Nuclear Receptor Activity and Liver Cancer Lesion Progression

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research & development

Introduction

The Virtual Liver project (v-Liver™) is aimed at producing decision support tools for evaluating chemical-induced adverse human liver outcomes across doses using *in vitro* data. As a proof of concept we are modeling nuclear receptor (NR)-mediated hepatocarcinogenesis. Chronic stimulation of some NRs is a non-genotoxic mechanism of rodent liver cancer with uncertain relevance to humans. Here we use ToxCast™ and ToxRefDB data to explore the relationship between human NR activities *in vitro*, and rodent hepatocarcinogenesis.

Objective

Organize environmental chemicals using the range of NR assays from ToxCast™

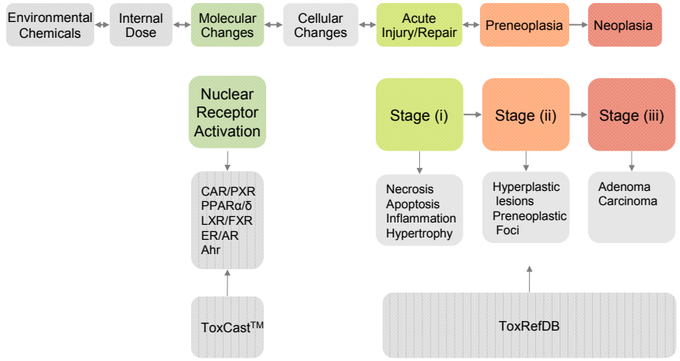
Stratify these chemicals according to severity of hepatic cancer lesion progression from ToxRefDB

Develop approach to compare human *in vitro* NR activity with rodent liver cancer

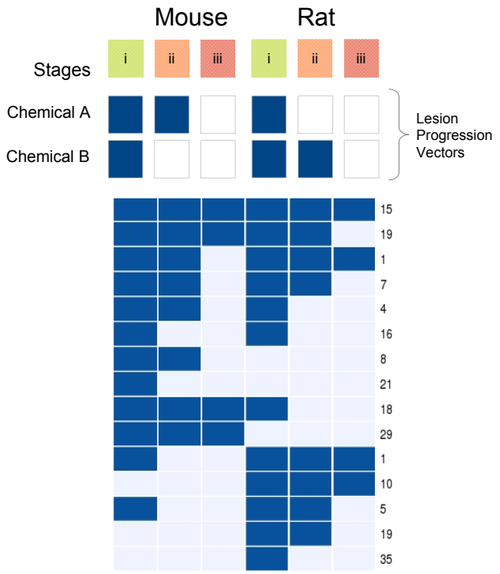
Identify relevant environmental chemicals for proof-of-concept model of NR-mediated liver cancer

Overview

Pathway to Liver Cancer



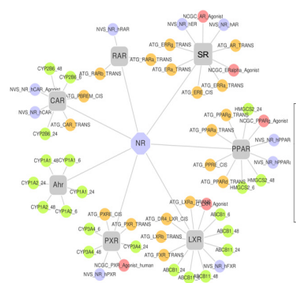
Cancer Lesion Progression (LP)



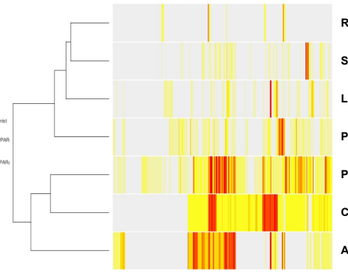
Chemicals grouped by similar Lesion Progression Vectors

Methods

Nuclear Receptor Activity



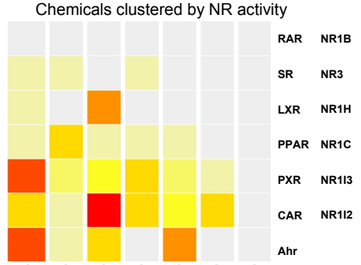
ToxCast Assays for NRs

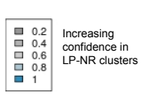


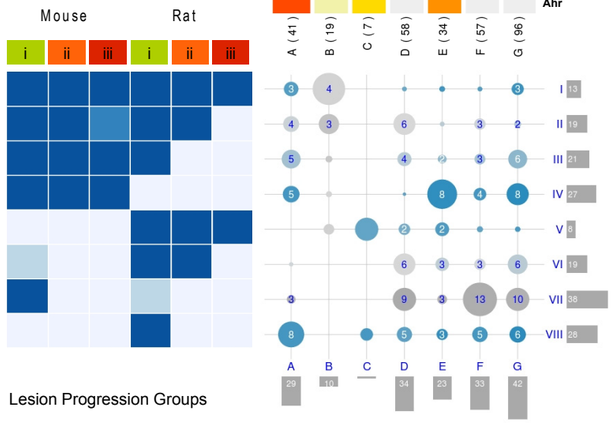
Aggregate NR activity for all chemicals

Human NR vs. Rodent LP

Chemicals clustered by NR activity







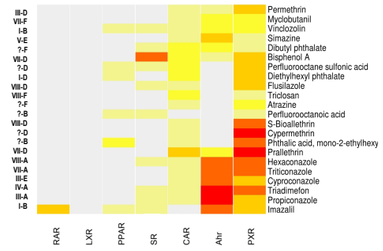
Lesion Progression Groups

Chemicals: NR vs. LP

	A	B	C	D	E	F	G
I	Fludioxonil Lactofen Oxadiazon	Diclofop-methyl Diclofop-methyl Diclofop-methyl Imazalil Malathion Vinclozolin		Diethylhexyl-phthalate	Carbaryl	Isoxaflutole	2,5-Pyridinedicarboxylic acid, dipropyl ester Pymetrozine Tepraloxydim
II	Bensulide Bensulide Dithiopyr MGK Triflumizole	Fentin Fluazinam Spirodiclofen		Buprofezin Fenarimol Fluthiacet-methyl Piperonyl butoxide Pyraflufen-ethyl Resmethrin	Fenamidone	Butafenacil Diphenylamine Fenoxycarb	Clodinafop-propargyl Pyrithiobac-sodium
III	Indoxacarb Iprodione Linuron Propiconazole Thiazopyr	Bromoxynil		Lindane Permethrin Prochloraz Propyzamide	Clofentezine Cyproconazole	Dicofol Difenoconazole Nitrapyrin	3-Iodo-2-propynylbutylcarbamate 3-Iodo-2-propynylbutylcarbamate Diazomet Fenoxaprop-ethyl
IV	Isoxaben Methidathion Triadimefon Triadimenol Tribufos	Cinmethylin		Hexythiazox	Benfluralin Benomyl Bifenazate Bromacil Fenitrothion Norflurazon Thiophanate-methyl Triflusulfuron-methyl	Maneb Pirimisulfuron-methyl Propoxur Terbacil	2-Phenylphenol Acephate Amitraz Bentazone Cloprop Clothianidin Demeton Dimethoate Thiodicarb
V		Cyclanilide	Tebufenpyrad	Ametryn Dimethenamid	Acetochlor Simazine	Dichlobenil	Mevinphos
VI	Tetraconazole			Azoxystrobin Butachlor Chlorpropham Flufenacet Pendimethalin Quinclorac	Boscalid Propanil Pyrimethanil	Oxasulfuron Sethoxydim Tralkoxydim	Clothianidin Ethephon Famoxadone Rimsulfuron Thiram Trichlorfon
VII	Fludolanil Oxyfluorfen Triticonazole			Bisphenol A Carfentrazone-ethyl cis,trans-Allethrin Fipronil Metalaxyl Prallethrin Prosulfuron Sulfentrazone Trifloxystrobin	Carboxin Dichloran Diuron	2,4-DB Butylate Chlorpyrifos-methyl Clorophene Fenbuconazole Flufenpyr-ethyl Flumiclorac-pentyl Fluoxastrobin Myclobutanil Prometon Prosulfuron Tefluthrin Triasulfuron	Acetamiprid Asulam Azamethiphos Cymoxanil Hexazinone Mesosulfuron-methyl Novaluron Prosulfuron Thiacloprid Thidiazuron
VIII	Cyprodinil Etoxazole Flumetralin Hexaconazole Methoxyfenozide Prosulone Pyraclostrobin Tebufenozide		Dimethomorph	Alachlor S-Bioallethrin Ethofumesate Flusilazole Fosthiazate	Acibenzolar-S-Methyl Picloram Thiabendazole	Emamectin benzoate Icaridin Paclobutrazol Penoxsulam Triclosan	2,4-Dichlorophenoxyacetic acid (2,4-D) Chlorsulfuron Chlorsulfuron Cyhalofop-butyl Dichlorprop Dichlorvos Mesotrione

Rows: LP groups, Cols: NR groups

v-Liver™ Chemicals



Results

Combinatorial activity of NRs summarized into small number of groups and most replicate chemicals cluster correctly

Initial literature analysis suggests similar NR activity across rodents and humans

Severity of rodent liver toxicity described by grade of cancer lesion progression

Aggregate human NR activity correlates with degree of rodent liver cancer lesion progression

Impact and Outcomes

Combinatorial NR activity is relevant to consider for environmental chemicals / mixtures

The analysis enabled the selection of 20 NR activating chemicals for developing the Virtual Liver

Apply these results to aid chemical prioritization for further testing

Next Steps: v-Liver™

Compare human *in vitro* NR activity with *in vivo* rodent data

Organize available knowledge about NR activity, downstream molecular pathways, cellular changes and tissue effects to evaluate human relevance

Develop predictive model of hepatic lobule to simulate the dose-dependent effects NR-activation in humans

References

Shah, I., Houck, K., Judson, R.S., Kavlock, R.J., Martin, M.T., Wambaugh, J., Dix, D.J. *Human Nuclear Receptor Activity Stratifies Rodent Hepatocarcinogens.* (Submitted)