Supporting Information

Assessment of Drug-Induced Liver Injury through cell morphology and gene expression analysis.

Vanille Lejal[1], Natacha Cerisier[1], David Rouquie[2,3], Olivier Taboureau[1]*

[1] Université Paris Cité, Inserm U1133, CNRS UMR 8251, Paris, France.

[2] Bayer SAS, Bayer Crop Science, 355 rue Dostoïevski, CS 90153, 06906, Valbonne Sophia-Antipolis, France.

[3] Université Côte d'Azur 3IA Interdisciplinary Institute in Artificial Intelligence, France.

Table of Contents

Supplementary Figures

Supplementary S1. Remaining pathway analysis of Cell-Painting features-based clusters of hepatotoxic compounds from the CP_DILIs_pos_neg dataset, and heatmaps and pathway analysis related to Cell-Painting features-based clusters of hepatotoxic compounds from the CP_DILIs_most_neg, CP_eTox_H_HT, CP_eTox_H_MF, CP_eTox_H_MFHB and CP_eTox_H_MFHC datasets.

- *CP_DILIs_pos_neg dataset*

Our analysis highlighted supplementary functional signaling pathways that could be related to hepatic injury. One of them deals with carbohydrate homeostasis. We noticed that hepatotoxic compounds of 39 affected gene expression coding associated with the apelin signaling pathway (Figure 6A). Apelin is a peptide that forms a ligand-receptor complex with the APJ receptor. Although the Apelin/APJ system plays a role in cardiac disease, in glycometabolism and fat metabolism and more generally in diabetic complications, it can contribute also in the liver to favor hepatic fibrosis and cirrhosis through an increased Fas production and apoptosis[1]. In addition, clusters 26 and 55 both had an impact on genes coding for proteins of the AGE-RAGE signaling pathway in diabetic complications. The coexistence of type 2 diabetes mellitus and Nonalcoholic Fatty Liver Disease (NAFLD) is known to be frequently observed[2,3]. Finally, Gene Ontology enrichment mentioned that clusters 23, 48 and 55 all had consequences on gene expression related to fat accumulation and sterol biosynthesis (Figure 6B) that are directly connected to steatosis and NAFLD too[4,5].

We already mentioned the perturbation of genes associated with hyperoxia, but a supplementary term related to the regulation of the oxygen levels concerning Hypoxia Inducible Factor 1 (HIF-1) was identified for hepatotoxic compounds of cluster 13 (Figure

6B). HIF-1 is a transcription factor that is activated in case of perturbations of the oxygen level in a cell. Studies of this compound and its mechanisms showed its implication in different types of liver injuries such as cirrhosis or liver cancer[6,7]. Moreover, mitochondrial cytochrome c, a marker of drug-induced hepatotoxicity[8], appeared to be a targeted area of hepatotoxic drugs of cluster 39 (Figure 6B).

Genes involved in the ER protein processing and more precisely in the ubiquitin proteasome pathway also were also mentioned as significantly differentially expressed by DILI compounds of cluster 55 (Figure 6B). The ubiquitin-proteasome complex has already been reported to be involved in liver injuries such as fibrosis or chronic liver diseases[9,10].

Hepatotoxic compounds of clusters 13, 16, 23, 26 and 55 lead to the differential expression of genes that are all involved in the regulation of the immune response and kinase activity (Figure 6B), which could hypothetically be linked to liver injuries. For example, the IL-17 signaling pathway is an actor of the immune response and development of DILI[11,12]. IL-17 can mediate the inflammatory and immune response through the activation of the MAPK cascade and the activation of NFκB[13]. Protein kinase activity is modified by clusters 23, 26 and 55 (Figure 6B), and NFκB, known for regulating immune response and for its implication in the development of hepatic inflammation, fibrosis or HCC[14], could be a stage in the development of liver injury resulting from a reaction of the immune system. Still regarding the protein kinase activity, we saw that ERB signaling pathway, also known as epidermal growth factor receptor (EGFR) signaling pathway, can be a key actor in inflammatory response and liver disease development[15]. Then, it has already been proved that phagocytosis, a mechanism of the immune response that is a deregulated pathway according to our enrichment analysis, can contribute to the progression of liver diseases[16].

Regarding the cellular compartments affected by the clusters of DILIs compounds, we noticed that genes related to spindle fibers organization and their role in mitosis were differentially expressed by clusters 30 and 55 (Figure 6B and 6C). Spindle fibers are part of the cytoskeleton and contribute to separating the chromosomes into two different cells during nuclear division, including mitosis. As already mentioned before, mitotic errors due to defaults during the separation of the genetic information of a cell can lead to liver fibrosis and hepatocellular carcinoma (HCC)[17].

The pathway analysis highlighted another loop of biological pathways that can end in liver fibrosis. Hepatotoxic compounds of cluster 17 acted on the expression of genes involved in response to hyperoxia and transforming growth factor beta (TGFβ) (Figure 6B). Lee S. et al. demonstrated that hyperoxia can generate an overexpression of TGFβ that can participate in the development of liver fibrosis[18]. More specifically, TGFβ can be at the origin of an inhibition of hepatocyte proliferation leading to the stop of liver growth and regeneration[19], which are BP that figured among those which were disrupted by the clusters 13, 41, 42, and 55 (Figure 6B).

Finally, according to the figure 6A, compounds of cluster 42 distorted the pathway affecting the role of proteoglycans in cancer, which could potentially include liver cancer[20].

- *CP_DILIs_most_neg dataset*

Figure S1. Heatmaps of pathways significantly deregulated by the Cell-Painting features-based clusters of hepatotoxic compounds from the CP_DILIs_most_neg dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green to white colors.
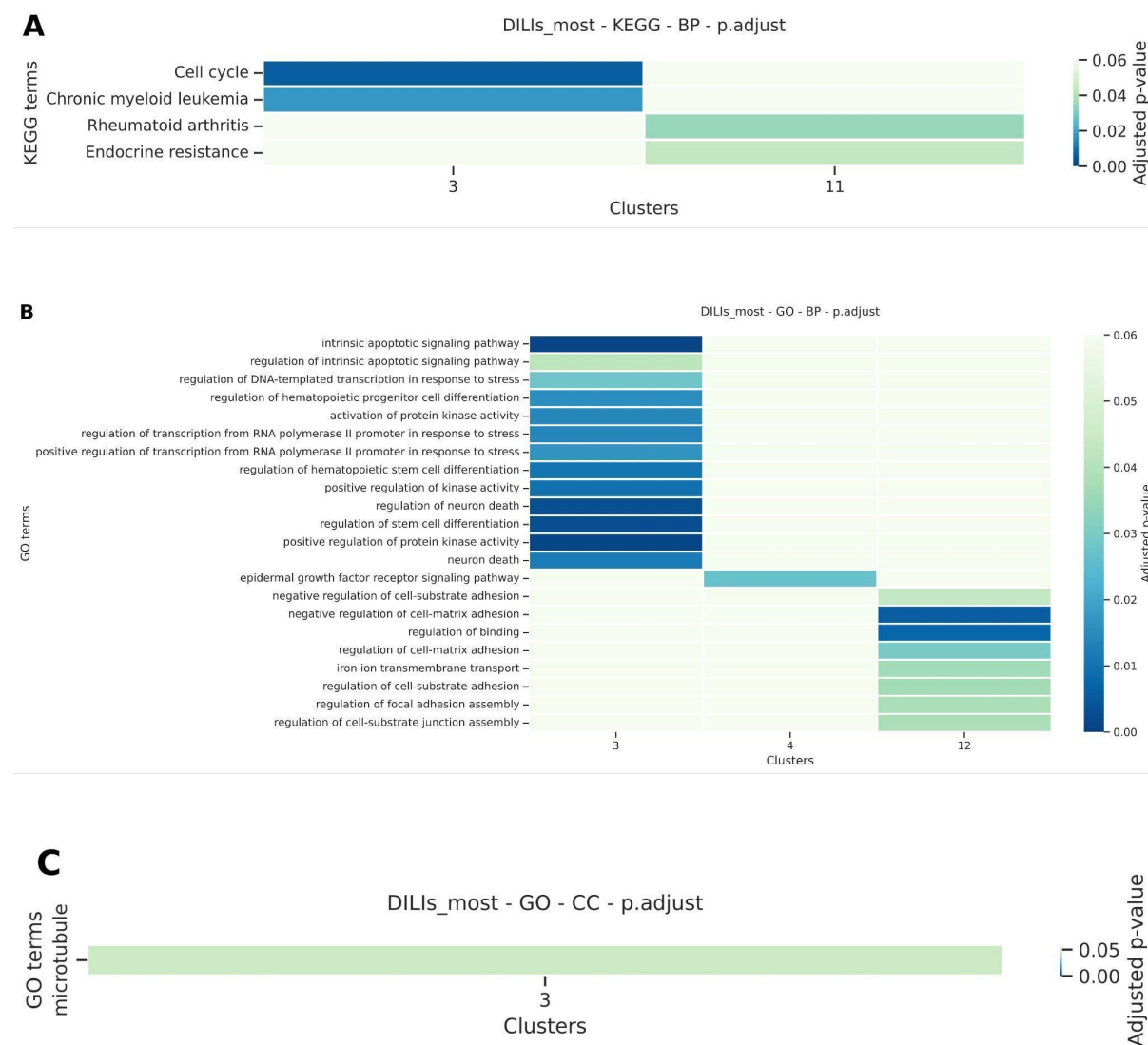
Among the 6 usable clusters of the CP_DILIs_most_neg dataset, only 4 clusters have enough chemicals with transcriptomics data to perform pathway enrichment analysis. Results of this dataset were very close to the observations we described with the CP_DILIs_pos_neg dataset in the manuscript. Significant perturbations on cell cycle, apoptosis, regulation of the kinase activity and immune response and microtubules organization (Figure S1) were obtained.

However, interesting supplementary pathways concerning the extracellular matrix (ECM) and cell-cell adhesion appeared in our analysis (Figure S1B). For example, cluster 12 affected negative regulation of focal adhesion, cell-substrate adhesion, regulation of binding and cell-matrix adhesion. Changes in extracellular properties such as thickening and association with deregulation of hepatic stellate cells were observed in case of liver fibrosis[21]. Cell adhesion molecules are generally very activated too in case of tissue inflammation and mediate the immune system response during the appearance of hepatic fibrosis[22]. Moreover, it has been demonstrated that an overactivation of ECM-producing cells trigger an overexpression of the ERBB receptors (mentioned before) leading to fibrosis[15].

- *CP_eTox_H_HT dataset*

Lots of biological pathways highlighted by the enrichment and pathway analysis of the CP_DILIs_eTox_H_HT dataset were similar with those obtained with the two DILIrank datasets and thus, already detailed. Among them, we can cite the cell cycle, the p53-mediated apoptosis signaling pathway, proteoglycans in cancer, carbohydrate homeostasis, cell growth and liver regeneration, the immune response mediated via NFκB activation, RNA splicing, mitosis and spindle organization, regulation of cell-matrix- adhesion, or ER protein processing (Figure S2A-B). At the cellular compartment level, we found again compartments that directly echoed the previous biological processes, as spliceosomes, the proteasome, and the membrane and cell-substrate junctions. However, some pathways affected by hepatotoxic compounds of the CP_eTox_H_HT dataset were new or allowed to complete some mechanisms.

For example, cell adhesion and ECM, that could be associated with liver injuries, are controlled by the RAP1 signaling pathway, itself affected by cluster 37 and 119[23].

Then, we saw with the DILIrank datasets that a potential mechanism of DILI was a perturbation of the carbohydrate homeostasis. According to the KEGG pathway analysis, the peroxisome proliferator-activated receptor (PPAR) signaling pathway was affected by DILI compounds of cluster 97 (Figure S2A). PPARs are known to modulate the lipid homeostasis, and dysfunctions of them may cause steatosis or liver cancer[24].

Regarding the kinase activity, clusters 43, 46, 119, 123, 135 and 137 have an effect on several pathways related to it, such as the MAPK and ERK signaling pathways. ERK is a cascade included in MAPK cascade involved into NFκB activation and the inflammatory response too[25].

On the subject of the drug-triggered inflammatory response, the pathway analysis of the CP_eTox_H_HT dataset showed that Tumor Necrosis Factor (TNF) signaling pathway and Fc receptor mediated signaling pathway including phagocytosis can both be impacted by hepatotoxic compounds (Figure S2A-B). Literature confirmed that these two pathways can be associated with liver diseases as nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC)[16,26]. Still regarding the immune response, KEGG enrichment pointed genes of the NOD-like receptor and c-type lectin receptor signaling pathways as significantly differentially expressed by respectively hepatotoxic compounds of the cluster 136, and 35 and 136 (Figure S2A). NOD-like receptors are actors of the immune response and can be associated with cases of fibrosis[27,28]. C-type lectin receptors are part of the immune system too and can be related to cirrhosis too[29].

We already detailed how endoplasmic reticulum (ER) protein processing and more particularly the ubiquitin-mediated proteolysis, can be linked to drug-induced liver injuries. Figure S2B showed that clusters can affect the activation of the unfolded protein response (UPR) pathway too, known to be able to cause the triggering of the ER stress. Thus, taken

together, ER and UPR pathways can have a huge contribution to the development of liver diseases such as steatosis, NAFLD or cholestatic liver diseases[30].

Finally, the third GO term was the regulation of the Notch signaling pathway. Notch pathway has a central role in tissue development and homeostasis and its involvement in the liver fibrosis, via for instance nitric oxide production, is known and demonstrated. Moreover, studies also revealed that Notch is connected to glucose and lipid metabolism, which are directly correlated to steatosis development[31].

According to heatmap of Figure S2B, mitochondria, which is an organelle known to be sensitive to hypoxia condition in case of liver injuries[32], appeared too as a targeted area of hepatotoxic drugs. Moreover, reactions to reactive oxygen species (ROS) and hypoxia were pointed out too (Figure S2B), and it has been demonstrated in literature that this could lead to hepatic inflammation and that it can be a process of DILI pathogenesis[33].

Figure S2. Heatmaps of pathways significantly deregulated by the Cell-Painting features-based clusters of hepatotoxic compounds from the CP_eTox_H_HT dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green to white colors.

B

S13

C

eTox_H_HT_pos - GO - CC - p.adjust

S14
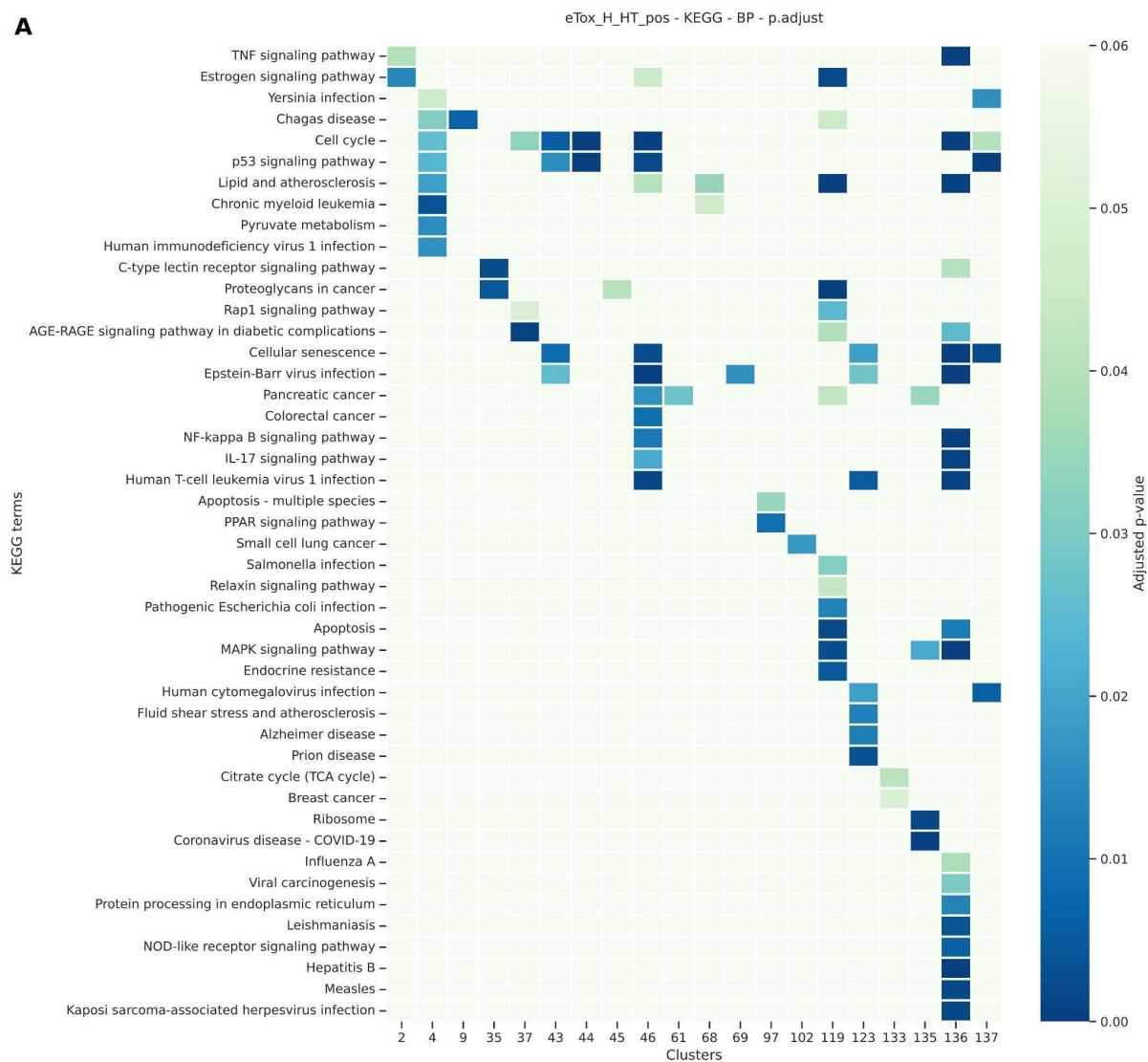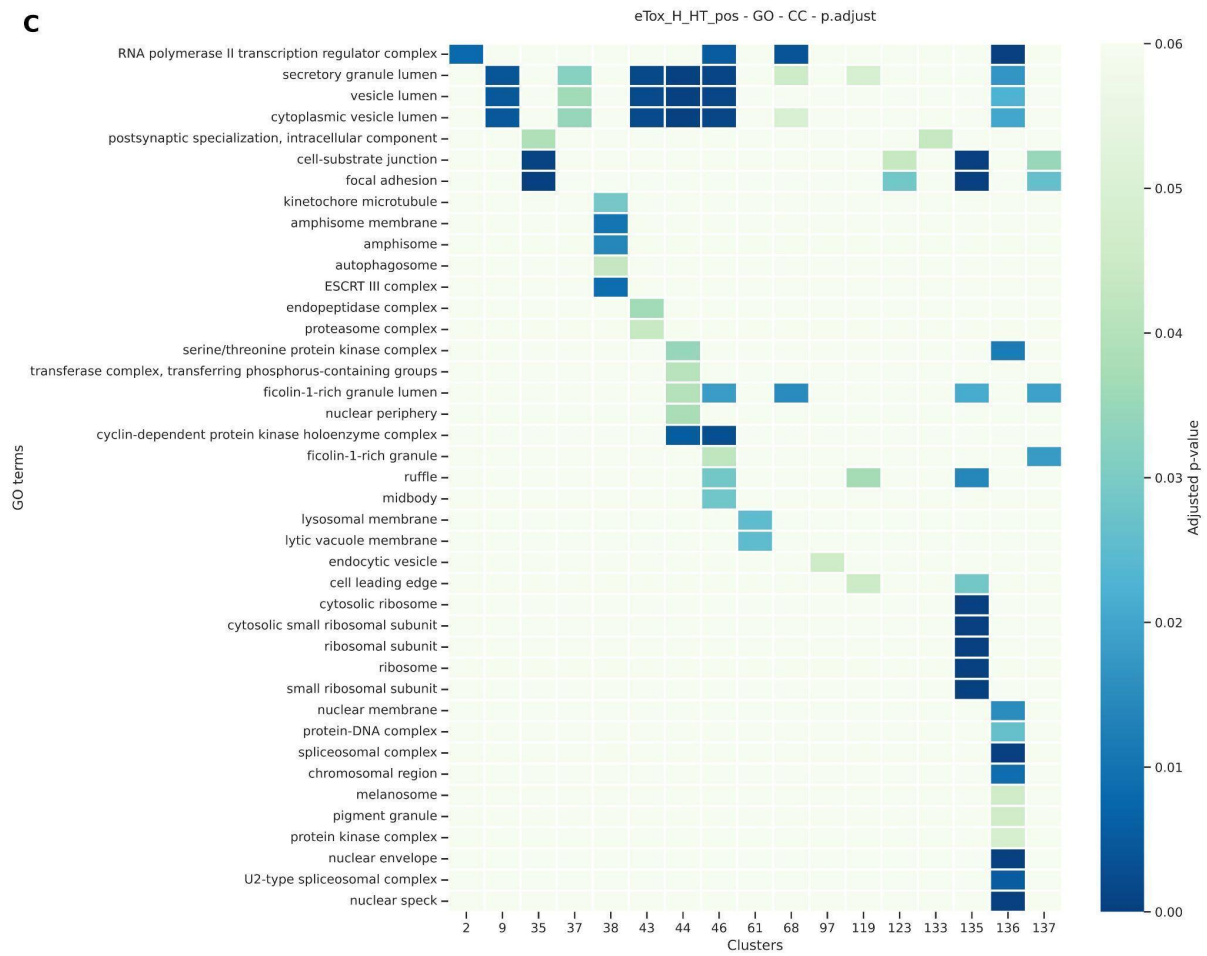
- *CP_eTox_H_MF dataset*

Figure S3. Heatmaps of pathways significantly deregulated by the Cell-Painting features-based clusters of hepatotoxic compounds from the CP_eTox_H_MF dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green to white colors.

B

GO terms

Clusters

S16

c

eTox_H_MF_pos - GO - CC - p.adjust
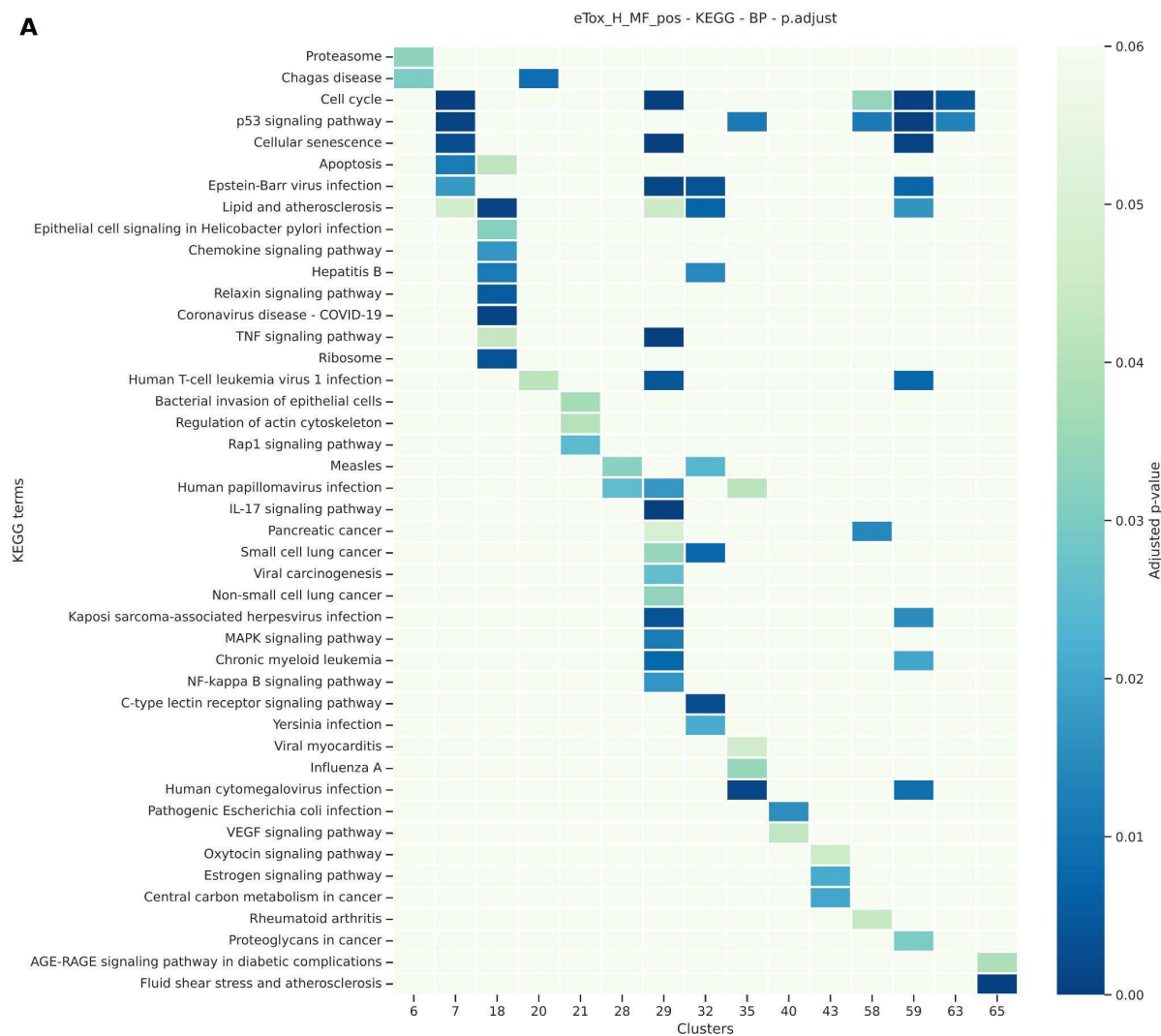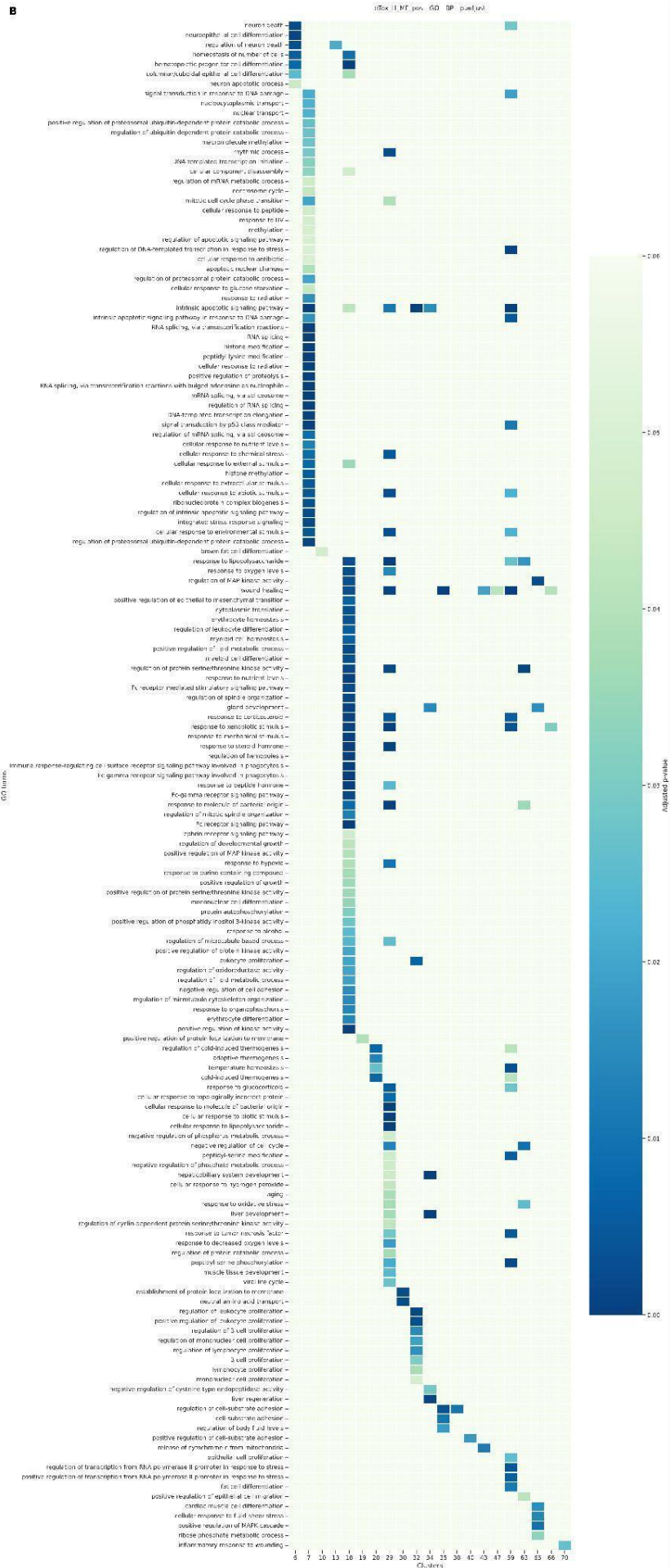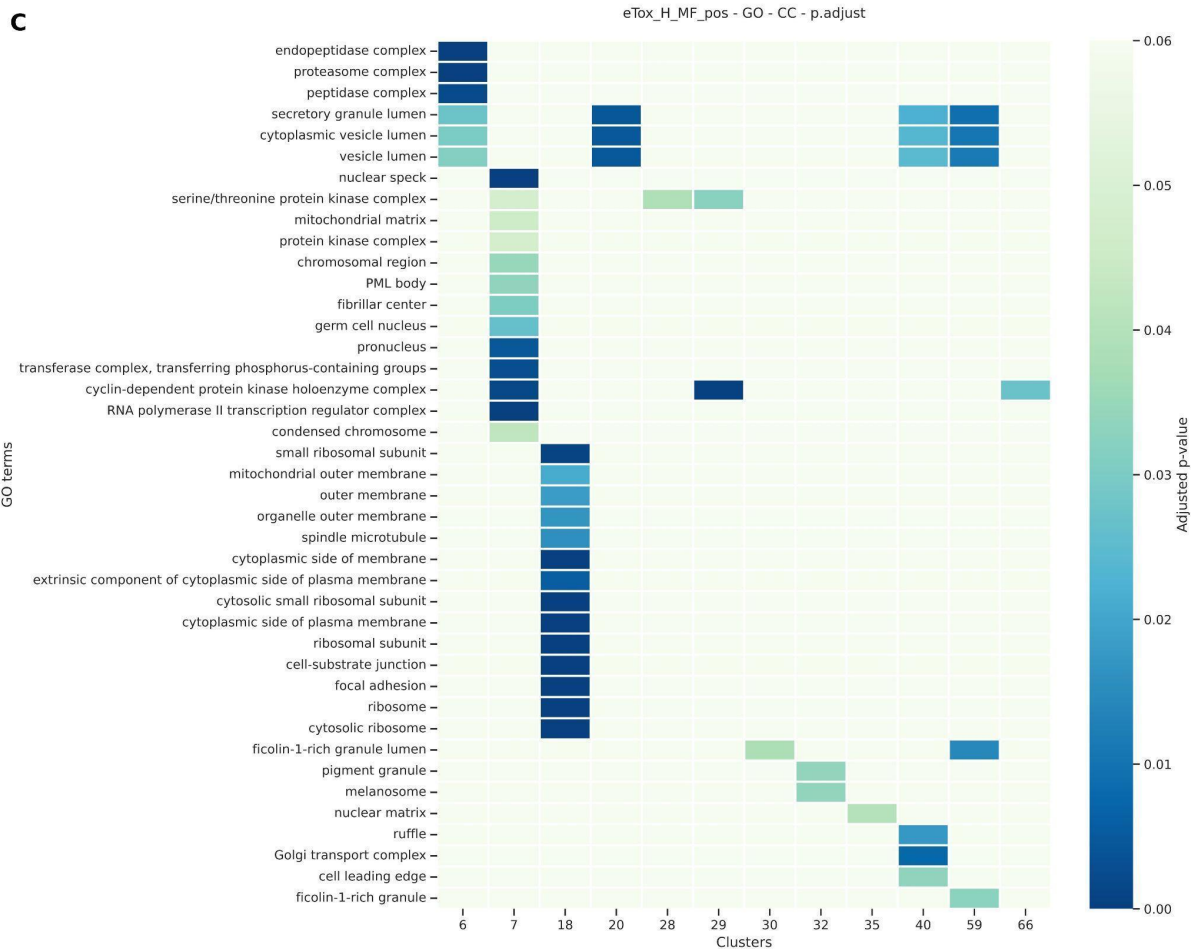
Many KEGG and GO terms that showed up from the pathway analysis dealt with terms already encountered previously: cell cycle, cell proliferation via NFκB, activation of the apoptotic pathway in response to stress and through the p53 factor, deregulation of the kinase activity including MAPK and ERK, microtubule and spindle organization, *etc* (Figure S3).

Only two new biological processes were highlighted. First is a perturbation of actin filament and non-membrane-bounded organelle assemblies (of which actin cytoskeleton is part of) (Figure S3A-B). Previous studies revealed that actin cytoskeleton could be linked firstly to hepatic fibrosis via the activation of hepatic stellate cell[34] and secondly to apoptosis[35].

Second is the ephrin receptor signaling pathway (Figure S3B). Ephrin receptors are types of receptor tyrosine kinase with a role in cell adhesion or in developmental processes for

example. However, studies on hepatic fibrosis in mice identified the EphB2 ephrin receptor as a prominent actor of liver fibrogenesis through an overactivation of the immune system[36,37].

- ### *CP_eTox_H_MFHB dataset*

Gene enrichment and pathway analysis of the CP_eTox_H_MFHB dataset gave close results from those observed with the CP_eTox_H_HT and CP_eTox_H_MF datasets (Figure S4).

Figure S4. Heatmaps of pathways significantly deregulated by the Cell-Painting features-based clusters of hepatotoxic compounds from the CP_eTox_H_MFHB dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green to white colors.

cTox_H_MFHB_pos - GO - BP - p.adjust

S19

c

eTox_H_MFHB_pos - GO - CC - p.adjust
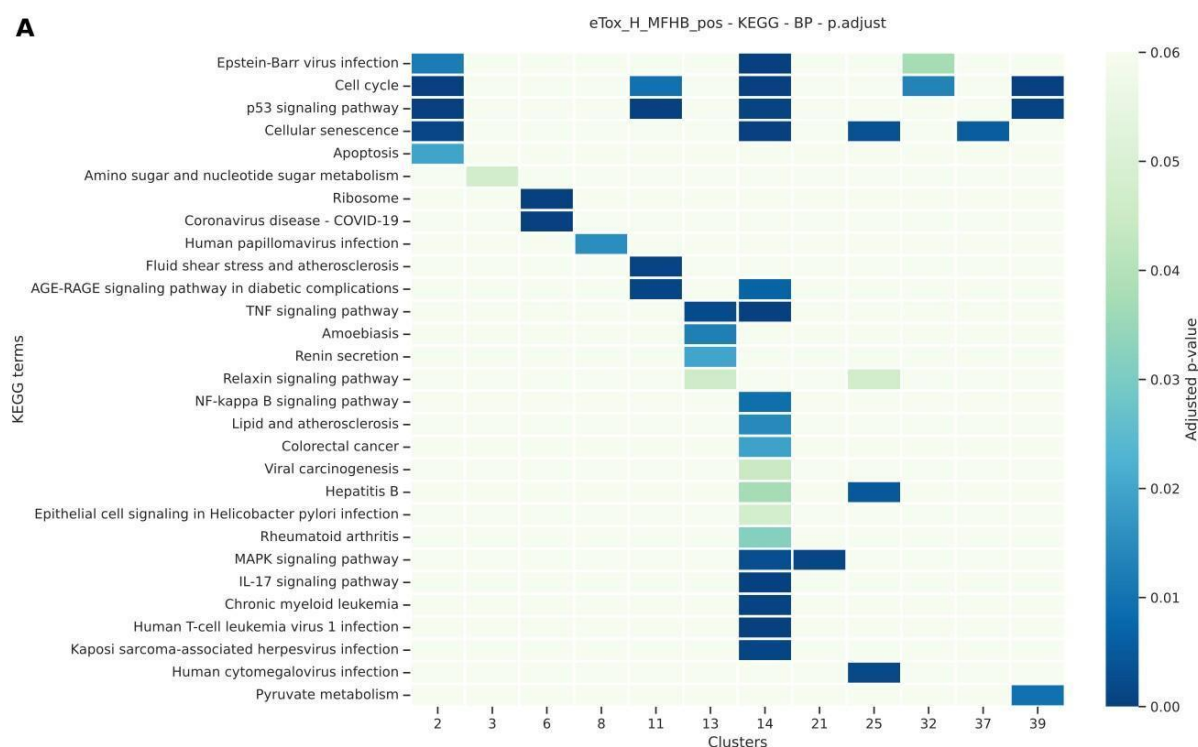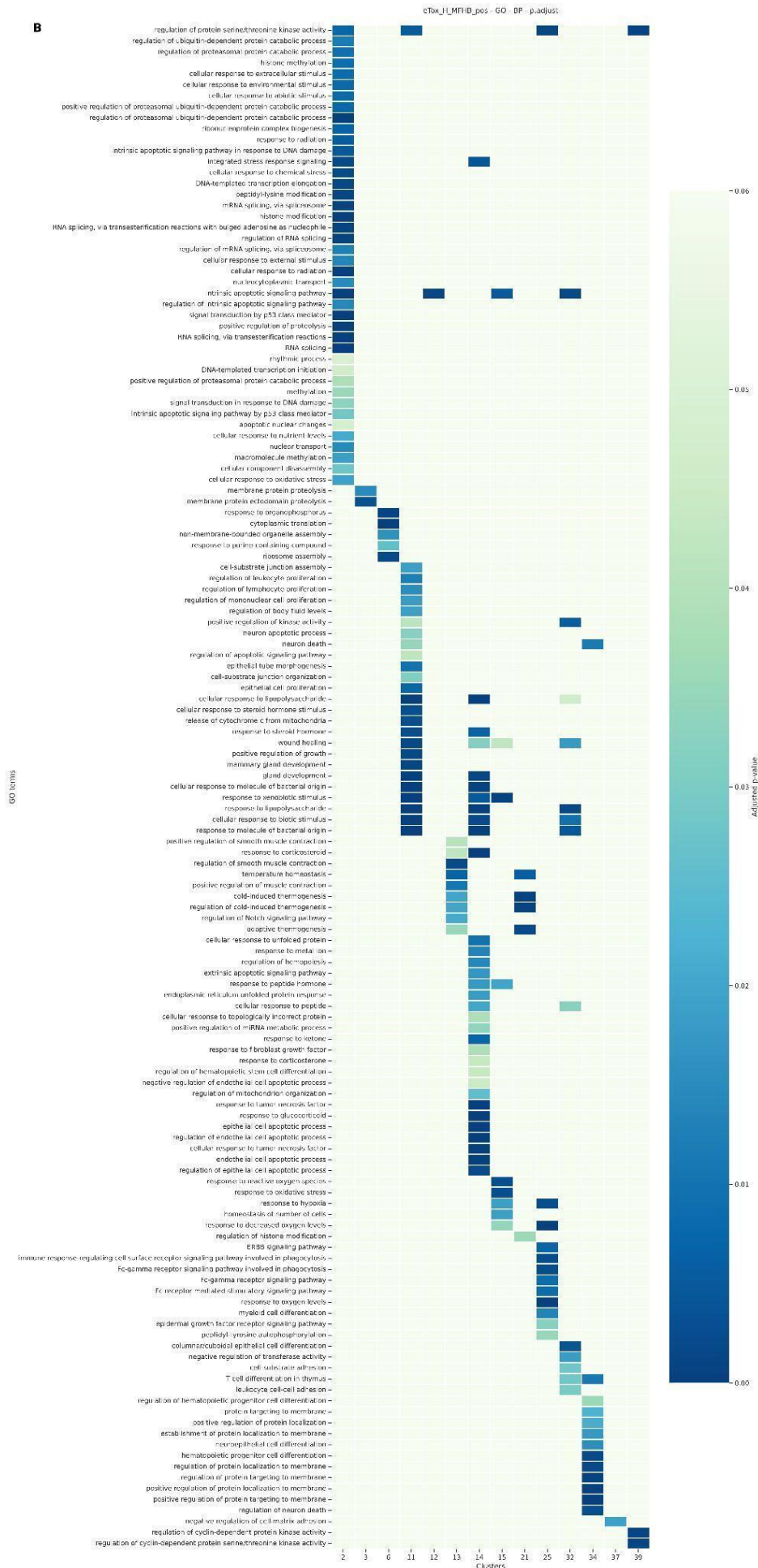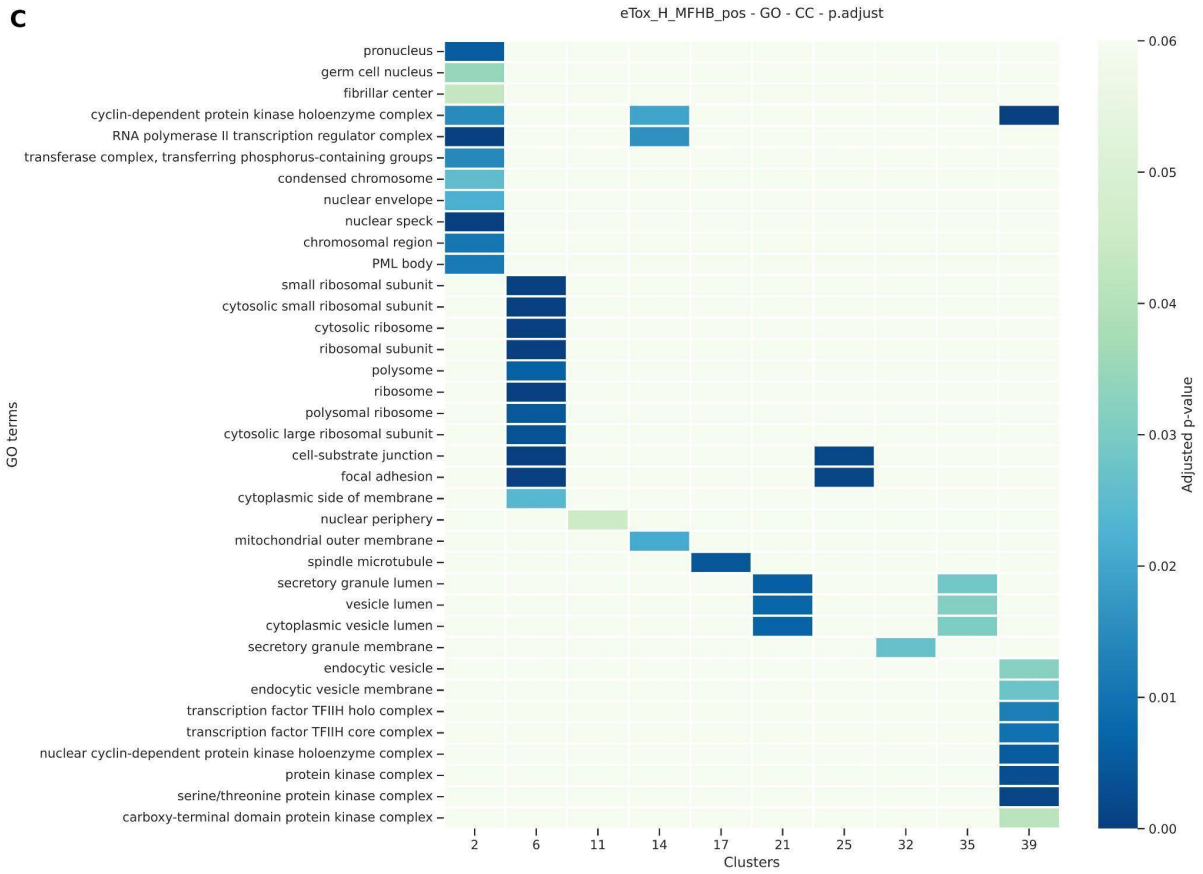
- *CP_eTox_H_MFHC dataset*

Results of the last eTox dataset CP_eTox_H_MFHC provided the same information about deregulated pathways that we detailed previously (Figure S5).

Figure S5. Heatmaps of pathways significantly deregulated by the Cell-Painting features-based clusters of hepatotoxic compounds from the CP_eTox_H_MFHC dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green to white colors.

B

C

eTox_H_MFHC_pos - GO - CC - p.adjust
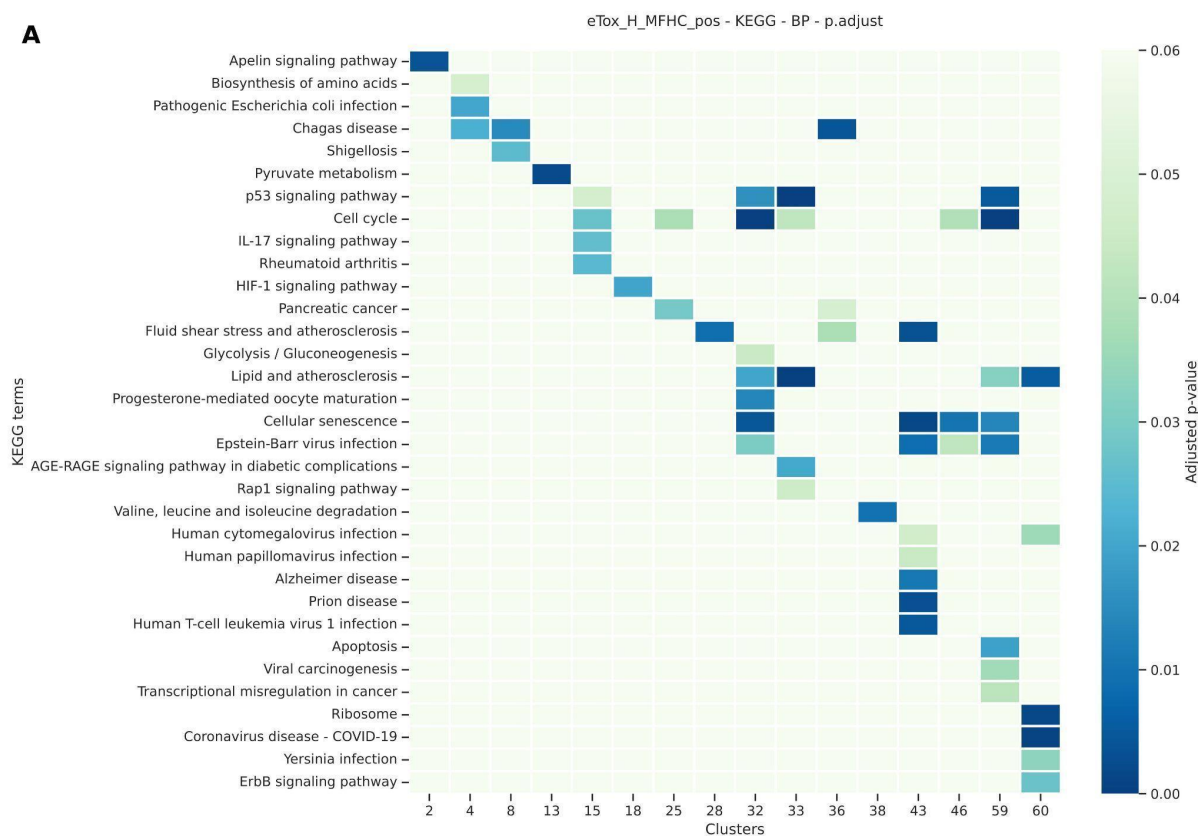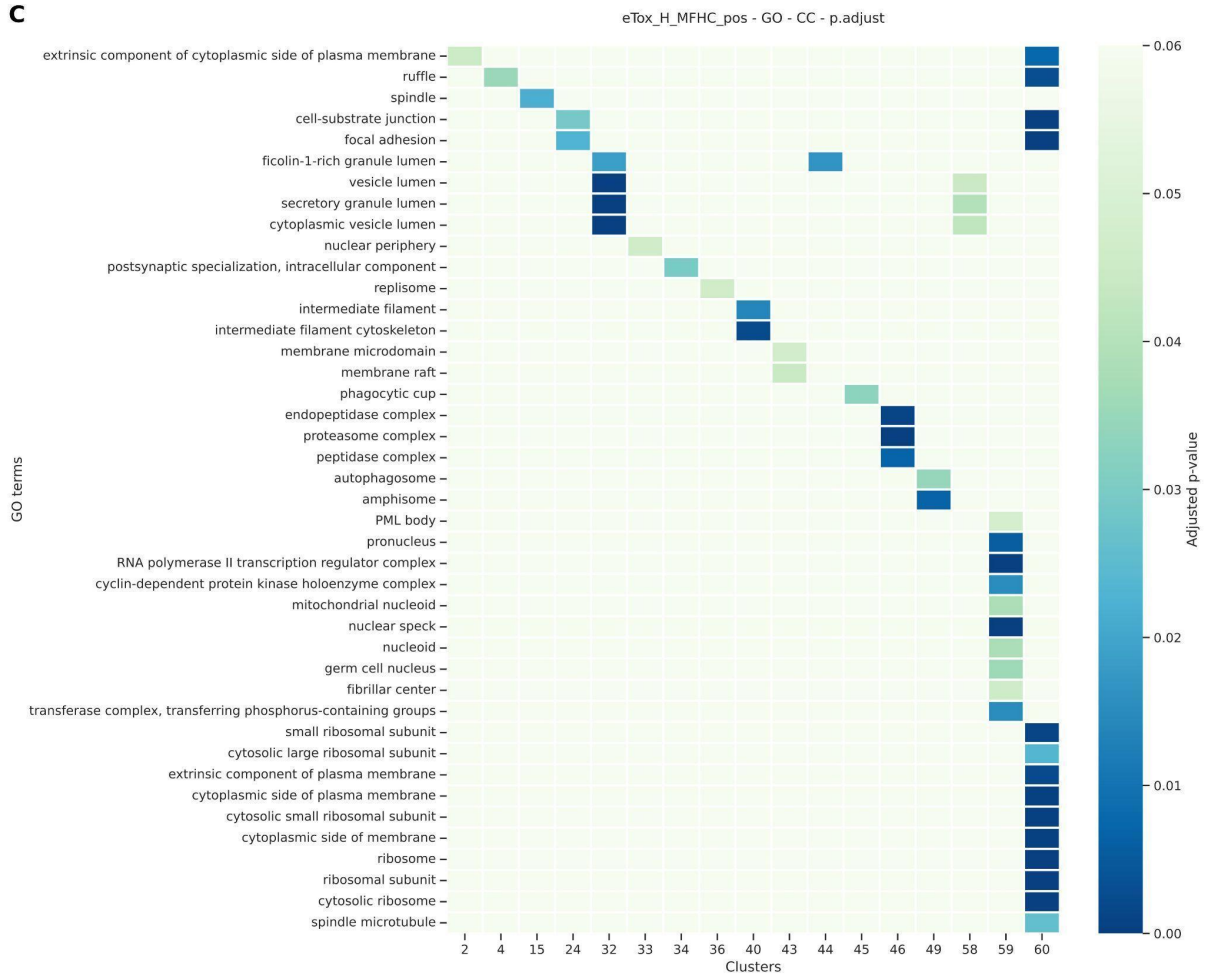
Supplementary S2. Analysis of permutation tests for CP_DILIs_pos_neg, CP_DILIs_most_neg, CP_eTox_H_HT, CP_eTox_H_MF, CP_eTox_H_MFHB, and CP_eTox_H_MFHC.

Figure S6. Histograms of validation set balanced accuracies obtained during the permutation tests with each best model according to CP_DILIs_pos_neg, CP_DILIs_most_neg, CP_eTox_H_HT, CP_eTox_H_MF, CP_eTox_H_MFHB and CP_eTox_H_MFHC datasets. A. Random Forest. B. Linear SVM. C. ElasticNet. Vertical red line represents the BA score obtained with the same model on original data.
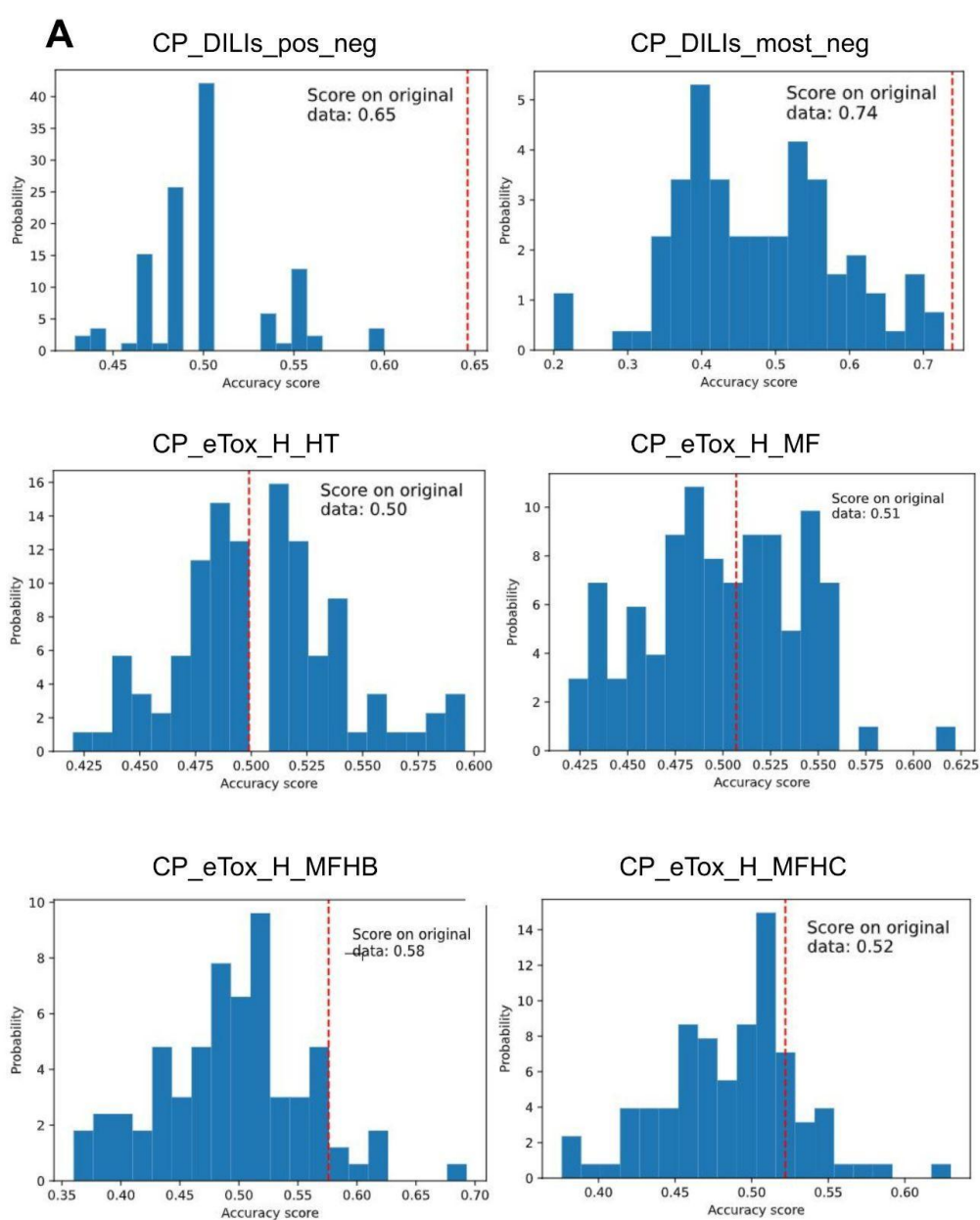
B

CP_DILIs_pos_neg
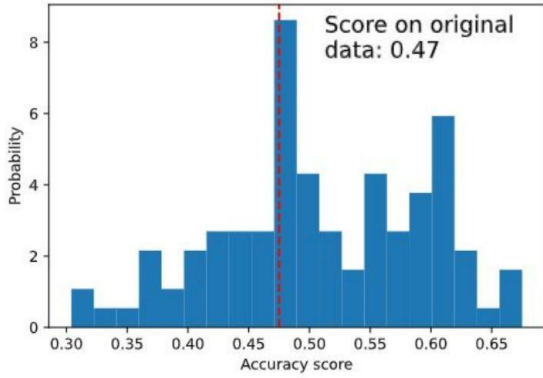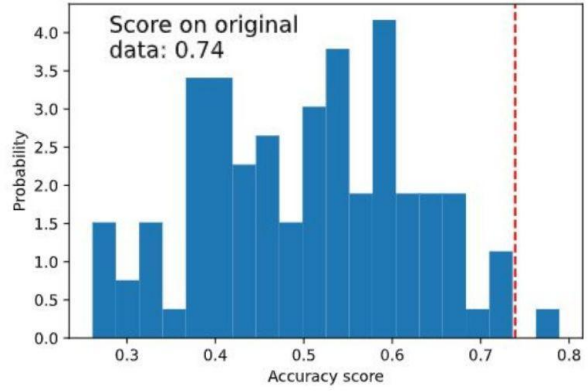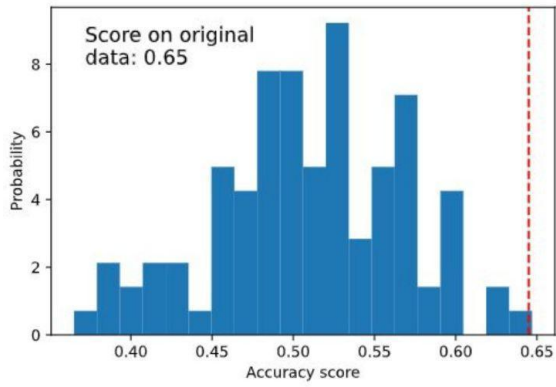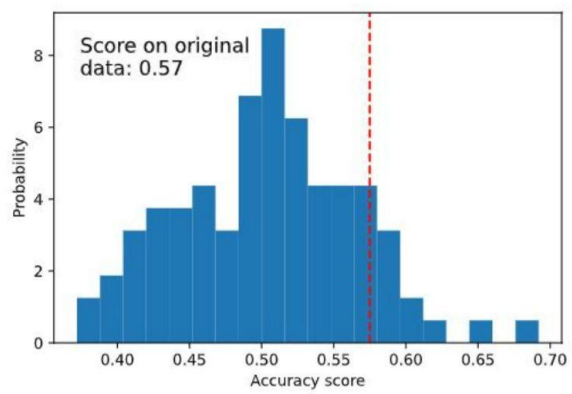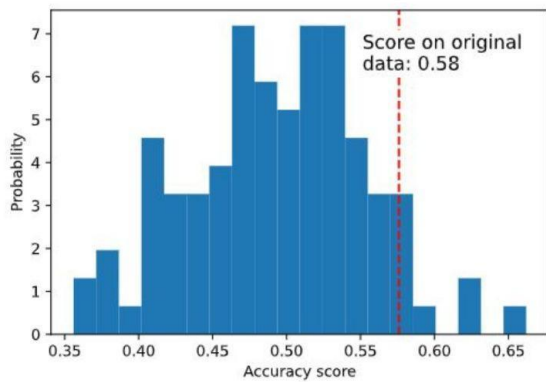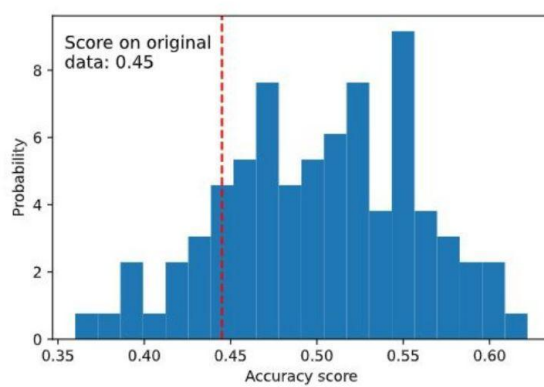
Score on original data: 0.47

CP_DILIs_most_neg

Score on original data: 0.74

CP_eTox_H_HT

Score on original data: 0.65

CP_eTox_H_MF

Score on original data: 0.57

CP_eTox_H_MFHB

Score on original data: 0.58

CP_eTox_H_MFHC

Score on original data: 0.45

C

CP_DILIs_pos_neg

Score on original data: 0.52

CP_DILIs_most_neg

Score on original data: 0.69

CP_eTox_H_HT

Score on original data: 0.57

CP_eTox_H_MF

Score on original data: 0.65

CP_eTox_H_MFHB

Score on original data: 0.52

CP_eTox_H_MFHC

Score on original data: 0.49
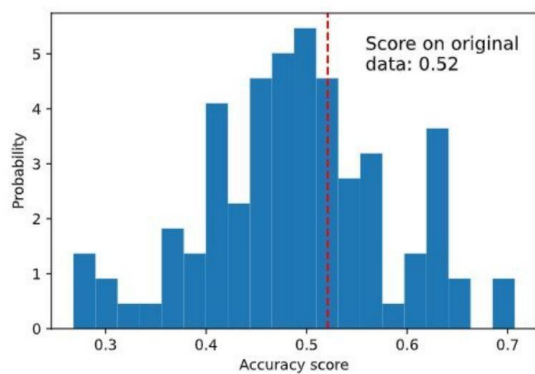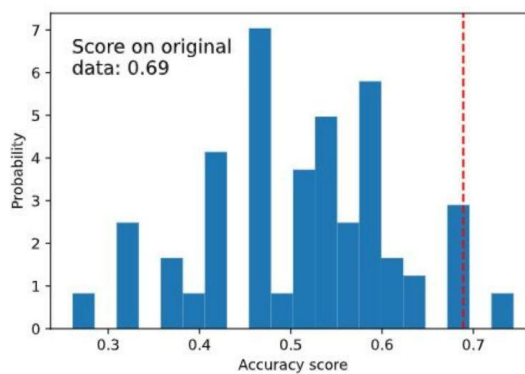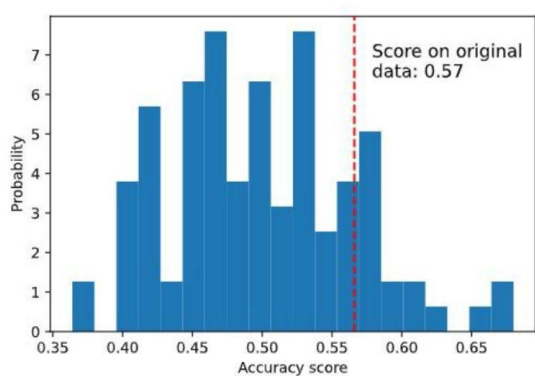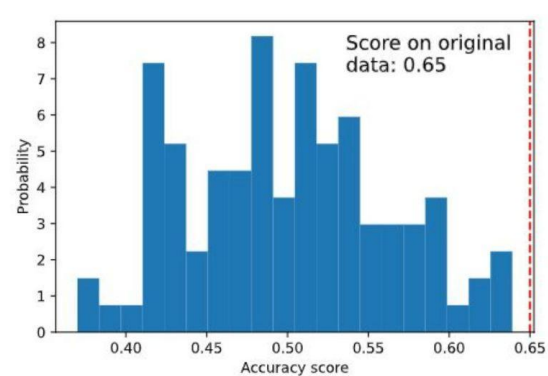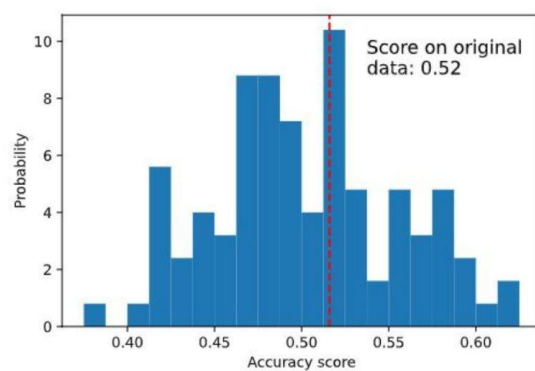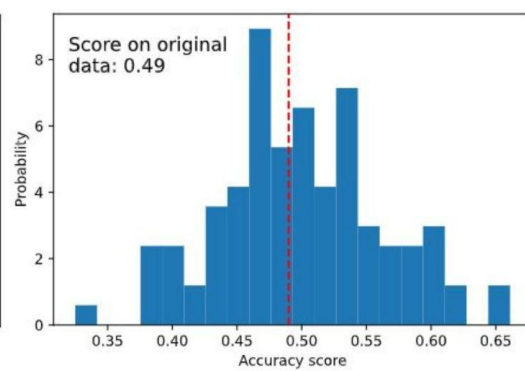
Supplementary S3. Heatmaps related to pathway analysis of the randomly created clusters from the hepatotoxic compounds of the CP_DILIs_pos_neg, CP_DILIs_most_neg, CP_eTox_H_HT, CP_eTox_H_MF, CP_eTox_H_MFHB and CP_eTox_H_MFHC datasets.

Figure S7. Heatmaps of pathways significantly deregulated by the randomly created clusters of hepatotoxic compounds from the CP_DILIs_pos_neg dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green.

DIUsPos - GO - BP - p.adjust

C

DILIsPos - GO - CC - p.adjust
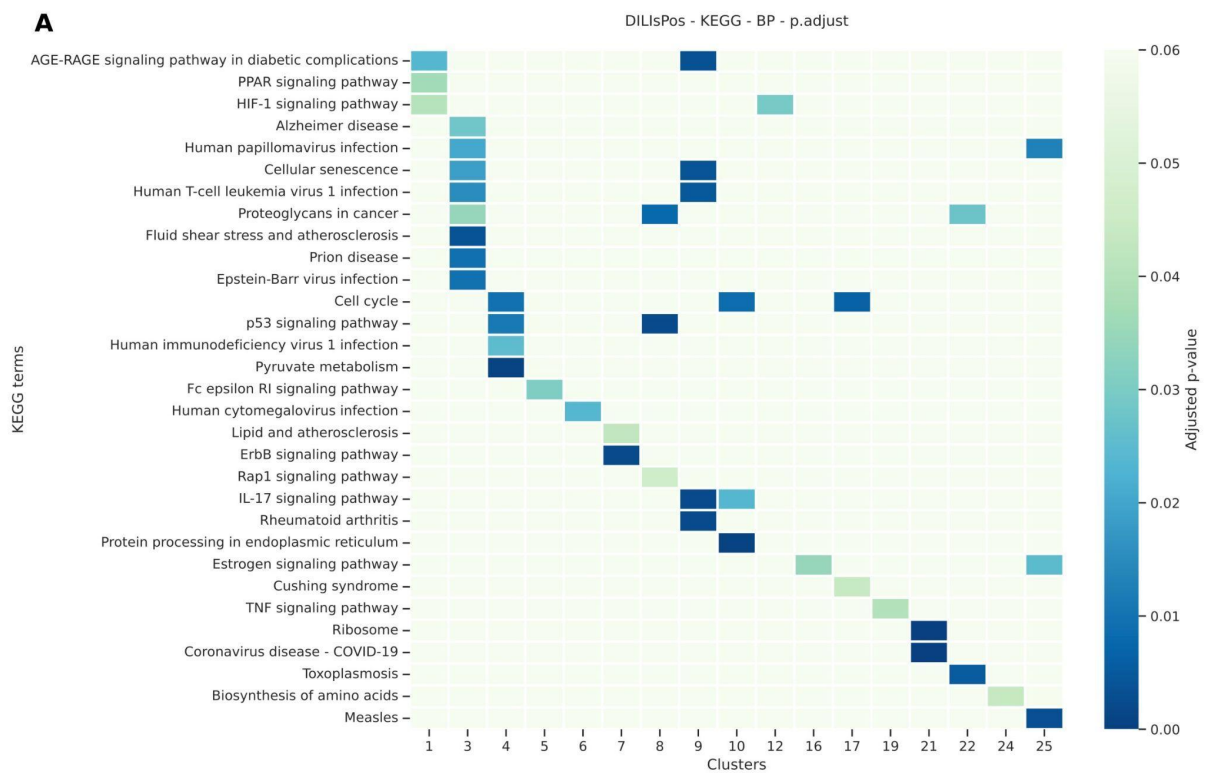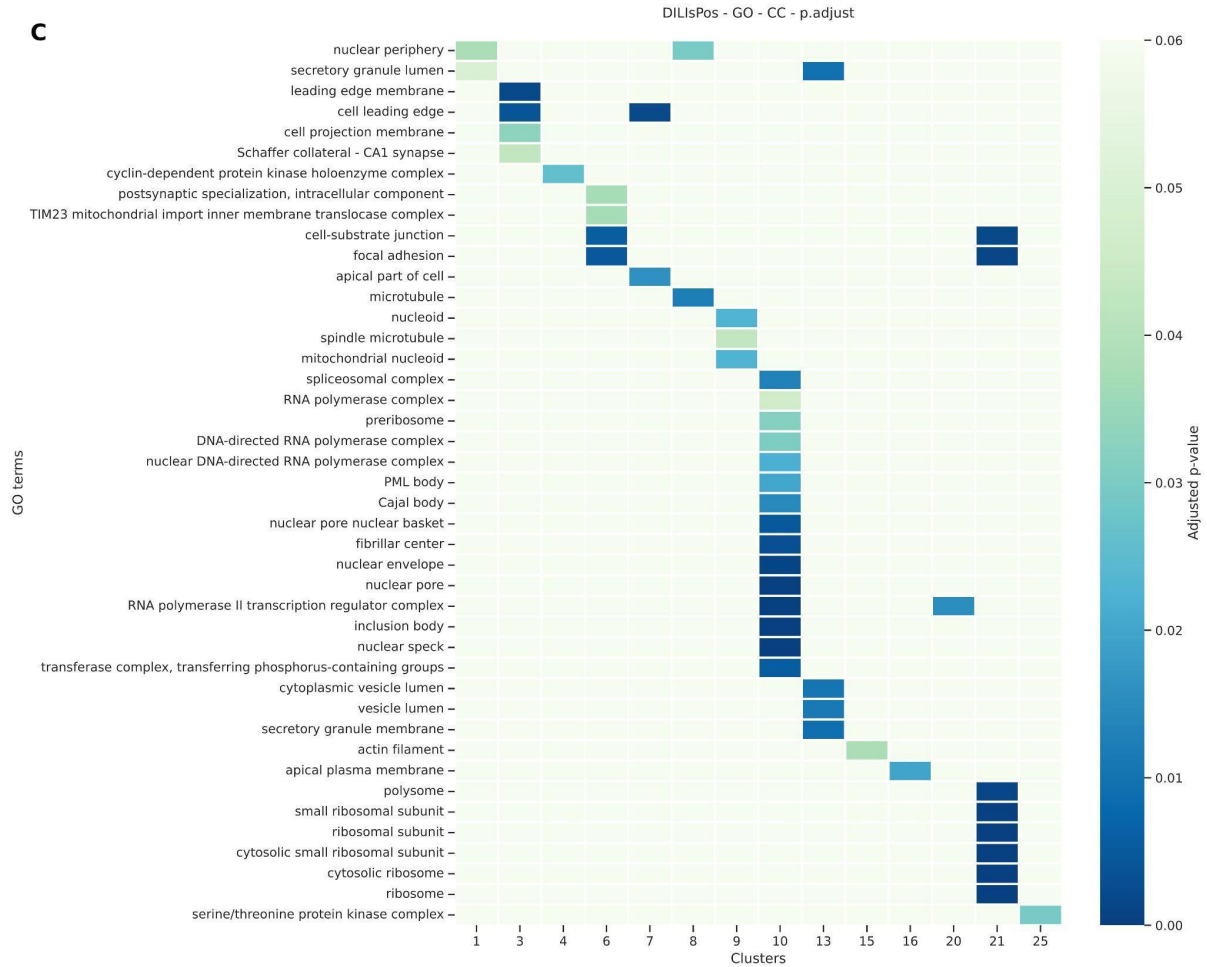
Figure S8. Heatmaps of pathways significantly deregulated by the randomly created clusters of hepatotoxic compounds from the CP_DILIs_most_neg dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green.

DILIsMost - GO - BP - p.adjust

DILIsMost - GO - CC - p.adjust

Figure S9. Heatmaps of pathways significantly deregulated by the randomly created clusters of hepatotoxic compounds from the CP_eTox_H_HT dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green.

c eTox_H_HT_pos - GO - CC - p.adjust
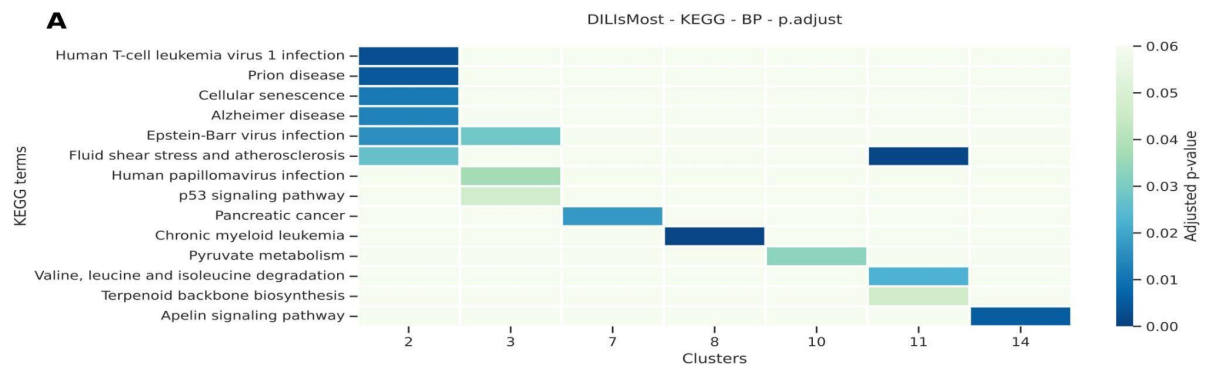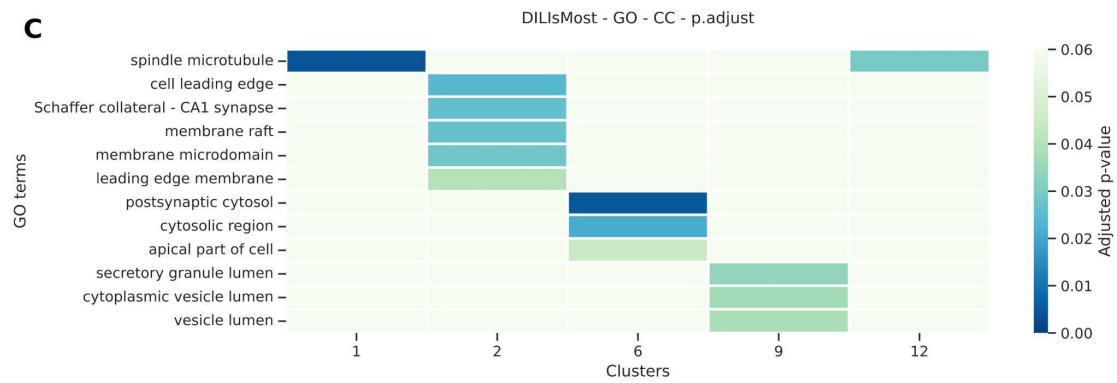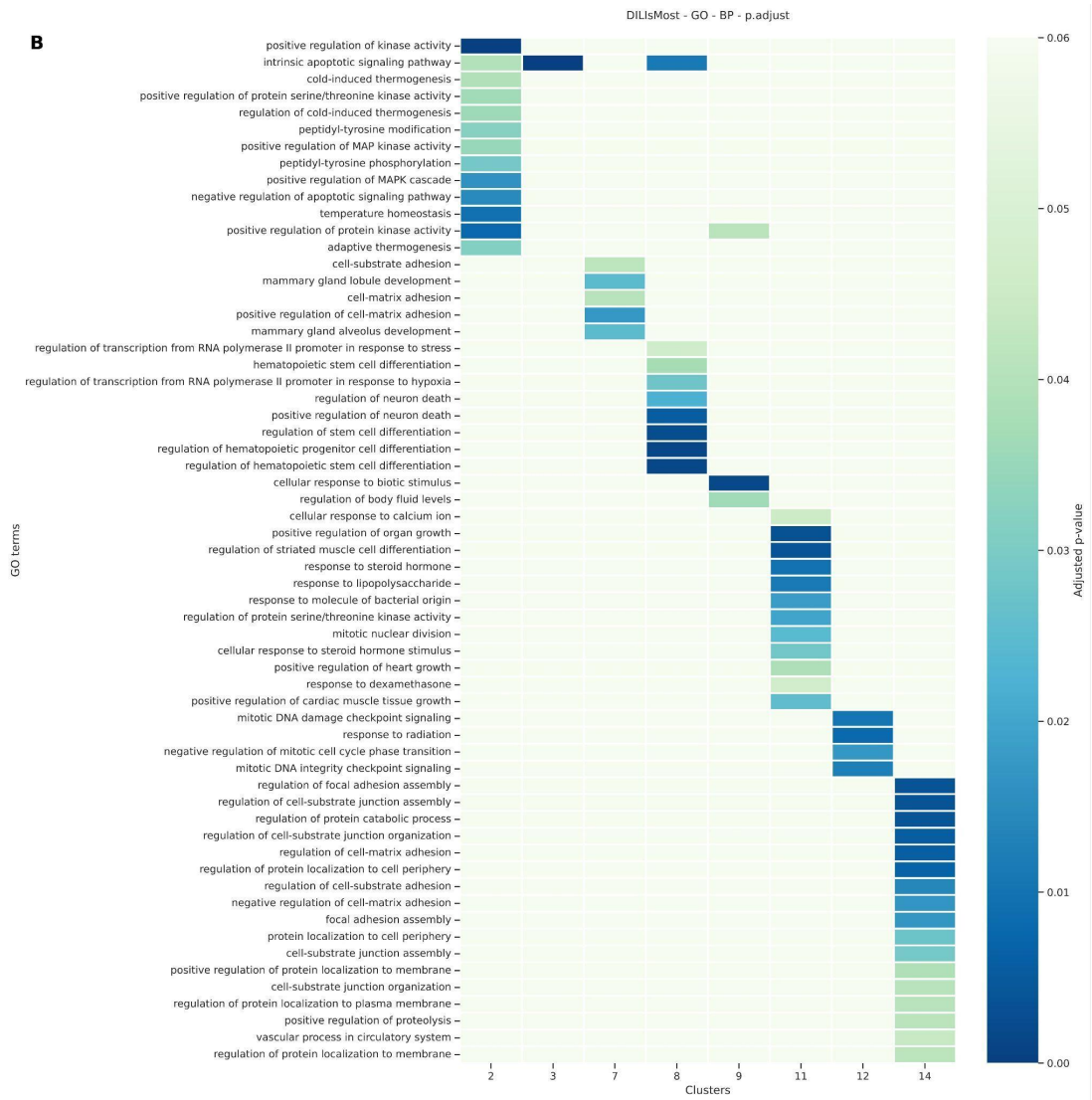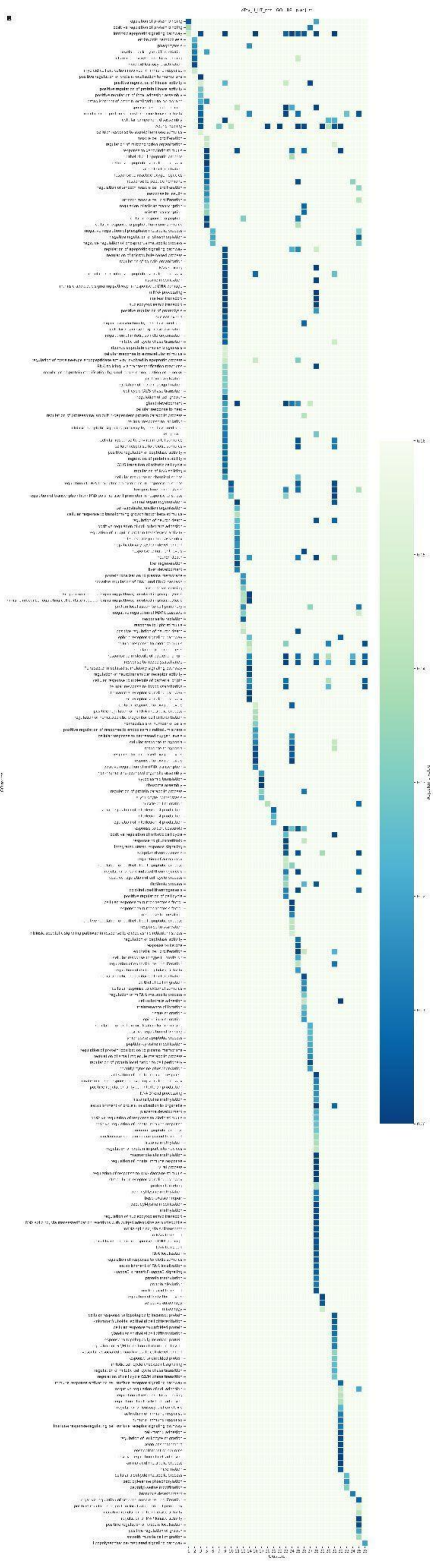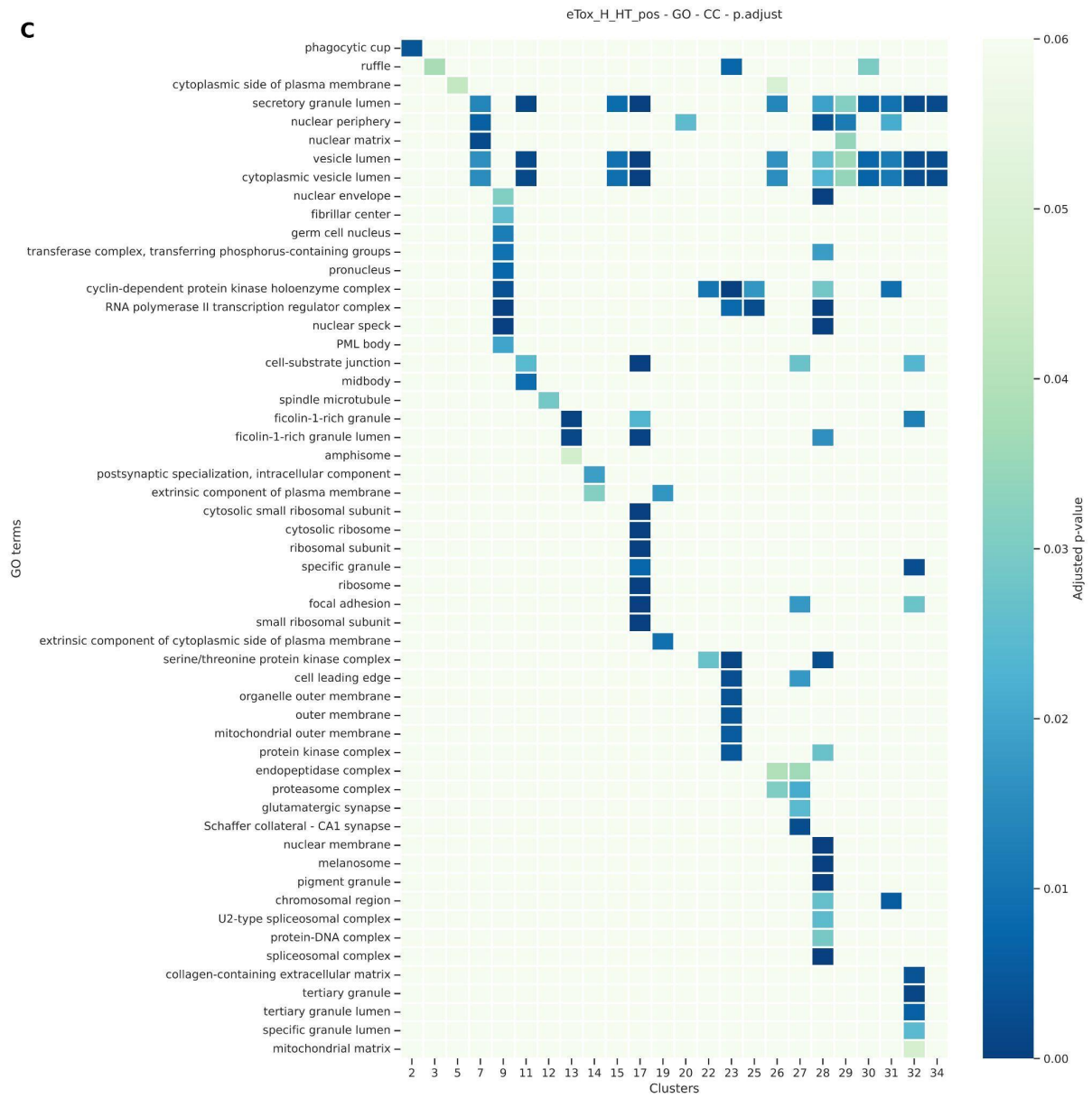
Figure S10. Heatmaps of pathways significantly deregulated by the randomly created clusters of hepatotoxic compounds from the CP_eTox_H_MF dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green.

B

eTox_H_MF_pos - GO - CC - p.adjust

C
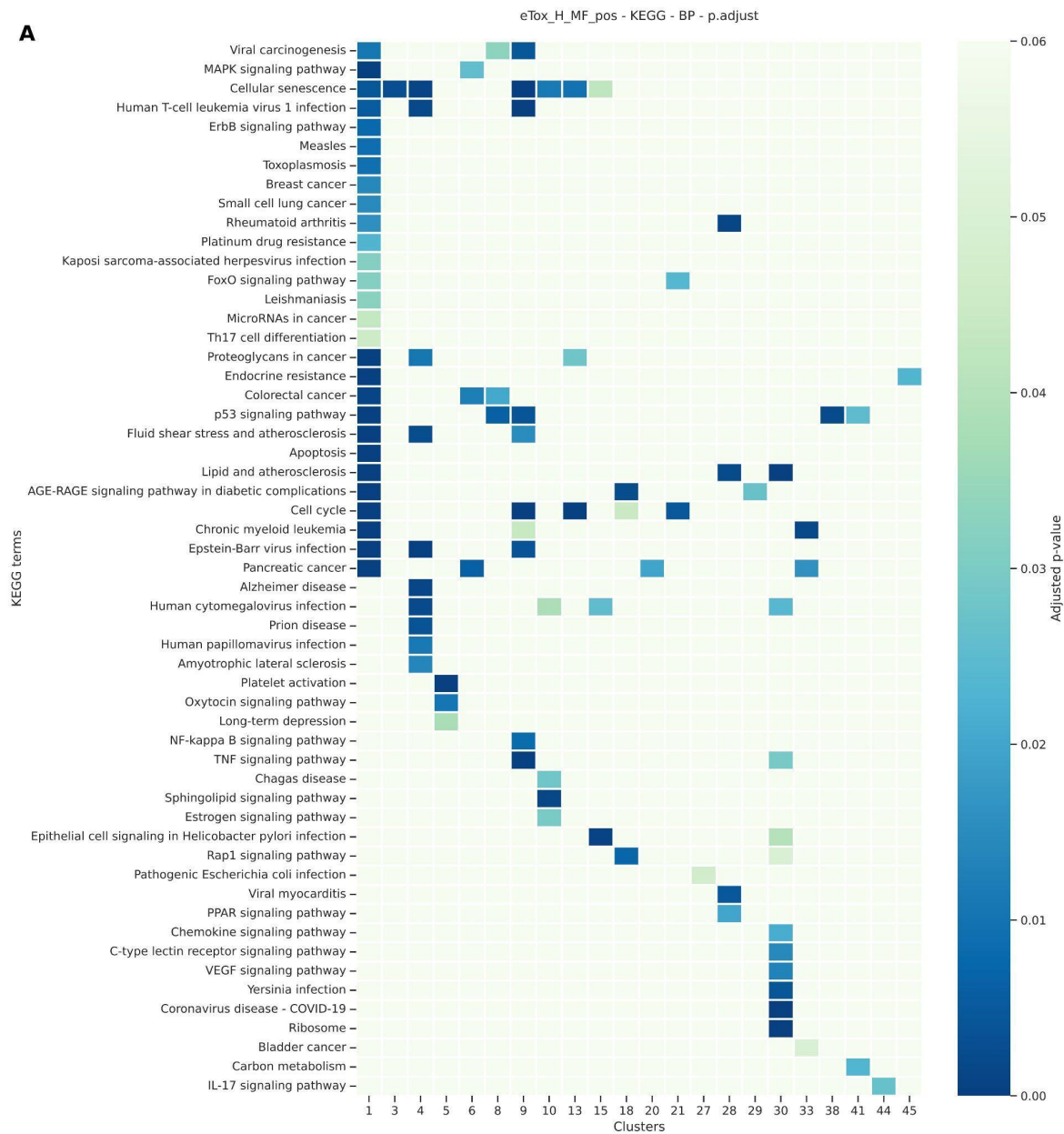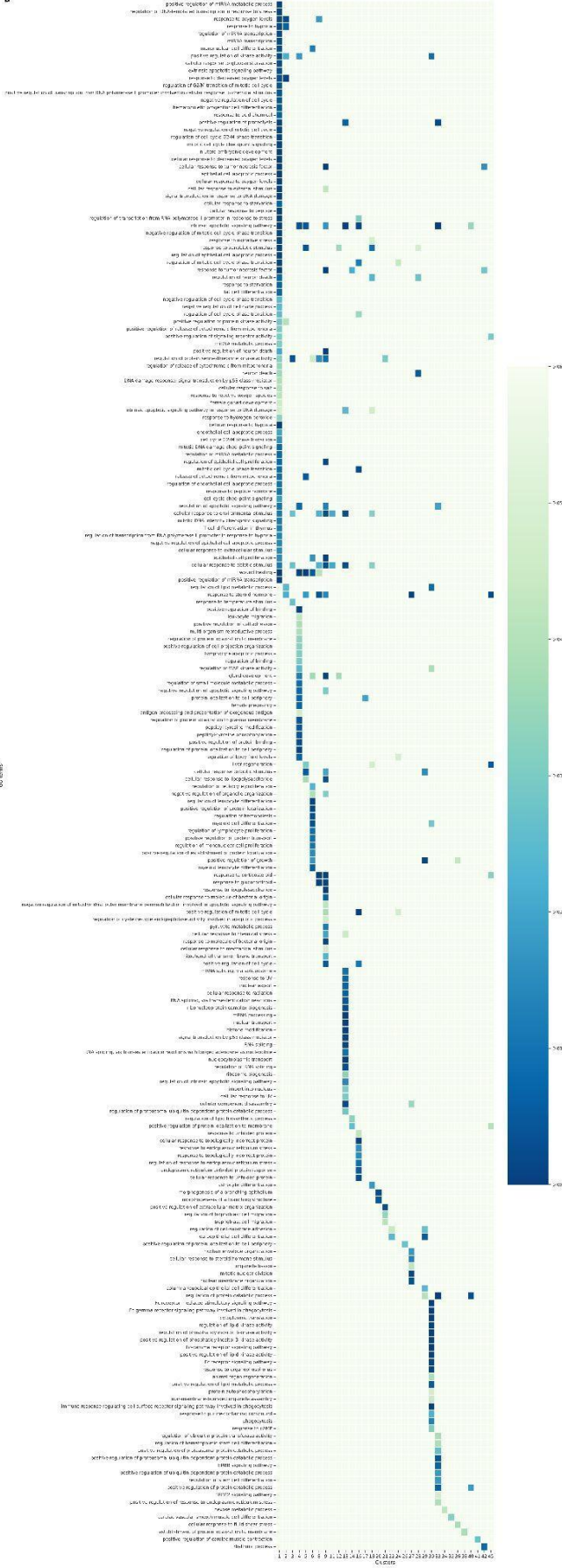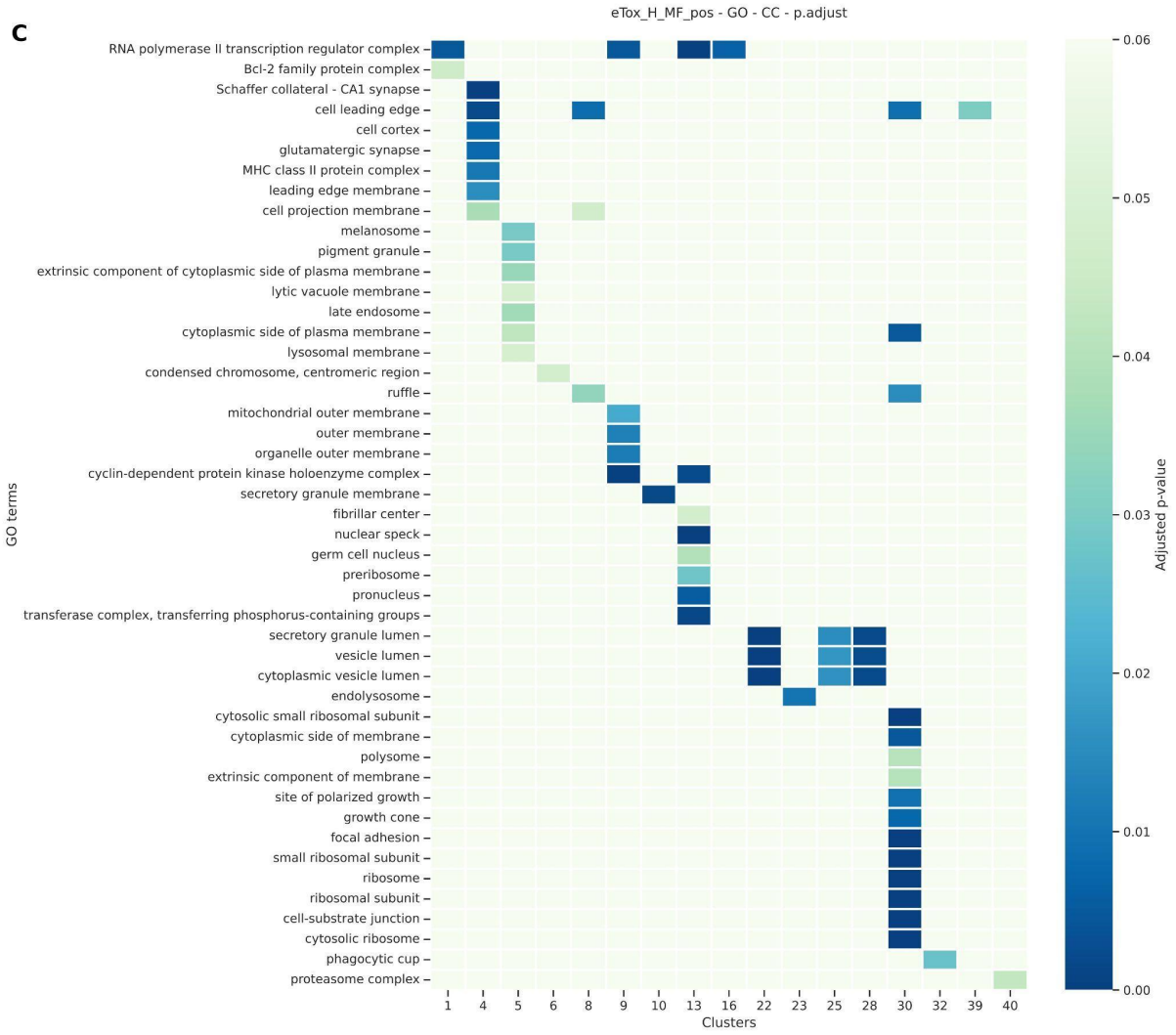
Figure S11. Heatmaps of pathways significantly deregulated by the randomly created clusters of hepatotoxic compounds from the CP_eTox_H_MFHB dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green.

eTox_H_MFHB_pos - GO - BP - p.adjust

C

eTox_H_MFHB_pos - GO - CC - p.adjust
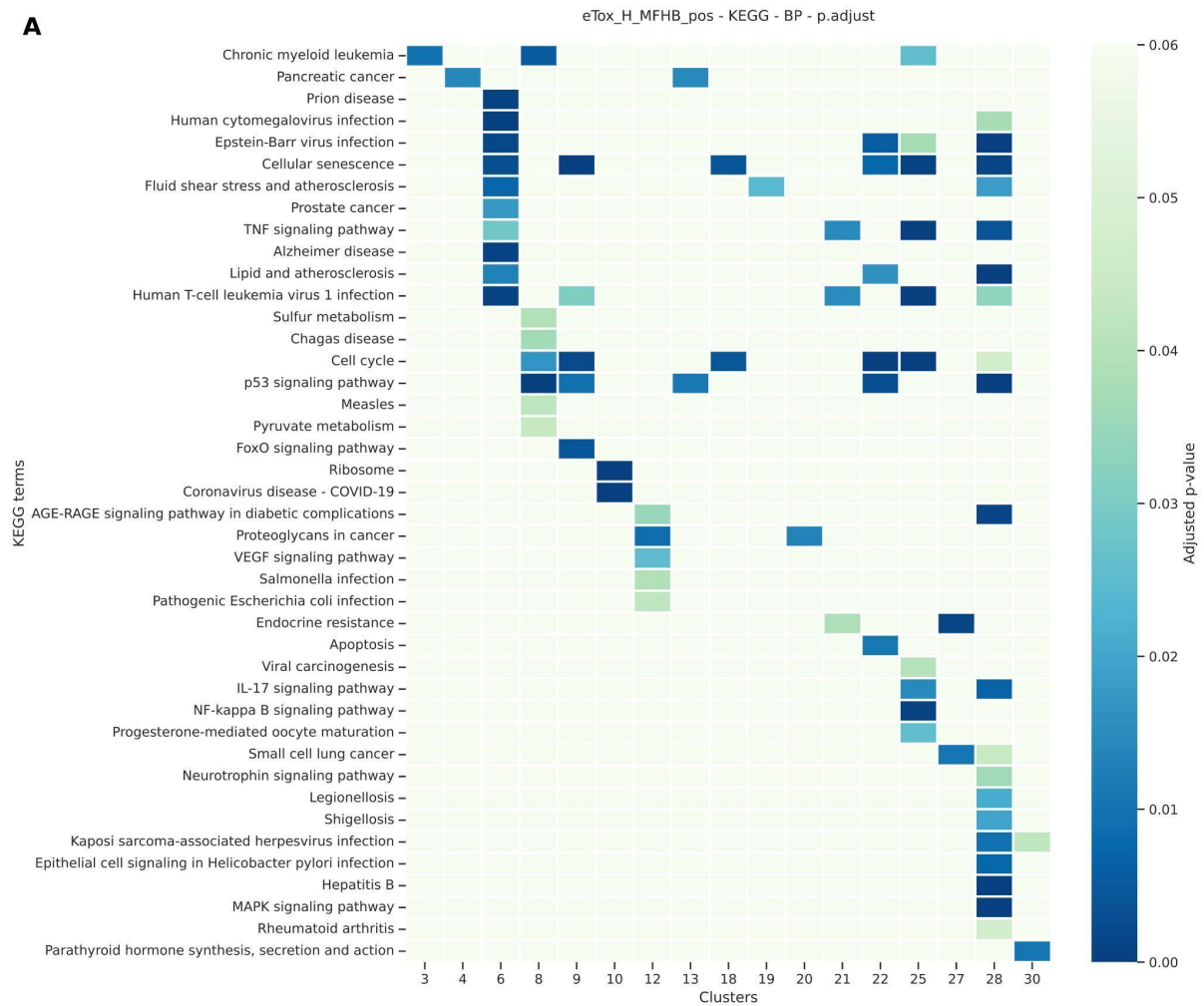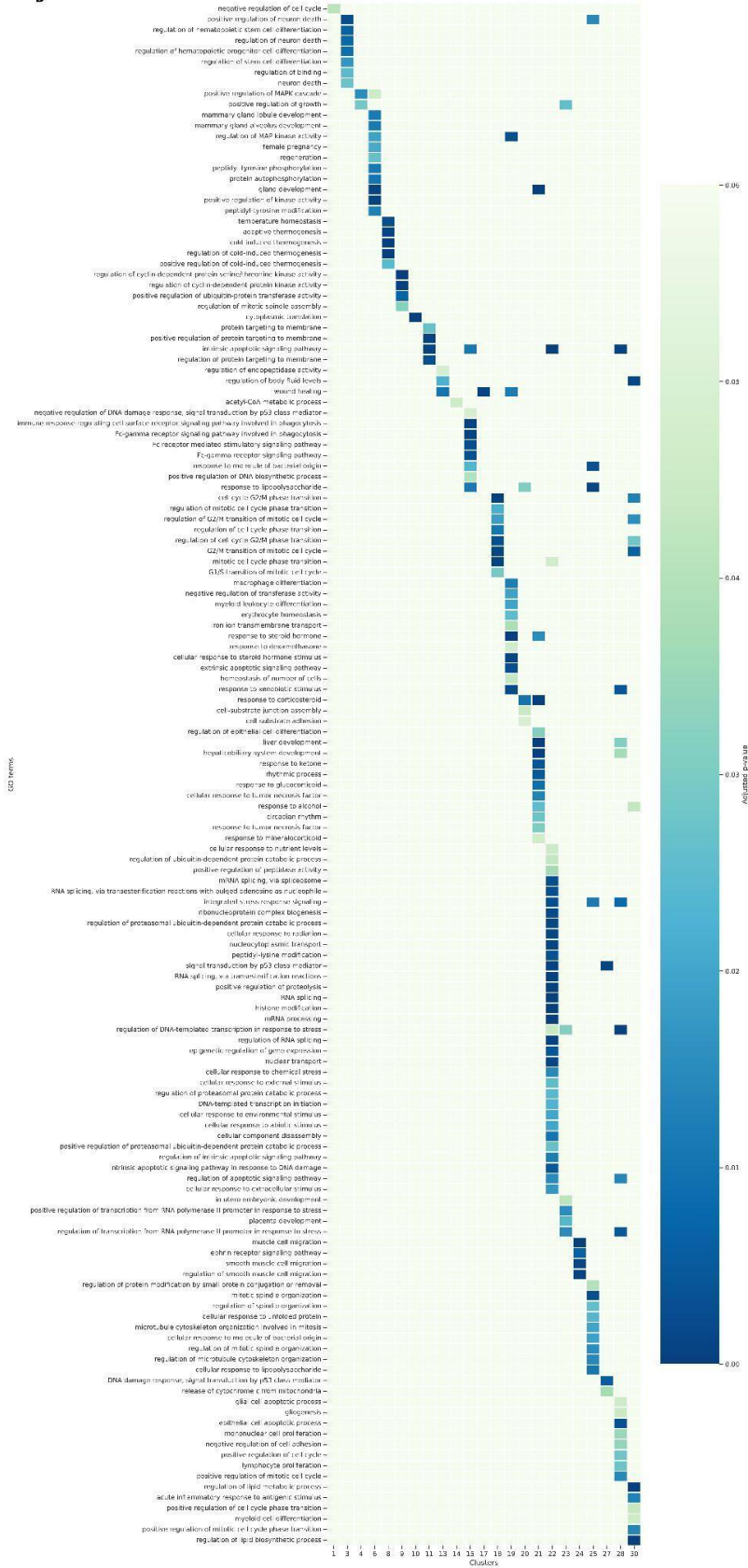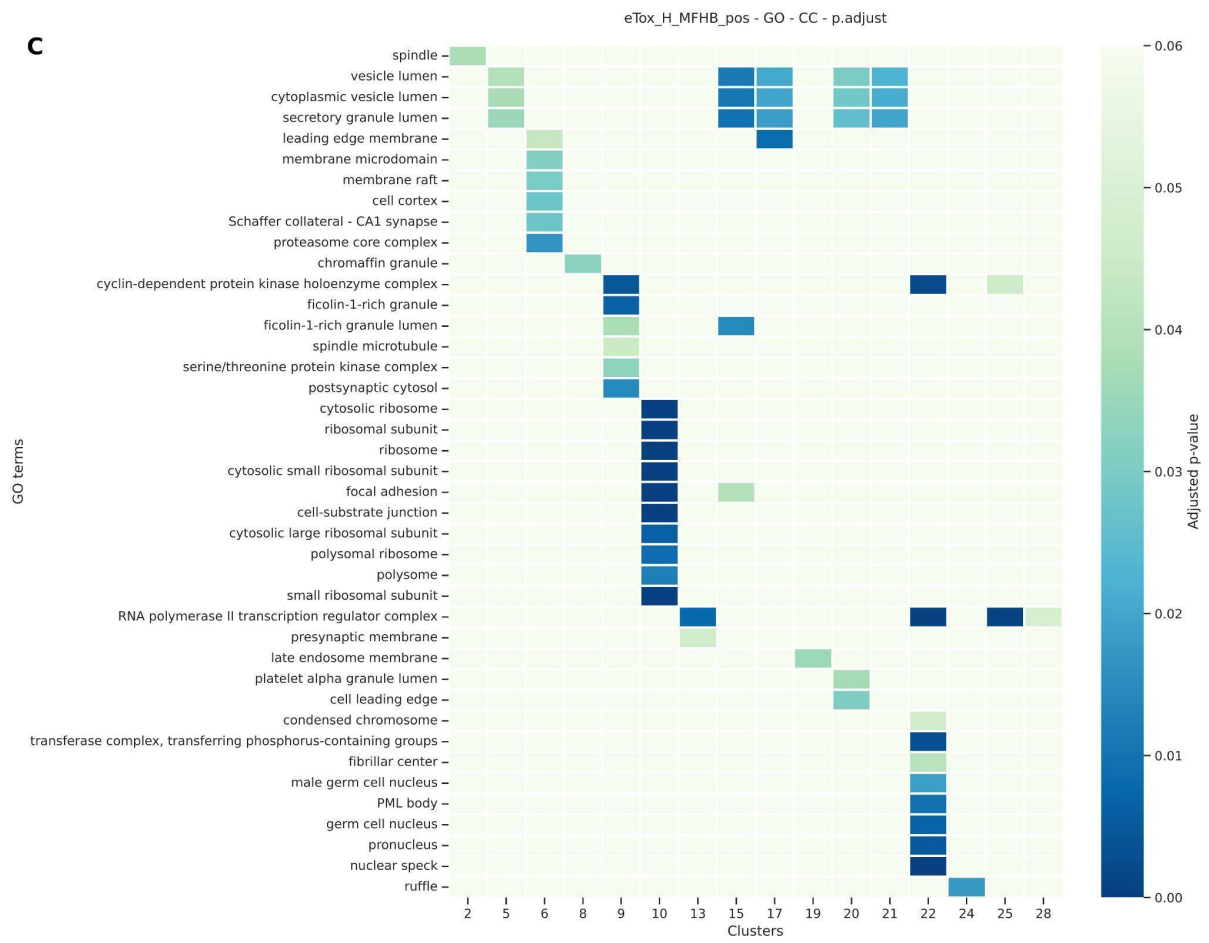
Figure S12. Heatmaps of pathways significantly deregulated by the randomly created clusters of hepatotoxic compounds from the CP_eTox_H_MFHC dataset. A. KEGG pathway analysis. B. GO BP pathway analysis. C. GO CC pathway analysis. Color scale is related to p-value. P-values equal or above 0.05 are in light green.

B

cTox H_MFHC pos - GO - BP - p.adjust

C

eTox_H_MFHC_pos - GO - CC - p.adjust
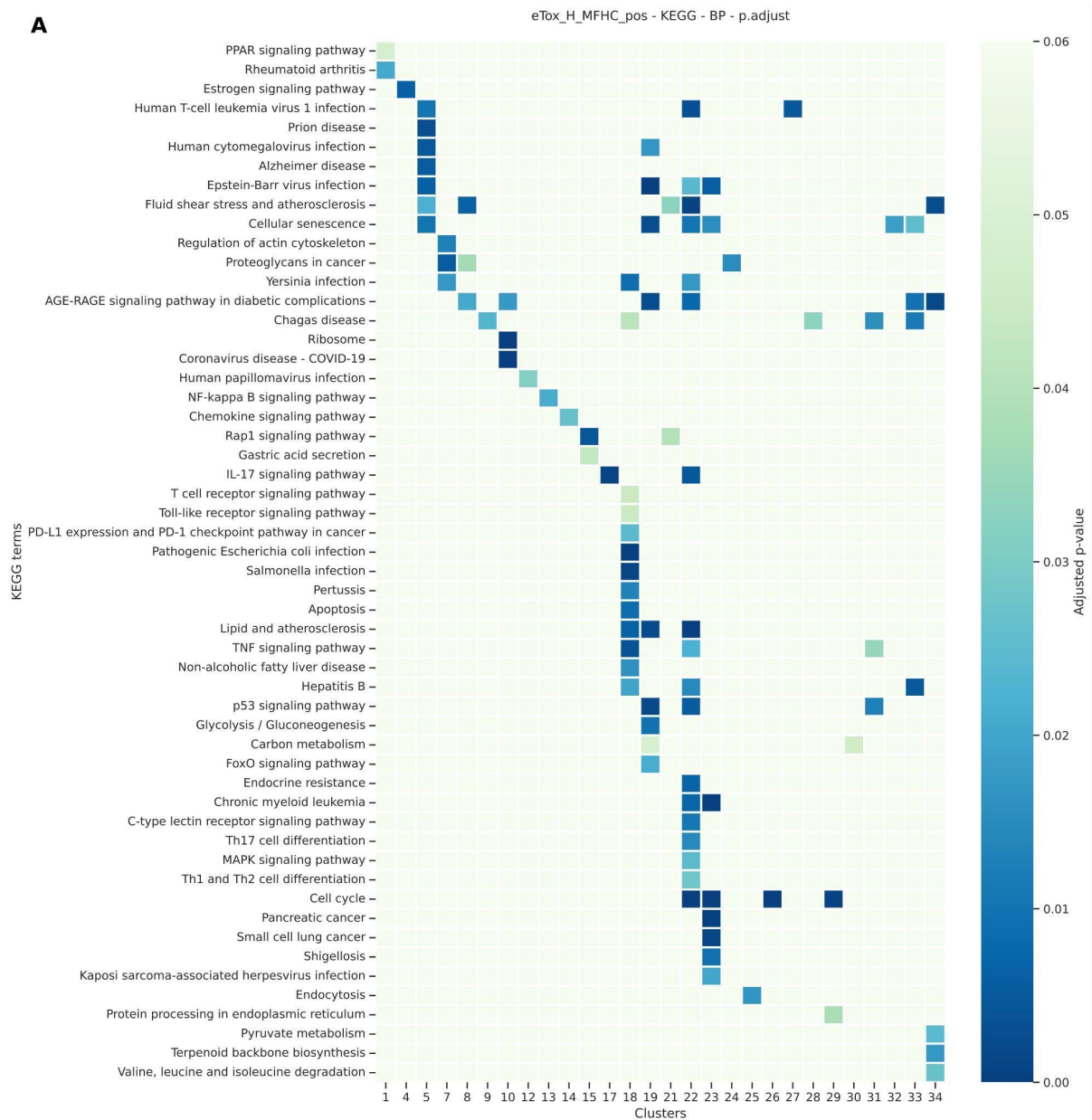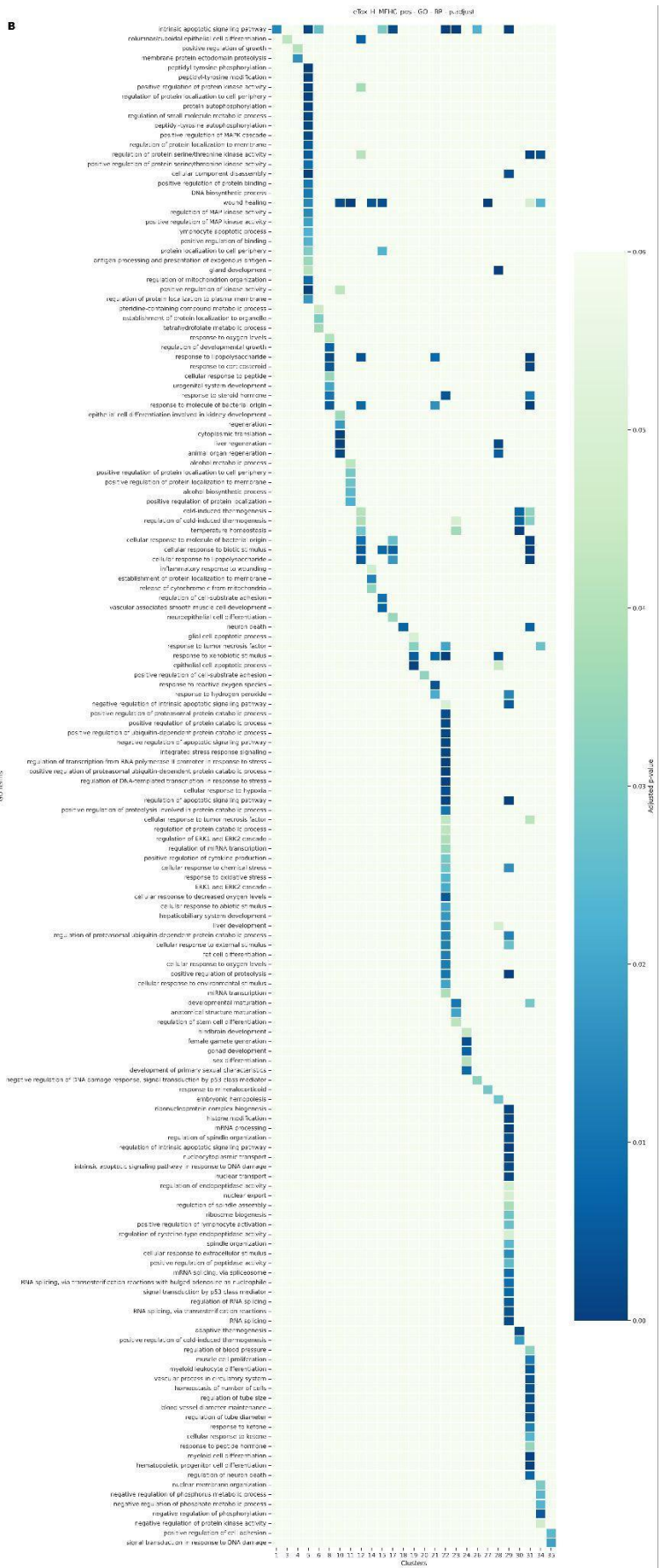
Supplementary Tables

Table S1. DILIrank and eTox compounds annotations (*see XLSX file*).

Table S2. Details of model parameters. Basic parameters describe parameters that are fixed and not included in the hyperparameter tuning.

Model	Basic parameters	Grid Search parameters
Random Forest	random_state = 1 criterion = 'gini' class_weight = 'balanced' n_jobs = -1	n_estimators: [100, 300, 500, 800, 1000] max_depth: [None, 5, 10, 20, 50]
Linear SVM	random_state = 1 class_weight = 'balanced'	penalty: ['l1', 'l2'] multi_class: ['ovr', 'crammer_singer'] max_iter: [1000, 2000, 4000] dual = [True, False]
ElasticNet	random_state = 1 class_weight = 'balanced' penalty = 'elasticnet' solver = 'saga' l1_ratio = 0.2	l1_ratio: [0.1, 0.12, 0.14, 0.16, 0.2, 0.3, 0.4, 0.5, 0.7, 0.8, 0.9] max_iter: [100, 50, 1000, 2000]

Table S3. Metrics formulas. Model efficiency was measured with balanced accuracy (BA), specificity (SP) and sensitivity (SN) metrics. 4 cases of prediction exist: True Positive (TP; Real positive predicted as such), False Positive (FP; Real negative predicted as positive), True Negative (TN; Real negative predicted as such), False Negative (FN; Real positive predicted as negative).

Metric	BA	SN	SP
Formula	$BA = \dfrac{SN + SP}{2}$	$SN = \dfrac{TN}{TN + FP}$	$SP = \dfrac{TP}{TP + FN}$

Table S4. Lists of selected features after feature selection.

Dataset	Compartement	Selected features
CP_DILIs_pos_neg	Cells	Cells_AreaShape_MeanRadius Cells_AreaShape_MedianRadius Cells_AreaShape_MinFeretDiameter Cells_AreaShape_MinorAxisLength Cells_Correlation_Costes_DNA_Mito Cells_Correlation_Costes_DNA_RNA Cells_Correlation_K_ER_AGP Cells_Correlation_RWC_ER_Mito Cells_Correlation_RWC_Mito_RNA Cells_Correlation_RWC_RNA_Mito Cells_Granularity_15_ER Cells_Granularity_2_AGP Cells_Granularity_2_ER Cells_Granularity_2_Mito

		Cells_Granularity_2_RNA
		Cells_Granularity_3_ER
		Cells_Intensity_LowerQuartileIntensity_ER
		Cells_Texture_AngularSecondMoment_AGP_10_0
		Cells_Texture_AngularSecondMoment_AGP_3_0
		Cells_Texture_AngularSecondMoment_AGP_5_0
		Cells_Texture_AngularSecondMoment_DNA_3_0
		Cells_Texture_Contrast_AGP_10_0
		Cells_Texture_Contrast_AGP_3_0
		Cells_Texture_Contrast_AGP_5_0
		Cells_Texture_Contrast_DNA_10_0
		Cells_Texture_Contrast_DNA_3_0
		Cells_Texture_Contrast_DNA_5_0
		Cells_Texture_Contrast_ER_10_0
		Cells_Texture_Contrast_ER_5_0
		Cells_Texture_Contrast_Mito_10_0
		Cells_Texture_Contrast_Mito_3_0
		Cells_Texture_Contrast_Mito_5_0
		Cells_Texture_Contrast_RNA_3_0
		Cells_Texture_Contrast_RNA_5_0
		Cells_Texture_Correlation_DNA_10_0
		Cells_Texture_Correlation_Mito_10_0
		Cells_Texture_Correlation_Mito_3_0
		Cells_Texture_Correlation_Mito_5_0
		Cells_Texture_Correlation_RNA_10_0
		Cells_Texture_Correlation_RNA_3_0
		Cells_Texture_Correlation_RNA_5_0
		Cells_Texture_DifferenceEntropy_AGP_10_0
		Cells_Texture_DifferenceEntropy_AGP_5_0

		Cells_Texture_DifferenceEntropy_DNA_3_0
		Cells_Texture_DifferenceEntropy_DNA_5_0
		Cells_Texture_DifferenceEntropy_ER_5_0
		Cells_Texture_DifferenceEntropy_Mito_10_0
		Cells_Texture_DifferenceEntropy_Mito_3_0
		Cells_Texture_DifferenceEntropy_Mito_5_0
		Cells_Texture_DifferenceEntropy_RNA_3_0
		Cells_Texture_DifferenceEntropy_RNA_5_0
		Cells_Texture_DifferenceVariance_AGP_10_0
		Cells_Texture_DifferenceVariance_AGP_5_0
		Cells_Texture_DifferenceVariance_DNA_10_0
		Cells_Texture_DifferenceVariance_DNA_5_0
		Cells_Texture_DifferenceVariance_ER_10_0
		Cells_Texture_DifferenceVariance_ER_5_0
		Cells_Texture_DifferenceVariance_Mito_10_0
		Cells_Texture_DifferenceVariance_Mito_3_0
		Cells_Texture_DifferenceVariance_Mito_5_0
		Cells_Texture_DifferenceVariance_RNA_3_0
		Cells_Texture_DifferenceVariance_RNA_5_0
		Cells_Texture_Entropy_AGP_10_0
		Cells_Texture_Entropy_AGP_3_0
		Cells_Texture_Entropy_AGP_5_0
		Cells_Texture_Entropy_DNA_3_0
		Cells_Texture_Gabor_AGP_10
		Cells_Texture_Gabor_DNA_10
		Cells_Texture_Gabor_Mito_10
		Cells_Texture_Gabor_RNA_10
		Cells_Texture_InfoMeas1_Mito_5_0
		Cells_Texture_InfoMeas1_RNA_3_0

		Cells_Texture_InfoMeas1_RNA_5_0
		Cells_Texture_InfoMeas2_Mito_3_0
		Cells_Texture_InfoMeas2_Mito_5_0
		Cells_Texture_InfoMeas2_RNA_10_0
		Cells_Texture_InfoMeas2_RNA_3_0
		Cells_Texture_InfoMeas2_RNA_5_0
		Cells_Texture_InverseDifferenceMoment_AGP_10_0
		Cells_Texture_InverseDifferenceMoment_AGP_3_0
		Cells_Texture_InverseDifferenceMoment_AGP_5_0
		Cells_Texture_InverseDifferenceMoment_DNA_3_0
		Cells_Texture_InverseDifferenceMoment_DNA_5_0
		Cells_Texture_InverseDifferenceMoment_Mito_3_0
		Cells_Texture_InverseDifferenceMoment_RNA_3_0
		Cells_Texture_InverseDifferenceMoment_RNA_5_0
		Cells_Texture_SumAverage_DNA_3_0
		Cells_Texture_SumEntropy_AGP_3_0
		Cells_Texture_SumVariance_AGP_3_0,
		Cells_Texture_SumVariance_Mito_10_0
		Cells_Texture_Variance_AGP_10_0
		Cells_Texture_Variance_AGP_3_0
		Cells_Texture_Variance_AGP_5_0
	Cytoplasm	Cytoplasm_AreaShape_MinFeretDiameter
		Cytoplasm_AreaShape_MinorAxisLength
		Cytoplasm_Correlation_Correlation_Mito_RNA
		Cytoplasm_Correlation_Costes_DNA_Mito
		Cytoplasm_Correlation_Costes_DNA_RNA
		Cytoplasm_Correlation_Overlap_DNA_ER
		Cytoplasm_Correlation_Overlap_DNA_Mito
		Cytoplasm_Correlation_RWC_DNA_Mito

		Cytoplasm_Correlation_RWC_Mito_DNA
		Cytoplasm_Correlation_RWC_Mito_RNA
		Cytoplasm_Correlation_RWC_RNA_DNA
		Cytoplasm_Correlation_RWC_RNA_Mito
		Cytoplasm_Granularity_15_ER
		Cytoplasm_Granularity_2_AGP
		Cytoplasm_Granularity_2_ER
		Cytoplasm_Granularity_2_Mito
		Cytoplasm_Granularity_2_RNA
		Cytoplasm_Granularity_3_ER
		Cytoplasm_Granularity_3_Mito
		Cytoplasm_Granularity_3_RNA
		Cytoplasm_Texture_AngularSecondMoment_AGP_3_0
		Cytoplasm_Texture_AngularSecondMoment_AGP_5_0
		Cytoplasm_Texture_Contrast_AGP_10_0
		Cytoplasm_Texture_Contrast_AGP_3_0
		Cytoplasm_Texture_Contrast_AGP_5_0
		Cytoplasm_Texture_Contrast_DNA_10_0
		Cytoplasm_Texture_Contrast_DNA_3_0
		Cytoplasm_Texture_Contrast_DNA_5_0
		Cytoplasm_Texture_Contrast_ER_10_0
		Cytoplasm_Texture_Contrast_Mito_10_0
		Cytoplasm_Texture_Contrast_Mito_3_0
		Cytoplasm_Texture_Contrast_Mito_5_0
		Cytoplasm_Texture_Contrast_RNA_3_0
		Cytoplasm_Texture_Contrast_RNA_5_0
		Cytoplasm_Texture_DifferenceEntropy_AGP_10_0
		Cytoplasm_Texture_DifferenceEntropy_AGP_5_0
		Cytoplasm_Texture_DifferenceEntropy_ER_10_0

		Cytoplasm_Texture_DifferenceEntropy_Mito_10_0
		Cytoplasm_Texture_DifferenceEntropy_Mito_5_0
		Cytoplasm_Texture_DifferenceEntropy_RNA_3_0
		Cytoplasm_Texture_DifferenceEntropy_RNA_5_0
		Cytoplasm_Texture_DifferenceVariance_AGP_10_0
		Cytoplasm_Texture_DifferenceVariance_DNA_10_0
		Cytoplasm_Texture_DifferenceVariance_DNA_3_0
		Cytoplasm_Texture_DifferenceVariance_DNA_5_0
		Cytoplasm_Texture_DifferenceVariance_ER_10_0
		Cytoplasm_Texture_DifferenceVariance_Mito_10_0
		Cytoplasm_Texture_DifferenceVariance_Mito_3_0
		Cytoplasm_Texture_DifferenceVariance_Mito_5_0
		Cytoplasm_Texture_DifferenceVariance_RNA_3_0
		Cytoplasm_Texture_DifferenceVariance_RNA_5_0
		Cytoplasm_Texture_Entropy_AGP_3_0
		Cytoplasm_Texture_Entropy_AGP_5_0
		Cytoplasm_Texture_Entropy_RNA_3_0
		Cytoplasm_Texture_Entropy_RNA_5_0
		Cytoplasm_Texture_Gabor_AGP_10
		Cytoplasm_Texture_Gabor_DNA_10
		Cytoplasm_Texture_Gabor_DNA_3
		Cytoplasm_Texture_Gabor_DNA_5
		Cytoplasm_Texture_Gabor_ER_10
		Cytoplasm_Texture_Gabor_Mito_10
		Cytoplasm_Texture_Gabor_Mito_5
		Cytoplasm_Texture_Gabor_RNA_10
		Cytoplasm_Texture_InverseDifferenceMoment_AGP_10_0
		Cytoplasm_Texture_InverseDifferenceMoment_AGP_3_0
		Cytoplasm_Texture_InverseDifferenceMoment_AGP_5_0

		Cytoplasm_Texture_InverseDifferenceMoment_Mito_3_0
		Cytoplasm_Texture_InverseDifferenceMoment_Mito_5_0
		Cytoplasm_Texture_InverseDifferenceMoment_RNA_3_0
		Cytoplasm_Texture_InverseDifferenceMoment_RNA_5_0
		Cytoplasm_Texture_SumEntropy_AGP_3_0
		Cytoplasm_Texture_SumVariance_AGP_10_0
		Cytoplasm_Texture_SumVariance_AGP_3_0
		Cytoplasm_Texture_SumVariance_AGP_5_0
		Cytoplasm_Texture_SumVariance_DNA_10_0
		Cytoplasm_Texture_SumVariance_ER_10_0
		Cytoplasm_Texture_SumVariance_ER_3_0
		Cytoplasm_Texture_SumVariance_ER_5_0
		Cytoplasm_Texture_Variance_AGP_10_0
		Cytoplasm_Texture_Variance_AGP_3_0
		Cytoplasm_Texture_Variance_AGP_5_0
		Cytoplasm_Texture_Variance_DNA_10_0
		Cytoplasm_Texture_Variance_DNA_5_0
		Cytoplasm_Texture_Variance_ER_10_0
		Cytoplasm_Texture_Variance_ER_3_0
		Cytoplasm_Texture_Variance_ER_5_0
	Nuclei	Nuclei_AreaShape_Compactness
		Nuclei_AreaShape_MaximumRadius
		Nuclei_AreaShape_Zernike_0_0
		Nuclei_Correlation_Costes_DNA_Mito
		Nuclei_Correlation_Costes_DNA_RNA
		Nuclei_Correlation_Overlap_Mito_AGP
		Nuclei_Granularity_13_ER
		Nuclei_Granularity_2_DNA
		Nuclei_Granularity_2_ER

		Nuclei_RadialDistribution_FracAtD_ER_4of4
		Nuclei_RadialDistribution_RadialCV_RNA_3of4
		Nuclei_Texture_AngularSecondMoment_DNA_3_0
		Nuclei_Texture_Contrast_AGP_5_0
		Nuclei_Texture_Contrast_DNA_10_0
		Nuclei_Texture_Contrast_DNA_3_0
		Nuclei_Texture_Contrast_DNA_5_0
		Nuclei_Texture_Contrast_RNA_5_0
		Nuclei_Texture_Correlation_DNA_10_0
		Nuclei_Texture_DifferenceEntropy_AGP_5_0
		Nuclei_Texture_DifferenceEntropy_DNA_10_0
		Nuclei_Texture_DifferenceEntropy_DNA_3_0
		Nuclei_Texture_DifferenceEntropy_DNA_5_0
		Nuclei_Texture_DifferenceVariance_AGP_5_0
		Nuclei_Texture_DifferenceVariance_DNA_10_0
		Nuclei_Texture_DifferenceVariance_DNA_3_0
		Nuclei_Texture_DifferenceVariance_DNA_5_0
		Nuclei_Texture_DifferenceVariance_Mito_5_0
		Nuclei_Texture_Entropy_DNA_3_0
		Nuclei_Texture_Entropy_RNA_3_0
		Nuclei_Texture_Gabor_AGP_10
		Nuclei_Texture_Gabor_DNA_10
		Nuclei_Texture_Gabor_Mito_10
		Nuclei_Texture_Gabor_RNA_10
		Nuclei_Texture_InfoMeas1_DNA_10_0
		Nuclei_Texture_InfoMeas1_ER_10_0
		Nuclei_Texture_InfoMeas2_DNA_10_0
		Nuclei_Texture_InfoMeas2_ER_10_0
		Nuclei_Texture_InverseDifferenceMoment_DNA_10_0

		Nuclei_Texture_InverseDifferenceMoment_DNA_3_0
		Nuclei_Texture_InverseDifferenceMoment_DNA_5_0
		Nuclei_Texture_InverseDifferenceMoment_RNA_3_0
		Nuclei_Texture_InverseDifferenceMoment_RNA_5_0
CP_DILIs_most_neg	Cells	Cells_AreaShape_Area
		Cells_AreaShape_MaximumRadius
		Cells_AreaShape_MeanRadius
		Cells_AreaShape_MedianRadius
		Cells_AreaShape_MinFeretDiameter
		Cells_AreaShape_MinorAxisLength
		Cells_Correlation_Correlation_Mito_ER
		Cells_Correlation_Costes_DNA_Mito
		Cells_Correlation_Costes_DNA_RNA
		Cells_Correlation_K_ER_RNA
		Cells_Correlation_RWC_DNA_Mito
		Cells_Correlation_RWC_ER_Mito
		Cells_Correlation_RWC_ER_RNA
		Cells_Correlation_RWC_Mito_ER
		Cells_Correlation_RWC_Mito_RNA
		Cells_Correlation_RWC_RNA_Mito
		Cells_Granularity_15_ER
		Cells_Intensity_LowerQuartileIntensity_ER
		Cells_Intensity_LowerQuartileIntensity_RNA
		Cells_Intensity_MassDisplacement_RNA
		Cells_Intensity_MaxIntensityEdge_DNA
		Cells_Intensity_MeanIntensityEdge_ER
		Cells_Intensity_MinIntensityEdge_ER
		Cells_Intensity_MinIntensityEdge_RNA
		Cells_Intensity_MinIntensity_ER

		Cells_Intensity_MinIntensity_RNA
		Cells_Intensity_StdIntensityEdge_DNA
		Cells_Intensity_UpperQuartileIntensity_DNA
		Cells_RadialDistribution_RadialCV_DNA_1of4
		Cells_RadialDistribution_RadialCV_DNA_2of4
		Cells_Texture_AngularSecondMoment_AGP_3_0
		Cells_Texture_AngularSecondMoment_AGP_5_0
		Cells_Texture_AngularSecondMoment_DNA_10_0
		Cells_Texture_AngularSecondMoment_DNA_3_0
		Cells_Texture_AngularSecondMoment_DNA_5_0
		Cells_Texture_Contrast_AGP_3_0
		Cells_Texture_Contrast_DNA_10_0
		Cells_Texture_Contrast_DNA_3_0
		Cells_Texture_Contrast_DNA_5_0
		Cells_Texture_Contrast_Mito_3_0
		Cells_Texture_Contrast_Mito_5_0
		Cells_Texture_Contrast_RNA_3_0
		Cells_Texture_Contrast_RNA_5_0
		Cells_Texture_Correlation_Mito_10_0
		Cells_Texture_Correlation_Mito_3_0
		Cells_Texture_Correlation_Mito_5_0
		Cells_Texture_Correlation_RNA_10_0
		Cells_Texture_Correlation_RNA_3_0
		Cells_Texture_Correlation_RNA_5_0
		Cells_Texture_DifferenceEntropy_AGP_10_0
		Cells_Texture_DifferenceEntropy_AGP_3_0
		Cells_Texture_DifferenceEntropy_AGP_5_0
		Cells_Texture_DifferenceEntropy_DNA_10_0
		Cells_Texture_DifferenceEntropy_DNA_3_0

		Cells_Texture_DifferenceEntropy_DNA_5_0
		Cells_Texture_DifferenceEntropy_Mito_3_0
		Cells_Texture_DifferenceEntropy_Mito_5_0
		Cells_Texture_DifferenceEntropy_RNA_10_0
		Cells_Texture_DifferenceEntropy_RNA_3_0
		Cells_Texture_DifferenceEntropy_RNA_5_0
		Cells_Texture_DifferenceVariance_AGP_5_0
		Cells_Texture_DifferenceVariance_ER_10_0
		Cells_Texture_DifferenceVariance_Mito_3_0
		Cells_Texture_DifferenceVariance_Mito_5_0
		Cells_Texture_DifferenceVariance_RNA_3_0
		Cells_Texture_DifferenceVariance_RNA_5_0
		Cells_Texture_Entropy_AGP_10_0
		Cells_Texture_Entropy_AGP_3_0
		Cells_Texture_Entropy_AGP_5_0
		Cells_Texture_Entropy_DNA_10_0
		Cells_Texture_Entropy_DNA_3_0
		Cells_Texture_Entropy_DNA_5_0
		Cells_Texture_Gabor_Mito_10
		Cells_Texture_Gabor_Mito_3
		Cells_Texture_Gabor_RNA_10
		Cells_Texture_Gabor_RNA_3
		Cells_Texture_Gabor_RNA_5
		Cells_Texture_InfoMeas1_Mito_10_0
		Cells_Texture_InfoMeas1_Mito_3_0
		Cells_Texture_InfoMeas1_Mito_5_0
		Cells_Texture_InfoMeas1_RNA_10_0
		Cells_Texture_InfoMeas1_RNA_3_0
		Cells_Texture_InfoMeas1_RNA_5_0

		Cells_Texture_InfoMeas2_Mito_10_0
		Cells_Texture_InfoMeas2_Mito_3_0
		Cells_Texture_InfoMeas2_Mito_5_0
		Cells_Texture_InfoMeas2_RNA_10_0
		Cells_Texture_InfoMeas2_RNA_3_0
		Cells_Texture_InfoMeas2_RNA_5_0
		Cells_Texture_InverseDifferenceMoment_AGP_10_0
		Cells_Texture_InverseDifferenceMoment_AGP_3_0
		Cells_Texture_InverseDifferenceMoment_AGP_5_0
		Cells_Texture_InverseDifferenceMoment_DNA_10_0
		Cells_Texture_InverseDifferenceMoment_DNA_3_0
		Cells_Texture_InverseDifferenceMoment_DNA_5_0
		Cells_Texture_InverseDifferenceMoment_Mito_3_0
		Cells_Texture_InverseDifferenceMoment_Mito_5_0
		Cells_Texture_InverseDifferenceMoment_RNA_3_0
		Cells_Texture_InverseDifferenceMoment_RNA_5_0
		Cells_Texture_SumAverage_DNA_10_0
		Cells_Texture_SumAverage_DNA_3_0
		Cells_Texture_SumAverage_DNA_5_0
		Cells_Texture_SumEntropy_DNA_10_0
		Cells_Texture_SumEntropy_DNA_3_0
		Cells_Texture_SumEntropy_DNA_5_0
		Cells_Texture_SumVariance_Mito_10_0
		Cells_Texture_Variance_DNA_3_0
		Cells_Texture_Variance_DNA_5_0
	Cytoplasm	Cytoplasm_AreaShape_Area
		Cytoplasm_AreaShape_Compactness
		Cytoplasm_AreaShape_Extent
		Cytoplasm_AreaShape_FormFactor

		Cytoplasm_AreaShape_MaximumRadius
		Cytoplasm_AreaShape_MeanRadius
		Cytoplasm_AreaShape_MedianRadius
		Cytoplasm_AreaShape_MinFeretDiameter
		Cytoplasm_AreaShape_MinorAxisLength
		Cytoplasm_AreaShape_Solidity
		Cytoplasm_AreaShape_Zernike_2_0
		Cytoplasm_Correlation_Correlation_Mito_RNA
		Cytoplasm_Correlation_Costes_DNA_Mito
		Cytoplasm_Correlation_Costes_DNA_RNA
		Cytoplasm_Correlation_K_ER_RNA
		Cytoplasm_Correlation_K_RNA_ER
		Cytoplasm_Correlation_Overlap_DNA_AGP
		Cytoplasm_Correlation_Overlap_DNA_ER
		Cytoplasm_Correlation_Overlap_DNA_RNA
		Cytoplasm_Correlation_RWC_AGP_DNA
		Cytoplasm_Correlation_RWC_DNA_AGP
		Cytoplasm_Correlation_RWC_DNA_Mito
		Cytoplasm_Correlation_RWC_DNA_RNA
		Cytoplasm_Correlation_RWC_ER_DNA
		Cytoplasm_Correlation_RWC_ER_Mito
		Cytoplasm_Correlation_RWC_Mito_DNA
		Cytoplasm_Correlation_RWC_Mito_ER
		Cytoplasm_Correlation_RWC_Mito_RNA
		Cytoplasm_Correlation_RWC_RNA_DNA
		Cytoplasm_Correlation_RWC_RNA_Mito
		Cytoplasm_Granularity_15_ER
		Cytoplasm_Granularity_2_ER
		Cytoplasm_Intensity_IntegratedIntensity_AGP

		Cytoplasm_Intensity_IntegratedIntensity_DNA
		Cytoplasm_Intensity_LowerQuartileIntensity_ER
		Cytoplasm_Intensity_MassDisplacement_RNA
		Cytoplasm_Intensity_MeanIntensityEdge_ER
		Cytoplasm_Intensity_MeanIntensity_ER
		Cytoplasm_Intensity_MedianIntensity_AGP
		Cytoplasm_Intensity_MedianIntensity_ER
		Cytoplasm_Intensity_MinIntensityEdge_ER
		Cytoplasm_Intensity_MinIntensityEdge_RNA
		Cytoplasm_Intensity_MinIntensity_ER
		Cytoplasm_Intensity_MinIntensity_RNA
		Cytoplasm_RadialDistribution_FracAtD_DNA_3of4
		Cytoplasm_Texture_AngularSecondMoment_AGP_3_0
		Cytoplasm_Texture_AngularSecondMoment_AGP_5_0
		Cytoplasm_Texture_Contrast_AGP_10_0
		Cytoplasm_Texture_Contrast_AGP_3_0
		Cytoplasm_Texture_Contrast_AGP_5_0
		Cytoplasm_Texture_Contrast_DNA_10_0
		Cytoplasm_Texture_Contrast_DNA_3_0
		Cytoplasm_Texture_Contrast_DNA_5_0
		Cytoplasm_Texture_Contrast_ER_10_0
		Cytoplasm_Texture_Contrast_RNA_3_0
		Cytoplasm_Texture_DifferenceEntropy_AGP_10_0
		Cytoplasm_Texture_DifferenceEntropy_AGP_3_0
		Cytoplasm_Texture_DifferenceEntropy_AGP_5_0
		Cytoplasm_Texture_DifferenceEntropy_ER_10_0
		Cytoplasm_Texture_DifferenceEntropy_Mito_10_0
		Cytoplasm_Texture_DifferenceEntropy_Mito_3_0
		Cytoplasm_Texture_DifferenceEntropy_Mito_5_0

		Cytoplasm_Texture_DifferenceEntropy_RNA_3_0
		Cytoplasm_Texture_DifferenceEntropy_RNA_5_0
		Cytoplasm_Texture_DifferenceVariance_AGP_3_0
		Cytoplasm_Texture_DifferenceVariance_DNA_10_0
		Cytoplasm_Texture_DifferenceVariance_DNA_3_0
		Cytoplasm_Texture_DifferenceVariance_DNA_5_0
		Cytoplasm_Texture_DifferenceVariance_Mito_10_0
		Cytoplasm_Texture_DifferenceVariance_Mito_5_0
		Cytoplasm_Texture_Entropy_AGP_3_0
		Cytoplasm_Texture_Entropy_AGP_5_0
		Cytoplasm_Texture_Entropy_RNA_3_0
		Cytoplasm_Texture_Gabor_AGP_10
		Cytoplasm_Texture_Gabor_DNA_10
		Cytoplasm_Texture_Gabor_DNA_3
		Cytoplasm_Texture_Gabor_DNA_5
		Cytoplasm_Texture_Gabor_ER_10
		Cytoplasm_Texture_Gabor_Mito_10
		Cytoplasm_Texture_InfoMeas1_DNA_3_0
		Cytoplasm_Texture_InfoMeas1_Mito_3_0
		Cytoplasm_Texture_InfoMeas1_Mito_5_0
		Cytoplasm_Texture_InfoMeas1_RNA_10_0
		Cytoplasm_Texture_InfoMeas1_RNA_3_0
		Cytoplasm_Texture_InfoMeas1_RNA_5_0
		Cytoplasm_Texture_InfoMeas2_Mito_3_0
		Cytoplasm_Texture_InfoMeas2_Mito_5_0
		Cytoplasm_Texture_InfoMeas2_RNA_3_0
		Cytoplasm_Texture_InverseDifferenceMoment_AGP_10_0
		Cytoplasm_Texture_InverseDifferenceMoment_AGP_3_0
		Cytoplasm_Texture_InverseDifferenceMoment_AGP_5_0

		Cytoplasm_Texture_InverseDifferenceMoment_Mito_3_0
		Cytoplasm_Texture_InverseDifferenceMoment_Mito_5_0
		Cytoplasm_Texture_InverseDifferenceMoment_RNA_3_0
		Cytoplasm_Texture_InverseDifferenceMoment_RNA_5_0
		Cytoplasm_Texture_SumEntropy_AGP_3_0
		Cytoplasm_Texture_SumVariance_AGP_3_0
		Cytoplasm_Texture_SumVariance_DNA_10_0
		Cytoplasm_Texture_Variance_AGP_10_0
		Cytoplasm_Texture_Variance_DNA_10_0
	Nuclei	Nuclei_Correlation_Costes_DNA_Mito
		Nuclei_Correlation_Costes_DNA_RNA
		Nuclei_Correlation_K_ER_RNA
		Nuclei_Granularity_10_DNA
		Nuclei_Granularity_13_ER
		Nuclei_Granularity_6_ER
		Nuclei_Granularity_9_DNA
		Nuclei_Granularity_9_RNA
		Nuclei_Texture_SumEntropy_DNA_10_0
CP_eTox_H_HT	Cells	Cells_Texture_Entropy_AGP_5_0
	Cytoplasm	/
	Nuclei	Nuclei_AreaShape_Orientation
		Nuclei_Texture_Variance_Mito_10_0
CP_eTox_H_MF	Cells	Cells_Correlation_Manders_RNA_ER
		Cells_Correlation_Overlap_Mito_AGP
		Cells_Correlation_Overlap_RNA_AGP
		Cells_Granularity_16_Mito
		Cells_Intensity_IntegratedIntensityEdge_Mito

		Cells_Texture_InfoMeas1_Mito_10_0
		Cells_Texture_InfoMeas1_Mito_5_0
		Cells_Texture_InfoMeas1_RNA_10_0
		Cells_Texture_InfoMeas1_RNA_3_0
		Cells_Texture_InfoMeas1_RNA_5_0
	Cytoplasm	Cytoplasm_Correlation_Overlap_RNA_AGP
		Cytoplasm_Granularity_16_Mito
		Cytoplasm_RadialDistribution_FracAtD_DNA_3of4
		Cytoplasm_Texture_Correlation_DNA_10_0
		Cytoplasm_Texture_Correlation_DNA_3_0
		Cytoplasm_Texture_Correlation_DNA_5_0
		Cytoplasm_Texture_DifferenceVariance_DNA_5_0
		Cytoplasm_Texture_InfoMeas1_Mito_3_0
		Cytoplasm_Texture_InfoMeas1_RNA_10_0
		Cytoplasm_Texture_InfoMeas1_RNA_5_0
		Cytoplasm_Texture_InfoMeas2_DNA_3_0
		Cytoplasm_Texture_InfoMeas2_Mito_3_0
		Cytoplasm_Texture_InfoMeas2_Mito_5_0
		Cytoplasm_Texture_InfoMeas2_RNA_10_0
	Nuclei	Nuclei_AreaShape_Zernike_3_1
		Nuclei_AreaShape_Zernike_8_8
		Nuclei_AreaShape_Zernike_9_7
		Nuclei_Correlation_RWC_DNA_ER
		Nuclei_Correlation_RWC_ER_DNA
		Nuclei_Granularity_16_Mito
CP_eTox_H_MHB	Cells	Cells_Correlation_Costes_AGP_RNA
		Cells_Correlation_K_ER_AGP
		Cells_Correlation_K_Mito_RNA

		Cells_Correlation_Manders_Mito_ER
		Cells_Correlation_Manders_RNA_ER
		Cells_Correlation_RWC_DNA_ER
		Cells_Correlation_RWC_RNA_ER
		Cells_Intensity_MeanIntensityEdge_Mito
		Cells_Intensity_StdIntensityEdge_ER
		Cells_RadialDistribution_RadialCV_ER_4of4
		Cells_RadialDistribution_RadialCV_Mito_2of4
	Cytoplasm	Cytoplasm_Correlation_Costes_AGP_RNA
		Cytoplasm_Correlation_K_AGP_ER
		Cytoplasm_Correlation_K_ER_AGP
		Cytoplasm_Correlation_Manders_AGP_ER
		Cytoplasm_Correlation_Manders_DNA_ER
		Cytoplasm_Correlation_Manders_Mito_ER
		Cytoplasm_Correlation_Manders_RNA_ER
		Cytoplasm_Intensity_LowerQuartileIntensity_Mito
		Cytoplasm_RadialDistribution_FracAtD_AGP_1of4
		Cytoplasm_RadialDistribution_FracAtD_AGP_2of4
		Cytoplasm_RadialDistribution_FracAtD_AGP_4of4
		Cytoplasm_RadialDistribution_FracAtD_ER_1of4
		Cytoplasm_RadialDistribution_FracAtD_ER_2of4
		Cytoplasm_RadialDistribution_FracAtD_ER_4of4
		Cytoplasm_RadialDistribution_FracAtD_Mito_2of4
		Cytoplasm_RadialDistribution_FracAtD_Mito_3of4
		Cytoplasm_RadialDistribution_FracAtD_Mito_4of4
		Cytoplasm_RadialDistribution_MeanFrac_ER_4of4
		Cytoplasm_RadialDistribution_MeanFrac_Mito_4of4
		Cytoplasm_RadialDistribution_RadialCV_ER_1of4
		Cytoplasm_Texture_Correlation_DNA_10_0

		Cytoplasm_Texture_Correlation_DNA_3_0
		Cytoplasm_Texture_Correlation_DNA_5_0
		Cytoplasm_Texture_InfoMeas1_DNA_10_0
		Cytoplasm_Texture_InfoMeas1_DNA_5_0
		Cytoplasm_Texture_InfoMeas1_Mito_10_0
		Cytoplasm_Texture_InfoMeas2_DNA_3_0
		Cytoplasm_Texture_InfoMeas2_DNA_5_0
		Cytoplasm_Texture_InfoMeas2_Mito_10_0
	Nuclei	Nuclei_AreaShape_Compactness
		Nuclei_AreaShape_FormFactor
		Nuclei_AreaShape_Zernike_6_6
		Nuclei_AreaShape_Zernike_8_8
		Nuclei_Correlation_RWC_DNA_ER
		Nuclei_Correlation_RWC_ER_DNA
		Nuclei_Granularity_10_Mito
		Nuclei_Granularity_10_RNA
CP_eTox_H_MFHC	Cells	Cells_Correlation_Manders_Mito_ER
		Cells_Correlation_Manders_RNA_ER
		Cells_Correlation_Overlap_Mito_AGP
		Cells_Correlation_Overlap_RNA_AGP
		Cells_Granularity_16_Mito
		Cells_Intensity_IntegratedIntensityEdge_Mito
		Cells_Texture_InfoMeas1_Mito_10_0
		Cells_Texture_InfoMeas1_Mito_5_0
		Cells_Texture_InfoMeas1_RNA_10_0
		Cells_Texture_InfoMeas1_RNA_3_0
		Cells_Texture_InfoMeas1_RNA_5_0
		Cells_Texture_InfoMeas2_Mito_10_0

		Cells_Texture_InfoMeas2_RNA_10_0
	Cytoplasm	Cytoplasm_AreaShape_Compactness
		Cytoplasm_AreaShape_Zernike_1_1
		Cytoplasm_Correlation_Manders_AGP_ER
		Cytoplasm_Correlation_Manders_DNA_ER
		Cytoplasm_Correlation_Manders_RNA_ER
		Cytoplasm_Correlation_Overlap_RNA_AGP
		Cytoplasm_Granularity_16_Mito
		Cytoplasm_Intensity_MassDisplacement_ER
		Cytoplasm_RadialDistribution_RadialCV_ER_1of4
		Cytoplasm_RadialDistribution_RadialCV_ER_2of4
		Cytoplasm_Texture_Correlation_DNA_3_0
		Cytoplasm_Texture_DifferenceVariance_DNA_5_0
		Cytoplasm_Texture_InfoMeas1_Mito_3_0
		Cytoplasm_Texture_InfoMeas1_Mito_5_0
		Cytoplasm_Texture_InfoMeas1_RNA_10_0
		Cytoplasm_Texture_InfoMeas1_RNA_5_0
		Cytoplasm_Texture_InfoMeas2_Mito_3_0
		Cytoplasm_Texture_InfoMeas2_Mito_5_0
		Cytoplasm_Texture_InfoMeas2_RNA_10_0
	Nuclei	Nuclei_AreaShape_Zernike_9_7
		Nuclei_Correlation_RWC_DNA_ER
		Nuclei_Granularity_14_RNA
		Nuclei_Granularity_16_Mito
		Nuclei_RadialDistribution_FracAtD_ER_3of4
		Nuclei_RadialDistribution_FracAtD_Mito_3of4

Table S5. Percentages of feature categories in each compartment and dataset before feature selection.

Compartment	Dataset	AreaShape	Correlation	Granularity	Intensity	RadialDistribution	Texture	Neighbors	Location	Number	Parent
Cells	CP_DILIs_most_neg	8.09	14.97	11.02	12.91	10.33	36.14	2.41	3.79	0.17	0.17
	CP_DILIs_pos_neg	8.09	14.97	11.02	12.91	10.33	36.14	2.41	3.79	0.17	0.17
	CP_eTox_H_HT	8.08	15.12	11.00	12.89	10.31	36.08	2.41	3.78	0.17	0.17
	CP_eTox_H_MF	8.08	15.12	11.00	12.89	10.31	36.08	2.41	3.78	0.17	0.17
	CP_eTox_H_MFHB	8.08	15.12	11.00	12.89	10.31	36.08	2.41	3.78	0.17	0.17
	CP_eTox_H_MFHC	8.08	15.12	11.00	12.89	10.31	36.08	2.41	3.78	0.17	0.17
Cytoplasm	CP_DILIs_most_neg	8.32	14.87	11.33	13.27	10.62	37.17	0.00	3.89	0.18	0.35
	CP_DILIs_pos_neg	8.32	14.87	11.33	13.27	10.62	37.17	0.00	3.89	0.18	0.35
	CP_eTox_H_HT	8.32	14.87	11.33	13.27	10.62	37.17	0.00	3.89	0.18	0.35
	CP_eTox_H_MF	8.32	14.87	11.33	13.27	10.62	37.17	0.00	3.89	0.18	0.35
	CP_eTox_H_MFHB	8.32	14.87	11.33	13.27	10.62	37.17	0.00	3.89	0.18	0.35
	CP_eTox_H_MFHC	8.32	14.87	11.33	13.27	10.62	37.17	0.00	3.89	0.18	0.35
Nuclei	CP_DILIs_most_neg	8.23	12.43	14.01	13.13	10.51	36.78	0.88	3.85	0.18	0.00
	CP_DILIs_pos_neg	8.23	12.43	14.01	13.13	10.51	36.78	0.88	3.85	0.18	0.00
	CP_eTox_H_HT	8.22	12.41	13.99	13.11	10.49	36.71	1.05	3.85	0.17	0.00
	CP_eTox_H_MF	8.22	12.41	13.99	13.11	10.49	36.71	1.05	3.85	0.17	0.00
	CP_eTox_H_MFHB	8.22	12.41	13.99	13.11	10.49	36.71	1.05	3.85	0.17	0.00
	CP_eTox_H_MFHC	8.22	12.41	13.99	13.11	10.49	36.71	1.05	3.85	0.17	0.00

Table S6. Percentages of feature categories in each compartment and dataset after feature selection.

Compartment	Dataset	AreaShape	Correlation	Granularity	Intensity	RadialDistribution	Texture	Neighbors	Location	Number	Parent
Cells	CP_DILIs_most_neg	3.03	18.79	6.06	9.09	11.52	49.09	2.42	0.0	0.0	0.0
	CP_DILIs_pos_neg	1.82	18.18	5.45	0.00	3.64	70.91	0.00	0.0	0.0	0.0
	CP_eTox_H_HT	18.18	18.18	18.18	9.09	0.00	36.36	0.00	0.0	0.0	0.0
	CP_eTox_H_MF	12.50	12.50	6.25	6.25	0.00	56.25	6.25	0.0	0.0	0.0
	CP_eTox_H_MFHB	5.26	31.58	31.58	31.58	0.00	0.00	0.00	0.0	0.0	0.0
	CP_eTox_H_MFHC	0.00	16.67	16.67	12.50	0.00	54.17	0.00	0.0	0.0	0.0
Cytoplasm	CP_DILIs_most_neg	6.35	26.19	7.94	11.90	5.56	42.06	0.00	0.0	0.0	0.0
	CP_DILIs_pos_neg	1.47	20.59	7.35	1.47	2.94	66.18	0.00	0.0	0.0	0.0
	CP_eTox_H_HT	0.00	0.00	11.11	0.00	0.00	88.89	0.00	0.0	0.0	0.0
	CP_eTox_H_MF	0.00	12.00	8.00	0.00	0.00	80.00	0.00	0.0	0.0	0.0
	CP_eTox_H_MFHB	0.00	28.57	25.00	28.57	0.00	17.86	0.00	0.0	0.0	0.0
	CP_eTox_H_MFHC	0.00	14.81	11.11	0.00	0.00	74.07	0.00	0.0	0.0	0.0
Nuclei	CP_DILIs_most_neg	2.27	25.00	38.64	6.82	22.73	0.00	4.55	0.0	0.0	0.0
	CP_DILIs_pos_neg	3.85	26.92	19.23	0.00	15.38	34.62	0.00	0.0	0.0	0.0
	CP_eTox_H_HT	30.77	0.00	15.38	30.77	7.69	15.38	0.00	0.0	0.0	0.0
	CP_eTox_H_MF	37.50	0.00	25.00	12.50	12.50	12.50	0.00	0.0	0.0	0.0
	CP_eTox_H_MFHB	25.00	2.78	19.44	30.56	13.89	8.33	0.00	0.0	0.0	0.0
	CP_eTox_H_MFHC	9.09	9.09	13.64	9.09	27.27	31.82	0.00	0.0	0.0	0.0

Table S7. Ratio of percentage in the selected features relative to the background percentage in the full set of features before selection.

Compartment	Dataset	AreaShape	Correlation	Granularity	Intensity	RadialDistribution	Texture	Neighbors	Location	Number	Parent
Cells	CP_DILIs_most_neg	0.374536	1.255177	0.549909	0.704105	1.115198	1.358329	1.004149	0.0	0.0	0.0
	CP_DILIs_pos_neg	0.224969	1.214429	0.494555	0.000000	0.352372	1.962092	0.000000	0.0	0.0	0.0
	CP_eTox_H_HT	2.250000	1.202381	1.652727	0.705198	0.000000	1.007761	0.000000	0.0	0.0	0.0
	CP_eTox_H_MF	1.547030	0.826720	0.568182	0.484872	0.000000	1.559035	2.593361	0.0	0.0	0.0
	CP_eTox_H_MFHB	0.650990	2.088624	2.870909	2.449961	0.000000	0.000000	0.000000	0.0	0.0	0.0
	CP_eTox_H_MFHC	0.000000	1.102513	1.515455	0.969744	0.000000	1.501386	0.000000	0.0	0.0	0.0
Cytoplasm	CP_DILIs_most_neg	0.763221	1.761264	0.700794	0.896760	0.523540	1.131558	NaN	0.0	0.0	0.0
	CP_DILIs_pos_neg	0.176683	1.384667	0.648720	0.110776	0.276836	1.780468	NaN	0.0	0.0	0.0
	CP_eTox_H_HT	0.000000	0.000000	0.980583	0.000000	0.000000	2.391445	NaN	0.0	0.0	0.0
	CP_eTox_H_MF	0.000000	0.806994	0.706090	0.000000	0.000000	2.152273	NaN	0.0	0.0	0.0
	CP_eTox_H_MFHB	0.000000	1.921318	2.206531	2.152977	0.000000	0.480495	NaN	0.0	0.0	0.0
	CP_eTox_H_MFHC	0.000000	0.995965	0.980583	0.000000	0.000000	1.992736	NaN	0.0	0.0	0.0
Nuclei	CP_DILIs_most_neg	0.275820	2.011263	2.758030	0.519421	2.162702	0.000000	5.170455	0.0	0.0	NaN
	CP_DILIs_pos_neg	0.467801	2.165728	1.372591	0.000000	1.463368	0.941272	0.000000	0.0	0.0	NaN
	CP_eTox_H_HT	3.743309	0.000000	1.099357	2.347063	0.733079	0.418959	0.000000	0.0	0.0	NaN
	CP_eTox_H_MF	4.562044	0.000000	1.786991	0.953471	1.191611	0.340507	0.000000	0.0	0.0	NaN
	CP_eTox_H_MFHB	3.041363	0.224013	1.389564	2.331045	1.324118	0.226914	0.000000	0.0	0.0	NaN
	CP_eTox_H_MFHC	1.105839	0.732474	0.974982	0.693364	2.599619	0.866794	0.000000	0.0	0.0	NaN

Table S8. P-values of the Fisher's Exact Test between the number of features before and after selection, for each compartment, feature category and dataset.

Compartment	Dataset	AreaShape	Correlation	Granularity	Intensity	RadialDistribution	Texture	Neighbors	Location	Number	Parent
Cells	CP_DILIs_most_neg	1.0	1	1.000000	1.000000	1.000000	0.014819	1	1.0	1	1
	CP_DILIs_pos_neg	1.0	1	1.000000	1.000000	1.000000	0.000498	1	1.0	1	1
	CP_eTox_H_HT	1.0	1	1.000000	1.000000	1.000000	0.119281	1	1.0	1	1
	CP_eTox_H_MF	1.0	1	1.000000	1.000000	1.000000	0.018943	1	1.0	1	1
	CP_eTox_H_MFHB	1.0	1	1.000000	0.532468	1.000000	1.000000	1	1.0	1	1
	CP_eTox_H_MFHC	1.0	1	1.000000	1.000000	1.000000	0.024501	1	1.0	1	1
Cytoplasm	CP_DILIs_most_neg	1.0	1	1.000000	1.000000	1.000000	0.041540	1	1.0	1	1
	CP_DILIs_pos_neg	1.0	1	1.000000	1.000000	1.000000	0.001026	1	1.0	1	1
	CP_eTox_H_HT	1.0	1	1.000000	1.000000	1.000000	0.001399	1	1.0	1	1
	CP_eTox_H_MF	1.0	1	1.000000	1.000000	1.000000	0.000235	1	1.0	1	1
	CP_eTox_H_MFHB	1.0	1	1.000000	0.549722	1.000000	0.558500	1	1.0	1	1
	CP_eTox_H_MFHC	1.0	1	1.000000	1.000000	1.000000	0.000638	1	1.0	1	1
Nuclei	CP_DILIs_most_neg	1.0	1	0.523671	1.000000	0.568663	1.000000	1	1.0	1	1
	CP_DILIs_pos_neg	1.0	1	1.000000	1.000000	0.566185	0.149866	1	1.0	1	1
	CP_eTox_H_HT	1.0	1	1.000000	0.528571	1.000000	1.000000	1	1.0	1	1
	CP_eTox_H_MF	1.0	1	1.000000	1.000000	1.000000	1.000000	1	1.0	1	1
	CP_eTox_H_MFHB	1.0	1	1.000000	0.545027	1.000000	1.000000	1	1.0	1	1
	CP_eTox_H_MFHC	1.0	1	1.000000	1.000000	0.289353	0.288294	1	1.0	1	1

Table S9. Cell Painting features-based clusters details and gene enrichment results. Compounds without gene expression data are displayed in italic.

CP_DILIs_pos_neg				
Cluster	**Compounds**	**Number of downregulated genes**	**Number of upregulated genes**	**Enrichment terms**
6	Carbamazepine *Ofloxacin* *Isradipine* *Aceclofenac*	21	17	/
13	Metoprolol Mexiletine Saquinavir Omeprazole *Sulfadiazine* *Captopril* *Valdecoxib* *Zonisamide* *Iproniazid* *Warfarin*	50	60	1 KEGG 3 GO BP 2 GO CC
16	Amiloride Pyrimethamine Mefenamic acid *Prednisone*	32	29	0 KEGG 4 GO BP 5 GO CC

	Prednisolone *Cefazolin*			
17	Glyburide Nimesulide Enalapril *Hydralazine* *Moxisylyte*	71	84	0 KEGG 5 GO BP 0 GO CC
23	Verapamil Fluoxetine Citalopram Falnidamol Metoclopramide Amiodarone Prochlorperazine Diclofenac *Cyclobenzaprine* *Baclofen*	169	191	6 KEGG 41 GO BP 5 GO CC
26	Mebendazole Amlodipine *Etoposide* *Paclitaxel*	37	57	5 KEGG 3 GO BP 0 GO CC
27	Ketorolac *Gemifloxacin*	13	8	/

	Sulindac *Chlorothiazide* *Norfloxacin* *Chlorcyclizine*			
30	Amitriptyline Clomipramine Tamoxifen Sildenafil Nefazodone Progesterone *Chlorpropamide* *Propylthiouracil* *Bromocriptine*	59	46	2 KEGG 13 GO BP 2 GO CC
31	Fluconazole Thiotepa Ketoprofen Riluzole *ChlorzoxazoneN* *Acetazolamide* *Deferoxamine*	60	39	/
35	Propafenone Doxepin Pantoprazole Oxaprozin *Cloxacillin*	62	61	0 KEGG 2 GO BP 2 GO CC

	Clotrimazole *Levothyroxine* *Methylprednisolone*			
39	Papaverine Estradiol Flutamide *Azathioprine* *Ibuprofen*	53	52	2 KEGG 5 GO BP 0 GO CC
41	Quinidine Modafinil *Ciprofloxacin* *Fipexide* *Trimethoprim* *Methazolamide* *Lansoprazole* *Cefoperazone*	33	37	0 KEGG 2 GO BP 0 GO CC
42	Cetirizine Finasteride Danazol *Acebutolol* *Disulfiram* *Ethionamide*	58	56	1 KEGG 2 GO BP 0 GO CC
48	Fenofibrate Carvedilol	59	46	0 KEGG 2 GO BP

Cluster	Compounds	Number of upregulated genes	Number of downregulated genes	Enrichment terms
	Metaxalone Procainamide Glipizide *Mefloquine* *Indomethacin* *Terbutaline* *Nitrofurantoin* *Dapsone*			0 GO CC
55	Mitoxantrone Doxorubicin Lovastatin Simvastatin Nortriptyline Imatinib	609	401	8 KEGG 50 GO BP 6 GO CC
CP_DILIs_most_neg				
Cluster	**Compounds**	**Number of upregulated genes**	**Number of downregulated genes**	**Enrichment terms**
3	Nilutamide Atomoxetine Amiodarone *Indomethacin* *Disulfiram*	64	60	2 KEGG 13 GO BP 1 GO CC
4	Etodolac Nialamide	135	103	0 KEGG 1 GO BP

	Diclofenac *Gemfibrozil*			0 GO CC
7	Nefazodone Clomipramine *Propylthiouracil* *Zidovudine* *Phenytoin*	22	15	/
11	Albendazole Riluzole *Acetazolamide* *cyclosporin A*	19	26	2 KEGG 0 GO BP 0 GO CC
12	Dantrolene Diltiazem Lamotrigine *Glafenine*	20	29	0 KEGG 8 GO BP 0 GO CC
16	Carbamazepine Mexiletine Clozapine *Iproniazid*	48	43	/
CP_eTox_H_HT				
2	Testosterone propionate	52	47	2 KEGG

	Celecoxib Saquinavir Estrone *Ethionamide*			18 GO BP 1 GO CC
4	Pinacidil Buspirone Tolazamide Metoprolol Dexamethasone Fexofenadine Ramacemide *Zolpidem* *Ofloxacin* *Iproniazid* *Carbimazole* *Ritodrine* *Metyrapone* *Valdecoxib*	105	90	8 KEGG 10 GO BP 0 GO CC
9	Cabergoline Enalapril Nimesulide Probenecid Pseudoephedrine Trazodone Clomethiazole Triamcinolone	74	87	1 KEGG 0 GO BP 3 GO CC

	Practolol				
	Leflunomide				
	Tolfenamic acid				
	Prednisone				
	Hydralazine				
	Hydrocortisone acetate				
	Valacyclovir				
	Azlocillin				
	Aceclofenac				
	Sulfachloropyridazine				
10	*Azelastine* *Azactam* *Zonisamide* Tolbutamide	27	23	/	
35	Glyburide Thalidomide Caffeine *Cefuroxime*	88	114	2 KEGG 16 GO BP 3 GO CC	
37	Haloperidol Pirfenidone Venlafaxine Doxylamine Benzthiazide Ticlopidine *Atenolol*	89	80	3 KEGG 5 GO BP 3 GO CC	

	Cinchophen *Nabumetone* *Methoxsalen*			
38	Proguanil Levonorgestrel *Diazepam* *Chlormezanone*	11	16	0 KEGG 0 GO BP 5 GO CC
39	Cyproheptadine *Cefoperazone* *Estrone sulfate* *4-Phenylbutyric acid* *Sulfathiazole* *Norfloxacin*	9	13	/
40	Pheniramine Diphenidol Tinidazole *Cephalothin* *Periciazine* *Niridazole* *Mephenytoin* *Levamisole*	33	38	/
43	Amiodarone Salmeterol Amoxapine	125	133	4 KEGG 26 GO BP 5 GO CC

	Mometasone furoate			
	Amiloride			S76
	Naftidrofuryl			
	Praziquantel			
	Prochlorperazine			
	Cyclobenzaprine			
	Indomethacin			
	Thiamphenicol			
	Piribedil			
	Letrozole			
44	Propafenone Niridazole Amitriptyline Simvastatin Chlorpromazine Tamoxifen Bepridil Mibefradil Nortriptyline Loxapine Fenofibrate Pizotifen Pindolol *Clotrimazole* *Astemizole* *Fluvastatine*	202	235	2 KEGG 15 GO BP 8 GO CC

45	Thiotepa Riluzole Quinapril Verapamil Progesterone *Terbutaline* *Chlorpropamide* *Etoposide* *Hycanthone* *Acetazolamide*	79	65	1 KEGG 4 GO BP 0 GO CC
46	Mesoridazine Pimozide Fluspirilene Flufenamic acid Mebendazole Albendazole Niclosamide Prazosin Paroxetine Nilutamide Flecainide Ornidazole *Hydroflumethiazide* *Bambuterol* *Colchicine* *AHZ9RYL9EW* *Azathioprine*	204	203	11 KEGG 45 GO BP 9 GO CC

57	Sertaconazole Phentolamine *Althiazide* *Acetohexamide* *Chlorzoxazone* *Propranolol*	20	17	0 KEGG 2 GO BP 0 GO CC
58	Ketoprofen Spironolactone Milrinone Perphenazine Metaxalone *Tolazoline* *Methylergonovine* *Chlorothiazide* *Disulfiram*	54	66	0 KEGG 6 GO BP 0 GO CC
59	Cilostazol Fluconazole Clomipramine *Enoxacin* *Miconazole*	67	55	0 KEGG 4 GO BP 0 GO CC
61	8-methyl-8-azabicyclo[3.2.1]oct-3-yl 1H-indole-3-carboxylate Trimethobenzamide Metoclopramide Papaverine	66	62	1 KEGG 1 GO BP 2 GO CC

	Bromhexine Nefazodone *Bromocriptine* *Propylthiouracil* *Torsemide* *Sulfamethoxazole* *Oxybutynin*			
68	Flunarizine Betahistine Norethindrone Alfuzosin Terfenadine Alrestatin *Deferoxamine* *Moxisylyte* *Moricizine* *Glafenine* *Imipramine*	108	97	2 KEGG 27 GO BP 4 GO CC
69	Talniflumate Rimexolone Fluticasone propionate Pyrimethamine Beclomethasone dipropionate Nialamide Flutamide Bezafibrate	151	161	1 KEGG 4 GO BP 0 GO CC

	Ketotifen				
	Pantoprazole				
	Ethacrynic acid				
	Meticrane				
	Piperacillin				
	Tianeptine				
	Phenytoin				
	Bergapten				
97	Falnidamol	71	44	2 KEGG	
	Fluoxetine			8 GO BP	
				1 GO CC	
	Sulfadimethoxine				
	Sulfaethidole				
102	Iopanoic acid	81	82	1 KEGG	
	Cefotiam			4 GO BP	
	Mepivacaine			0 GO CC	
	Ketorolac				
	Chlorthalidone				
	Mirtazapine				
	Sildenafil				
	Metaproterenol				
	Indapamide				
	Trichlormethiazide				
	Suprofen				
	Pentobarbital				
	Repaglinide				

	Prednisolone *Clidinium* *Cyclizine*			
103	Carteolol Fenoterol Ciprofibrate *Tegaserod* *Lomefloxacin* *Phenacemide*	41	45	/
107	Pentoxifylline Isocarboxazid Ondansetron Triflupromazine Amantadine	92	78	/
118	Fenbufen Valsartan Methocarbamol Raloxifene *Lansoprazole*	43	43	0 KEGG 3 GO BP 0 GO CC
119	Loperamide Estradiol Diltiazem Primaquine Ciglitazone Doxepin	103	105	13 KEGG 18 GO BP 3 GO CC

		Sulfisoxazole			
		Famciclovir			
		Famotidine			
		Methazolamide			
		Furosemide			
		Gliclazide			
		Trimethoprim			
		Sulfacetamide			
		Phthalylsulfathiazole			
		Hydroxyzine			
		Atrazine			
		Diphenylpyraline			
		Metamizole			
		Sulfamethizole			
123		Diflunisal	248	408	7 KEGG
		Omeprazole			7 GO BP
		Perindopril			2 GO CC
		Iocetamic acid			
		Metronidazole			
131		Propofol	22	20	/
		Primidone			
		Nomifensine			
		Pefloxacin			
		Molindone			
133		Risperidone	16	35	2 KEGG
		Tranilast			3 GO BP

				1 GO CC
	Baclofen *Xylometazoline* *Liothyronine* *Benazepril* *Chlorotrianisene*			
135	Trimipramine Tolmetin Statil Guanfacine Clozapine Domperidone Cimetidine Triamterene Disopyramide *Selegiline* *Flurbiprofen*	143	129	4 KEGG 5 GO BP 10 GO CC
136	Candesartan cilexetil Digoxin Penicillin g Naproxen Benzbromarone Omacetaxine mepesuccinate *Quinethazone* *Pilocarpine*	308	592	20 KEGG 48 GO BP 15 GO CC
137	Atomoxetine	165	112	5 KEGG

| | | | | 11 GO BP |
| | | | | 4 GO CC |

Oxaprozin

Dicloxacillin

Meclofenamic acid

Dantrolene

Bumetanide

Lidocaine

Bupropion

Olmesartan medoxomil

Mefenamic acid

Lovastatin

Adenosine

Methapyrilene

Zopiclone

Sulfamethoxypyridazine

CP_eTox_H_MF

Cluster	Compounds	Number of upregulated genes	Number of downregulated genes	Enrichment terms
2	Ornidazole Meclofenamic acid *Letrozole* *Methapyrilene*	22	18	/
6	Amiloride Beclomethasone dipropionate Trazodone	78	89	2 KEGG 8 GO BP 6 GO CC

	Triamcinolone Amantadine Dexamethasone acetate *Meticrane* *Hydrocortisone acetate* *Prednisolone* *Prednisone* *Piperacillin*			
7	Propofol Digoxin Daunorubicin *Molindone* *Valacyclovir*	402	405	6 KEGG 47 GO BP 13 GO CC
8	Omeprazole *Adenosine* *Hydrochlorothiazide* *Azactam*	24	28	/
10	Carteolol Buspirone Clozapine Carbamazepine Estrone *Ofloxacin* *Metyrapone*	68	58	0 KEGG 1 GO BP 0 GO CC

13	Fexofenadine Fenoterol Saquinavir Phenylbutazone Mexiletine Candesartan cilexetil Metoprolol *Sulfadiazine* *Lomefloxacin* *Tegaserod* *Zonisamide* *Trichlormethiazide*	80	70	0 KEGG 1 GO BP 0 GO CC
18	Celecoxib Lidocaine Thalidomide Clomethiazole Moxonidine Metolazone Disopyramide Mesoridazine Domperidone *Chlorotrianisene* *Nitrofurantoin* *Zomepirac* *Phenacemide* *Galantamine*	138	153	9 KEGG 55 GO BP 14 GO CC

19	Prochlorperazine Pravastatin Perindopril *Hydroflumethiazide* *Indapamide*	30	34	0 KEGG 1 GO BP 0 GO CC
20	Penicillin g Diazoxide Pseudoephedrine Alfuzosin *Carbimazole* *Metronidazole* *4-Phenylbutyric acid* *Selegiline* *Flurbiprofen* *Pentobarbital*	60	54	2 KEGG 0 GO BP 3 GO CC
21	Testosterone propionate Methysergide *Aceclofenac* *Diphenhydramine* *Benazepril*	27	20	3 KEGG 0 GO BP 0 GO BP
22	Methocarbamol Probenecid Enalapril Gatifloxacin Ondansetron	58	43	/

	Liothyronine *Azelastine* *Tolfenamic acid* *Tocainide* *Acebutolol* *Pilocarpine* *Sulfamethoxypyridazine* *Cinchophen*			
24	Atenolol *Chlormezanone* *Proguanil* *Mephenytoin*	5	2	/
25	Metaxalone Cyproheptadine *Methoxsalen* *Sulfathiazole*	20	22	/
28	Cimetidine Pentoxifylline *Sulfaethidole* *Hydralazine* *Levamisole* *Niridazole* *Sulfamerazine*	46	40	2 KEGG 4 GO BP 1 GO CC

29	Salmeterol Raloxifene Benzbromarone Olmesartan medoxomil Mefenamic acid Pimozide Imatinib Carvedilol Diclofenac Dibenzepin *Cyclobenzaprine* *Loratadine*	149	142	16 KEGG 38 GO BP 2 GO CC
30	Bendroflumethiazide Flecainide Dydrogesterone Procainamide *Zolpidem* *Dichlorophen*	57	66	0 KEGG 2 GO BP 1 GO CC
32	Caffeine Risperidone Ketotifen Cilostazol *Ketoconazole* *Xylometazoline*	89	104	7 KEGG 10 GO BP 2 GO CC
34	Mometasone furoate	54	54	0 KEGG

	Fluticasone propionate			6 GO BP
	Rimexolone			0 GO CC
	Pyrimethamine			
	Praziquantel			
	Triamterene			
	Nafcillin			
35	Trifluoperazine Nortriptyline Simvastatin *Imipramine*	70	55	5 KEGG 4 GO BP 1 GO CC
38	Modafinil Danthron Sulfisoxazole *Lansoprazole* *Methazolamide* *Trimethoprim* *Gliclazide* *Cefoperazone*	28	33	0 KEGG 1 GO BP 0 GO CC
40	Primaquine Famciclovir Bisacodyl Diltiazem *Furosemide* *Famotidine*	59	52	2 KEGG 1 GO BP 6 GO CC

	Hydroxyzine				
	Sulfacetamide				
	Phthalylsulfathiazole				
	Diphenylpyraline				
43	Trimipramine Levonorgestrel Estradiol Fenofibrate Lamotrigine Norethindrone *Clotrimazole*	74	73	3 KEGG 2 GO BP 0 GO CC
47	Pheniramine Propafenone Amoxapine Oxaprozin Doxepin *Melatonin* *Doxazosin* *Diazepam* *Glafenine* *Cloxacillin*	75	82	0 KEGG 1 GO BP 0 GO CC
58	Mebendazole Albendazole Etodolac *Colchicine*	66	68	4 KEGG 0 GO BP 0 GO CC

	AHZ9RYL9EW			
59	Bumetanide Naproxen Mibefradil Bepridil Amiodarone Loxapine Perphenazine Atomoxetine Finasteride Lovastatin *Fluvastatine*	191	206	10 KEGG 24 GO BP 4 GO CC
60	Diphenidol Nimesulide *Phenytoin* *Moxisylyte*	25	18	/
61	Clemastine Paroxetine Naftidrofuryl *Clidinium* *Bromocriptine*	57	59	/
63	Ketoprofen Promazine Mirtazapine	123	118	2 KEGG 6 GO BP 0 GO CC

	Fluoxetine Niridazole Pizotifen *Repaglinide* *Propranolol*			
64	Triflupromazine Haloperidol Flunarizine Quinapril	82	68	/
65	Thiotepa Amitriptyline Trimethobenzamide Tamoxifen *Disulfiram* *Etoposide* *Acetazolamide* *Astemizole*	63	44	2 KEGG 6 GO BP 0 GO CC
66	Verapamil Phentolamine Progesterone Protriptyline *Chlorpropamide* *Nabumetone* *Chlorzoxazone*	91	86	0 KEGG 2 GO BP 1 GO CC

Cluster	Compounds	Number of upregulated genes	Number of downregulated genes	Enrichment terms
68	Clomipramine Nefazodone *Tolazoline* *Chlorothiazide*	22	15	/
70	Fluconazole Mepivacaine Riluzole *Terbutaline* *Propylthiouracil*	28	31	0 KEGG 1 GO BP 0 GO CC
74	Ketorolac *Enoxacin* *Cyclizine* *Acetohexamide*	13	8	/
CP_eTox_H_MFHB				
Cluster	**Compounds**	**Number of upregulated genes**	**Number of downregulated genes**	**Enrichment terms**
2	Digoxin Daunorubicin Mebendazole Imatinib *Acetaminophen* *Clotrimazole*	410	421	5 KEGG 43 GO BP 11 GO CC

3	Flunarizine Clomipramine Fluconazole Levonorgestrel *Chlorpropamide*	53	38	1 KEGG 2 GO BP 0 GO CC
6	Disopyramide Raloxifene *Propranolol* *Lansoprazole* *Nabumetone* *Zonisamide*	51	53	2 KEGG 5 GO BP 11 GO BP
7	Flecainide Quinapril Propofol *Imipramine*	42	45	/
8	Diclofenac Fenofibrate Pantoprazole *Sotalol* *Methapyrilene*	31	31	1 KEGG 0 GO BP 0 GO CC
11	Amoxapine Trifluoperazine Nilutamide	135	124	4 KEGG 26 GO BP 1 GO CC

	Pizotifen Nortriptyline Tamoxifen Loperamide Ketoprofen Fluoxetine			
12	Doxepin Propafenone Haloperidol Triflupromazine Cilostazol *Cyclobenzaprine* *Cloxacillin*	96	106	0 KEGG 1 GO BP 0 GO CC
13	Risperidone Valsartan Moxonidine Finasteride *Propylthiouracil* *Diphenylpyraline* *Valacyclovir* *Diazepam* *Disulfiram* *Clidinium*	39	57	4 KEGG 8 GO BP 0 GO CC
14	Pimozide Albendazole	92	79	18 KEGG 33 GO BP

	Lovastatin			3 GO CC
	Astemizole			
	Etoposide			
15	Trimipramine	172	178	0 KEGG
	Practolol			
	Doxylamine			
	Verapamil			
	Carvedilol			
	Paroxetine			
	Protriptyline			0 KEGG
	Chlorpromazine			9 GO BP
	Dipyridamole			0 GO CC
	Progesterone			
	Sulfadimethoxine			
	Cyclizine			
	Repaglinide			
	AHZ9RYL9EW			
17	Thiabendazole	13	27	0 KEGG
	Leflunomide			0 GO BP
	Zolpidem			1 GO CC
	Prednisone			
21	Chlorthalidone	96	100	1 KEGG
	Chloroquine			5 GO BP
	Glipizide			3 GO CC
	Metoprolol			

	Omeprazole Rofecoxib Metolazone Lidocaine *Flurbiprofen* *Cyclothiazide* *Quinethazone* *Cefoxitin*			
25	Candesartan cilexetil Lamotrigine Olmesartan medoxomil Dicloxacillin Thalidomide *Hydroxyzine* *Cefazolin* *Atenolol* *Lomefloxacin* *Pilocarpine* *Cefoperazone*	73	62	4 KEGG 12 GO BP 2 GO CC
32	Etodolac Proguanil Mometasone furoate Clemastine Milrinone Estradiol Atomoxetine	126	103	2 KEGG 13 GO BP 1 GO CC

	Dantrolene Amitriptyline Metoclopramide *Sulfamethoxazole* *Althiazide* *Azathioprine*			
34	Procainamide Pravastatin Phenylbutazone Methocarbamol Nefazodone Mirtazapine Amantadine *Trichlormethiazide* *Furosemide* *Acetohexamide* *Galantamine* *Chlorothiazide*	68	76	0 KEGG 13 GO BP 0 GO CC
35	Penicillin g Cyclopenthiazide Dibenzepin *Carbimazole* *Ofloxacin* *Metronidazole*	49	42	0 KEGG 0 GO BP 3 GO CC
36	Clomethiazole	30	27	/

	Enalapril Ketorolac *Enoxacin* *Chlorzoxazone*			
37	Pentoxifylline Flutamide Diltiazem Ketotifen Estrone *Diphenhydramine* *Phenytoin*	65	64	1 KEGG 1 GO BP 0 GO CC
38	Spironolactone *Torsemide* *Gliclazide* *Meticrane* *Indapamide* *Doxazosin* *Hydroflumethiazide*	13	22	/
39	Cyproheptadine Dexamethasone Tolazamide Tinidazole *Prednisolone* *Hydrocortisone acetate*	53	57	3 KEGG 3 GO BP 9 GO CC

41	Bendroflumethiazide Cimetidine *Estrone sulfate* *Piperacillin*	50	55	/
43	Meclofenamic acid *Chlormezanone* *Hydrochlorothiazide* *Ritodrine*	15	3	/

CP_eTox_H_MFHC				
Cluster	**Compounds**	**Number of upregulated genes**	**Number of downregulated genes**	**Enrichment terms**
2	Papaverine Flutamide *Azathioprine* *Torsemide* *Ethacrynic acid* *Bergapten*	28	32	1 KEGG 4 GO BP 1 GO CC
4	Diltiazem Famciclovir Bisacodyl *Hydroxyzine* *Methazolamide*	46	43	3 KEGG 0 GO BP 1 GO CC

	Sulfacetamide *Famotidine* *Diphenylpyraline* *Phthalylsulfathiazole*			
8	Pheniramine Propafenone Amoxapine Oxaprozin Doxepin Pantoprazole Dantrolene Glipizide *Glafenine* *Cloxacillin* *Diazepam* *Doxazosin*	94	102	2 KEGG 11 GO BP 0 GO CC
13	Ticlopidine Dicloxacillin Sulfisoxazole Trioxsalen Modafinil *Trimethoprim* *Gliclazide* *Indomethacin*	50	47	1 KEGG 3 GO BP 0 GO CC
15	Mebendazole Albendazole	84	86	4 KEGG 5 GO BP

	Etodolac Mepivacaine Metaxalone *Colchicine* *AHZ9RYL9EW* *Hydralazine*			1 GO CC
18	Alrestatin Sildenafil Fluconazole Ketorolac *Phenytoin* *Oxybutynin* *Propylthiouracil* *Enoxacin* *Acetohexamide*	48	41	1 KEGG 2 GO BP 0 GO CC
24	Protriptyline Amitriptyline Phentolamine Flunarizine Clomipramine	107	87	0 KEGG 0 GO BP 2 GO CC
25	Riluzole Clemastine Milrinone Mirtazapine *Terbutaline*	36	53	2 KEGG 3 GO BP 0 GO CC

	Sulfadimethoxine			
26	Nefazodone *Chlorpropamide* *Deferoxamine* *Sulfamethoxazole* *Tolazoline*	11	6	/
28	Thiotepa Tamoxifen Prazosin *Hycanthone* *Etoposide* *Acetazolamide* *Astemizole*	55	40	1 KEGG 18 GO BP 0 GO CC
32	Fluoxetine Amiodarone Perphenazine Loxapine Atomoxetine Salmeterol Raloxifene Triflupromazine Haloperidol Verapamil Quinapril Pizotifen	215	191	7 KEGG 27 GO BP 4 GO CC

	Propranolol			
	Cyclobenzaprine			
	Dichlorophen			
33	Simvastatin Chlorpromazine Mibefradil Bepridil Lovastatin Trifluoperazine Nortriptyline Paroxetine Loperamide Imatinib *Imipramine* *Fluvastatine*	187	200	5 KEGG 14 GO BP 1 GO CC
34	Carvedilol Niridazole Thiabendazole Bupropion Pseudoephedrine Mefenamic acid Praziquantel *Cefoxitin* *Selegiline* *Flurbiprofen* *Sulfaethidole*	97	85	0 KEGG 0 GO BP 1 GO CC

	Repaglinide *Zopiclone*			
36	Risperidone Fluticasone propionate Pyrimethamine Mometasone furoate Tolmetin Spironolactone Pentoxifylline *Benazepril*	71	74	3 KEGG 9 GO BP 1 GO CC
37	Cyproheptadine Ketotifen Rimexolone Bendroflumethiazide Primidone Diclofenac *Atenolol* *Sulfathiazole* *Ketoconazole*	77	87	0 KEGG 5 GO BP 0 GO CC
38	Glyburide Nimesulide Testosterone propionate Doxylamine Proguanil	97	106	1 KEGG 12 GO BP 0 GO CC
40	Enalapril	27	16	0 KEGG

	Probenecid			0 GO BP
				2 GO CC
	Tocainide			
	Sulfamethoxypyridazine			
	Acetaminophen			
	Cinchophen			
	Liothyronine			
	Cyclizine			
42	Methysergide Propofol *Aceclofenac* *Valacyclovir* *Azelastine*	27	20	/
43	Diflunisal Dexamethasone Rofecoxib Chloroquine Brinzolamide *Cefazolin* *Pilocarpine* *Letrozole*	257	405	8 KEGG 18 GO BP 2 GO CC
44	Omeprazole Prochlorperazine Tinidazole Diazoxide	47	62	0 KEGG 0 GO BP 1 GO CC

	Cefoperazone *Indapamide* *Adenosine* *Azactam* *Carbimazole* *Metyrapone* *Pentobarbital* *4-Phenylbutyric acid* *Baclofen*			
45	Triamcinolone Leflunomide Ondansetron *Ritodrine* *Tolfenamic acid* *Diphenhydramine* *Prednisone* *Zomepirac* *Valdecoxib* *Methapyrilene* *Nomifensine* *Ciprofloxacin*	38	35	0 KEGG 2 GO BP 1 GO CC
46	Olmesartan medoxomil Beclomethasone dipropionate Amiloride *Zolpidem* *Prednisolone*	34	29	3 KEGG 0 GO BP 3 GO CC

	Piperacillin *Hydrocortisone acetate*			
49	Lidocaine Metolazone Dexamethasone acetate *Galantamine* *Phenacemide*	34	52	0 KEGG 1 GO BP 2 GO CC
53	Saquinavir Metoprolol Fexofenadine Candesartan cilexetil Mexiletine Phenylbutazone *Lomefloxacin* *Zonisamide* *Sulfadiazine*	68	55	0 KEGG 1 GO BP 0 GO CC
58	Domperidone Pravastatin Trazodone Buspirone Clozapine Dibenzepin Nafcillin	58	63	0 KEGG 7 GO BP 2 GO CC
59	Digoxin Daunorubicin	416	422	8 KEGG 41 GO BP

	Perindopril Caffeine *Suprofen*			10 GO CC
60	Bumetanide Naproxen Disopyramide Thalidomide Celecoxib	113	121	6 KEGG 26 GO BP 14 GO CC
62	Gatifloxacin Valsartan Benzbromarone Flecainide *Aminopyrine* *Theophylline*	46	48	/

Table S10. Details of the number of Cell Painting features based clusters and their mean size.

	Number of final valid clusters (>= 4 compounds)	Mean size of final valid clusters (>= 4 compounds)
CP_DILIs_pos_neg	15	7
CP_DILIs_most_neg	6	4.3
CP_eTox_H_HT	31	10
CP_eTox_H_MF	34	7.1
CP_eTox_H_MFHB	22	7.4

CP_eTox_H_MFHC	28	8.1

Table S11. Comparison of machine learning models for hepatotoxicity prediction based on Cell Painting features. Balanced accuracies (BA), sensitivities (SN) and specificities (SP) were calculated during cross-validation (mean of scores across all folds), on the training set and on the validation set. Selected features refer to features remaining after the feature selection step.

Dataset		Random Forest	Linear SVM	ElasticNet
All features				
CP_DILIs_pos_neg	Cross Validation	BA: 0.506 SN: 0.984 SP: 0.027	BA: 0.502 SN: 0.699 SP: 0.305	BA: 0.493 SN: 0.53 SP: 0.457
	Training set	BA: 1 SN: 1 SP:1	BA: 1 SN: 1 SP: 1	BA: 0.809 SN: 0.725 SP: 0.893
	Validation set	BA: 0.464 SN: 0.929 SP: 0	BA: 0.371 SN: 0.643 SP: 0.099	BA: 0.436 SN: 0.571 SP: 0.301

CP_DILIs_most_neg	Cross Validation	BA: 0.518 SN: 0.404 SP: 0.632	BA: 0.523 SN: 0.448 SP: 0.598	BA: 0.511 SN: 0.515 SP: 0.507
	Training set	BA: 1 SN: 1 SP: 1	BA: 1 SN: 1 SP: 1	BA: 1 SN: 1 SP: 1
	Validation set	BA: 0.522 SN: 0.444 SP: 0.6	BA: 0.478 SN: 0.556 SP: 0.4	BA: 0.583 SN: 0.667 SP: 0.499
CP_eTox_H_HT	Cross Validation	BA: 0.5 SN: 1 SP: 0	BA: 0.502 SN: 0.727 SP: 0.279	BA: 0.477 SN: 0.671 SP: 0.283
	Training set	BA: 1 SN: 1 SP: 1	BA: 1 SN: 1 SP: 1	BA: 0.981 SN: 0.962 SP: 1
	Validation set	BA: 0.5 SN: 1 SP: 0	BA: 0.472 SN: 0.786 SP: 0.158	BA: 0.532 SN: 0.696 SP: 0.368
CP_eTox_H_MF	Cross Validation	BA: 0.501 SN: 0.982 SP: 0.02	BA: 0.481 SN: 0.659 SP: 0.303	BA: 0.471 SN: 0.441 SP: 0.5
	Training set	BA: 1 SN: 1 SP: 1	BA: 1 SN: 1 SP: 1	BA: 0.657 SN: 0.549 SP: 0.765
	Validation set	BA: 0.479 SN: 0.958 SP: 0	BA: 0.572 SN: 0.708 SP: 0.436	BA: 0.587 SN: 0.521 SP: 0.653
CP_eTox_H_MFHB	Cross Validation	BA: 0.52 SN: 0.283 SP: 0.757	BA: 0.493 SN: 0.472 SP: 0.514	BA: 0.503 SN: 0.472 SP: 0.536
	Training set	BA: 1 SN: 1 SP: 1	BA: 1 SN: 1 SP: 1	BA: 0.725 SN: 0.689 SP: 0.761

	Validation set	BA: 0.356 SN: 0.062 SP: 0.65	BA: 0.46 SN: 0.406 SP: 0.514	BA: 0.409 SN: 0.25 SP: 0.568
CP_eTox_H_MFHC	Cross Validation	BA: 0.562 SN: 0.802 SP: 0.323	BA: 0.506 SN: 0.566 SP: 0.446	BA: 0.526 SN: 0.467 SP: 0.585
	Training set	BA: 0.994 SN: 1 SP: 0.988	BA: 1 SN: 1 SP: 1	BA: 0.678 SN: 0.601 SP: 0.755
	Validation set	BA: 0.376 SN: 0.674 SP: 0.078	BA: 0.414 SN: 0.558 SP: 0.27	BA: 0.375 SN: 0.442 SP: 0.308
Selected features				
CP_DILIs_pos_neg	Cross Validation	BA: 0.573 SN: 0.95 SP: 0.198	BA: 0.567 SN: 0.732 SP: 0.402	BA: 0.59 SN: 0.611 SP: 0.569
	Training set	BA: 1 SN: 1 SP: 1	BA: 0.987 SN: 0.974 SP: 1	BA: 0.737 SN: 0.706 SP: 0.768
	Validation set	BA: **0.646** SN: 0.893 SP: 0.399	BA: 0.475 SN: 0.75 SP: 0.2	BA: 0.521 SN: 0.643 SP: 0.399
CP_DILIs_most_neg	Cross Validation	BA: 0.567 SN: 0.468 SP: 0.666	BA: 0.567 SN: 0.554 SP: 0.579	BA: 0.603 SN: 0.593 SP: 0.614
	Training set	BA: 1 SN: 1 SP: 1	BA: 1 SN: 1 SP: 1	BA: 0.676 SN: 0.638 SP: 0.714
	Validation set	BA: **0.739** SN: 0.778 SP: 0.7	BA: **0.739** SN: 0.778 SP: 0.7	BA: **0.689** SN: 0.778 SP: 0.6
CP_eTox_H_HT	Cross Validation	BA: 0.537 SN: 0.887	BA: 0.555 SN: 0.567	BA: 0.57 SN: 0.558

		SP: 0.187	SP: 0.543	SP: 0.581
	Training set	BA: 0.917 SN: 0.969 SP: 0.865	BA: 0.642 SN: 0.639 SP: 0.645	BA: 0.626 SN: 0.589 SP: 0.663
	Validation set	BA: 0.499 SN: 0.839 SP: 0.159	BA: **0.645** SN: 0.554 SP: 0.736	BA: 0.566 SN: 0.554 SP: 0.578
CP_eTox_H_MF	Cross Validation	BA: 0.529 SN: 0.819 SP:0.24	BA: 0.533 SN: 0.581 SP: 0.485	BA: 0.541 SN: 0.573 SP: 0.509
	Training set	BA: 0.966 SN: 0.963 SP: 0.969	BA: 0.679 SN: 0.648 SP: 0.71	BA: 0.661 SN: 0.63 SP: 0.692
	Validation set	BA: 0.507 SN: 0.667 SP: 0.347	BA: 0.575 SN: 0.542 SP: 0.608	BA: **0.65** SN: 0.604 SP: 0.696
CP_eTox_H_MFHB	Cross Validation	BA: 0.6 SN: 0.469 SP: 0.731	BA: 0.565 SN: 0.531 SP: 0.6	BA: 0.59 SN: 0.542 SP: 0.638
	Training set	BA: 1 SN: 1 SP: 1	BA: 0.702 SN: 0.667 SP: 0.737	BA: 0.656 SN: 0.617 SP: 0.695
	Validation set	BA: 0.576 SN: 0.531 SP: 0.621	BA: 0.576 SN: 0.531 SP: 0.621	BA: 0.516 SN: 0.438 SP: 0.594
CP_eTox_H_MFHC	Cross Validation	BA: 0.582 SN: 0.712 SP: 0.452	BA: 0.533 SN: 0.549 SP: 0.517	BA: 0.555 SN: 0.465 SP: 0.646
	Training set	BA: 0.949 SN: 0.926 SP: 0.972	BA: 0.701 SN: 0.667 SP: 0.735	BA: 0.633 SN: 0.519 SP: 0.747
	Validation set	BA: 0.522 SN: 0.698	BA: 0.445 SN: 0.581	BA: 0.49 SN: 0.442

	SP: 0.346	SP: 0.309	SP: 0.538

Table S12. Percentage of balanced accuracies higher after training and prediction on a permuted dataset than after training and prediction on the non-permuted dataset.

	Random Forest	**Linear SVM**	**ElasticNet**
CP_DILIs_pos_neg	0	60	32
CP_DILIs_most_neg	0	1	2
CP_eTox_H_HT	49	1	16
CP_eTox_H_MF	42	12	0
CP_eTox_H_MFHB	7	6	40
CP_eTox_H_MFHC	15	82	55

Table S13. Machine learning models performance for hepatotoxicity prediction based on Cell Painting features with Recursive Feature Elimination (RFE) included in the loop of training. RFE estimator used is a Random Forest algorithm. Stratified 2 times 5-fold cross-validation was included in the training procedure. Balanced accuracies (BA), sensitivities (SN) and specificities (SP) were calculated during cross-validation (mean of scores across all folds), on the training set and on the validation set.

Dataset		ElasticNet
CP_DILIs_pos_neg	Cross Validation	BA: 0.523 SN: 0.533 SP: 0.519
	Training set	BA: 0.769 SN: 0.699 SP: 0.839
	Validation set	BA: 0.468

		SN: 0.536 SP: 0.4
CP_DILIs_most_neg	Cross Validation	BA: 0.587 SN: 0.594 SP: 0.58
	Training set	BA: 0.989 SN: 0.979 SP: 0.999
	Validation set	BA: 0.522 SN: 0.444 SP: 0.6
CP_eTox_H_HT	Cross Validation	BA: 0.508 SN: 0.671 SP: 0.346
	Training set	BA: 0.976 SN: 0.953 SP: 0.999
	Validation set	BA: 0.507 SN: 0.75 SP: 0.264
CP_eTox_H_MF	Cross Validation	BA: 0.545 SN: 0.614 SP: 0.477
	Training set	BA: 0.559 SN: 0.623 SP: 0.495
	Validation set	BA: 0.349 SN: 0.438 SP: 0.26
CP_eTox_H_MFHB	Cross Validation	BA: 0.582 SN: 0.542 SP: 0.621
	Training set	BA: 0.621

		SN: 0.594 SP: 0.648
	Validation set	BA: 0.532 SN: 0.469 SP: 0.595
CP_eTox_H_MFHC	Cross Validation	BA: 0.513 SN: 0.634 SP: 0.392
	Training set	BA: 0.531 SN: 0.675 SP: 0.387
	Validation set	BA: 0.471 SN: 0.558 SP: 0.384

Table S14. Randomly created cluster details and gene enrichment results. Compounds without gene expression data are displayed in italic.

CP_DILIs_pos_neg				
Cluster	Compounds	Number of downregulated genes	Number of upregulated genes	Enrichment terms
1	Cetirizine Metoclopramide Fluoxetine Falnidamol *Azathioprine* *Levothyroxine*	88	59	3 KEGG 8 GO BP 2 GO CC

	Sulfamethizole *Isradipine*			
2	Risperidone Pantoprazole Doxorubicin Cyproheptadine Carvedilol Propofol *Chlorothiazide* *Bromocriptine*	129	85	0 KEGG 2 GO BP 0 GO CC
3	Bendroflumethiazide Valsartan Atomoxetine Diflunisal Venlafaxine *Methoxsalen* *Ethionamide* *Cinchophen*	267	405	8 KEGG 14 GO BP 4 GO CC
4	Pravastatin Tolazamide Metoprolol Benzbromarone Etodolac *Zidovudine* *Cefdinir* *Aceclofenac*	90	83	4 KEGG 11 GO BP 1 GO CC

5	Labetalol Clozapine Isotretinoin Enalapril *Cyclobenzaprine* *Imipramine* *Clotrimazole* *Warfarin*	90	81	1 KEGG 2 GO BP 0 GO CC
6	Thalidomide Procainamide Alfuzosin Chloroquine *Methylprednisolone* *Metronidazole* *Letrozole* *Chlorcyclizine*	66	62	2 KEGG 9 GO BP 4 GO CC
7	Haloperidol Danazol Citalopram Nimesulide Riluzole Propafenone *Etoposide*	109	137	2 KEGG 3 GO BP 2 GO CC
8	Amlodipine Carbamazepine	90	95	3 KEGG 1 GO BP

	Finasteride			2 GO CC
	Simvastatin			
	Phenytoin			
	Mefloquine			
	Indomethacin			
9	Lovastatin Ropinirole Nilutamide Penicillin g Imatinib *Glafenine* *Dapsone*	105	83	5 KEGG 4 GO BP 3 GO CC
10	Tamoxifen Mitoxantrone Amiloride Glyburide Sirolimus *Cefoperazone* *Ofloxacin*	105	83	3 KEGG 61 GO BP 15 GO CC
11	Disulfiram Ondansetron Valacyclovir Sildenafil Mirtazapine Ibuprofen	49	37	0 KEGG 1 GO BP 0 GO CC

	Repaglinide			
12	Pyrimethamine Celecoxib Verapamil Norfloxacin *Propylthiouracil* *Lansoprazole* *Deferoxamine*	48	51	1 KEGG 14 GO BP 0 GO CC
13	Flutamide Fluconazole Triamterene Flecainide *Nomifensine* *Trimethoprim* *Hydralazine*	47	52	0 KEGG 1 GO BP 4 GO CC
14	Diltiazem Trazodone Tinidazole Nefazodone Nialamide *Acetazolamide* *Atenolol*	110	97	/
15	Dicloxacillin Oxaprozin	80	66	0 KEGG 4 GO BP

	Omeprazole Quinapril *Chlorpropamide* *Gemifloxacin* *Ciprofloxacin*			1 GO CC
16	Diclofenac Dantrolene Clomipramine Thiotepa *Chlormezanone* *Famotidine* *Cefazolin*	60	53	1 KEGG 3 GO BP 1 GO CC
17	Amitriptyline Mefenamic acid Ketorolac Paclitaxel *Cloxacillin* *Baclofen* *Sulfathiazole*	54	50	2 KEGG 4 GO BP 0 GO CC
18	Doxepin Albendazole Ticlopidine Nafcillin *Methazolamide*	32	40	0 KEGG 3 GO BP 0 GO CC

	Sulfadiazine *Zonisamide*			
19	Metaxalone *Nitrofurantoin* *Chlorzoxazone* *Cefuroxime* *Paclitaxel* *Prednisone* *cyclosporin A*	/	/	/
20	Amiodarone Ketoprofen Mebendazole Bupropion *Hydrochlorothiazide* *Terbutaline* *Fipexide*	78	84	0 KEGG 37 GO BP 1 GO CC
21	Mexiletine Disopyramide Paroxetine Glipizide Progesterone *Iproniazid* *Acebutolol*	98	94	2 KEGG 4 GO BP 8 GO CC
22	Estradiol	85	104	2 KEGG

	Modafinil Chlorpromazine Spironolactone Naproxen Thiabendazole *Prednisolone*			7 GO BP 0 GO CC
23	Leflunomide Lamotrigine Felodipine Papaverine Prochlorperazine *Moxisylyte* *Acetaminophen*	44	59	0 KEGG 9 GO BP 0 GO CC
24	Tolmetin Perphenazine Glimepiride *Sulindac* *Cefotaxime* *Levofloxacin* *Captopril*	47	49	1 KEGG 2 GO BP 0 GO CC
25	Fenofibrate Cimetidine Nortriptyline Saquinavir	63	58	3 KEGG 5 GO BP 1 GO CC

Cluster	Compounds	Number of upregulated genes	Number of downregulated genes	Enrichment terms
	Gemfibrozil *Benazepril* *Valdecoxib*			
CP_DILIs_most_neg				
1	Thiabendazole Leflunomide *Chlorzoxazone* *Levofloxacin*	13	27	0 KEGG 0 GO BP 1 GO CC
2	Atomoxetine Carbamazepine Diflunisal *Zidovudine*	250	389	6 KEGG 13 GO BP 5 GO CC
3	Albendazole Clomipramine Labetalol *Fipexide*	61	48	3 KEGG 1 GO BP 0 GO CC
4	Benzbromarone Etodolac *cyclosporin A*	54	43	/

	Iproniazid			
5	Clozapine Fluconazole *Cinchophen* *Sulfathiazole*	23	18	/
6	Diclofenac Danazol *Glafenine* *Sulindac*	47	40	0 KEGG 0 GO BP 3 GO CC
7	Mexiletine Nilutamide *Phenytoin* *Gemfibrozil*	26	24	1 KEGG 5 GO BP 0 GO CC
8	Amiodarone *Moxisylyte* *Nitrofurantoin* *Nomifensine*	/	/	/
9	Falnidamol Riluzole Nortriptyline Flutamide	65	53	0 KEGG 3 GO BP 3 GO CC
10	Diltiazem	21	17	1 KEGG

Cluster	Compounds	Number of	Number of	Enrichment
	Ticlopidine *Ciprofloxacin* *Indomethacin*			0 GO BP 0 GO CC
11	Tamoxifen Lamotrigine Mefenamic acid *Azathioprine*	41	29	3 KEGG 12 GO BP 0 GO CC
12	Imatinib *Acetazolamide* *Disulfiram* *Propylthiouracil*	/	/	/
13	Isotretinoin Nialamide Nimesulide *Chlormezanone*	108	96	0 KEGG 0 GO BP 0 GO CC
14	Dantrolene Papaverine Nefazodone *Acetaminophen*	26	35	1 KEGG 17 GO BP 0 GO CC
CP_eTox_H_HT				
Cluster	**Compounds**	**Number of**	**Number of**	**Enrichment**

		upregulated genes	downregulated genes	terms
1	Metoclopramide Bendroflumethiazide Enalapril Methysergide Doxepin Mexiletine Promazine *Torsemide* *Etoposide* *Chlorzoxazone* *Sulfamerazine*	86	93	3 KEGG 3 GO BP 0 GO CC
2	Carteolol Risperidone Talniflumate Spironolactone *Loratadine* *Prednisolone* *Periciazine* *Cefoxitin* *Nabumetone* *Dapsone*	41	66	1 KEGG 6 GO BP 1 GO CC
3	Atomoxetine Tamoxifen Amoxapine	105	97	0 KEGG 11 GO BP 3 GO CC

	Sertaconazole Trioxsalen Mibefradil Guanfacine Papaverine *AHZ9RYL9EW* *Gemfibrozil* *Xylometazoline*			
4	Betahistine Famciclovir Trimipramine Quinapril Probenecid Danthron Perindopril Leflunomide *Chlormezanone* *Pentobarbital*	85	87	3 KEGG 0 GO BP 0 GO CC
5	Mepivacaine Isocarboxazid Pizotifen Cefotiam Saquinavir Statil *Zonisamide*	68	73	5 KEGG 17 GO BP 1 GO CC

	Glafenine			
	Fipexide			
	Diphenylpyraline			
	Furosemide			
6	Mebendazole Trimethobenzamide Simvastatin Propafenone Haloperidol *Chlorothiazide* *Valdecoxib* *Azathioprine* *Zolpidem* *Iproniazid*	94	99	4 KEGG 3 GO BP 0 GO CC
7	Buspirone Amantadine Sildenafil Propofol Lidocaine Cyproheptadine *Cloxacillin* *Hydroflumethiazide* *Sulfaethidole* *Baclofen*	74	79	0 KEGG 1 GO BP 5 GO CC
8	Finasteride	/	/	/

	Clidinium			
	Metaproterenol			
	Hydrochlorothiazide			
	Imipramine			
	Fluvastatine			
	Metamizole			
	Tegaserod			
9	Candesartan cilexetil Dicloxacillin Caffeine Estradiol Daunorubicin Mesoridazine *Methylergonovine* *Almotriptan* *Terbutaline* *Zomepirac*	443	405	8 KEGG 41 GO BP 9 GO CC
10	Bumetanide Naftidrofuryl Methocarbamol Clomipramine Protriptyline Niridazole *Ethionamide* *Galantamine* *Cefazolin*	119	121	0 KEGG 5 GO BP 0 GO CC

	Trimethoprim				
11	Verapamil Dexamethasone acetate Mometasone furoate Pindolol Glyburide Chlorthalidone Doxylamine Fluconazole *Acetazolamide* *Sulfamethoxazole*	147	165	6 KEGG 15 GO BP 5 GO CC
12	Albendazole Amitriptyline Imatinib Nefazodone Fexofenadine *Zopiclone* *Valacyclovir* *Ketoconazole* *Piribedil* *Sulfadiazine*	61	53	1 KEGG 11 GO BP 1 GO CC
13	Ketotifen Bromhexine Venlafaxine Proguanil Thiabendazole	71	80	2 KEGG 0 GO BP 3 GO CC

	Sulfacetamide *Famotidine* *Acetohexamide* *Norfloxacin* *Hycanthone*			
14	Fenoterol Thalidomide Clomethiazole Diazoxide *Melatonin* *Metyrapone* *Levofloxacin* *Hydroxyzine* *Molindone* *Oxybutynin*	42	63	5 KEGG 16 GO BP 2 GO CC
15	Triflupromazine Rimexolone Procainamide Bisacodyl Trifluoperazine *Propylthiouracil* *Sulfachloropyridazine* *Atrazine* *Ciprofloxacin* *Nomifensine*	75	71	0 KEGG 0 GO BP 3 GO CC

16	Dydrogesterone Levonorgestrel Ondansetron Tolbutamide Olmesartan medoxomil Nafcillin Lamotrigine Amiodarone *Moricizine* *Modafinil*	124	125	6 KEGG 14 GO BP 0 GO CC
17	Salmeterol Timolol Flecainide Fenoldopam Disopyramide *Thiamphenicol* *Tolfenamic acid* *Enoxacin* *Sulfadimethoxine* *Piperacillin*	90	93	2 KEGG 5 GO BP 13 GO CC
18	Clozapine Nialamide Pyrimethamine Pantoprazole *Tocainide*	100	88	/

	Indapamide *Deferoxamine* *Diazepam* *Gliclazide* *Colchicine*			
19	Dexamethasone Carvedilol Flutamide Pravastatin *Niridazole* *Hydrocortisone acetate* *Prednisone* *Moxisylyte* *4-Phenylbutyric acid*	52	42	0 KEGG 0 GO BP 2 GO CC
20	Triamterene Bupropion Nimesulide Sulfisoxazole Testosterone propionate Fenbufen *Aminopyrine* *Cyclothiazide* *Megestrol acetate*	70	67	0 KEGG 2 GO BP 1 GO CC
21	Triamcinolone Pirfenidone Fluticasone propionate Bezafibrate	36	37	0 KEGG 3 GO BP 0 GO CC

	Theophylline *Quinethazone* *Sulfamethoxypyridazine* *Methazolamide* *Meticrane* *Clotrimazole*			
22	Ciprofibrate Primaquine Benzbromarone Progesterone *Dichlorophen* *Lansoprazole* *Tolazoline* *Bergapten* *Methoxsalen* *Sulfamethizole*	36	44	1 KEGG 1 GO BP 2 GO CC
23	Alrestatin Pimozide Cimetidine Flufenamic acid Valsartan Nilutamide *Bromocriptine* *Cefoperazone* *Benazepril* *Tiaprofenic acid*	123	128	15 KEGG 24 GO BP 9 GO CC

24	Beclomethasone dipropionate Thiotepa Loperamide Digoxin Ornidazole Paroxetine *Pefloxacin* *Ticlopidine* *Althiazide* *Ethacrynic acid*	120	128	13 KEGG 20 GO BP 0 GO CC
25	Rofecoxib 8-methyl-8-azabicyclo[3.2.1]oct-3-yl 1H-indole-3-carboxylate Phentolamine Tolazamide Celecoxib *Indomethacin* *Diphenhydramine* *Pilocarpine* *Levamisole* *Methapyrilene*	84	76	16 KEGG 29 GO BP 2 GO CC
26	Practolol Amiloride Diphenidol Metolazone Chloroquine Trazodone	119	122	2 KEGG 21 GO BP 6 GO CC

	Phenacemide			
	Suprofen			
	Niclosamide			
	Propranolol			
27	Dibenzepin Meclofenamic acid Nortriptyline Fluspirilene Diflunisal *Sotalol* *Acebutolol* *Aceclofenac* *Diltiazem* *Acetaminophen*	278	414	10 KEGG 12 GO BP 7 GO CC
28	Prazosin Mirtazapine Ketorolac Iopanoic acid Tolmetin Omacetaxine mepesuccinate Ciglitazone *Selegiline* *Disulfiram*	319	584	22 KEGG 53 GO BP 19 GO CC
29	Riluzole Falnidamol Clemastine	90	75	1 KEGG 5 GO BP 5 GO CC

	Cyclopenthiazide *Cephalothin* *Captopril* *Repaglinide* *Metronidazole* *Letrozole* *Penicillin g*			
30	Diclofenac Pseudoephedrine Brinzolamide Metaxalone Glipizide *Tranilast* *Cefuroxime* *Phenytoin* *Ritodrine* *Miconazole*	57	59	1 KEGG 7 GO BP 4 GO CC

31	Fenofibrate Praziquantel Terfenadine Metoprolol Omeprazole Loxapine *Adenosine* *Estrone* *Sulfathiazole*	125	104	7 KEGG 31 GO BP 6 GO CC
32	Milrinone Lovastatin Cilostazol 3-Methylcholanthrene Phenylbutazone Flunarizine Norethindrone *Azlocillin* *Doxazosin* *Estrone sulfate*	497	658	2 KEGG 19 GO BP 12 GO CC
33	Cabergoline Alfuzosin Perphenazine Bepridil Tinidazole *Cinchophen*	84	120	0 KEGG 4 GO BP 0 GO CC

	Cyclizine *Chlorpropamide* *Trichlormethiazide* *Mephenytoin*			
34	Altretamine Etodolac Raloxifene Domperidone Chlorpromazine *Chlorotrianisene* *Hydralazine* *Flurbiprofen* *Azactam* *Nitrofurantoin*	101	99	0 KEGG 4 GO BP 3 GO CC
35	Ramacemide Mefenamic acid Carbamazepine Ketoprofen Dipyridamole Prochlorperazine Dantrolene *Carbimazole* *Astemizole* *Bambuterol*	76	75	0 KEGG 21 GO BP 0 GO CC
36	Moxonidine Pinacidil	114	94	0 KEGG 6 GO BP

	Pentoxifylline			0 GO CC
	Oxaprozin			
	Primidone			
	Benzthiazide			
	Naproxen			
	Tianeptine			
	Cinoxacin			
37	Gatifloxacin	46	30	/
	Pheniramine			
	Fluoxetine			
	Azelastine			
	Iocetamic acid			
	Liothyronine			
	Lomefloxacin			
	Phthalylsulfathiazole			
	Cyclobenzaprine			
	Atenolol			

CP_eTox_H_MF

Cluster	Compounds	Number of upregulated genes	Number of downregulated genes	Enrichment terms
1	Estradiol	102	102	28 KEGG
	Primaquine			80 GO BP
	Ticlopidine			2 GO CC
	Digoxin			

	Fexofenadine *Chlorotrianisene* *Cyclobenzaprine* *Famotidine*			
2	Dicloxacillin Trioxsalen Pheniramine Dipyridamole *Sulfaethidole* *Azactam* *Nomifensine* *Cefoperazone*	35	45	0 KEGG 8 GO BP 0 GO CC
3	Penicillin g Omeprazole Promazine Benzthiazide Carvedilol *Tolfenamic acid* *Baclofen* *Chlorothiazide*	116	107	1 KEGG 4 GO BP 0 GO CC
4	Bendroflumethiazide Trazodone Praziquantel Simvastatin Diflunisal	288	433	10 KEGG 25 GO BP 7 GO CC

	Sotalol *Pilocarpine* *Dichlorophen*			
5	Pizotifen Caffeine Norethindrone Naftidrofuryl Diclofenac *Nitrofurantoin* *Letrozole* *Lomefloxacin*	88	94	3 KEGG 8 GO BP 7 GO CC
6	Lamotrigine Domperidone Celecoxib *Norfloxacin* *Galantamine* *Liothyronine* *Suprofen* *Chlorzoxazone*	52	44	3 KEGG 17 GO BP 1 GO CC
7	Protriptyline Ketoprofen Clomethiazole Prazosin *Metronidazole*	88	81	0 KEGG 0 GO BP 0 GO CC

	Deferoxamine *Glafenine*			
8	Glyburide Cimetidine Triamcinolone Mebendazole *Indomethacin* *Trichlormethiazide* *Tegaserod*	110	135	3 KEGG 8 GO BP 3 GO CC
9	Amitriptyline Pimozide Cyclopenthiazide Perphenazine Tolazamide *AHZ9RYL9EW* *Zopiclone*	95	108	10 KEGG 30 GO BP 5 GO CC
10	Dibenzepin Milrinone Mesoridazine Gatifloxacin Ketotifen *Doxazosin* *Gemfibrozil*	65	81	5 KEGG 0 GO BP 1 GO CC
11	Meclofenamic acid	52	29	0 KEGG

	Oxaprozin			2 GO BP
				0 GO CC
	Sulfathiazole			
	Ciprofloxacin			
	Lansoprazole			
	Prednisolone			
	Prednisone			
12	Spironolactone	61	53	0 KEGG
	Nortriptyline			
	Dydrogesterone			
	Salmeterol			2 GO BP
				0 GO CC
	Fluvastatine			
	Chlormezanone			
	Megestrol acetate			
13	Pravastatin	415	387	3 KEGG
	Methysergide			
	Triflupromazine			
	Betahistine			26 GO BP
	Daunorubicin			8 GO CC
	Sulfamethizole			
	Carbimazole			
14	Estrone	36	24	0 KEGG
	Albendazole			3 GO BP
	Candesartan cilexetil			0 GO CC
	Acebutolol			

	Sulfamerazine			
	Sulfadimethoxine			
	Iocetamic acid			
15	Moxonidine Olmesartan medoxomil *Cinchophen* *Quinethazone* *Tocainide* *Propranolol* *Diphenylpyraline*	29	31	3 KEGG 0 GO BP 0 GO CC
16	Terfenadine Propofol Cyproheptadine Doxepin Flunarizine *Cefuroxime* *Captopril*	73	76	0 KEGG 14 GO BP 1 GO CC
17	Fenofibrate Metolazone Flecainide Carteolol Sildenafil Quinapril *Enoxacin*	69	74	0 KEGG 1 GO BP 0 GO CC

18	Imatinib Risperidone Doxylamine *Levofloxacin* *Furosemide* *Clidinium* *Metyrapone*	51	54	3 KEGG 8 GO BP 0 GO CC
19	Pantoprazole Fluticasone propionate Pseudoephedrine *Cefoxitin* *Oxybutynin* *Zonisamide* *Hydroxyzine*	20	31	/
20	Nilutamide Mexiletine Thiabendazole Metoprolol *Molindone* *Selegiline* *Diazepam*	42	39	1 KEGG 2 GO BP 0 GO CC
21	Timolol Progesterone Rofecoxib	35	26	2 KEGG 1 GO BP 0 GO CC

	Colchicine *Theophylline* *Ketoconazole* *Gliclazide*			
22	Amantadine Loperamide Verapamil Brinzolamide Diltiazem Metoclopramide *Acetaminophen*	77	83	0 KEGG 2 GO BP 3 GO CC
23	Perindopril Nefazodone Diazoxide *Bromocriptine* *Phenytoin* *Zolpidem* *Methapyrilene*	25	28	0 KEGG 0 GO BP 1 GO CC
24	Bupropion Clomipramine Loxapine *Diphenhydramine* *Althiazide* *Repaglinide* *Hydroflumethiazide*	80	44	0 KEGG 3 GO BP 0 GO CC

25	Trifluoperazine Trimethobenzamide Ornidazole Alfuzosin *Aminopyrine* *Phenacemide* *Clotrimazole*	43	43	0 KEGG 0 GO BP 3 GO CC
26	Phentolamine Propafenone Paroxetine Pentoxifylline Bepridil Primidone *Etoposide*	96	116	0 KEGG 1 GO BP 0 GO CC
27	Mibefradil Proguanil Tamoxifen Lidocaine *Cyclothiazide* *Azathioprine* *Levamisole*	41	45	1 KEGG 7 GO BP 0 GO CC
28	Clozapine Chlorthalidone Chlorpromazine Lovastatin	108	92	4 KEGG 3 GO BP 3 GO CC

	Fluoxetine *Ritodrine* *Bergapten*			
29	Probenecid Buspirone Mefenamic acid Papaverine Benzbromarone *Hycanthone* *Phthalylsulfathiazole*	63	57	1 KEGG 6 GO BP 0 GO CC
30	Thalidomide Bisacodyl Famciclovir Tolmetin Disopyramide *Valacyclovir* *Methoxsalen*	112	110	11 KEGG 22 GO BP 15 GO CC
31	Flutamide Finasteride Rimexolone Practolol *Meticrane* *Sulfamethoxypyridazine* *Sulfachloropyridazine*	41	50	0 KEGG 0 GO BP 0 GO CC

32	Pyrimethamine Phenylbutazone Mepivacaine Cabergoline *Atenolol* *Benazepril* *Piperacillin*	27	45	0 KEGG 0 GO BP 1 GO CC
33	Amiodarone Dantrolene Riluzole Trimipramine Prochlorperazine Levonorgestrel *Aceclofenac*	68	102	3 KEGG 14 GO BP 0 GO CC
34	Metaxalone Diphenidol Ketorolac *Flurbiprofen* *Hydralazine* *Cefazolin* *Zomepirac*	40	31	0 KEGG 1 GO BP 0 GO CC
35	Clemastine Saquinavir Triamterene Nimesulide	46	48	0 KEGG 1 GO BP 0 GO CC

	Methocarbamol Fluconazole *Cloxacillin*			
36	Bumetanide Dexamethasone Naproxen Thiotepa *Imipramine* *Valdecoxib* *Azlocillin*	75	60	0 KEGG 2 GO BP 0 GO CC
37	Etodolac Danthron *Pentobarbital* *Hydrochlorothiazide* *Torsemide* *Melatonin* *Indapamide*	49	40	0 KEGG 0 GO BP 0 GO CC
38	Fenoterol Atomoxetine Amoxapine *Astemizole* *Tolazoline* *Sulfadiazine* *Ethionamide*	56	47	1 KEGG 1 GO BP 0 GO CC

39	Testosterone propionate Mirtazapine Venlafaxine *Dapsone* *Cyclizine* *Azelastine* *Sulfacetamide*	37	35	0 KEGG 0 GO BP 1 GO CC
40	Amiloride Haloperidol Carbamazepine *Hydrocortisone acetate* *Moricizine* *Loratadine* *Methazolamide*	44	50	0 KEGG 3 GO BP 1 GO CC
41	Sulfisoxazole Tinidazole Ondansetron Beclomethasone dipropionate *Niridazole* *Ethacrynic acid* *Chlorpropamide*	49	48	2 KEGG 1 GO BP 0 GO CC
42	Glipizide Procainamide Mometasone furoate	33	26	0 KEGG 3 GO BP 0 GO CC

	Mephenytoin *Acetazolamide* *Nabumetone* *Xylometazoline*			
43	Raloxifene Modafinil Niridazole Enalapril *Estrone sulfate* *Moxisylyte* *Propylthiouracil*	41	46	0 KEGG 0 GO BP 0 GO CC
44	Nafcillin Dexamethasone acetate Leflunomide Cilostazol Chloroquine *Acetohexamide* *Terbutaline*	84	97	1 KEGG 0 GO BP 0 GO CC
45	Alrestatin Valsartan *Trimethoprim* *Sulfamethoxazole* *4-Phenylbutyric acid* *Disulfiram* *Adenosine*	34	29	1 KEGG 5 GO BP 0 GO CC

	CP_eTox_H_MFHB			
Cluster	**Compounds**	**Number of upregulated genes**	**Number of downregulated genes**	**Enrichment terms**
1	Paroxetine Verapamil Practolol Benzthiazide *Acetaminophen* *Letrozole* *Quinethazone* *Propylthiouracil*	76	71	0 KEGG 1 GO BP 0 GO CC
2	Metolazone Finasteride Estrone Chlorthalidone Phenylbutazone Cyclopenthiazide *Trichlormethiazide* *Cefazolin*	46	64	0 KEGG 0 GO BP 1 GO CC
3	Doxepin Raloxifene Amiodarone *Cyclizine*	45	67	1 KEGG 7 GO BP 0 GO CC

	Trimethoprim *Deferoxamine* *Indomethacin*			
4	Nilutamide Carbamazepine Venlafaxine *Piperacillin* *Glafenine* *Estrone sulfate* *Althiazide*	44	36	1 KEGG 2 GO BP 0 GO CC
5	Metoclopramide Primidone Fluoxetine *Metronidazole* *Zonisamide* *Phenytoin* *Flurbiprofen*	55	38	0 KEGG 0 GO BP 3 GO CC
6	Moxonidine Diflunisal Alfuzosin Dicloxacillin *Repaglinide* *Azelastine* *Benazepril*	248	399	10 KEGG 11 GO BP 6 GO CC
7	Perindopril	23	33	/

	Saquinavir Methocarbamol *Azlocillin* *Enoxacin* *Zolpidem* *Pilocarpine*			
8	Gatifloxacin Chloroquine Flecainide Tolazamide *Acetohexamide* *Cyclobenzaprine* *Sotalol*	70	75	7 KEGG 5 GO BP 1 GO CC
9	Tinidazole Quinapril Progesterone Ketotifen *Cyclothiazide* *Chlormezanone* *Cefoperazone*	58	67	5 KEGG 4 GO BP 6 GO CC
10	Risperidone Pyrimethamine Disopyramide *Valacyclovir*	50	65	2 KEGG 1 GO BP 10 GO CC

	Diazepam			
	Azathioprine			
	Cefoxitin			
11	Mexiletine Metoprolol Protriptyline Haloperidol Pravastatin *Methapyrilene* *Diphenhydramine*	102	93	0 KEGG 4 GO BP 0 GO CC
12	Candesartan cilexetil Mirtazapine Famciclovir Ticlopidine *Hydrochlorothiazide* *Ciprofloxacin* *Hydroxyzine*	61	51	5 KEGG 0 GO BP 0 GO CC
13	Ornidazole Mebendazole Valsartan Flunarizine Simvastatin *Meticrane* *Etoposide*	100	85	2 KEGG 3 GO BP 2 GO CC

14	Loperamide Proguanil Carvedilol Fenofibrate Diltiazem *Tegaserod* *Hydrocortisone acetate*	55	52	0 KEGG 1 GO BP 0 GO CC
15	Thalidomide Cilostazol Lamotrigine Thiabendazole Atomoxetine Nefazodone *Torsemide*	106	96	0 KEGG 9 GO BP 5 GO CC
16	Spironolactone Dexamethasone Dibenzepin Clomipramine Propafenone *Sulfadimethoxine* *Gliclazide*	50	64	/
17	Fexofenadine Trimipramine Etodolac Fluvastatine	74	58	0 KEGG 1 GO BP 4 GO CC

	Propranolol *Famotidine* *Pheniramine*			
18	Imatinib Cimetidine Olmesartan medoxomil Modafinil *Chlorotrianisene* *Sulfamethoxazole* *Nitrofurantoin*	73	67	2 KEGG 8 GO BP 0 GO CC
19	Tamoxifen Pizotifen Lidocaine Dipyridamole *Norfloxacin* *Atenolol* *Imipramine*	64	75	1 KEGG 13 GO BP 1 GO CC
20	Flutamide Prochlorperazine Glyburide Enalapril Pentoxifylline Bendroflumethiazide *Nabumetone*	100	121	1 KEGG 4 GO BP 5 GO CC

21	Riluzole Celecoxib Mometasone furoate Pantoprazole Penicillin g *Prednisone* *Clotrimazole*	83	75	3 KEGG 14 GO BP 3 GO CC
22	Daunorubicin Procainamide Digoxin *Cefuroxime* *Diphenylpyraline* *Hydroflumethiazide* *Chlorzoxazone*	401	405	6 KEGG 35 GO BP 10 GO CC
23	Amantadine Diclofenac Bumetanide *Indapamide* *Astemizole* *Loratadine* *Carbimazole*	66	64	0 KEGG 6 GO BP 0 GO CC
24	Ketoprofen Triflupromazine Dantrolene Chlorpromazine	73	70	0 KEGG 4 GO BP 1 GO CC

	Doxazosin *Levofloxacin* *Clidinium*			
25	Ondansetron Clomethiazole Pimozide Leflunomide Omeprazole *Furosemide* *Ketoconazole*	94	101	10 KEGG 13 GO BP 2 GO CC
26	Milrinone Levonorgestrel Trifluoperazine Clemastine *Gemfibrozil* *Acetazolamide* *Galantamine*	33	55	/
27	Ketorolac Estradiol Fluconazole Glipizide *Prednisolone* *Lansoprazole* *Chlorpropamide*	59	42	2 KEGG 3 GO BP 0 GO CC

Cluster	Compounds	Number of upregulated	Number of downregulated	Enrichment terms
28	Amoxapine Lovastatin Rofecoxib Terfenadine Amitriptyline *Lomefloxacin* *Disulfiram*	98	87	20 KEGG 16 GO BP 1 GO CC
29	Meclofenamic acid Cyproheptadine Doxylamine Clozapine Nimesulide *Captopril* *Ritodrine*	64	47	/
30	Trazodone Albendazole Propofol Nortriptyline *AHZ9RYL9EW* *Cloxacillin* *Chlorothiazide*	47	40	2 KEGG 12 GO BP 0 GO CC

CP_eTox_H_MFHC

Cluster	Compounds	Number of upregulated	Number of downregulated	Enrichment terms

		genes	genes	
1	Perphenazine Fluoxetine Bupropion Dibenzepin *Selegiline* *Methoxsalen* *Azathioprine* *Dapsone* *Cyclizine*	82	68	2 KEGG 1 GO BP 2 GO CC
2	Pyrimethamine Modafinil Sulfisoxazole Propafenone *Cinchophen* *Cloxacillin* *Zopiclone* *Zolpidem* *Methapyrilene*	37	49	/
3	Clemastine Carbamazepine Primidone Omeprazole *Pentobarbital* *Norfloxacin*	66	67	0 KEGG 1 GO BP 0 GO CC

5	*Acebutolol* *Pilocarpine* *Sotalol*			
4	Cabergoline Dipyridamole Pantoprazole Flunarizine Albendazole Nilutamide Thiotepa *Phthalylsulfathiazole* *Tocainide*	98	95	1 KEGG 2 GO BP 0 GO CC
5	Mesoridazine Diflunisal Diclofenac Clomipramine Mibefradil Diltiazem *Sulfacetamide* *Hydrocortisone acetate* *Nomifensine*	272	419	7 KEGG 26 GO BP 7 GO CC
6	Protriptyline Terfenadine Timolol *Hycanthone*	99	87	0 KEGG 4 GO BP 0 GO CC

	Carbimazole			
	Ethionamide			
	Letrozole			
	Methazolamide			
	Prednisolone			
7	Caffeine Domperidone Methysergide *Galantamine* *Aceclofenac* *Moricizine* *Ketoconazole* *Chlorzoxazone*	53	40	3 KEGG 0 GO BP 5 GO CC
8	Glyburide Phentolamine Danthron Tolmetin Ticlopidine *Hydroxyzine* *Acetohexamide* *Bergapten*	101	103	3 KEGG 8 GO BP 0 GO CC
9	Doxepin Glipizide *Diphenhydramine* *Cefoperazone*	15	21	1 KEGG 0 GO BP 1 GO CC

	Acetazolamide *Tegaserod* *Sulfathiazole* *Phenytoin*			
10	Norethindrone Prazosin Fenoterol Alfuzosin Disopyramide Riluzole *Lansoprazole* *Ritodrine*	103	96	3 KEGG 7 GO BP 9 GO CC
11	Fluconazole Pravastatin Oxaprozin Cyproheptadine Prochlorperazine Rimexolone *Benazepril* *Hydrochlorothiazide*	74	64	0 KEGG 6 GO BP 0 GO CC
12	Cimetidine Procainamide Nortriptyline Amiloride Mefenamic acid Praziquantel	108	78	1 KEGG 11 GO BP 7 GO CC

	Ethacrynic acid *Glafenine*			
13	Probenecid Risperidone Thiabendazole *Etoposide* *Baclofen* *Megestrol acetate* *Cyclobenzaprine* *Cefoxitin*	26	37	1 KEGG 0 GO BP 0 GO CC
14	Pizotifen Carvedilol Mepivacaine Niridazole Fexofenadine *Diazepam* *Valdecoxib* *Sulfamethoxypyridazine*	81	86	1 KEGG 4 GO BP 4 GO CC
15	Pentoxifylline Simvastatin Triamcinolone Bendroflumethiazide Naftidrofuryl *Flurbiprofen*	81	83	2 KEGG 6 GO BP 2 GO CC

	Terbutaline *AHZ9RYL9EW*			
16	Phenylbutazone Dexamethasone acetate Fenofibrate Mirtazapine *Fluvastatine* *Indapamide* *Trimethoprim* *Cefazolin*	44	58	0 KEGG 0 GO BP 1 GO CC
17	Metaxalone Diazoxide Perindopril Haloperidol *Sulfaethidole* *Nitrofurantoin* *Oxybutynin* *Bromocriptine*	38	51	1 KEGG 5 GO BP 1 GO CC
18	Famciclovir *Chlorpropamide* *Prednisone* *Repaglinide* *Metronidazole* *Sulfamerazine* *Tolazoline*	/	/	/

	Torsemide			
19	Lovastatin Enalapril Dexamethasone Ketorolac Flutamide Ketotifen *Phenacemide* *Theophylline*	106	85	9 KEGG 4 GO BP 2 GO CC
20	Ketoprofen Benzbromarone Practolol Betahistine *Iocetamic acid* *Hydralazine* *Levofloxacin* *Zonisamide*	46	37	0 KEGG 1 GO BP 0 GO CC
21	Trioxsalen Bepridil Raloxifene Proguanil Lamotrigine Doxylamine *Valacyclovir* *4-Phenylbutyric acid*	93	106	2 KEGG 5 GO BP 2 GO CC

22	Bumetanide Digoxin Papaverine Atomoxetine Alrestatin *Metyrapone* *Liothyronine* *Tolfenamic acid*	100	112	18 KEGG 35 GO BP 2 GO CC
23	Fluticasone propionate Rofecoxib Amiodarone Venlafaxine Naproxen Loxapine *Aminopyrine* *Diphenylpyraline*	94	98	8 KEGG 6 GO BP 0 GO CC
24	Pseudoephedrine Progesterone Estradiol Candesartan cilexetil *Captopril* *Moxisylyte* *Disulfiram* *Ciprofloxacin*	52	49	1 KEGG 5 GO BP 0 GO CC
25	Ondansetron	45	38	1 KEGG

	Testosterone propionate Leflunomide Nefazodone *Famotidine* *Colchicine* *Doxazosin* *Mephenytoin*			0 GO BP 0 GO CC
26	Tinidazole Amitriptyline Milrinone Triflupromazine Cilostazol *Astemizole* *Dichlorophen* *Suprofen*	93	95	1 KEGG 2 GO BP 0 GO CC
27	Pheniramine Celecoxib Nimesulide Penicillin g Trifluoperazine *Azlocillin* *Deferoxamine* *Adenosine*	78	66	1 KEGG 2 GO BP 4 GO CC
28	Beclomethasone dipropionate Buspirone	54	56	2 KEGG 7 GO BP

	Mometasone furoate			4 GO CC
	Verapamil			
	Lidocaine			
	Indomethacin			
	Sulfadimethoxine			
	Enoxacin			
29	Thalidomide Paroxetine Metoprolol Brinzolamide Daunorubicin Finasteride Levonorgestrel *Sulfadiazine*	430	415	2 KEGG 32 GO BP 9 GO CC
30	Loperamide Etodolac Dantrolene Chloroquine Nafcillin Bisacodyl *Trichlormethiazide* *Azactam*	100	92	1 KEGG 5 GO BP 3 GO CC
31	Mexiletine Moxonidine Valsartan	92	88	3 KEGG 28 GO BP 1 GO CC

	Trazodone Salmeterol Tolazamide *Propranolol* *Lomefloxacin*			
32	Carteolol Dicloxacillin Saquinavir Olmesartan medoxomil *Zomepirac* *Atenolol* *Cefuroxime* *Gliclazide*	57	42	1 KEGG 0 GO BP 1 GO CC
33	Spironolactone Amoxapine Quinapril Metolazone Propofol *Azelastine* *Acetaminophen* *Imipramine*	60	76	4 KEGG 0 GO BP 0 GO CC
34	Sildenafil Tamoxifen Mebendazole Gatifloxacin	63	66	5 KEGG 8 GO BP 2 GO CC

	Imatinib *Clotrimazole* *Nabumetone* *Loratadine*			
35	Flecainide Chlorpromazine Trimipramine Clozapine *Sulfamethizole* *Piperacillin* *Propylthiouracil* *Sulfamethoxazole*	63	79	0 KEGG 2 GO BP 3 GO CC

REFERENCES

(1) Lv, X.; Kong, J.; Chen, W.-D.; Wang, Y.-D. The Role of the Apelin/APJ System in the Regulation of Liver Disease. *Front. Pharmacol.* **2017**, *8*, 221. https://doi.org/10.3389/fphar.2017.00221.

(2) Dharmalingam, M.; Yamasandhi, Pg. Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus. *Indian J. Endocrinol. Metab.* **2018**, *22* (3), 421. https://doi.org/10.4103/ijem.IJEM_585_17.

(3) Asadipooya, K.; Lankarani, K. B.; Raj, R.; Kalantarhormozi, M. RAGE Is a Potential Cause of Onset and Progression of Nonalcoholic Fatty Liver Disease. *Int. J. Endocrinol.* **2019**, *2019*, 1–11. https://doi.org/10.1155/2019/2151302.

(4) Malhotra, P.; Gill, R. K.; Saksena, S.; Alrefai, W. A. Disturbances in Cholesterol Homeostasis and Non-Alcoholic Fatty Liver Diseases. *Front. Med.* **2020**, *7*, 467. https://doi.org/10.3389/fmed.2020.00467.

(5) Simonen, P.; Kotronen, A.; Hallikainen, M.; Sevastianova, K.; Makkonen, J.; Hakkarainen, A.; Lundbom, N.; Miettinen, T. A.; Gylling, H.; Yki-Järvinen, H. Cholesterol Synthesis Is Increased and Absorption Decreased in Non-Alcoholic Fatty Liver Disease Independent of Obesity. *J. Hepatol.* **2011**, *54* (1), 153–159. https://doi.org/10.1016/j.jhep.2010.05.037.

(6) Ju, C.; Colgan, S. P.; Eltzschig, H. K. Hypoxia-Inducible Factors as Molecular Targets for Liver Diseases. *J. Mol. Med.* **2016**, *94* (6), 613–627. https://doi.org/10.1007/s00109-016-1408-1.

(7) Chu, Q.; Gu, X.; Zheng, Q.; Zhu, H. Regulatory Mechanism of HIF-1α and Its Role in Liver Diseases: A Narrative Review. *Ann. Transl. Med.* **2022**, *10* (2), 109–109. https://doi.org/10.21037/atm-21-4222.

(8) Miller, T. J.; Knapton, A.; Adeyemo, O.; Noory, L.; Weaver, J.; Hanig, J. P. Cytochrome c: A Non-Invasive Biomarker of Drug-Induced Liver Injury. *J. Appl. Toxicol.* **2008**, *28* (7), 815–828. https://doi.org/10.1002/jat.1347.

(9) Mercado-Gómez, M.; Lopitz-Otsoa, F.; Azkargorta, M.; Serrano-Maciá, M.; Lachiondo-Ortega, S.; Goikoetxea-Usandizaga, N.; Rodríguez-Agudo, R.; Fernández-Ramos, D.; Bizkarguenaga, M.; Juan, V. G.; Lectez, B.; Aloria, K.; Arizmendi, J. M.; Simon, J.; Alonso, C.; Lozano, J. J.; Avila, M. A.; Banales, J. M.; Marin, J. J. G.; Beraza, N.; Mato, J. M.; Elortza, F.; Barrio, R.; Sutherland, J. D.; Mayor,

U.; Martínez-Chantar, M. L.; Delgado, T. C. Multi-Omics Integration Highlights the Role of Ubiquitination in CCl4-Induced Liver Fibrosis. *Int. J. Mol. Sci.* **2020**, *21* (23), 9043. https://doi.org/10.3390/ijms21239043.

(10)   Park, J.-S.; Ma, H.; Roh, Y.-S. Ubiquitin Pathways Regulate the Pathogenesis of Chronic Liver Disease. *Biochem. Pharmacol.* **2021**, *193*, 114764. https://doi.org/10.1016/j.bcp.2021.114764.

(11)   Tang, Y.; Bian, Z.; Zhao, L.; Liu, Y.; Liang, S.; Wang, Q.; Han, X.; Peng, Y.; Chen, X.; Shen, L.; Qiu, D.; Li, Z.; Ma, X. Interleukin-17 Exacerbates Hepatic Steatosis and Inflammation in Non-Alcoholic Fatty Liver Disease. *Clin. Exp. Immunol.* **2011**, *166* (2), 281–290. https://doi.org/10.1111/j.1365-2249.2011.04471.x.

(12)   Adams, D. H.; Ju, C.; Ramaiah, S. K.; Uetrecht, J.; Jaeschke, H. Mechanisms of Immune-Mediated Liver Injury. *Toxicol. Sci.* **2010**, *115* (2), 307–321. https://doi.org/10.1093/toxsci/kfq009.

(13)   Monin, L.; Gaffen, S. L. Interleukin 17 Family Cytokines: Signaling Mechanisms, Biological Activities, and Therapeutic Implications. *Cold Spring Harb. Perspect. Biol.* **2018**, *10* (4), a028522. https://doi.org/10.1101/cshperspect.a028522.

(14)   Elsharkawy, A. M.; Mann, D. A. Nuclear Factor-KB and the Hepatic Inflammation-Fibrosis-Cancer Axis. *Hepatology* **2007**, *46* (2), 590–597. https://doi.org/10.1002/hep.21802.

(15)   Berasain, C.; Avila, M. A. The EGFR Signalling System in the Liver: From Hepatoprotection to Hepatocarcinogenesis. *J. Gastroenterol.* **2014**, *49* (1), 9–23. https://doi.org/10.1007/s00535-013-0907-x.

(16)   Wen, Y.; Lambrecht, J.; Ju, C.; Tacke, F. Hepatic Macrophages in Liver Homeostasis and Diseases-Diversity, Plasticity and Therapeutic Opportunities. *Cell. Mol. Immunol.* **2021**, *18* (1), 45–56. https://doi.org/10.1038/s41423-020-00558-8.

(17)   Tahmasebi-Birgani, M.; Ansari, H.; Carloni, V. Defective Mitosis-Linked DNA Damage Response and Chromosomal Instability in Liver Cancer. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer* **2019**, *1872* (1), 60–65. https://doi.org/10.1016/j.bbcan.2019.05.008.

(18)   Lee, S. H. Hyperoxia Accelerates Progression of Hepatic Fibrosis by Up-Regulation of Transforming Growth Factor-β Expression. *WJG* **2014**, *20* (11), 3011. https://doi.org/10.3748/wjg.v20.i11.3011.

(19)   Böhm, F.; Köhler, U. A.; Speicher, T.; Werner, S. Regulation of Liver Regeneration by Growth Factors and Cytokines. *EMBO Mol Med* **2010**, *2* (8), 294–305.

https://doi.org/10.1002/emmm.201000085.

(20)   Baghy, K. Proteoglycans in Liver Cancer. World J. Gastroenterol. 2016, 22 (1), 379. https://doi.org/10.3748/wjg.v22.i1.379.

(21)   Herrera, J.; Henke, C. A.; Bitterman, P. B. Extracellular Matrix as a Driver of Progressive Fibrosis. J. Clin. Invest. 2018, 128 (1), 45–53. https://doi.org/10.1172/JCI93557.

(22)   Hintermann; Christen. The Many Roles of Cell Adhesion Molecules in Hepatic Fibrosis. Cells 2019, 8 (12), 1503. https://doi.org/10.3390/cells8121503.

(23)   Boettner, B.; Van Aelst, L. Control of Cell Adhesion Dynamics by Rap1 Signaling. Curr. Opin. Cell Biol. 2009, 21 (5), 684–693. https://doi.org/10.1016/j.ceb.2009.06.004.

(24)   Wang, Y.; Nakajima, T.; Gonzalez, F. J.; Tanaka, N. PPARs as Metabolic Regulators in the Liver: Lessons from Liver-Specific PPAR-Null Mice. Int. J. Mol. Sci. 2020, 21 (6), 2061. https://doi.org/10.3390/ijms21062061.

(25)   Schulze-Osthoff, K.; Ferrari, D.; Riehemann, K.; Wesselborg, S. Regulation of NF-KB Activation by MAP Kinase Cascades. Immunobiology 1997, 198 (1–3), 35–49. https://doi.org/10.1016/S0171-2985(97)80025-3.

(26)   Coffin, C. S.; Fraser, H. F.; Panaccione, R.; Ghosh, S. Liver Diseases Associated with Anti-Tumor Necrosis Factor-Alpha (TNF-α) Use for Inflammatory Bowel Disease: Inflamm. Bowel Dis. 2011, 17 (1), 479–484. https://doi.org/10.1002/ibd.21336.

(27)   Calcagno, D. M.; Chu, A.; Gaul, S.; Taghdiri, N.; Toomu, A.; Leszczynska, A.; Kaufmann, B.; Papouchado, B.; Wree, A.; Geisler, L.; Hoffman, H. M.; Feldstein, A. E.; King, K. R. NOD‑like Receptor Protein 3 Activation Causes Spontaneous Inflammation and Fibrosis That Mimics Human NASH. Hepatology 2022, 76 (3), 727–741. https://doi.org/10.1002/hep.32320.

(28)   Zhong, Y.; Kinio, A.; Saleh, M. Functions of NOD-Like Receptors in Human Diseases. Front. Immunol. 2013, 4. https://doi.org/10.3389/fimmu.2013.00333.

(29)   Schierwagen, R.; Uschner, F. E.; Ortiz, C.; Torres, S.; Brol, M. J.; Tyc, O.; Gu, W.; Grimm, C.; Zeuzem, S.; Plamper, A.; Pfeifer, P.; Zimmer, S.; Welsch, C.; Schaefer, L.; Rheinwalt, K. P.; Clària, J.; Arroyo, V.; Trebicka, J.; Klein, S. The Role of Macrophage-Inducible C-Type Lectin in Different Stages of Chronic Liver Disease. Front. Immunol. 2020, 11, 1352. https://doi.org/10.3389/fimmu.2020.01352.

(30)   Liu, X.; Green, R. M. Endoplasmic Reticulum Stress and Liver Diseases. Liver Res. 2019, 3 (1), 55–64. https://doi.org/10.1016/j.livres.2019.01.002.

(31)   Adams, J.; Jafar-Nejad, H. The Roles of Notch Signaling in Liver Development

and Disease. Biomolecules 2019, 9 (10), 608. https://doi.org/10.3390/biom9100608.

(32)   Chiu, D. K.-C. Hypoxia Regulates the Mitochondrial Activity of Hepatocellular Carcinoma Cells through HIF/HEY1/PINK1 Pathway. 2019, 16.

(33)   Bhogal, R. H.; Curbishley, S. M.; Weston, C. J.; Adams, D. H.; Afford, S. C. Reactive Oxygen Species Mediate Human Hepatocyte Injury during Hypoxia/Reoxygenation. Liver Transpl. 2010, 16 (11), 1303–1313. https://doi.org/10.1002/lt.22157.

(34)   Cui, X.; Zhang, X.; Yin, Q.; Meng, A.; Su, S.; Jing, X.; Li, H.; Guan, X.; Li, X.; Liu, S.; Cheng, M. F-Actin Cytoskeleton Reorganization Is Associated with Hepatic Stellate Cell Activation. Mol. Med. Rep. 2014, 9 (5), 1641–1647. https://doi.org/10.3892/mmr.2014.2036.

(35)   Desouza, M.; Gunning, P. W.; Stehn, J. R. The Actin Cytoskeleton as a Sensor and Mediator of Apoptosis. BioArchitecture 2012, 2 (3), 75–87. https://doi.org/10.4161/bioa.20975.

(36)   Mimche, P. N.; Brady, L. M.; Bray, C. F.; Lee, C. M.; Thapa, M.; King, T. P.; Quicke, K.; McDermott, C. D.; Mimche, S. M.; Grakoui, A.; Morgan, E. T.; Lamb, T. J. The Receptor Tyrosine Kinase EphB2 Promotes Hepatic Fibrosis in Mice. Hepatology 2015, 62 (3), 900–914. https://doi.org/10.1002/hep.27792.

(37)   Mimche, P. N. EphB2 Receptor Tyrosine Kinase Promotes Hepatic Fibrogenesis in Mice via Activation of Hepatic Stellate Cells. Sci. Rep. 2018, 14.