Supplementary Materials and Legends

Identification of Early Liver Toxicity Gene Biomarkers Using Comparative Supervised Machine Learning

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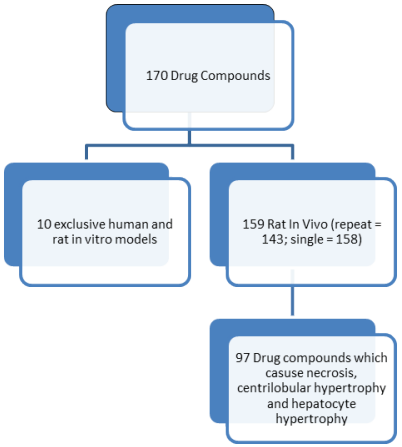
Supplementary Figure 1: A. Overview of the compounds in TG-GATES data. **B.** Experimental design. Timeline and doses used for experiments in TG-GATES database **C.** Flow chart for development of the ML pipeline.

All graphs are generated using Graph is generated using Powerpoint software (Microsoft Corporation, Seattle, WA, USA).

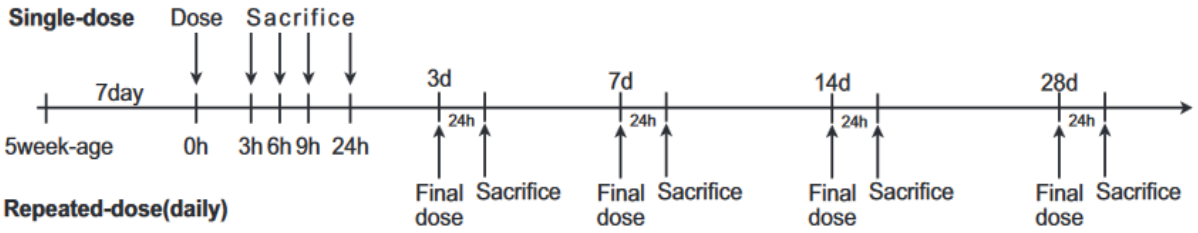
Supplementary Figure 2: GSEA analysis of clusters related to Figure 2. Upper panel graphs are generated by Graphpad© Prism8 software (GraphPad Software Inc., La Jolla, CA, www.graphpad.com). Lower panels are generated using Gene Set Enrichment Analysis software (https://www.gsea-msigdb.org/gsea/index.jsp) [31,32].

Supplementary Figure 3: Evaluation of average ROC for gene sets up to **A.** 50 and **B.** 100 . Figures are generated using Tableau software (Seattle, WA, USA, https://www.tableau.com/).

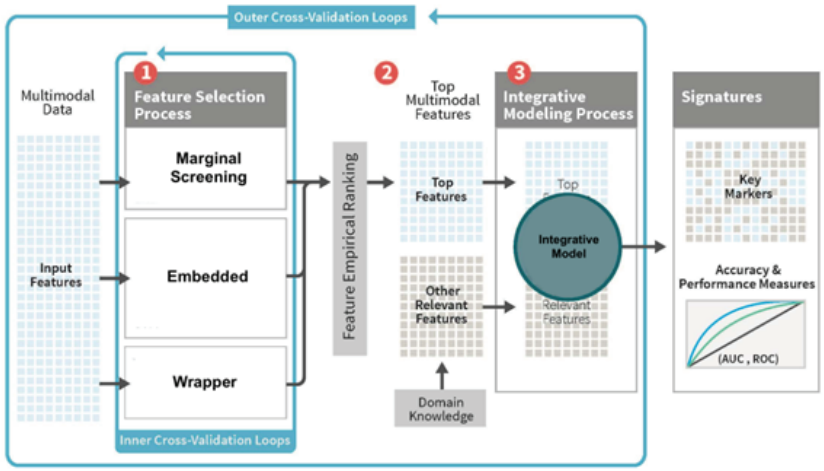
A

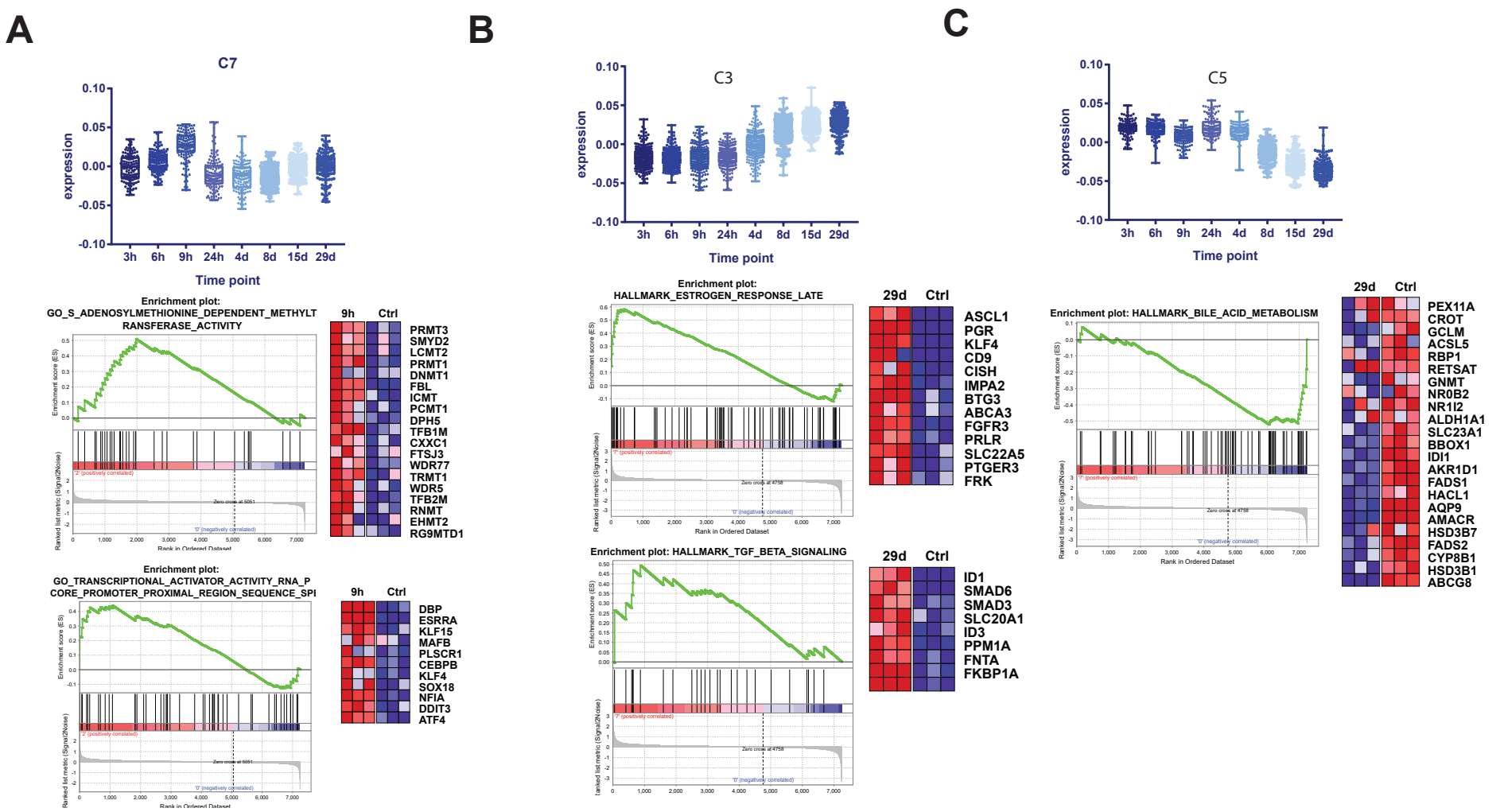

170 Drug Compounds
10 exclusive human and rat in vitro models
159 Rat In Vivo (repeat = 143; single = 158)
97 Drug compounds which casuse necrosis, centrilobular hypertrophy and hepatocyte hypertrophy

B


Single-dose
Dose
Sacrifice
7day
5week-age
0h
3h 6h 9h 24h
3d
7d
14d
28d
24h
Final dose
Sacrifice
Repeated-dose(daily)

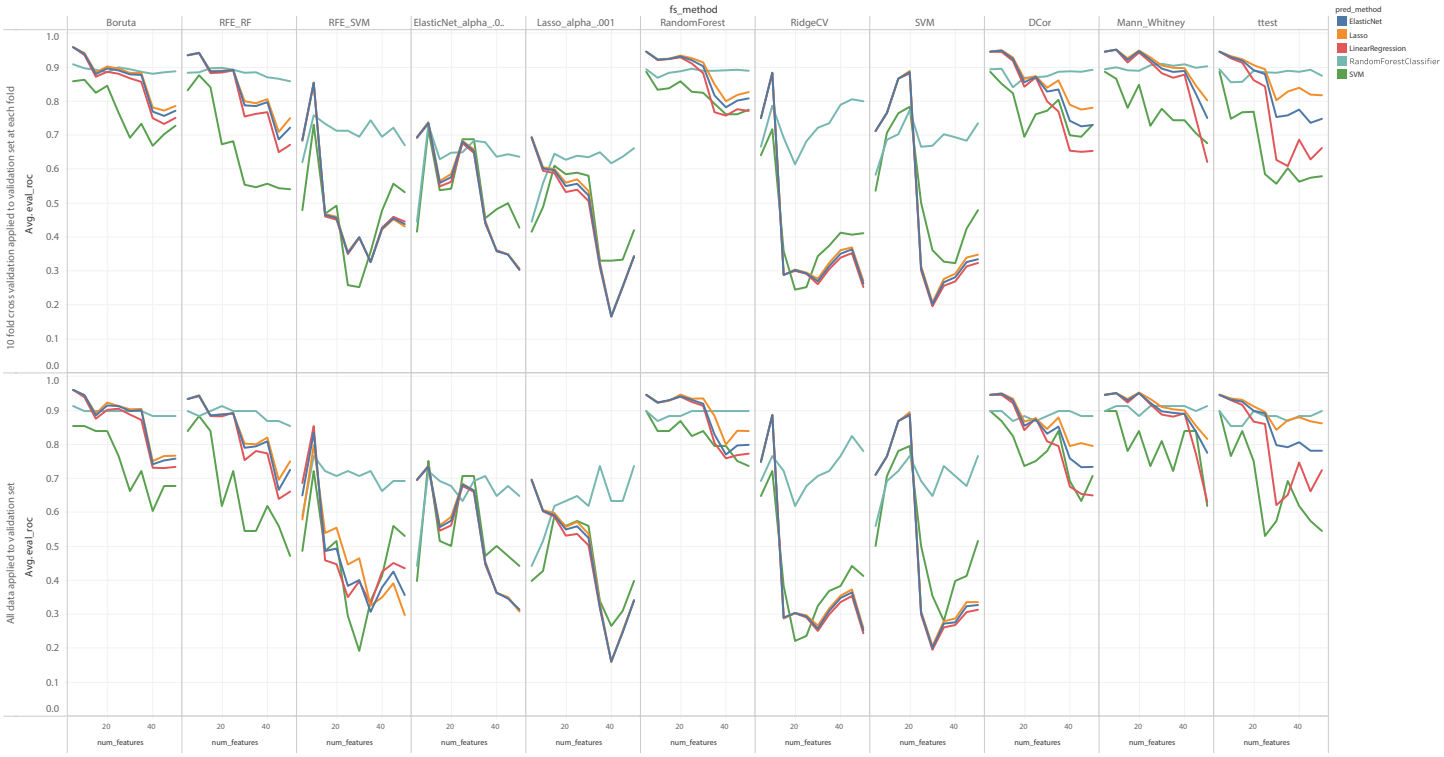
C


Outer Cross-Validation Loops
Multimodal Data
1
Feature Selection Process
Marginal Screening
Embedded
Wrapper
Input Features
Inner Cross-Validation Loops
Feature Empirical Ranking
2
Top Multimodal Features
Top Features
Other Relevant Features
Domain Knowledge
3
Integrative Modeling Process
Top
Integrative Model
Relevant Features
Signatures
Key Markers
Accuracy & Performance Measures
(AUC , ROC)


A
C7
expression
0.10
0.05
0.00
-0.05
-0.10
3h 6h 9h 24h 4d 8d 15d 29d
Time point
Enrichment plot:
GO_S_ADENOSYLMETHIONINE_DEPENDENT_METHYLTRANSFERASE_ACTIVITY
9h Ctrl
PRMT3
SMYD2
LCMT2
PRMT1
DNMT1
FBL
ICMT
PCMT1
DPH5
TFB1M
CXXC1
FTSJ3
WDR77
TRMT1
WDR5
TFB2M
RNMT
EHMT2
RG9MTD1
Enrichment plot:
GO_TRANSCRIPTIONAL_ACTIVATOR_ACTIVITY_RNA_POLYMERASE_II_CORE_PROMOTER_PROXIMAL_REGION_SEQUENCE_SPI
9h Ctrl
DBP
ESRRA
KLF15
MAFB
PLSCR1
CEBPB
KLF4
SOX18
NFIA
DDIT3
ATF4
B
C3
expression
0.10
0.05
0.00
-0.05
-0.10
3h 6h 9h 24h 4d 8d 15d 29d
Time point
Enrichment plot:
HALLMARK_ESTROGEN_RESPONSE_LATE
29d Ctrl
ASCL1
PGR
KLF4
CD9
CISH
IMPA2
BTG3
ABCA3
FGFR3
PRLR
SLC22A5
PTGER3
FRK
Enrichment plot: HALLMARK_TGF_BETA_SIGNALING
29d Ctrl
ID1
SMAD6
SMAD3
SLC20A1
ID3
PPM1A
FNTA
FKBP1A
C
C5
expression
0.10
0.05
0.00
-0.05
-0.10
3h 6h 9h 24h 4d 8d 15d 29d
Time point
Enrichment plot: HALLMARK_BILE_ACID_METABOLISM
29d Ctrl
PEX11A
CROT
GCLM
ACSL5
RBP1
RETSAT
GNMT
NR0B2
NR1I2
ALDH1A1
SLC23A1
BBOX1
IDI1
AKR1D1
FADS1
HACL1
AQP9
AMACR
HSD3B7
FADS2
CYP8B1
HSD3B1
ABCG8

A

Validation Results/Up tp 50 genes



The trend of average of eval_roc for num_features broken down by fs_method vs. wix_run_id (group). Color shows details about pred_method. The data is filtered on wix_run_id, which keeps 12 of 12 members. The view is filtered on pred_method, fs_method, wix_run_id (group) and num_features. The pred_method filter keeps ElasticNet, Lasso, LinearRegression, RandomForestClassifier and SVM. The fs_method filter excludes ElasticNet_alpha_.01 and Lasso_alpha_.01. The wix_run_id (group) filter keeps 10 fold cross validation applied to validation set at each fold and All data applied to validation set. The num_features filter ranges from 5.00 to 50.00.

B

Validation Results/Up tp 100 genes