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Title Page

Transcriptomic hepatotoxicity signature of Chlorpromazine after short- and long-term exposure in primary Human sandwich cultures

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Running title Page

Chorpromazine toxicity on human hepatocytes sandwich cultures

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Abbreviations:

CPZ: Chlorpromazine

CYP450: Cytochrome P450

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DMSO: Dimethyl Sulfoxide

EGTA: ethylene glycol tetraacetic acid

FBS: Fetal Bovine Serum

IPA: Ingenuity Pathways Analysis

LPS: Lipopolysaccharide

PHH: Primary Human Hepatocytes

RT: Room Temperature

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Abstract

Drug induced liver injury is the most frequent reason for market-withdrawal of approved drugs and is difficult to predict in animal models. Here, we analyzed transcriptomic data derived from short- and long-term cultured primary human hepatocytes (PHH) exposed to the well-known human hepatotoxin Chlorpromazine (CPZ). Samples were collected from five PHH cultures after short-term (1 and 3 days) and long-term (14 days) repeat daily treatment with 0.1 or 0.2 µM CPZ, corresponding to Cmax. Two PHH cultures were additionally treated with 1 µM CPZ, and the three others with 0.02 µM CPZ. Differences in the total number of gene changes were seen between donors and over time of treatment. Specific transcriptomic hepatotoxicity signatures were created for CPZ and consisted of inflammation/hepatitis, cholestasis and liver proliferation in all 5 donors, as well as of fibrosis and steatosis that were observed in 4/5 donors. Necrosis was present in 3/5 donors, and an indicative signature of cirrhosis was observed after long-term 14-day repeat treatment also in 3/5 donors. The inter-donor variability in the inflammatory response to CPZ treatment was associated with variability in the strength of the response of the transcriptomic hepatotoxicity signatures, suggesting that features of inflammation could be related to the idiosyncratic hepatotoxic effects of CPZ in humans.

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Introduction

Drug induced liver injury is the most frequent reason cited for market-withdrawal of approved drugs (Lee, 2003). In order to detect hepatotoxic effects as early as possible in the process of drug development, *in vitro* liver models, such as primary hepatocytes, are increasingly being used (Tuschl et al., 2008; Gomez-Lechon et al., 2010). Primary hepatocytes have been shown to be the most relevant model for predicting *in vivo* xenobiotic metabolism (Blanchard et al., 2005; Foster et al., 2011), drug-drug interaction through a reversible or time-dependent inhibition of CYP450s (Zhao et al., 2005; Soars et al., 2007; Gomez-Lechon et al., 2010), interference with transporters (Soars et al., 2007; De Bruyn et al., 2011) and for drug toxicity (Richert et al., 2003; Liguori et al., 2005; Li, 2009).

Microarray analysis has great utility for the elucidation of underlying mechanisms of hepatotoxicity (Richert et al., 2008; Lauer et al., 2009). In addition, large inter-individual variability has been observed in both the basal expression (Rogue et al., 2012) and in response to treatment of many genes related to drug metabolism: Liguori at al., (2005) showed that after 24 hours treatment of trovofloxacin, gene changes varied across four different primary human hepatocytes (PHH) cultures. We (Abadie-Viollon et al., 2010) have shown an important inter-donor variability in the response of three PHH cultures to a 72-hour exposure to reference CYP450 inducers, and Goyak et al. (2008) reported that only a small set of genes was consistently deregulated across ten PHH cultures, whereas relatively large gene sets were regulated uniquely in a given PHH culture in response to 24 hours exposure to reference inducers.

To date mainly short-term exposure *in vitro* toxicity studies have been reported (Lauer et al., 2009; Gerets et al., 2012), but effects in humans during long-term medication needs also to be evaluated and thus long-term repeat-dose toxicity assessments in *in vitro* systems need to be performed. The expression of many liver-specific genes decrease during the initial stage of cultivation of PHHs (Boess et al., 2003; Richert et al., 2006), often associated with declines in metabolic capacities (Richert et al., 2002; Binda et al., 2003; Madan et al., 2003). They are however maintained at acceptable levels over time in long-term cultures using sandwich configuration and appropriate medium (Hewitt et al., 2007;

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Tuschl et al., 2009; Mueller et al., 2012). Prolonged exposure studies of PHH to drugs affecting major toxicity and metabolism pathways, such as ethanol during 14 days (van Pelt et al., 2003) or diclofenac during 23 days (Mueller et al., 2012) have indicated a good *in vivo / in vitro* correlation.

Chlorpromazine (CPZ) is the most widely used phenothiazine neuroleptic for the treatment of schizophrenic patients (Wojcikowski et al., 2010). CPZ clearance was demonstrated to be dependent on the patient's bodyweight and lifestyle which is a major problem for its therapeutic use (Pantuck et al., 1982; Chetty et al., 1994). An inter-donor CYP450 polymorphism is also recognized for CPZ pharmacokinetics, since it is extensively metabolized by CYP2D6 and CYP1A2 (Yeung et al., 1993; Yoshii et al., 2000). CPZ has been reported to be cytotoxic and several of its metabolites, generated by both rat and human metabolism, are known to be equally or more cytotoxic than CPZ itself (Abernathy et al., 1977; Tavoloni and Boyer, 1980; Yeung et al., 1993). A species-difference in the *in vitro* sensitivity of hepatocytes in monocultures has been reported, with an EC_{50} as low as 9 ± 6 µM CPZ in human (Gerets et al., 2012) compared to 110 µM in rat (Zhang et al., 2011) hepatocytes. An incidence of 1-2 % cholestasis has been reported in patients treated with CPZ at therapeutic doses of 2 to 5 mg/kg (Boelsterli et al., 1987; Horikawa et al., 2003; de Abajo et al., 2004). In contrast, CPZ was not hepatotoxic in pre-clinical toxicity studies: for example, CPZ did not cause cholestasis after 3 week repeated-dosing at the highest dose level of 20 mg/kg in rats (Tsao et al., 1983). More recently, Buchweitz et al. (2002) demonstrated the appearance of cholestasis in rats after one dose of CPZ (70mg/kg bodyweight) given 2 hours after LPS administration. Involvement of an inflammatory process could indeed underlie the idiosyncrasy of CPZ since, in humans, CPZ-induced cholestasis has been associated with an infiltration of inflammatory cells, such as neutrophils and lymphocytes (Moradpour et al., 1994).

In the present study the mRNA expression profile of PHH's was analyzed after single- and repeat-dose treatment of CPZ, with the aim to address mechanisms as well as inter-individual variability of PHH.

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Material and methods

Chemicals and solutions

William's E medium GlutaMAX™, fetal bovine serum (FBS), insulin-transferrin-selenium (ITS), sodium pyruvate, gentamycin and Geltrex™ were purchased from Invitrogen (Fisher, Illkirch, France). Insulin, penicillin/streptomycin, dexamethasone, bovine serum albumin, dimethyl sulfoxide (DMSO), Percoll®, collagenase and chlorpromazine hydrochloride were from Sigma-Aldrich (St-Quentin-Fallavier, France). Hepatocyte maintenance medium (HMM™) was from Lonza (Verviers, Belgium).

Isolation of primary human hepatocytes (PHH)

Human liver tissue was obtained from resections from patients undergoing partial liver hepatectomy for therapy of hepatic tumors, with permission of the national ethics committees and regulatory authorities (Table 1). Biopsies (20-100 g) were removed from the safety margin of the tissue resected near the tumor. Human hepatocytes were isolated using a two-step perfusion technique as previously described by Richert et al. (2004) and Lecluyse and Alexandre (2010). Briefly, two to four hepatic vessels were cannulated and perfused with 0.5 mM EGTA-containing buffer for 10 min and then with a 0.02 % collagenase-containing buffer for 20 min at 37°C. At the end of the perfusion, the resection was removed from the perfusion system and immersed into warm HBSS containing 10 % FBS (suspension buffer). Using tissue forceps and scissors, the Glisson's capsule was gently torn and the hepatocytes released into the medium following gentle shaking and passing the tissue between the tissue forceps, leaving behind the connective tissue and any undigested material. The cells were filtered through 850, 400 and 100 µm meshes and then centrifuged at 80 *g* for 5 min at room temperature (RT). Cells were washed once in suspension buffer and once in Percoll®-containing buffer (final concentration 28.8 %) at 168 *g* for 20 min at RT. The hepatocytes were washed again in suspension buffer at 80 *g* for 5 min at RT and cell viability and number were determined using the Trypan blue (0.4 %) exclusion method. Only preparations with more than 70 % cell viability were used for further experiments.

Exposure to CPZ for cell viability

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To determine the toxicity of CPZ, PHH suspensions obtained after isolation was seeded onto collagen I coated 96-well plates (Biocoat®, Dutscher, France) at 0.05 x 10^6 viable cells per well in 100 µL William's E medium supplemented with 10 % FBS, 4 µg/mL insulin, 1 µM dexamethasone and gentamycin (50 µg/mL). After overnight culturing, the monolayer was overlaid with 350 µg/mL Geltrex™ in seeding medium without FBS for 24 hours. Seven concentrations of CPZ were tested; 0 – 1 – 10 – 20 – 30 - 40 and 50 µM and either a resazurin or a MTT test was performed after 1, 3 and 14 days of treatment. For the resazurin assay, cell monolayers were incubated for 30 min with 450 µM resazurin and fluorescence was measured with an excitation wavelength at 530-560 nm and an emission wavelength at 590 nm. For the MTT assay, cell monolayers were incubated for 30 min with thiazolyl blue tetrazolium bromide (1 mg/mL), the supernatant was removed and 100 µL per well of DMSO was added. After gentle shaking, the absorbance was measured at 595 nm. For the two assays, results were expressed as a percentage versus the vehicle control.

Culture and exposure to CPZ for transcriptomic analysis

The PHH suspension obtained after isolation was seeded as described in "*Exposure to CPZ for cell viability*" onto collagen I coated 6-well plates (Biocoat®, Dutscher, France) at 2 x 10^6 viable cells per well. Forty eight hours after seeding, treatment with CPZ was started. The culture medium consisted of Hepatocyte Maintenance Medium (HMM™) supplemented with 1 % ITS, 100 nM dexamethasone and 50 µg/mL gentamycin. Medium was renewed every day and a new overlay with Geltrex™ (350 µg/mL) was applied 6, 9 and 13 days after seeding.

Stock solutions of CPZ were made in DMSO: 0.01, 0.05, 0.1 and 0.5 mM CPZ. Stock solutions of CPZ were diluted in appropriate medium to obtain 0.02, 0.1, 0.2 and 1 µM. Compound containing medium was renewed every day until day 13. Cells not treated with CPZ but receiving only the vehicle (DMSO) served as the control.

RNA extraction

After 1, 3 and 14 days of CPZ treatment, RNA was extracted for whole transcriptome analysis. Cells were washed with PBS 1X and scraped in RNA protect Cell Reagent (Qiagen). After centrifugation,

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cells were lysed in RLT Buffer plus (Qiagen) complemented with 1 % 2-mercapto-ethanol, pipetted onto a QIAshredder spin column (Qiagen) and centrifuged for 2 min at 13800 *g* to be sure of full homogenization. The lysates were kept at -80°C until RNA extraction.

Total RNA was extracted using the RNeasy Plus Mini Kit from Qiagen (Hilden, Germany) on the automated QIAcube™ robotic workstation (Qiagen), both according to the manufacturer's protocols. The RNA quantity was assessed with the NanoDrop 2000 (Thermo Fisher Scientific, Waltham (MA), USA), while the quality was determined with the Agilent 2100 Bioanalyzer (Agilent Technologies, Waldbronn, Germany).

Transcriptomics Processing

Biotinylated cRNA was amplified with the Illumina® TotalPrep™-96 RNA Amplification kit (Ambion®) according to the manufacturer's protocol. After assessing the quantity (NanoDrop 2000) and the quality (Agilent 2100 Bioanalyzer) of the labeled cRNA it was hybridized onto the appropriate Illumina® BeadChips (HumanHT-12_v4). The BeadChips were washed and stained using the Little Dipper® Microarray Processor (SciGene Corporation, Sunnyvale (CA), USA) and subsequently scanned with the Illumina® BeadArray Reader (Illumina Inc., San Diego (CA), USA). The GenomeStudio® Data Analysis Software (Illumina) was used to check the quality of the transcriptomic raw data and to make it accessible for further processing (Illumina, 2010). Transcriptomic raw data were log2 transformed and quantile normalized before statistical analysis. Quantile normalization was performed as outlined in Bolstad et al. (2003) using the application package 'preprocessCore' (http://www.bioconductor.org) written for the open-source statistical software R (http://www.R-project.org). Microarray data are available in the ArrayExpress database (www.ebi.ac.uk/arrayexpress) under accession number E-MTAB-1747.

Data processing and Analysis

Due to a large donor-to-donor variability the transcriptomics results of the five PHH preparations were analyzed separately. Fold change values were calculated to compare gene expression measurements between corresponding time-matched vehicle controls and CPZ treatment conditions. Genes with a

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fold change value larger than 2 were regarded as up-regulated while genes with a fold change value smaller than - 2 were regarded as down-regulated. The total number of deregulated genes was plotted against treatment time and PHH donor, to visualize time and donor effects on these numbers.

For each PHH donor and each time point, hepatic pathway hypotheses were generated using the Ingenuity Pathway Analysis® v.7.0 (IPA, Ingenuity System, CA) software. A pathway was selected when at least 2/3 donors treated with 0.02 µM CPZ, 3/5 donors with 0.1 or 0.2 µM CPZ or 1/2 donors with 1 µM have a p-value ≤ 0.05 (this IPA®-derived p-value is calculated via Fisher's Exact Test and reflects the likelihood that the association between a set of genes and a certain pathway is due to random chance).

A heatmap illustrating fold change values of the genes involved in the identified hepatic signatures were created within the Analyst™ software (Genedata, Basel, Switzerland). To classify deregulated genes in hepatic signatures, the genes assigned to the different hepatic pathways according to IPA® (supplemental table 1) were validated manually using current literature. In addition, these hepatic signatures were expanded by further additional deregulated genes known to be involved in hepatotoxicity, taken from literature (NCBI – Gene and PubMed, Weizmann Institute of Science - The GeneCards Human Gene Database).

The number of deregulated genes per hepatic signature was calculated separately for each hepatic signature, PHH donor, CPZ treatment concentration and treatment time. Dot plots created with R, version 2.14.1, were used to compare numbers of deregulated genes across hepatic signatures, donors and treatment times.

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Results

a. Treatment concentrations for transcriptomic analysis

Within the European Seventh Framework Program Predict-IV (FP7/2007-2013) the CPZ repeat-treatment protocol of PHH was set to a daily exposure over a 14-day period with a concentration causing a maximum of 10 % decrease in cell viability (TC_{10}) and with a presumed non-cytotoxic concentration being $1/10^{th}$ of TC_{10}.

To determine the TC_{10} of CPZ in PHH, a preliminary cytotoxicity experiment was performed using a range of CPZ concentrations. Cell viability was assessed after short-term (1 day and 3 days) and long-term (14 days) CPZ repeat daily exposure. A large inter-donor variability in the response to CPZ cytotoxicity was observed, since the TC_{10} varied between 1 and 18 µM and TC_{50} between 3 and 35 µM from 13 donors after 3 days of treatment (Figure 1) and ranged between 0.2 and 1 µM in three donors treated daily up to 14 days. As this range of concentrations corresponded to reported Cmax in patients (0.16 µM) (Borges et al., 2011), PHH (n = 5) were treated with 0.1 or 0.2 µM, i.e. TC_{10}, and in addition either with 1 µM (n = 2), i.e. ten-fold TC_{10} or with 0.02 µM (n = 3) CPZ, i.e. $1/10^{th}$ of TC_{10}.

b. Hepatotoxicity signatures of CPZ

A total of 34,693 genes were included in the transcriptomic analysis. Figure 2 shows a large variability between donors as well as between treatment times with respect to the total number of gene expression changes. With respect to short-term treatment, the total number of gene expression changes for a given donor ranged between 8 and 1062 genes after 1 day of treatment and between 22 and 188 genes after 3 days of treatment. After 14 days repeated treatment, the total number of gene expression changes per donor varied between 32 and 1499. The number of common genes deregulated at each time point for a given donor varied between 0 and 9, suggesting little biological significance for these genes. Indeed, these were pseudogenes and genes involved in cellular homeostasis (e.g. PCK1 and HNRNPA2B1) that were not included in the hepatic signatures described hereafter. This large variability indicates that a global analysis of gene expression data only makes sense when looking at each donor in isolation.

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Therefore, when looking into specific pathways of hepatotoxicity, we analyzed the five donors and the three CPZ treatment times individually.

Firstly, functional analysis with Ingenuity Pathway Analysis® (IPA) software was conducted on the whole gene expression profiles. Several hepatotoxicity signatures of CPZ at 0.1 or 0.2 μM were identified (table 2). Cholestasis, fibrosis, hepatitis, inflammation, liver proliferation, necrosis, GSH depletion and steatosis were identified both after short-term (1 or 3 days) and long-term (14 days) CPZ treatment, while genes related to the pathway giving rise to a signature of cirrhosis were deregulated only after 14 days.

These IPA®-derived hepatic signatures were thereafter expanded by further deregulated genes known to be involved in liver toxicity as illustrated in Figure 3. Signatures of liver inflammation/hepatitis, liver proliferation and cholestasis were present in all donors. Cholestasis-related genes were observed as early as the first exposure and in 5/5 donors, this effect was maintained over the entire treatment time. Signatures of fibrosis/cirrhosis, and steatosis were present in 4/5 donors and steatosis was represented with a minimum of one deregulated gene after short-term treatment and two deregulated genes after prolonged treatment. Necrosis/GSH depletion/oxidative stress was present in 3/5 donors.

Even though the hepatotoxicity signatures were to some degree present in all donors, differences could be highlighted: for example, PHH donor S251110 showed signs of necrosis only after short-term treatment with CPZ but no signs of fibrosis/cirrhosis, indicating only transient effects. PHH donor S301110 showed signs of fibrosis only after short-term treatment and no signs of cirrhosis, whereas liver inflammation appeared only after long-term treatment and no signs of necrosis were seen. PHH donor S1045 gave no signs of steatosis or necrosis. PHH donor B1050 showed no induction of steatosis after long-term treatment. PHH donor M291110 was the only donor showing all hepatic signatures both in short- and long-term CPZ treatment.

In order to better capture the time-dependent and donor-dependent hepatotoxicity response to CPZ treatment, we compared the number of gene expression changes across hepatic signatures, donors and

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treatment times (Figure 4). The number of gene expression changes after 3 days of treatment was less pronounced in all of the 5 PHH donors as compared to 1 or 14 days of treatment.

Of particular relevance was the fact that at 1 and 14 days of CPZ treatment, donors with a large number of gene changes related to liver inflammation/hepatitis (M291110 and B1050) also showed large numbers of gene changes related to other specific hepatotoxic signatures.

With treatment concentrations of 0.02 µM (i.e. $1/10^{th}$ of Cmax (n = 3)) fewer gene changes were observed and with 1 µM (i.e. 10-fold Cmax (n = 2)) more gene changes were observed, but 85 % and 66 % of those genes were also deregulated with Cmax (0.1 or 0.2 µM) treatment concentrations, respectively (data not shown). Therefore, we can conclude that whatever the concentration used the hepatic signatures were overall similar (Table 2) indicating that we could not define a concentration that did not induce adverse effects. Genes related to necrosis, GSH depletion, steatosis, fibrosis, cholestasis, inflammation, hepatitis and liver proliferation pathways were deregulated both after short- and long-term treatment. Signs of cirrhosis were observed both after short- and long-term of treatment with 1 µM of CPZ, while at 0.1 and 0.2 µM signs of cirrhosis appeared only after 14 days of treatment.

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Discussion

After a 14 day treatment period with increasing concentrations of CPZ, the highest non-cytotoxic concentration observed in PHH was between 0.2 and 1 µM. These results are in accordance with the TC_{50} (9 ± 6 µM after 48 hours of treatment in PHH) reported by Gerets et al. (2012). The fact that these concentrations of CPZ are close to the reported Cmax levels in humans (Borges et al., 2011) prompted us to choose PHH repeat-treatment concentrations of 0.1 or 0.2 µM (n = 5), as well as $1/10^{th}$ (0.02 µM, n = 3) and the 10-fold concentration (1 µM, n = 2) for transcriptomics analysis.

In the present study, we found that after 3 days of treatment fewer gene changes were induced compared to days 1 and 14. We (Richert et al., 2009) have previously described that genes deregulated after 24 hours treatment are not automatically deregulated after 72 hours, and this could represent an adaptation phase after the primary acute response on day 1. Nevertheless, repeat exposure for up to 14 days provided valuable additional information in some donors (S251110, M291110 and S1045) and gave further insight into the mechanism of long-term CPZ induced hepatotoxicity.

The CYP1A gene, one of the main CYP450 involved in CPZ metabolism (Wojcikowski et al., 2010) and producing a metabolite more toxic than the parent (Tavoloni and Boyer, 1980), was found to be up-regulated in the present study after the first day and up to 14-days of treatment at 0.1 and 0.2 µM (2-fold) and 1 µM (3-fold) in PHH. However, other mechanisms than increased CYP1A1/2-reactive metabolite formation are involved in CPZ cytotoxicity towards human hepatocytes, since a similar increase was observed in rat hepatocytes exposed to 1 µM CPZ without any overt signs of cytotoxicity (unpublished data). Inter-individual CYP2D6 dependent reactive metabolite formation seems not to be directly related to toxicity. Indeed, donor B1050 displayed the highest expression in CYP2D6 (between 3- to 9-fold that of the 4 other donors) and a CYP2D6 activity of 1.5 pmol/min/mg cell protein compared to 0.5 pmol/min/mg cell protein for donor S1045, but was not more susceptible to CPZ toxicity than the latter (see also discussion below).

The global hepatic signature obtained after 0.1 or 0.2 µM CPZ treatment generated using the Ingenuity Pathway Analysis® (IPA) software was comparable in the five PHH cultures. Cholestasis is the main

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form of hepatotoxicity described in patients treated with CPZ, with an incidence of 1-2 % after treatment with therapeutic doses (Boelsterli et al., 1987; Regal et al., 1987). In 5/5 donors the gene expression changes are indicative of, according to IPA analysis, the cholestasis pathway. The hepatocyte uptake transporter NTCP (SLC10A1) has been described to be down-regulated during cholestasis (Lee and Boyer, 2000; Zollner et al., 2001). In the present study, NTCP (SLC10A1) was down-regulated in 3/5 donors, after the first day of treatment at 0.02 and 0.2 µM (M291110 and S301110) and after 14-day of treatment at 0.1 µM (S1045). OCT (SLC22A1) was down-regulated in 2/5 PHH donor exposed to short- (M291110) and long-term (S1045) 0.1 or 0.2 µM CPZ. The expression of the hepatocyte efflux transporter BSEP (ABCB11) has been reported to be either decreased (Zollner et al., 2001) or not affected (Lee and Boyer, 2000; Demeilliers et al., 2006) in patients with liver cholestatis. In the present study, BSEP, p-gp (ABCB1) and BCRP (ABCG2) were not transcriptionally deregulated at any treatment time in any of the donors after CPZ treatment. Since CPZ is known to inhibit uptake transporters, such as OCT1 (SLC22A1) and also efflux transporters such as BSEP (ABCB11), p-gp (ABCB1) and BCRP (ABCG2) (Pedersen et al., 2008), the results of the present study suggest a cellular feed-back regulation at the transcriptional level of the uptake but not secretory transporter proteins to counteract the inhibition of canalicular transport of bile acids. Down-regulation of CYP7A1, which is a major CYP450 involved in bile acid synthesis (Demeilliers et al., 2006), has also been described in cholestatic patients. CYP7A1 was deregulated in 3/5 donors, up-regulated in two donors, after short-term (B1050) or long-term treatment (S251110) and down-regulated in M291110 after long-term treatment. Taken together, these data highlight feed-back regulations at the transcriptional level by human hepatocytes exposed to CPZ reflecting their attempts to reverse disturbances in bile acid homeostasis.

Fibrosis degenerating into cirrhosis was also described in patients with a lower sulfoxidation capacity (Larrey and Pageaux, 1997; Brind, 2007). Indeed, sulfoxidation mediates CPZ detoxification (Wojcikowski et al., 2010) and a poor capacity of sulfoxidation leads to an accumulation of toxic metabolites that could cause fibrosis and, eventually cirrhosis. From the five studied PHH donors, two (M291110 and S301110) displayed transcriptional signs of fibrosis at both 0.02 and 0.2 µM, with no

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signs of cirrhosis whereas in two other donors (S1045 and B1050) fibrosis and cirrhosis were highlighted both after short and long-term treatment, which might suggest a poor capacity of sulfoxidation in these donors. Our data did not indicate expression changes of genes involved in sulfoxidation, suggesting that changes at the post-translational level, not measurable by transcriptomics, might possibly lead to these adverse effects.

Signs of liver steatosis were also evident in PHH cultures treated with CPZ: up-regulation of the CYP2E1 gene in 3/5 donors (M291110, S301110, S1045) and of the CYP4A11 gene in 2/5 donors (M291110 and S301110), two markers involved in lipid metabolism and known to be induced in patients with steatohepatitis (Jansen, 2004).

In the present study, transcriptomic data showed gene expression changes related to signs of necrosis, possibly due to the treatment with a concentration close to the $TC_{10,}$ thus causing cell damage. S251110 PHH culture showed signs of necrosis only after short-term treatment whereas M291110 and B1050 showed these signs both after short- and long-term treatment. Liver regeneration has been described to be a defense mechanism of the liver to cytotoxicity (Lee, 2003; Hinson et al., 2010). The early signaling components TNFα and IL-6 secretion are known to cause up-regulation of genes involved in liver regeneration, such as STAT1, MAPK, or IGFBP1 and also up-regulation of vascular endothelial growth factor gene (VEGF) (Li et al., 2002). In the present study a strong up-regulation of IL-6 was accompanied by an up-regulation of MAPK9, IGFBP1, IL1RN and VEGFA (M291110) or STAT1 (S1045), while down-regulation of TNFα and IL-6 genes was accompanied by a down-regulation of IGFBP1, IL1RN and STAT1 genes (B1050). All of these genes involved in liver regeneration were hardly affected when early signaling was not or only slightly deregulated (S251110 and S301110).

IL-6 and TNFα are also widely described to promote inflammatory events through the expansion and activation of T-cells, differentiation of B-cells, and the induction of acute-phase reactants by hepatocytes (Jones et al., 2001). TNFα gene polymorphisms are known to result in variable TNF production which leads to inter-individual drug toxicity in human (Louis et al., 1998). Interestingly,

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when an inflammatory event was induced prior to CPZ treatment, cholestasis could be induced in rats (Buchweitz et al., 2002). In the present study, up-regulation of IL-6 gene expression (M291110 and S1045) was accompanied by an up-regulation of the IL-8 gene, another interleukin induced during liver inflammation, as well as several chemokines and chemokine receptors, such as CCL2 or CXCL2 genes. When the IL-6 gene was down-regulated (B1050), many chemokine and receptor genes were also down-regulated and when the IL-6 gene was not deregulated (S251110 and S301110), no other genes of this IL-6 dependent inflammatory pathway were deregulated. It is also noteworthy that donors with TNF/IL-6 deregulated pathways (M291110, S1045 and B1050) presented more genes deregulated in other pathways, including cholestasis and fibrosis/cirrhosis. Taken together, these results support the hypothesis that features of inflammation could be related to the idiosyncratic effects of CPZ (Roth et al., 2003)

In summary, short- and long-term *in vitro* exposure of PHH to CPZ at concentrations close to human Cmax (0.1 or 0.2 µM) induced six hepatotoxicity-related transcriptomic signatures: cholestasis, fibrosis/cirrhosis, liver proliferation, necrosis, liver inflammation/hepatitis and steatosis. Inter-donor variability in the inflammatory response of human hepatocyte cultures to CPZ treatment was associated with variability in the strength of these transcriptomic hepatoxicity signatures. Taken together, these results further suggest that features of inflammation could be related to the idiosyncratic hepatotoxic effects of CPZ in humans and that pathway-specific analysis of gene expression profiles in individual human donor hepatocytes are associated with increased susceptibility to toxic effects of drugs.

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Autorship Contributions

Participated in research design: Parmentier, Truisi, Stanzel, Richert

Conducted experiments: Parmentier, Truisi and Alexandre

Contributed analytic tools: Moenks, Lukas and Truisi

Performed data analysis: Parmentier, Truisi, Stanzel, Kopp-Schneider and Moenks

Wrote or contributed to the writing of the manuscript: Parmentier, Richert, Truisi, Mueller, Stanzel, Kopp-Schneider, Lukas, Alexandre and Hewitt

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Footnotes

Céline Parmentier and Germaine L Truisi contributed equally to the work presented in this manuscript.

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Figure legends

Fig.1: Toxicity of CPZ after 3 days of treatment. The black line represents mean viability of 13 donors (in % of untreated control). The grey area reflects variability between the 13 donors, with area borders illustrating minimum and maximum viability of the donors. Viability was assessed by MTT or resazurin assays (see Material and Methods).

Fig.2 : Barplot representing the total number of genes which changed at least a 2-fold (as compared to untreated control) for the five PHH cultures after 1, 3 and 14 days at 0.1 or 0.2 µM of CPZ treatment.

Fig.3 : Heatmap illustrating fold change values (red: up-regulation; green: down-regulation; black: [-1.3, 1.3]) of genes involved in hepatic signatures that were generated for five PHH donors treated after 1, 3 and 14 days at 0.1-0.2 µM of CPZ.

Fig.4 : Number of up- or downregulated genes per hepatic signature (● = inflammation & hepatitis, ■ = cholestasis, ▲ = fibrosis & cirrhosis, ○ = steatosis, □ = necrosis & GSH depletion & oxidative stress, × = general cellular metabolism, + = DME) obtained for the five PHH cultures (A) after 1 day, (B) after 3 days and (C) after 14 days of treatment with 0.1 or 0.2 µM of CPZ .

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Table.1: characteristics of the 5 human donors used for the transcriptomics analysis.

M = male, F = female.

Donor ID	Sex	Age (years)	Pathology
S251110	M	63	Colorectal adenocarcinoma
M291110	F	66	Colorectal adenocarcinoma
S301110	M	60	Colorectal adenocarcinoma
S1045	M	75	HepaticTumor
B1050	M	63	Hydatid cyst

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Table. 2: Transcriptomic signature of PHH after short- (1 or 3 days) and long-term (14 days) treatment with (a) 0.02 µM (3 donors), (b) 0.1-0.2 µM (5 donors) or (c) 1 µM (2 donors) CPZ. These signatures were obtained with Ingenuity Pathway Analysis® software, a specific pathway was selected when highlighted with a p-value < 0.05 in at least 2 donors (a), 3 donors (b) or one donor (c).

(a) 0.02 µM			(b) 0.1 or 0.2 µM			(c) 1 µM		
Short-term treatment		Long-term treatment	Short-term treatment		Long-term treatment	Short-term treatment		Long-term treatment
Day 1	Day 3	Day 14	Day 1	Day 3	Day 14	Day 1	Day 3	Day 14
Cholestasis	Cholestasis	Cholestasis	Cholestasis	-	Cholestasis	Cholestasis	Cholestasis	Cholestasis
Fibrosis	Fibrosis	Fibrosis	Fibrosis	Fibrosis	Fibrosis	Fibrosis	Fibrosis	Fibrosis
-	Cirrhosis	Cirrhosis	-	-	Cirrhosis	Cirrhosis	Cirrhosis	Cirrhosis
GSH depletion	GSH depletion	GSH depletion	-	GSH depletion	GSH depletion	GSH depletion	GSH depletion	GSH depletion
Necrosis	Necrosis	Necrosis	-	-	Necrosis	Necrosis	Necrosis	Necrosis
Hepatitis	Hepatitis	Hepatitis	Hepatitis	-	Hepatitis	Hepatitis	Hepatitis	Hepatitis
-	-	-	-	-	Inflammation	Inflammation	Inflammation	Inflammation
Liver proliferation	Liver proliferation	Liver proliferation	Liver proliferation	Liver proliferation	Liver proliferation	Liver proliferation	Liver proliferation	Liver proliferation
-	Steatosis	Steatosis	Steatosis	Steatosis	Steatosis	Steatosis	Steatosis	Steatosis

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Figure 1

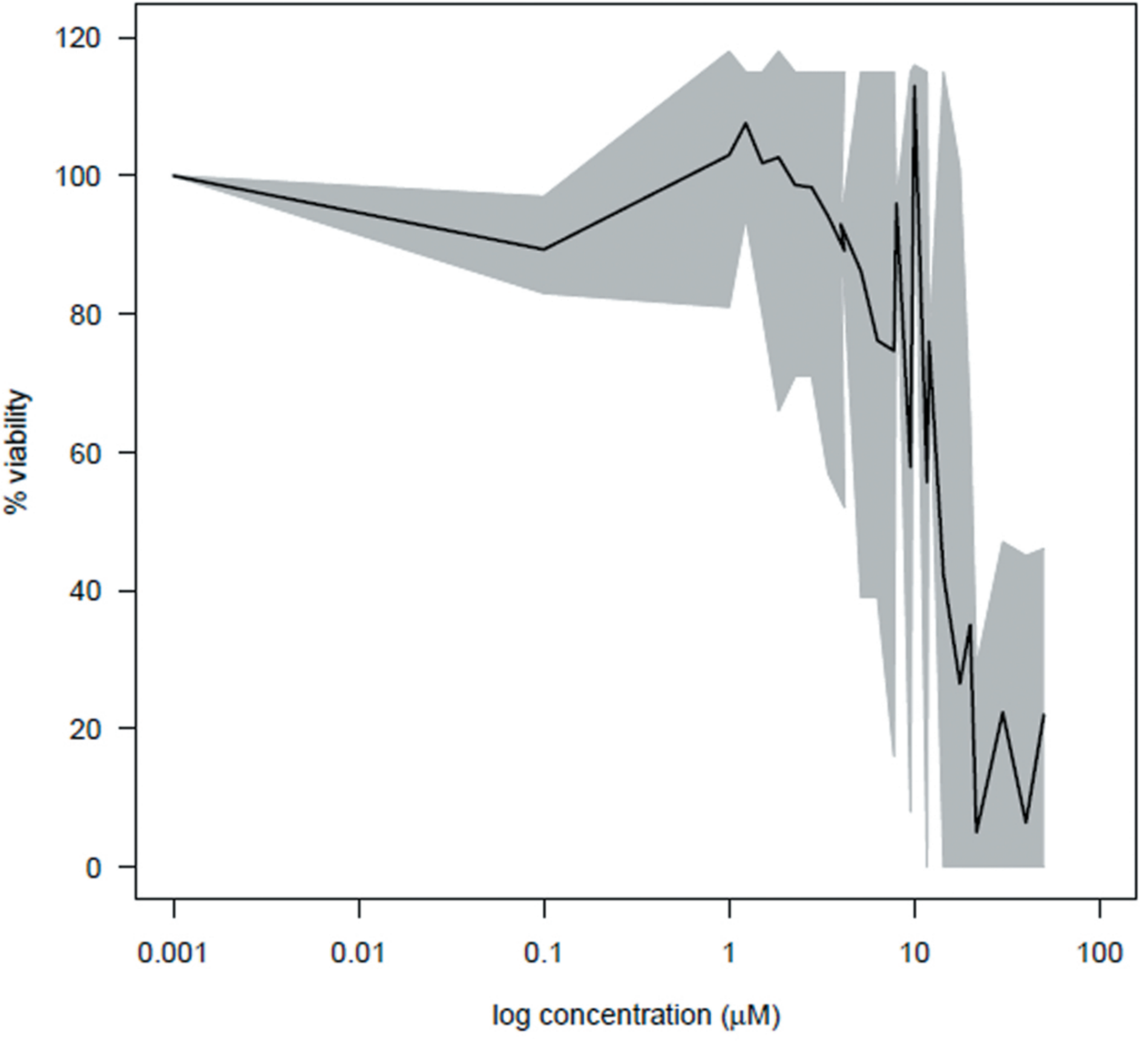

120
100
80
60
40
20
0
% viability
0.001
0.01
0.1
1
10
100
log concentration (μM)

Figure 2

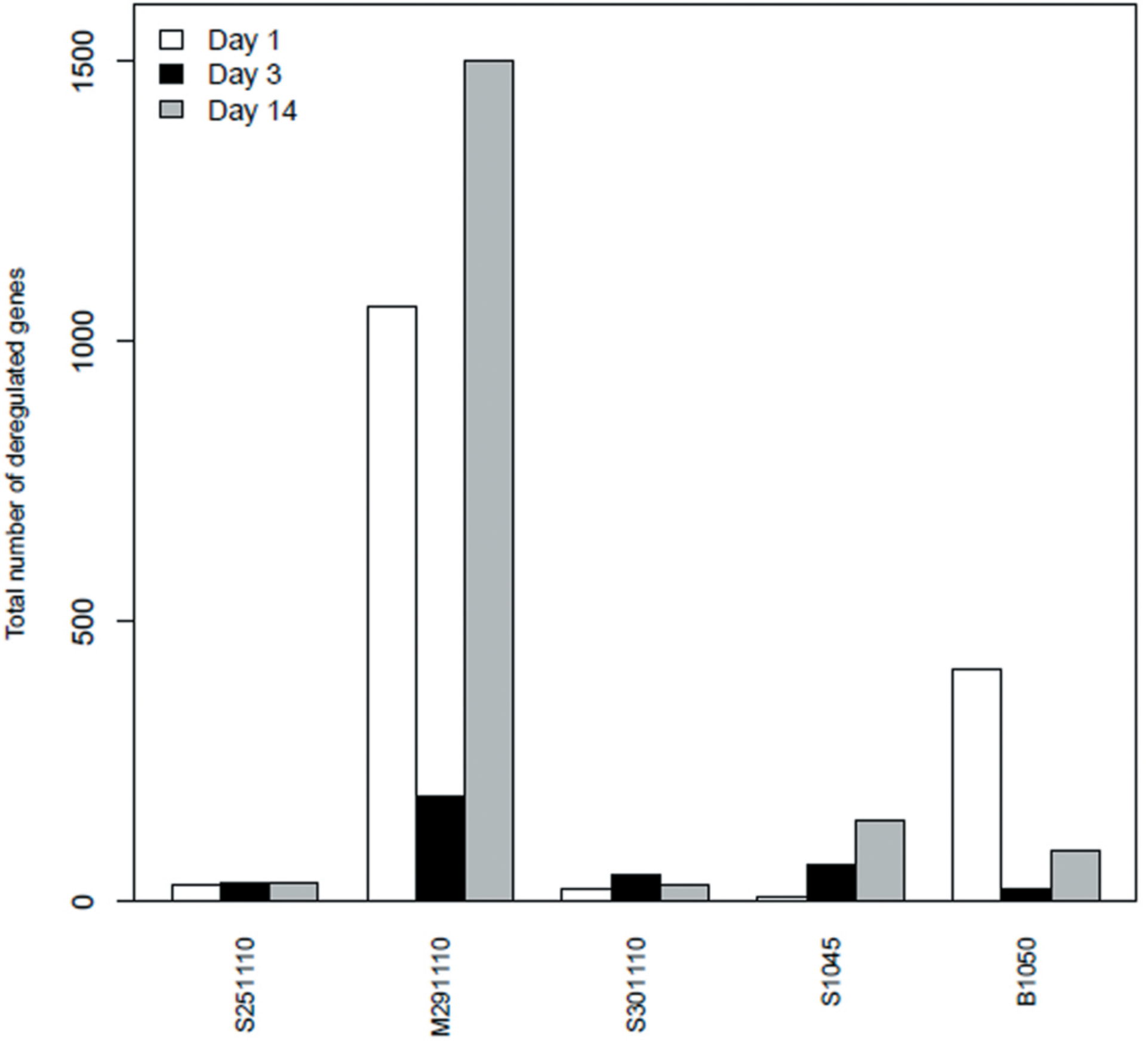
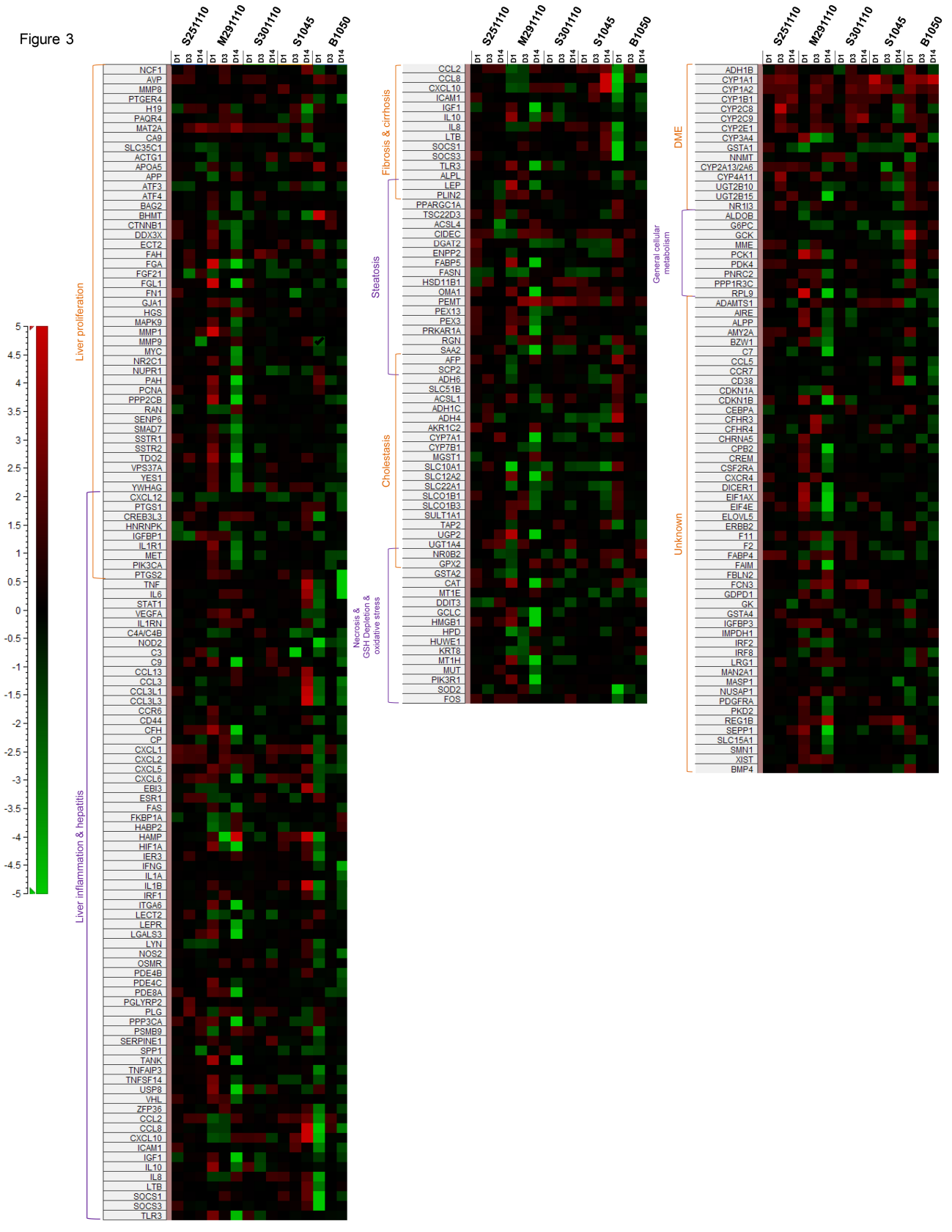

Day 1
Day 3
Day 14
Total number of deregulated genes
0
500
1000
1500
S251110
M291110
S301110
S1045
B1050

Figure 3


S251110
M291110
S301110
S1045
B1050
D1
D3
D14
Liver proliferation
Liver inflammation & hepatitis
Necrosis & GSH Depletion & oxidative stress
Cholestasis
Steatosis
Fibrosis & cirrhosis
General cellular metabolism
DME
Unknown
NCF1
AVP
MMP8
PTGER4
H19
PAQR4
MAT2A
CA9
SLC35C1
ACTG1
APOA5
APP
ATF3
ATF4
BAG2
BHMT
CTNNB1
DDX3X
ECT2
FAH
FGA
FGF21
FGL1
FN1
GJA1
HGS
MAPK9
MMP1
MMP9
MYC
NR2C1
NUPR1
PAH
PCNA
PPP2CB
RAN
SENP6
SMAD7
SSTR1
SSTR2
TDO2
VPS37A
YES1
YWHAQ
CXCL12
PTGS1
CREB3L3
HNRNPK
IGFBP1
IL1R1
MET
PIK3CA
PTGS2
TNF
IL6
STAT1
VEGFA
IL1RN
C4A/C4B
NOD2
C3
C9
CCL13
CCL3
CCL3L1
CCL3L3
CCR6
CD44
CFH
CP
CXCL1
CXCL2
CXCL5
CXCL6
EBI3
ESR1
FAS
FKBP1A
HABP2
HAMP
HIF1A
IER3
IFNG
IL1A
IL1B
IRF1
ITGA6
LECT2
LEPR
LGALS3
LYN
NOS2
OSMR
PDE4B
PDE4C
PDE8A
PGLYRP2
PLG
PPP3CA
PSMB9
SERPINE1
SPP1
TANK
TNFAIP3
TNFSF14
USP8
VHL
ZFP36
CCL2
CCL8
CXCL10
ICAM1
IGF1
IL10
IL8
LTB
SOCS1
SOCS3
TLR3
CCL2
CCL8
CXCL10
ICAM1
IGF1
IL10
IL8
LTB
SOCS1
SOCS3
TLR3
ALPL
LEP
PLIN2
PPARGC1A
TSC22D3
ACSL4
CIDEC
DGAT2
ENPP2
FABP5
FASN
HSD11B1
OMA1
PEMT
PEX13
PEX3
PRKAR1A
RGN
SAA2
AFP
SCP2
ADH6
SLC51B
ACSL1
ADH1C
ADH4
AKR1C2
CYP7A1
CYP7B1
MGST1
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SLC12A2
SLC22A1
SLCO1B1
SLCO1B3
SULT1A1
TAP2
UGP2
UGT1A4
NR0B2
GPX2
GSTA2
CAT
MT1E
DDIT3
GCLC
HMGB1
HPD
HUWE1
KRT8
MT1H
MUT
PIK3R1
SOD2
FOS
ADH1B
CYP1A1
CYP1A2
CYP1B1
CYP2C8
CYP2C9
CYP2E1
CYP3A4
GSTA1
NNMT
CYP2A13/2A6
CYP4A11
UGT2B10
UGT2B15
NR1I3
ALDOB
G6PC
GCK
MME
PCK1
PDK4
PNRC2
PPP1R3C
RPL9
ADAMTS1
AIRE
ALPP
AMY2A
BZW1
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CCL5
CCR7
CD38
CDKN1A
CDKN1B
CEBPA
CFHR3
CFHR4
CHRNA5
CPB2
CREM
CSF2RA
CXCR4
DICER1
EIF1AX
EIF4E
ELOVL5
ERBB2
F11
F2
FABP4
FAIM
FBLN2
FCN3
GDPD1
GK
GSTA4
IGFBP3
IMPDH1
IRF2
IRF8
LRG1
MAN2A1
MASP1
NUSAP1
PDGFRA
PKD2
REG1B
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SLC15A1
SMN1
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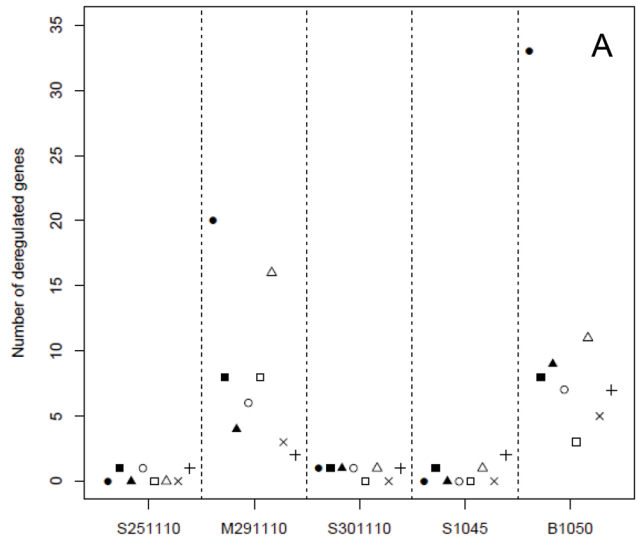
Figure 4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25
30
35
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M291110
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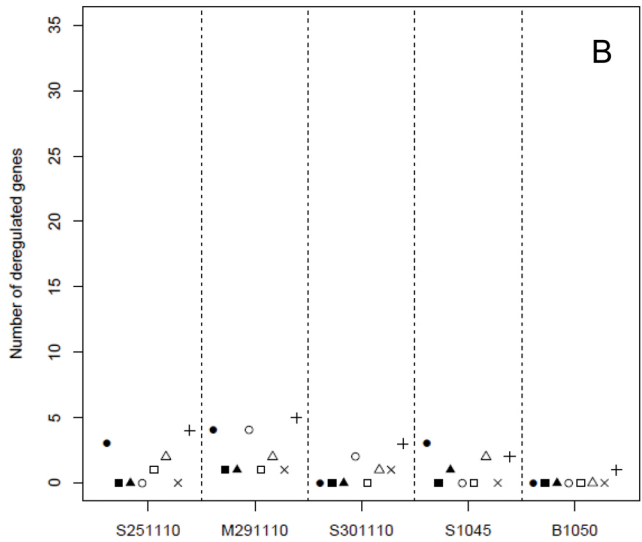
B1050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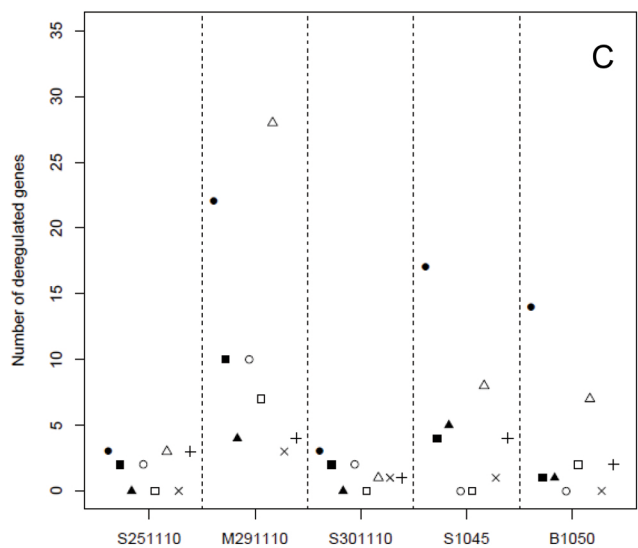
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S301110
S1045
B1050

DMD # 52415

Transcriptomic hepatotoxicity signature of Chlorpromazine after short- and long-term exposure in primary Human sandwich cultures

Céline Parmentier, Germaine L Truisi, Konrad Moenks, Sven Stanzel, Arno Lukas, Annette Kopp-Schneider, Eliane Alexandre, Philip G Hewitt, Stefan O Mueller and Lysiane Richert

Drug Metabolism and Disposition

classification of up- and down-regulated genes by CPZ in human hepatocyte sandwich cultures within hepatotoxicity signatures as defined by the IPA software

										S251110			M291110			S301110			S1045			B1050		
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis	Steatosis	cholestasis	necrosis & GSH depletion & oxidative stress	SYMBOL		PROBE_ID	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis	Steatosis		necrosis & GSH depletion & oxidative stress	IL10	Interleukin 10	ILMN_2073307	1,2	-1,0	-1,1	3,4	1,0	-2,5	1,6	-1,6	-1,3	1,1	1,1	1,1	-1,1	-1,1	-1,2
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	MMP9	matrix metallopeptidase 9	ILMN_1796316	1,2	1,2	-3,2	1,1	1,3	1,3	1,2	1,1	-1,2	1,0	1,1	1,6	-1,8	1,0	-1,4
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	SERPINE1	serpin peptidase inhibitor, clade E	ILMN_1744381	1,2	1,0	1,3	1,3	1,2	-1,3	1,2	-1,1	2,1	-1,2	-1,2	-1,1	-1,3	1,0	-1,3
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	SOCS1	suppressor of cytokine signaling 1	ILMN_1774733	1,1	1,0	-1,0	1,0	1,3	1,3	1,1	1,0	-1,0	1,5	1,4	2,6	-4,6	1,1	-1,4
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	STAT1	signal transducer and activator of transcription 1	ILMN_1777325	-1,0	1,1	1,0	-1,1	-1,2	1,1	-1,0	1,1	-1,1	-1,0	-1,1	2,5	-2,4	-1,0	-1,1
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis				CXCL12	chemokine (C-X-C motif) ligand 12 (not in liver)	ILMN_1791447	-1,4	1,0	-1,4	-1,3	-1,3	-1,2	1,1	1,0	-1,5	-1,8	-1,2	-1,1	-1,3	1,1	-2,0
inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis				PTGS1	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	ILMN_2339835	1,1	1,1	1,4	1,0	-1,1	1,1	1,0	-1,1	1,1	-1,0	-1,0	1,5	1,4	1,1	-2,0
inflammation & hepatitis	liver proliferation			cholestasis	necrosis & GSH depletion & oxidative stress	FAS	Fas (TNF receptor superfamily, member 6)	ILMN_2319077	1,1	-1,0	-1,2	1,4	1,1	-2,8	-1,3	-1,2	1,1	-1,1	-1,3	-1,4	-1,4	-1,1	-1,2
inflammation & hepatitis	liver proliferation			cholestasis		SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	ILMN_1776112	-1,3	1,3	-1,1	-4,9	-1,1	-1,4	-2,2	1,2	-1,3	-1,4	-1,5	-3,7	3,0	1,2	1,1
inflammation & hepatitis	liver proliferation			cholestasis		SLCO1B1	solute carrier organic anion transporter family, member 1B1	ILMN_1771118	1,4	1,1	1,2	1,0	1,4	-2,2	-1,1	1,2	-1,2	1,1	-1,0	1,1	2,2	1,1	-1,1
inflammation & hepatitis	liver proliferation				necrosis & GSH depletion & oxidative stress	FAIM	Fas apoptotic inhibitory molecule	ILMN_2351548	1,1	-1,0	1,1	2,4	-1,1	-5,3	1,1	-1,1	1,2	-1,1	1,0	1,0	-1,1	1,1	-1,0
inflammation & hepatitis	liver proliferation				necrosis & GSH depletion & oxidative stress	HMGB1	high mobility group box 1	ILMN_1791466	1,4	1,2	1,3	2,7	-1,1	-7,3	-1,1	1,0	1,3	1,2	-1,2	-1,3	1,6	-1,1	1,0
inflammation & hepatitis	liver proliferation					CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	ILMN_1715715	-1,3	-1,0	-1,0	-1,1	-1,3	1,2	-1,2	1,3	1,1	-1,1	-1,3	1,0	2,4	-1,2	1,0
inflammation & hepatitis	liver proliferation					IL1R1	interleukin 1 receptor	ILMN_1810584	1,2	1,1	1,1	2,8	1,0	-2,8	1,0	-1,1	1,2	1,0	1,1	1,2	1,1	-1,1	1,1
inflammation & hepatitis		fibrosis & cirrhosis	Steatosis	cholestasis	necrosis & GSH depletion & oxidative stress	IL6	Interleukin 6	ILMN_1699651	-1,0	-1,1	-1,1	-1,0	1,6	1,6	-1,2	1,1	-1,1	1,1	-1,0	3,4	-2,3	-1,2	-5,5
inflammation & hepatitis		fibrosis & cirrhosis	Steatosis		necrosis & GSH depletion & oxidative stress	CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	ILMN_1665437	-1,0	2,3	1,6	-1,1	2,0	1,6	1,1	1,3	1,1	-1,2	1,5	1,2	1,0	1,5	-1,1
inflammation & hepatitis		fibrosis & cirrhosis	Steatosis			CCL2	alcoholic hepatitis	ILMN_1720048	1,2	1,5	1,6	-2,1	-1,3	1,7	1,2	1,0	1,2	1,6	1,2	2,7	-3,4	1,4	-1,5
inflammation & hepatitis		fibrosis & cirrhosis	Steatosis			CD44	CD44 molecule	ILMN_1803429	-1,0	-1,3	-1,1	1,5	-1,2	1,0	-1,1	-1,1	-1,1	-1,1	1,0	1,5	-2,2	-1,0	-1,5
inflammation & hepatitis		fibrosis & cirrhosis	Steatosis			LEP	leptin	ILMN_2207505	1,0	-1,2	-1,3	4,0	1,2	-3,0	1,1	1,2	-1,0	1,0	1,4	1,1	-1,3	-1,0	-1,1
inflammation & hepatitis		fibrosis & cirrhosis	Steatosis			SPP1	secreted phosphoprotein 1	ILMN_2374449	-1,1	1,1	-2,6	-1,1	1,5	-1,3	1,1	-1,1	-1,1	-1,2	-1,2	-1,7	-1,5	1,1	-2,1
inflammation & hepatitis		fibrosis & cirrhosis		cholestasis		IL8	interleukin 8	ILMN_1666733	1,1	1,1	1,2	-1,3	-1,3	1,5	1,1	1,1	1,5	1,4	1,0	2,1	-3,2	1,2	-1,2
inflammation & hepatitis		fibrosis & cirrhosis				CCL5	chemokine ligand 5	ILMN_1773352	1,2	-1,1	-1,0	-1,1	-1,2	-1,1	-1,0	1,1	-1,2	-1,1	1,2	2,3	-1,4	1,1	-2,2
inflammation & hepatitis		fibrosis & cirrhosis				CCL8	chemokine ligand 8	ILMN_1772964	1,3	-1,2	-1,1	-1,4	-1,4	1,0	-1,1	1,0	1,0	1,2	1,1	35,1	-9,3	1,1	-3,0
inflammation & hepatitis		fibrosis & cirrhosis				CCR7	chemokine receptor	ILMN_1715131	1,0	1,1	-1,0	-1,0	-1,1	-1,3	1,2	1,0	-1,1	1,1	-1,2	1,1	1,1	-1,1	-2,2
inflammation & hepatitis		fibrosis & cirrhosis				CXCL10	chemokine (C-X-C motif) ligand 10 (IP-10)	ILMN_1791759	-1,1	1,3	1,1	-1,9	-1,7	1,5	1,4	1,6	-1,3	-1,1	2,1	7,4	-4,9	-1,2	-1,1
inflammation & hepatitis		fibrosis & cirrhosis				LTB	lymphotoxin beta	ILMN_2376204	1,3	1,0	1,0	-1,2	1,3	-1,1	1,1	-1,1	1,0	1,1	-1,1	2,2	-3,6	1,1	1,3
inflammation & hepatitis		fibrosis & cirrhosis				TLR3	toll-like receptor 3	ILMN_2155708	1,3	-1,0	1,2	2,8	1,2	-4,6	1,4	-1,4	1,2	-1,1	-1,0	-1,1	-1,3	1,1	-1,1
inflammation & hepatitis			Steatosis		necrosis & GSH depletion & oxidative stress	C3	complement 3	ILMN_1762260	-1,0	1,1	1,7	-1,5	1,1	1,0	-1,0	-1,2	1,7	-1,4	-9,2	-1,2	-2,1	1,1	-1,9
inflammation & hepatitis			Steatosis		necrosis & GSH depletion & oxidative stress	IGFBP1	insulin-like growth factor binding protein 1	ILMN_1728445	-1,6	-2,4	2,2	1,4	1,5	-1,5	-1,0	-1,5	1,1	1,2	1,1	1,0	-1,5	-1,1	-1,3
inflammation & hepatitis			Steatosis		necrosis & GSH depletion & oxidative stress	SOD2	superoxide dismutase 2, mitochondrial	ILMN_1792922	1,0	-1,3	-1,1	1,0	1,4	-1,8	-1,2	1,2	-1,1	-1,2	-1,1	1,8	-2,1	1,0	1,3
inflammation & hepatitis			Steatosis			PDE4B	phosphodiesterase 4B, cAMP-specific	ILMN_1782922	-1,1	-1,0	1,1	-1,1	-1,1	-1,0	-1,0	1,0	1,1	1,1	-1,4	1,5	-1,3	-1,2	-2,1
inflammation & hepatitis			Steatosis			PEMT	phosphatidylethanolamine N-methyltransferase	ILMN_1689116	1,0	1,0	1,0	-1,0	3,2	3,5	2,0	3,0	2,6	-1,0	1,2	1,2	2,1	-1,1	-1,0
inflammation & hepatitis			Steatosis			PDE4C	phosphodiesterase 4C, cAMP-specific	ILMN_1761277	1,1	-1,0	1,1	2,4	-1,1	-1,3	-1,1	1,2	1,0	1,1	1,0	1,0	-1,3	-1,0	-1,0
inflammation & hepatitis			Steatosis			PDE8A	phosphodiesterase 8A	ILMN_1699767	1,3	1,0	-1,0	1,9	1,5	-4,5	1,2	1,0	1,1	1,0	1,0	1,1	1,0	1,1	1,4
inflammation & hepatitis				cholestasis	necrosis & GSH depletion & oxidative stress	ESR1	estrogen receptor	ILMN_1678535	-1,2	1,6	1,7	-1,3	-1,4	-1,0	-1,2	1,6	1,1	-1,1	-1,8	-1,2	2,1	1,1	-1,2
inflammation & hepatitis				cholestasis		ALPP	alkaline phosphatase, placental	ILMN_1693789	-1,1	-1,1	-1,1	2,8	1,0	-1,7	1,2	-1,4	1,0	1,1	-1,1	-1,4	-1,0	1,0	-1,2
inflammation & hepatitis				cholestasis		SCP2	sterol carrier protein 2	ILMN_1694776	1,1	1,0	-1,0	-2,1	1,2	-1,0	-1,1	1,2	-1,1	1,3	-1,3	-1,0	1,1	1,5	-1,1
inflammation & hepatitis					necrosis & GSH depletion & oxidative stress	FKBP1A	FK506 binding protein 1A	ILMN_2333367	-1,3	-1,1	-1,1	-2,2	-1,3	1,5	-1,1	1,0	-1,2	-1,3	1,1	-1,0	-1,2	1,1	1,2
inflammation & hepatitis					necrosis & GSH depletion & oxidative stress	IL1RN	interleukin 1 receptor antagonist	ILMN_1774874	-1,1	1,2	-1,2	1,1	1,6	1,5	1,1	-1,1	1,0	1,1	-1,1	1,4	-2,2	1,1	-1,4
inflammation & hepatitis					necrosis & GSH depletion & oxidative stress	MAPK9	mitogen-activated protein kinase 9	ILMN_2400297	-1,0	-1,1	1,0	2,1	-1,1	-2,6	-1,1	-1,2	-1,1	-1,1	-1,0	-1,1	-1,1	-1,0	-1,2
inflammation & hepatitis					necrosis & GSH depletion & oxidative stress	NR2C1	nuclear receptor subfamily 2, group C, member 1	ILMN_1728983	1,3	1,1	1,2	2,1	1,2	-3,2	1,2	-1,3	1,1	1,0	-1,2	-1,1	-1,1	1,1	-1,1
inflammation & hepatitis						AIRE	autoimmune regulator	ILMN_2261519	-1,0	1,0	1,0	2,5	-1,0	-2,0	1,3	-1,7	-1,2	-1,1	1,2	1,1	1,0	1,2	1,3
inflammation & hepatitis						AMY2A	amylase, alpha 2A	ILMN_1801303	1,4	1,5	1,2	1,2	2,1	-2,2	1,2	-1,1	1,0	-1,0	1,0	1,1	2,6	1,0	1,1
inflammation & hepatitis						CCL3L1	chemokine (C-C motif) ligand 3-like 1	ILMN_2218856	1,5	1,2	-1,2	-1,1	1,0	1,2	1,1	-1,1	-1,1	-1,1	-1,3	3,6	-2,3	1,2	-2,7
inflammation & hepatitis						CCL3L3	chemokine (C-C motif) ligand 3-like 3	ILMN_2105573	1,2	1,1	-1,5	-1,1	-1,2	1,1	-1,1	-1,1	-1,2	-1,4	-1,3	6,3	-2,6	1,1	-2,3
inflammation & hepatitis						CXCL1	chemokine (C-X-C motif) ligand 1 gro-a	ILMN_1787897	1,9	1,5	1,6	-1,1	1,6	-1,0	1,2	-1,3	1,8	1,7	1,9	2,6	-2,2	-1,2	-1,0
inflammation & hepatitis						CXCL2	chemokine (C-X-C motif) ligand 2 gro-b	ILMN_1682636	1,8	1,5	1,4	1,1	2,0	1,6	1,3	1,1	1,3	1,2	-1,3	1,1	-2,0	1,1	-1,4
inflammation & hepatitis						CXCL5	chemokine (C-X-C motif) ligand 5	ILMN_2171384	1,2	-1,0	1,2	2,4	1,5	-1,3	1,4	-1,1	1,0	1,8	1,3	5,4	-2,2	-1,3	-1,2
inflammation & hepatitis						CXCL6	chemokine (C-X-C motif) ligand 6	ILMN_2161577	1,3	1,4	2,0	1,6	-1,2	-3,6	1,0	-1,5	2,0	1,4	1,1	1,8	-1,5	1,0	1,1
inflammation & hepatitis						EBI3	Epstein-Barr virus induced 3	ILMN_1802653	-1,2	-1,2	-1,3	-1,4	-1,2	-1,2	-1,1	1,0	1,0	-1,3	-1,1	3,2	-1,9	1,0	-1,2
inflammation & hepatitis						ICAM1	intercellular adhesion molecule 1	ILMN_1812226	1,5	-1,1	1,0	1,0	-1,1	-1,3	1,0	-1,2	1,2	-1,1	1,8	1,6	-3,1	1,0	-1,5
inflammation & hepatitis						IFNG	interferon, gamma	ILMN_2207291	1,2	-1,1	1,0	-1,1	-1,1	1,1	-1,1	1,2	-1,0	1,1	-1,2	1,2	-1,3	1,0	-3,3
inflammation & hepatitis						IMPDH1	IMP (inosine 5'-monophosphate) dehydrogenase	ILMN_1676515	-1,1	-1,0	1,0	-1,6	1,0	2,1	1,0	1,2	-1,2	1,3	1,2	1,1	1,1	-1,1	-1,5
inflammation & hepatitis						IRF1	interferon regulatory factor 1	ILMN_1708375	-1,1	-1,1	1,2	-1,3	1,7	1,1	1,3	-1,0	-1,3	-1,0	-1,1	1,6	-2,7	1,1	-1,7
inflammation & hepatitis						LECT2	leukocyte cell-derived chemotaxin	ILMN_1717557	1,1	1,5	1,0	-2,1	-1,4	1,1	-1,4	1,1	-2,0	-1,1	-1,3	-1,4	1,8	-1,1	-1,0
inflammation & hepatitis						LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	ILMN_1781155	-1,0	-1,3	-1,5	-1,4	1,1	1,2	-1,1	1,0	-1,2	1,1	1,0	1,3	-2,1	-1,1	1,0
inflammation & hepatitis						MAN2A1	mannosidase, alpha, class 2A, member 1	ILMN_2147435	-1,2	-1,0	-1,1	1,1	-1,1	-2,1	1,0	-1,1	-1,1	1,0	-1,2	1,1	1,2	-1,1	-1,1
inflammation & hepatitis						NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha	ILMN_1773154	-1,1	1,1	1,3	-1,1	1,3	1,5	1,0	1,0	-1,0	1,2	-1,1	1,3	-2,0	1,1	-1,2
inflammation & hepatitis						PPP3CA	protein phosphatase 3, catalytic subunit, alpha isozyme	ILMN_2044226	1,5	1,0	1,4	2,1	-1,2	-5,8	1,2	-1,3	1,1	-1,1	-1,0	-1,1	1,4	-1,0	-1,0
inflammation & hepatitis						TANK	TRAF family member-associated NFKB activator	ILMN_2292387	1,2	1,1	1,3	3,8	1,0	-8,1	1,0	-1,1	1,0	-1,0	1,1	-1,0	1,2	-1,2	-1,1
inflammation & hepatitis						TNF	tumor necrosis factor	ILMN_1728106	1,2	1,1	1,0	-1,1	1,0	1,1	1,0	1,1	1,1	1,1	-1,1	3,3	-1,6	1,1	-4,8
inflammation & hepatitis						TNFAIP3	tumor necrosis factor, alpha-induced protein 3	ILMN_1702691	1,2	1,1	1,3	-1,1	1,2	-1,1	1,0	-1,0	-1,1	1,3	1,1	1,3	-2,9	1,2	-1,1
inflammation & hepatitis						USP8	ubiquitin specific peptidase 8	ILMN_2094587	1,1	1,0	1,1	3,0	1,0	-5,5	1,8	-1,5	1,5	-1,0	1,1	-1,2	1,1	-1,0	1,0
inflammation & hepatitis						ZFP36	zinc finger protein 36, C3H type, homolog	ILMN_1720829	1,2	1,0	-1,2	1,2	1,9	1,2	1,2	-1,2	1,1	1,2	1,0	1,5	-2,9	1,1	-1,0
inflammation & hepatitis						C4A/C4B	complement 4 (inflammation)	ILMN_2179533	1,2	-1,0	-1,0	-1,7	-1,3	1,0	1,1	1,4	1,2	-1,1	-2,5	-1,7	-1,2	1,1	-1,6
inflammation & hepatitis						NOD2	nucleotide-binding oligomerization domain containing 2	ILMN_1762594	-1,0	-1,2	-1,1	1,3	1,2	-1,2	-1,0	-1,1	-1,0	1,1	1,0	-1,1	-5,2	-1,3	-1,9
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	F11	coagulation factor	ILMN_1807101	-1,3	1,5	-1,1	1,5	2,2	-2,0	1,4	1,5	1,2	1,0	1,1	1,3	1,3	1,0	-1,0
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	IGF1	insulin-like growth factor 1	ILMN_2056087	-1,3	1,2	1,2	1,9	-1,1	-5,1	1,2	-1,5	-1,1	1,2	1,5	1,2	-1,5	-1,1	1,2
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	LEPR	leptin receptor	ILMN_2234956	1,1	-1,1	-1,2	1,7	-1,0	-3,9	-1,2	-1,2	-1,1	1,2	1,2	-1,0	1,1	-1,1	-1,2
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	NOS2	nitric oxide synthase 2, inducible	ILMN_3249361	1,2	1,1	-1,3	1,1	1,0	1,1	1,1	-1,0	-1,4	1,0	-1,3	1,0	-1,2	1,1	-2,7
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	PLG	plasminogen	ILMN_1714446	-1,0	2,3	1,3	-1,4	1,7	1,4	-1,2	1,4	1,4	-1,2	-1,0	-1,6	1,3	1,2	-1,2
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	PTGS2	prostaglandin-endoperoxide synthase 2	ILMN_2054297	1,1	1,1	-1,1	1,8	1,4	1,2	-1,2	-1,1	-1,0	1,6	-1,1	1,3	-1,1	1,0	-3,5
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	XDH	xanthine dehydrogenase	ILMN_1712632	1,3	1,2	-1,2	-1,4	1,4	-1,1	-1,1	1,7	-1,0	1,1	-1,3	1,2	2,1	-1,0	-1,5
	liver proliferation	fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	NCF1	neutrophil cytosolic factor 1	ILMN_1697309	1,1	1,3	1,0	1,2	1,4	1,1	1,1	1,1	-1,2	-1,0	-1,1	2,6	-1,6	1,0	-1,4
	liver proliferation	fibrosis & cirrhosis				ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	ILMN_1673566	1,4	1,1	-1,5	-1,0	1,7	1,3	1,1	-1,0	1,4	1,3	1,2	2,4	-2,2	1,0	-1,5
	liver proliferation	fibrosis & cirrhosis				ALPL	alkaline phoshatase	ILMN_1701603	-1,0	-1,1	1,1	1,2	1,4	-1,0	-1,2	-1,2	-1,1	1,3	1,2	1,1	-2,7	1,5	-1,2
	liver proliferation	fibrosis & cirrhosis				CTGF	connective tissue growth factor	ILMN_2115125	1,1	1,2	1,4	-1,1	-1,1	1,2	-1,5	-1,0	1,2	1,0	-1,3	-1,3	2,4	1,0	1,1
	liver proliferation	fibrosis & cirrhosis				CTNNB1	cell growth and adhesion (catenine)	ILMN_1651617	1,3	1,2	1,0	1,7	-1,5	-2,4	-1,3	1,0	1,2	1,0	-1,1	-1,1	-1,3	1,0	-1,0
	liver proliferation	fibrosis & cirrhosis				CXCR4	chemokine receptor 4	ILMN_2320888	1,6	-1,1	-1,1	-1,2	2,0	1,0	1,2	1,3	1,1	1,0	-1,3	-1,1	1,2	-1,1	-1,5
	liver proliferation	fibrosis & cirrhosis				F2	coagulation factor II (blood coagulation cascade) role in inflammation	ILMN_3249291	1,0	-1,2	-1,2	1,2	-1,5	-2,5	1,1	1,6	-1,0	1,1	1,0	-1,2	1,3	-1,7	1,4
	liver proliferation	fibrosis & cirrhosis				LGALS3	lectin, galactoside-binding, soluble	ILMN_1803788	1,2	0,0	1,6	2,6	-1,2	-5,4	1,2	-1,1	-1,0	-1,1	1,2	1,1	1,3	1,2	-1,2
	liver proliferation	fibrosis & cirrhosis				SMAD7	SMAD family member 7	ILMN_2203896	1,1	-1,1	-1,2	1,7	-1,3	-3,6	-1,3	-1,1	-1,2	-1,1	-1,2	-1,1	-1,1	-1,2	-1,3

inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis	Steatosis	cholestasis	necrosis & GSH depletion & oxidative stress	SYMBOL		PROBE_ID	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14
	liver proliferation	fibrosis & cirrhosis				AVP	arginine vasopressin (stimulate VEGF in kidney)	ILMN_2230117	1,6	1,5	1,1	-1,0	1,5	-1,1	1,4	1,4	1,1	1,1	1,0	-1,2	2,3	1,5	1,0
	liver proliferation	fibrosis & cirrhosis				MMP8	matrix metallopeptidase 8 (cell proliferation)	ILMN_1736026	-1,1	-1,0	1,1	1,0	1,1	-1,0	1,1	-1,0	1,2	2,0	1,1	-1,1	-1,2	-1,1	1,0
	liver proliferation			Steatosis		necrosis & GSH depletion & oxidative stress	CDKN1A	ILMN_1784602	1,0	-1,2	-1,1	-1,4	-1,8	2,2	-1,0	1,0	-1,0	-1,1	-1,1	1,1	-1,1	1,1	-1,3
	liver proliferation			Steatosis			BHMT	ILMN_1656638	1,1	1,2	1,1	-1,6	1,2	1,2	-1,5	1,3	-1,2	-1,6	-1,1	-3,0	5,8	1,3	1,1
	liver proliferation			Steatosis			IL1B	ILMN_1775501	-1,1	-1,2	1,1	1,5	1,2	-1,2	1,2	1,1	1,1	1,4	1,1	7,7	-4,0	-1,1	-2,1
	liver proliferation			steatosis			PTGER4	ILMN_1795930	-1,1	1,1	-1,1	-1,1	1,1	-1,0	1,2	1,4	-1,1	1,0	-1,1	1,7	-1,6	-1,1	-2,6
	liver proliferation			steatosis			NR1I3	ILMN_2330697	1,2	1,9	1,1	-1,3	1,4	1,2	1,2	1,3	1,1	-1,0	1,0	-2,1	1,8	1,3	1,1
	liver proliferation				cholestasis		ADH1C	ILMN_1740717	-1,3	1,3	1,2	-1,2	-1,1	-1,2	-1,8	1,3	1,0	-1,0	-1,0	-1,7	2,7	-1,2	1,3
	liver proliferation				cholestasis		CYP7A1	ILMN_1749575	-1,0	1,1	2,4	1,0	-1,1	-10,0	1,1	-1,3	-1,6	-2,2	-1,2	-3,9	5,3	-1,2	1,1
	liver proliferation				cholestasis		SLC22A1	ILMN_1715742	-1,2	1,1	-1,0	-2,6	1,0	-1,8	-1,3	-1,1	-1,2	-1,5	-1,2	-2,2	2,4	1,0	-1,1
	liver proliferation				cholestasis		SLCO1B3	ILMN_1687319	1,2	-1,1	1,3	1,9	1,9	-2,5	1,0	-1,1	-1,4	-1,2	-1,2	-1,9	1,8	-1,2	1,0
	liver proliferation					necrosis & GSH depletion & oxidative stress	CPB2	ILMN_2391436	-1,2	1,3	1,1	1,7	-1,2	-5,2	-1,1	-1,2	1,0	1,1	1,3	-1,1	1,0	-1,0	-1,1
	liver proliferation					necrosis & GSH depletion & oxidative stress	DICER1	ILMN_2349831	-1,2	1,2	-1,0	3,1	-1,2	-4,2	-1,1	1,1	1,2	-1,0	1,0	-1,0	-1,0	-1,4	1,1
	liver proliferation					necrosis & GSH depletion & oxidative stress	FAH	ILMN_1781536	1,0	1,5	1,1	-1,2	-1,0	1,7	1,1	2,5	1,5	-1,0	1,2	-1,1	1,7	1,0	1,0
	liver proliferation					necrosis & GSH depletion & oxidative stress	FGA	ILMN_2280203	-1,0	1,3	-1,1	5,1	-1,5	-17,1	-1,3	-1,2	-1,4	-1,1	-1,1	-1,0	-1,3	1,1	-1,0
	liver proliferation					necrosis & GSH depletion & oxidative stress	MET	ILMN_1715175	1,1	1,0	1,0	1,8	-1,2	-3,2	-1,1	-1,3	1,1	1,0	-1,0	-1,0	-1,1	-1,3	-1,3
	liver proliferation					necrosis & GSH depletion & oxidative stress	MT1H	ILMN_1683923	-1,2	-1,1	1,0	2,9	-1,4	-5,0	-1,1	-1,4	-1,4	-1,1	2,0	-1,1	-1,3	1,2	-1,2
	liver proliferation					necrosis & GSH depletion & oxidative stress	MYC	ILMN_2110908	1,0	-1,2	1,1	1,1	-1,2	-3,5	1,0	-1,3	1,1	-1,1	1,1	1,1	-1,9	-1,2	1,0
	liver proliferation					necrosis & GSH depletion & oxidative stress	PIK3R1	ILMN_2398235	1,2	1,1	1,2	2,6	-1,2	-5,4	-1,1	-1,2	1,1	1,0	-1,0	1,0	-1,1	1,0	-1,1
	liver proliferation					necrosis & GSH depletion & oxidative stress	SOCS3	ILMN_2156250	1,3	-1,2	-1,3	-1,0	-1,1	-1,0	-1,2	1,0	-1,1	1,2	1,2	1,3	-4,2	-1,0	-1,4
	liver proliferation					necrosis & GSH depletion & oxidative stress	MT1E	ILMN_1718968	-1,1	-1,1	-1,2	1,1	1,2	1,3	-1,1	1,0	-1,1	1,1	-1,9	-1,0	-1,6	-1,2	-2,0
	liver proliferation						ACTG1	actin, gamma 1	ILMN_1704961	1,0	-1,1	-1,0	-1,7	-1,1	1,2	1,0	-1,3	2,0	-1,4	2,1	1,5	-1,1	-1,1	-1,2
	liver proliferation						AKR1C2	aldo-keto reductase family 1, member C2	ILMN_1719154	2,2	1,3	1,0	-1,1	-1,1	2,2	1,1	-1,2	-1,3	-1,1	-2,1	-1,0	1,0	-1,0	1,0
	liver proliferation						APP	amyloid beta (A4) precursor protein	ILMN_1653283	1,3	-1,2	1,2	-2,2	-1,0	1,7	1,3	-1,0	-1,1	-1,6	-1,2	1,1	-1,2	1,1	-1,1
	liver proliferation						ATF3	activating transcription factor 3	ILMN_2374865	-1,3	-1,4	1,1	1,2	-1,1	1,1	1,0	-1,1	-1,1	-1,2	1,3	-1,6	-2,3	1,0	-1,6
	liver proliferation						ATF4	activating transcription factor 4	ILMN_2358457	1,0	-1,2	1,1	1,3	-1,1	-2,2	-1,2	1,4	1,1	1,1	-1,0	-1,0	1,1	-1,0	-1,0
	liver proliferation						BAG2	BCL2-associated athanogene 2	ILMN_3244893	-1,0	-1,2	1,0	1,6	1,0	-2,4	1,1	-1,3	-1,0	1,1	1,1	1,0	1,4	-1,1	1,3
	liver proliferation						BZW1	basic leucine zipper and W2 domains 1	ILMN_1793846	1,3	-1,0	-1,2	2,0	-1,4	-2,8	-1,1	1,1	1,0	1,1	1,1	-1,1	1,0	1,1	-1,1
	liver proliferation						C7	complement component 7	ILMN_1687848	1,1	-1,0	-1,6	-1,0	1,1	-4,5	1,1	1,0	-1,1	1,0	1,1	-1,3	1,0	1,2	-1,2
	liver proliferation						C9	complement 9	ILMN_1767831	-1,1	1,6	-1,0	2,4	1,0	-5,4	1,3	-1,2	1,5	1,1	-1,2	-1,1	1,0	1,2	-1,3
	liver proliferation						CFHR3	complement factor H-related 3	ILMN_1805799	-1,1	1,1	-1,2	1,3	3,4	-1,3	-1,2	1,1	-1,2	-1,3	1,2	-1,5	-1,0	-1,1	-1,4
	liver proliferation						CFHR4	complement factor H-related 4	ILMN_1665855	1,2	1,2	-1,4	-1,0	3,1	1,3	1,2	-1,0	-1,2	1,5	-1,6	-1,3	-1,1	1,1	-1,2
	liver proliferation						CP	ferroxidase	ILMN_1813206	-1,1	1,1	-1,3	1,3	1,9	-2,1	1,0	-1,8	1,2	-1,1	1,1	1,2	-1,7	1,1	-1,2
	liver proliferation						CREB3L3	cAMP responsive element binding protein 3-like	ILMN_1779524	1,3	1,5	1,2	-1,0	1,6	1,9	1,6	1,0	-1,2	1,1	1,3	2,0	-4,5	1,3	1,2
	liver proliferation						CREM	cAMP responsive element modulator1	ILMN_1745318	1,2	1,0	1,2	2,4	1,0	-2,6	1,1	1,1	-1,0	1,4	1,2	-1,2	1,2	1,1	1,0
	liver proliferation						CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	ILMN_1807291	2,0	2,6	2,4	1,0	1,5	1,9	1,0	1,5	1,6	4,9	1,9	1,1	3,1	3,1	4,7
	liver proliferation						CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 1	ILMN_1683607	1,8	1,7	1,8	-1,1	2,5	1,4	1,2	2,2	1,7	2,9	2,2	-1,3	2,0	1,6	2,0
	liver proliferation						CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	ILMN_1670652	1,0	1,9	-1,1	-1,1	1,5	1,3	-1,3	2,2	3,4	-1,7	1,3	-2,4	2,3	1,7	1,3
	liver proliferation						DDX3X	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked	ILMN_1728870	1,4	1,1	-1,0	2,5	1,0	-2,6	1,0	-1,0	1,2	-1,0	1,1	1,0	-1,4	-1,1	1,0
	liver proliferation						DGAT2	diacylglycerol O-acyltransferase 2	ILMN_1681520	2,1	1,1	1,2	1,2	1,2	-2,2	-1,8	-1,4	1,1	-1,2	1,1	1,1	1,5	-1,3	-1,0
	liver proliferation						ECT2	epithelial cell transforming sequence 2 oncogene	ILMN_1717173	1,1	-1,2	1,1	1,9	-1,0	-2,3	1,2	1,0	1,1	1,1	1,0	1,5	-2,0	-1,1	-1,0
	liver proliferation						EIF1AX	eukaryotic translation initiation factor 1A, X-linked	ILMN_1813240	1,4	-1,1	-1,0	3,6	-1,1	-5,1	1,3	-1,2	1,8	-1,1	1,0	1,0	-1,3	1,1	-1,0
	liver proliferation						EIF4E	eukaryotic translation initiation factor 4E	ILMN_2050761	1,1	1,3	1,3	3,0	-1,4	-5,6	1,0	-1,4	1,1	1,0	1,0	-1,1	-1,0	1,0	1,1
	liver proliferation						ERBB2	epidermal growth factor	ILMN_1717902	1,0	-1,1	-1,0	-1,2	-1,2	1,1	-1,2	1,0	-1,0	-1,2	-1,8	-1,1	2,2	-1,0	-1,2
	liver proliferation						FCN3	ficolin	ILMN_2349771	1,2	1,2	1,0	-1,3	2,3	2,8	1,1	2,3	3,0	1,1	1,2	1,3	-1,2	1,2	-1,2
	liver proliferation						FGL1	fibrogen like 1	ILMN_1672872	1,1	1,2	1,2	5,1	-1,0	-16,5	1,4	-1,2	1,1	1,2	-1,1	1,0	-1,4	1,0	1,0
	liver proliferation						FN1	fibronectin 1	ILMN_1778237	1,6	1,1	-1,1	-1,2	-1,1	1,1	-1,1	1,1	-1,3	-1,1	-2,6	-1,3	-1,1	-1,1	-1,2
	liver proliferation						GDPD1	glycerophosphodiester phosphodiesterase domain containing 1	ILMN_2106265	-1,2	-1,2	-1,2	1,8	1,1	-2,1	1,1	1,0	-1,0	1,0	-1,1	-1,2	1,1	-1,1	-1,2
	liver proliferation						HAMP	hepcidin antimicrobial peptide	ILMN_1729188	1,1	-1,2	-1,2	1,5	-8,0	5,5	-1,3	-1,3	-1,0	1,9	2,1	5,8	-3,7	1,4	1,1
	liver proliferation						HGS	hepatocyte growth factor-regulated tyrosine kinase substrate1	ILMN_1715994	-1,0	1,2	-1,1	-1,3	-1,0	2,1	1,3	1,1	-1,2	1,1	1,2	1,1	-1,2	1,2	1,1
	liver proliferation						HIF1A	hypoxia inducible factor 1, alpha subunit	ILMN_2379788	1,0	1,1	-1,0	2,9	-1,7	-7,4	-1,1	1,0	-1,1	1,1	-1,1	2,0	-2,3	-1,1	-1,2
	liver proliferation						HUWE1	HECT, UBA and WWE domain containing 1, E3 ubiquitin protein ligase	ILMN_1790987	1,1	1,0	1,1	-1,1	-2,0	-1,2	-1,2	-1,4	1,1	1,0	1,0	-1,1	-1,1	1,2	1,0
	liver proliferation						IGFBP3	insulin-like growth factor binding protein 3	ILMN_1746085	-1,1	-1,0	1,3	2,1	2,2	-1,1	1,2	-1,4	1,2	-1,4	1,4	-1,4	-1,7	-1,1	1,2
	liver proliferation						MAD1L1	MAD1 mitotic arrest deficient-like 1	ILMN_2358074	-1,1	1,3	1,1	1,2	1,0	-1,9	1,0	1,3	-1,4	-1,2	1,2	-1,3	2,5	1,1	-1,0
	liver proliferation						MASP1	mannan-binding lectin serine peptidase 1	ILMN_2240866	-1,1	1,2	1,0	1,2	1,2	-1,2	1,2	-1,2	-1,2	-1,3	-1,1	-2,2	1,0	1,1	-1,1
	liver proliferation						MAT2A	methionine adenosyltransferase II, alpha	ILMN_1737298	1,2	1,5	2,9	2,1	1,7	3,2	1,4	1,5	1,5	1,6	-1,1	1,8	1,2	1,4	-1,1
	liver proliferation						NNMT	nicotinamide N-methyltransferase	ILMN_1715508	-1,2	1,0	-1,1	-1,1	1,2	2,0	2,0	-1,4	-1,1	1,1	1,3	1,3	-2,6	1,2	-1,2
	liver proliferation						NUPR1	nuclear protein, transcriptional regulator, 1	ILMN_2404688	1,1	-1,1	1,1	-1,1	-1,3	1,5	1,3	1,2	-2,0	-1,0	1,2	-1,4	1,6	1,2	1,0
	liver proliferation						OSMR	oncostatin M receptor	ILMN_2205999	1,1	-1,0	-1,2	-1,2	1,4	-1,0	1,4	-1,1	1,4	-1,0	1,4	1,2	-2,1	1,2	-1,1
	liver proliferation						PDGFRA	platelet-derived growth factor receptor, alpha polypeptide	ILMN_2086470	1,2	-1,0	-1,1	1,9	1,1	-2,6	-1,1	-1,2	-1,0	1,5	-1,3	1,3	-1,9	1,0	-1,2
	liver proliferation						PGLYRP2	peptidoglycan recognition protein 2	ILMN_1701778	-1,0	2,1	1,1	1,0	1,3	1,0	-1,1	1,2	1,1	-1,5	1,1	-2,0	1,4	1,5	1,0
	liver proliferation						PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	ILMN_1705468	-1,0	1,0	1,1	1,4	1,1	-2,1	-1,0	-1,1	1,1	-1,0	-1,1	1,1	1,0	-1,1	-1,2
	liver proliferation						PPP2CB	protein phosphatase 2, catalytic subunit, beta isozyme	ILMN_1768582	-1,2	-1,2	1,1	3,9	1,1	-13,7	-1,1	1,3	1,2	-1,0	-1,1	-1,1	1,0	-1,1	-1,2
	liver proliferation						PRKAR1A	protein kinase, cAMP-dependent, regulatory, type I, alpha	ILMN_2389590	1,3	1,1	1,1	2,8	1,1	-4,4	1,3	-1,3	1,1	1,0	-1,0	-1,2	1,1	1,3	-1,1
	liver proliferation						PSMB9	proteasome (prosome, macropain) subunit, beta type, 9	ILMN_2376108	-1,0	1,2	1,4	-2,3	-1,1	2,1	1,3	1,2	-1,1	-1,1	1,1	1,0	-2,6	1,1	-1,5
	liver proliferation						RAN	member RAS oncogene family	ILMN_3307930	-1,4	1,0	1,0	-1,8	-1,7	2,0	-1,0	1,1	-1,1	1,0	1,2	1,2	-1,4	1,0	1,3
	liver proliferation						REG1B	regenerating islet-derived 1 beta	ILMN_1681462	1,0	-1,3	-1,2	1,4	1,5	4,0	1,0	1,0	1,1	1,4	1,5	2,9	-1,2	1,2	1,3
	liver proliferation						RPL9	ribosomal protein L9	ILMN_2408415	1,2	-1,0	1,2	5,1	-1,1	-8,5	1,1	-1,9	1,2	-1,0	-1,2	-1,0	-1,0	1,0	-1,0
	liver proliferation						SENP6	SUMO1/sentrin specific peptidase 6	ILMN_2054236	1,0	1,2	1,1	1,3	-1,1	-2,1	1,1	-1,1	-1,0	1,0	-1,2	-1,0	-1,1	-1,2	-1,3
	liver proliferation						SLC15A1	PEPT-1	ILMN_1652857	-1,2	-1,0	1,1	1,5	-1,2	-3,0	-1,1	-1,1	1,0	-1,2	-1,1	-1,3	1,5	-1,2	1,3
	liver proliferation						SSTR1	somatostatin receptor 1	ILMN_2069745	1,4	1,0	1,1	1,4	1,3	-2,2	-1,0	-1,1	1,0	-1,1	1,2	-1,0	1,4	1,0	1,1
	liver proliferation						SSTR2	somatostatin receptor 2	ILMN_2152257	-1,2	-1,1	-1,1	2,7	-1,1	-2,9	1,0	-1,4	1,1	1,0	1,1	-1,1	-1,3	-1,2	-1,2
	liver proliferation						TDO2	tryptophan 2,3-dioxygenase	ILMN_2172091	1,3	1,9	1,3	3,5	1,3	-11,7	-1,0	1,3	1,0	1,1	1,1	1,2	1,2	-1,1	-1,0
	liver proliferation						UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	ILMN_1697967	-1,1	1,6	2,1	-1,7	1,6	1,1	-1,0	1,2	2,2	1,4	1,3	1,0	1,0	1,5	1,3
	liver proliferation						VPS37A	vacuolar protein sorting 37 homolog A	ILMN_1711139	1,1	-1,3	1,1	1,9	1,0	-2,3	1,2	-1,3	1,3	-1,2	1,2	-1,2	1,1	-1,3	-1,1
	liver proliferation						XIST	X (inactive)-specific transcript	ILMN_1764573	-1,2	-1,2	-1,0	1,5	2,3	1,9	-1,0	-1,1	-1,1	-1,0	1,2	1,0	1,0	-1,1	-1,0
	liver proliferation						YWHAG	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide	ILMN_1750145	1,1	1,0	-1,0	2,2	-1,0	-3,2	1,5	-1,6	1,6	1,0	1,3	1,1	1,2	-1,1	-1,2
	liver proliferation						H19	imprinted maternally expressed transcript (non-protein coding)	ILMN_2148527	-1,5	1,4	1,3	1,2	1,6	-1,5	1,0	-1,1	-1,2	-1,1	1,6	-3,6	1,4	-1,1	1,0
	liver proliferation						PAQR4	progestin and adipoQ receptor family member IV	ILMN_1660793	-1,0	-1,0	-1,2	-1,2	1,5	1,3	1,0	1,1	1,1	-1,3	1,3	-2,1	1,2	1,1	1,0
	liver proliferation						CA9	Carbonic Anhydrase IX	ILMN_1725139	-1,0	1,1	-1,0	1,3	1,3	-1,0	1,1	-1,0	1,0	-1,3	1,1	-2,5	-1,0	-1,2	-1,2
	liver proliferation						SLC35C1	solute carrier family 35, member C1	ILMN_1680104	-1,2	-1,2	-1,8	-1,4	-1,1	1,3	-1,1	-1,3	1,0	1,0	-1,2	1,3	-2,0	-1,1	-1,1
	liver proliferation						FOS	FBJ murine osteosarcoma viral oncogene homolog	ILMN_1669523	1,5	1,2	1,4	1,4	1,3	1,2	-1,1	-1,1	1,4	1,1	-1,2	1,0	-2,4	-1,2	-1,3
	liver proliferation						BMP4	bone morphogenetic protein 4 (not in liver)	ILMN_1740900	1,0	1,1	1,5	-1,3	-1,2	1,1	-1,3	1,2	1,0	-1,2	-1,2	-1,3	2,4	-1,0	1,1
		fibrosis & cirrhosis	Steatosis		necrosis & GSH depletion & oxidative stress	KRT8	keratin 8	ILMN_1753584	-1,1	1,1	-1,3	-2,1	-1,8	1,5	-1,3	1,2	1,1	1,0	1,0	1,1	1,2	1,1	1,3
		fibrosis & cirrhosis		cholestasis	necrosis & GSH depletion & oxidative stress	CAT	catalase	ILMN_2151739	1,3	1,3	1,3	3,2	1,0	-6,7	1,5	-1,4	-1,1	-1,1	-1,2	-1,3	2,2	1,2	-1,0
		fibrosis & cirrhosis		cholestasis		CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	ILMN_1701661	-1,1	-1,1	1,1	1,1	-1,5	-2,2	1,1	-1,0	1,0	-1,0	1,1	1,1	-1,2	-1,0	1,0
		fibrosis & cirrhosis		cholestasis		PAH	phenylalanine hydroxylase	ILMN_2218104	1,1	1,2	1,1	2,9	-1,1	-12,7	-1,3	1,0	-1,0	-1,1	-1,2	-1,2	2,7	-1,0	1,1
		fibrosis & cirrhosis			necrosis & GSH depletion & oxidative stress	CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	ILMN_1772206	1,1	-1,0	-1,0	3,0	-3,8	-2,6	-1,1	-1,1	1,5	1,1	-1,3	-1,5	3,6	1,1	-1,6

inflammation & hepatitis	liver proliferation	fibrosis & cirrhosis	Steatosis	cholestasis	necrosis & GSH depletion & oxidative stress	SYMBOL		PROBE_ID	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14	D1	D3	D14
		fibrosis & cirrhosis				CCL13	chemokine ligand 13	ILMN_1783593	1,2	1,0	1,1	1,2	1,2	1,3	-1,1	1,3	1,3	-1,2	1,1	2,7	-1,0	-1,1	1,0
		fibrosis & cirrhosis				CCL3	chemokine (C-C motif) ligand 3	ILMN_1671509	-1,2	1,0	-1,4	-1,2	-1,3	1,3	1,1	1,1	-1,1	-1,2	1,0	3,5	-1,8	-1,1	-2,3
		fibrosis & cirrhosis				CCR6	chemokine (C-C motif) receptor 6	ILMN_2387696	1,1	-1,1	1,0	2,1	-1,1	-1,2	1,1	-1,3	-1,0	-1,1	-1,1	-1,1	1,2	1,1	1,4
		fibrosis & cirrhosis				CD38	CD38 molecule	ILMN_2233783	-1,1	-1,1	1,0	-1,2	1,1	1,1	1,1	1,1	1,0	1,0	1,1	2,9	-2,7	-1,0	-1,8
		fibrosis & cirrhosis				CSF2RA	colony stimulating factor 2 receptor, alpha, low-affinity	ILMN_2376458	1,0	-1,1	1,0	2,2	1,1	-2,0	1,1	1,0	-1,0	1,1	1,0	-1,2	-1,0	1,0	-1,0
		fibrosis & cirrhosis				FBLN2	fibumin 2	ILMN_1774602	1,2	-1,0	1,0	-1,2	-1,1	2,2	-1,2	-1,0	-1,0	-1,1	1,1	-1,0	-1,1	-1,1	1,1
		fibrosis & cirrhosis				HABP2	hyaluronan binding protein	ILMN_1737041	-1,0	0,0	1,1	-2,6	-1,4	1,5	-1,3	1,0	1,1	-1,3	-1,4	-1,2	1,1	1,0	1,2
		fibrosis & cirrhosis				HNRNPK	heterogeneous nuclear ribonucleoprotein K	ILMN_3260017	-1,7	1,1	1,2	1,1	-2,0	-1,2	-1,2	-1,0	1,1	1,3	-1,0	1,1	-1,3	1,0	-1,0
		fibrosis & cirrhosis				IL1A	interleukin 1, alpha	ILMN_1658483	1,0	1,0	1,1	1,1	1,0	1,1	-1,2	1,2	1,1	1,1	-1,1	1,1	-1,2	1,2	-2,4
		fibrosis & cirrhosis				ITGA6	integrin alpha 6	ILMN_2359287	1,1	-1,1	-1,2	2,4	-1,2	-4,9	1,2	-1,1	1,1	1,3	-1,2	-1,0	-1,0	-1,1	1,0
		fibrosis & cirrhosis				MMP1	matrix metallopeptidase 1	ILMN_1726448	1,1	-1,2	1,4	5,4	1,4	-1,5	1,2	1,2	-1,2	1,3	1,2	1,1	-1,0	1,4	1,3
		fibrosis & cirrhosis				PCNA	proliferating cell nuclear antigen	ILMN_1694177	1,3	-1,0	1,0	2,3	1,1	-2,6	1,1	1,0	1,1	-1,1	-1,0	1,1	1,2	-1,0	-1,0
		fibrosis & cirrhosis				PKD2	polycystic kidney disease 2	ILMN_1807300	1,2	1,1	1,1	1,4	-1,1	-2,3	1,0	1,0	1,0	-1,1	-1,1	1,1	1,1	-1,0	1,1
		fibrosis & cirrhosis				VEGFA	vascular endothelial growth factor A	ILMN_2375879	-1,2	-1,0	1,2	1,6	2,3	1,2	2,0	-1,1	-1,1	1,2	-1,1	1,1	-1,0	-1,1	-1,1
		fibrosis & cirrhosis				SLC51B	solute carrier family 51, beta subunit	ILMN_1750312	1,2	1,1	-1,2	1,2	-1,0	-1,3	1,1	-1,0	1,0	1,3	-1,3	1,1	2,1	1,2	1,0
			Steatosis		necrosis & GSH depletion & oxidative stress	CDKN1B	cyclin-dependent kinase inhibitor 1B	ILMN_2196347	1,4	-1,1	1,2	3,1	1,2	-6,5	1,4	-1,7	-1,1	1,0	1,1	-1,1	1,1	1,0	-1,1
			Steatosis		necrosis & GSH depletion & oxidative stress	G6PC	glucose-6-phosphatase, catalytic subunit	ILMN_1738414	-1,0	1,1	1,1	1,1	-1,5	-1,6	-1,0	-1,0	-2,1	1,0	-1,0	-1,2	2,0	-1,2	1,2
			steatosis		necrosis & GSH depletion & oxidative stress	PPARGC1A	peroxisome proliferative activated receptor, gamma, coactivator 1 alpha	ILMN_1750062	1,1	1,0	1,4	1,0	-1,1	1,2	-1,2	-1,2	1,1	-1,0	-1,1	-1,2	2,3	1,0	-1,1
			steatosis			ACSL4	acyl-CoA synthetase long-chain family member 4	ILMN_2391458	1,1	-1,2	-3,2	-1,1	1,0	1,7	1,1	1,1	1,0	-1,0	-1,1	1,1	-1,1	-1,0	-1,1
			Steatosis			CIDEC	cell death-inducing DFFA-like effector c1	ILMN_2174437	1,4	1,5	-2,0	-1,5	2,1	1,9	1,6	1,1	-1,2	1,0	-1,1	1,4	-1,2	-1,1	-1,1
			Steatosis			CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	ILMN_1735816	-1,2	3,3	-1,0	-1,2	2,1	1,1	1,2	1,2	1,1	-1,1	1,3	-1,9	1,3	-1,1	1,1
			Steatosis			ELOVL5	fatty acid elongase	ILMN_2174369	-1,1	-1,1	-1,2	1,4	-1,3	-2,4	-1,1	-1,1	1,1	1,2	-1,4	1,0	1,1	-1,4	-1,0
			Steatosis			FABP4	fatty acid binding protein	ILMN_1773006	2,1	2,0	-1,1	-1,4	1,3	2,0	1,1	1,6	-1,0	-1,4	-1,5	-1,7	1,0	-1,4	-1,2
			Steatosis			FABP5	fatty acid binding protein	ILMN_1696302	1,4	-1,2	1,1	3,5	1,1	-4,8	1,3	-1,0	-1,2	1,1	-1,1	1,2	-1,0	-1,0	-1,2
			Steatosis			FASN	fatty acid synthetase	ILMN_1784871	-1,5	-1,3	-1,0	-1,9	-2,4	1,2	1,3	1,1	-1,3	-1,2	-1,5	-1,4	1,4	1,0	1,0
			Steatosis			FGF21	fibroblast growth factor 21	ILMN_1772789	-1,1	-2,8	1,3	-1,7	-1,2	1,0	1,1	-1,2	-1,4	-1,2	-1,0	-1,4	1,3	-1,2	1,2
			Steatosis			GCK	glucokinase glucose metabolism	ILMN_1676437	-1,2	-1,0	1,1	-1,1	1,0	1,1	-1,2	1,2	-1,1	1,0	-1,1	-2,1	4,3	1,4	-1,0
			Steatosis			HSD11B1	hydroxysteroid (11-beta) dehydrogenase	ILMN_2389501	-1,3	1,8	-1,0	-1,2	1,6	1,3	1,1	2,0	2,1	1,2	1,3	1,2	1,0	-1,0	-1,1
			Steatosis			OMA1	OMA1 zinc metallopeptidase homolog	ILMN_2094938	1,4	1,1	1,1	2,5	1,1	-5,4	-1,1	1,2	-1,2	1,3	1,1	1,0	1,5	1,3	1,1
			Steatosis			PCK1	phosphoenolpyruvate carboxykinase 1	ILMN_2197381	1,3	-1,1	-1,3	4,4	2,3	-2,5	1,1	-1,1	1,1	-1,0	1,2	1,3	3,0	1,4	1,9
			Steatosis			PEX13	peroxisomal biogenesis factor 13	ILMN_2113957	1,5	1,2	1,1	1,7	1,1	-2,4	-1,4	1,0	-1,0	1,0	-1,1	1,1	1,1	-1,4	1,0
			Steatosis			PEX3	peroxisomal biogenesis factor 3	ILMN_2057389	1,4	1,0	1,1	1,8	1,4	-2,9	-1,1	-1,2	1,3	-1,0	-1,2	-1,1	1,4	-1,1	-1,1
			Steatosis			PLIN2	perilipin 2 (	ILMN_2138765	-1,2	1,2	-1,3	1,5	2,1	-1,1	1,4	1,2	1,1	-1,0	1,1	-1,2	1,0	-1,4	1,1
			Steatosis			PNRC2	proline-rich nuclear receptor coactivator 2	ILMN_1778957	1,2	-1,1	1,1	1,7	1,5	-2,5	1,1	1,0	1,3	1,0	-1,0	1,0	-1,1	-1,1	-1,2
			steatosis			SAA2	serum amyloid A2	ILMN_1728262	-1,1	-1,1	1,4	1,0	-1,5	-5,1	1,3	-1,5	-1,4	-1,1	1,3	1,2	-1,2	2,5	1,0
			Steatosis			VHL	von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase	ILMN_2376625	1,3	1,2	1,1	1,9	1,5	-2,3	1,1	1,1	-1,1	1,2	-1,0	-1,0	-1,1	-1,1	1,0
			steatosis			TSC22D3	TSC22 domain family, member 3 (lien avec IL10)	ILMN_2376403	1,3	-1,1	1,6	-1,3	1,3	1,1	-1,0	-1,2	1,3	1,0	-1,0	-1,4	2,0	1,1	1,0
				cholestasis	necrosis & GSH depletion & oxidative stress	GSTA2	glutathione S-transferase alpha 2	ILMN_3251540	1,5	1,1	-1,3	-2,3	-1,0	-1,3	1,0	-1,1	-1,6	-1,7	-1,4	-1,2	1,4	2,0	1,1
				cholestasis	necrosis & GSH depletion & oxidative stress	NR0B2	nuclear receptor subfamily 0, group B, member 2	ILMN_2220978	-1,0	-1,0	-1,6	-1,4	1,1	-1,1	-1,4	-1,2	-1,9	-1,1	-1,1	1,6	1,8	1,2	2,3
				cholestasis		ACSL1	acyl-CoA synthetase long-chain family member 1	ILMN_1684585	1,2	-1,3	1,1	2,2	1,1	-2,1	1,5	1,2	1,4	1,1	1,0	1,0	1,3	-1,1	-1,1
				cholestasis		ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	ILMN_1797912	-1,1	1,5	-1,6	-1,0	-1,1	-1,2	-1,2	1,1	-2,0	-1,1	-1,2	-2,2	4,5	1,1	1,0
				cholestasis		GJA1	gap junction protein	ILMN_1727087	1,3	-1,2	-1,1	2,1	1,6	-2,1	1,3	1,1	1,2	-1,0	1,1	-1,3	1,1	-1,0	-1,1
				cholestasis		GK	glycerol kinase	ILMN_1725471	-1,1	1,1	-2,1	-1,0	1,5	1,3	1,2	1,1	1,0	1,3	1,3	1,9	-1,7	1,0	-1,1
				cholestasis		GPX2	glutathione peroxidase	ILMN_2133205	-1,2	1,1	1,1	-1,5	-1,1	2,2	1,3	1,5	1,1	1,0	1,0	1,4	-1,9	1,3	1,0
				cholestasis		MGST1	microsomal glutathione S-transferase 1	ILMN_1803033	-1,4	-1,0	1,2	-1,2	1,1	2,1	1,1	1,1	-1,2	1,2	-1,1	-1,2	1,2	1,2	-1,2
				cholestasis		MUT	methylmalonyl CoA mutase	ILMN_2078074	1,2	-1,0	1,3	1,1	1,0	-2,3	-1,1	-1,0	-1,0	1,1	1,1	1,1	1,6	-1,2	1,1
				cholestasis		SLC12A2	solute carrier family 12 (sodium/potassium/chloride transporters)	ILMN_2059452	1,0	1,2	1,1	2,9	-1,1	-6,2	1,3	-1,2	-1,1	-1,1	0,0	1,0	-1,1	-1,0	1,1
				cholestasis		SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	ILMN_2404795	-1,1	-1,1	-1,1	2,1	1,0	-1,2	1,1	1,1	-1,1	1,1	-1,0	1,0	-1,2	1,2	-1,1
				cholestasis		TAP2	transporter 2, ATP-binding cassette, sub-family B	ILMN_1777565	1,2	-1,0	1,1	-1,4	1,2	1,2	-1,1	1,5	-1,0	1,0	-1,2	1,6	-2,9	1,0	-1,4
				cholestasis		UGP2	UDP-glucose pyrophosphorylase 2	ILMN_2284181	1,2	-1,0	1,6	4,4	-1,1	-9,4	1,1	1,0	-1,2	-1,0	-1,1	-1,3	1,1	-1,3	-1,1
				cholestasis		UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	ILMN_1742444	0,0	1,9	-1,1	1,2	-1,1	-1,6	-1,3	1,0	-1,2	-1,1	-1,5	-1,8	1,8	1,1	1,3
				cholestasis		UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	ILMN_1739624	-1,2	1,3	1,9	1,1	1,2	-8,1	-1,0	-1,1	1,0	-1,1	-1,1	-1,5	1,8	1,2	-1,0
				cholestasis		ADH6	alcohol dehydrogenase 6 (alcolhol metabolization)	ILMN_1691175	-1,1	1,5	1,2	-1,4	1,2	1,0	-1,1	1,2	-1,2	-1,2	-1,4	-1,8	2,2	1,2	-1,2
					necrosis & GSH depletion & oxidative stress	CFH	complement factor H	ILMN_1698144	1,0	1,5	1,5	3,6	1,3	-7,4	-1,1	1,0	-1,1	1,1	-1,1	-1,1	1,1	1,0	-1,2
					necrosis & GSH depletion & oxidative stress	CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	ILMN_1693338	1,1	1,7	2,7	1,1	1,4	1,4	-1,2	1,4	1,4	1,3	1,3	1,7	1,4	1,3	1,5
					necrosis & GSH depletion & oxidative stress	DDIT3	DNA-damage inducible transcripts	ILMN_1676984	-1,4	-2,0	1,5	-1,1	-1,1	1,1	1,0	-1,2	-1,7	-1,0	1,1	-1,3	-1,1	-1,1	1,2
					necrosis & GSH depletion & oxidative stress	GCLC	glutamate-cysteine ligase, catalytic subunit	ILMN_2215194	1,2	1,2	1,2	1,9	-1,4	-5,6	1,2	-1,3	1,1	-1,2	-1,3	-1,2	1,3	-1,1	-1,3
					necrosis & GSH depletion & oxidative stress	GSTA4	glutathione S-transferase alpha 4	ILMN_1771964	1,1	1,4	1,1	1,0	1,3	1,2	-1,3	1,1	-1,2	1,1	-1,0	-1,1	2,2	1,2	-1,0
					necrosis & GSH depletion & oxidative stress	GSTA5	glutathione S-transferase alpha 5	ILMN_1788122	1,3	1,1	-1,2	1,5	-1,6	-1,9	1,3	-1,5	-1,4	-1,3	-1,2	-1,2	2,1	1,9	-1,0
					necrosis & GSH depletion & oxidative stress	GSTM1	glutathione S-transferase mu 1	ILMN_1668134	1,0	1,4	1,3	-1,0	-1,4	1,1	-1,0	-1,0	1,1	-1,3	-1,3	-1,4	2,0	1,1	-1,4
					necrosis & GSH depletion & oxidative stress	IER3	immediate early response 3	ILMN_1682717	1,0	1,3	1,2	1,0	1,3	1,4	1,3	1,2	1,1	1,3	1,3	1,8	-3,1	-1,2	-1,1
					necrosis & GSH depletion & oxidative stress	IRF2	interferon regulatory factor 2	ILMN_2090607	-1,2	-1,0	1,2	1,4	-1,6	-2,1	-1,2	-1,1	-1,0	-1,3	-1,0	1,1	-1,2	-1,3	-1,4
					necrosis & GSH depletion & oxidative stress	IRF8	interferon regulatory factor 8	ILMN_1666594	1,1	1,0	-1,2	-1,5	1,1	1,4	-1,1	1,1	-1,1	1,1	-1,2	1,2	-2,3	1,2	-2,0
					necrosis & GSH depletion & oxidative stress	RGN	regucalcin	ILMN_1707592	1,2	1,2	1,2	-1,4	1,9	1,3	-1,1	1,6	1,7	-1,3	-1,3	-1,5	2,5	1,0	1,2
					necrosis & GSH depletion & oxidative stress	SEPP1	selenoprotein P, plasma, 1	ILMN_2204826	1,0	-1,0	1,4	2,9	-1,1	-11,9	1,2	-1,2	-1,3	1,1	-1,1	-1,2	2,1	1,2	1,1
					necrosis & GSH depletion & oxidative stress	TNFSF14	tumor necrosis factor (ligand) superfamily, member 14	ILMN_2363392	1,0	1,1	1,2	2,7	1,2	-1,5	1,1	1,2	-1,0	-1,3	-1,1	1,1	-2,0	-1,0	-1,1
					necrosis & GSH depletion & oxidative stress	YES1	v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1	ILMN_1691466	-1,2	1,0	1,3	1,9	1,0	-3,2	1,1	-1,3	1,2	-1,0	-1,1	-1,2	1,0	-1,1	-1,1