Improved quantitative models of chemical toxicity based on combined application of chemical and biological molecular descriptors

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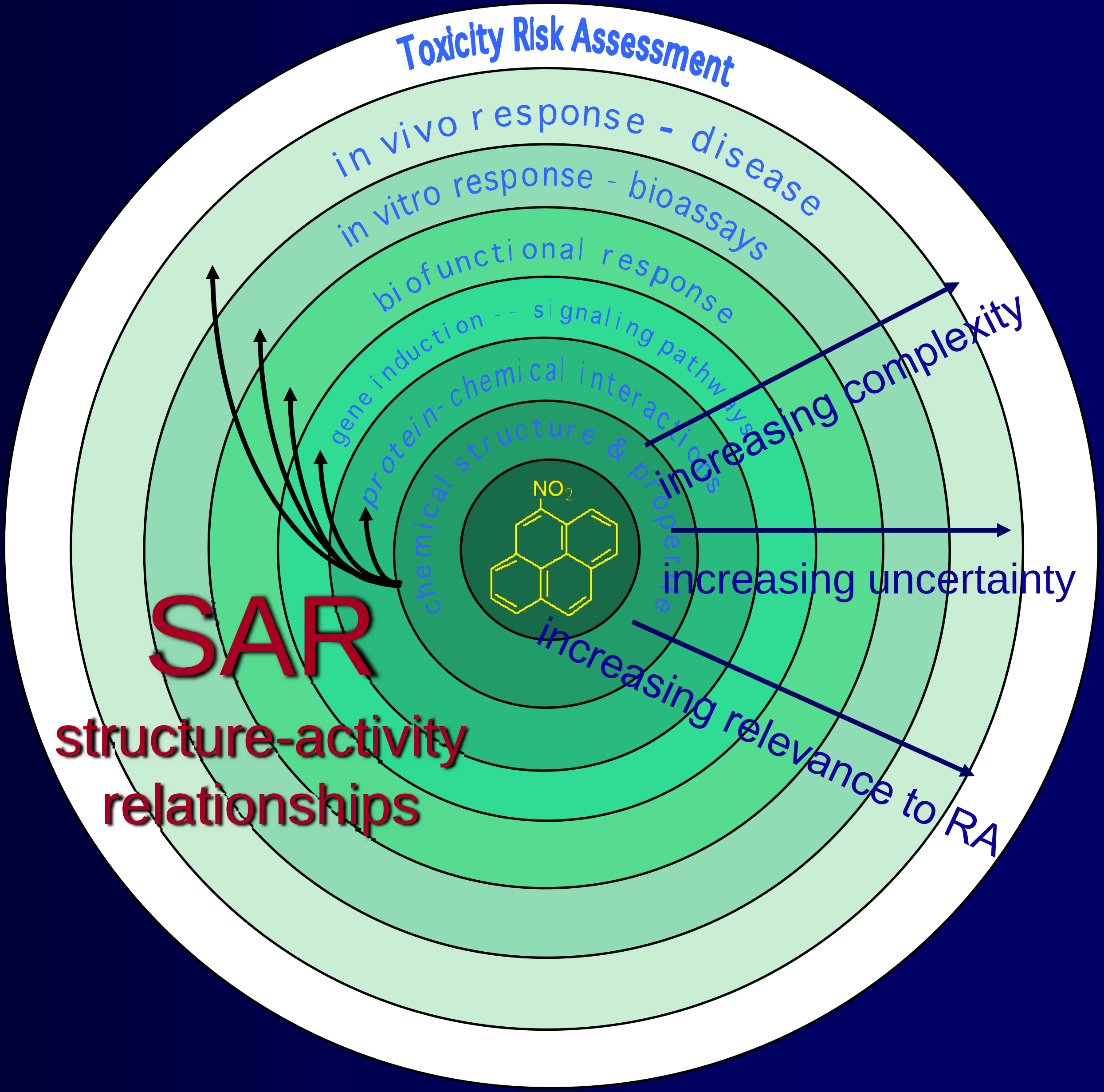
Outline

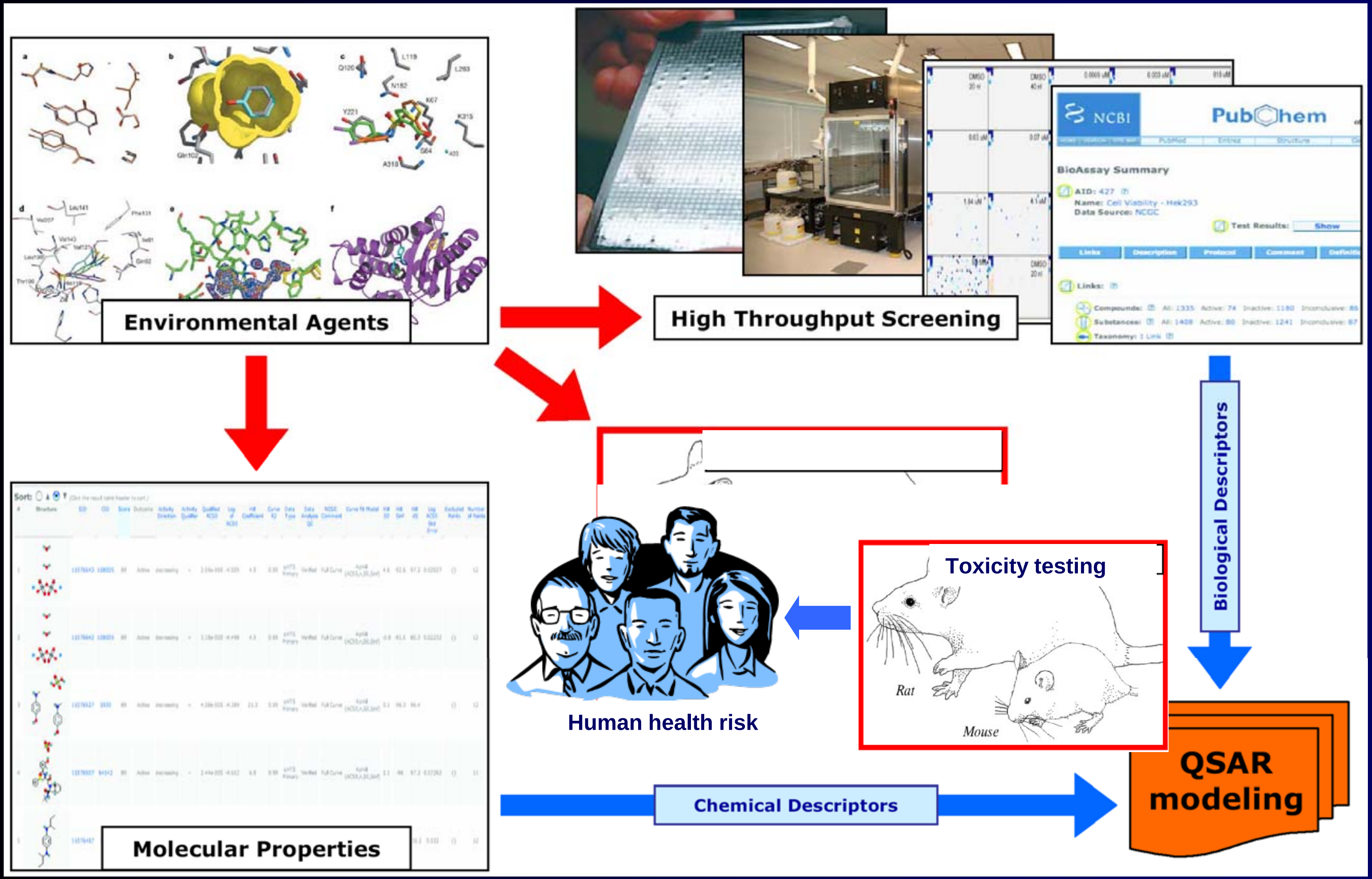
- Overall project vision: exploiting the entire structure – *in vitro* – *in vivo* continuum
- (briefly) Predictive QSAR Modeling Workflow
- Applications
  - novel data partitioning approach based on in vitro – in vivo correlations: Hierarchical QSAR modeling of rodent toxicity
  - analysis of ToxCAST data
    - Modeling of ToxRefDB endpoints using chemical descriptors only
    - Modeling selected *in vivo* end points using hierarchical QSAR modeling

Chemocentric view of biological data



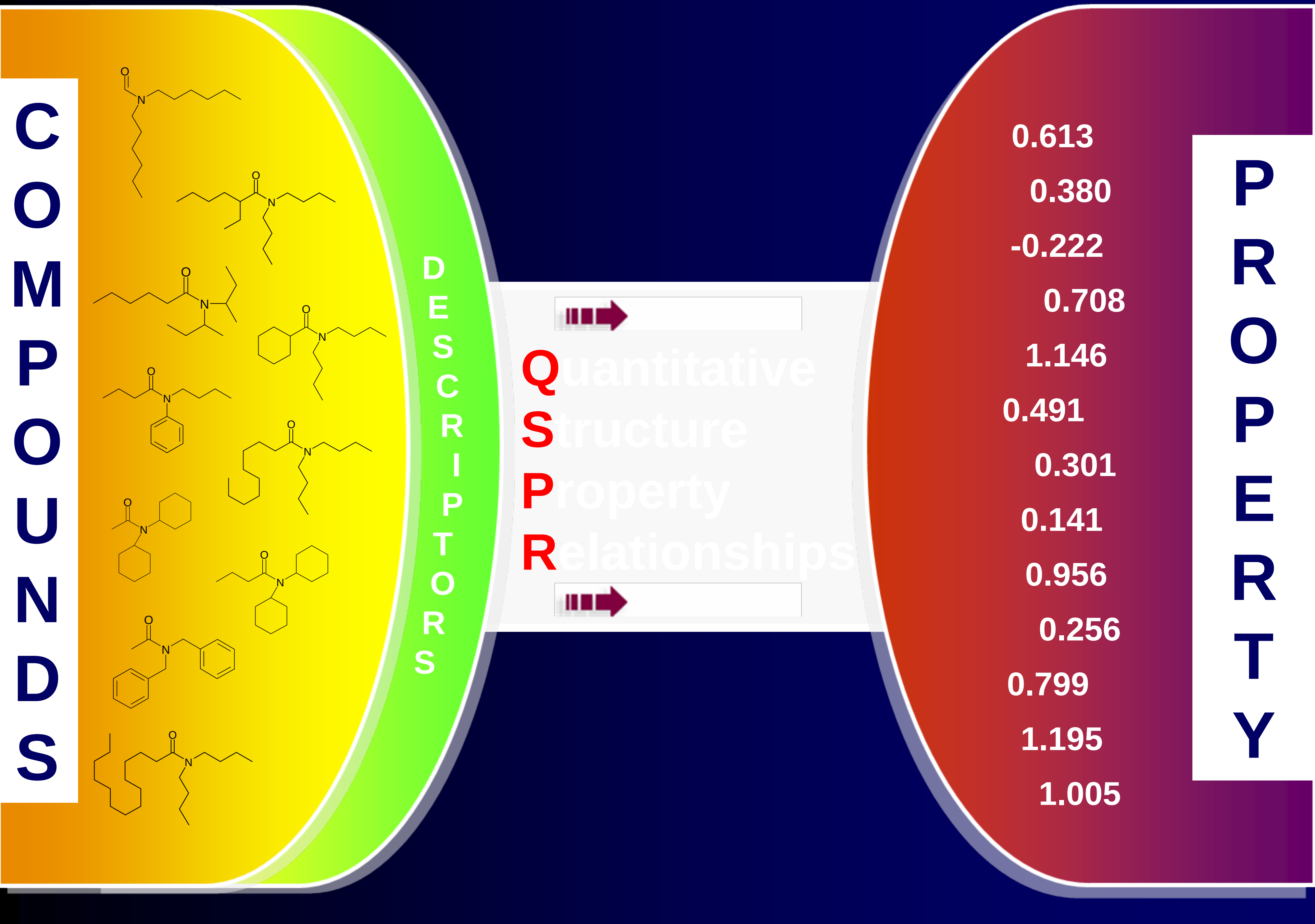
Slide courtesy of Dr. Ann Richard (EPA)

Chemical Structure – *in vitro* – *in vivo* Toxicity Data Continuum.



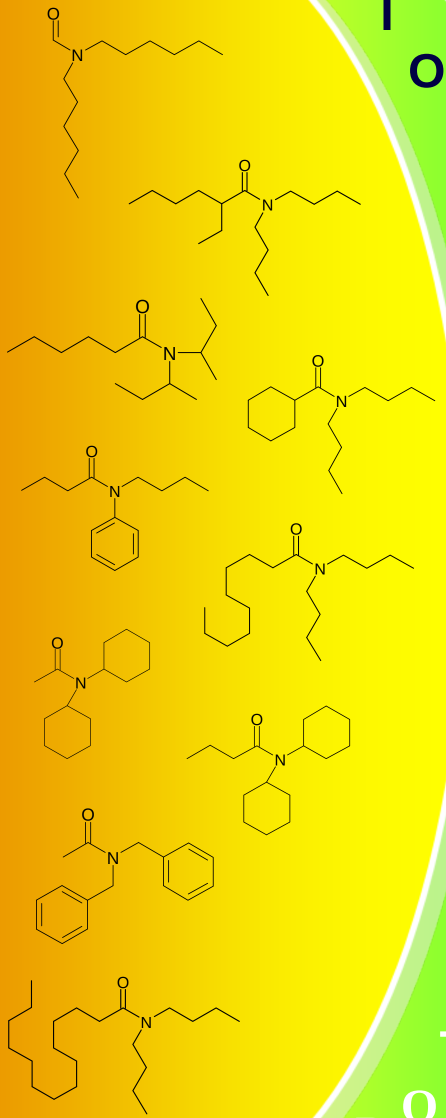
Slide is courtesy of Dr. Ivan Rusyn (UNC)

Principles of QSAR/QSPR modeling



Principle of QSAR/QSPR modeling

COMPOUNDS



BIOPROFILES + DESCRIPTORS

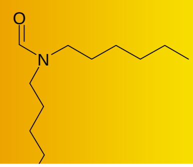
Quantitative **S**tructure **P**roperty **R**elationships

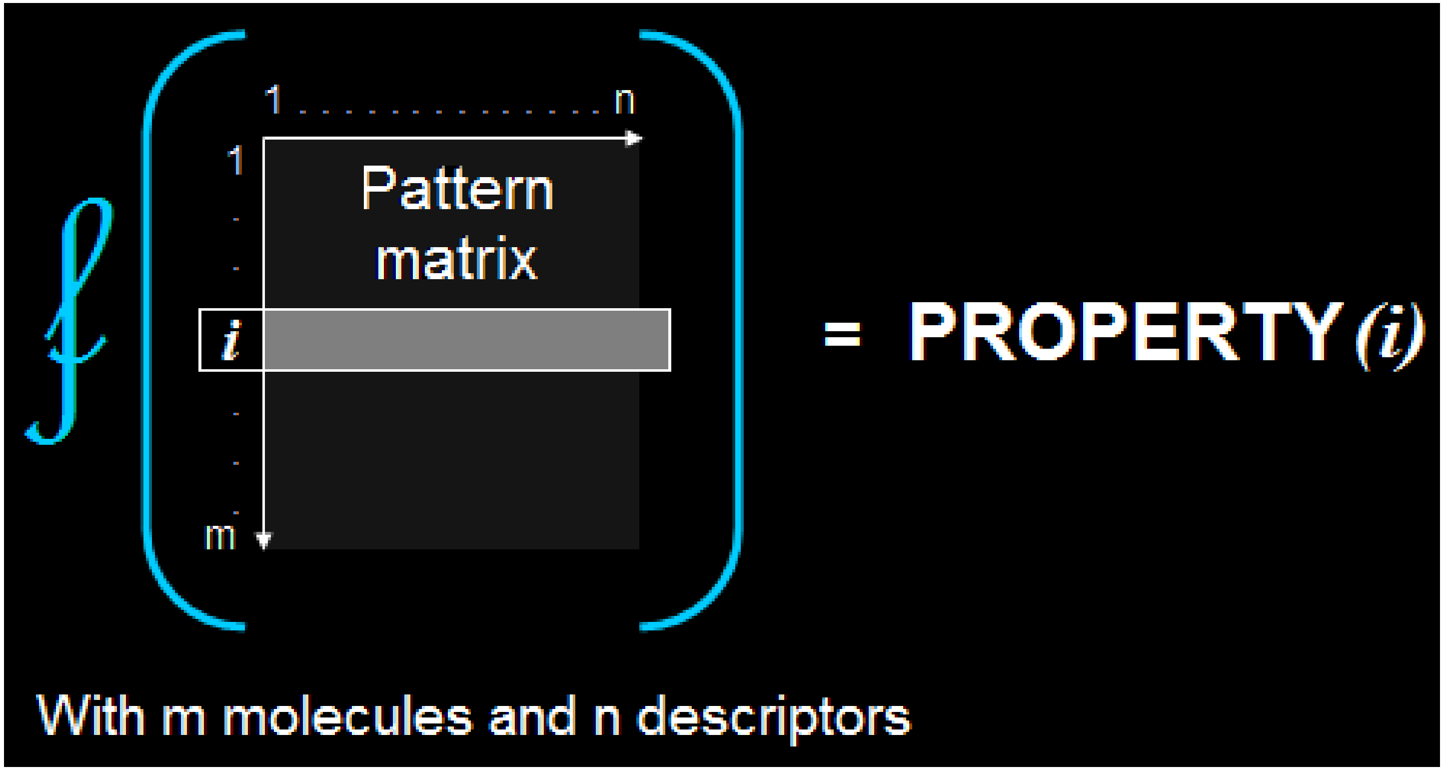
0.613
0.380
-0.222
0.708
1.146
0.491
0.301
0.141
0.956
0.256
0.799
1.195
1.005

PROPERTY

Principles of QSAR/QSPR modeling

C O M P O U N D S



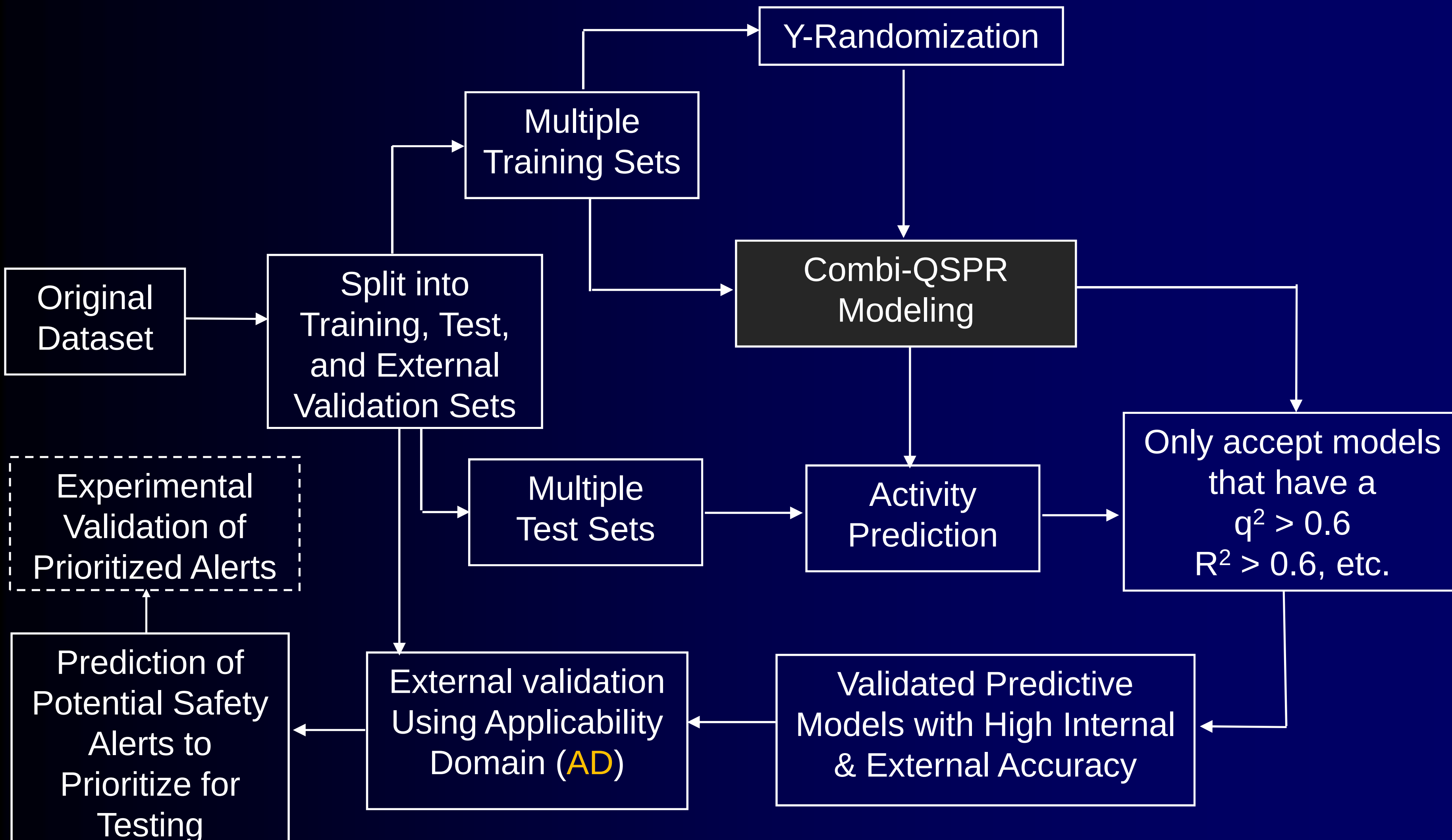


0.613

1.005

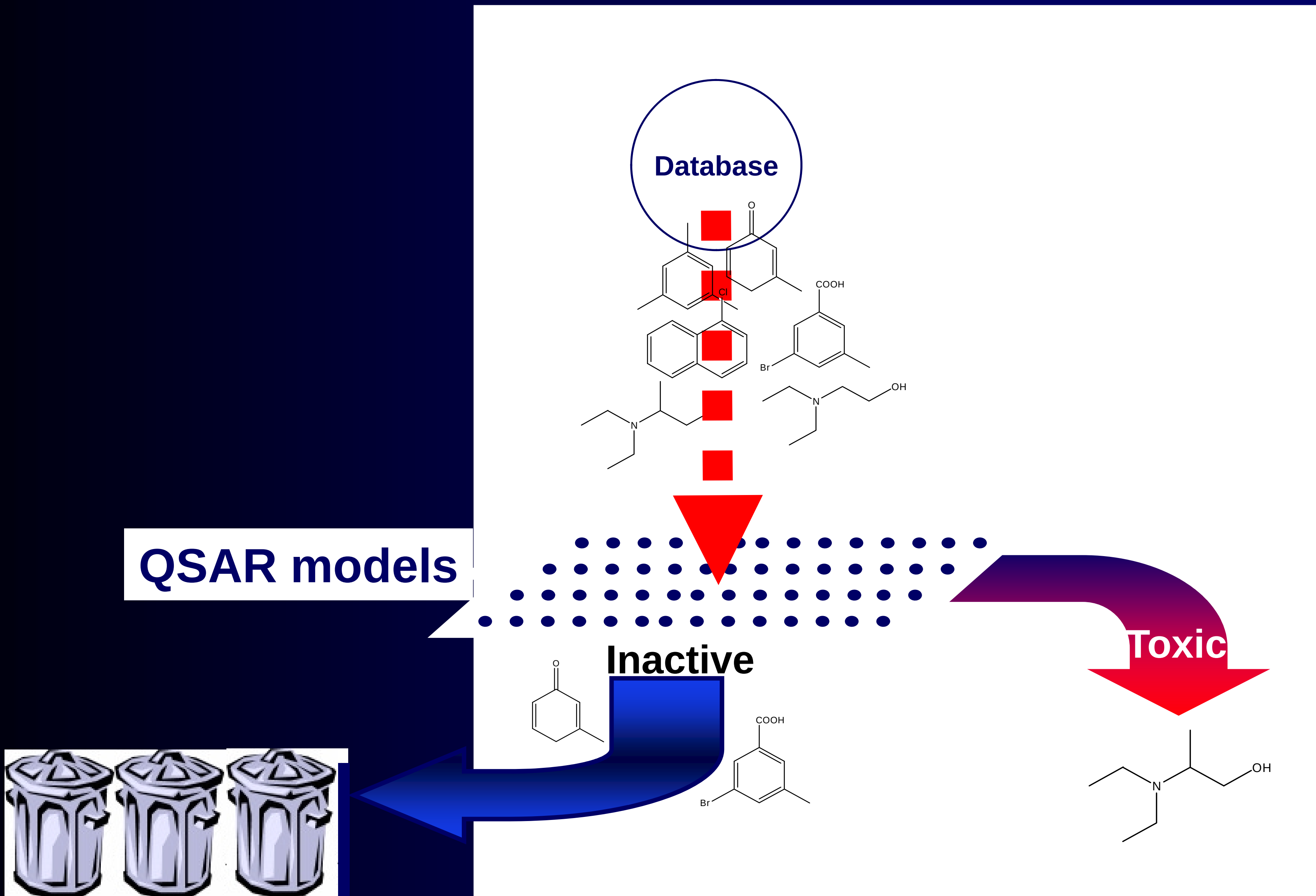
P R O P E R T Y

Predictive QSAR Workflow*



Tropsha, A., Golbraikh, A. Predictive QSAR Modeling Workflow, Model Applicability Domains, and Virtual Screening. Curr. Pharm. Des., 2007, 13, 3494-3504.

Compound prioritization using QSAR models



Experimental Study I: A Two-step Hierarchical QSAR Modeling Workflow for Predicting *in vivo* Chemical Toxicity*

*Zhu, Rusyn, Wright, et al, EHP, 2009(8), 1257-64; in collaboration with Ann Richard, NCCT, US EPA

ZEBET Database* and Data Preparation

361 compounds — cytotoxicity IC50 and both rat and/or mouse LD50

291 compounds — inorganics, mixtures and heavy metal salts are removed

253 compounds — both in vitro IC50 values and rat LD50 results

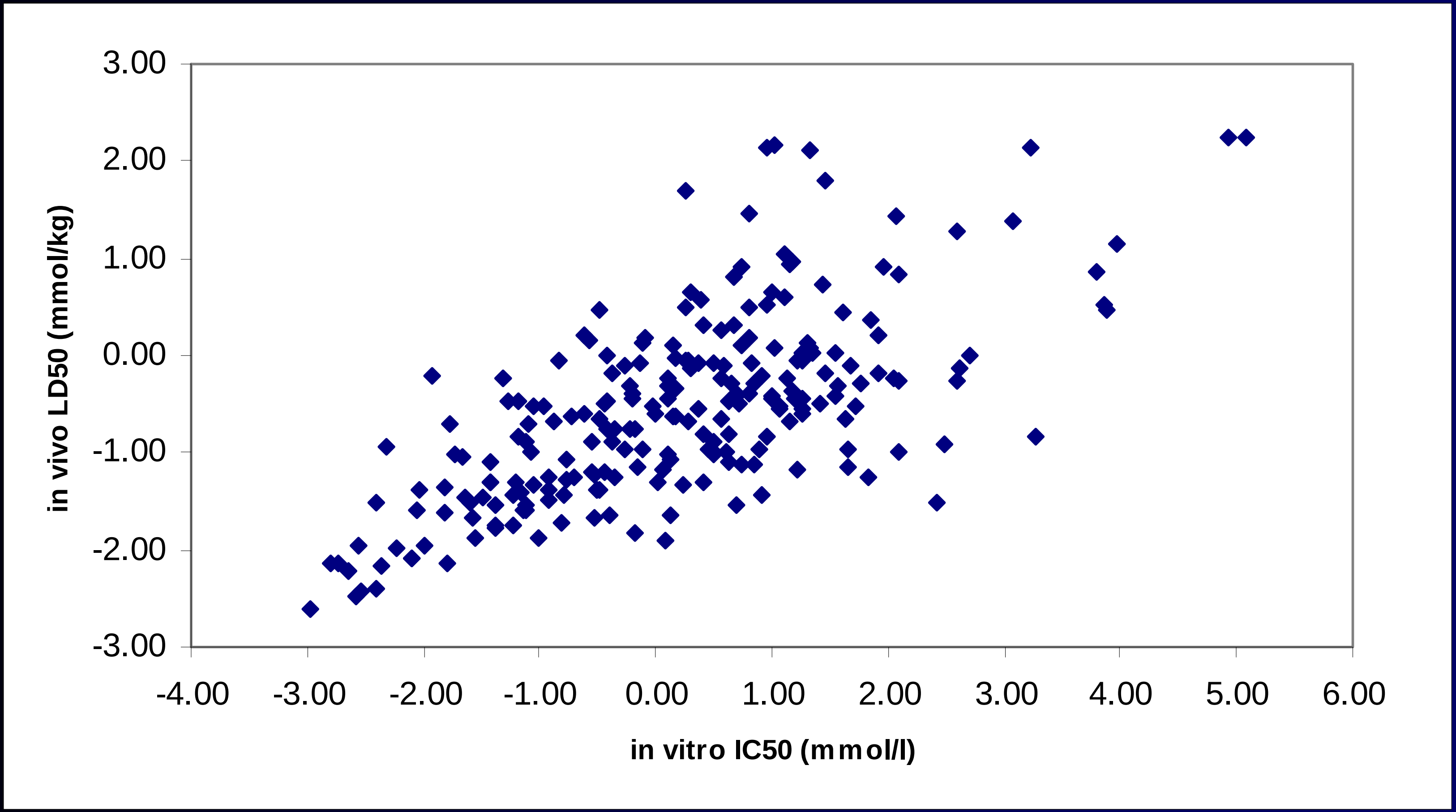
Random split

230 compounds modeling set

23 compounds validation set

**The ZEBET database was provided by Dr. Ann Richard (EPA)*

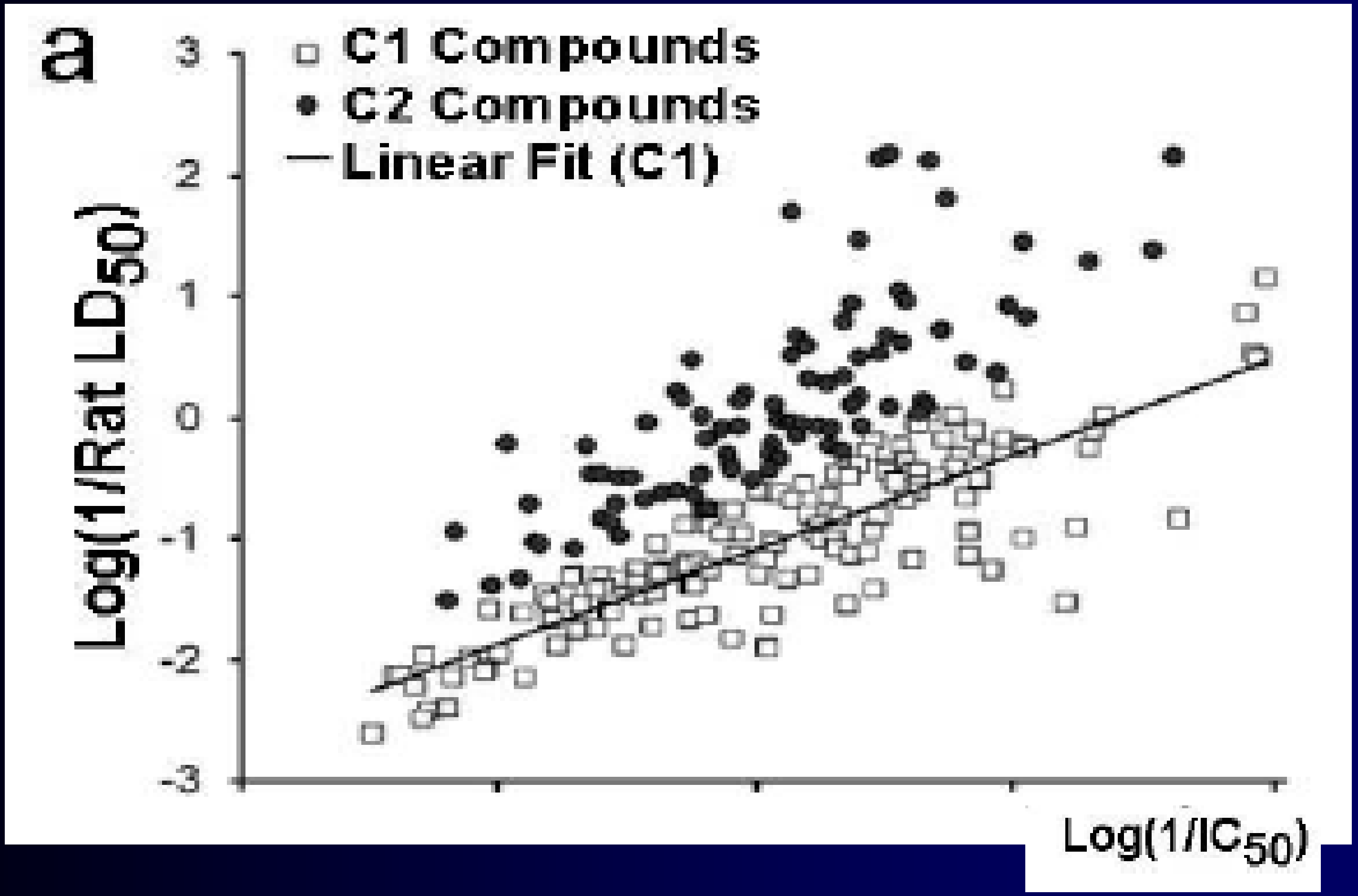
(Rather) poor in vitro-in vivo Correlation Between IC50 and Rat LD50 Values



$R^2=0.46$

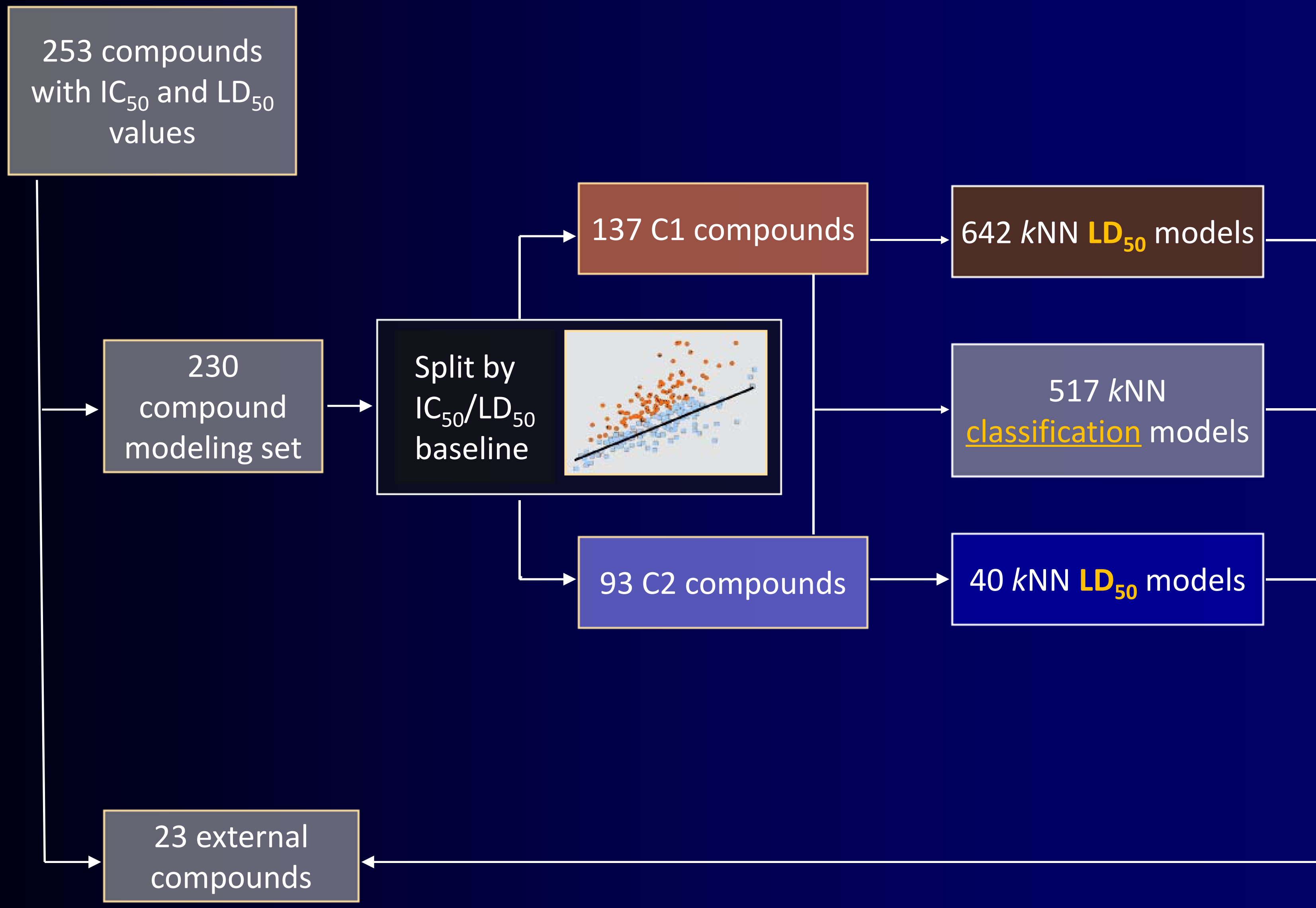
Data partitioning based on the moving regression approach

- IC50 vs. rat LD50 values

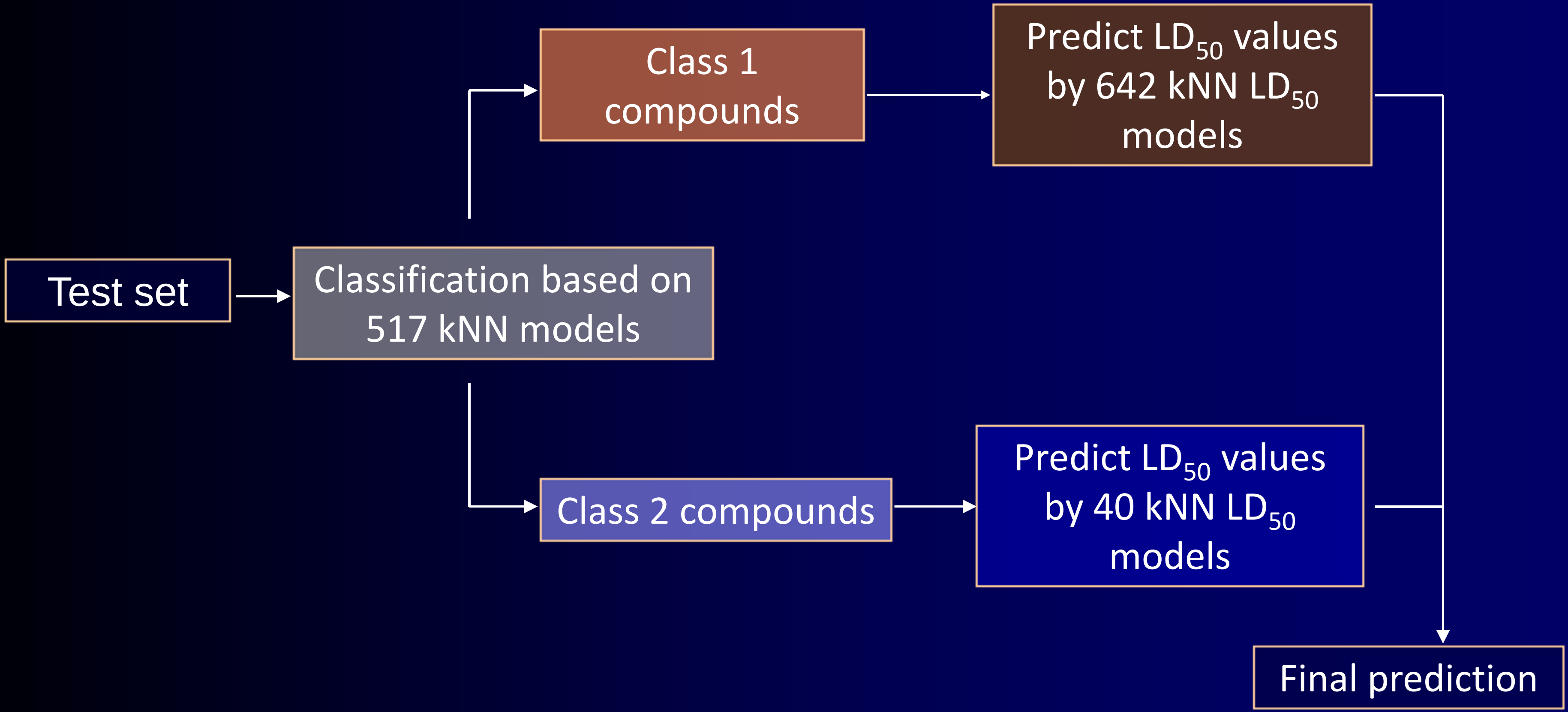


R^2=0.74 for Class 1 compounds

Modeling Workflow



Prediction Workflow



Classification of the Rat LD50 Values for the External Set of 23 Compounds

No AD:
Classification rate = 62%

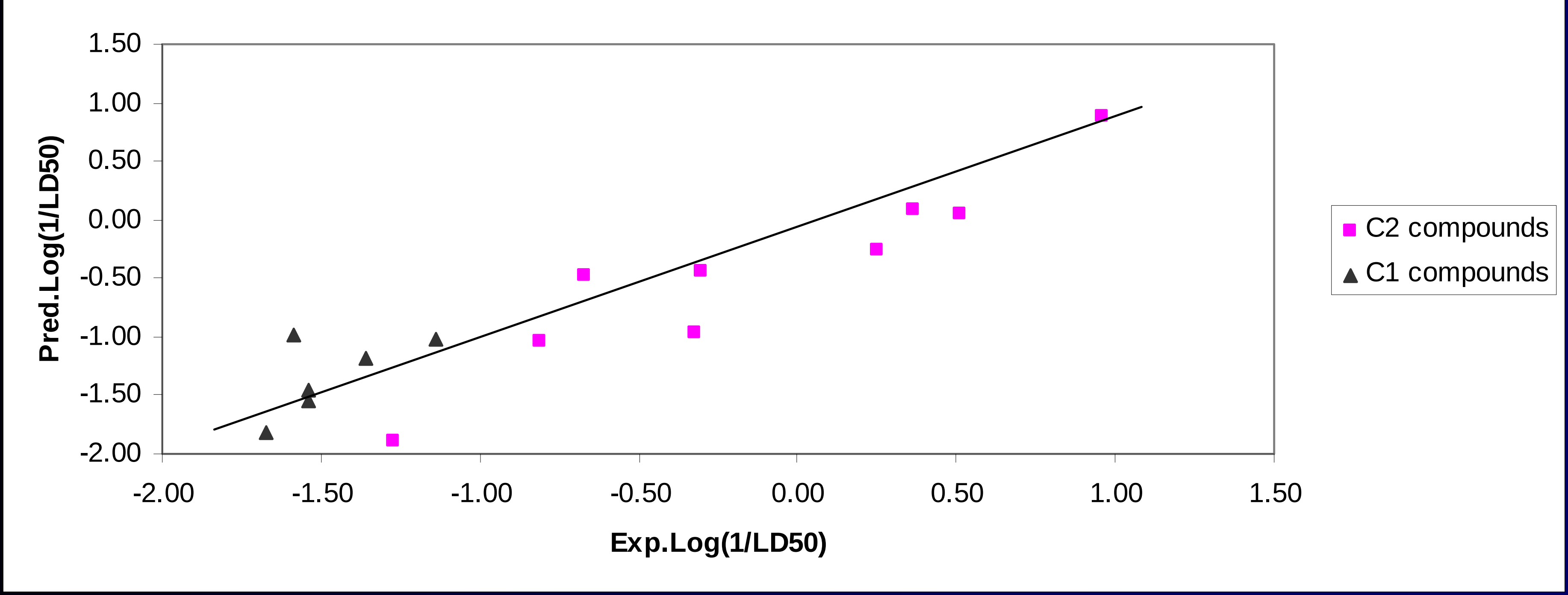
	Pred. C1	Pred. C2
Exp. C1	7	2
Exp. C2	6	5

With AD:
Classification rate = 78%

	Pred. C1	Pred. C2
Exp. C1	6	0
Exp. C2	4	5

Prediction of the Rat LD50 Values of the External 23 Compounds

- R^2=0.79, *MAE*=0.37, Coverage=74% (17 out of 23)



Experimental Study II:

Analysis of ToxCAST data:

(i) ToxRefDB Overview

(ii) Application of Hierarchical QSAR Approach

ToxRefDB* Summary

I. Effective Dose, in mg/kg/day

Chronic toxicity: CHR_Mouse (7); CHR_Rat (14)

Developmental toxicity: DEV_Rabbit (18); DEV_Rat (18)

Reproductive toxicity: Multigeneration, MGR_Rat (19)

-LTD, HTD - Lowest and Highest Tested Doses (10)

II. Category data:

- Supplementary carcinogenicity data,

lesions/tumors of various organs: Mouse (174); Rat(174)

- OPP Carcinogenic potential (2)

*http://www.epa.gov/NCCT/toxrefdb/

Toxcast Assays (08-07-2009). 320 chemical entries

Source	#	Type	Species	Description	Endpoint	Max. test conc.(μM)	≠0	0	N/A
ACEA	7	*In vitro*	*Human*	Cell-growth and morphology	IC50	100	17%	83%	0%
Attagene	73	*In vitro*	*Human*	Transcription factors	LEL	100	8%	92%	0%
BioSeek	174	*In vitro*	*Human*	BioMap system (pharmac.targets, adverse effects), protein markers	LEL	40	11%	89%	0%
Cellumen	57	*In vitro*	*Human*	Cellular toxicity indicators	IC50	200	11%	89%	0%
CellzDirect	42	*In vitro*	*Human*	Gene expression change (transport proteins, metabolic enzymes, etc)	LEL	40	17%	83%	0%
Gentronix	1	*In vitro*	*Human*	HTS (Genotoxicity)	LEL	200	10%	90%	0%
NCGC	18	*In vitro*	*Human(23); Rat(1)*	HTS (Nuclear receptor, cell viability and p53 assays)	IC50	200	3%	97%	0%
NovaScreen	239	*In vitro (biochem)*	*Human(146); Rat(67); Mouse(2); Rabbit(2); Pig(1); Guinea Pig(10); Sheep(2); Cow(9)*	HTS (ADME-Tox, enzyme, nuclear receptor, GPCR)	IC50	20 & 50	3%	97%	0%
Solidus	4	*In vitro*	*Human*	Cytotoxicity	LC50	960	22%	78%	0%
Genes	315	*Mapped*	*Human(231); Rat(65); Mouse(2); Pig(1); Guinea Pig(6); Sheep(2); Cow(8)*	values = min. LEL (over all the assays relevant to the particular gene)	LEL	-	9%	91%	0%
Pathways	438	*Mapped*	*Human(425); Rat(7); Mouse(6)*	min.LEL if > 5 mapped assays	LEL	-	8%	92%	0%
ToxRefDB	76	*In vivo*	*Rat(51); Mouse(7); Rabbit(18)*	In-vivo animal toxicity (mg/kg/day)	LEL	≈10g/kg/day	11%	68%	21%
ToxRefDB	10	*In vivo*	*Rat(6); Mouse(2); Rabbit(2)*	In-vivo animal toxicity (mg/kg/day)	LTD, HTD	HTD	79%	0%	21%
	348	*In vivo*	*Rat(174); Mouse(174)*	Carcinogenicity data	Binary	-	2%	77%	21%
OPP Carc	2	*In vivo*	*Rodents*	Human carcinogen risk judgement	Score	-	22%	46%	32%

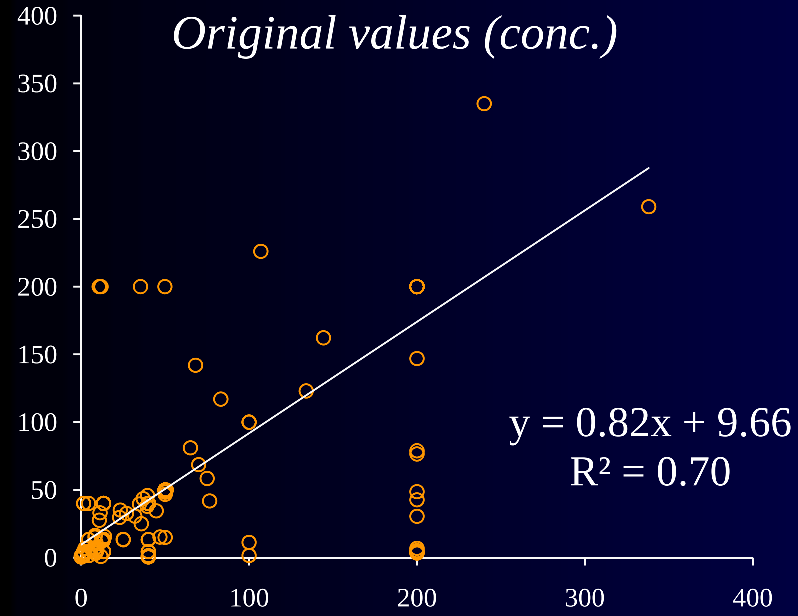
LEL – lowest effective level; LTD, HTD – lowest, highest tested dose

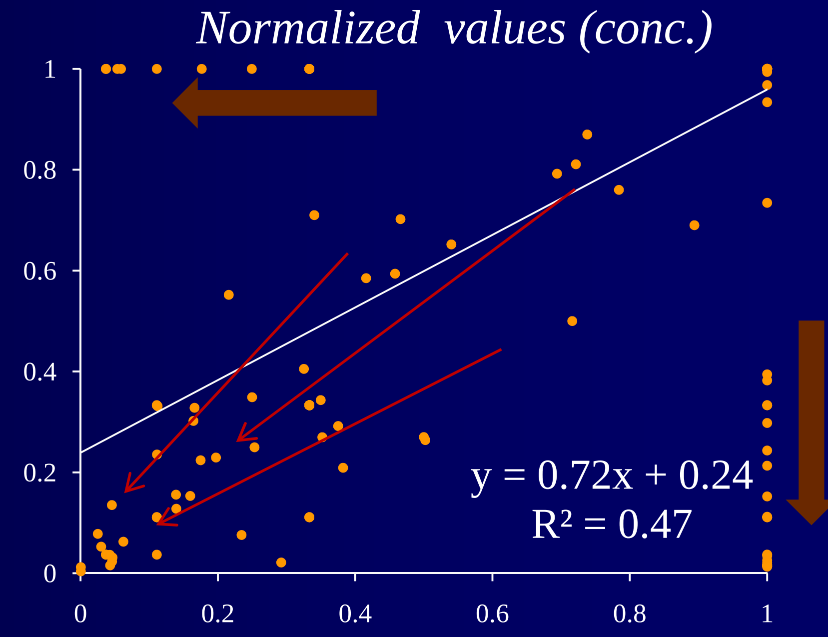
Comparison of the ToxCAST *in vitro* Assay Results for Duplicates/Triplicates (QC)

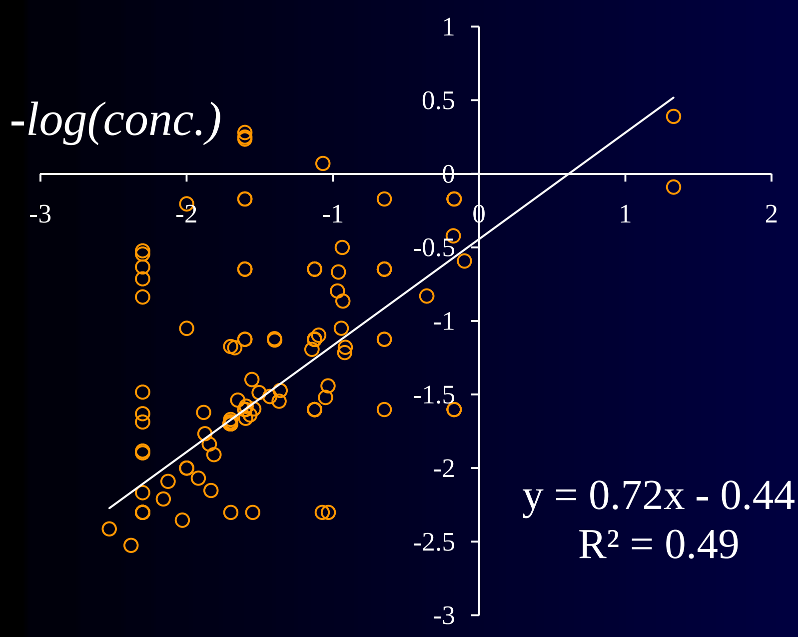
	Assay->	Total	ACEA	ATG	BSK	Cellu	CLZD	NVS	NCGC	Total	ACEA	ATG	BSK	Cellu	CLZD	NVS	NCGC
	n=	*610*	*7*	*73*	*174*	*57*	*42*	*239*	*18*	*610*	*7*	*73*	*174*	*57*	*42*	*239*	*18*
CAS	**Chemical**	R correlation coefficients (-log [Conc.])								# of non-zero signals							
55406-53-6	3-Iodo-2-propynyl-butylcarbamate	0.70	0.91	NA	0.57	0.40	0.44	0.93	NA	90	4	0	48	15	1	17	0
741-58-2	Bensulide	0.87	0.38	0.97	0.16	0.35	0.47	0.91	1.00	83	2	4	14	12	17	30	2
64902-72-3	Chlorsulfuron	0.67	NA	NA	-0.03	NA	0.00	1.00	NA	1	0	0	1	0	0	0	0
84-74-2	Dibutyl phthalate	0.74	NA	0.60	0.02	-0.02	0.02	0.95	NA	22	0	4	12	1	1	4	0
51338-27-3	Diclofop-methyl	0.88	1.00	0.97	0.22	0.45	0.31	0.26	1.00	23	2	4	11	1	3	1	2
759-94-4	EPTC	0.89	NA	NA	-0.01	NA	0.98	0.00	NA	3	0	0	0	0	3	0	0
66441-23-4	Fenoxaprop-ethyl	0.85	NA	0.33	-0.02	0.10	0.00	0.03	NA	21	0	1	17	2	0	1	0
94125-34-5	Prosulfuron	0.86	NA	0.66	-0.02	NA	0.71	0.50	NA	9	0	1	3	0	5	1	0
		R correlation coefficients (binary data)								Accuracy (binary data) = (TP + TN)/(TP+TN+FP+							
55406-53-6	3-Iodo-2-propynyl-butylcarbamate	0.74	0.73	NA	0.70	0.47	0.48	0.89	NA	0.93	0.86	0.99	0.86	0.74	0.93	0.98	1.00
741-58-2	Bensulide	0.76	0.55	0.94	0.56	0.43	0.76	0.94	1.00	0.94	0.79	0.99	0.90	0.75	0.87	0.99	1.00
64902-72-3	Chlorsulfuron	0.07	NA	NA	0.07	NA	NA	NA	NA	0.97	0.71	0.99	0.91	0.98	0.95	1.00	1.00
84-74-2	Dibutyl phthalate	0.49	NA	0.52	0.48	0.49	0.38	0.81	NA	0.94	0.57	0.90	0.89	0.95	0.88	0.99	1.00
51338-27-3	Diclofop-methyl	0.53	1.00	1.00	0.40	0.48	0.45	0.35	1.00	0.95	1.00	1.00	0.86	0.92	0.85	0.99	1.00
759-94-4	EPTC	0.27	NA	NA	-0.04	NA	1.00	NA	NA	0.98	0.86	1.00	0.92	1.00	1.00	1.00	1.00
66441-23-4	Fenoxaprop-ethyl	0.53	NA	0.43	0.65	0.35	NA	0.35	NA	0.95	0.71	0.95	0.90	0.89	0.98	0.98	1.00
94125-34-5	Prosulfuron	0.47	NA	0.70	0.23	NA	0.77	1.00	NA	0.98	1.00	0.99	0.93	0.98	0.94	1.00	1.00

triplicate results are averaged; shaded cells reflect significant # of signals

ToxCast Assays comparison example : 3-Iodo-2-propynylbutylcarbamate

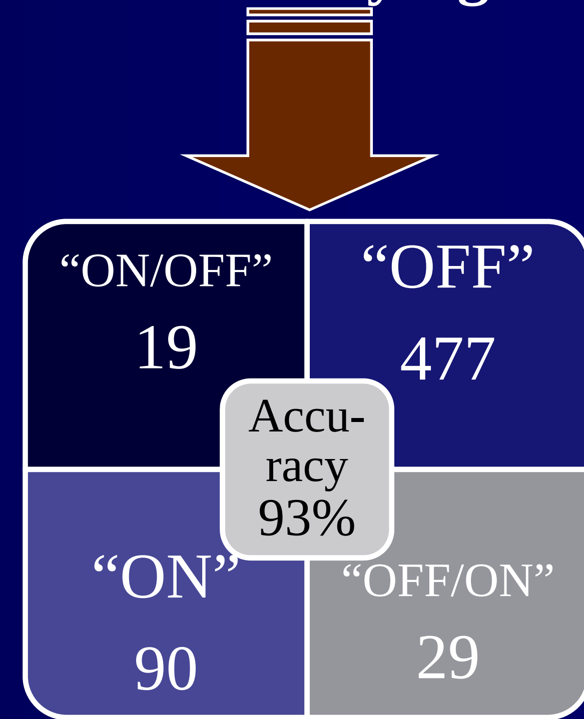






Quantitave data too "noisy"…

Binary signal



Data Curation

- *In-vitro* assays: 615→ 284
  - Remove one of two highly correlated (R^2 >0.95) assays and low-signal (<10 non-zero entries) assays
- Chemicals: 320 → 230~250
  - duplicate structures, mixtures, inorganic compounds, macromolecules were removed
  - Kept only those for which ***in-vivo*** data is available

    (may vary for different endpoints)

Focusing on a small subset of data: Multi-Generation Rat Toxicity

- Important: Reproductive Toxicity
- 3 out of 19 assays with the highest fraction of actives chosen for initial studies:

  MGR_Rat_Kidney (78 actives)

  MGR_Rat_Liver (110 actives)

  MGR_Rat_ViabilityPND4 (70 actives)

Conventional QSAR Modeling

- Using chemical descriptors only:

  -1224 Dragon chemical descriptors

- QSAR approaches:

  - Random Forest (RF)

  - SVM linear kernal

  - SVM rbf kernel

Breiman L. Machine Learning 45 (2001): 5-32

5-Fold Cross Validation Result

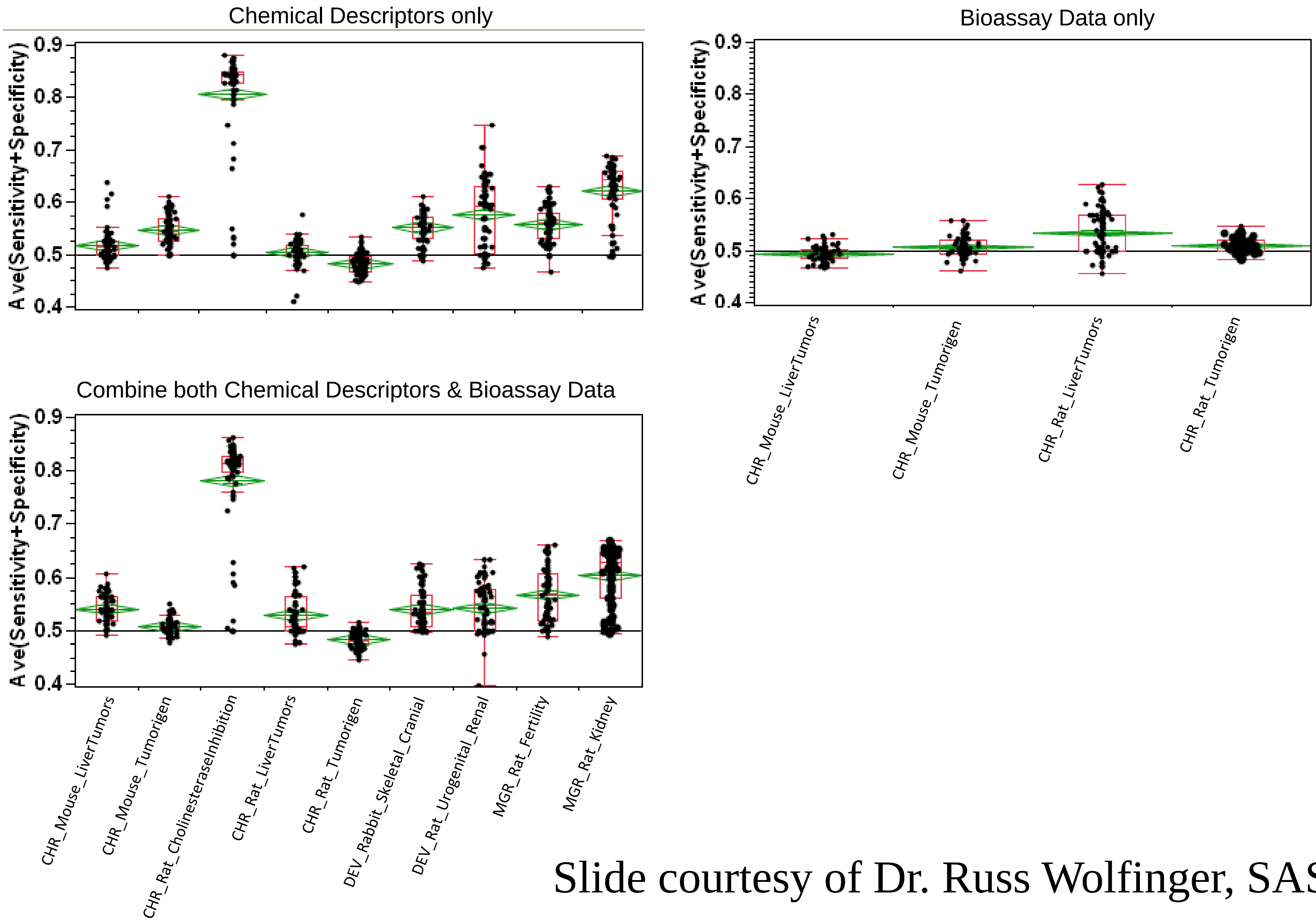
	MGR_Rat Kidney	MGR_Rat Liver	MGR_Rat ViabilityPND4
RF sensitivity	0.22	0.53	0.12
RF specificity	0.90	0.75	0.93
RF CCR	**0.56**	**0.64**	**0.53**
SVM_linear sensitivity	0.35	0.56	0.32
SVM_linear specificity	0.65	0.64	0.73
SVM_linear CCR	**0.50**	**0.60**	**0.53**
SVM_rfb sensitivity	0.37	0.61	0.23
SVM_rfb specificity	0.81	0.69	0.83
SVM_rfb CCR	**0.59**	**0.65**	**0.53**

$$CCR = \frac{1}{K}\sum_{k=1}^{K}\frac{N_k^{corr}}{N_k^{total}}$$

In vivo toxicity prediction using either biological or hybrid (chemical plus biological descriptors)

- Using ToxCAST bioassay results as biological descriptors did not result in any statistically significant models.
- The use of hybrid (biological + chemical descriptors) did not improve the results either.
- These results are similar to the analysis of ToxCAST data by the SAS team.

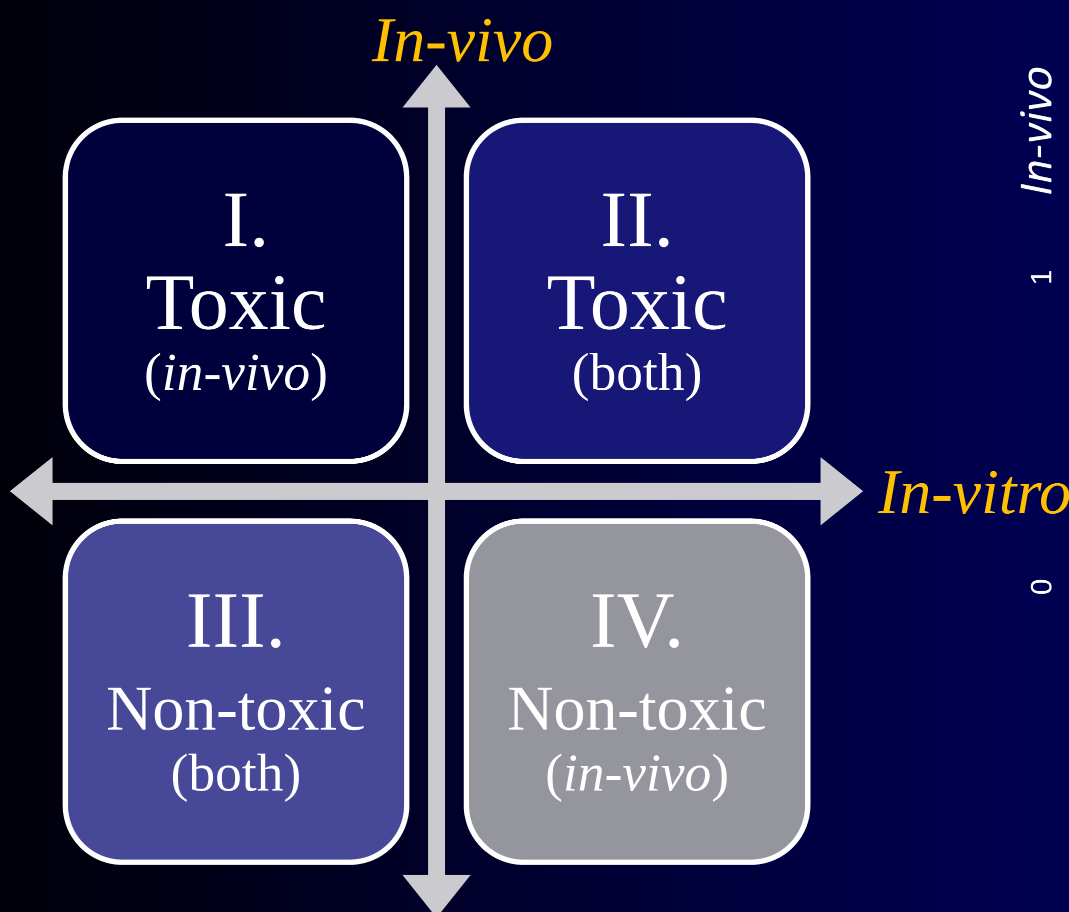
Prediction Comparison Based on Ave (Sensitivity + Specificity)

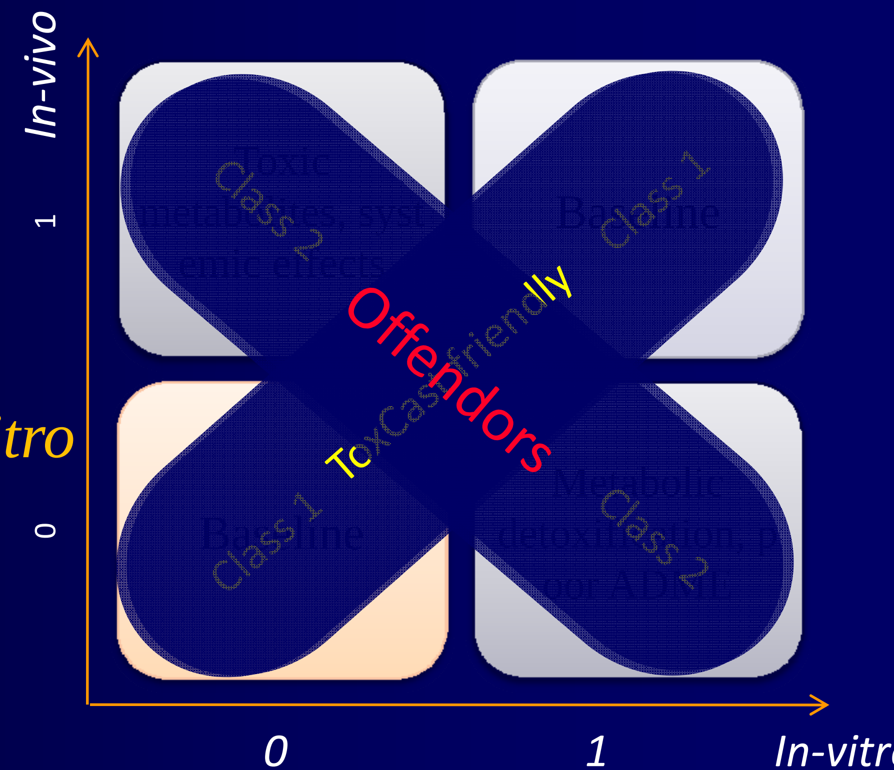


Slide courtesy of Dr. Russ Wolfinger, SAS

Data partitioning based on *in vitro-in vivo* correlations as part of the QSAR Modeling workflow

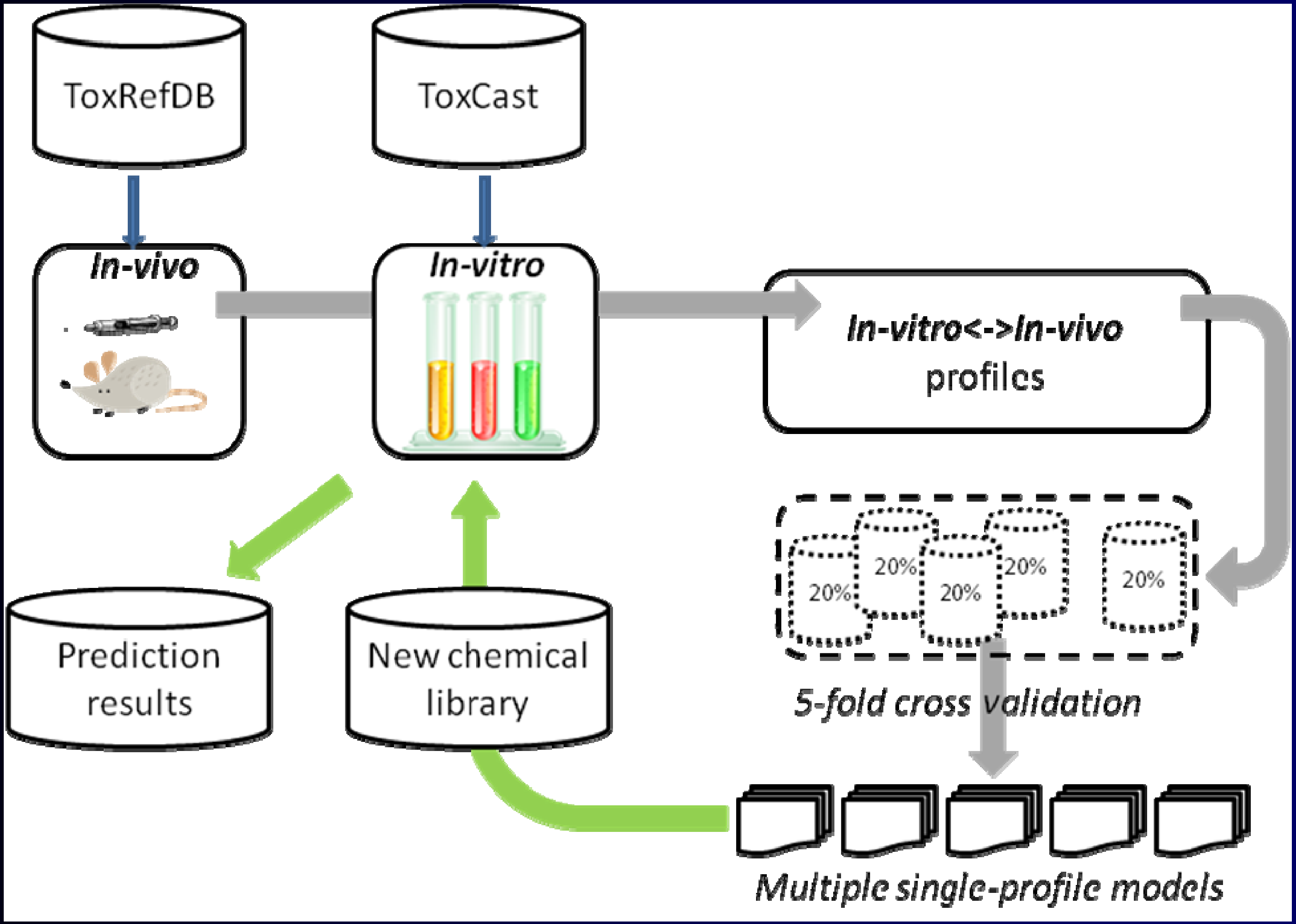
For <u>each</u> In-vitro vs. *In-vivo* profile (~1000 combinations):



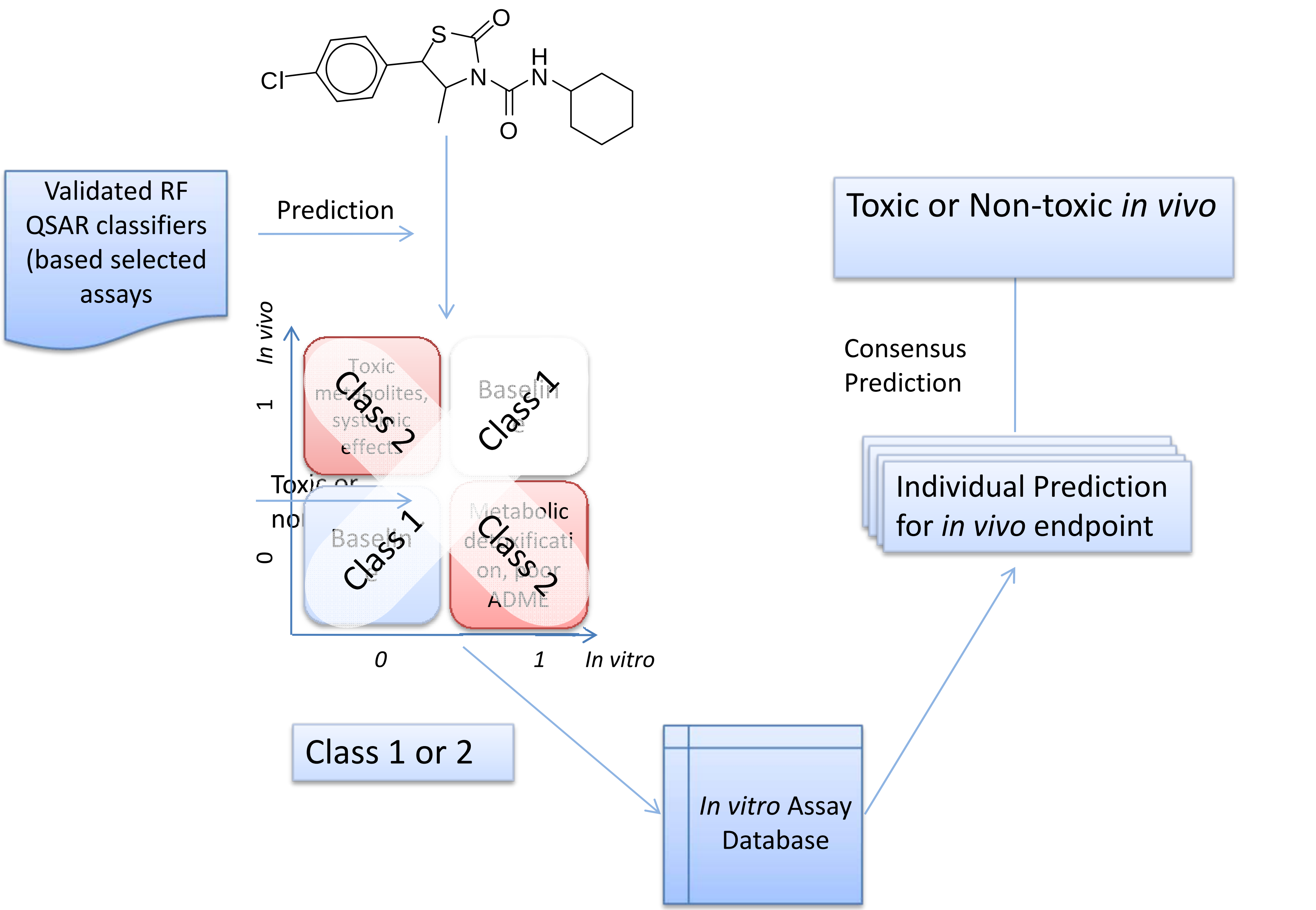


- Binary classification QSAR for "baseline" (II & III) vs. off-line (I & IV) using chemical descriptors only

Modeling Workflow for ~1000 in vitro – in vivo Series Using Various QSAR Approaches and Dragon descriptors



External prediction workflow



General Consensus Prediction Gave the Similar Prediction Accuracy Compared to Conventional QSAR Model

	MGR_Rat Kidney		**MGR_Rat Liver**		**MGR_Rat ViabilityPND4**	
	Hybrid	Chemical	Hybrid	Chemical	Hybrid	Chemical
RF sensitivity	0.25	0.22	0.6	0.53	0.12	0.12
RF specificity	0.88	0.90	0.77	0.75	0.93	0.93
RF CCR	**0.57**	**0.56**	**0.69**	**0.64**	**0.53**	**0.53**
SVM_linear sensitivity	0.37	0.35	0.56	0.56	0.34	0.32
SVM_linear specificity	0.68	0.65	0.67	0.64	0.73	0.73
SVM_linear CCR	**0.53**	**0.50**	**0.61**	**0.60**	**0.53**	**0.53**
SVM_rfb sensitivity	0.35	0.37	0.6	0.61	0.25	0.23
SVM_rfb specificity	0.81	0.81	0.7	0.69	0.83	0.83
SVM_rfb CCR	**0.58**	**0.59**	**0.65**	**0.65**	**0.54**	**0.53**

Possible Reasons for the Lack of Significant Improvement

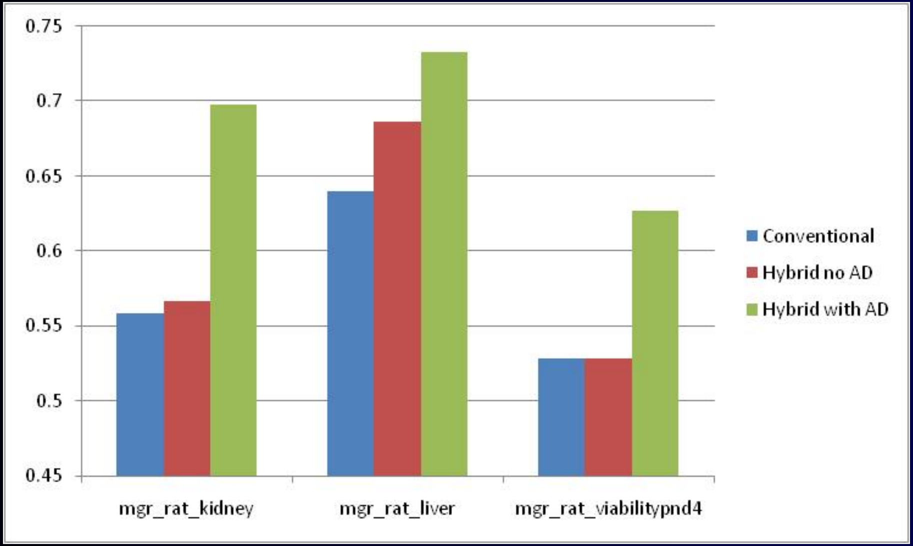
- 1. The quality of the data
- 2. Too many irrelevant bioassays were included in the consensus prediction

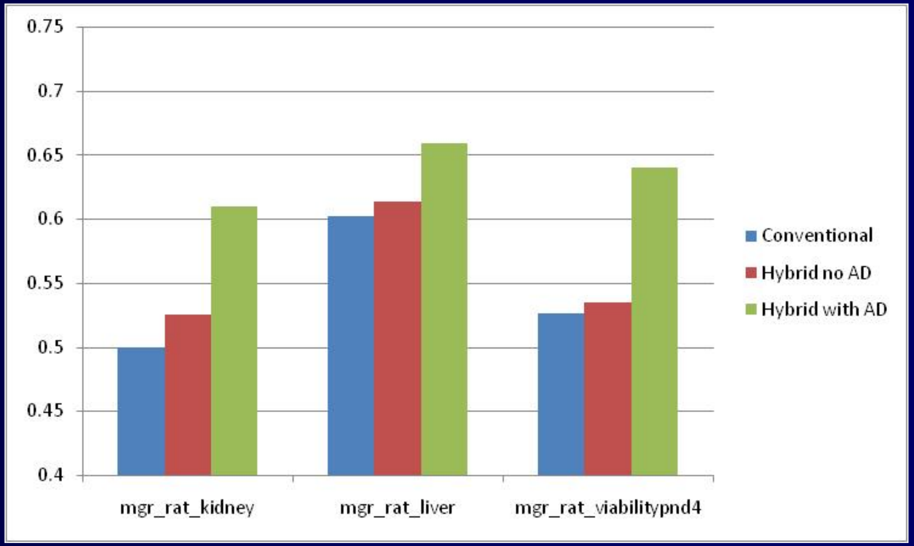
- Solution: the use of more restrictive threshold for active/inactive definitions as a special <u>Applicability Domain</u>
- >0.7 instead of 0.5 was used to define actives; <0.1 instead of 0.5 was used to define inactives.

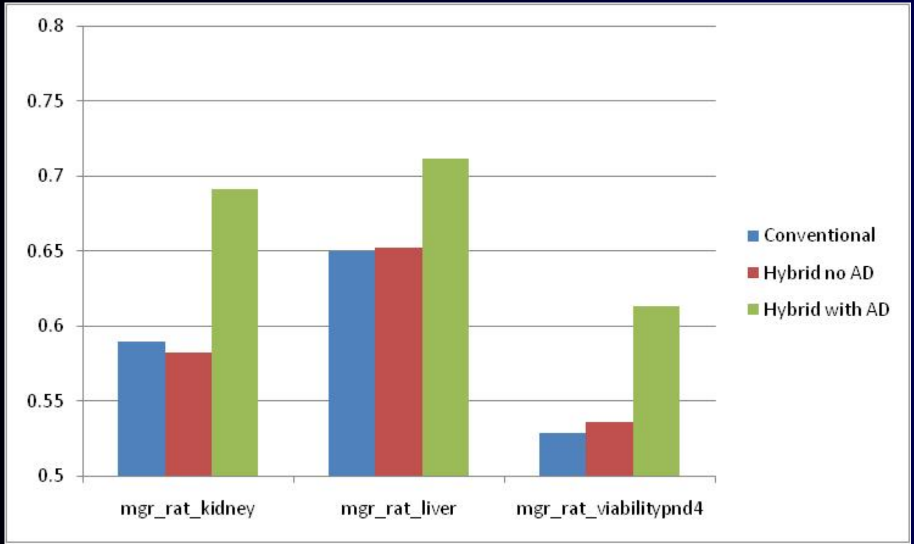
General Consensus Prediction Gave Clear Better Prediction Accuracy with Applicability Domain

	MGR_Rat Kidney		MGR_Rat Liver		MGR_Rat ViabilityPND4	
	Hybrid	Chemical	Hybrid	Chemical	Hybrid	Chemical
RF sensitivity	0.56	0.22	0.77	0.53	0.33	0.12
RF specificity	0.84	0.90	0.70	0.75	0.92	0.93
RF CCR	**0.70**	**0.56**	**0.73**	**0.64**	**0.63**	**0.53**
SVM_linear sensitivity	0.70	0.35	0.86	0.56	0.71	0.32
SVM_linear specificity	0.52	0.65	0.46	0.64	0.57	0.73
SVM_linear CCR	**0.61**	**0.50**	**0.66**	**0.60**	**0.64**	**0.53**
SVM_rfb sensitivity	0.68	0.37	0.86	0.61	0.48	0.23
SVM_rfb specificity	0.71	0.81	0.56	0.69	0.75	0.83
SVM_rfb CCR	**0.69**	**0.59**	**0.71**	**0.65**	**0.61**	**0.53**

Comparison of Prediction Accuracy (CCR) of Conventional and Hybrid QSAR Models







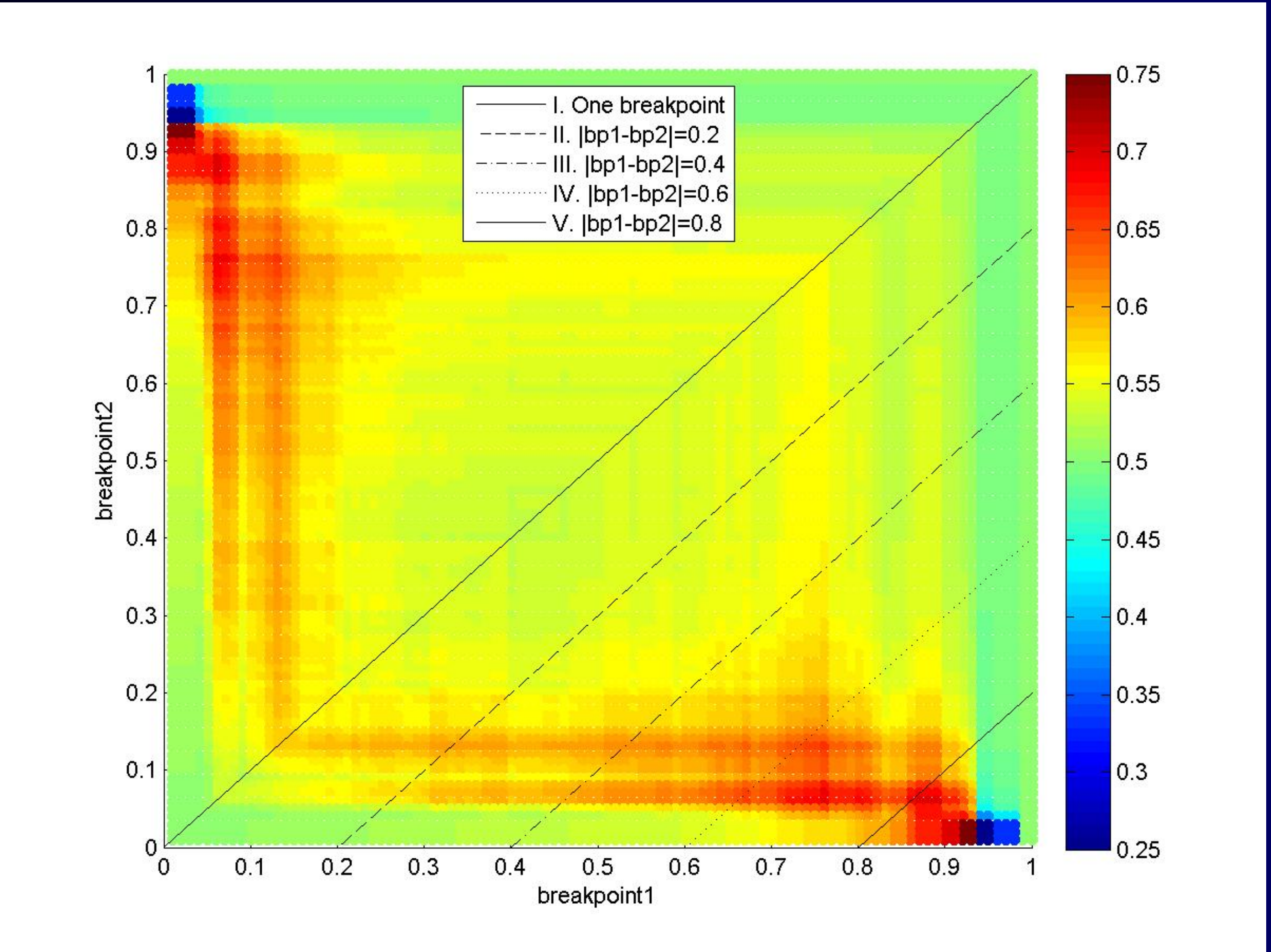
- RF Models
- SVM linear kernel models
- SVM rbf kernel models

The Coverage is Reasonable for the Resulting Models

	MGR_Rat Kidney	MGR_Rat Liver	MGR_Rat ViabilityPND4
RF	0.41	0.56	0.40
SVM_linear	0.61	0.66	0.64
SVM_rbf	0.43	0.53	0.38

Using Different Thresholds Could Result in Different Prediction Accuracy

SVM_rbf MGR_Rat ViabilityPND4 results:

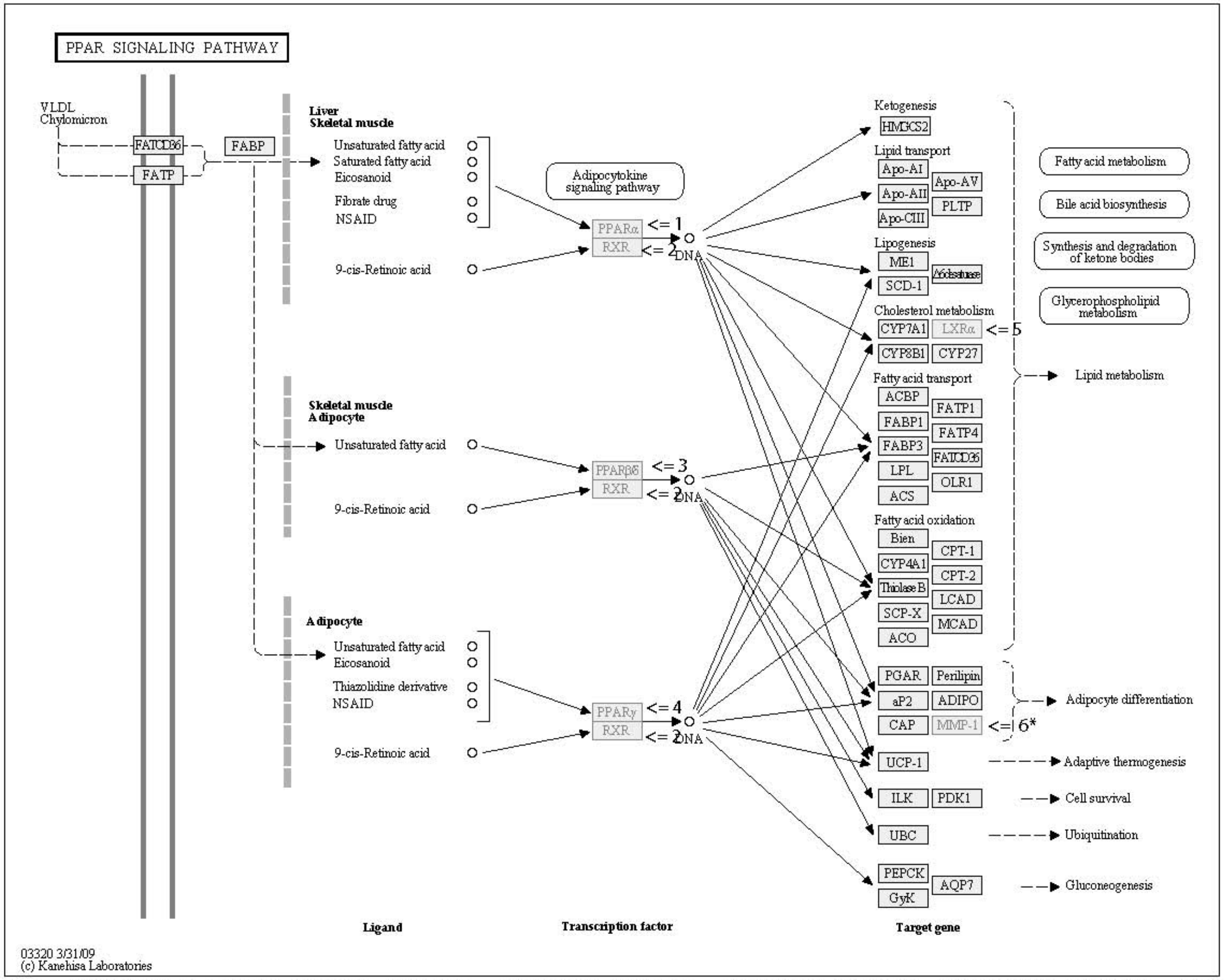


The Use of Toxicological Pathway Information to Improve the Model*

- There are three groups of data could be relevant to toxicological pathways:
  - Attagene: 73 assays;
  - BioSeek: 174 assays;
  - NovaScreen: 239 assays.

*All pathway information was provided by Dr. Shawn Gomez

Example of Some ToxCast Assays That Could be Mapped onto Pathways



1) PPARA hsa:5465 K07294 ATG_PPARa_TRANS & ATG_PPRE_CIS & NVS_NR_hPPARa

2) ATG_RXRa_TRANS & ATG_RXRb_TRANS RXRA hsa:6256 K08524 & RXRB hsa:6257 K08525

3) PPARD hsa:5467 K04504 ATG_PPARd_TRANS

4) PPARG hsa:5468 K08530 ATG_PPARg_TRANS & NVS_NR_hPPARg

5) NR1H3 hsa:10062 k08536 ATG_DR4_LXR_CIS & ATG_LXRa_TRANS

*6) MMP1 hsa:4312 k01388 BSK_BE3C_MMP1 & BSK_hDFCGF_MMP1 & NVS_ENZ_hMMP1

Obtained from Dr. Shawn Gomez

Overview of the ToxCast Assays that have been mapped to pathways (so far)

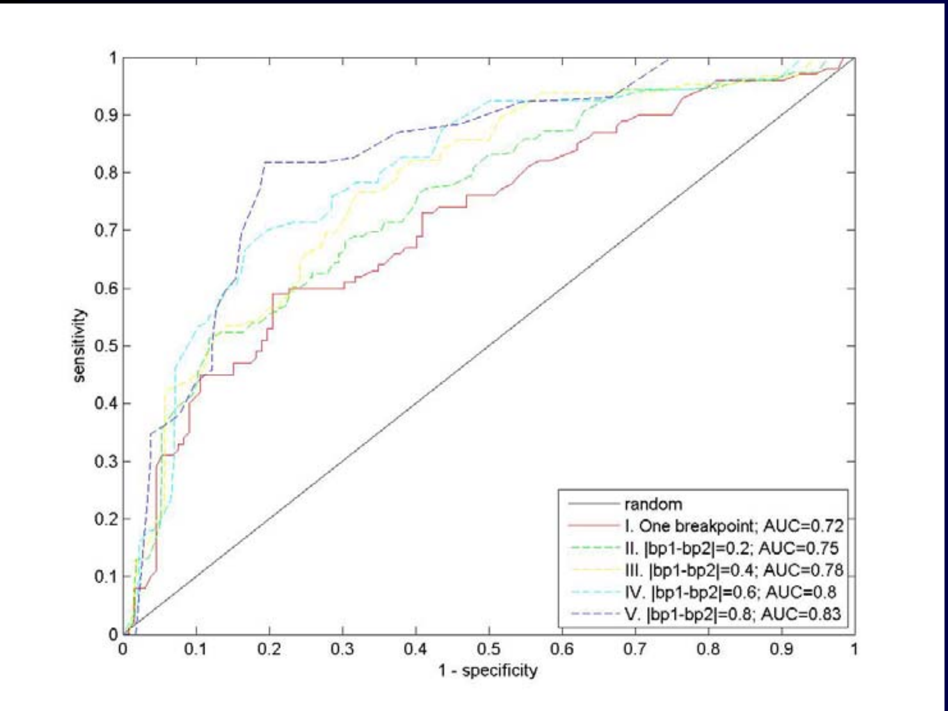
	Nm. of assays	**Nm. of assays (no low active %)**
JAK-STAT Signaling Pathway	8	0
PPAR Signaling Pathway	13	7
Focal adhesion	14	5
T cell receptor signaling pathway	13	4
TGF-beta signaling pathway	10	6
Toll-like receptor signaling pathway	25	20
Apoptosis	15	9
Wnt signaling pathway	10	2
Adipocytokine signaling pathway	12	4
Leukocyte transendothelial migration	11	9
MAPK signaling pathway	24	14
ErbB signaling pathway	11	3
Natural killer cell mediated cytotoxicity	13	4
Cell cycle	9	3
p53 signaling pathway	7	4
BMPR2 interaction with PPARG	8	6
All	95	54

Using 54 ToxCast Pathway-mapped Assays for Consensus Prediction

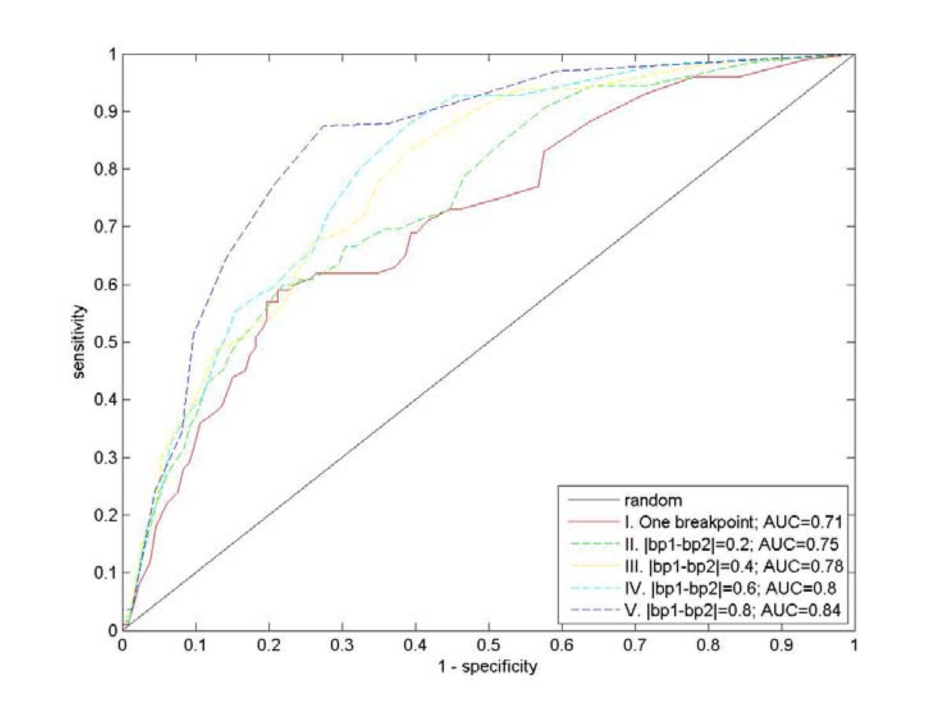
	MGR_Rat Kidney		**MGR_Rat Liver**		**MGR_Rat ViabilityPND4**	
	CCR	Coverage	CCR	Coverage	CCR	Coverage
RF all assays	0.70	0.41	0.73	0.56	0.63	0.4
54 pathway assays	**0.67**	**0.48**	**0.72**	**0.6**	**0.60**	**0.46**
23 pathway assays	0.65	0.44	0.73	0.55	0.58	0.4
10 pathway assays	0.62	0.43	0.71	0.5	0.54	0.36
SVM_linear all assays	0.61	0.38	0.66	0.42	0.64	0.32
54 pathway assays	**0.64**	**0.4**	**0.63**	**0.42**	**0.64**	0.29
23 pathway assays	0.63	0.28	0.57	0.31	0.64	0.22
10 pathway assays	0.6	0.28	0.54	0.24	0.61	0.2
SVM_rfb all assays	0.69	0.43	0.71	0.53	0.61	0.38
54 pathway assays	**0.69**	**0.45**	**0.71**	**0.53**	**0.68**	**0.36**
23 pathway assays	0.67	0.38	0.69	0.4	0.64	0.29
10 pathway assays	0.64	0.28	0.67	0.32	0.53	0.2

The Comparison between General Consensus and Pathway Consensus Results

RF MGR_Rat Liver all 284 models

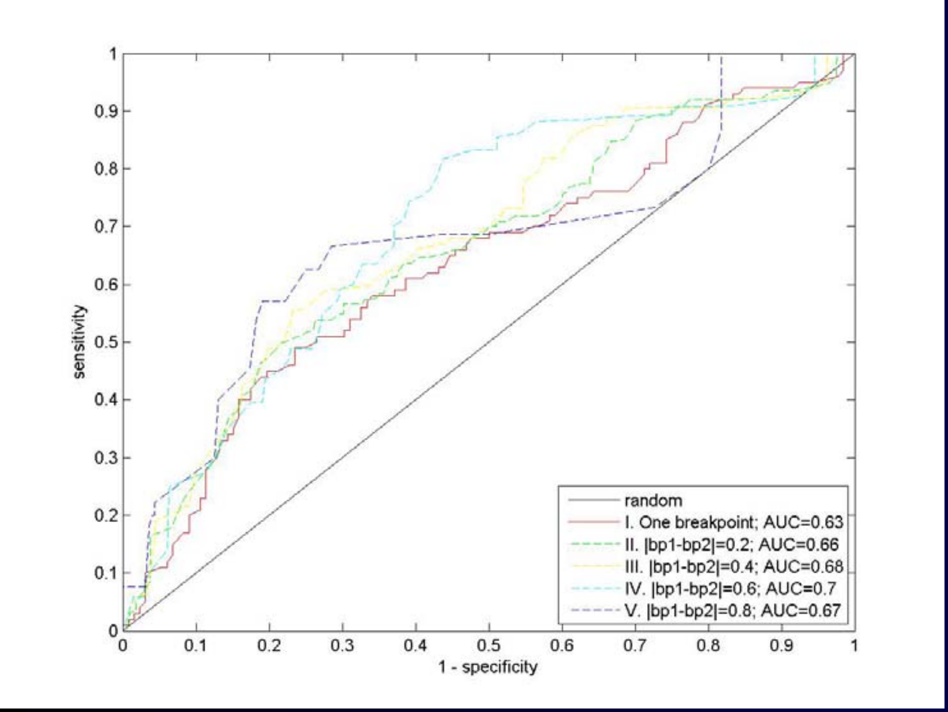


RF MGR_Rat Liver 54 pathway models

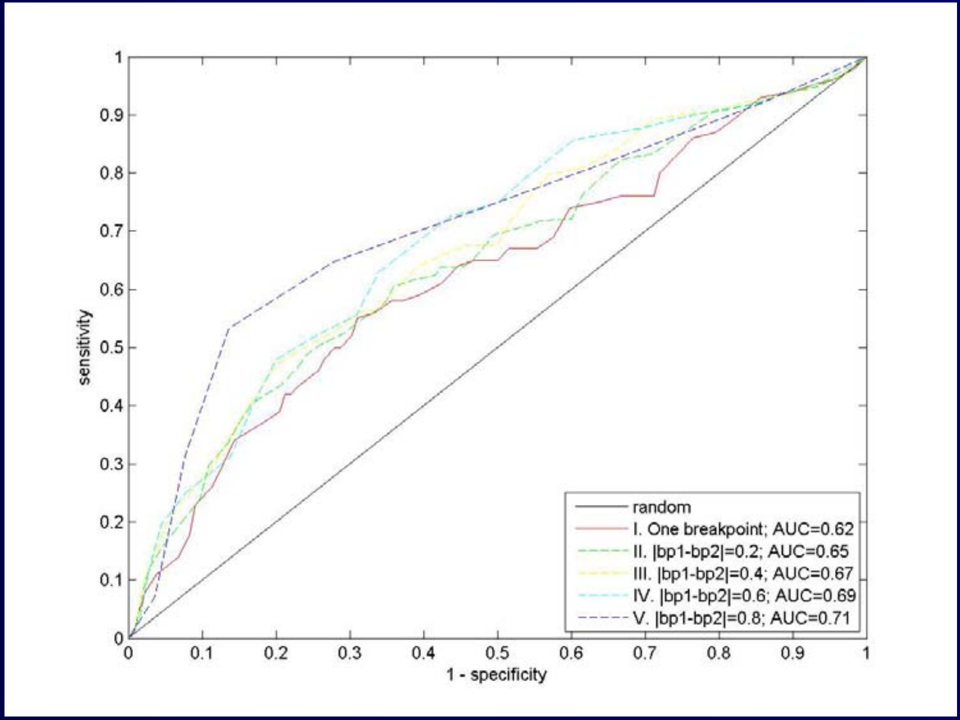


The Comparison between General Consensus and Pathway Consensus Results II

SVM_linear MGR_Rat Liver all 284 models

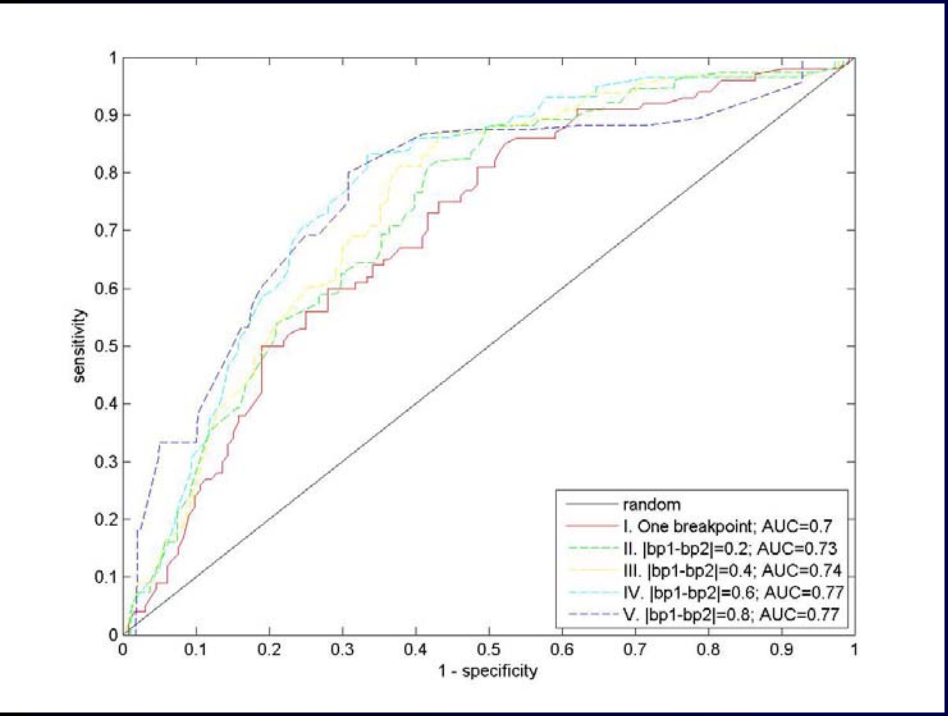


SVM_linear MGR_Rat Liver 54 pathway models

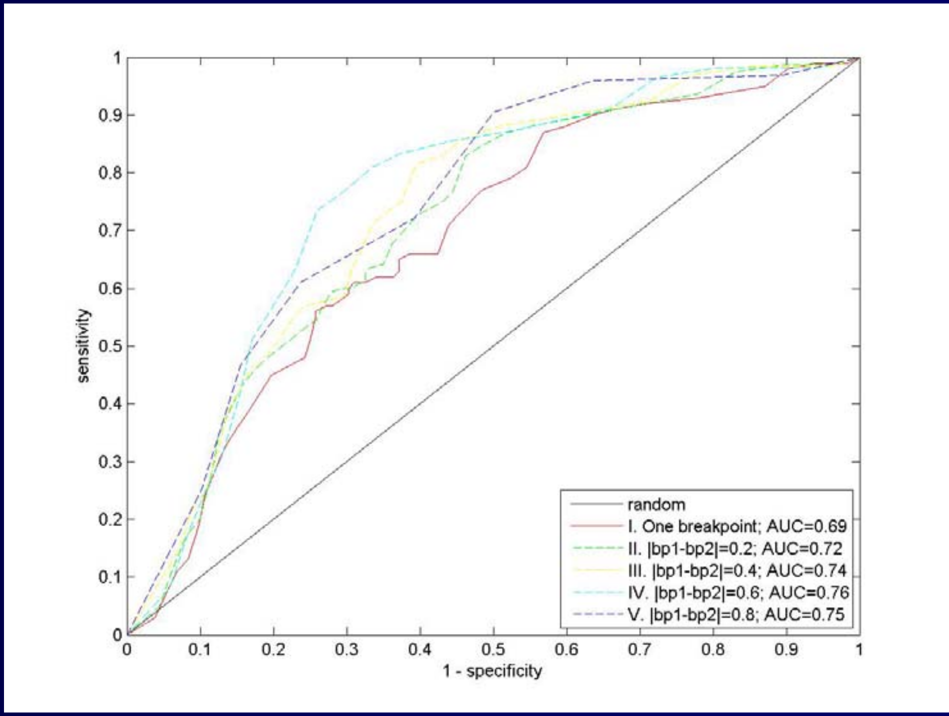


The Comparison between General Consensus and Pathway Consensus Results III

SVM_rbf MGR_Rat Liver all 284 models



SVM_rbf MGR_Rat Liver 54 pathway models



Using Individual Pathways for MGR_Rat Liver Modeling

	RF		**SVM_linear**		**SVM_rbf**	
	CCR	Coverage	CCR	Coverage	CCR	Coverage
All 54	0.73	0.56	0.66	0.42	0.71	0.53
PPAR (7)	**0.77**	**0.47**	0.54	0.3	0.61	0.35
Focal adhesion (5)	**0.7**	**0.57**	**0.7**	**0.46**	**0.72**	**0.52**
T cell (4)	0.69	0.7	0.61	0.4	0.64	0.49
TGF-beta (6)	**0.73**	**0.52**	0.57	0.54	**0.72**	**0.58**
Toll-like (20)	**0.71**	**0.61**	0.59	0.39	**0.69**	**0.43**
Apoptosis (9)	0.69	0.30	0.60	0.32	0.67	0.35
Wnt (2)	0.66	0.74	0.59	0.53	0.66	0.58
Adipocytokine (4)	**0.70**	**0.62**	0.60	0.4	0.58	0.47
Leukocyte (9)	**0.71**	**0.59**	0.59	0.45	**0.72**	**0.54**
MAPK (14)	**0.72**	**0.63**	0.61	0.41	**0.71**	**0.49**
ErbB (3)	**0.70**	**0.56**	**0.68**	**0.35**	0.66	0.41
Natural killer cell (4)	0.66	0.76	**0.65**	**0.62**	**0.69**	**0.64**
Cell cycle (3)	0.69	0.65	0.62	0.68	**0.69**	**0.75**
p53 (4)	0.64	0.66	0.62	0.52	0.66	0.59
BMPR2 (6)	**0.72**	**0.4**	**0.63**	**0.24**	**0.70**	**0.29**

Using Individual Pathways for MGR_Rat Kidney Modeling

	RF		**SVM_linear**		**SVM_rbf**	
	CCR	Coverage	CCR	Coverage	CCR	Coverage
All 54	0.67	0.48	0.64	0.4	0.69	0.45
PPAR (7)	**0.71**	**0.3**	0.51	0.5	0.6	0.29
Focal adhesion (5)	0.62	0.49	0.56	0.53	0.65	0.5
T cell (4)	0.61	0.63	**0.61**	**0.45**	0.58	0.47
TGF-beta (6)	0.61	0.49	0.58	0.53	0.64	0.59
Toll-like (20)	**0.64**	**0.51**	**0.64**	**0.33**	**0.66**	**0.38**
Apoptosis (9)	0.61	0.49	**0.62**	**0.29**	**0.66**	**0.30**
Wnt (2)	0.57	0.75	0.56	0.62	0.58	0.65
Adipocytokine (4)	0.63	0.51	0.57	0.44	0.60	0.45
Leukocyte (9)	**0.65**	**0.53**	**0.61**	**0.41**	**0.67**	**0.48**
MAPK (14)	0.61	0.62	**0.65**	**0.44**	0.64	0.49
ErbB (3)	0.61	0.59	0.59	0.49	0.59	0.52
Natural killer cell (4)	0.61	0.71	**0.61**	**0.56**	0.63	0.6
Cell cycle (3)	0.56	0.72	0.56	0.69	0.62	0.77
p53 (4)	0.60	0.63	0.53	0.5	0.61	0.53
BMPR2 (6)	**0.70**	**0.31**	0.57	0.2	0.63	0.28

Using Individual Pathways for MGR_Rat ViabilityPND4 Modeling

	RF		**SVM_linear**		**SVM_rbf**	
	CCR	Coverage	CCR	Coverage	CCR	Coverage
All 54	0.63	0.4	0.64	0.32	0.61	0.38
PPAR (7)	**0.63**	**0.3**	0.52	0.25	0.5	0.26
Focal adhesion (5)	0.56	0.43	0.59	0.39	0.53	0.41
T cell (4)	0.51	0.62	0.54	0.43	0.54	0.46
TGF-beta (6)	0.53	0.4	**0.61**	**0.39**	**0.60**	**0.5**
Toll-like (20)	0.58	0.47	**0.61**	**0.27**	**0.65**	**0.30**
Apoptosis (9)	**0.60**	**0.46**	**0.63**	**0.23**	**0.60**	**0.27**
Wnt (2)	0.53	0.76	0.48	0.60	0.52	0.63
Adipocytokine (4)	0.51	0.52	0.56	0.39	0.5	0.37
Leukocyte (9)	**0.63**	**0.46**	0.58	0.37	0.55	0.44
MAPK (14)	0.53	0.57	**0.61**	**0.35**	0.56	0.63
ErbB (3)	0.54	0.56	0.56	0.41	0.51	0.46
Natural killer cell (4)	0.54	0.72	**0.61**	**0.54**	**0.63**	**0.57**
Cell cycle (3)	0.48	0.66	0.52	0.65	0.53	0.77
p53 (4)	0.56	0.63	0.54	0.61	0.57	0.54
BMPR2 (6)	0.57	0.3	0.55	0.22	**0.59**	**0.26**

Future Studies

- Go deeply to each pathway assay model
  - Significant tests
  - Any chemical scaffold could be identified?
- Combine different pathway models to achieve predictions with higher accuracy
- Model analysis to identify significant assay-chemical combinations that are predictive of *in vivo* outcomes
- Apply model prospectively to prioritise new compounds for ToxCast testing.

Conclusions and plans

- Focus on accurate prediction of <u>external</u> datasets is much more critical than accurate fitting of existing data: validate, <u>then</u> interpret!
  - validation!!!
  - applicability domain
  - consensus prediction using all acceptable models
  - Ideally, experimental validation of a <u>small</u> number of computational hits
  - Outcome: decision support tools in selecting future experimental screening sets
- HTS and –omics data may be insufficient to achieve the desired accuracy of the end point property prediction BUT should be explored as biodescriptors in combination with chemical descriptors
  - New computational approaches (e.g., hierarchical QSAR)
  - Understanding of <u>both</u> chemistry and biology

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