Various application of transcriptional profiling in regulatory toxicology

Tier 1
High-throughput *in vitro* transcriptomics

Tier 2
High-throughput screening

Tier 3
In vivo and organ model transcriptomics

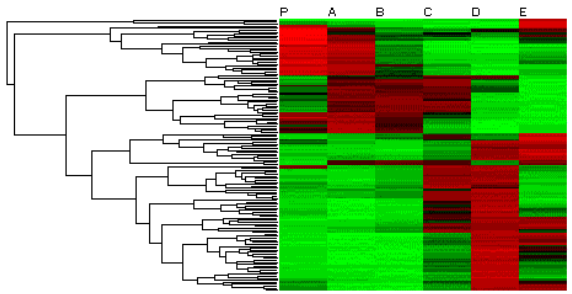
Tier 4
Conventional tests

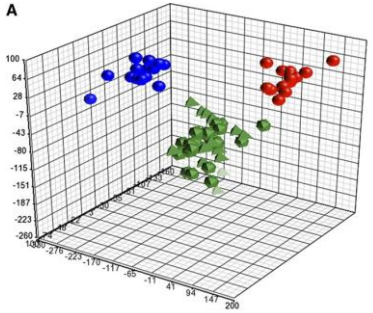
But how to efficiently analyze and interpret toxicogenomic data?

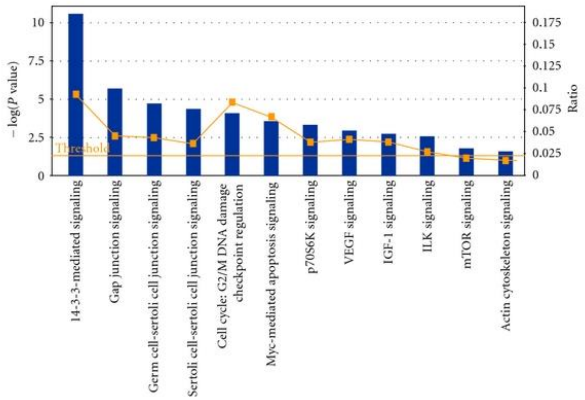
Large gene lists

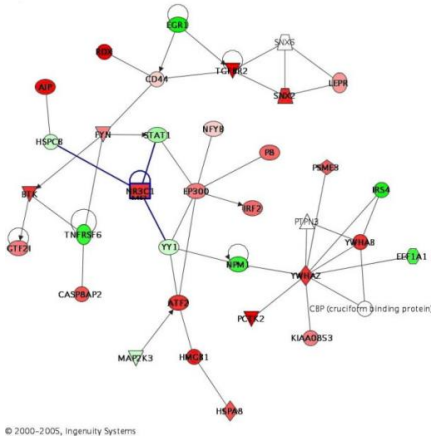
			25mg/kg/day		50mg/kg/day		75mg/kg/day	
Agilent Probe	Accession Number	Gene Symbol	FDR p-value	Fold change	FDR p-value	Fold change	FDR p-value	Fold change
55 P1963017	NM 001082543	Stfa1	0.89	2	0	9.9	0	78.5
66 P133397	NM 145126	Chi3l4	0.97	1.3	0	5.2	0	36.6
55 P2114187	XM 884904	LOC620515	0.95	1.4	0.05	3.7	0	29.2
51 P464703	NM 021443	Ccl8	0	6.6	0	13.8	0	16.7
66 P139618	NM 001082545	Stfa2	0.59	2.2	0	4.4	0	15.5
55 P2007756	NM 008470	Krt16	0.43	2.3	0	7.3	0	13.3
52 P398925	NM 173869	Stfa2l1	0.91	1.6	0.02	2.8	0	11.4
55 P2028949	NR 002880	Defb48-ps	0.98	1.2	0.07	2.5	0	9
55 P1998943	NM 145211	Oas1a	0.19	2.4	0	5.1	0	8.9
55 P2103698	NM 015783	Isg15	0.53	2.1	0	4.6	0	8.8
55 P2174143	NM 009265	Sprr1b	0.84	1.8	0	3.7	0	8.5
51 P386870	NM 011472	Sprr2f	0.94	1.5	0.04	3	0	7.2
51 P113906	NM 025467	Gkn2	0.53	4.3	0.5	3	0.01	6.8
51 P167292	NM 009892	Chi3l3	0.98	-1.2	0.84	1.4	0	6.4
66 P116206	NM 013756	Defb3	0.96	1.2	0.3	1.7	0	5.7
55 P2062246	NM 001145164	Tgtp2	0.64	2.2	0	4.4	0	5.6
66 P128537	NM 015783	Isg15	0.84	1.5	0	2.7	0	5.4
55 P1998471	NM 009114	S100a9	0.57	2.1	0	4.1	0	5.2
55 P1978465	NM 023124	H2-Q8	0.92	1.6	0.03	3	0	5.1
66 P138462	NM 011474	Sprr2h	0.97	1.2	0.15	2.3	0	5
51 P304170	NM 023386	Rtp4	0.75	1.6	0	3	0	5
55 P2135064	NM 008204	H2-M2	0.76	1.7	0.01	2.3	0	5
55 P1979828	NR 003548	Sprr2g	0.9	1.5	0	2.7	0	4.6
55 P2112005	NM 009362	Tff1	0.55	3.1	0.04	4.3	0	4.6
51 P504815	NM 025288	Stfa3	1	1	0.41	1.9	0	4.6
55 P1955372	NM 011477	Sprr2k	0.66	1.7	0	2.3	0	4.5
52 P104658	NM 008476	Krt6a	0.94	1.4	0.02	3.2	0	4.5
66 P101935	NM 010669	Krt6b	0.92	1.5	0.01	2.7	0	4.5
51 P303160	NM 007482	Arg1	0.81	1.7	0	3.3	0	4.5
51 P126275	NM 010669	Krt6b	0.92	1.5	0.01	2.9	0	4.5
51 P112355	NM 018738	Iqtp	0.68	2	0	4.1	0	4.4
55 P2021585	NM 009362	Tff1	0.5	3.2	0.01	4.5	0.01	4.3
55 P2016462	NM 021274	Cxcl10	0.89	1.6	0	3	0	4.3
51 P100997	NM 201363	Serpinb3c	0.06	2	0	3.1	0	4.3
55 P1970144	AK049846	Slc16a14	0.97	1.2	0.17	1.9	0	4.3
52 P68883	NM 183026	Defb14	0.26	2.1	0	3.6	0	4
55 P1965303	NM 013505	Dsc2	0.9	1.3	0.04	1.8	0	4
55 P2016034	NM 001033207	Nlrc5	0	2.2	0	2.7	0	3.8
30 P01019307			0.93	1.3	0	2.1	0	3.8
66 P114244	XM 001478461	Gm3914	0.96	1.3	0.05	2.5	0	3.8
51 P198434	NM 001001892	H2-K1	0.73	1.6	0.01	2.4	0	3.7
55 P2003746	NM 009126	Serpinb3a	0.74	1.5	0	2.3	0	3.6
55 P2410304	NM 001146275	Iigp1	0.59	1.8	0	3.1	0	3.6
55 P2472435	NM 018734	Gbp3	0.87	1.5	0	2.9	0	3.6

Complex analyses and interpretations









Phenotype?

Acceptable exposure levels?

NTP: simplified pipeline

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66 P139618	NM 001082545	Stfa2	0.59	2.2	0	4.4	0	15.5
55 P2007756	NM 008470	Krt16	0.43	2.3	0	7.3	0	13.3
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51 P386870	NM 011472	Sprr2f	0.94	1.5	0.04	3	0	7.2
51 P113906	NM 025467	Gkn2	0.53	4.3	0.5	3	0.01	6.8
51 P167292	NM 009892	Chi3l3	0.98	-1.2	0.84	1.4	0	6.4
66 P116206	NM 013756	Defb3	0.96	1.2	0.3	1.7	0	5.7
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55 P1978465	NM 023124	H2-Q8	0.92	1.6	0.03	3	0	5.1
66 P138462	NM 011474	Sprr2h	0.97	1.2	0.15	2.3	0	5
51 P304170	NM 023386	Rtp4	0.75	1.6	0	3	0	5
55 P2135064	NM 008204	H2-M2	0.76	1.7	0.01	2.3	0	5
55 P1979828	NR 003548	Sprr2g	0.9	1.5	0	2.7	0	4.6
55 P2112005	NM 009362	Tff1	0.55	3.1	0.04	4.3	0	4.6
51 P504815	NM 025288	Stfa3	1	1	0.41	1.9	0	4.6
55 P1955372	NM 011477	Sprr2k	0.66	1.7	0	2.3	0	4.5
52 P104658	NM 008476	Krt6a	0.94	1.4	0.02	3.2	0	4.5
66 P101935	NM 010669	Krt6b	0.92	1.5	0.01	2.7	0	4.5
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51 P126275	NM 010669	Krt6b	0.92	1.5	0.01	2.9	0	4.5
51 P112355	NM 018738	Ietp	0.68	2	0	4.1	0	4.4
55 P2021585	NM 009362	Tff1	0.5	3.2	0.01	4.5	0.01	4.3
55 P2016462	NM 021274	Cxcl10	0.89	1.6	0	3	0	4.3
51 P100997	NM 201363	Serpinb3c	0.06	2	0	3.1	0	4.3
55 P1970144	AK049846	Slc16a14	0.97	1.2	0.17	1.9	0	4.3
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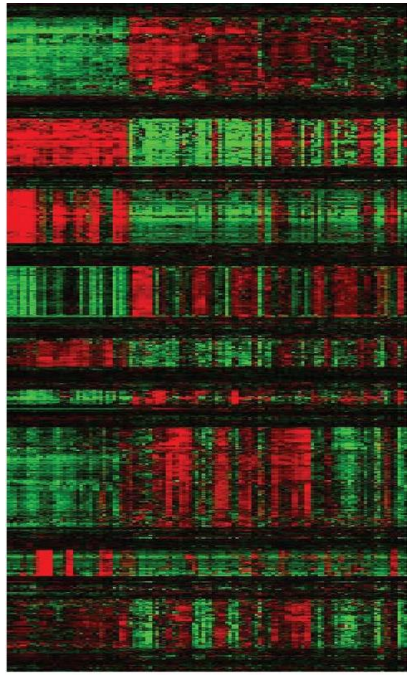
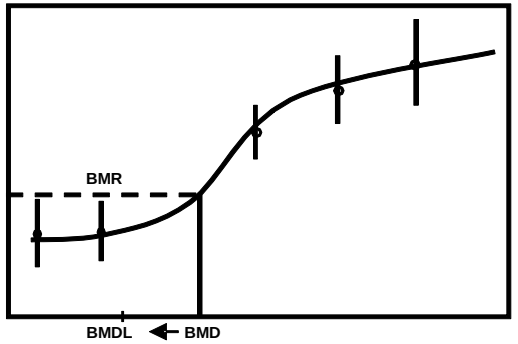
55 P2016034	NM 001033207	Nlrc5	0	2.2	0	2.7	0	3.8
30 P01019307			0.93	1.3	0	2.1	0	3.8
66 P114244	XM 001478461	Gm3914	0.96	1.3	0.05	2.5	0	3.8
51 P198434	NM 001001892	H2-K1	0.73	1.6	0.01	2.4	0	3.7
55 P2003746	NM 009126	Serpinb3a	0.74	1.5	0	2.3	0	3.6
55 P2410304	NM 001146275	Iigp1	0.59	1.8	0	3.1	0	3.6
55 P2472435	NM 018734	Gbp3	0.87	1.5	0	2.9	0	3.6

Hallmark signatures



Identify transcriptomic Point of Departure

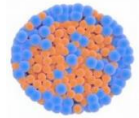


Regulatory decision

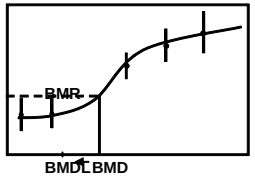
(screening, prioritization, interim POD)

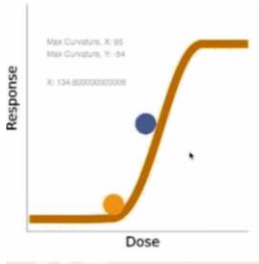
Expert panel questions

Study designs?

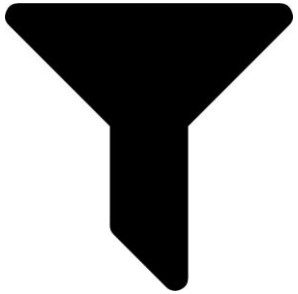


Models?



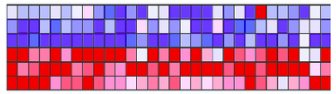


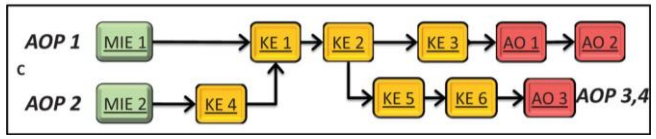
Filters?

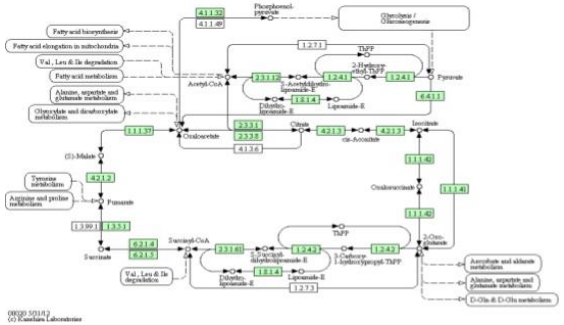


Gene lists

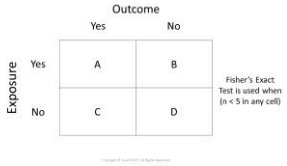
Gene sets? Biological interpretation?







Gene sets?



GSEA
Gene Set Enrichment Analysis

Group median vs key gene

Identify transcriptomic Point of Departure