Table S1. Cellular composition of the liver

Cell type	***Function***
Hepatocytes	Polygon-shaped polarized epithelial cells with abundant microvilli on the apical side. Most cells contain one nucleus. Most of the nuclei are diploid. Hepatocytes are responsible for the metabolic, endocrine, and secretory functions of the liver. The maintenance of hepatocyte metabolism requires an oxygenation of ~1 nmol/s/10^6 cells (Nahmias et al. 2007)
Sinusoidal endothelial cells	Specialized endothelial cells. They do not produce basal lamina and form a porous *fenestrated* barrier. The *fenestrae* diameter is ~0.1 µm-0.3 µm. An exchange of soluble factors between the hepatocytes and the blood occurs through the *fenestrae*.
Kupffer cells	Specialized hepatic macrophages placed on the luminal surface of the sinusoids. They have high endocytic and phagocytic capacity.
Pit cells	Natural killer cells, e.g. against tumor cells and viral infections.
Stellate cells	The myofibroblast stellate cells are in the space of Dissé lying between the hepatocytes and the sinusoids epithelium. They synthesize the ECM, are involved in matrix degradation, contract the sinusoid, regulate the sinusoidal diameter and tone, and store retinoids (e.g. vitamin A). Function as resident mesenchymal stem cells in the liver.
Portal fibroblasts	Fibroblasts surrounding the biliary tree.

Table S2. Liver ECM composition

ECM proteins	***Liver-specific localization of ECM proteins***
Collagen type I	Perisinusoidal space, at any point between the portal area and the central vein.
Collagen type I, III, V, VI	Interstitium of the portal area.
Tenascin	Interstitium of the portal area.
Fibronectin	Abundant in the space of Disse. Interstitium of the portal area.
Basement membrane (laminin, entactin, perlecan, collagen IV, heparin sulfate proteoglycan)	Portal area (coating the *bile ductule*, the *portal venule*, and the *hepatic arteriole*)
Elastin	Abundant in portal tracts. Not present in the sinusoidal walls.

Adapted from (Martinez-Hernandez and Amenta 1993; Hunt et al. 2009).

Table S3. Effects of β-catenin signaling on the expression of drug metabolism-associated nuclear receptors in murine liver cells: tumors with activated β-catenin (*Ctnnb1**), mice with *Alb-Cre*-driven conditional hepatocyte-specific knockout of *Ctnnb1* (*Ctnnb1*^{ko}), and Wnt3a-treated hepatocyte cultures *in vitro* (*in vitro* +Wnt). Arrows indicate up- or down-regulation; numbers in brackets indicate relevant literature.

Gene product	***Ctnnb1****	***Ctnnb1***^{ko}	***in vitro* +Wnt**
AhR mRNA	↑ (Stahl et al. 2005; Braeuning et al. 2007a)	↓ (Braeuning, 2009; Braeuning et al. 2011)	↑ (Hailfinger et al. 2006; Braeuning et al. 2011)
AhR protein		↔ (Braeuning et al. 2011)	
CAR mRNA	↑ (Giera et al. 2010)	↓ (Braeuning et al. 2009; Giera et al. 2010; Braeuning et al. 2011)	↔ (Braeuning et al. 2011)
CAR protein		↓ (Braeuning et al. 2011)	
PXR mRNA		↓ (Braeuning 2009)	↑ (Braeuning et al. 2011)

Table S4. Effects of β-catenin signaling on the expression of drug metabolism-associated genes from phase I in murine liver cells: tumors with activated β-catenin (*Ctnnb1**), mice with *Alb-Cre*-driven conditional hepatocyte-specific knockout of *Ctnnb1* ($Ctnnb1^{ko}$), transgenic mouse hepatocytes with expression of activated human β-Catenin^{S33Y} ($CTNNB1^{S33Y}$), and Wnt3a-treated hepatocyte cultures *in vitro* (*in vitro* +Wnt). Arrows indicate up- or down-regulation; numbers in brackets indicate relevant literature.

Gene product	*Ctnnb1**	$Ctnnb1^{ko}$	$CTNNB1^{S33Y}$	*in vitro* +Wnt
Cyp1a1 mRNA	↑ (Loeppen et al. 2005)	↔ / ↑ (Sekine et al. 2006; Tan et al. 2006; Braeuning et al. 2009, 2011)		↑ (Hailfinger et al. 2006; Braeuning et al. 2009, 2011)
Cyp1a2 mRNA	↑ (Braeuning et al. 2007a)	↓ (Sekine et al. 2006; Tan et al. 2006; Braeuning et al. 2009, 2011)		↑ (Braeuning et al. 2011)
Cyp1a protein	↑ (Loeppen et al. 2005; Schreiber et al. 2011)	↓ (Sekine et al. 2006; Tan et al. 2006; Braeuning et al. 2009, 2010, 2011)	↑ (Schreiber et al. 2011)	
Cyp2a4/5 mRNA	↑ (Braeuning et al. 2007a)	↓ (Tan et al. 2006)		
Cyp2b9 mRNA		↑ (Tan et al. 2006)		
Cyp2b10 mRNA	↑ (Loeppen et al. 2005; Stahl et al. 2005)	↑ (Tan et al. 2006; Braeuning et al. 2009)		↑ (Hailfinger et al. 2006; Braeuning et al. 2011)
Cyp2b20 mRNA	↑ (Stahl et al. 2005)			
Cyp2b protein	↑ (Loeppen et al. 2005)			
Cyp2c29 mRNA		↓ (Sekine et al. 2006)		
Cyp2c38 mRNA	↑ (Braeuning et al. 2007a)			
Cyp2c55 mRNA	↑ (Stahl et al. 2005; Braeuning et al. 2007a)			
Cyp2c mRNA		↓ (Braeuning et al. 2009, 2010, 2011)		↑ (Braeuning et al. 2011)
Cyp2c protein	↑ (Loeppen et al. 2005; Hailfinger et al. 2006)	↓ (Braeuning et al. 2009 and 2011)	↑ (Braeuning et al. 2011)	
Cyp2d9 mRNA		↓ (Tan et al. 2006)		
Cyp2e1 mRNA	↑ (Loeppen et al.	↓ (Sekine et al. 2006;		↑ (Hailfinger et al.

	2005)	Tan et al. 2006; Braeuning et al. 2011)		2006; Braeuning et al. 2011)
Cyp2e1 protein	↑ (Loeppen et al. 2005; Hailfinger et al. 2006; Schreiber et al. 2011)	↓ (Sekine, 2006; Tan et al. 2006; Schreiber et al. 2011; Braeuning et al. 2010, 2011)	↑ (Schreiber et al. 2011; Braeuning et al. 2011)	
Cyp2f2 mRNA	↓ (Stahl et al. 2005; Braeuning et al. 2007a)	↑ (Braeuning et al. 2009)		
Cyp3a11 mRNA		↔ (Sekine et al. 2006)		
Cyp3a mRNA		↑ (Braeuning et al. 2009)		↑ (Braeuning et al. 2011)
Cyp3a protein	↑ (Loeppen et al. 2005)	↑ (Braeuning et al. 2009)		
Cyp4a14 mRNA		↓ (Braeuning et al. 2009)		

Table S5. Effects of β-catenin signaling on the expression of drug metabolism-associated genes from phase II in murine liver cells: tumors with activated β-catenin (*Ctnnb1**), mice with *Alb-Cre*-driven conditional hepatocyte-specific knockout of *Ctnnb1* ($Ctnnb1^{ko}$), transgenic mouse hepatocytes with expression of activated human β-Catenin^{S33Y} ($CTNNB1^{S33Y}$), and Wnt3a-treated hepatocyte cultures *in vitro* (*in vitro* +Wnt). Arrows indicate up- or down-regulation; numbers in brackets indicate relevant literature.

Gene product	***Ctnnb1****	***Ctnnb1*^{ko}**	***CTNNB1*^{S33Y}**	***in vitro* +Wnt**
GSTa4 mRNA	↑ (Stahl et al. 2005; Braeuning et al. 2012)			
GSTa4 protein	↑ (Strathmann et al. 2007)	↓ (Braeuning, 2012)		
GSTa mRNA		↓ (Braeuning et al. 2009)		
GSTk1 mRNA	↓ (Stahl et al. 2005; Braeuning, 2012)			
GSTm1 mRNA	↑ (Stahl et al, 2005; Braeuning et al, 2007a; Braeuning, 2012)			
GSTm1 protein	↑ (Strathmann et al. 2007)	↓ (Braeuning, 2012)		
GSTm2 mRNA	↑ (Stahl et al. 2005; Braeuning et al. 2007; Giera et al. 2010)	↓ (Braeuning et al. 2009; Giera et al. 2010)		↑ (Giera et al. 2010)
GSTm2 protein	↑ (Strathmann, 2007)			
GSTm3 mRNA	↑ (Stahl et al. 2005; Braeuning et al. 2007; Giera et al. 2010)	↓ (Braeuning et al. 2009; Giera et al. 2010)		↑ (Giera et al. 2010)
GSTm4 mRNA	↑ (Stahl et al. 2005; Braeuning, 2012)			
GSTm6 mRNA	↑ (Stahl et al. 2005; Braeuning et al. 2007; Giera et al. 2010)	↓ (Braeuning et al. 2009; Giera et al. 2010)		↑ (Giera et al. 2010)
GSTm6 protein	↑ (Strathmann et al. 2007)			
GSTm protein	↑ (Strathmann et al. 2007; Hailfinger et al. 2006; Giera et al. 2010; Braeuning, 2012)	↓ (Braeuning et al. 2009; Giera et al. 2010)	↑ (Giera et al. 2010)	↑ (Giera et al. 2010)
GSTp1 mRNA	↑ (Strathmann et al.			

	2007)			
GSTt2 mRNA	↑ (Stahl et al. 2005; Braeuning, 2012)			
GSTt3 mRNA	↑ (Stahl et al. 2005; Braeuning, 2012)			
Ugt1a6 mRNA		↓ (Braeuning et al. 2009)		

Table S6. Composition and enzyme activities [U/mg lyophilisate] of the collagenase P batches from Roche (Mannheim, Germany) (A. Nüssler et al, *unpublished data*).

Information on Lot	**Collagenase Lot number**				
	11914427	**10957731**	**11779821**	**1259322**	**13439520**
Date of expiration	03.2008	07.2011	06.2012	09.2013	03.2014
Collagenase [U/mg]	2.85	2.52	1.90	1.80	1.70
Clostripain [U/mg]	7.10	32.58	33.100	21.442	32.496
Protease [U/mg]	158.0	100.6	51.7	48.8	40.8
Trypsin [U/mg]	1.370	2.010	4.370	4.311	2.241

Table S7. NTP 2006 TCDD Bioassay Histology – MOA and Key Event Possibility for Primary Liver Cell Research.

Histological Endpoint	**Cancer Bioassay Observations**	**Primary Liver Cell Research Areas and Comments**
Hypertrophy	• Statistically significant by 14 weeks at 22 ng/kg/day	Due largely to core-battery enzyme induction with expansion of smooth endoplasmic reticulum. In-vitro uptake studies for deriving "*in-vitro-to-in-vivo*" extrapolation could provide estimates of human intake dosages of dioxin to induce enzyme induction.
Multinucleated Hepatocytes	• Statistically elevated by 31 weeks at 46 ng/kg/day • At two years the 10 ng/kg/day and higher dosages demonstrate statistically significant increases. • Multinucleated cells contained 2 and, frequently, more than 10 nucleii.	• Is this an adaptive response, analogous to polyploidy, that renders hepatocytes senescent and prone to apoptosis rather than being available for replication and differentiation in to an altered hepatic cell and eventual focus? • Is this evidence of AhR-induced disregulation of cytokinesis? • What is the origin of these cells, e.g., old polydiploid hepatocytes, hepatocytes from Zones 1 and 2 reflecting newer cells, or maybe even stem cells? Are there cell markers that could identify where these hepatocytes are originating? • Dose-response evaluation of this finding, when coupled to "*in-vitro-to-in-vivo*" extrapolation could be used to improve human health risk assessment for TCDD.
Pigmentation	• By 31 weeks, and at 10 ng/kg/day, this observation was statistically elevated. By 2-years the incidence is still statistically significant at 10 ng/kg/day but not at the lower 3 ng/kg/day dosage.	• This suggests an iron-overload, Kupffer cell response, that may reflect AhR-associated inhibition of porphyrin metabolism and the accumulation of porphyrins with enhanced iron accumulation in hepatocytes. • Since hematomacrosis is a risk factor in hepatocellular carcinoma this endpoint could be a contributing key event to the overall tumor promotion MOA for sustained AhR activation. Or, it could simply be a by-stander event whereby kupffer cells accumulate iron as they

		phagocytize hepatocytes damged by porphyrin-related iron accumulation.
Mixed Cell Focus	• Statistically significant by 53 weeks and at 46 ng/kg/day.	• Can liver cell culture systems be extended sufficiently in time so that naturally occurring mutations could be promoted with sustained AhR activation?
Diffuse Steatosis	• Statistically elevated at 100 ng/kg/day by 31 weeks and by 2-years diffuse fat accumulation occurred as low as 10 ng/k/day	• Non-alcoholic fatty liver disease is a risk factor for liver cancer. • Increases in Scd1 in rat hepatocytes could be further studied as a mechanism for fatty acid accumulation (Angrish et al. 2011) for the purposes of dosimetry/risk assessment and for evaluating human versus rat sensitivity.
Bile Duct Fibrosis	• Begins to appear by 53 weeks at 46 and 100 ng/kg/day but the observations were not statistically significant. By 2-years, portal fibrosis is statistically elevated at both the 46 and 100 ng/kg/day dosages.	• The role of stem cells and stellate cells, coupled to changes in stellate cells linked to fibrosis, e.g., reduction in retinoid levels, or in how sustained AhR activation alters normal differentiation of these cell types, e.g., cell surface markers, could be evaluated in primary cultures.
Bile Duct Hyperplasia	• At 53 weeks this was statisitically elevated at 100 ng/kg/day. By 2-years, the response was elevated at the 22 ng/kg/day dosages and above.	• The bile duct fibrosis and hyperplasia endpoints could be evaluated together.
Oval cell hyperplasia	• Elevated by 2-years at dosages of 3, 22, 46 and 100 ng/kg/day but not at 10 ng/kg/day suggesting the 3 ng/kg/day finding is due to chance, e.g., only 2/54 animals. • Oval cell hyperplasia was not observed at 53 weeks or earlier.	• AhR activation on stem cell biology/differentiation would be invaluable for examining many of the histological observations classified under the term “hepatopathy”.

Table S8. Authors and their contributions to the review. Each author/institute was asked to write two to three pages on a selected topic. Some contributions were combined due to an overlap of information; therefore, this table lists the topics attributed to each author.

Author(s)	**Affiliation and contact email**	**Contribution**
N. J. Hewitt	SWS, Erzhausen, Germany. nickyhewittltd@yahoo.co.uk	Recent advances in methods of cryopreservation of hepatocytes. This author was the main editor of the review and co-author communication.
P. Godoy J. Hengstler	Leibniz Research Centre for Working Environment and Human Factors IFADO, D44139, Dortmund, Germany Godoy@ifado.de, Hengstler@ifado.de	Topics covering the dilemma of cultured hepatocytes: the switch from a resting to a proliferation primed state and a second section on cross talk between liver cells during hepatotoxicity with a focus on inflammation and the relevance of non-parenchymal cell types. Also contributed the section on toxicogenomics and in vitro liver toxicity prediction. Contribution to editing and collation of tables and figures, as well as co-author communication.
A. Widera, R. Stöber	Leibniz Research Centre for Working Environment and Human Factors IFADO, D44139, Dortmund, Germany	Provided standard operating procedures for the isolation and culture of mouse and rat hepatocytes.
A. Gibson, R. Eakins, C.E.P. Goldring, D. J. Naisbitt, C. Rowe, B.K. Park	Centre for Drug Safety Science, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK B.K.Park@liverpool.ac.uk	Perspectives to predict idiosyncratic drug-induced liver injury in vitro: (metabolism and immune-related) mechanisms of DILI and in vitro models and biomarkers.
B. Burkhardt, A.K. Nüssler	Eberhard Karls University Tübingen, BG Trauma Center, Siegfried Weller Institut, D72076 Tübingen, Germany Britta.Burkhardt@med.uni-tuebingen.de andreas.nuessler@googlemail.com	Optimized isolation of human hepatocytes: isolation, culture and transport, as well as their pitfalls and limitations. These authors also provided an SOP on the isolation of human hepatocytes.
C. Schelcher, W. E. Thasler	Ludwig Maximilians University of Munich, Department of Surgery, Liver Regeneration, Core facility - human in vitro models of the liver, Munich, Germany Wolfgang.Thasler@med.uni-muenchen.de	

G. Damm, M. Glanemann	Charité University Medicine Berlin, Department of General-, Visceral- and Transplantation Surgery, D13353 Berlin, Germany	
D. Häussinger	Clinic for Gastroenterology, Hepatology and Infectious Diseases, Heinrich-Heine-University, Düsseldorf, Germany. Moorenstrasse 5, D40225 Düsseldorf, Germany verena.keitel@med.uni-duesseldorf.de haeussin@uni-duesseldorf.de Johannes.Bode@med.uni-duesseldorf.de	The isolated perfused liver
V. Keitel		Bile acid receptors in liver
J. Bode, U. Albrecht		Communication of liver macrophages and hepatocytes
C.-S. Cho, Y.-J. Choi, B. Singh	Department of Agricultural Biotechnology and Research Institute for Agriculture and Life Sciences, Seoul National University, Seoul 151-921, Korea chocs@snu.ac.kr	Effect of 3D scaffolds on hepatocyte functions. Importance of the extracellular matrix and the effect of porosity, galactose ligand and glycosaminoglycan in the 3-D scaffold on hepatocellular behaviours.
B. Stieger, C. Guyot	Department of Clinical Pharmacology and Toxicology, University Hospital, 8091 Zurich, Switzerland bstieger@kpt.uzh.ch	Transporter polarity of hepatocytes, hepatocyte in vitro systems (sandwich and organoid cultures) in basic research.
J. Mwinyi, G.A. Kullak-Ublick	Department of Clinical Pharmacology and Toxicology, University Hospital, 8091 Zurich, Switzerland bstieger@kpt.uzh.ch	Transcriptional and microRNA dependent regulation of genes involved in hepatic drug and bile acid metabolism and transport
G. Camussi, V. Fonsato	Department of Medical Sciences, University of Torino, 10126 Turin, Italy giovanni.camussi@unito.it	Isolation and characterization of stem cell populations from human liver
C. Tetta	Fresenius Medical Care, Bad Homburg, Germany	
K. Sá Ferreira,	GRK 1104 From Cells to Organs, Molecular Mechanisms of Organogenesis, Faculty of Biology, University of Freiburg, Freiburg, Germany	In vitro hepatocyte systems to study apoptosis in the liver.
K. Sá Ferreira, C. Borner	Institute of Molecular Medicine and Cell Research, University of Freiburg, Freiburg, Germany christoph.borner@uniklinik-freiburg.de	
A. Lutz, K. Schmich, I. Merfort	Department of Pharmaceutical Biology and Biotechnology, University of Freiburg, Freiburg, Germany	
P. Olinga	University of Groningen, Department of Pharmacy, Division of Pharmaceutical Technology and Biopharmacy, 9713 AV Groningen, The Netherlands P.olinga@rug.nl	Precision cut liver slices.

A. Ramachandran, H. Jaeschke	Department of Pharmacology, Toxicology & Therapeutics, University of Kansas Medical Center. Kansas City, KS 66160, USA hjaeschke@kumc.edu	Mechanisms of liver injury: intracellular signaling networks controlling drug-induced hepatocyte death and their modulation by culture conditions.
V. Rogiers, J. Fraczek, J. Bolleyn, M. Vinken, T. Vanhaecke	Department Of Toxicology, Centre For Pharmaceutical Research, Faculty Of Medicine And Pharmacy, Vrije Universiteit Brussel, B1090 Brussels, Belgium vrogiers@vub.ac.be	Epigenetic and posttranscriptional mechanisms as novel anti dedifferentiation strategies for primary hepatocytes in culture.
K. Ito	Research Institute of Pharmaceutical Sciences, Musashino University, 1-1-20 Shinmachi, Nishitokyo-shi, Tokyo 202-8585, Japan k-ito@musashino-u.ac.jp	Hepatocyte in vitro systems for prediction of specific toxic mechanisms. Drug-drug interactions: prediction of enzyme induction, inhibition, transporter and enzyme interplay, active uptake, and clearance
Y. Sugiyama	Sugiyama Laboratory, RIKEN Innovation Center, RIKEN, Yokohama Biopharmaceutical R&D Center, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan ychi.sugiyama@riken.jp	
J. Hrach	FORIM GMBH, D68165 Mannheim, Germany jenshrach@hotmail.com	Toxicogenomics and in vitro liver toxicity prediction.
P.G. Hewitt	Merck KGaA, D64283 Darmstadt, Germany Philip.Hewitt@merckgroup.com	
S. Messner, J.M. Kelm	InSphero AG, 8952 Schlieren, Switzerland simon.messner@insphero.com jens.kelm@insphero.com	The hepatosphere model.
J. Böttger, R. Gebhardt	Institute of Biochemistry, Faculty of Medicine, University of Leipzig, Leipzig, D04103, Leipzig, Germany jan.boettger@medizin.uni-leipzig.de Rolf.Gebhardt@medizin.uni-leipzig.de	Culture of hepatocytes and non-parenchymal cells on cell culture microchips: Microfluidic in vitro systems – advances and status for a physiologically relevant sinusoid-like liver cell culture device and techniques for isolating pericentral and periportal hepatocytes from rodent livers.
M. Matz-Soja, R. Gebhardt	Institute of Biochemistry, Faculty of Medicine, University of Leipzig, Leipzig, Germany. Johannisallee 30, 04103, Leipzig, Germany Madlen.Matz@medizin.uni-leipzig.de Rolf.Gebhardt@medizin.uni-leipzig.de	Current techniques for investigating zonal heterogeneity of hepatocytes
F. Pampaloni, N. Ansari, E. H.K. Stelzer	Buchmann Institute for Molecular Life Sciences (BMLS), Goethe University Frankfurt, Max-von-Laue-Str. 15, D60438 Frankfurt am Main, Germany francesco.pampaloni@physikalischebiologie.de Nariman.Ansari@physikalischebiologie.de	Technological advancements in Bio-engineering and the artificial liver: the importance of the third dimension.

A. Braeuning, M. Schwarz	Institute of Experimental and Clinical Pharmacology and Toxicology, Dept. of Toxicology, Wilhelmstr. 56, 72074 Tübingen, Germany albert.braeuning@uni-tuebingen.de michael.schwarz@uni-tuebingen.de	Wnt/β-catenin signaling, an undercover pathway relevant for expression of many important drug metabolizing enzymes in hepatocytes.
S. Hoehme, D. Drasdo	Interdisciplinary Center for Bioinformatics, University of Leipzig, D04107 Leipzig, Germany; INRIA (French National Institute for Research in Computer Science and Control), 8153 Le Chesnay Cedex, France dirk.drasdo@inria.fr	Progress in Systems Biology and image analysis
J.J. Xu	Merck & Co, USA jinghai_xu@merck.com	High throughput screening and prediction models for idiosyncratic human hepatotoxicants and the use of image analysis.
S. Dooley, C. Meyer	Department of Medicine II, Section Molecular Hepatology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany steven.dooley@medma.uni-heidelberg.de christoph.meyer@medma.uni-heidelberg.de	Technological advancements of co-cultures with hepatocytes and non-parenchymal cells and crosstalk with stellate cells.
L. Gustavsson	Center for Molecular Pathology, Department of Laboratory Medicine (Malmö), Lund University, Jan Waldenströms gata 59, SE-205 02 Malmö, Sweden Lena.Gustavsson@med.lu.se	Effect of cryopreservation on transporter function
D. Maltman [1], A. Hayward[2], S.A. Przyborski[1,2]	(1) Reinnervate Limited, NETPark Incubator, Thomas Wright Way, Sedgefield TS21 3FD, UK; (2) Biological and Biomedical Sciences, Durham University, Durham DH1 3LE, UK stefan.przyborski@durham.ac.uk	Practical applications and features of various methods for routine 3D cell culture of Liver Hepatocytes – natural and synthetic scaffolds.
Neil R. Cameron	Department of Chemistry, Durham University, Durham DH13LE, UK	
D. Hallifax, J .B. Houston	Centre for Applied Pharmacokinetic Research (CAPKR), School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Oxford Road, Manchester, M13 9PT, UK Brian.Houston@manchester.ac.uk	Prediction of clearance in the liver
E.L. LeCluyse, S. Bhattacharya, P. McMullen, C.G. Woods, K. M. Yarborough, L. Pluta, P. Lu, J. Dong, J. Pi, M.E. Andersen	The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina, USA ELeCluyse@thehamner.org sbhattacharya@thehamner.org mandersen@thehamner.org	PPARα pathway reconstruction in primary human hepatocytes
E.L. LeCluyse	The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina, USA ELeCluyse@thehamner.org	Studying the Role of the Aryl Hydrocarbon Receptor and Dioxin

R.A. Budinsky, J. C. Rowlands	Toxicology and Environmental Research & Consulting, The Dow Chemical Company, Midland, Michigan, USA. JCRowlands@dow.com RABudinsky@dow.com	Toxicity in Primary Liver Cells.
M. J. Gómez-Lechón[1,2] M. T. Donato[1,2,3]	(1) Unidad de Hepatología Experimental. IIS Hospital La Fe, Avda Campanar 21, 46009-Valencia, Spain. (2) CIBERehd, Fondo de Investigaciones Sanitarias, Barcelona, Spain (3) Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Universidad de Valencia, Spain. gomez_mjo@gva.es donato_mte@gva.es	Metabolically competent hepatic cells by gene engineering for drug hepatotoxicity testing. The need of metabolically competent hepatic cells for drug hepatotoxicity testing, Cells expressing CYPs and Phase II enzymes permanently/transiently for drug screening.
J. Luebke-Wheeler	jluebkewheeler@gmail.com	Stem and Precursor cells: Hepatocyte cells from stem cells
H.-G. Holzhütter	Universitätsmedizin Berlin (Charité), Institut für Biochemie Abteilung Mathematische Systembiochemie, Charitéplatz 1, D10117 Berlin, Germany hergo@charite.de	Metabolic modelling to guide and support experimentation on hepatocytes: use of mathematical models for the interpretation of experimental data and generation of testable hypothesis.
C. Hellerbrand	Department of Medicine I; University Hospital Regensburg, D93053 Regensburg, Germany Claus.Hellerbrand@klinik.uni-regensburg.de	Hepatocellular lipid accumulation in vitro - a model system to study pathophysiological mechanisms in non-alcoholic fatty liver disease.
U. Dahmen	Experimental Transplantation Surgery, Department of General, Visceral and Vascular Surgery, Friedrich-Schiller-University Jena, 07745 Jena, Germany Uta.Dahmen@med.uni-jena.de	Provided figure 1B
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S. Hammad	Department of Forensic Medicine and Veterinary Toxicology, Faculty of Veterinary Medicine, South Valley University, Qena, Egypt	Provided staining and confocal imaging of hepatospheres for Figure 18
G. Groothuis	Department of Pharmacy, Pharmacokinetics Toxicology and Targeting, University of Groningen A. Deusinglaan 1, 9713 AV Groningen, The Netherlands g.m.m.groothuis@rug.nl	Transporters