DrugMatrix™

Drug Signature Documentation

DrugMatrix Online 1.0

June 2007

Liver Signatures

Hepatomegaly

Signature_identifier: SV0642001R5QU
Array Platform: Affymetrix RG230 v2
Type: Body and Organ Weights
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused liver weight increase.

Training Set Description: Liver expression data from 0.25, 1 day experiments inducing relative liver weight higher than the historical control mean by 2 standard deviations (10 experiments, 8 compounds, including BETAMETHASONE, ARTEMISININ, DEXAMETHASONE, GENTIAN VIOLET, ITRACONAZOLE) were used as the positive class in defining this signature. The negative class was composed of 0.25, 1 day experiments with relative liver weight within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 61.2
Specificity (% True Negative): 99.1
Log Odds Ratio: 5.2

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: DEXAMETHASONE_150mpk_1d = 2.18, FLUOCINOLONE ACETONIDE_2.5mpk_1d = 1.61, BETAMETHASONE_79mpk_1d = 1.34.

Serum bilirubin and alkaline phosphatase increase

Signature_identifier: SV0663003R5QU
Array Platform: Affymetrix RG230 v2
Type: Clinical Pathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused serum bilirubin and alkaline phosphatase increase.

Training Set Description: Liver expression data from 3, 5, 7 day experiments inducing serum total bilirubin and alkaline phosphatase levels at least 1.5 fold over control values in at least 2/3 animals (9 experiments, 7 compounds, including 1-NAPHTHYL ISOTHIOCYANATE, CHLOROFORM, DIETHYLSTILBESTROL, ETHINYLESTRADIOL, MICONAZOLE) were used as the positive class in defining this signature. The negative class was composed of experiments with serum total bilirubin and alkaline phosphatase levels less than 1.2-fold and greater 0.75-fold in all 3 animals at all doses on days 3, 5, and 7.

Sensitivity (% True Positive): 51.2
Specificity (% True Negative): 99.3
Log Odds Ratio: 5

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: MICONAZOLE_920mpk_5d = 3.27, 1-NAPHTHYL ISOTHIOCYANATE_60mpk_7d = 3.15, 1-NAPHTHYL ISOTHIOCYANATE_30mpk_7d = 2.10.

Hypoalbuminemia

Signature_identifier: SV0562035R5QU
Array Platform: Affymetrix RG230 v2
Type: Clinical Pathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused albumin decrease.

Training Set Description: Liver expression data from 3, 5, 7 day experiments reducing serum albumin lower than the historical control mean by 2 standard deviations and other timepoints for positive treatments (54 experiments, 33 compounds, including ALLYL ALCOHOL, INDOMETHACIN, LPS, ROFLUMILAST, SULINDAC) were used as the positive class in defining this signature. The negative class was composed of 3, 5, 7 day experiments with serum albumin within 1 standard deviation of historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 69.3
Specificity (% True Negative): 94.2
Log Odds Ratio: 3.6

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: ETODOLAC_24mpk_5d = 5.05, MELOXICAM_33mpk_5d = 4.30, KETOROLAC_48mpk_5d = 3.84.

Serum alanine aminotransferase increase

Signature_identifier: SV0290422R5QU
Array Platform: Affymetrix RG230 v2
Type: Clinical Pathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused serum alanine aminotransferase increase.

Training Set Description: Liver expression data from 3, 5, 7 day experiments inducing serum alanine aminotransferase levels above the 98 percentile of all treatments and other timepoints for positive treatments (29 experiments, 14 compounds, including 1-NAPHTHYL ISOTHIOCYANATE, CARBON TETRACHLORIDE, ANASTROZOLE, MICONAZOLE, VINBLASTINE) were used as the positive class in defining this signature. The negative class was composed of 3, 5, 7 day experiments with serum alanine aminotransferase levels between the 40 and 55 percentile, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 87.5
Specificity (% True Negative): 97
Log Odds Ratio: 5.3

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: ETODOLAC_24mpk_5d = 6.56, AMINOSALICYLIC ACID_2337mpk_1d = 6.27, ROFLUMILAST_17mpk_4d = 6.19.

Thrombocytopenia

Signature_identifier: SA0562068R40340QU
Array Platform: Affymetrix RG230 v2
Type: Clinical Pathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused platelet count decrease.

Training Set Description: Liver expression data from 0.25, 1, 3, 5, 7 day experiments reducing blood platelet counts lower than the historical control mean by 2 standard deviations and other timepoints for positive treatments (15 experiments, 9 compounds, including BIS(2-ETHYLHEXYL)PHTHALATE, FLUOCINOLONE ACETONIDE, LEFLUONOMIDE, LPS, VINBLASTINE) were used as the positive class in defining this signature. The negative class was composed of 0.25, 1, 3, 5, 7 day experiments with blood platelet counts within 1 standard deviation of historical control mean, but not other doses of compounds in the positive class..

Sensitivity (% True Positive): 40
Specificity (% True Negative): 98.2
Log Odds Ratio: 3.6

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: VINBLASTINE_0.3mpk_5d = 1.68, LEFLUONOMIDE_60mpk_5d = 1.01, LPS_1.25mpk_3d = 1.

Leukopenia

Signature_identifier: SV0562087R5QU
Array Platform: Affymetrix RG230 v2
Type: Clinical Pathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused leukocyte count decrease.

Training Set Description: Liver expression data from 0.25, 1, 3, 5, 7 day experiments reducing leukocyte counts lower than the historical control mean by 2 standard deviations and other doses and timepoints of positive treatments (33 experiments, 15 compounds, including CARMUSTINE, DOXORUBICIN, ETODOLAC, LEFLUNOMIDE, PROCARBAZINE) were used as the positive class in defining this signature. The negative class was composed of 0.25, 1, 3, 5, 7 day experiments with leukocyte counts within 1 standard deviation of historical control mean.

Sensitivity (% True Positive): 67.9
Specificity (% True Negative): 98.1
Log Odds Ratio: 4.7

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: EPIRUBICIN_2.7mpk_3d = 2.74, VINBLASTINE_0.3mpk_5d = 2.44, DOXORUBICIN_3mpk_5d = 2.32.

Lymphopenia

Signature_identifier: SV0562059R5QU
Array Platform: Affymetrix RG230 v2
Type: Clinical Pathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused lymphocyte decrease.

Training Set Description: Liver expression data from 3, 5, 7 day experiments reducing absolute lymphocyte counts lower than the historical control mean by 2 standard deviations and other timepoints for positive treatments (20 experiments, 11 compounds, including BETAMETHASONE, CHLORAMBUCIL, DEXAMETHASONE, DOXORUBICIN, THIOGUANINE) were used as the positive class in defining this signature. The negative class was composed of 3, 5, 7 day experiments with absolute lymphocyte counts within 1 standard deviation of historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 75
Specificity (% True Negative): 99.9
Log Odds Ratio: 7.6

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: THIOGUANINE_12mpk_3d = 2.16, DEXAMETHASONE_1mpk_3d = 1.67, HYDROCORTISONE_56mpk_3d = 1.66.

Neutrophilia

Signature_identifier: SV0567012R5QU
Array Platform: Affymetrix RG230 v2
Type: Clinical Pathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused neutrophil count increase.

Training Set Description: Liver expression data from 3, 5, 7 day experiments inducing neutrophil counts higher than the historical control mean by 2 standard deviations and other timepoints for positive treatments (67 experiments, 37 compounds, including SULINDAC, KETOROLAC, IBUPROFEN, 4,4'-METHYLENEDIANILINE, 1,1-DICHLOROETHENE) were used as the positive class in defining this signature. The negative class was composed of 3, 5, 7 day experiments with absolute segmented neutrophil counts within 1 standard deviation of historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 73.7
Specificity (% True Negative): 93.6
Log Odds Ratio: 3.7

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: NYSTATIN_134mpk_3d = 1, IBUPROFEN_263mpk_5d = 1, 4,4'-METHYLENEDIANILINE_81mpk_5d = 1.

Hepatic fibrosis

Signature_identifier: SV0651050R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic fibrosis.

Training Set Description: Liver expression data from <=7 day experiments inducing hepatic fibrosis with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combination (22 experiments, 6 compounds, including 1-NAPHTHYL ISOTHIOCYANATE, 4,4'-METHYLENEDIANILINE, ALLYL ALCOHOL, CARMUSTINE, CROTAMITON) were used as the positive class in defining this signature. The negative class was composed of <=7 day experiments that did not cause hepatic fibrosis (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 58.9
Specificity (% True Negative): 99.5
Log Odds Ratio: 5.6

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: 1-NAPHTHYL ISOTHIOCYANATE_30mpk_7d = 2.26, ALLYL ALCOHOL_32mpk_1d = 1.39, LOMUSTINE_8.75mpk_5d = 1.26.

Bile duct hyperplasia

Signature_identifier: SV0650090R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused bile duct hyperplasia.

Training Set Description: Liver expression data from >=3 day experiments inducing bile duct hyperplasia in at least 2 of 3 animals or additional earlier timepoints for positive compound-dose combination (18 experiments, 9 compounds, including 1-NAPHTHYL ISOTHIOCYANATE, 4,4'-METHYLENEDIANILINE, CARVEDILOL, LOMUSTINE, VINBLASTINE) were used as the positive class in defining this signature. The negative class was composed of >=3 day experiments that did not cause bile duct hyperplasia, but not other doses of compounds in the positive class or experiments causing bile duct hyperplasia in 1 of 3 animals.

Sensitivity (% True Positive): 56.9
Specificity (% True Negative): 99.6
Log Odds Ratio: 5.7

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: 4,4'-METHYLENEDIANILINE_81mpk_5d = 2.09, CARMUSTINE_16mpk_5d = 2.04, 1-NAPHTHYL ISOTHIOCYANATE_60mpk_7d = 1.76.

Bile duct hyperplasia, early gene expression

Signature_identifier: SV0620027R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused bile duct hyperplasia at a later time-point.

Training Set Description: Liver expression data from 3 day experiments inducing bile duct hyperplasia with a ridit p-value <=0.05 at later time-points (10 experiments, 9 compounds, including 1-NAPHTHYL ISOTHIOCYANATE, 4,4'-METHYLENEDIANILINE, CARVEDILOL, LOMUSTINE, VINBLASTINE) were used as the positive class in defining this signature. The negative class was composed of 3 day experiments that did not cause bile duct hyperplasia (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 43.8
Specificity (% True Negative): 98.8
Log Odds Ratio: 4.2

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: 4,4'-METHYLENEDIANILINE_81mpk_5d = 2.13, VINBLASTINE_0.3mpk_5d =2, CARMUSTINE_16mpk_5d = 1.75.

Hepatic eosinophilia

Signature_identifier: SV0651095R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic eosinophilia.

Training Set Description: Liver expression data from <=7 day experiments inducing diffuse hepatocellular cytoplasmic eosinophilia with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combination (30 experiments, 8 compounds, including AMINOSALICYLIC ACID, BEZAFIBRATE, CERIVASTATIN, FENOFIBRATE, PIRINIXIC ACID) were used as the positive class in defining this signature. The negative class was composed of <=7 day experiments that did not cause hepatocellular eosinophilia (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 57.5
Specificity (% True Negative): 98.8
Log Odds Ratio: 4.7

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: NAFENOPIN_338mpk_5d = 2.69, NAFENOPIN_338mpk_3d = 2.31, PIRINIXIC ACID_364mpk_5d = 2.

Hepatic eosinophilia, early gene expression

Signature_identifier: SV0651105R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic eosinophilia at a later time-point.

Training Set Description: Liver expression data from <=1 day experiments inducing diffuse hepatocellular cytoplasmic eosinophilia with a ridit p-value <=0.05 at later timepoints or additional earlier timepoints for positive compound-dose combination (13 experiments, 8 compounds, including AMINOSALICYLIC ACID, BEZAFIBRATE, CERIVASTATIN, FENOFIBRATE, PIRINIXIC ACID) were used as the positive class in defining this signature. The negative class was composed of <=1 day experiments that did not cause hepatocellular cytoplasmic eosinophilia (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 48.3
Specificity (% True Negative): 99.1
Log Odds Ratio: 4.6

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: SIMVASTATIN_1200mpk_3d = 2.63, FENOFIBRATE_100mpk_3d = 2.32, CERIVASTATIN_7mpk_3d = 2.27.

Hepatic centrilobular inflammatory infiltrate

Signature_identifier: SV0651068R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic centrilobular inflammatory infiltrate.

Training Set Description: Liver expression data from <=7 day experiments inducing hepatic centrilobular inflammatory cell infiltrate with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combination (15 experiments, 6 compounds, including 1,1-DICHLOROETHENE, CLOFIBRATE, DIGOXIN, LPS, LOMEFLOXACIN) were used as the positive class in defining this signature. The negative class was composed of <=7 day experimentsthat did not cause hepatic inflammatory cell infiltrate (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 40.8
Specificity (% True Negative): 98.9
Log Odds Ratio: 4.1

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: LPS_1.25mpk_0.25d = 2.68, LPS_1.25mpk_1d = 1.20, ETODOLAC_24mpk_5d = 1.12.

Hepatic inflammatory infiltrate, early gene expression

Signature_identifier: SV0651144R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic Inflammatory cell infiltrate at a later time-point.

Training Set Description: Liver expression data from <=1 day experiments inducing hepatic lymphoid inflammatory cell infiltrate with a ridit p-value <=0.05 at later timepoints or additional earlier timepoints for positive compound-dose combination (6 experiments, 4 compounds, including 1,1-DICHLOROETHENE, DIGOXIN, LPS, 4,4'-METHYLENEDIANILINE) were used as the positive class in defining this signature. The negative class was composed of <=1 day experiments that did not cause hepatic inflammatory cell infiltrate (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 61.7
Specificity (% True Negative): 99.8
Log Odds Ratio: 6.2

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: MELOXICAM_33mpk_5d = 4.33, SULINDAC_132mpk_5d = 3.73, RUFLUOMILAST_17mpk_4d = 3.63.

Hepatic centrilobular lipid accumulation, microvesicular

Signature_identifier: SV0650122R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic centrilobular lipid accumulation, microvesicular.

Training Set Description: Liver expression data from >=3 day experiments inducing hepatic centrilobular lipid accumulation, microvesicular in at least 2 of 3 animals or additional earlier timepoints for positive compound-dose combination (10 experiments, 4 compounds, including SULINDAC, MICONAZOLE, INDOMETHACIN, CHLOROFORM) were used as the positive class in defining this signature. The negative class was composed of >=3 day experiments that did not cause hepatic lipid accumulation (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 43.8
Specificity (% True Negative): 98.8
Log Odds Ratio: 4.1

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: MICONAZOLE_920mpk_5d = 2.50, CHLOROFORM_600mpk_1d = 2.39, MICONAZOLE_920mpk_3d = 1.

Hepatic lipid accumulation, macrovesicular

Signature_identifier: SA0652002R40000QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic lipid accumulation, macrovesicular.

Training Set Description: Liver expression data from <=7 day experiments inducing hepatic lipid accumulation, macrovesicular with a ridit p-value <0.05 or additional earlier timepoints for positive compound-dose combination (70 experiments, 18 compounds, including CARBON TETRACHLORIDE, CLOTRIMAZOLE, ETHINYLESTRADIOL, HYDRAZINE, MICONAZOLE) were used as the positive class in defining this signature. The negative class was composed of <=7 day experiments that did not cause hepatic lipid accumulation (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 50.4
Specificity (% True Negative): 98.8
Log Odds Ratio: 4.4

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: MICONAZOLE_920mpk_3d = 2.40, CLOTRIMAZOLE_178mpk_5d = 2.16, MICONAZOLE_920mpk_5d = 1.55.

Hepatic hypertrophy, centrilobular

Signature_identifier: SV0651136R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic centrilobular hypertrophy.

Training Set Description: Liver expression data from <=7 day experiments inducing hepatic centrilobular hypertrophy with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combination (29 experiments, 9 compounds, including ANASTROZOLE, FLUCONAZOLE, NORETHINDRONE ACETATE, PHENOBARBITAL, SAFROLE) were used as the positive class in defining this signature. The negative class was composed of <= 7 day experiments that did not cause hepatic hypertrophy (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 45
Specificity (% True Negative): 98.6
Log Odds Ratio: 4.1

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: DEXAMETHASONE_1mpk_5d = 1.51, SAFROLE_488mpk_5d = 1.44, MICONAZOLE_920mpk_5d = 1.01.

Hepatic necrosis

Signature_identifier: SA0651115R34000QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused hepatic necrosis.

Training Set Description: Liver expression data from <=7 day experiments inducing hepatic nonzonal necrosis with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combination (40 experiments, 11 compounds, including 1-NAPHTHYL ISOTHIOCYANATE, ALLYL ALCOHOL, ANASTROZOLE, CLOTRIMAZOLE, LORAZEPAM) were used as the positive class in defining this signature. The negative class was composed of <=7 day experiments that did not cause hepatic necrosis (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 33.1
Specificity (% True Negative): 96.1
Log Odds Ratio: 2.5

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: 1-NAPHTHYL ISOTHIOCYANATE_30mpk_3d = 1.10, EPIRUBICIN_2.7mpk_5d = 1.02, BETAMETHASONE_79mpk_1d =1.01.

Hepatocellular hypertrophy, diffuse

Signature_identifier: SV0651020R5QU
Array Platform: Affymetrix RG230 v2
Type: Histopathology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused diffuse hepatocellular hypertrophy.

Training Set Description: Liver expression data from <=7 day experiments inducing diffuse hepatocellular hypertrophy with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combination (37 experiments, 9 compounds, including PIRINIXIC ACID, CARMUSTINE, FENOFIBRATE, FLUVASTATIN, VINBLASTINE) were used as the positive class in defining this signature. The negative class was composed of <=7 day experiments that did not cause hepatocellular hypertrophy (ridit p-value>=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 59.7
Specificity (% True Negative): 98.1
Log Odds Ratio: 4.3

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: NAFENOPIN_338mpk_5d = 3.31, NAFENOPIN_338mpk_3d = 2.95, PIRINIXIC ACID_364mpk_3d = 2.63.

Pregnane X receptor activation

Signature_identifier: SV0126005R5QU
Array Platform: Affymetrix RG230 v2
Type: Literature
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with compounds reported in the literature as pregnane X receptor activators.

Training Set Description: Liver expression data from medium and high dose experiments with compounds reported in the literature as pregnane X receptor activators (22 experiments, 5 compounds, including CLOTRIMAZOLE, CYPROTERONE ACETATE, DEXAMETHASOME, MICONAZOLE, MIFEPRISTONE) were used as the positive class in defining this signature. The negative class was composed of experiments with compounds known not to be pregnane X receptor activators.

Sensitivity (% True Positive): 95.6
Specificity (% True Negative): 98.7
Log Odds Ratio: 7.3

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: DEXAMETHASONE_150mpk_3d = 3.83, ANASTROZOLE_400mpk_5d = 3.74, DEXAMETHASONE_150mpk_.25d = 3.32.

Cholesterol biosynthesis inhibitor

Signature_identifier: SV0599213R5QU
Array Platform: Affymetrix RG230 v2
Type: Structure Activity Class
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with compounds having the DrugMatrix activity class annotation cholesterol biosynthesis inhibitor.

Training Set Description: Liver expression data from 3, 5, 7 day high dose experiments with the activity class annotation cholesterol biosynthesis inhibitor (7 experiments, 4 compounds, including CERIVASTATIN, FLUVASTATIN, LOVASTATIN, SIMVASTATIN) were used as the positive class in defining this signature. The negative class was composed of all other liver 3, 5, 7 day high dose experiments.

Sensitivity (% True Positive): 100
Specificity (% True Negative): 100
Log Odds Ratio: 13.3

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: SIMVASTATIN_1200mpk_3d = 1.83, FLUVASTATIN_94mpk_5d = 1.60, FLUVASTATIN_94mpk_3d = 1.41.

Thyroperoxidase inhibitor

Signature_identifier: SV0599426R5QU
Array Platform: Affymetrix RG230 v2
Type: Structure Activity Class
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with compounds having the DrugMatrix activity class annotation thyroperoxidase inhibitor.

Training Set Description: Liver expression data from 0.25, 1, 3, 5 ,7 day high dose experiments with the activity class annotation thyroperoxidase inhibitor (8 experiments, 3 compounds, including CARBIMAZOLE, METHIMAZOLE, PROPYLTHIOURACIL) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5, 7 day high dose experiments

Sensitivity (% True Positive): 34.4
Specificity (% True Negative): 99.9
Log Odds Ratio: 6.7

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: CARBIMAZOLE_400mpk_5d = 1.21, PROPYLTHIOURACIL_625mpk_1d = 1.11, CARBIMAZOLE_400mpk_3d = 1.

Toxicant, DNA alkylator

Signature_identifier: SV0599162R5QU
Array Platform: Affymetrix RG230 v2
Type: Structure Activity Class
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with compounds having the DrugMatrix structure activity class annotation toxicant, DNA alkylator.

Training Set Description: Liver expression data from 3, 5 ,7 day high dose experiments with the structure activity class annotation toxicant, DNA alkylator (10 experiments, 6 compounds, including 2-ACETYLAMINOFLUORENE, 4,4'-METHYLENEDIANILINE, AFLATOXIN B1, HYDRAZINE, N-NITROSODIETHYLAMINE) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5, 7 day high dose experiments.

Sensitivity (% True Positive): 48.2
Specificity (% True Negative): 99.2
Log Odds Ratio: 4.7

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: AFLATOXIN B1_0.3mpk_5d = 2.04, AFLATOXIN B1_0.3mpk_3d = 1.24, 2-ACETYLAMINOFLUORENE_30mpk_3d = 1.

Peroxisome proliferator

Signature_identifier: SV0594006R5QU
Array Platform: Affymetrix RG230 v2
Type: Structure Activity Class and Pharmacology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with compounds having the DrugMatrix activity class annotation peroxisome proliferator.

Training Set Description: Liver expression data from <=7 day experiments with the activity class annotation peroxisome proliferator (41 experiments, 8 compounds, including BEZAFIBRATE, CLOFIBRATE, FENOFIBRATE, GEMFIBROZIL, PIRINIXIC ACID) were used as the positive class in defining this signature. The negative class was composed of all other liver <=7 day experiments, but not valproic acid, ticrynafen, or experiments with the structure activity class annotation PPAR gamma agonist, thiazolidinedione, antidiabetic.

Sensitivity (% True Positive): 71.2
Specificity (% True Negative): 99.8
Log Odds Ratio: 7.2

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: FENOFIBRATE_100mpk_7d = 4.76, PIRINIXIC ACID_364mpk_3d = 3.29, BEZAFIBRATE_617mpk_7d = 3.24.

Glucocorticoid and mineralocorticoid receptor agonist

Signature_identifier: SV0594002R5QU
Array Platform: Affymetrix RG230 v2
Type: Structure Activity Class and Pharmacology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with compounds having the DrugMatrix activity class annotation glucocorticoid and mineralocorticoid receptor agonist

Training Set Description: Liver expression data from <=7 day experiments with the activity class annotation glucocorticoid and mineralocorticoid receptor agonist (21 experiments, 7 compounds, including BETAMETHASONE, DEXAMETHASONE, FLUOCINOLONE ACETONIDE, HYDROCORTISONE, CORTISONE) were used as the positive class in defining this signature. The negative class was composed of all other liver <=7 day experiments, but not compounds that bind the glucocorticoid receptor with >=70% inhibition.

Sensitivity (% True Positive): 59.4
Specificity (% True Negative): 99.2
Log Odds Ratio: 5.3

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: BETAMETHASONE_79mpk_5d = 1.82, BETAMETHASONE_79mpk_1d = 1.47, HYDROCORTISONE_56mpk_3d = 1.27.

Estrogen receptor agonist

Signature_identifier: SV0594024R5QU
Array Platform: Affymetrix RG230 v2
Type: Structure Activity Class and Pharmacology
Tissue: LIVER

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment causes a pattern of gene expression changes specifically associated with compounds having the DrugMatrix activity class annotation estrogen receptor agonist

Training Set Description: Liver expression data from <=7 day high dose experiments with the activity class annotation estrogen receptor agonist (16 experiments, 5 compounds, including BETA-ESTRADIOL, DIETHYLSTILBESTROL, ESTRIOL, ETHINYLESTRADIOL, MESTRANOL) were used as the positive class in defining this signature. The negative class was composed of all other liver <=7 day high dose experiments, but not experiments with the structure activity class annotation estrogen receptor antagonist/agonist, or toxicant, estrogen receptor agonist, or compounds that bind the estrogen receptor alpha and beta with >70% inhibition.

Sensitivity (% True Positive): 88.5
Specificity (% True Negative): 99.3
Log Odds Ratio: 7

High Scoring Treatments: The three highest scalar product scores against this Signature among DrugMatrix treatments are: ESTRIOL_313mpk_5d = 3.89, MESTRANOL_250mpk_5d = 3.66, BETA-ESTRADIOL_150mpk_5d = 2.96.

Heart Signatures

Lymphopenia

Signature_identifier: SA0560070R40000RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused lymphocyte decrease.

Training Set Description: Heart expression data from 0.25, 1, 3, 5 and 7 day experiments reducing absolute lymphocyte counts lower than the historical control mean by 2 standard deviations (21 experiments, 11 compounds, including CHLORAMBUCIL, CYCLOPHOSPHAMIDE, DAUNORUBICIN, DEXAMETHASONE, FLUDROCORTISONE ACETATE) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5 and 7 day heart experiments with absolute lymphocyte counts within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 81.7
Specificity (% True Negative): 99.9
Log Odds Ratio: 8.7

Adrenergic agonist

Signature_identifier: SA0666001R34280RU
Array Platform: Codelink RU1
Type: Literature
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds reported in the literature as adrenergic receptor agonists.

Training Set Description: Heart expression data from <=7 day experiments at high dose with the activity class annotation adrenergic receptor agonist (35 experiments, 11 compounds, including CLONIDINE, DOBUTAMINE, EPINEPHRINE, ISOPRENALINE, METHYLDOPA) were used as the positive class in defining this signature. The negative class was composed of all other <=7 day high dose heart experiments, but not compounds that bind adrenergic receptors alpha 1A, 1B, 1D, 2A, 2B, 2C and beta 1, 2 and 3 with >=70%.

Sensitivity (% True Positive): 43.8
Specificity (% True Negative): 97.8
Log Odds Ratio: 3.5

Hypoalbuminemia

Signature_identifier: SV0560021R5NU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused albumin decrease.

Training Set Description: Heart expression data from 3, 5 and 7 day experiments reducing albumin level lower than the historical control mean by 2 standard deviations and other doses for positive treatments (31 experiments, 18 compounds, including ACROLEIN, BENZETHONIUM CHLORIDE, CELEXIB, CLEMASTINE, PRAMOXINE) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day heart experiments with albumin level within 1 standard deviation of the historical control mean, but not other time points of compounds in the positive class.

Sensitivity (% True Positive): 48.1
Specificity (% True Negative): 98.4
Log Odds Ratio: 4.1

DNA damage, intercalation

Signature_identifier: SA0592024R20509RU
Array Platform: Codelink RU1
Type: Structure Activity Class and Pharmacology
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation DNA damage, intercalation.

Training Set Description: Heart expression data from <=7 day experiments with the structure activity class annotation DNA intercalator or DNA intercalator, anthracyclin (18 experiments, 5 compounds, including DAUNORUBICIN, DOXORUBICIN, EPIRUBICIN, IDARUBICIN, MITOXANTRONE) were used as the positive class in defining this signature. The negative class was composed of all other <=7 day heart experiments, but not compounds with the structure activity class annotation of DNA damager or toxicant, DNA damaging.

Sensitivity (% True Positive): 86.8
Specificity (% True Negative): 99.7
Log Odds Ratio: 7.5

Glucocorticoid and mineralocorticoid agonist

Signature_identifier: SV0597002R5RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation glucocorticoid and mineralocorticoid receptor agonist.

Training Set Description: Heart expression data from 0.25 and 1 day low dose experiments with activity class annotation glucocorticoid and mineralocorticoid receptor agonist (7 experiments, 7 compounds, including ALDOSTERONE, CORTISONE, FLUDROCORTISONE ACETATE, FLUOCINOLONE ACETONIDE, HYDROCORTISONE) were used as the positive class in defining this signature. The negative class was composed of all other heart 0.25 and 1 day low dose experiments.

Sensitivity (% True Positive): 58.3
Specificity (% True Negative): 98.9
Log Odds Ratio: 4.8

Cardiac cellular infiltration

Signature_identifier: SV0660005R5RU
Array Platform: Codelink RU1
Type: Histopathology
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused cardiac cellular infiltrate.

Training Set Description: Heart expression data from <=7 day experiments inducing heart cellular infiltration with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combinations (21 experiments, 7 compounds, including ACONITINE, ALLYLAMINE, DOBUTAMINE, METOPROLOL, TERBUTALINE) were used as the positive class in defining this signature. The negative class was composed of all other <=7 day heart experiments that did not cause cardiac cellular infiltration (ridit p-value >= 0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 50. 6
Specificity (% True Negative): 98.6
Log Odds Ratio: 4.3

Neutrophilia

Signature_identifier: SA0565012R40000RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused neutrophil increase.

Training Set Description: Heart expression data from 3, 5 and 7 day experiments inducing neutrophil count higher than the historical control mean by 2 standard deviations and other doses for positive treatments (47 experiments, 30 compounds, including ACROLEIN, CELECOXIB, CLEMASTINE, DEXAMETHASONE, ROFLUMILAST) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day heart experiments with neutrophil counts within 1 standard deviation of the historical control mean, but not other time points of compounds in the positive class.

Sensitivity (% True Positive): 47.1
Specificity (% True Negative): 99.0
Log Odds Ratio: 4.5

PDE4 inhibitor

Signature_identifier: SV0597192R5RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation PDE4 inhibitor.

Training Set Description: Heart expression data from 0.25, 1, 3, 5 and 7 day low dose experiments with the structure activity class annotation PDE4 inhibitor (10 experiments, 4 compounds, including PICLAMILAST, ROFLUMILAST, ROLIPRAM, SCH-351591) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5, 7 day low dose heart experiments.

Sensitivity (% True Positive): 50.0
Specificity (% True Negative): 99.4
Log Odds Ratio: 5.2

Peroxisome proliferator

Signature_identifier: SA0597193R14740RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation peroxisome proliferator.

Training Set Description: Heart expression data from 0.25, 1, 3, 5 and 7 day low dose experiments with activity class annotation peroxisome proliferator (7 experiments, 3 compounds, including BEZAFIBRATE, FENOFIBRATE, CLOFIBRIC ACID) were used as the positive class in defining this signature. The negative class was composed of all other heart 0.25, 1, 3, 5 and 7 day low dose experiments.

Sensitivity (% True Positive): 55.7
Specificity (% True Negative): 99.6
Log Odds Ratio: 5.8

Toxicant, DNA damaging

Signature_identifier: SV0597065R5RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: HEART

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation toxicant, DNA damager.

Training Set Description: Heart expression data from 3, 5 ,7 day low dose experiments with the activity class annotation toxicant, DNA damaging (10 experiments, 5 compounds, including 1, 2, 3-TRICHLOROPROPANE, 2-AMINO-4-NITROPHENOL, ACROLEIN, CHLOROBENZENE, FURAN) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5, 7 day low dose heart experiments.

Sensitivity (% True Positive): 62.5
Specificity (% True Negative): 99.3
Log Odds Ratio: 5.4

Kidney Signatures

Lymphopenia

Signature_identifier: SV0561103R5RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused lymphocyte decrease.

Training Set Description: Kidney expression data from 0.25, 1, 3, 5 and 7 day experiments reducing absolute lymphocyte counts lower than the historical control mean by 2 standard deviations (25 experiments, 19 compounds, including AMIKACIN, CARBOPLATIN, DAUNORUBICIN, FLUDROCORTISONE ACETATE, NETILMICIN) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5 and 7 day kidney experiments with absolute lymphocyte counts within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 87.0
Specificity (% True Negative): 99.4
Log Odds Ratio: 7.0

Hypoalbuminemia

Signature_identifier: SA0561029R40000RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused albumin decrease.

Training Set Description: Kidney expression data from 3, 5 and 7 day experiments reducing albumin level lower than the historical control mean by 2 standard deviations (74 experiments, 43 compounds, including 4,4'-METHYLENEDIANILINE, AMPIROXICAM, AZAURIDINE, CALCITRIOL, FLURBIPROFEN) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day heart experiments with albumin level within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 60.2
Specificity (% True Negative): 98.7
Log Odds Ratio: 4.7

Angiotensin converting enzyme (ACE) inhibitor

Signature_identifier: SA0593009R14400RU
Array Platform: Codelink RU1
Type: Structure Activity Class and Pharmacology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation angiotensin converting enzyme (ACE) inhibitor.

Training Set Description: Kidney expression data from <=7 day experiments at high dose with the structure activity class annotation angiotensin converting enzyme (ACE) inhibitor (19 experiments, 6 compounds, including BENAZEPRIL, CAPTOPRIL,ENALAPRIL, LISINOPRIL, QUINAPRIL) were used as the positive class in defining this signature. The negative class was composed of all other <=7 day high dose kidney experiments, but not compounds with the activity class annotation of RAAS inhibitors.

Sensitivity (% True Positive): 48.6
Specificity (% True Negative): 99.8
Log Odds Ratio: 6.1

Angiotensin receptor AT1 antagonist

Signature_identifier: SA0613117R34375RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation PDE4 inhibitor.

Training Set Description: Kidney expression data from 0.25, 1, 3, 5 and 7 day low dose experiments with the activity class annotation angiotensin receptor AT1 antagonist (9 experiments, 3 compounds, including CANDESARTAN, LOSARTAN, VALSARTAN) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5 and 7 day low dose kidney experiments, but not compounds with the activity class annotation of RAAS inhibitors.

Sensitivity (% True Positive): 55
Specificity (% True Negative): 100
Log Odds Ratio: 9.5

DNA intercalator, anthracycline-like

Signature_identifier: SV0613073R5NU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation DNA intercalator, anthracycline-like.

Training Set Description: Kidney expression data from 3, 5 and 7 day experiments with the activity class annotation DNA intercalator anthracycline (12 experiments, 4 compounds, including DAUNORUBICIN, DOXORUBICIN, EPIRUBICIN, IDARUBICIN) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day kidney experiments, but not compounds with the activity class annotation of DNA damager.

Sensitivity (% True Positive): 78.7
Specificity (% True Negative): 99.9
Log Odds Ratio: 7.9

Erythrocyte count increase

Signature_identifier: SV0566121R5RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused erythrocyte count increase.

Training Set Description: Kidney expression data from 0.25, 1, 3, 5 and 7 day experiments inducing erythrocyte counts higher than the historical control mean by 2 standard deviations (12 experiments, 9 compounds, including AMIKACIN, CARBOPLATIN, FURAN, NEOMYCIN, ROXITHROMYCIN) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5 and 7 day kidney experiments with erythrocyte counts within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 53
Specificity (% True Negative): 99.2
Log Odds Ratio: 4.9

Estrogen receptor alpha binding

Signature_identifier: SA0608062R40140RU
Array Platform: Codelink RU1
Type: Pharmacology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that bind to the estrogen receptor alpha in vitro.

Training Set Description: Kidney expression data from 0.25, 1, 3, 5, 7 day low dose experiments with compounds that bind the estrogen receptor alpha with an IC50 <= 1 micromolar (10 experiments, 3 compounds, including 4-NONYLPHENOL, BETA-ESTRADIOL, DIETHYLSTILBESTROL) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5, 7 day low dose kidney experiments for compounds that bind the estogen receptor alpha with <70% inhibition.

Sensitivity (% True Positive): 69.2
Specificity (% True Negative): 99.9
Log Odds Ratio: 8.0

Glucocorticoid and mineralocorticoid receptor agonist

Signature_identifier: SA0598107R34280RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation glucocorticoid and mineralocorticoid receptor agonist.

Training Set Description: Kidney expression data from 3, 5 and 7 day low dose experiments with the activity class annotation glucocorticoid and mineralocorticoid receptor agonist (15 experiments, 8 compounds, including ALDOSTERONE, DEXAMETHASONE, HYDROCORTISONE, PREDNISOLONE, PREDNISONE) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day low dose kidney experiments.

Sensitivity (% True Positive): 63.7
Specificity (% True Negative): 99.9
Log Odds Ratio: 7.2

Renal tubular hyaline droplet accumulation, early gene expression

Signature_identifier: SV0661001R5NU
Array Platform: Codelink RU1
Type: Histopathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused renal tubular hyaline droplet accumulation.

Training Set Description: Kidney expression data from <=1 day experiments inducing hyaline droplet accumulation in at least 2 of 3 animals at later time points (7 experiments, 7 compounds, including HEXACHLOROETHANE, ACETONE, 1,4-DICHLOROBENZENE, 4-NITROTOLUENE, D-LIMONENE) were used as the positive class in defining this signature. The negative class was composed of all other <=1 day kidney experiments that did not cause hyaline droplet accumulation in all animals, but not lower doses for positive treatments.

Sensitivity (% True Positive): 43.3
Specificity (% True Negative): 98.8
Log Odds Ratio: 4.1

Renal tubular dilatation

Signature_identifier: SV0662007R5RU
Array Platform: Codelink RU1
Type: Histopathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused renal cortex tubular dilatation.

Training Set Description: Kidney expression data from <=7 day experiments inducing renal cortex tubular dilatation with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combinations (12 experiments, 4 compounds, including NIMESULIDE, 1-NAPHTHYL ISOTHIOCYANATE, ALLOPURINOL, PENCICLOVIR) were used as the positive class in defining this signature. The negative class was composed of all other <=7 day kidney experiments that did not cause renal cortex tubular dilatation (ridit p-value >=0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 47
Specificity (% True Negative): 99.4
Log Odds Ratio: 5.0

Renal tubular necrosis, early gene expression

Signature_identifier: SV0662004R5RU
Array Platform: Codelink RU1
Type: Histopathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused renal cortex tubular necrosis.

Training Set Description: Kidney expression data from <=1 day experiments inducing renal cortex tubular necrosis with a ridit p-value <=0.05 for compound-dose combinations at later time points (10 experiments, 8 compounds, including BACITRACIN, CALCITRIOL, CISPLATIN, GENTAMICIN, LEAD(II) ACETATE) were used as the positive class in defining this signature. The negative class was composed of all other <=1 day kidney experiments that did not cause renal cortex tubular necrosis (ridit p-value >= 0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 46.2
Specificity (% True Negative): 98.7
Log Odds Ratio: 4.1

Renal tubular necrosis

Signature_identifier: SV0662005R5NU
Array Platform: Codelink RU1
Type: Histopathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused cortex tubule necrosis in kidney.

Training Set Description: Kidney expression data from <=7 day experiments inducing renal cortex tubular necrosis with a ridit p-value <=0.05 or additional earlier timepoints for positive compound-dose combinations (28 experiments, 8 compounds, including VANCOMYCIN, 2-AMINO-4-NITROPHENOL, BACITRACIN, LEAD(II) ACETATE, CALCITRIOL) were used as the positive class in defining this signature. The negative class was composed of all other <=7 day kidney experiments that did not cause renal cortex tubular necrosis (ridit p-value >= 0.5), but not lower doses for positive treatments.

Sensitivity (% True Positive): 62.9
Specificity (% True Negative): 99.4
Log Odds Ratio: 5.6

Renal tubular hyaline droplet accumulation

Signature_identifier: SV0661011R5NU
Array Platform: Codelink RU1
Type: Histopathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused renal tubular hyaline droplet accumulation.

Training Set Description: Kidney expression data from >=3 day experiments inducing renal tubular hyaline droplet accumulation in at least 2 of 3 animals (14 experiments, 7 compounds, including 1,4-DICHLOROBENZENE, ACETONE, D-LIMONENE, GENTAMICIN, HEXACHLOROETHANE) were used as the positive class in defining this signature. The negative class was composed of all other >=3 day kidney experiments that did not cause renal tubular hyaline droplet accumulation in any animal, but not lower doses for positive treatments.

Sensitivity (% True Positive): 56.7
Specificity (% True Negative): 99.0
Log Odds Ratio: 4.8

Leukocytosis

Signature_identifier: SV0561020R5RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused leukocyte count decrease.

Training Set Description: Kidney expression data from 3, 5 and 7 day experiments reducing leukocyte counts lower than the historical control mean by 2 standard deviations (15 experiments, 8 compounds, including AMIKACIN, CYTARABINE, DOXORUBICIN, LEFLUNOMIDE, OXALIPLATIN) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day kidney experiments with leukocyte counts within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 65
Specificity (% True Negative): 99.3
Log Odds Ratio: 5.6

Neutrophilia

Signature_identifier: SA0566012R40000RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused neutrophil increase.

Training Set Description: Kidney expression data from 3, 5 and 7 day experiments inducing neutrophil counts higher than the historical control mean by 2 standard deviations (80 experiments, 42 compounds, including VALDECOXIB, ROXARSONE, PENCICLOVIR, LOVASTATIN, MELOXICAM, FLUOCINOLONE ACETONIDE) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day kidney experiments with neutrophil counts within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 53.6
Specificity (% True Negative): 98.4
Log Odds Ratio: 4.2

Peroxisome proliferator

Signature_identifier: SA0598027R40340RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation peroxisome proliferator.

Training Set Description: Kidney expression data from 0.25 and 1 day low dose experiments with the activity class annotation peroxisome proliferator (8 experiments, 4 compounds, including BEZAFIBRATE, CHLOFIBRATE, FENOFIBRATE, GEMFIBROZIL) were used as the positive class in defining this signature. The negative class was composed of all other 0.25 and 1 day low dose kidney experiments.

Sensitivity (% True Positive): 77.5
Specificity (% True Negative): 99.5
Log Odds Ratio: 6.4

Renin-angiotension-aldosterone synthesis inhibitor

Signature_identifier: SA0598338R14340RU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation renin-angiotensin-aldosterone synthesis inhibitor.

Training Set Description: Kidney expression data from 0.25, 1, 3, 5, 7 day experiments with the activity class annotation RAAS inhibitor (31 experiments, 10 compounds, including CANDESARTAN, QUINAPRIL, LOSARTAN, ENALAPRIL, VALSARTAN) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5, 7 day kidney experiments.

Sensitivity (% True Positive): 66.8
Specificity (% True Negative): 99.7
Log Odds Ratio: 6.5

Nephromegaly

Signature_identifier: SV0644006R5NU
Array Platform: Codelink RU1
Type: Body and Organ Weights
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused an increase in kidney weight.

Training Set Description: Kidney expression data from 0.25, 1, 3, 5, 7 day experiments with compounds that caused a relative kidney weight higher than historical control mean by over 2 standard deviations (28 experiments, 21 compounds, including ACECLOFENAC, ALLOPURINOL, CALCITRIOL, LEAD(IV) ACETATE, NIMESULIDE) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5, 7 day kidney experiments with relative kidney weight within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 46.2
Specificity (% True Negative): 99.2
Log Odds Ratio: 4.7

Renal tubular nephrosis

Signature_identifier: SV0661023R5RU
Array Platform: Codelink RU1
Type: Histopathology
Tissue: KIDNEY

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused renal tubular nephrosis.

Training Set Description: Kidney expression data from <=1 day experiments inducing renal tubular nephrosis in at least 2 of 3 animals for compound-dose combinations at later time points (15 experiments, 13 compounds, including ALLOPURINOL, PENCICLOVIR, BECITRACIN, CISPLATIN, LEAD(IV) ACETATE) were used as the positive class in defining this signature. The negative class was composed of all other <=1 day kidney experiments that did not cause renal tubular nephrosis in any animal, but not lower doses for positive treatments.

Sensitivity (% True Positive): 40
Specificity (% True Negative): 98.4
Log Odds Ratio: 3.7

Bone Marrow Signatures

Lymphopenia

Signature_identifier: SV0559022R5RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: BONE MARROW

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused lymphocyte decrease.

Training Set Description: Bone marrow expression data from 3, 5, 7 day experiments reducing absolute lymphocyte counts lower than the historical control mean by 2 standard deviations (9 experiments, 5 compounds, including BETAMETHASONE, CHLORAMBUCIL, CLOBETASOL PROPIONATE, HYDROCORTISONE, THIOGUANINE) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5, 7 day bone marrow experiments with absolute lymphocyte counts within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 65
Specificity (% True Negative): 99.1
Log Odds Ratio: 5.3

Glucocorticoid and mineralocorticoid agonist

Signature_identifier: SV0596054R5NU
Array Platform: Codelink RU1
Type: Structure Activity Class
Tissue: BONE MARROW

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds having the DrugMatrix structure activity class annotation glucocorticoid and mineralocorticoid receptor agonist.

Training Set Description: Bone marrow expression data from 0.25, 1, 3, 5 and 7 day low dose experiments with activity class annotation glucocorticoid and mineralocorticoid receptor agonist (9 experiments, 3 compounds, including BETAMETHASONE, CLOBETASOL PROPIONATE, HYDROCORTISONE) were used as the positive class in defining this signature. The negative class was composed of all other 0.25, 1, 3, 5 and 7 day low dose bone marrow experiments.

Sensitivity (% True Positive): 93.3
Specificity (% True Negative): 99.5
Log Odds Ratio: 7.8

Neutrophilia

Signature_identifier: SV0564004R5RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: BONE MARROW

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused neutrophil increase.

Training Set Description: Bone marrow expression data from 3, 5 and 7 day experiments inducing neutrophil counts higher than the historical control mean by 2 standard deviations and other doses for positive treatments (11 experiments, 8 compounds, including 1-NAPHTHYL ISOTHIOCYANATE, BETAMETHASONE, CLOBETASOL PROPIONATE, HYDROCORTISONE, METHOTREXATE) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day bone marrow experiments with neutrophil counts within 1 standard deviation of the historical control mean, but not other timepoints of compounds in the positive class.

Sensitivity (% True Positive): 65
Specificity (% True Negative): 99.5
Log Odds Ratio: 5.8

Spleen Signatures

Alkaline phosphatase increase

Signature_identifier: SA0568018R20375RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: SPLEEN

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused serum alkaline phsphatase increase.

Training Set Description: Spleen expression data from 3, 5 and 7 day experiments inducing alkyline phosphatase level higher than the historical control mean by 2 standard deviations (9 experiments, 4 compounds, including DIETHYLSTILBESTROL, METHOTREXATE, THIOGUANINE, CARMUSTINE) were used as the positive class in defining this signature. The negative class was composed of 3, 5 and 7 day spleen experiments with alkyline phosphatase level within 1 standard deviation of the historical control mean, but not other timepoints of compounds in the positive class.

Sensitivity (% True Positive): 60
Specificity (% True Negative): 99.8
Log Odds Ratio: 6.3

Aspartate Aminotransferase Increase

Signature_identifier: SV0568022R5NU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: SPLEEN

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused serum aspartate aminotransferase increase.

Training Set Description: Spleen expression data from 3, 5 and 7 day experiments inducing aspartate aminotransferase level higher than the historical control mean by 2 standard deviations and other doses and time points for positive treatments (10 experiments, 4 compounds, including N-NITROSODIETHYLAMINE, N,N-DIMETHYLFORMAMIDE, LOMUSTINE, CARMUSTINE) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day spleen experiments with aspartate aminotransferase level within 1 standard deviation of the historical control mean, but not other timepoints of compounds in the positive class.

Sensitivity (% True Positive): 51.2
Specificity (% True Negative): 98.9
Log Odds Ratio: 4.4

Total bilirubin increase

Signature_identifier: SA0568014R20375RU
Array Platform: Codelink RU1
Type: Clinical Pathology
Tissue: SPLEEN

Signature Interpretation: A positive score against this Drug Signature indicates that the query treatment caused a pattern of gene expression changes specifically associated with DrugMatrix compounds that caused total bilirubin increase.

Training Set Description: Spleen expression data from 3, 5 and 7 day experiments inducing total bilirubin level higher than the historical control mean by 2 standard deviations (6 experiments, 3 compounds, including CARMUSTINE, DIETHYLSTILBESTROL, CYCLOSPORIN A) were used as the positive class in defining this signature. The negative class was composed of all other 3, 5 and 7 day spleen experiments with total bilirubin level within 1 standard deviation of the historical control mean, but not other doses of compounds in the positive class.

Sensitivity (% True Positive): 58.3
Specificity (% True Negative): 98.8
Log Odds Ratio: 4.7