The predictive toxicogenomics space (PTGS) modeling tool captures diverse cellular and organ toxicity mechanisms and serves for in vitro model-driven prediction of drug-induced liver injury

Roland Grafström & Pekka Kohonen

Karolinska Institutet
Karolinska Innovations/Predictomics AB
Stockholm, Sweden
Misvik Biology Oy, Turku, Finland

Roland

Pekka

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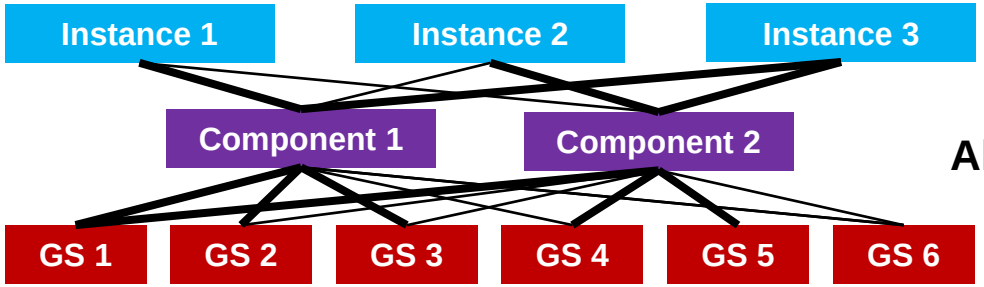
(The authors have financial interest in the subject area of the presentation)

Contact information: roland.grafstrom@ki.se; grafstromrc@gmail.com; predictomicsab@gmail.com

”Toxicogenomics Space” is defined by ”omics” components predictive of cytotoxicity

Connectivity Map (3062 instances)



Latent Dirichlet Allocation component models (100)

Molecular Signatures Database (1321 gene sets)

Connectivity Map
(1217 compounds)
(100 components)
(MCF7, HL60, PC3)

→

Cross-over data set
222 compounds
492 instances

↓

←

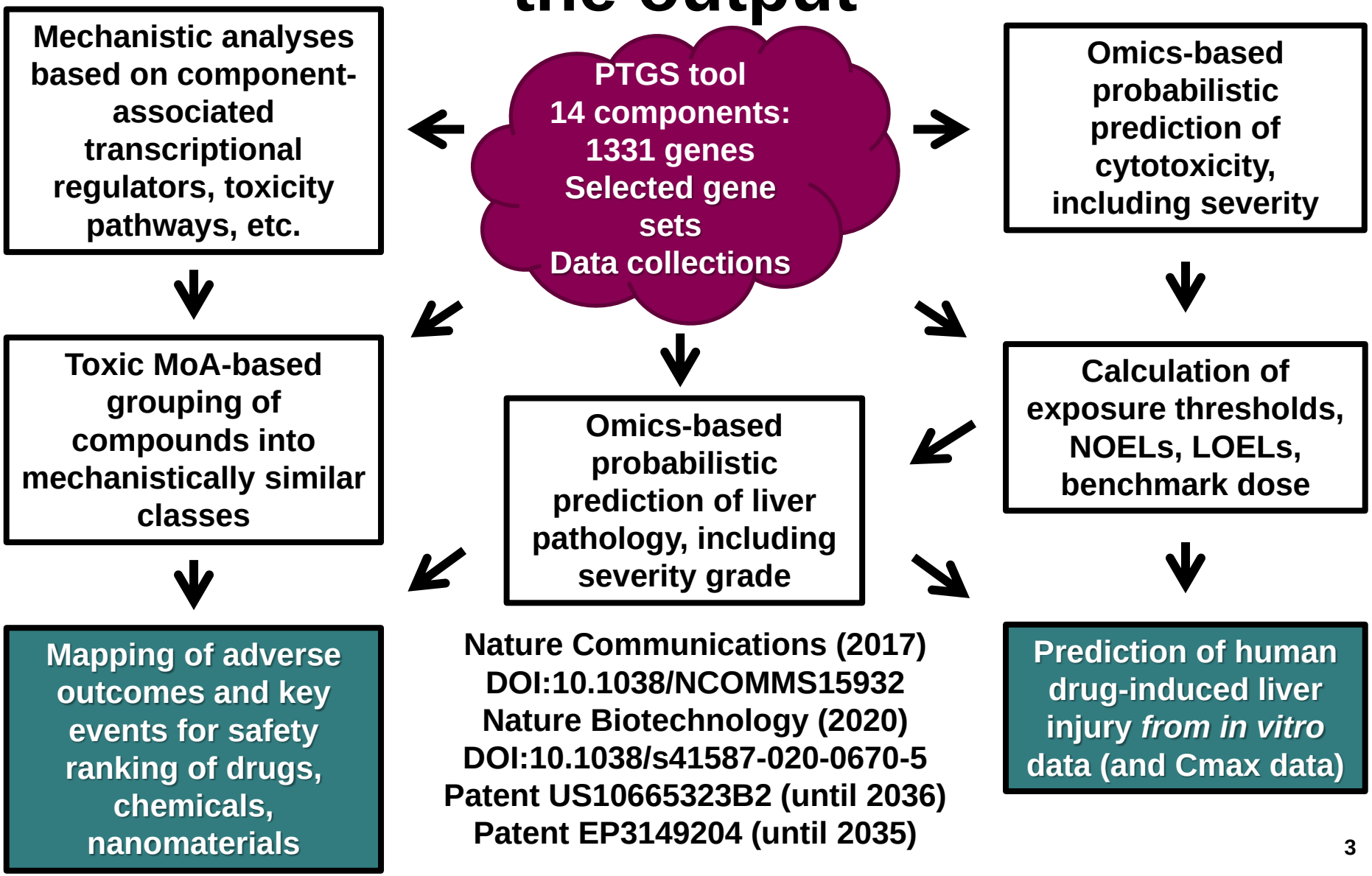
NCI-60 DTP
(100000 compounds)
(59 cell lines)
(GI50/TGI/LC50 data)

Predictive Toxicogenomic Space (PTGS)

14 of the 100 component models, 1331 genes

Component-based scoring	**Gene set-based scoring**
(tests if the 14 components are more active than the other 86 components)	(tests if the PTGS-associated genes are more active in the treated vs. non-treated)

The PTGS safety scoring concept – the output



Nature Communications (2017)
DOI:10.1038/NCOMMS15932
Nature Biotechnology (2020)
DOI:10.1038/s41587-020-0670-5
Patent US10665323B2 (until 2036)
Patent EP3149204 (until 2035)

Big Data analyses: central to generating/applying the PTGS tool

- Connectivity Map: 7000 profiles and >140 million gene expression points (**1309 compounds**); LINCS L1000 dataset with >1.3 million profiles **(~20000 compounds, 4500 knockdowns, and 3000 over-expressions)**; The LINCS dataset incorporates groups of mechanistically similar compounds/perturbations in **171 Perturbation Classes** for easier mode-of-action analysis
- NCI-60 DTP database: toxicity data for >**100 000 compounds**
- TG-GATEs toxicogenomics database has >20000 profiles and >800 million data points (**170 compounds, 157 in hepatocytes**); Drugmatrix > 5000 profiles (**> 200 compounds, 125 in hepatocytes**)
- Ingenuity Pathway Analysis Knowledgebase: > **3 million** literature **references**
- Molecular Signatures Database v7.5.1 has 9 collections of experimentally defined signatures and pathways (Hallmark: **50 sets**, C2: **6366 sets)**
- Gene Ontology project (2022-3) has **43699 GO terms,** 7,838,790 annotations, based on > **169,555** peer-reviewed **publications**
- AOP Knowledge Base (2022-4): AOPWiki has AOPs (**387**), Key Events (**1553**), KE Relationships (**2224**) and Stressors (**738**); Events (MIE, KE and AO) are mapped to the Gene Ontology (**327 GO terms**)
- Drug Induced Liver Injury Rank (DILIrank) consists of **1,036 FDA-approved drugs**, divided by their potential to cause liver injury (DILI-concern): 192 Most, 278 Less and 312 No and 254 Ambiguous; DILIst has a binary classification of **1279 drugs** by human hepatotoxicity

DILI assessments with the Predictive Toxicogenomics Space (PTGS) concept (>500 million data points applied)

Data sets	Compounds	Tests	Samples	Data points
TG-GATEs rat repeated dose 28-day study, prediction concept/validation (MA)	143	1689	6765	128 651 751
TG-GATEs human hepatocytes, prediction concept/validation (MA)	157	941	2605	90 669 391
TG-GATEs rat hepatocytes, prediction concept/validation (MA)	145	1260	3370	76 692 128
DrugMatrix rat liver, in vivo, repeated dose, validation (MA)	201	654	2218	56 752 735
DrugMatrix rat hepatocytes, validation (MA)	126	268	939	25 671 374
Benchmark dose (BMD) rat liver, *in vivo*, validation (RNA-seq/MA comparison)	1	12	60	986 788
HepG2 cell model, TempO-Seq S1500+, validation (HTTr)	81	160	489	5 730 967
DILI prediction, rat liver, *in vivo*, blinded study, validation (MA)	1	4	24	891 746
Human and rat liver, *in vitro* systems comparison, blinded study, validation (MA)	3	87	439	14 427 646
DILI prediction, rat liver, *in vivo*, blinded study, validation (MA)	1	6	45	1 236 342
DILI prediction/BMD, human liver spheroids, validation (HTTr)	28	560	2774	67 779 442
DILI prediction, human liver spheroids, LINCS L1000+Inferred, validation (HTTr)	28	560	2774	44 018 024
DILI prediction, human liver spheroids, blinded study, validation (RNA-seq)	27	87	269	6 084 001
DILI prediction, human liver spheroids, quantitative AOP analysis (HTTr)	28	560	2774	4 641 178
DILI prediction, human liver spheroids, grouping, AOP-based principles (HTTr)	28	560	2774	4 641 794
Total	***998***	***7 408***	***28 319***	***528 875 307***

Unique compounds 453; 231 with DILI information (FDA DILIRank DB): 85 Most-DILI-concern, 87 Less, 27 Ambiquous and 32 No-DILI-concern; 119 compounds in total (74 Most, 36 Less, 14 No, 13 Ambiguous, 18 Unclassified).

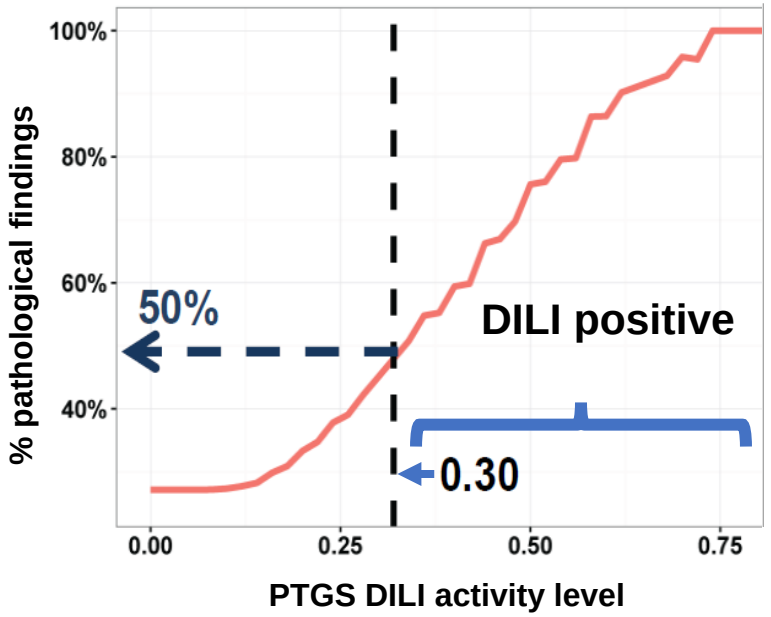
In vitro **model predictions included 119 compounds of which *92* were correctly predicted *(77%).***

The blinded rat liver analyses each confirmed DILI positivity of a ”false-negative” compound

Study calculations include raw data and derived analyses data of gene expression at transcriptome level.
“Blinded study” indicates unrevealed compound identity and/or DILI classification at start of analysis.
MA = microarray technology, HTTr = High-throughput platforms, RNA-seq = RNA sequencing technology

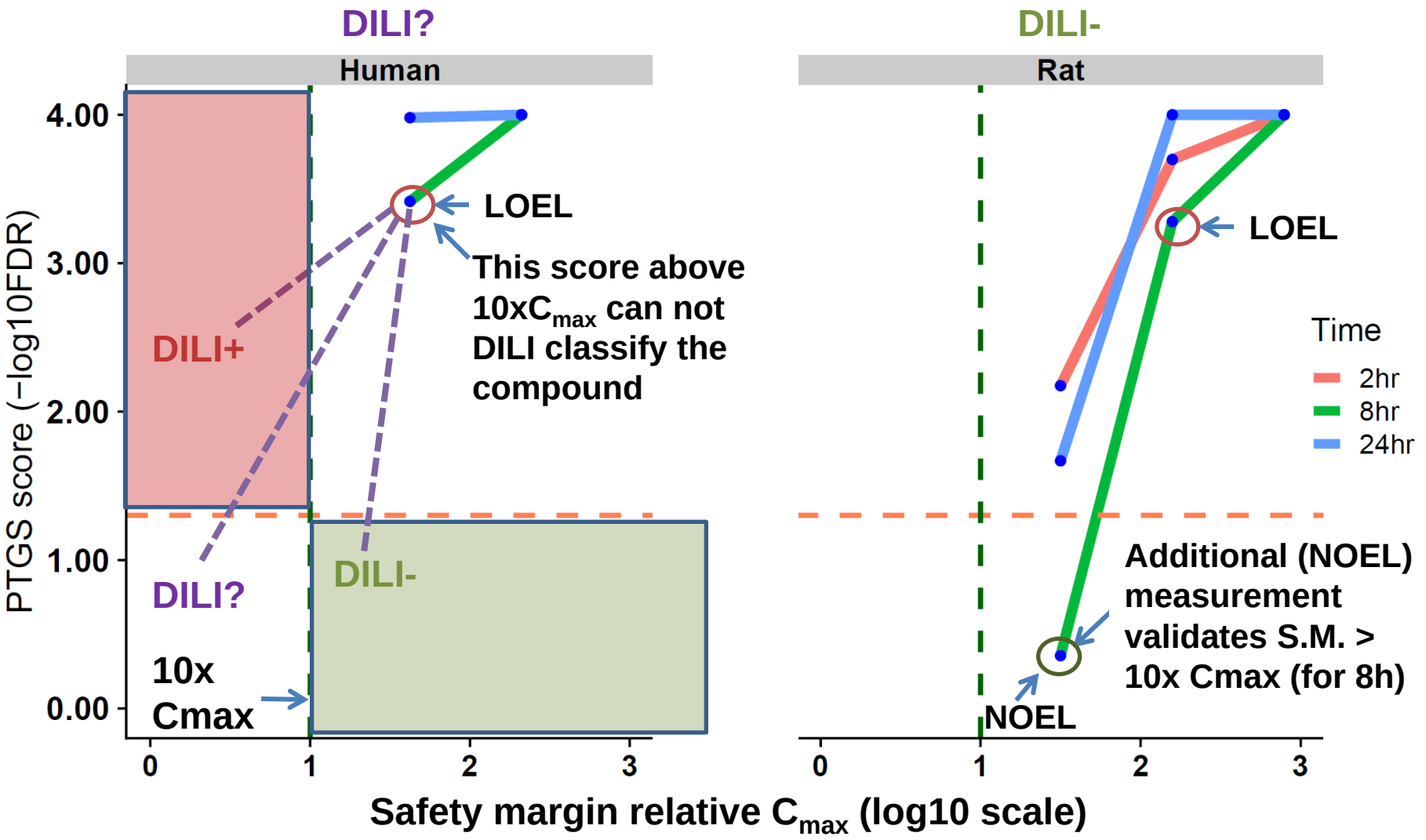
Scoring concepts for DILI and cytotoxicity prediction: defining LOELs

- **Gene set enrichment analysis, adjusted p-value (stat significance; FDR <0.05)**
  - ***R/Bioconductor limma* rotation-based testing (10000 rotations)**
  - **Tests whether PTGS changes relative control**
  - **Uses all gene expression information, not just DEGs**
- **Activity score relative TG-GATEs or the Connectivity Map (biological effect, > 50% effect probability)**
  - **Use the proportion of genes in set(s) altered by the exposure as a score**
  - **Compared directly to the TG-GATEs rat 28-day liver data (1667 treatments) for DILI and Connectivity Map /NCI-60 DTP for cytotoxicity (492 treatments)**
  - **Point where at least 50% of treatments have pathological/cytotoxic effects (DILI/GI50) is used as the threshold**



Nature Communications (2017) DOI:10.1038/NCOMMS15932

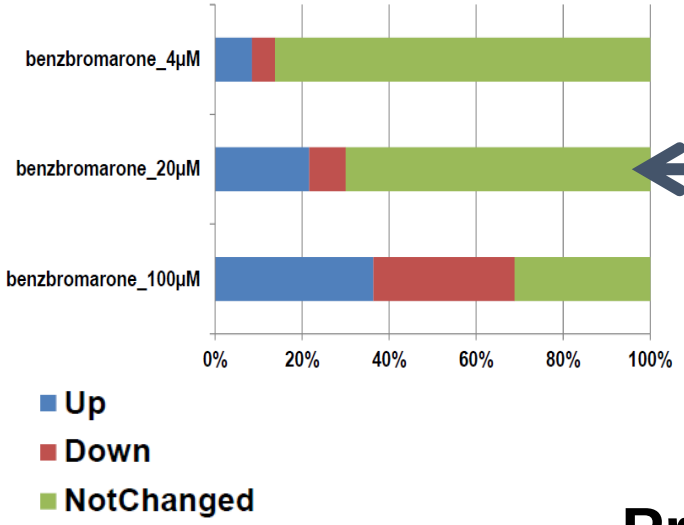
Example: DILI/organ tox-prediction with cell culture data



Data from TG-GATEs, human and rat hepatocytes: hydroxycine is a DILI-negative compound (negative control in the Kohonen et al. 2017 study)

The PTGS safety scoring concept examplified with TG-GATEs data (Benzbromarone, 4-100 µM; 8 h, human hepatocytes, therapeutic $C_{max, total}$ 6.6 µM)

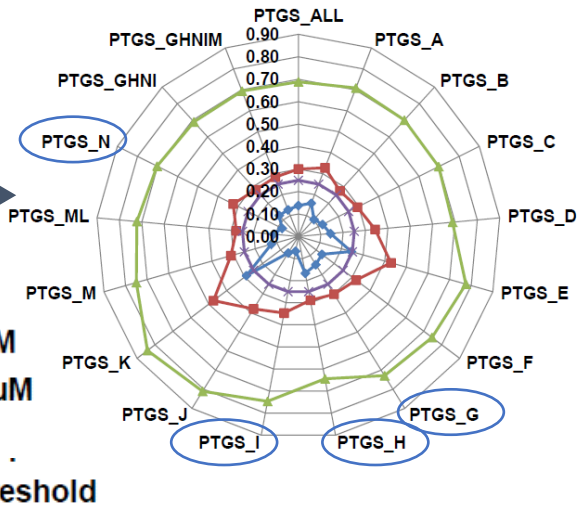
PTGS gene set/space activity



PTGS

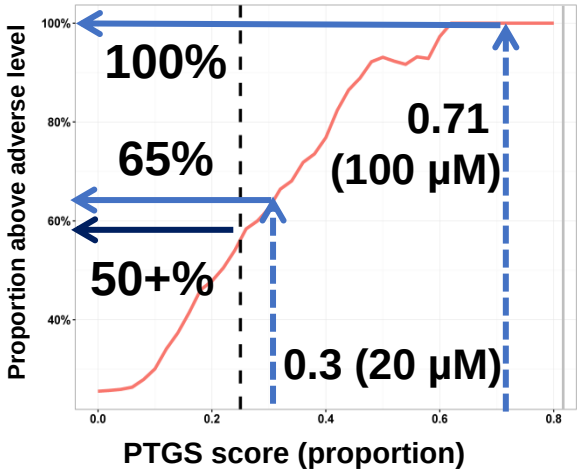
14 components
1331 genes
Selected gene sets, Data collections

PTGS component MoA

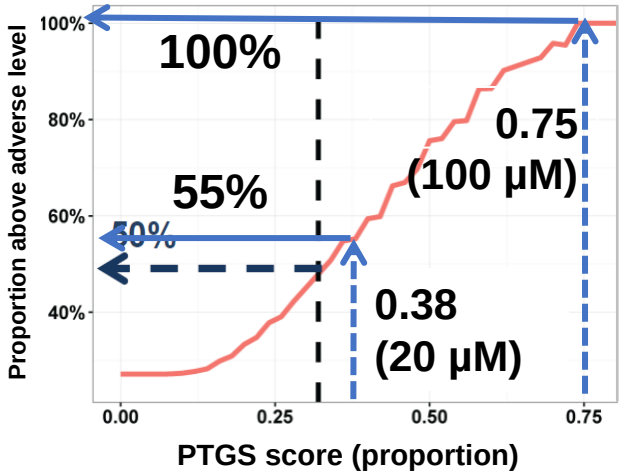


Probabilistic prediction of

Cytotoxicity LOEL (20 µM)

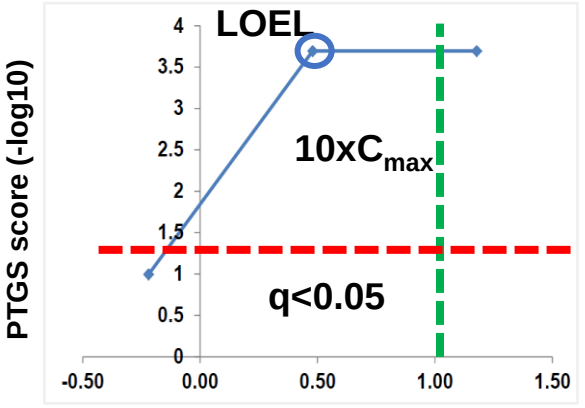


DILI LOEL (20 µM)



Human DILI (DILI +)

Safety margin (0.5; 3.3x)



TG-GATEs analyses validated the PTGS scoring concept for organ toxicity effects in liver from in vitro data

- **PTGS components G, H, I and N served for probabilistic prediction of rat liver injury (1689 treatments; up to 28 days)**

- **PTGS scoring captured/predicted:**

  -All pathological states (17/17), the severity grade and proportion of affected animals/rats; 143 compounds

  -Dose-response effects in rat/human hepatocytes; 157 compounds

  -Human drug-induced liver injury (DILI) better than existing commercial tests (68 compounds); prediction is further enhanced when the scoring is combined with other tests

  -MIEs and KEs in AOPs for liver injury (e.g., fibrosis, steatosis, cholestasis)

Kohonen et al, Nature Communications, 2017

PTGS concept enables component-based MoA analysis; G,H, I, N components are applied to liver toxicity prediction; (Component activations also serves for compound grouping)

Component	Toxicity-associated biological and cellular mechanisms
A, B, C, G, H, I, N	PPARa/RXRa Activation, Peroxisome Proliferators via PPARa, LXR/RXR Activation, VDR/RXR Activation, RAR Activation, Aryl Hydrocarbon Receptor Signaling, NF-kB Signaling, Oxidative Stress, NRF2-mediated Oxidative Stress Response, TGF-b Signaling, Transmembrane Potential of Mitochondria, Anti-Apoptosis, Cell Cycle: G1/S Checkpoint Regulation, p53 Signaling
D	TGF-b Signaling, PPARa/RXRa Activation
E, K	Cell Cycle: G1/S Checkpoint Regulation and G2/M DNA Damage Checkpoint Regulation, Aryl Hydrocarbon Receptor Signaling, p53 Signaling, Notch signaling, E2F/MYC targets, peroxisome
L	Cellular aldehyde metabolic process (HMGCL, ABAT, ADH5, PGD)
F	Regulation of transcription, DNA-dependent, positive regulation of transcription from RNA polymerase II promoter, UV response
J	RNA polymerase II promoter regulation, IL2-STAT5 signaling
M	tRNA charging, unfolded protein response, MTORC1 signaling

10

Capture of TG-GATEs phenotypes by PTGS liver predictive components (G,H,N,I)

Pathological Phenotypes	PTGS_H	PTGS_N	PTGS_I	PTGS_G
slight.Single.cell.necrosis (I)	0.00	0.00	3.61	0.00
Present, any phenotype (N)	0.00	2.18	0.00	0.00
slight.Increased.mitosis (G)	1.06	0.00	0.00	2.11
minimal.Vacuolization.cytoplasmic (H)	1.57	1.07	0.00	0.00
Minimal, any phenotype (N)	0.00	2.75	0.00	0.00
P.Necrosis (H)	5.39	0.00	0.00	1.04
P.Proliferation.bile.duct (H)	4.67	1.31	0.00	3.63
minimal.Fibrosis(H)	4.15	2.07	0.00	0.00
minimal.Necrosis (N)	2.68	2.89	0.00	1.08
minimal.Change.acidophilic (H)	2.63	0.00	0.00	0.00
P.Change.acidophilic (H)	2.48	1.77	0.00	1.19
minimal.Cellular.infiltration (H)	2.20	2.00	0.00	1.40
P.Cellular.infiltration (H)	2.05	1.51	0.00	1.13
slight.Proliferation.bile.duct (H)	2.01	1.70	1.23	0.00
P.Fibrosis (H)	1.89	0.00	0.00	1.33
slight.Change.acidophilic (H)	1.77	0.00	1.52	0.00
P.Degeneration.granular.eosinophilic (N)	1.14	1.55	0.00	0.00
minimal.Degeneration.granular.eosinophilic (N)	0.00	2.88	0.00	1.01
Moderate, any phenotype (N)	0.00	2.54	0.00	0.00
P.Microgranuloma (N)	0.00	2.48	0.00	0.00
P.DEAD (N)	0.00	2.19	0.00	2.18
minimal.Microgranuloma N)	0.00	1.56	0.00	0.00
moderate.Degeneration.granular.eosinophilic (G)	0.00	1.39	0.00	1.89
minimal.Change.eosinophilic (I)	0.00	0.00	5.58	0.00
P.Single.cell.necrosis (I)	0.00	0.00	4.73	0.00
minimal.Single.cell.necrosis (I)	0.00	0.00	4.50	0.00
P.Change.eosinophilic (I)	0.00	0.00	3.51	0.00
minimal.Ground.glass.appearance (I)	0.00	0.00	1.80	0.00
P.Vacuolization.cytoplasmic (I)	0.00	0.00	1.59	0.00
P.Degeneration.fatty (G)	0.00	0.00	0.00	1.98

Derived using RandomForest regression

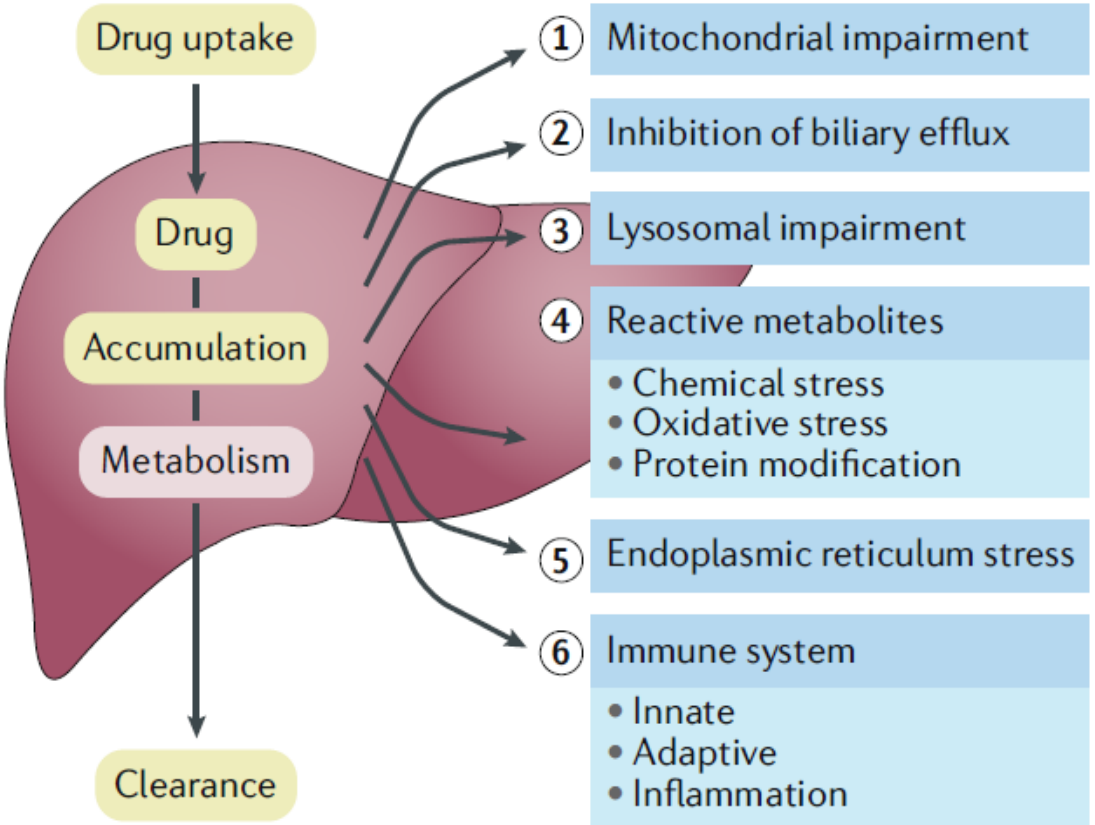
PTGS covers key characteristics of human hepatotoxicants

Key Characteristic	Gene Ontology	IPA ToxLists
Is reactive and/or is metabolized (bioactivated) to reactive moieties	E, G, K, N	A, B, C, G, N
Causes death (apoptosis and/or necrosis) of liver cells	A, B, C, D, F, G, I, N	A, B, C, D, E, F, G, H, I, N
Affects liver cell proliferation and/or tissue regeneration	A, B, C, D, E, F, G, H, I, K, N	A, B, C, D, E, F, G, H, I, K, N
Disrupts transport function		A, B, C, D, E, G, H, I, N
Induces oxidative stress	B, C, D, E, G, H, I	A, B, C, D, E, G, H, N
Triggers immune-mediated responses in liver	B, C, F, G, H, I, J, N	
Causes mitochondrial dysfunction	G, M	C, G, I
Activates stress signaling pathways	A, B, C, D, E, F, G, I, K	B, C, D, E, F, G, K, N
Causes cholestasis		A, B, C, G, I, N
Disrupts cellular cytoskeleton	C, D, H, I, N	
Causes liver fibrosis	D, I	B, I, N
Disrupts liver metabolism, including of lipids and proteins	B, C, D, E, F, G, H, I, J	

Key Characteristics Table from Rusyn et al. Hepatology. 74: 3486–3496, 2021

Based on enrichment/overrepresentation analysis of PTGS components ($p < 0.01$)

PTGS components capture toxic mechanisms associated to DILI

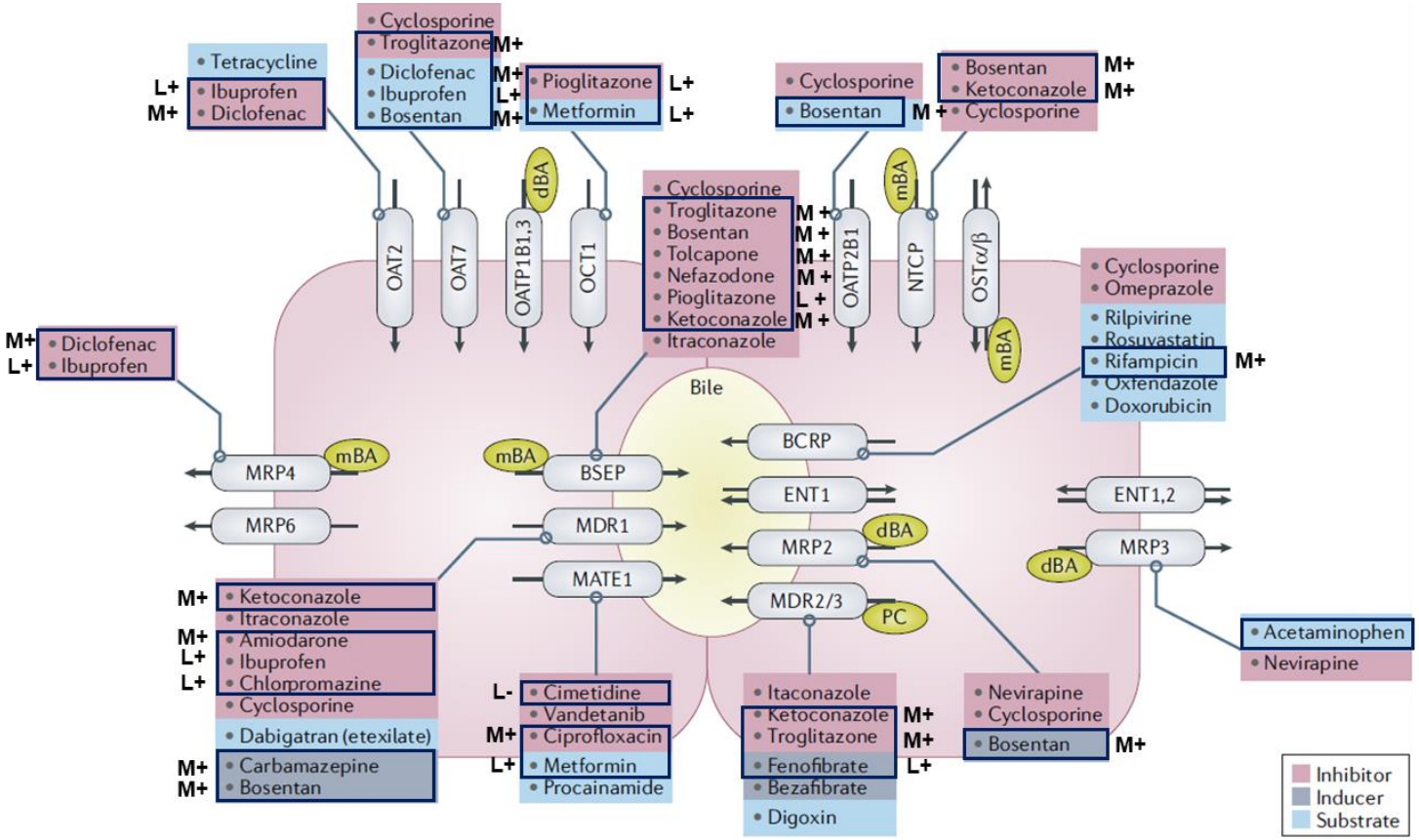


	Gene Ontology	IPA ToxLists
1 Mitochondrial impairment	B, C, G, I, M	C, G, I
2 Inhibition of biliary efflux		A, B, C, D, E, F, G, H, I, K, N
3 Lysosomal impairment	H	
4 Reactive metabolites		
• Chemical stress	A, C, F, M	A, B, C, G, N
• Oxidative stress	B, D, G, I	A, B, C, D, E, G, H, N
• Protein modification	G	
5 Endoplasmic reticulum stress	B, D	
6 Immune system	B, N	
• Innate	B, C, J	
• Adaptive	B	
• Inflammation	B, G, I, N	

Figure adapted from Weaver et al, Nature Reviews-Drug Discovery, 2020

Based on enrichment/overrepresentation analysis of PTGS components ($p < 0.01$)

PTGS scoring in vitro captures effectively DILI concerns related to hepatobilary transport (33 of 34 DILI-inducing drug molecular actions captured)



PTGS analyses data combined from public and client liver model experiments

M = Most DILI concern compounds
L = Less DILI concern compounds

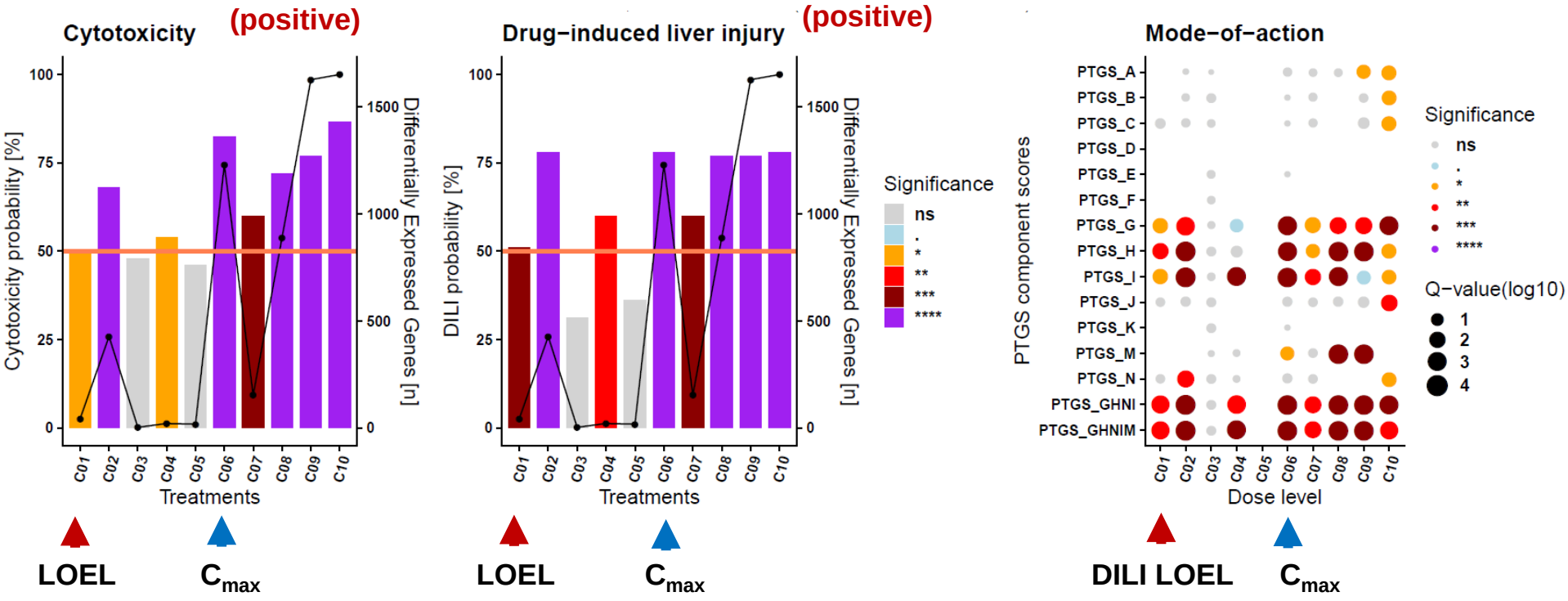
\+ = PTGS LOEL DILI positive scores
\- = PTGS LOEL DILI negative scores

Cimetidine is negative in TG-GATEs rat and human hepatocytes

Figure adapted from Weaver et al, Nature Reviews-Drug Discovery, 2020

DILI predictions founded in AOPs via quantitative analysis (PTGS qAOP workflow assesses 27 liver AOPs)

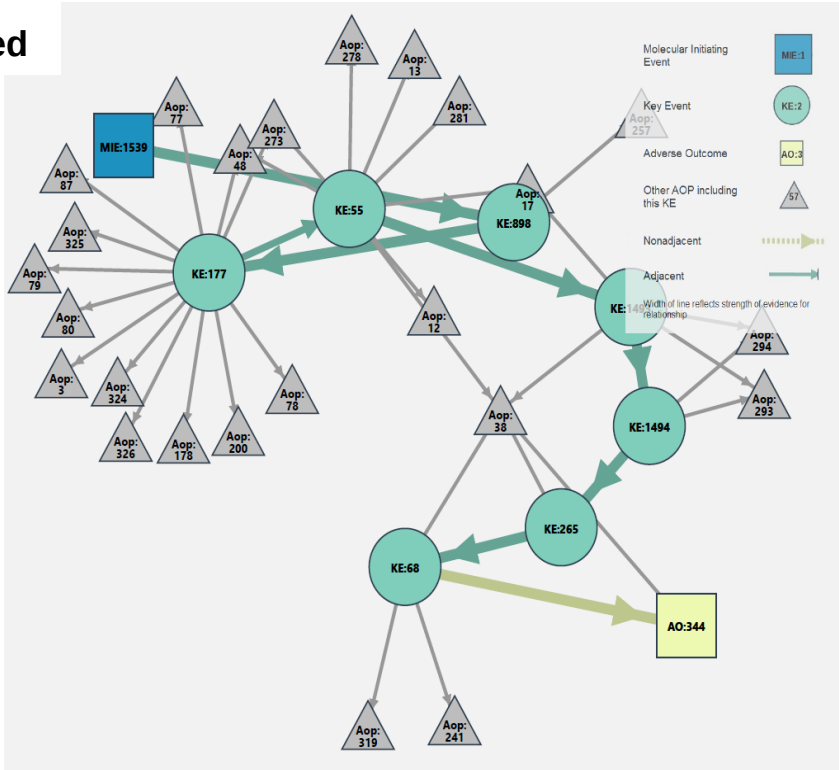
Example: a most−DILI−Concern compound X that causes liver fibrosis and steatosis (from a client study where 27 of 28 compounds were correctly classified by the PTGS tool)



Cytotoxicity and DILI LOEL: ~1 µM, C01 (Plasma C_{max} at C06, 2x concentration increase at each step)

AOP 144: Endocytic lysosomal uptake leading to liver fibrosis

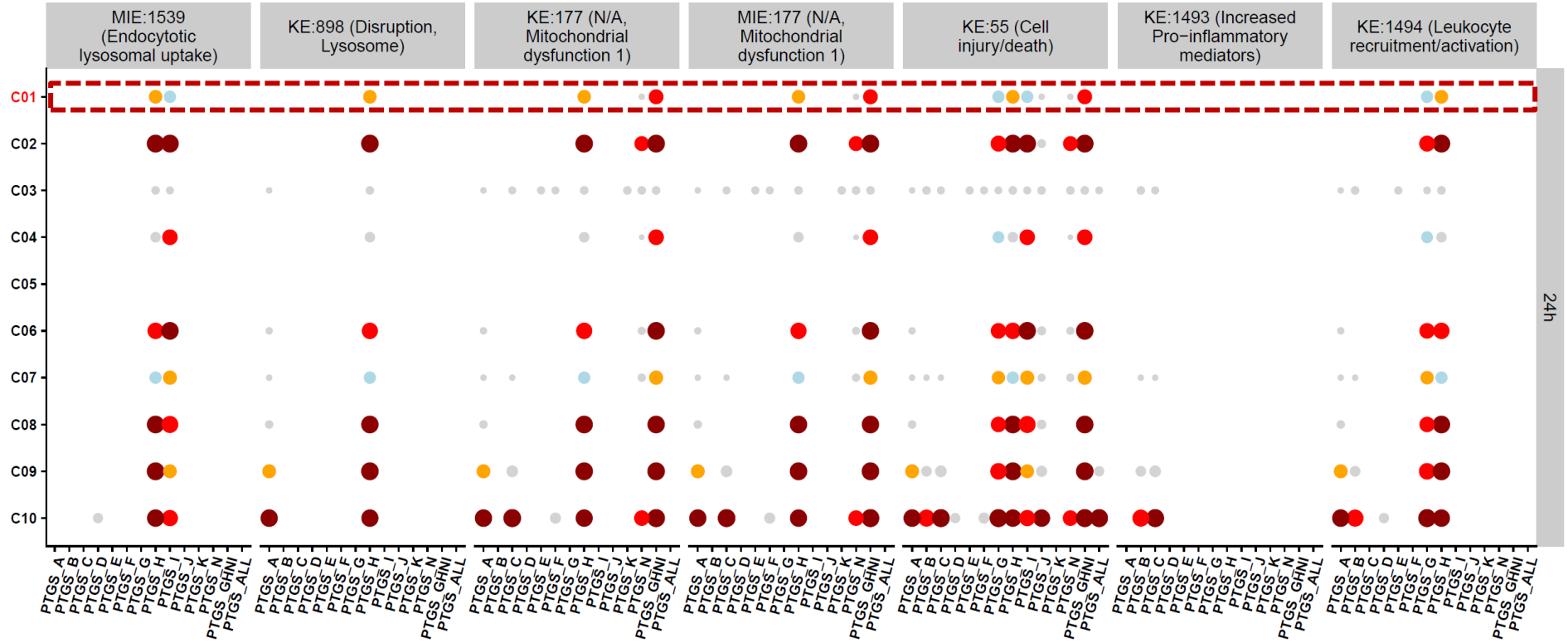
Type	Event ID	Title	PTGS annotated
MIE	1539	Endocytotic lysosomal uptake	X
KE	898	Disruption, Lysosome	X
KE	177*	Mitochondrial dysfunction 1	X
KE	55	Cell injury/death	X
KE	1493	Increased pro-inflammatory mediators	X
KE	1494	Leucocyte recruitment/activation	X
KE	265	Activation, stellate cells	
KE	68	Accumulation, collagen	
AO	344	Liver fibrosis	X



*KE 177 is also an MIE

Compound X. Aop:144 (Events=6/9 annotated by PTGS), Endocytic lysosomal uptake leading to liver fibrosis (PTGS DILI LOEL 24h: C01)

(Quantitative estimates via multiple testing corrected p-values)



PTGS Component MoA analysis using competitive GSEA (the 14 toxicity-associated vs the non-toxicity 86 components of the LDA-compressed cMap). Six of six PTGS-annotated events positive within the concentration series

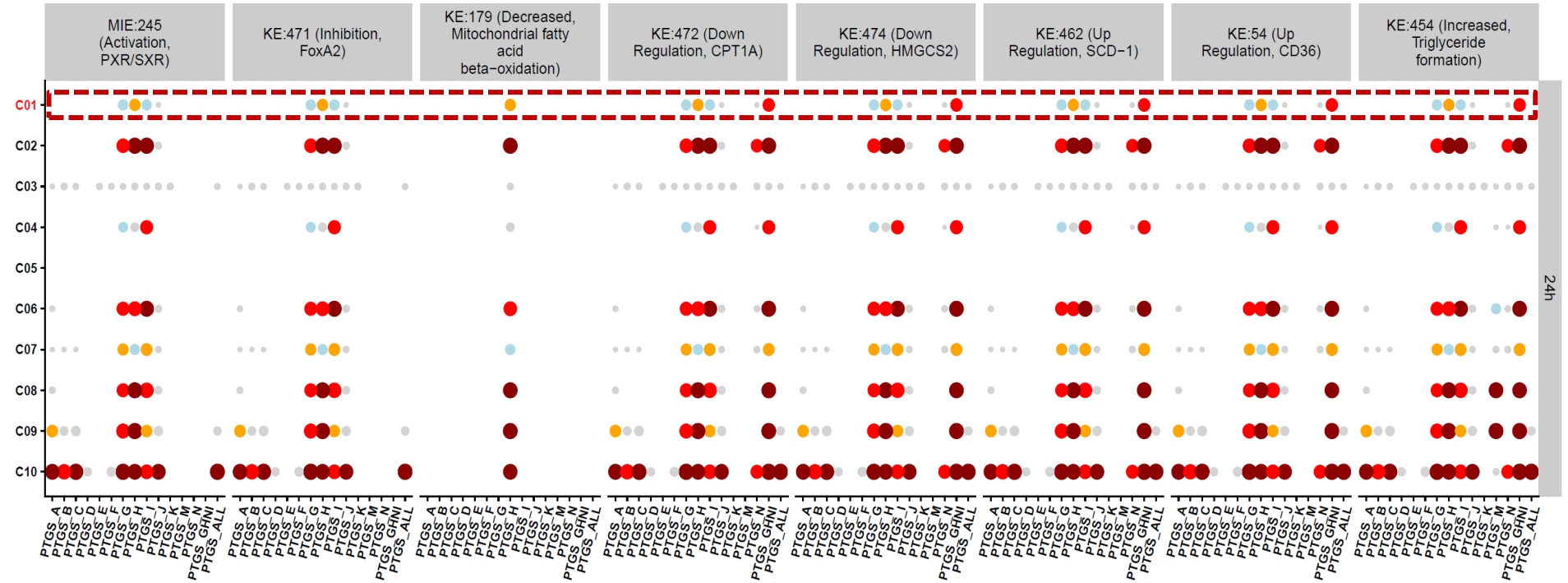
Significance

ns	q>0.1	
.	q<0.1	
*	q<0.05	
**	q<0.01	
***	q<0.001	

PTGS DILI LOEL

Compound X activates all steatosis AOPs (9 of 27 AOPs) Aop:60 (Events=8/12 annotated by PTGS), NR1I2 (Pregnane X Receptor, PXR) activation leading to hepatic steatosis (PTGS DILI LOEL 24h: C01)

(Quantitative estimates via multiple testing corrected p-values)



PTGS Component MoA analysis using competitive GSEA (the 14 toxicity-associated vs the non-toxicity 86 components of the LDA-compressed cMap). All PTGS-annotated events positive within the concentration series

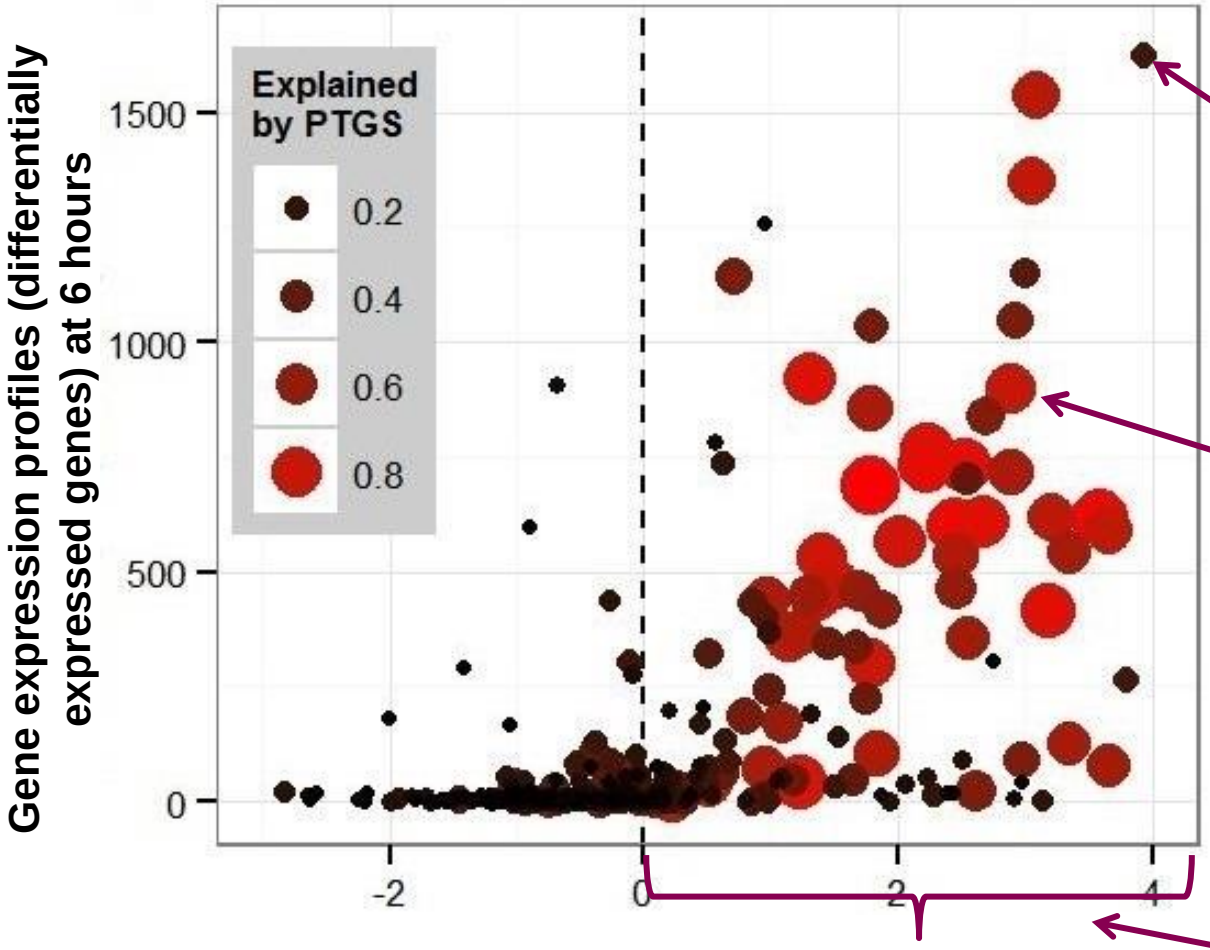
Significance

ns	q>0.1	PTGS DILI LOEL
.	q<0.1	
*	q<0.05	
**	q<0.01	
***	q<0.001	

The toxicity scoring concept is based on broad variations in gene alterations and toxicity effects

The score from 6h omics data predicts growth inhibition manifested at a later time point, i.e., 48h. A red color score of 1 would indicate that 100% of the gene expression changes couple with above GI50-levels of toxicity.

Cross-over data (Connectivity Map 2.0): MCF7/PC3/HL60 cells



Each dot represents one Affymetrix microarray. N = 492; 222 compounds

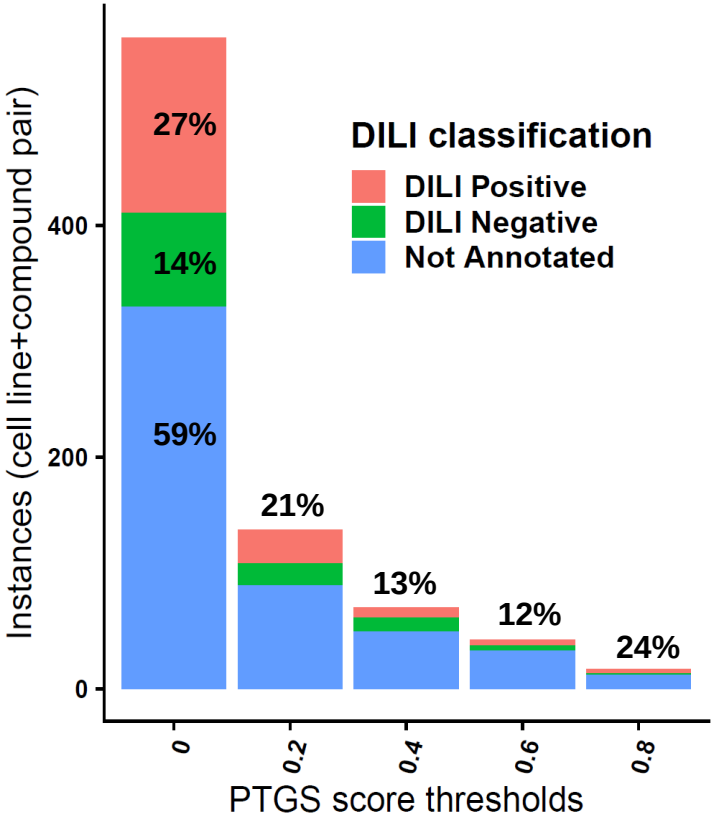
Size and color (red) of the dot indicates the magnitude of the PTGS score

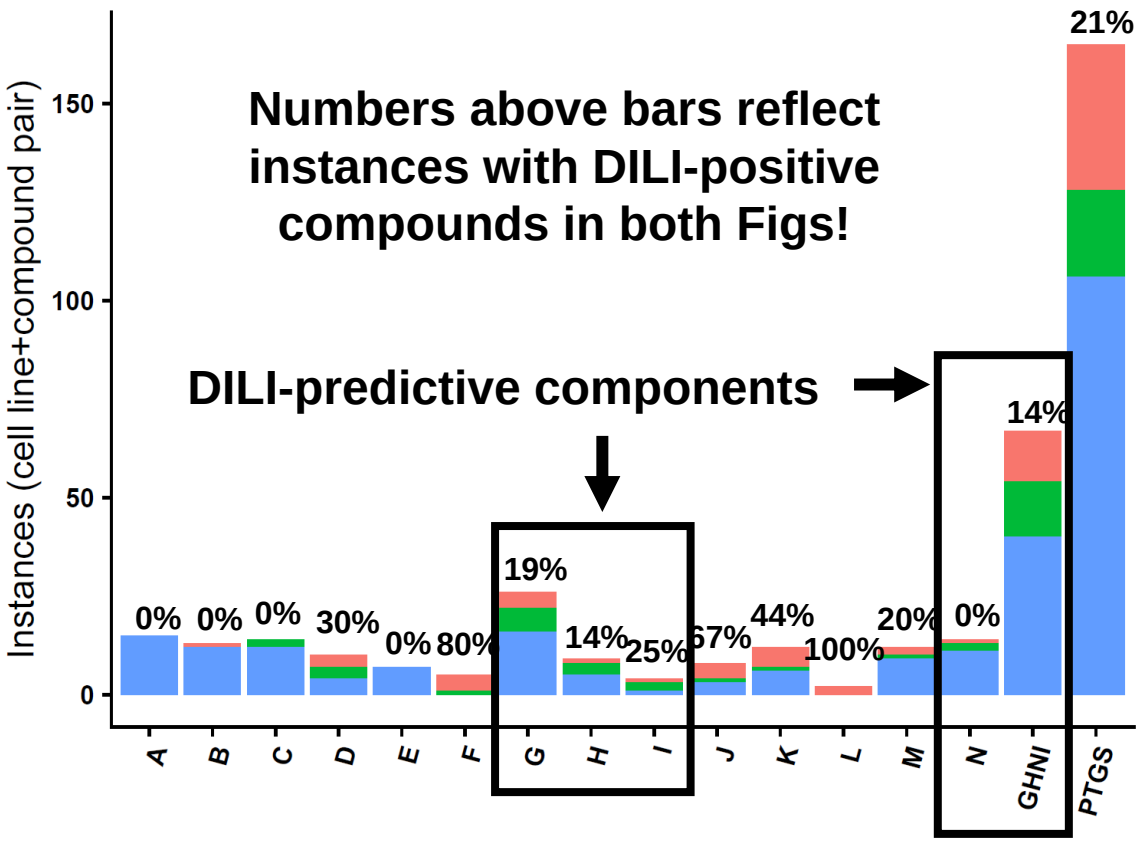
PTGS components become active beyond GI50 level of toxicity

DILI compound annotations (%): the PTGS-modelled CMAP-NCI60 data set vs. the PTGS components

(PTGS scores and DILI predictive components do not enrich DILI compounds!)

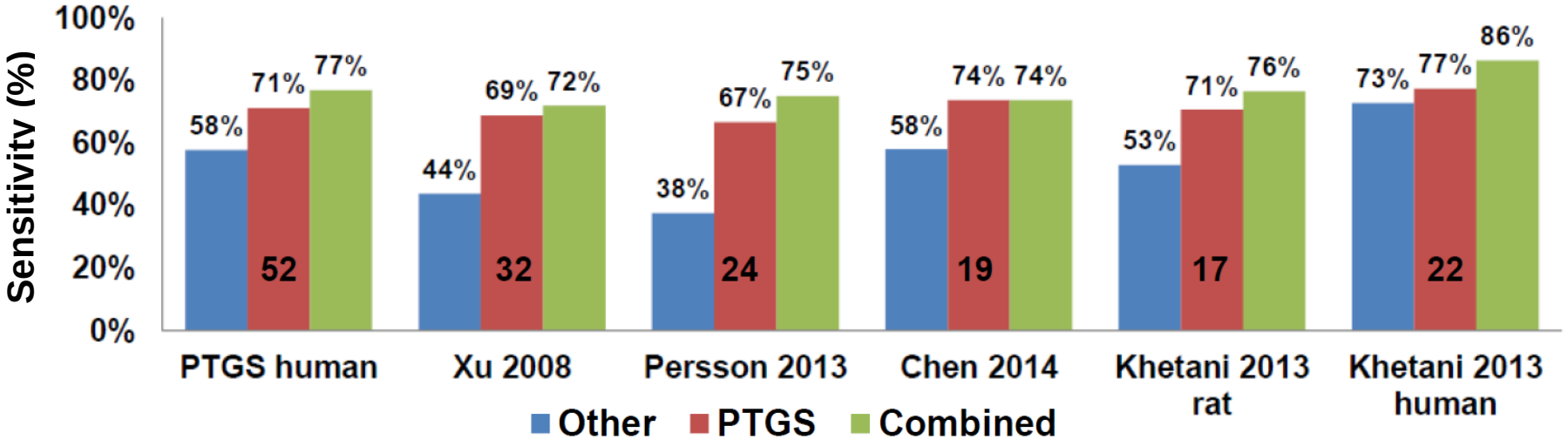
CMAP-NCI60 overlay: 222 compounds / 492 instances





Similar absent enrichment for DILI compounds is seen for the complete cMap
Compound annotations from: Thakkar et al. Drug Discovery Today, 2019

PTGS-based predictions of DILI outperform and enhance the predictions of other approaches (concept of augmented intelligence and not a “Stand-Alone”-tool)



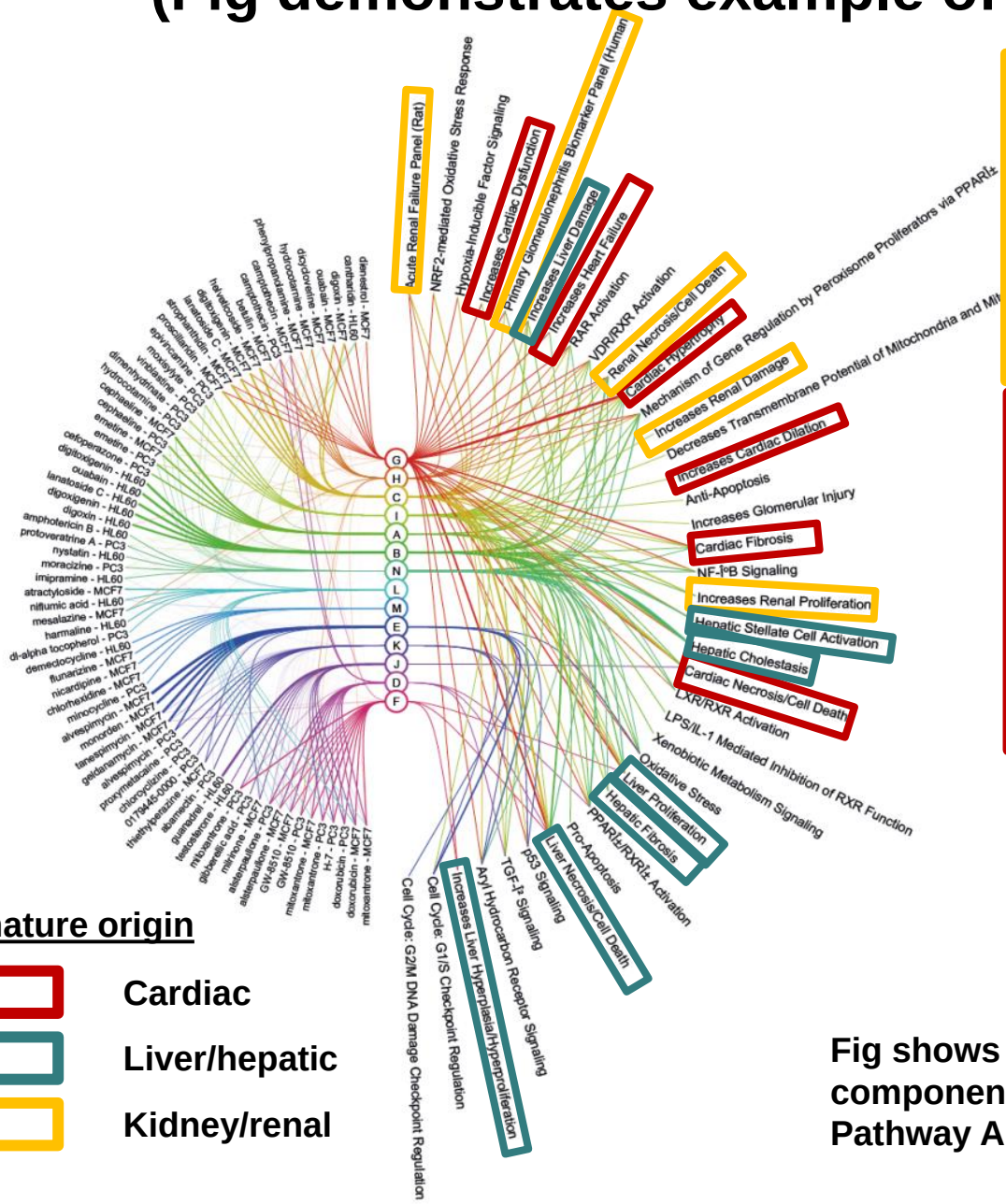
PTGS results (based on rat hepatocyte profiles) compared to other *in vitro* approaches, including PTGS-based analysis of human hepatocytes; numbers of matching compounds indicated inside the red bar; all analysis at 100% specificity

Xu et al. 2008 human hepatocyte imaging assays at 24 h
Persson et al. 2013 HepG2 cells with four mechanistic endpoints at 24-72 h
Chen et al. 2014 rat hepatocyte imaging assays at 24-48 h combined with high lipophilicity (logP ≥ 3) + High Daily Dose (DD ≥ 100 mg)
Khetani et al. 2013 human/rat micro-patterned human hepatocyte co-cultures with repeated dosing over 7-14 days

Our suggested approach to PTGS-DILI predictions

- **Unsupervised use of the toxicogenomics space** (covers approx. 70% of chemical space) relative the compound selection. Refer collaborators to cMap and Cmap-NCI60 compound lists
- **Study (compound identity) can be blinded or not**, but we request information on the predictivity also for non-disclosed compounds
- **Human liver microtissue or well-characterized hepatocyte models under a defined in-house culture protocol.** Set PTGS safety margin based on the experimental data with 10x as starting point. Include reference compounds
- **Apply in parallel other in vitro prediction methods** with proven specificity, e.g., Vorrink et al, 2018 claims 100%; (PTGS DILI analysis with TG-GATEs used 100% specificity to calibrate the prediction model)
- **Integrate PTGS in multi-test AI-driven DILI prediction model**, explainable (and not a black box) to the extent possible

PTGS covers other organ toxicities besides liver
(Fig demonstrates example of explainable AI)



Kidney
- Acute Renal Failure Panel (Rat)
- Primary Glomerulonephritis Biomarker Panel (human)
- Renal Necrosis / Cell Death
- Increases Renal Damage
- Increases Renal Proliferation

Heart
- Increases cardiac dysfunction
- Increases Heart Failure
- Cardiac Hyperthropy
- Increases Cardiac dilation
- Cardiac fibrosis
- Cardiac Necrosis / Cell death

Example related to heart:
G connects strongly to cardiac hypertrophy and cardiac fibrosis

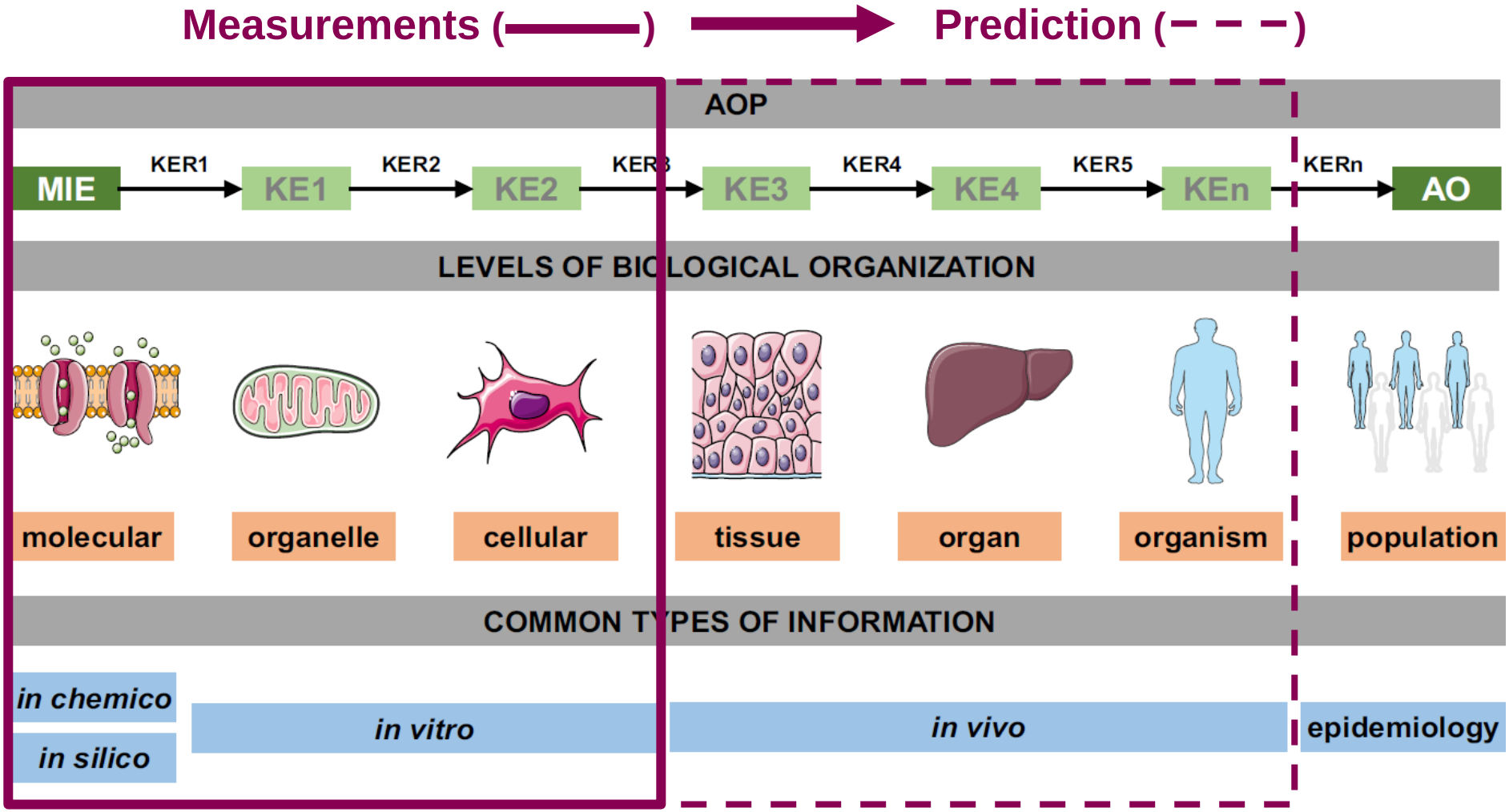
signature origin

- Cardiac
- Liver/hepatic
- Kidney/renal

Fig shows overlap analysis of PTGS component-based gene sets versus Ingenuity Pathway Analysis ToxLists collection

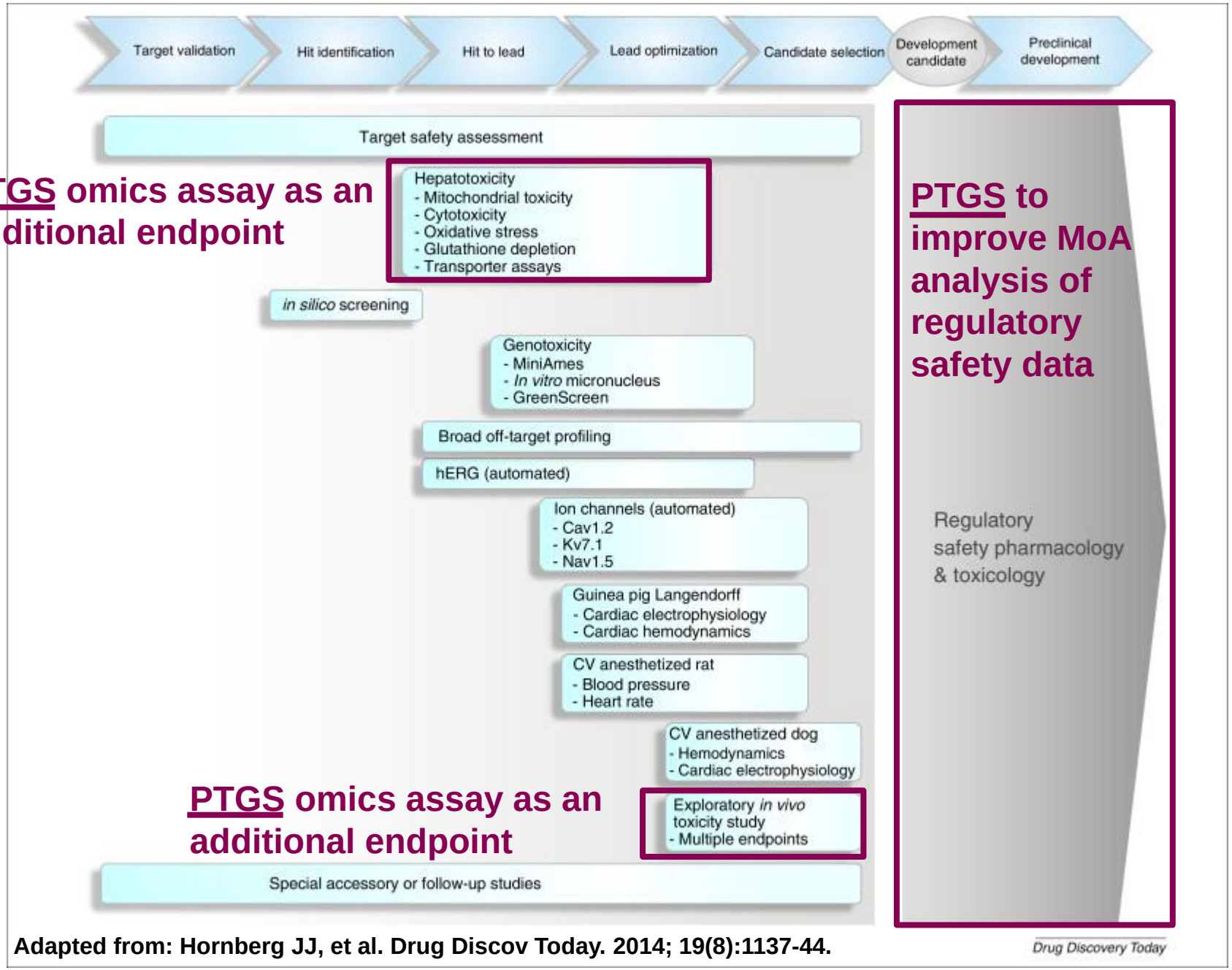
The “PTGS AOPome” captures GO-annotated toxicity events

(Example 1: 27/32 Liver AOPs exhibit 107 PTGS-accessible vs. 188 GO-accessible events)
(Example 2: 22/32 Lung AOPs exhibit 30 PTGS-accessible vs. 50 GO-accessible events)



Adapted from: Vinken et al., Arch Toxicol, 91, 3697–3707, 2017

Applying PTGS scoring in drug discovery and DILI prediction



PTGS omics assay as an additional endpoint

PTGS omics assay as an additional endpoint

PTGS to improve MoA analysis of regulatory safety data

Adapted from: Hornberg JJ, et al. Drug Discov Today. 2014; 19(8):1137-44.

Considering PTGS applicability to grouping/connectivity mapping/read-across (structural vs. transcriptomics distances)

- **Structural/physiochemical similarity** is the starting point if available in most evaluations (a regulatory demand)
- **Biological (pertubational) similarity** is potentially a complement or alternative for compounds undergoing metabolism (e.g., many DILI-associated compounds cause side-effects due to metabolism).
- **Biological (pertubational) similarity** is potentially an alternative also for “Unknown, Variable Composition Biologicals” (UVCB) and “Advanced multi-component (nano)materials” (e.g., where decay, leaching, etc. changes the composition) and for evaluating mixture effects generally
- **For grouping purpose, the PTGS tool today includes 10+ component-based and AOP-based analysis methods** where initial definition of PTGS-LOELs serves as a sensitive, low-toxicity effect starting point
- Kohonen et al, 2017 study provides already grouping analysis from defining Cmap compound-associations to the 14 PTGS componentss

Our safety testing H2020 EU-projects variably involve tiered high throughput testing methodologies and PTGS

Gov4Nano Implementation of risk governance: meeting the needs of nanotechnology (Jan 2019-Dec 2022); *KI*; **Penny Nymark lead, omics, FAIR**

NanoSolveIT Innovative nanoinformatics models and tools: towards a solid, verified and Integrated approach to predictive (eco)toxicology (Jan 2019-Dec 2022); *Misvik* ***(HTS, qAOP workflow developments)***

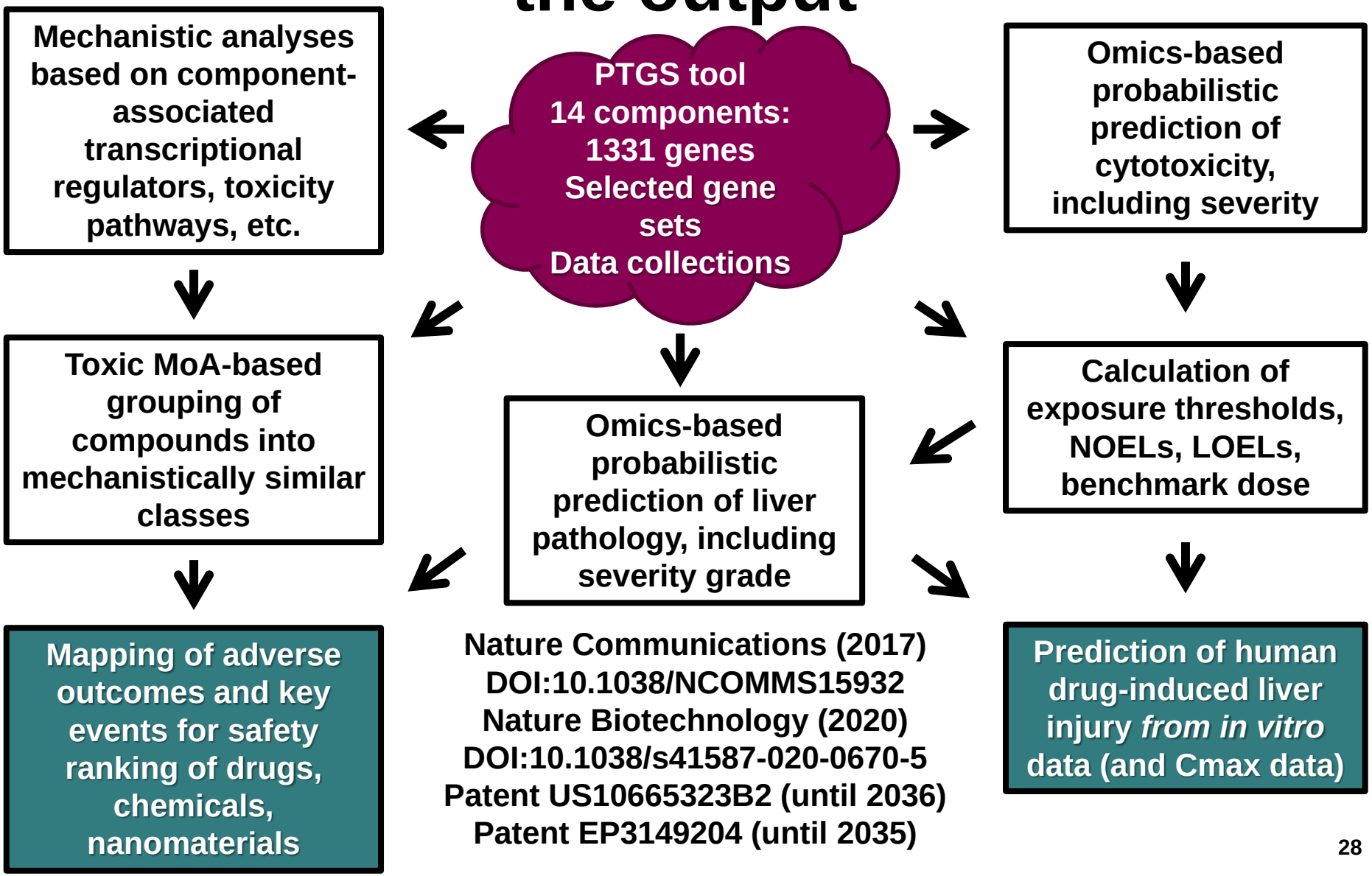
SABYDOMA Safety by design of nanomaterials-from lab manufacture to governance and communication: progressing up the TRL ladder" (April 2020-March 2024); *Misvik (**HTS, on-line model predictive control concept)***

HARMLESS Advanced high aspect ratio and multicomponent materials: towards comprehensive intelligent testing and safe by design strategies (Jan 2021-Dec 2024); *KI & Misvik* ***(tiered HTS; multiomics, AOP-based grouping)***

RISK-HUNT3R Risk assessment of chemicals integrating human centric next generation testing strategies promoting the 3Rs (June 2021-May 2026); *KI*; **Pekka Kohonen lead (DILI, multiomics, next generation risk assessment)**

PrecisionTox Toward precision toxicology: new approach methodologies for chemical safety (Jan 2021-May 2026); *Misvik*; **Vesa Hongisto lead (HTS for individual susceptibility biomarkers)**

The PTGS safety scoring concept – the output



Nature Communications (2017)
DOI:10.1038/NCOMMS15932
Nature Biotechnology (2020)
DOI:10.1038/s41587-020-0670-5
Patent US10665323B2 (until 2036)
Patent EP3149204 (until 2035)

PTGS concept- inherent capabilities

- Serves as a giant AOP-applicable toxicity biomarker that captures/describes dose response and MoA
- Can be applied in high throughput manner to diverse types of model systems and types of transcriptomics data: microarray, RNA seq, feature sets (EPA/NTP S1500+; LINCS L1000)
- Initial selection of toxicity-related genes serves to cover multiple toxicity pathways and to avoid unspecific gene expression noise
- Analysis is standardized, driven by data completeness and quality considerations, arbitrary differential gene expression cut-offs are eliminated, and all gene expression levels are taken into account (FAIR principle applied = reliable + transparent)
- The algorithm and bioinformatics processing concept applying GSEA outperforms common tests for analyzing cytotoxicity; PTGS test is commonly 1-2 order of magnitude more sensitive
- Scoring concept enables IVIVE both with or without PBPK data/modeling results and clinical data (e.g., Cmax values)

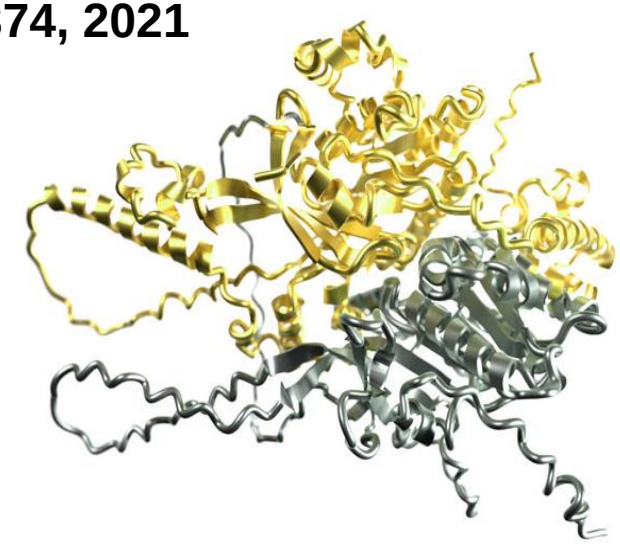
PTGS Implementation: “the new kid on the block”

- **PTGS constructed to decrease uncertainties in results**; builds on “Big Data” analysis and explainable AI/informatics methodology
- **Not complex in general terms**: gene expression changes bridging low to overt toxicity, coupled additionally to MoA via an easy to grasp low number of components
- **Toxicity/DILI predictions derived by a transparent two-component scoring metric and algorithms;** 14 gene set-based, variably overlapping component models is the basis
- **Ultra-sensitive toxicity detection** applicable in multiple cell types/tissues and contexts: molecular read across, safe-by-design, pharmacovigilance, etc.

PTGS Implementation: “the new kid on the block”

- **Effective drug side effects prediction implicates broader applicability,** i.e., to safety assessment of agents generally in consumer products (generates a “toxicity/hazard warning” with a potential turn-over of 2-3 weeks for 20+ compounds)
- **PTGS-driven toxicity predictions founded in AOPs**: validates the results relative animal and human risk assessment-relevant data
- Overall, **agrees with “replacement” under 3R** (1R), and might facilitate an **“one animal species testing regimen supported with NAM-derived data”** (instead of 2 species) in diverse regulations
- PTGS use agrees with **tiered testing** approaches and **complementarity** to established tools and methods

HUMPHREYS et al., SCIENCE 374, 2021



AI – based prediction of protein structures

“AI will not replace toxicologists, but those who don’t use AI will be replaced by those who do”

Stefan Platz
AstraZeneca
Senior Vice President of Clinical Pharmacology and Safety Sciences

SOT/EUROTOX Debate: Is There a Role for Artificial Intelligence and Machine Learning in Risk Decisions?

Is there NO role for artificial intelligence and machine learning in risk decisions!

frontiers in Artificial Intelligence

Disclaimer

The presenter actually thinks that A.I. is the best thing for toxicology since the-dose-makes-the-poison, i.e., hazard-is-not-risk

SOT SAN DIEGO
MARCH 27–31, 2022

Thomas Hartung: SOT/EUROTOX 2022 debate on AI

Contact details:

- Professor Roland Grafström, Institute of Environmental Medicine, Karolinska Institutet, Nobels väg 13, Box 210, 171 77 Stockholm, Sweden; roland.grafstrom@ki.se

- Predictomics AB, Sturegatan 38, lgh 1201, 114 36 Stockholm, Sweden; predictomicsab@gmail.com, grafstromrc@gmail.com (CEO: Roland Grafström)

- Misvik Biology OY, Karjakatu 35B, 205 20 Turku, Finland; Rantala@misvik.com (CEO: Juha Rantala)