56	28.19	19.47	28.78	27
Tolcapone	1. Severe clinical DILI	75.85	110	66.06	141.5	98
Troglitazone	1. Severe clinical DILI	16.61	26.26	14.85	14.7	18
Trovafloxacin	1. Severe clinical DILI	>1000	>1000	>1000	>1000	>1000
Valproic Acid	1. Severe clinical DILI	25554	25792	>25,000	25028	25458
Diclofenac	2. High clinical DILI concern	336.7	551.9	316.2	382.2	397
Rosiglitazone	2. High clinical DILI concern	226.9	297.6	200.2	250	244
Acetaminophen	3. Low clinical DILI concern	10388	17339	>10,000	>10,000	13864
Chlorpromazine	3. Low clinical DILI concern	29.84	26.57	31.33	28.1	29
Pioglitazone	3. Low clinical DILI concern	>500	>500	>500	>500	>500
Dexamethasone	4: Enzyme elevations in clinic	>1250	>1250	>1250	>1250	>1250
Flumazenil	5. No DILI	>1250	>1250	>1250	>1250	>1250

- Lot pool: three lots of PHHs were mixed at 1:1:1 after thawing, then used to set up spheroid culture

➢ Spheroid from pooled PHHs showed comparable IC_{50} to the mean IC_{50} of 3 individual lots – potentially an approach to reduce lot-to-lot variation

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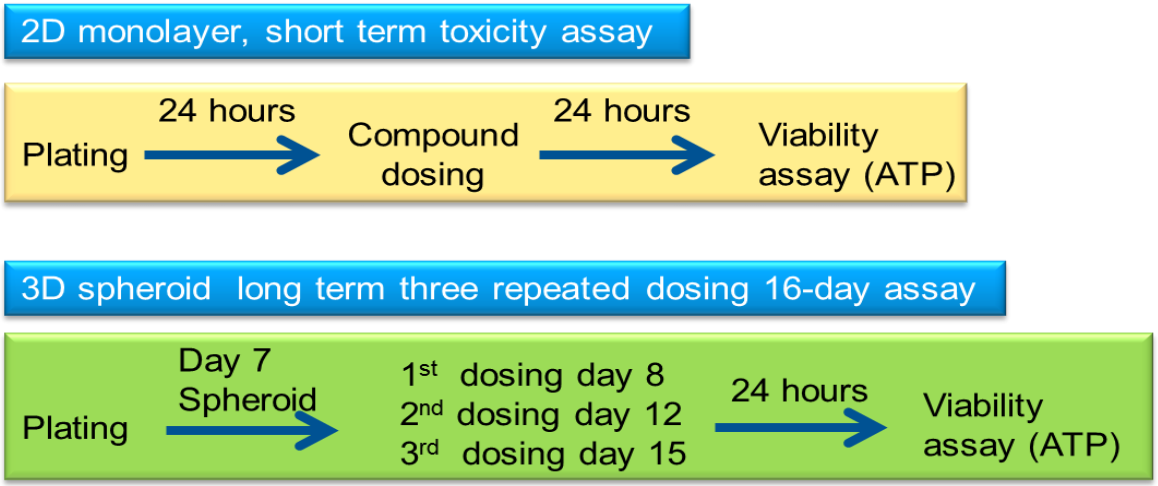
Testing DILI Compounds in 3D PHH Spheroids vs. 2D Monolayer (3 PHH Lots)

- Hepatocytes in 2D culture are short-lived for ~7 days.
- 3D spheroid culture supports long-term hepatocyte viability in culture for up to 4 weeks.
- 3D spheroid culture is capable of testing chronic liver toxicity with repeated dosing.



DILI Category	Compound	C_{max} (µM)
1. Severe	Amiodarone	5.3
	Bosentan	7.4
	Nefazodone	4.3
	Tolcapone	47.6
	Troglitazone	6.4
	Trovafloxacin	5.0
	Valproic Acid	693.4
2. High concern	Diclofenac	10.1
	Rosiglitazone	1
3. Low concern	Acetaminophen	165.4
	Chlorpromazine	0.9
	Pioglitazone	2.95
4: Enzyme elevation	Dexamethasone	0.2
5. No DILI	Flumazenil	1.1

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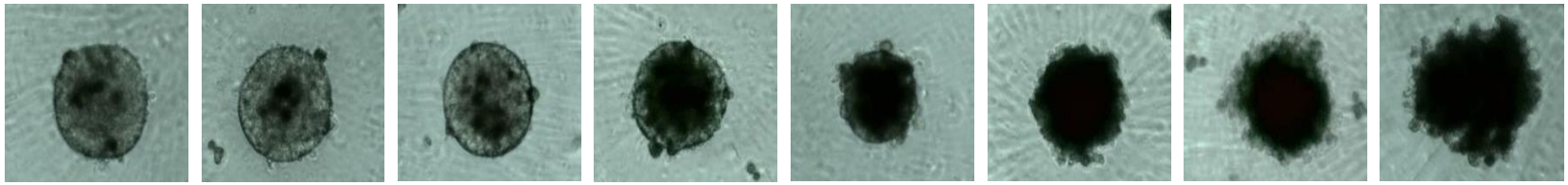
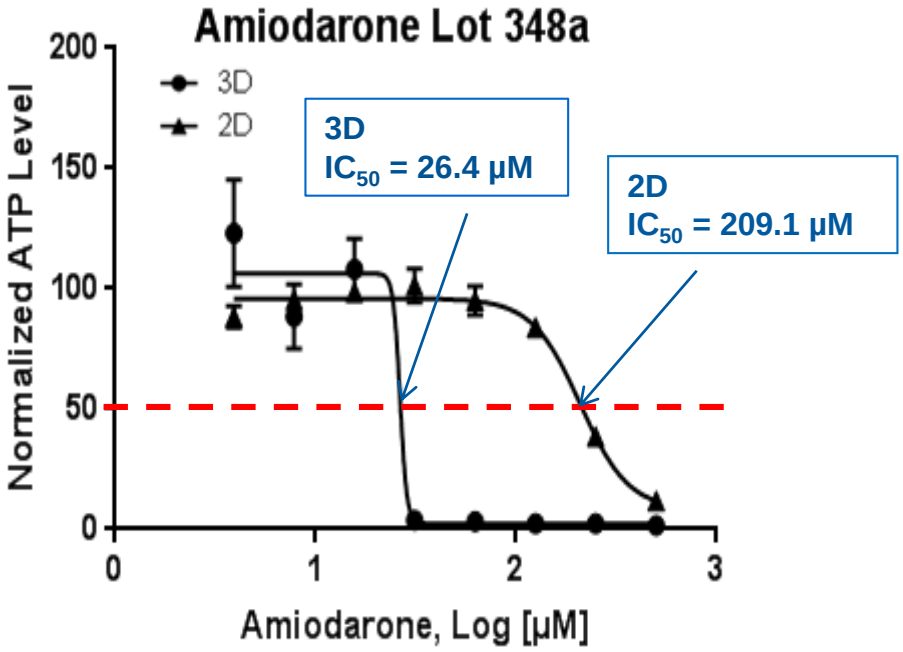
Example DILI Compound Dose Response Curve



Conc. (µM) 3.9 → 500.0



Spheroids show increased sensitivity (lower IC_{50} values) to DILI compound treatment compared to 2D cultures.

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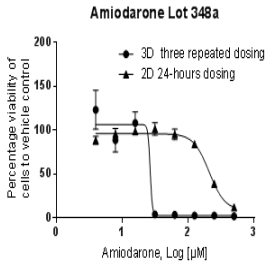
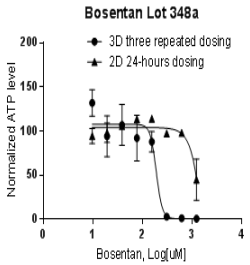
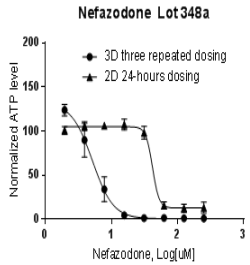
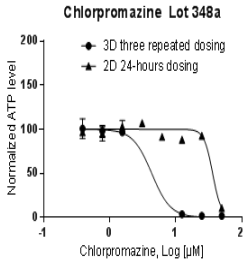
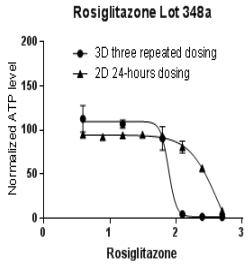
Dose Response Curves Show 3D Spheroids are More Sensitive to DILI Compound Treatment than 2D PHH Culture

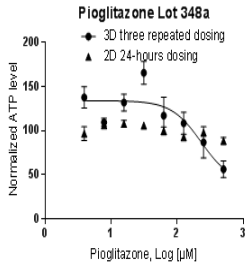


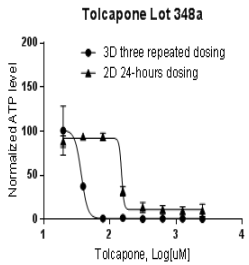


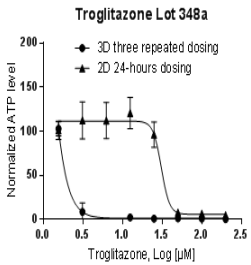


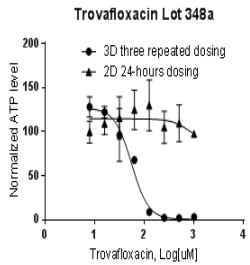


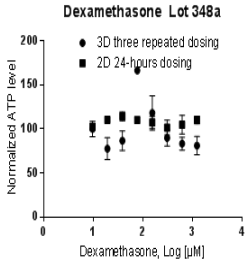


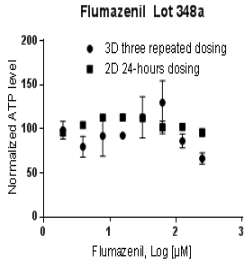












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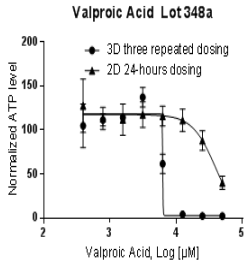

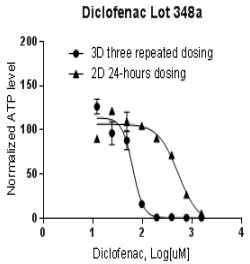

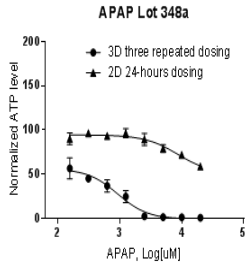

- 3 PHH lots tested in 3D vs. 2D culture.
- 3D spheroids showed increased sensitivity to DILI compound treatment.

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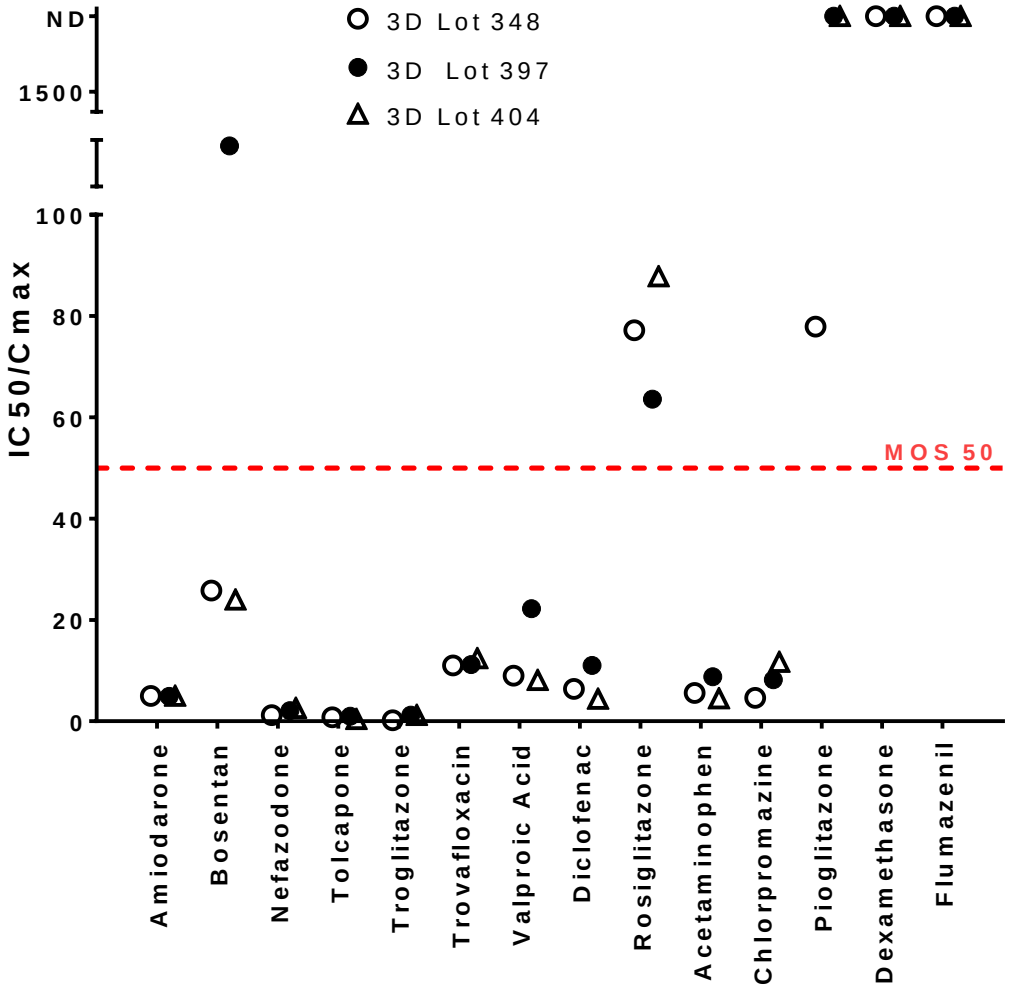
IC_{50}/C_{max} (MOS) of Liver Spheroids from 3 PHH Lots



- Comparable MOS values between spheroids from different PHH lots
- Differential responses to structurally related compounds Troglitazone, Rosiglitazone, and Pioglitazone

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Initial Testing Shows 3D PHH Are 3X More Sensitive vs. 2D Monolayer (MOS 25)

Compound	Clinical C_{max} (µM)	Margin of Safety (IC50/Cmax)	
		2D	3D
Amiodarone	5.3	27.7	5.0
Bosentan	7.43	67.6	39.0
Nefazodone	4.26	9.7	2.0
Tolcapone	47.58	2.8	0.6
Troglitazone	6.39	4.4	0.8
Trovafloxacin	5.02	199.2	11.5
Valproic Acid	693.43	39.0	13.1
Diclofenac	10.13	42.1	7.1
Rosiglitazone	1.04	319.0	88.5
Acetaminophen	165.38	90.7	5.1
Chlorpromazine	0.94	36.3	8.2
Pioglitazone	2.95	169.7	84.9
Dexamethasone	0.22	5580.4	5580.4
Flumazenil	1.12	1115.0	223.0

- Margin of safety (MOS) = IC_{50}/C_{max}
  - Predict *in vivo* liver toxicity
  - MOS 25 as a threshold
- For 12 DILI compounds
  - 3D predicted 9 toxic compounds (75%)
  - 2D predicted only 3 (25%)
- Data calculated from 3 PHH lots in either 2D or 3D cultures

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Selection of 100 Compounds for Hepatotoxicity Tests with PHH 2D Culture or 3D Spheroids

DILI Severity Category	No. of Compounds	
1. Severe clinical DILI	17	**DILI**
2. High clinical DILI concern	22	
3. Low clinical DILI concern	24	
4. Enzyme Elevations in Clinic	17	**Control**
5. No DILI	20	
Total	100	

1. Proctor et al, Arch Toxicol. 2017; 91(8): 2849–2863.

2. Garside et al Toxicology In Vitro 2014; 28(2): 171-181

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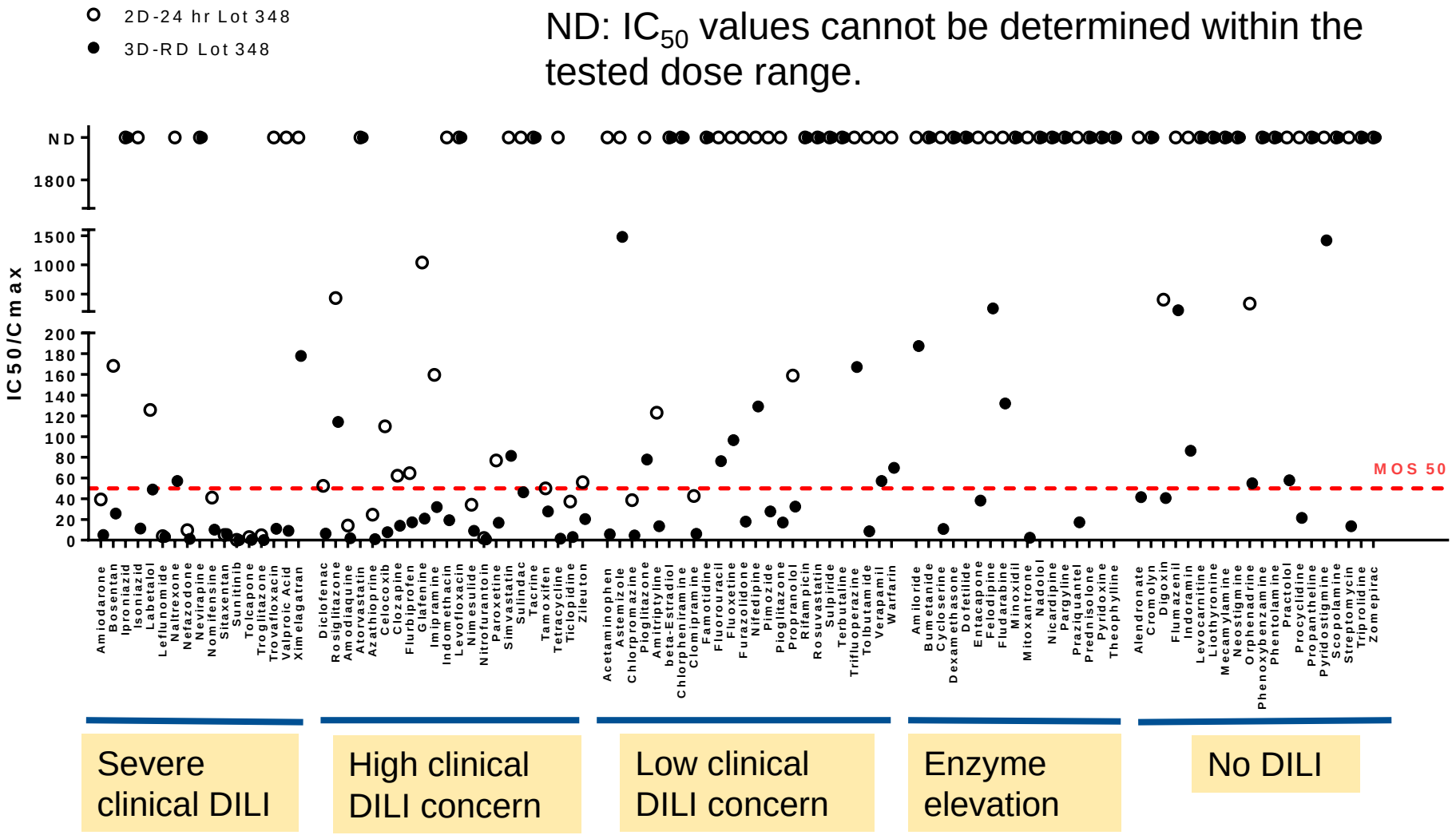
3D PHH Liver Spheroids Show Superior Sensitivity to DILI Compound Treatment



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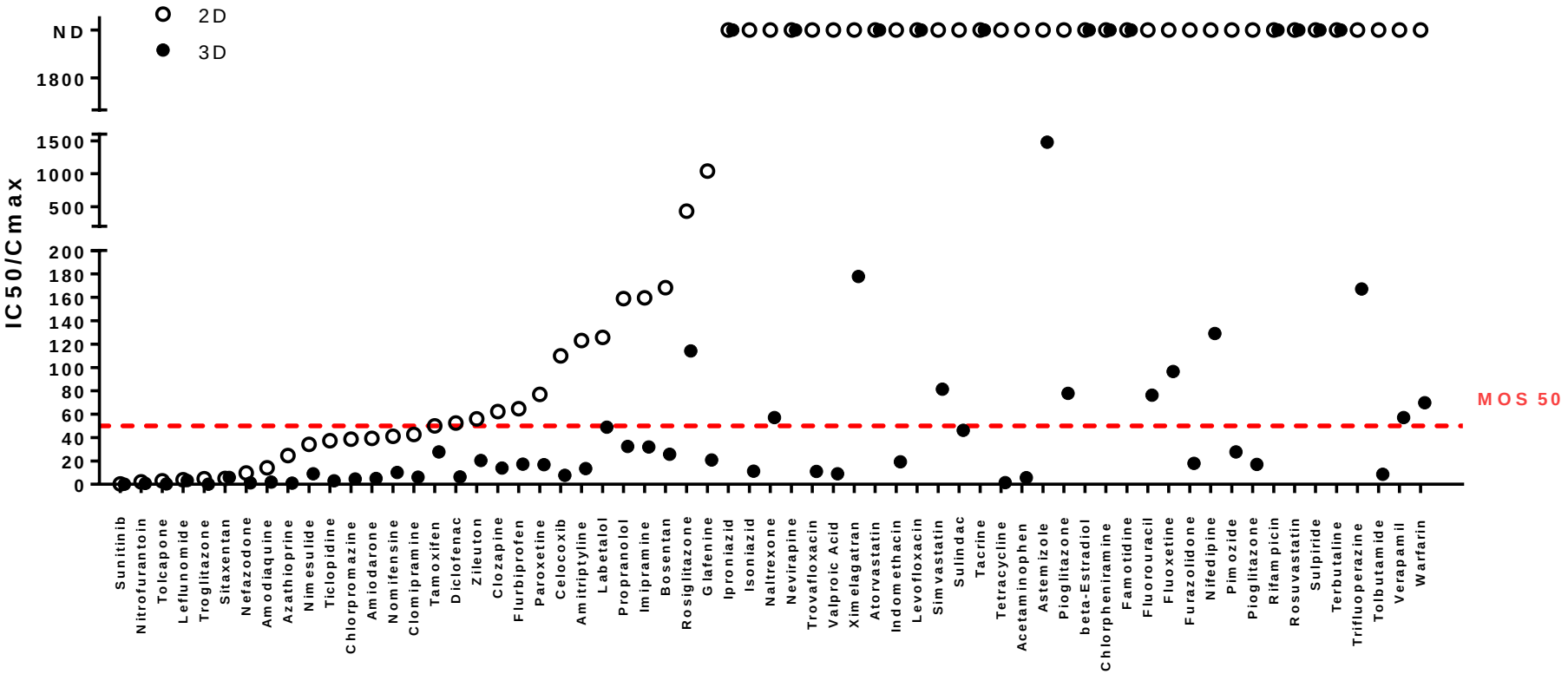
3D PHH Liver Spheroids Show Superior Sensitivity to DILI Compound Treatment (continued)



DILI compounds = Categories 1, 2, and 3

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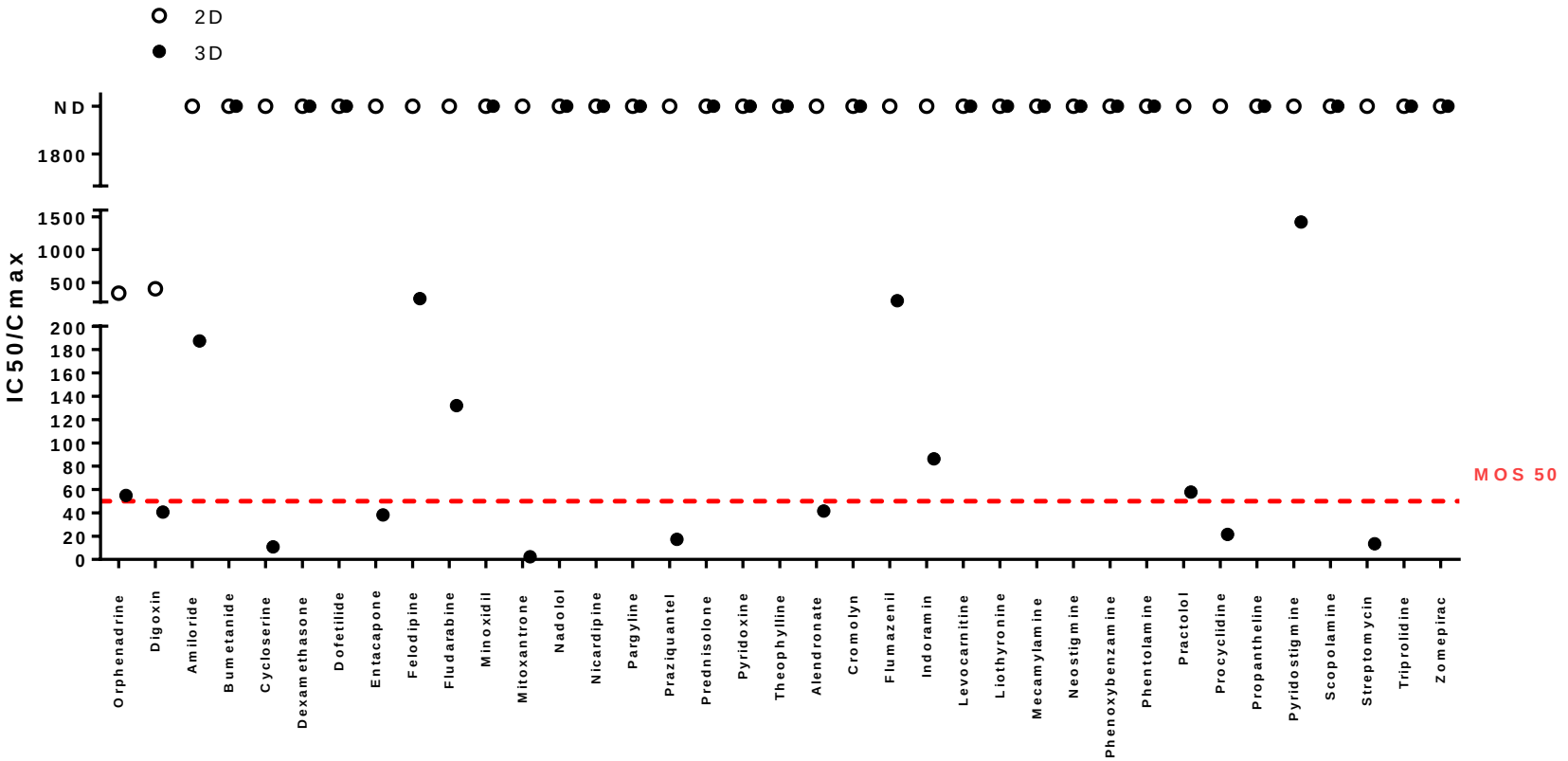
3D PHH Liver Spheroids Show Superior Sensitivity to DILI Compound Treatment (continued)



Control compounds = Categories 4 and 5

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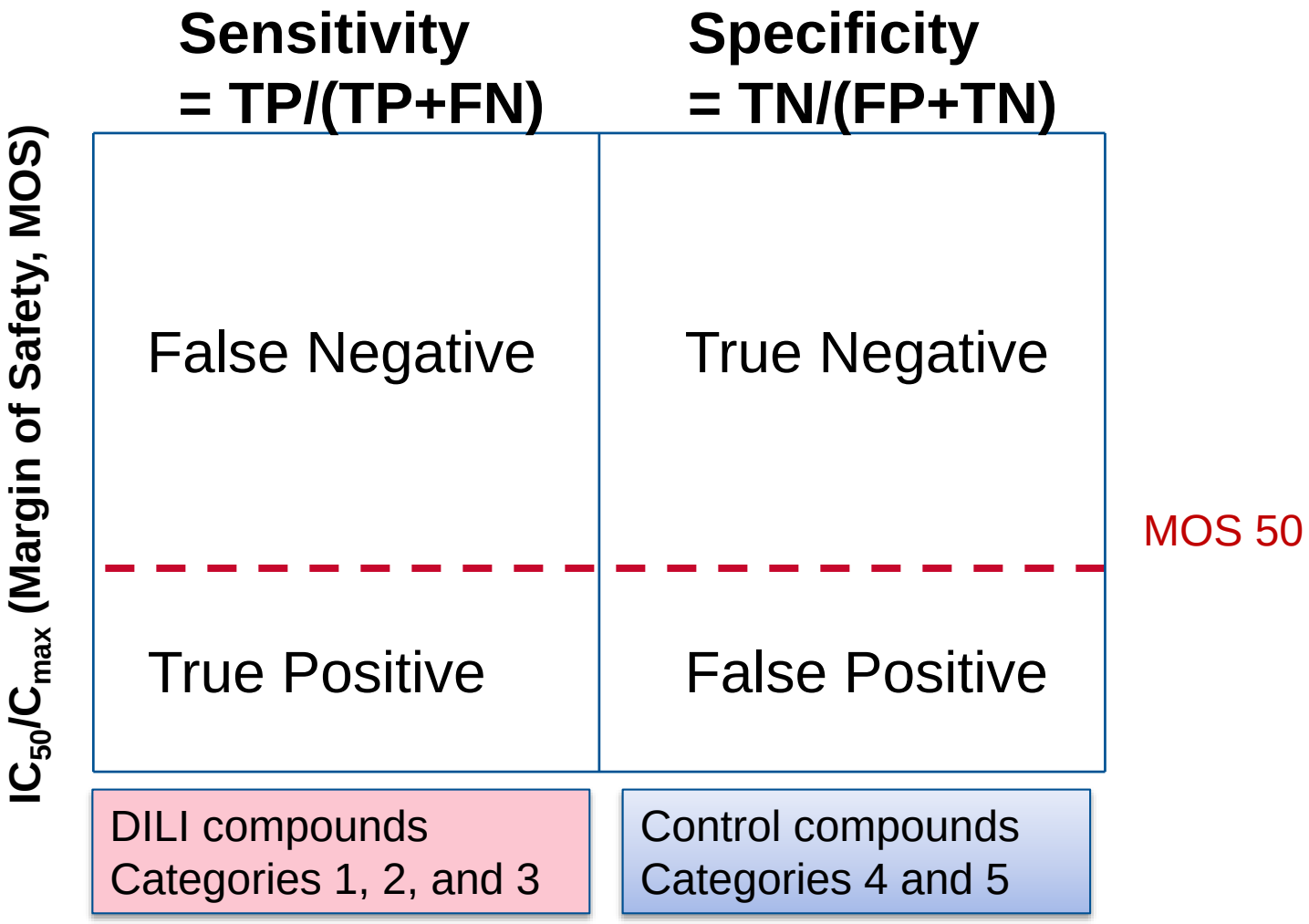
PHH 3D vs. 2D Hepatotoxicity Assay Performance



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2D and 3D Hepatotoxicity Assay Performance

2D Hepatotoxicity Assay; IC50/Cmax (MOS) 50

DILI severity category	# of Compound	TP	TN	FP	FN
1. Severe clinical DILI	17	7	0	0	10
2. High clinical DILI concern	22	6	0	0	16
3. Low clinical DILI concern	24	2	0	0	22
4. Enzyme Elevations in Clinic	17	0	17	0	0
5. No DILI	20	0	20	0	0
Total	100	15	37	0	48

3D Hepatotoxicity Assay; IC50/Cmax (MOS) 50

DILI severity category	# of Compound	TP	TN	FP	FN
1. Severe clinical DILI	17	13	0	0	4
2. High clinical DILI concern	22	17	0	0	5
3. Low clinical DILI concern	24	9	0	0	15
4. Enzyme Elevations in Clinic	17	0	14	3	0
5. No DILI	20	0	17	3	0
Total	100	39	31	6	24

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3D PHH Spheroids Hepatotoxicity Assay Shows 2-3X Improvement in Sensitivity vs. 2D

MOS Threshold	10		25		50	
Assay	**3D**	**2D**	**3D**	**2D**	**3D**	**2D**
Sensitivity	32%	11%	51%	14%	62%	24%
Specificity	95%	100%	86%	100%	84%	100%

IC_{50} values measured from 2D and 3D hepatotoxicity assays are corrected with clinical C_{max} (not shown) for 100 tested drugs that belong to five DILI severity categories. To compare the performance for 2D and 3D liver spheroids, assay sensitivity and specificity are calculated using MOS thresholds 10X, 25X, and 50Xx, respectively.

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Alternative Hepatic Cell Model: Corning® HepatoCells

Issues with PHH

- ❑ Limited supply
- ❑ Large lot-to-lot variability
- ❑ Need to qualify every lot (costly and time consuming)

Industry Needs

- ❑ Renewable alternative hepatocyte model
- ❑ Primary hepatocyte-like morphology and phenotype
- ❑ Consistent performance, eliminating the need to pre-qualify lot

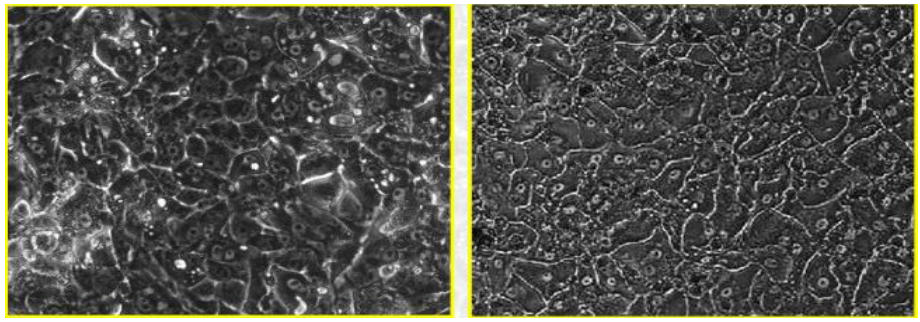
Corning Solution

HepatoCells - a renewable hepatocyte model

Key Features of Corning HepatoCells

- Derived from primary human hepatocytes
- Maintain mature hepatocyte-like morphology (prominent nuclei, bile canalicular structures)
- Homogeneous population of cells
- Wild type genotype for important cytochrome P450s (CYP2D6, CYP2C9, CYP2C19)
- Low lot-lot variability
- Large lot sizes

Corning HepatoCells **PHH**



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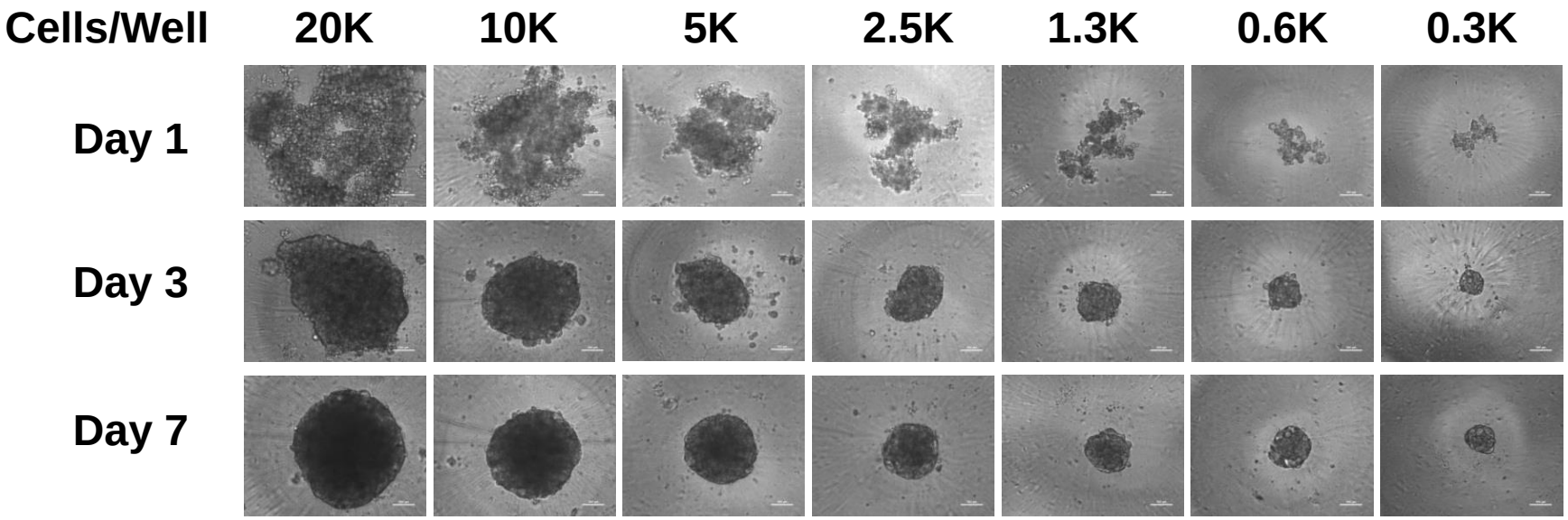
Corning® HepatoCells Can be Grown as 3D Spheroids



Bar = 100 µm

- Cells seeded on 384-well Corning spheroid microplate
- Cultured up to 7 days (pictures taken day 1, 3, 4, 6, and 7)
- No media changes during the first 2 days; then from days 3 to 7, half media change every other day

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Preliminary Hepatotoxicity Results for 3D Corning® HepatoCells vs. 3D PHH

Compound list	DILI Severity Category	PHH IC_{50} µM (Average of 3 PHH lots)	Corning HepatoCells
		3D-24 hrs.	3D-24 hrs.
Amiodarone	1. Severe clinical DILI	229	599.2
Bosentan	1. Severe clinical DILI	886	1222
Nefazodone	1. Severe clinical DILI	27	66
Tolcapone	1. Severe clinical DILI	98	205.8
Troglitazone	1. Severe clinical DILI	18	53.7
Trovafloxacin	1. Severe clinical DILI	>1000	na
Valproic Acid	1. Severe clinical DILI	25458	na
Diclofenac	2. High clinical DILI concern	397	1651
Rosiglitazone	2. High clinical DILI concern	244	391.7
Acetaminophen	3. Low clinical DILI concern	13864	17131
Chlorpromazine	3. Low clinical DILI concern	29	23.8
Pioglitazone	3. Low clinical DILI concern	>500	ND
Dexamethasone	4. Enzyme elevations in clinic	>1250	na
Flumazenil	5. No DILI	>1250	ND

3D Corning HepatoCells results are mostly within ~2-3X of 3D PHH

(na = not tested; ND = not determined)

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PHH 3D Spheroid Summary and Next Steps

- We have developed a 3D liver spheroid culture protocol
- Screened >30 PHH lots for 3D spheroid culture
- Established 3D hepatotoxicity assay
  - 3D spheroids show superior sensitivity
- Preliminary hepatotoxicity data with Corning® HepatoCells shows good correlation with 3D PHH

Next Steps

- Evaluate co-culture liver spheroids (PHH and NPCs)
- Explore other applications with 3D liver spheroids

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Agenda

- Background on 3D liver models
- Spheroid culture with primary human hepatocytes (PHHs)
- PHH 3D spheroids for liver toxicity screening
- **Overview of Corning® Gentest℠ Contract Research Services**
- Q&A

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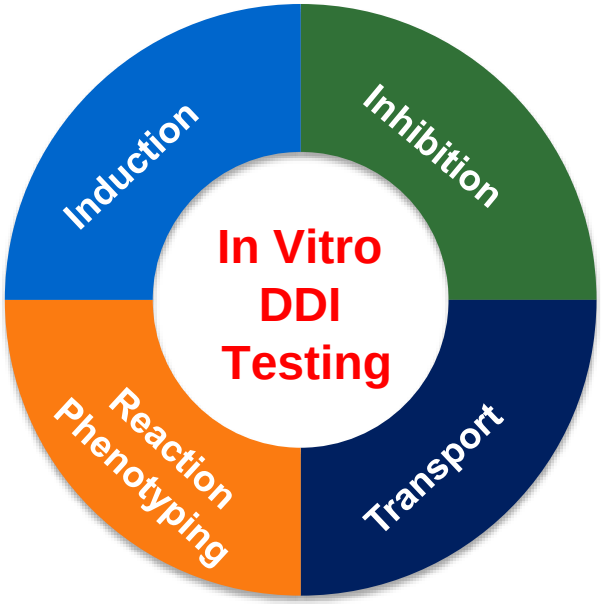
Corning® Gentest℠ Contract Research Services

Corning® Gentest℠ *In Vitro* ADME Services Overview



Underpinned by a foundation of Analytical Chemistry and Quality function support

Enzyme Induction
In vitro models in human hepatocytes that enable prediction enzyme induction *in vivo*. Multiple endpoints including EC_{50} and E_{max}. Rapid turnaround and conventional methods aligned with regulatory guidance.

Enzyme Inhibition
Reversible and time-dependent enzyme inhibition studies. Major and minor CYPs, UGTs, and other enzymes. IC_{50} values, K_I, k_{inact}; aligned with regulatory guidance. Microsomes & hepatocytes. Fully validated LC/MS/MS based methods.

Transporter
SLC Corning® TransportoCells™, P-gp/MRP/BCRP/BSEP membranes and vesicles, MDR1 LLC-PK1, Caco-2 using state-of-the-art Corning consumables; aligned with regulatory guidance.

Reaction Phenotyping
Enzyme identification using Corning Supersomes™ enzymes, chemicals, antibodies, HLM

Metabolic Stability, CL_{int} in Human and Animal Microsomes and Hepatocytes
Assays performed in human and animal microsomes and hepatocytes to predict the intrinsic clearance or metabolic half life of a test article

CYP Induction and Inhibition
CYP induction in cryopreserved human and animal hepatocytes
CYP inhibition in microsomes

Permeability and Transport
Permeability testing and P-gp transport and inhibition screening across Caco-2 , MDR1-LLC-PK1 and MDCK monolayers

Plasma Protein Binding
High throughput, cost-effective equilibrium dialysis method

Custom Designed Studies
Unusual drug metabolizing enzymes, custom expression, hepatocytes studies, assay transfers

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In Vitro ADME Services for Drug Development

Enzyme Induction

In vitro models in human hepatocytes that enable prediction enzyme induction *in vivo*. Multiple endpoints including EC_{50} and $E_{max,}$ RIS and R_3 analysis. Rapid turnaround and conventional methods aligned with regulatory guidance.

Enzyme Inhibition

Reversible and time-dependent enzyme inhibition studies. Major and minor CYPs, UGTs, and other enzymes. IC_{50} values, K_I, k_{inact}; aligned with regulatory guidance. Microsomes & hepatocytes. Fully validated LC/MS/MS based methods.

Transporter

SLC Corning® TransportoCells™, P-gp/MRP/BCRP/BSEP membranes and vesicles, MDR1 LLC-PK1, Caco-2 using state-of-the-art Corning consumables; aligned with regulatory guidance.

Reaction Phenotyping

Enzyme identification using Corning Supersomes™ enzymes, chemicals, antibodies, HLM.

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In Vitro ADME Services for Drug Development

Metabolic Stability, CL_{int} in Human and Animal Microsomes and Hepatocytes

Assays performed in human and animal microsomes and hepatocytes to predict the intrinsic clearance or metabolic half life of a test article.

CYP Induction and Inhibition

- CYP induction in cryopreserved human and animal hepatocytes
- CYP inhibition in microsomes

Permeability and Transport

Permeability testing and P-gp transport and inhibition screening across Caco-2, MDR1-LLC-PK1, and MDCK monolayers

Plasma Protein Binding /Blood to Plasma Partitioning

PPB (RAD equilibrium dialysis method) and BPP across human and animal species

Custom Designed Studies

Unusual drug metabolizing enzymes, custom expression, hepatocytes studies, assay transfers

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Trusted Corning® Gentest℠ Contract Research Services Team

- Contract Research Services team committed to:
  - State-of-the-art science
    - Integrated new product and services development
    - Multiple publications from our scientists
    - Corning designed services - using Corning reagents and consumables
  - Regulatory requirements and guidance
    - GLP services since 1996
    - 100% acceptance of data by regulatory agencies
    - Long track record of successful customer audits
  - Outstanding customer service and support
    - Personalized, direct Sponsor-to-Study Director communication
    - Fully committed and experienced leadership team
- Located in Woburn, Massachusetts

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