



EDCMET Scientific Results

WP1

In silico methods to identify endocrine disrupting effects of chemicals



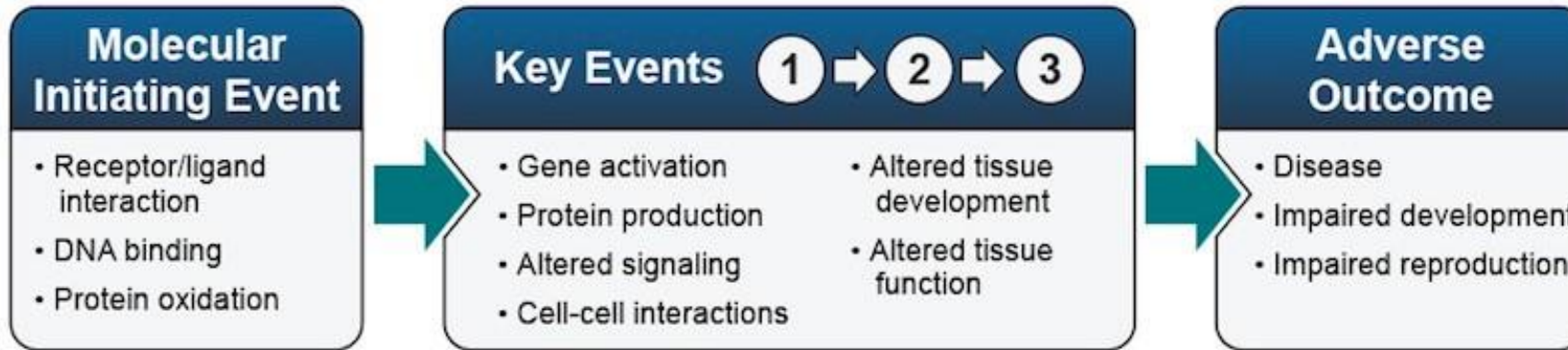
WP1 Aim



WP1 will develop and validate novel screening approaches that can be used stand-alone or in a linked, hybrid approach.

These approaches will follow a traditional AOP paradigm, identifying MIEs and predicting the emergent adverse biological phenotype







Deliverable	Title
D1.1	A validated molecular modelling approach to identify interactions between proteins and EDs
D1.2	Preliminary list of proteins most likely to interact with EDs
D1.3	A list of proteins most likely to interact with EDs
D1.4	A binding energy interaction map to explore the quantitative interaction of EDs with proteins, as part of the overall risk assessment model
D1.5	A validated classification system linking ED exposure to adverse outcome
D1.6	Preliminary list of potential biomarkers of exposure and effect for EDs
D1.7	A list of potential biomarkers of exposure and effect for EDs
D1.8	A systems toxicology tool to predict emergent metabolic phenotype from ED exposure

D1.1: A validated molecular modelling approach to identify interactions between proteins and EDs

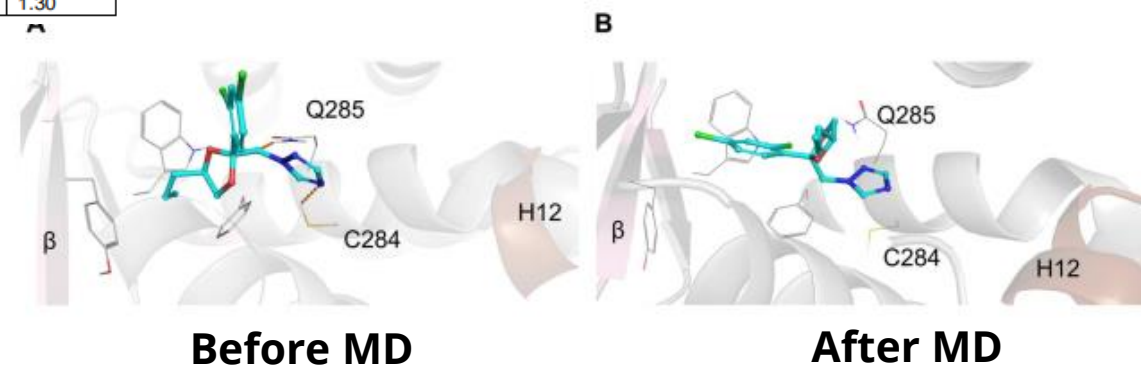
Molecular Initiating Event

- Receptor/ligand interaction
- DNA binding
- Protein oxidation

NR	PDB ID	Resolution (Å)	Docking score	RMSD
PXR	4X1F	1.44	-10.77	0.45
CAR	1XVP	2.60	-11.46	0.85
FXR	6HL1	1.60	-5.42	0.69
LXR α	3IPQ	2.00	-17.90	0.42
LXR β	2P54	2.30	-14.07	1.46
PPAR α	4XLD	1.79	-12.50	0.80
PPAR γ	4XLD	2.45	-8.93	0.21
TR β	1XZX	2.50	-10.72	1.10
VDR	3CS4	2.00	-12.83	1.09
AR	2AM9	1.64	-11.85	0.06
ER	1GWR	2.4	-11.22	0.40
GR	1M2Z	2.5	-12.44	0.20

	PXR				
	PDB ID	1NRL	4XF1	4XHD	5A86
	Resolution(Å)	2.0	1.55	2.40	2.25
1NRL-ligand	Docking Score	-7.04	-6.86	-6.91	-7.491
	RMSD	1.30	0.18	1.96	0.02
4XF1-ligand	Docking Score	-6.89	-10.77	-7.11	-7.93
	RMSD	1.2	0.05	0.20	0.02
4XHD-ligand	Docking Score	-9.63	-8.00	-10.06	-8.71
	RMSD	0.03	0.02	1.30	1.7
5A86-ligand	Docking Score	-7.97	-8.83	-8.99	-8.05
	RMSD	0.38	0.02	1.70	1.30

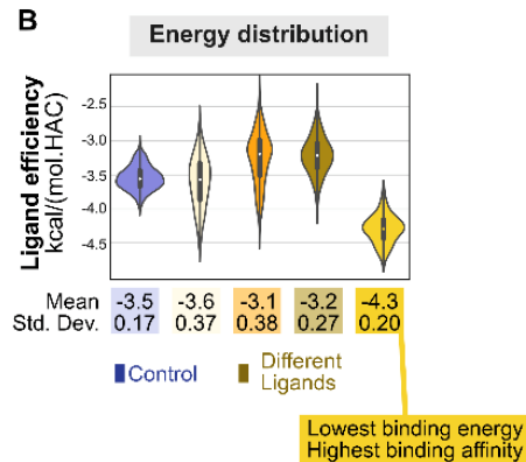
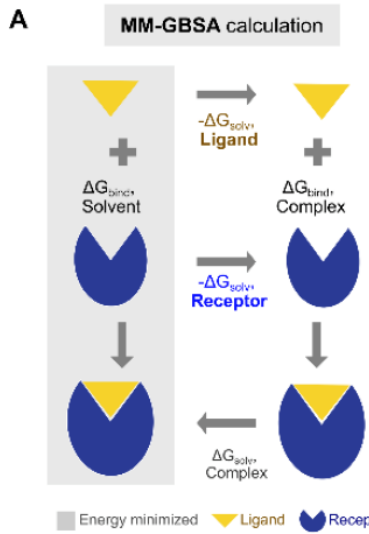
PXR – Propiconazole



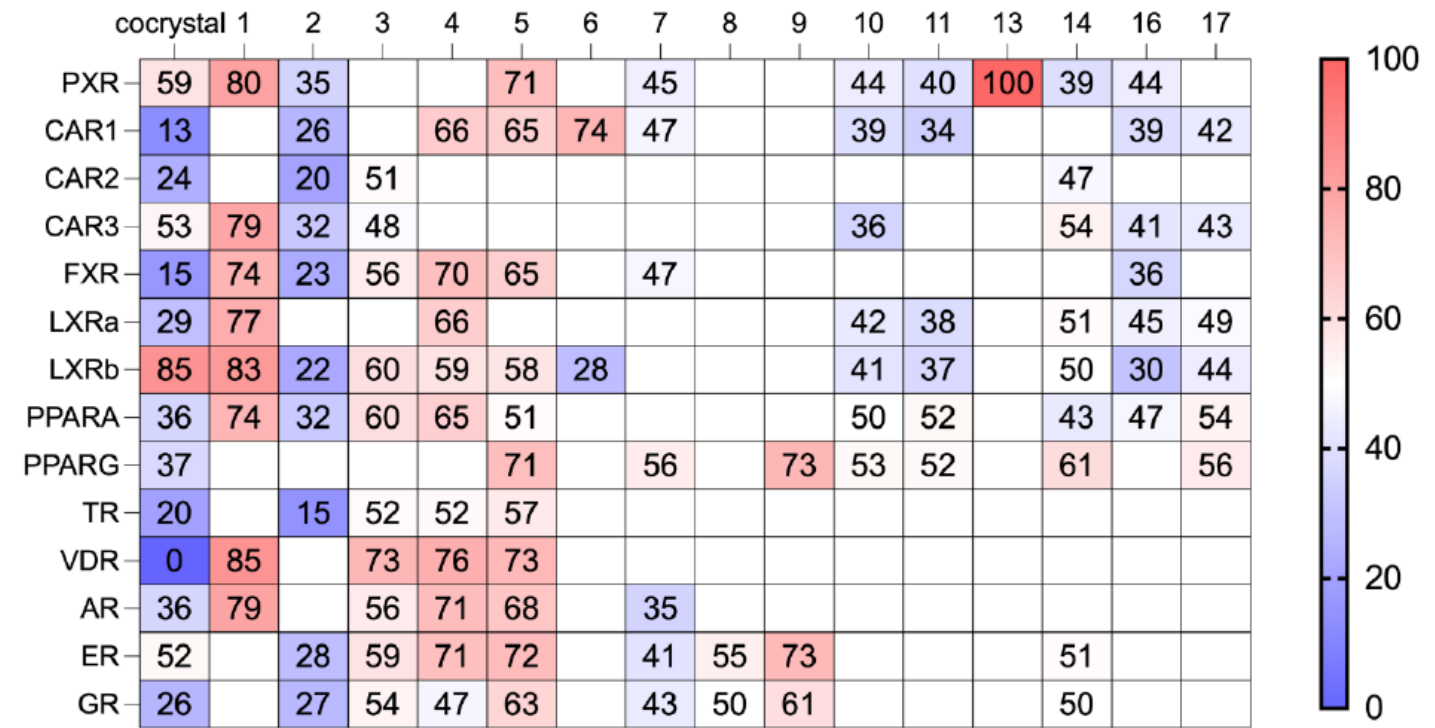
D1.4: A binding energy interaction map to explore the quantitative interaction of EDs with proteins

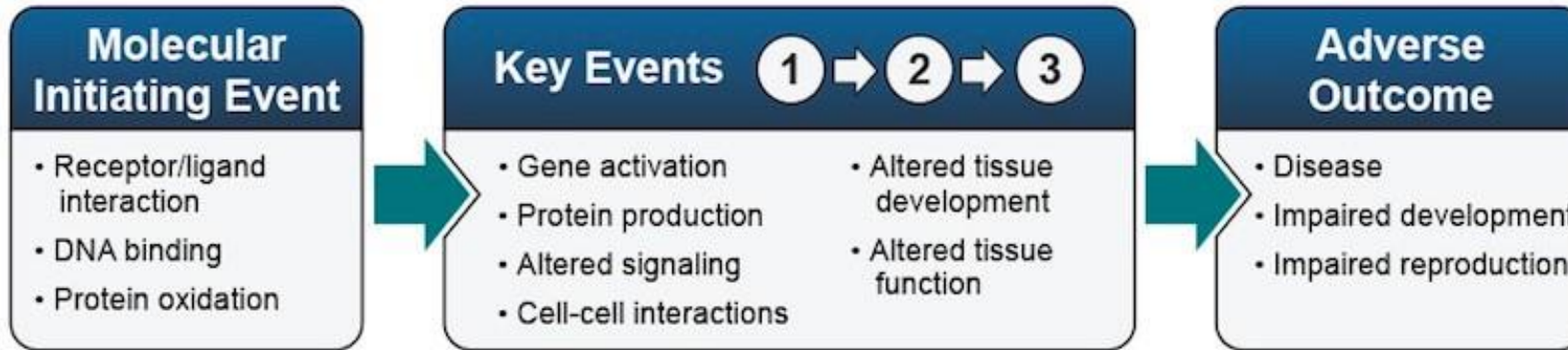
Molecular Initiating Event

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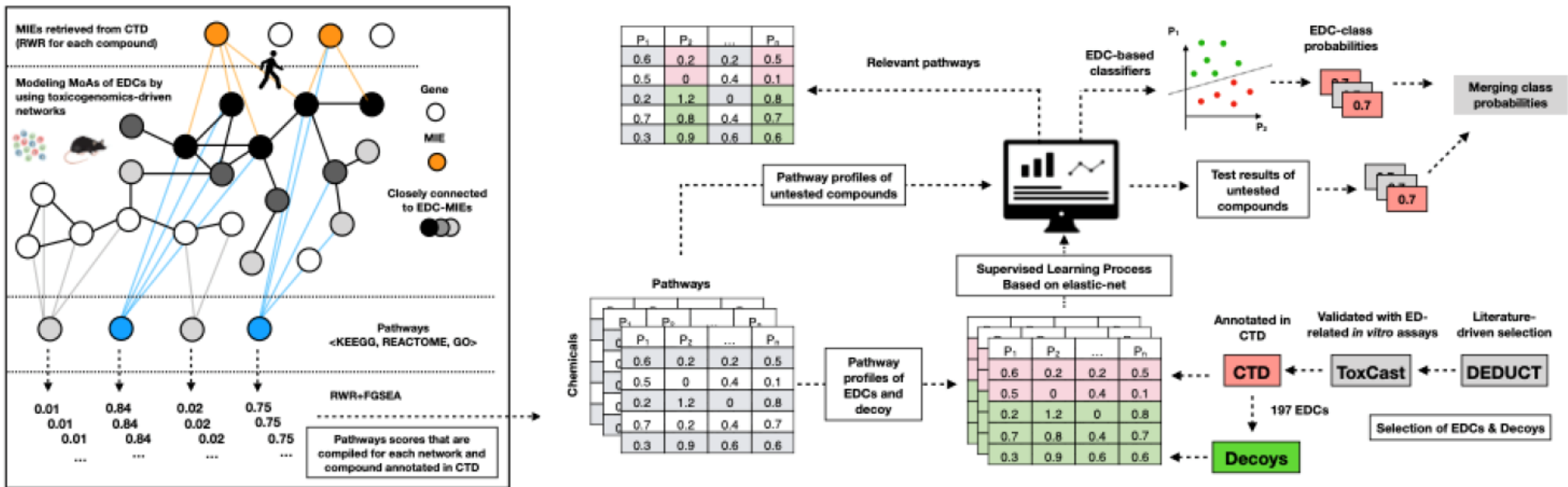


ED	Compound	CAS
1	Atrazine	1912-24-9
2	Bis(2-ethylhexyl) phthalate (DEHP)	117-81-7
3	Bisphenol A (BPA)	80-05-7
4	Carbofuran	1563-66-2
5	3OH-Carbofuran	16655-82-6
6	Cypermethrin	52315-07-8
7	Dichlorodiphenyldichloroethylene (DDE)	72-55-9
8	Diethylstilbestrol (DES)	56-53-1
9	Mono-(2-ethylhexyl) phthalate (MEHP)	4376-20-9
10	PCB 118	31508-00-6
11	PCB 153	35065-27-1
12	Perfluorooctanoic acid (PFOA)	335-67-1
13	Perfluorooctanesulfonic acid (PFOS)	1763-23-1
14	Propiconazole	60207-90-1
15	Tributyltin chloride (TBT)	1461-22-9
16	Triphenyl phosphate (TPP/TPHP)	115-86-6
17	Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	13674-87-8

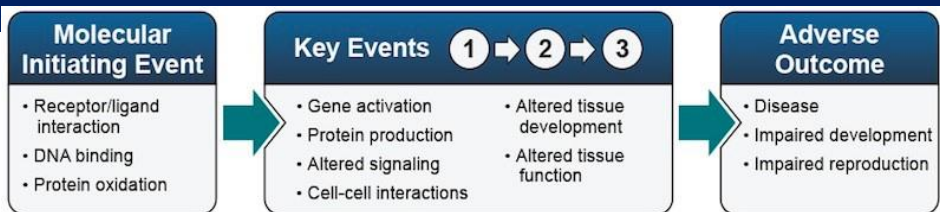




D1.5: A validated classification system linking ED exposure to adverse outcome



Sakhteman et al (2021) *Env. Int.* 156: 106751.



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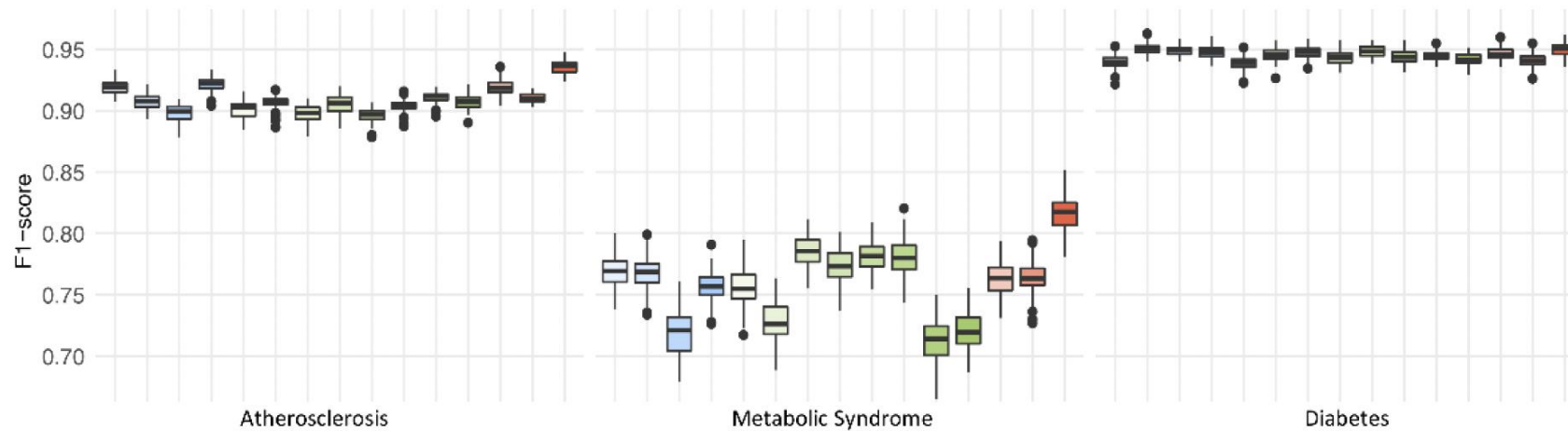


	Test Set 1		Test Set 2		Test Set 3	
	Average	Harmonic S	Average	Harmonic S	Average	Harmonic S
EDC score > 0.6	113	125	165	177	48	48
EDC score < 0.6	26	14	27	15	4	4
Tot. EDCs	139	139	192	192	52	52
Accuracy	81%	89%	86%	92%	92%	92%

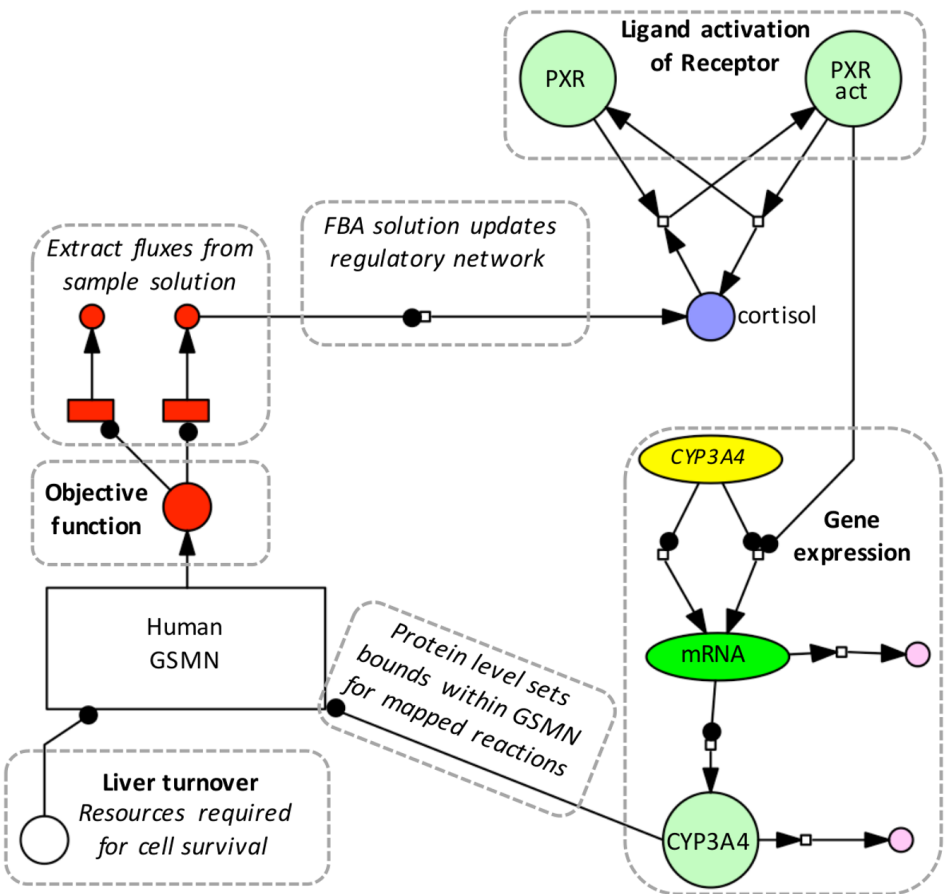
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B

Classification of EDC/+AO .vs EDC/-AO



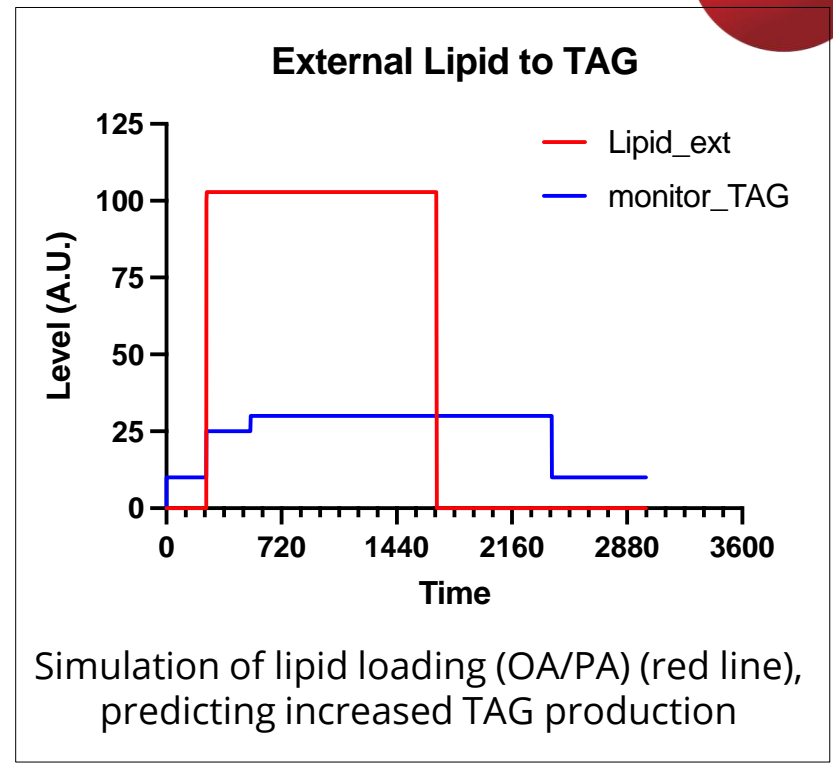
D1.8: A systems toxicology tool to predict emergent metabolic phenotype from ED exposure



Hepatonet 1
 Exchange rxns
 Internal rxns
 SF DMEM external pool
 Transport limited by CORE rates

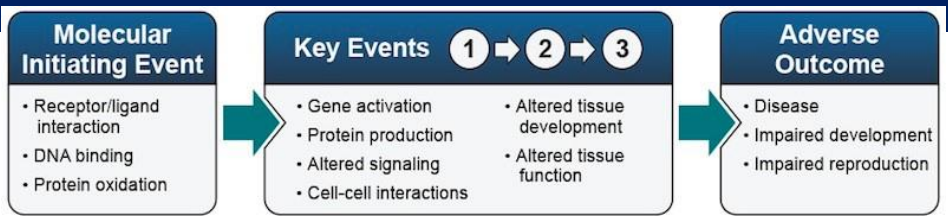
NR Gene Regulatory Networks
 AR; CAR FXR; GR; LXR; PPAR α ;
 PPAR γ ; PXR; SHP

Direct Target Genes	166
Single NR	117 (70%)
Multiple NRs	49 (30%)
Reactions regulated	306 (12%)

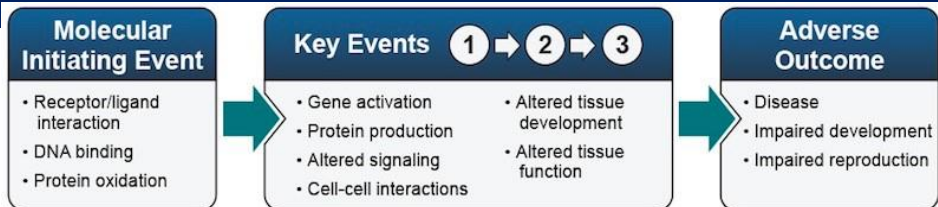
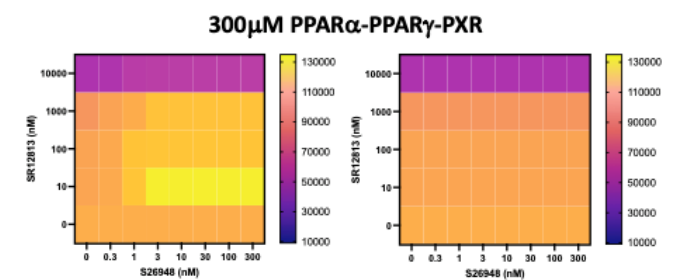
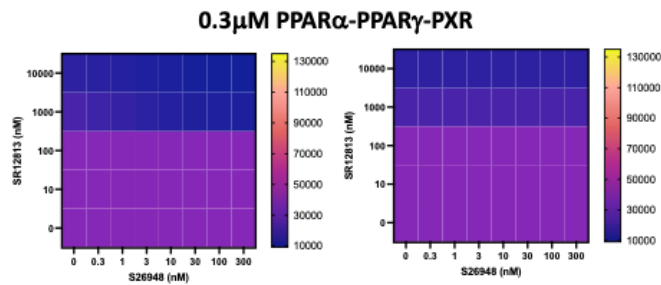
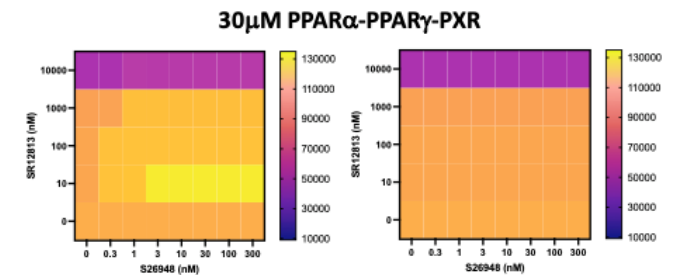
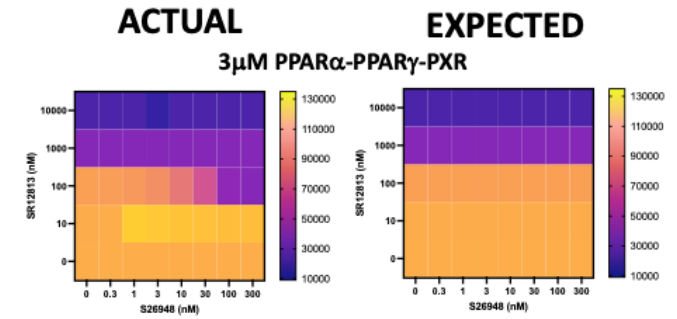
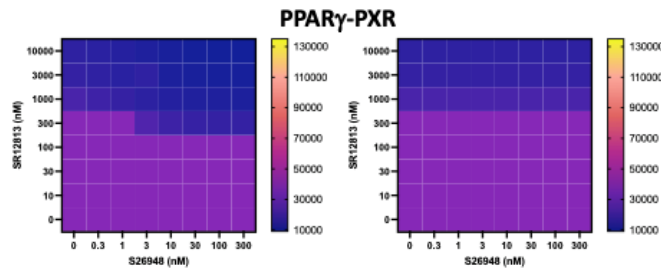
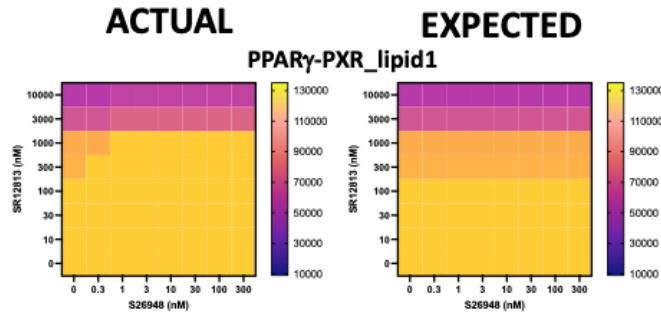
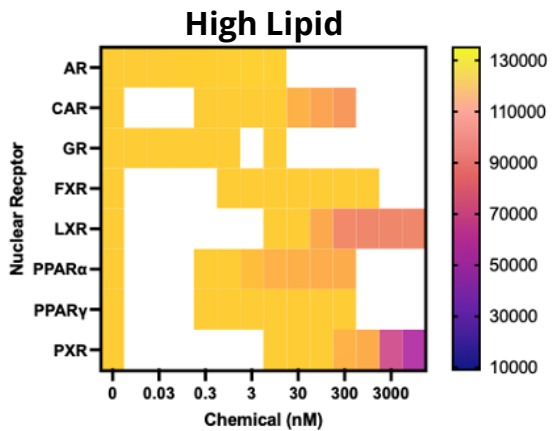
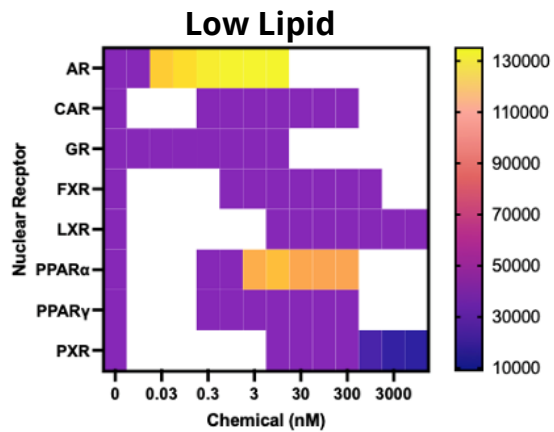


Wu et al. 2016, npj Systems Biology & Applications 6:16032

Maldonado et al. 2018, npj Systems Biology & Applications 4:33



D1.8: A systems toxicology tool to predict emergent metabolic phenotype from ED exposure



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Thank you!

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