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Applicability of systems biology in toxicology

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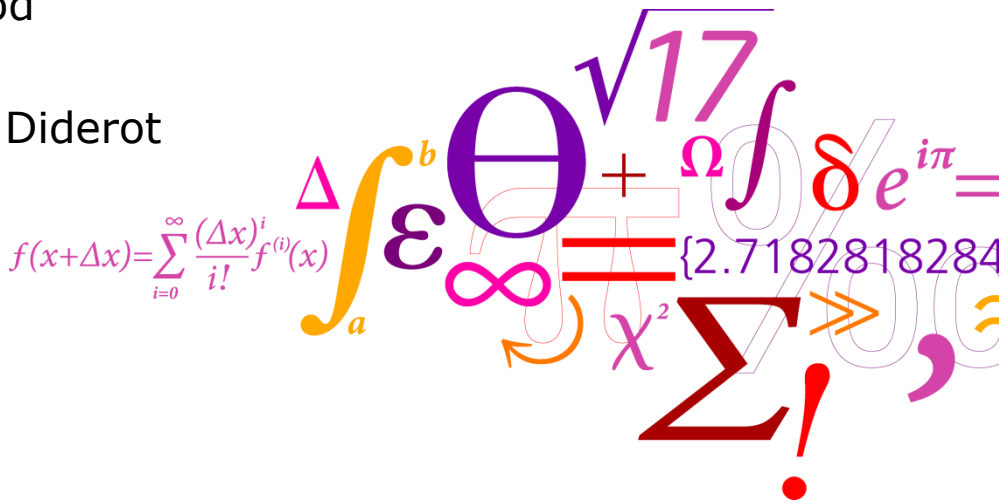

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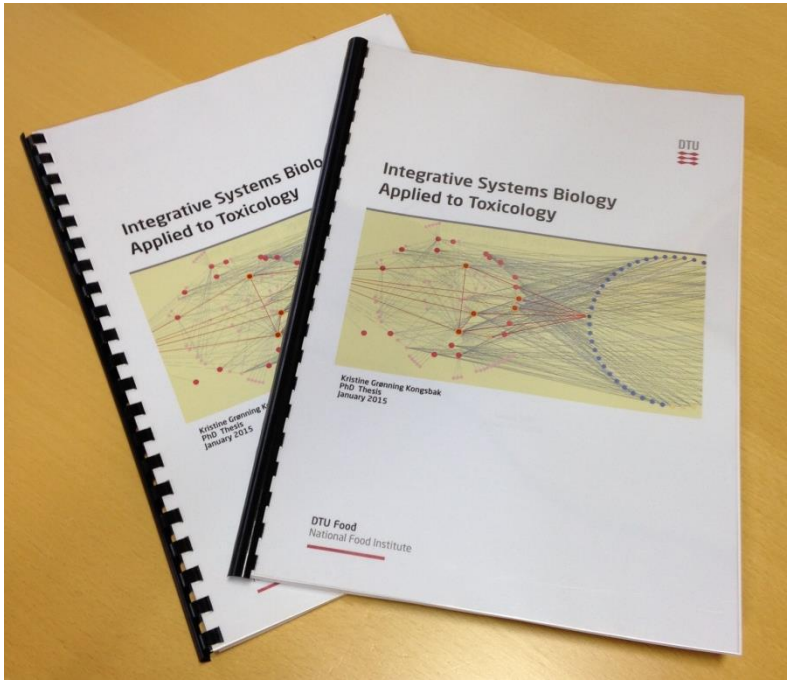
Outline

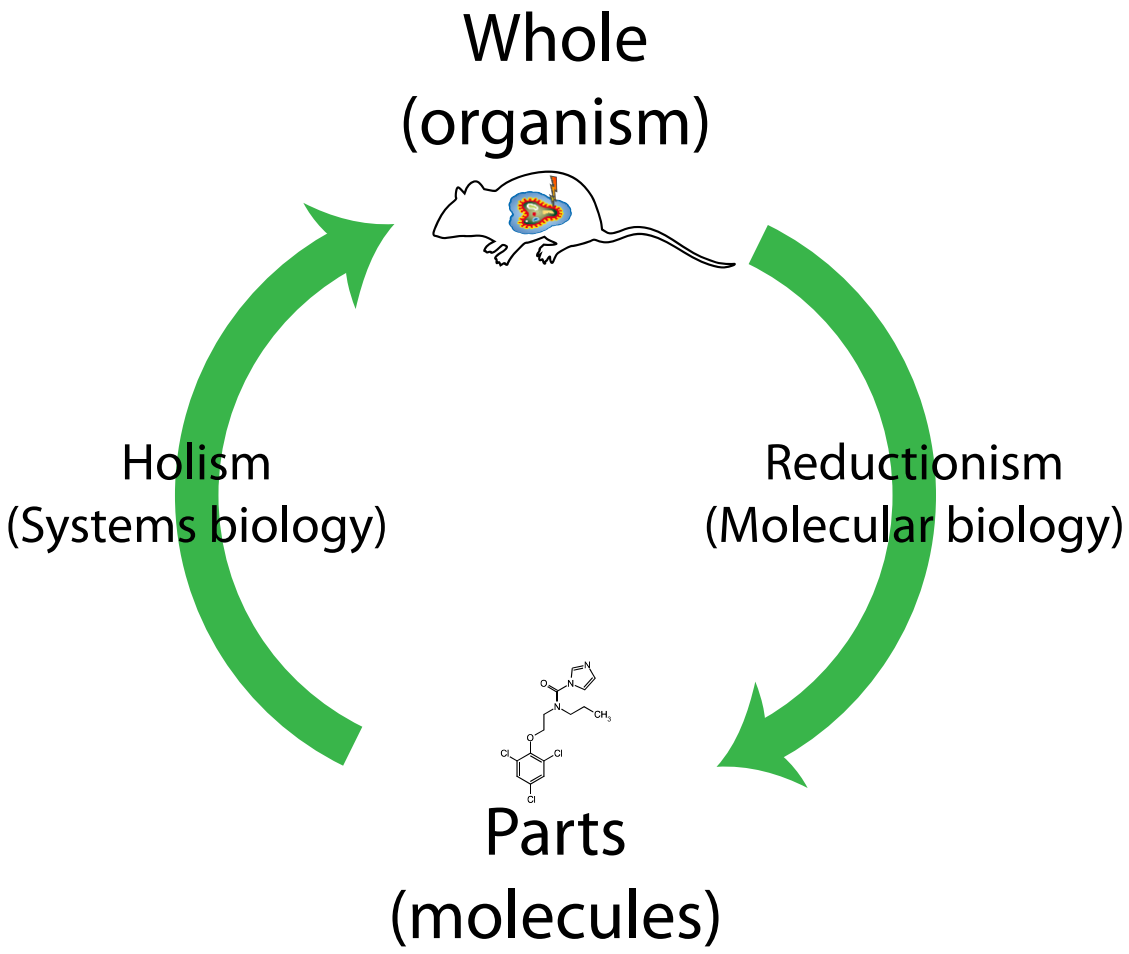
- Background/scope
  - What is systems biology?
- Computational toxicology projects
  - Integrative systems biology
  - Predictive modeling

Scope

- Assess whether (integrative) systems biology methods can supplement traditional *in vivo* and *in vitro* toxicological investigations.



What is systems biology?



PROJECTS

Integrative systems biology

Modeling ToxCast™ Data

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BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology, 2014, **115**, 45–49 Doi: 10.1111/bcpt.12216

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MiniReview

Applicability of Computational Systems Biology in Toxicology

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A Computational Approach to Mechanistic and Predictive Toxicology of Pesticides

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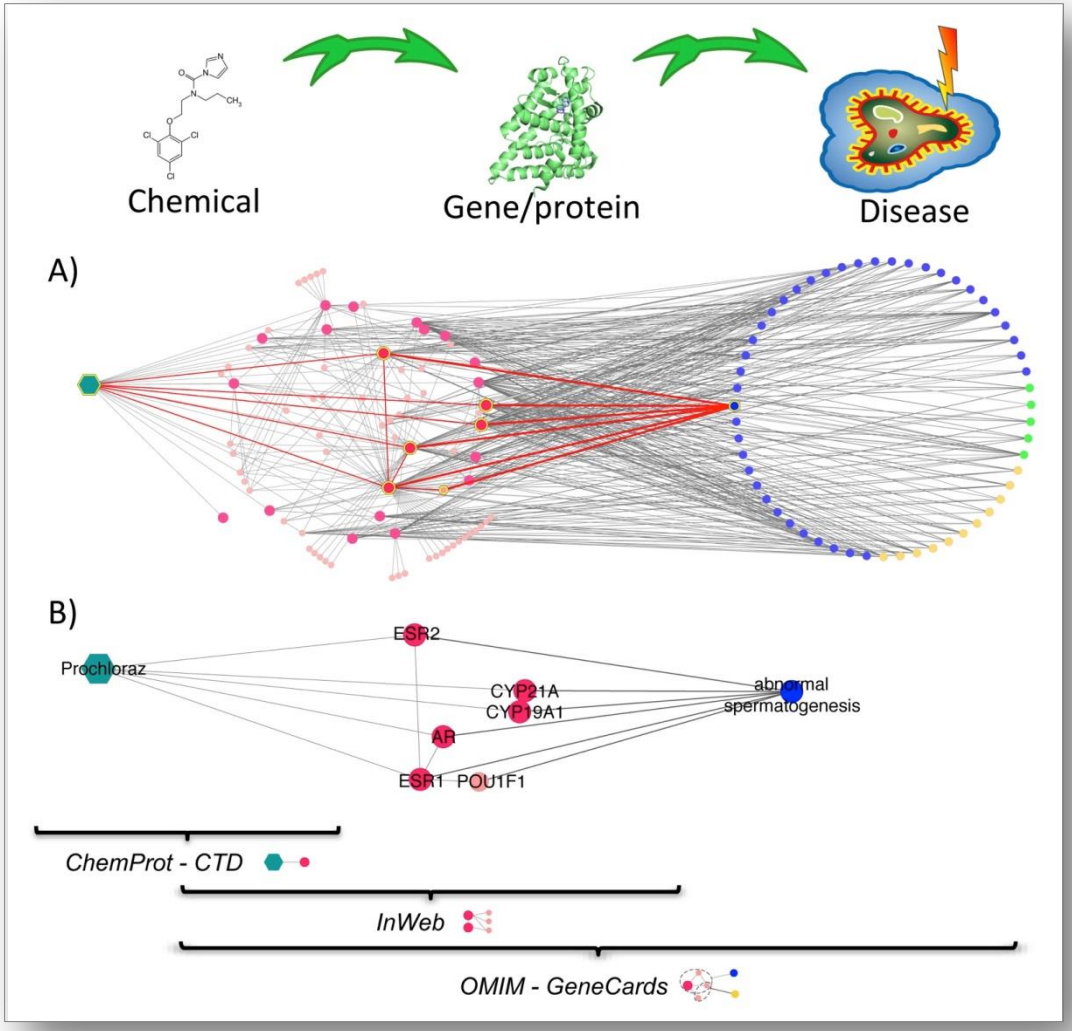
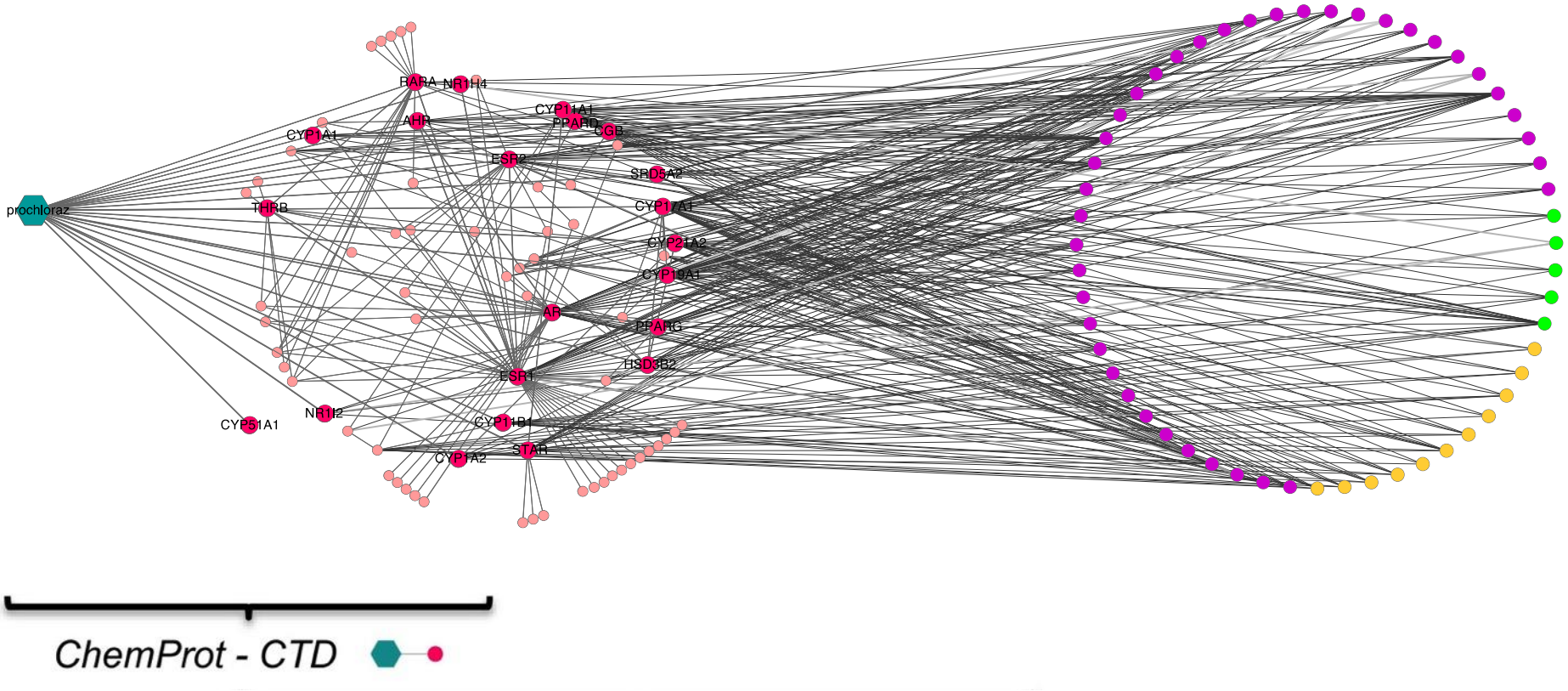
Integrative systems biology

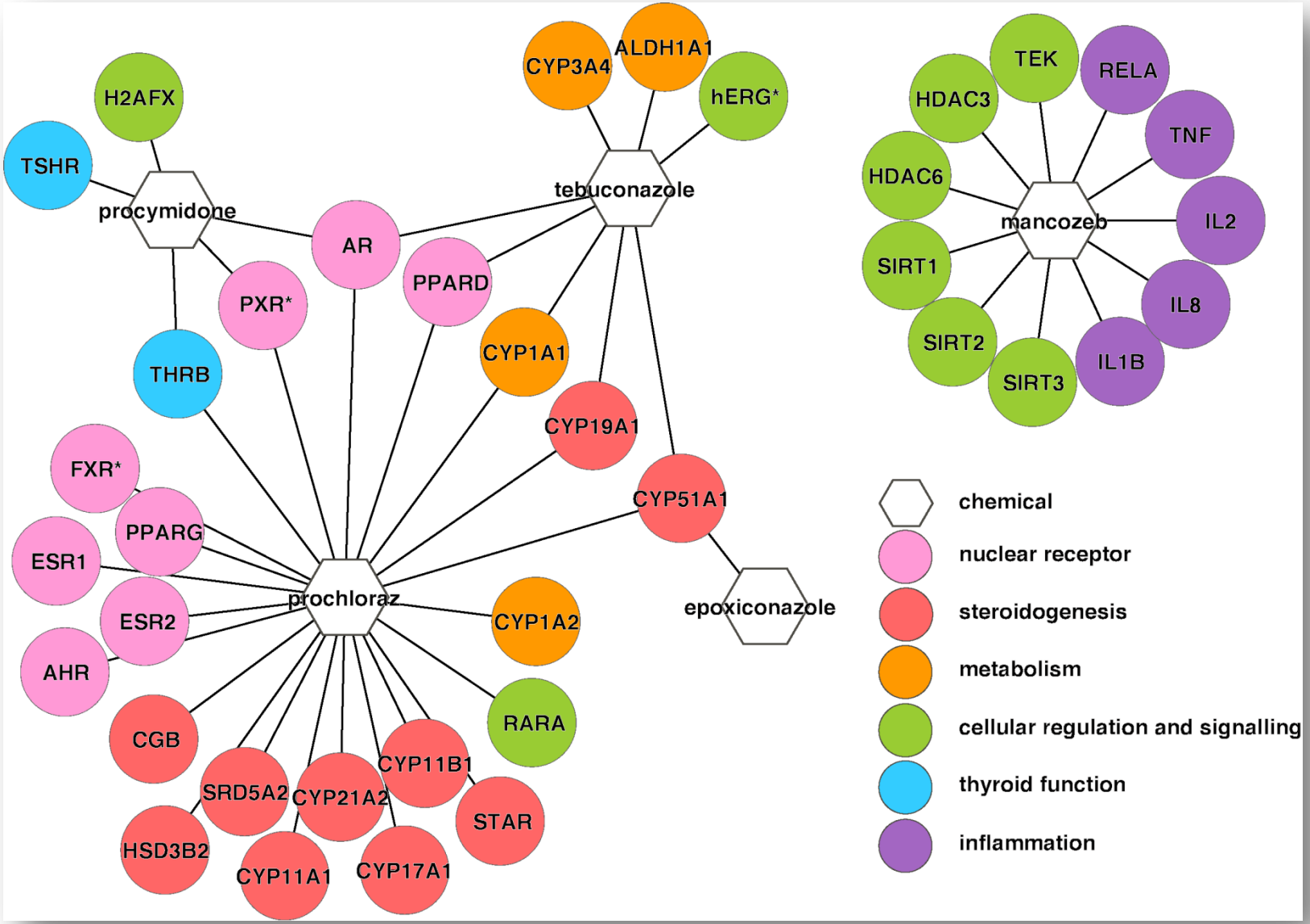


[Kongsbak *et al.* 2014]

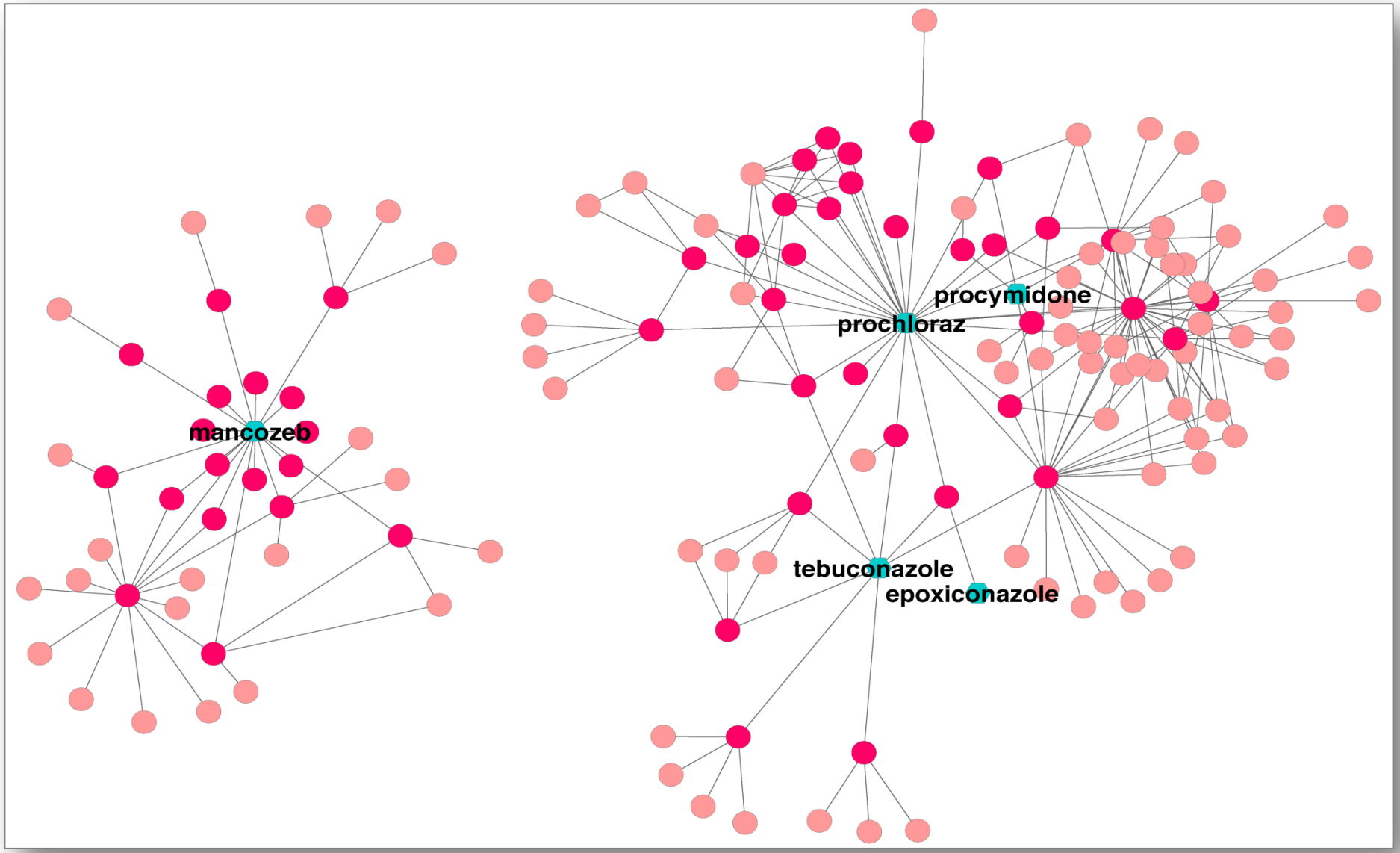
Integrative systems biology (cont'd)



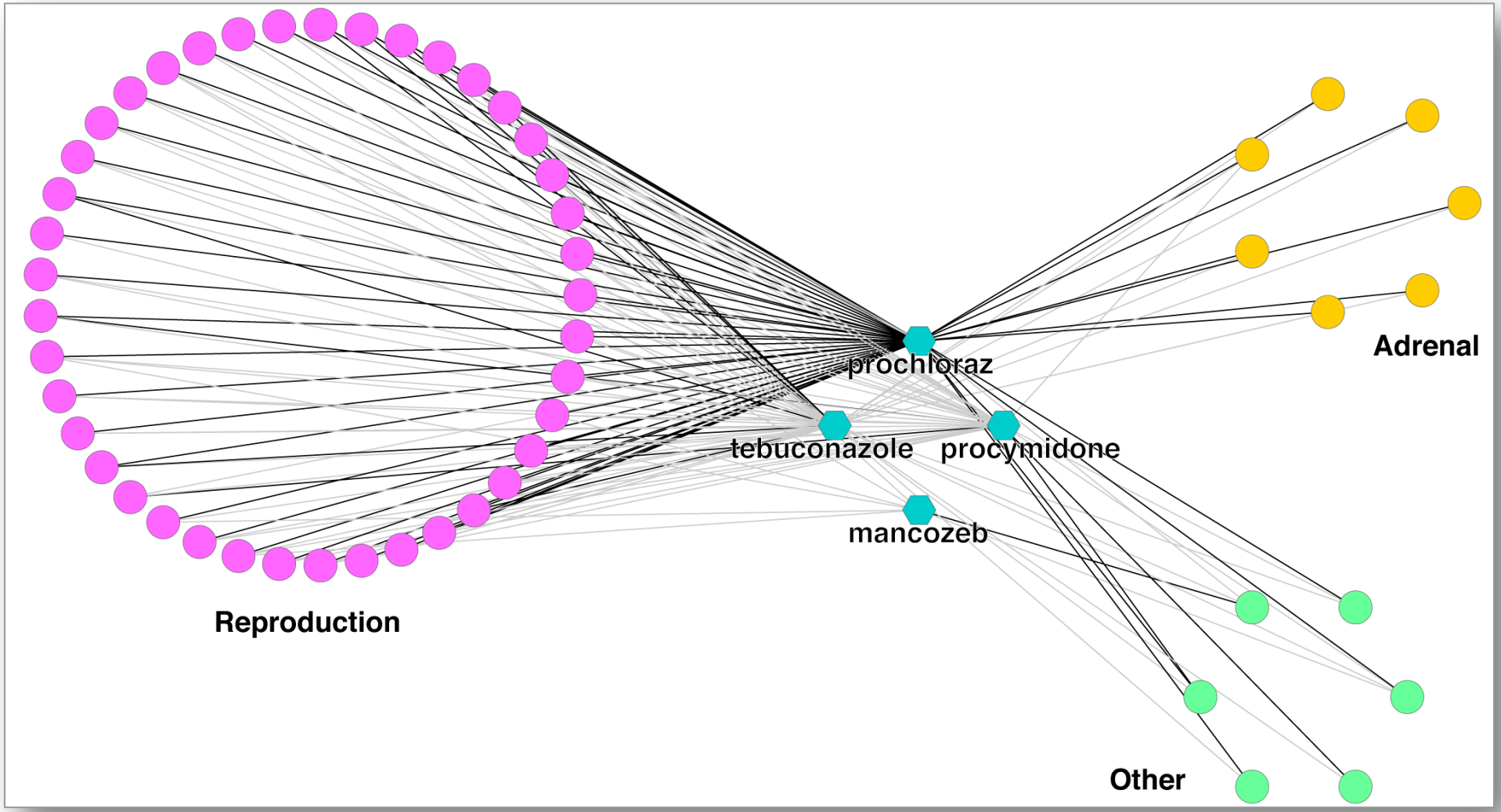
Integrative systems biology (cont'd)



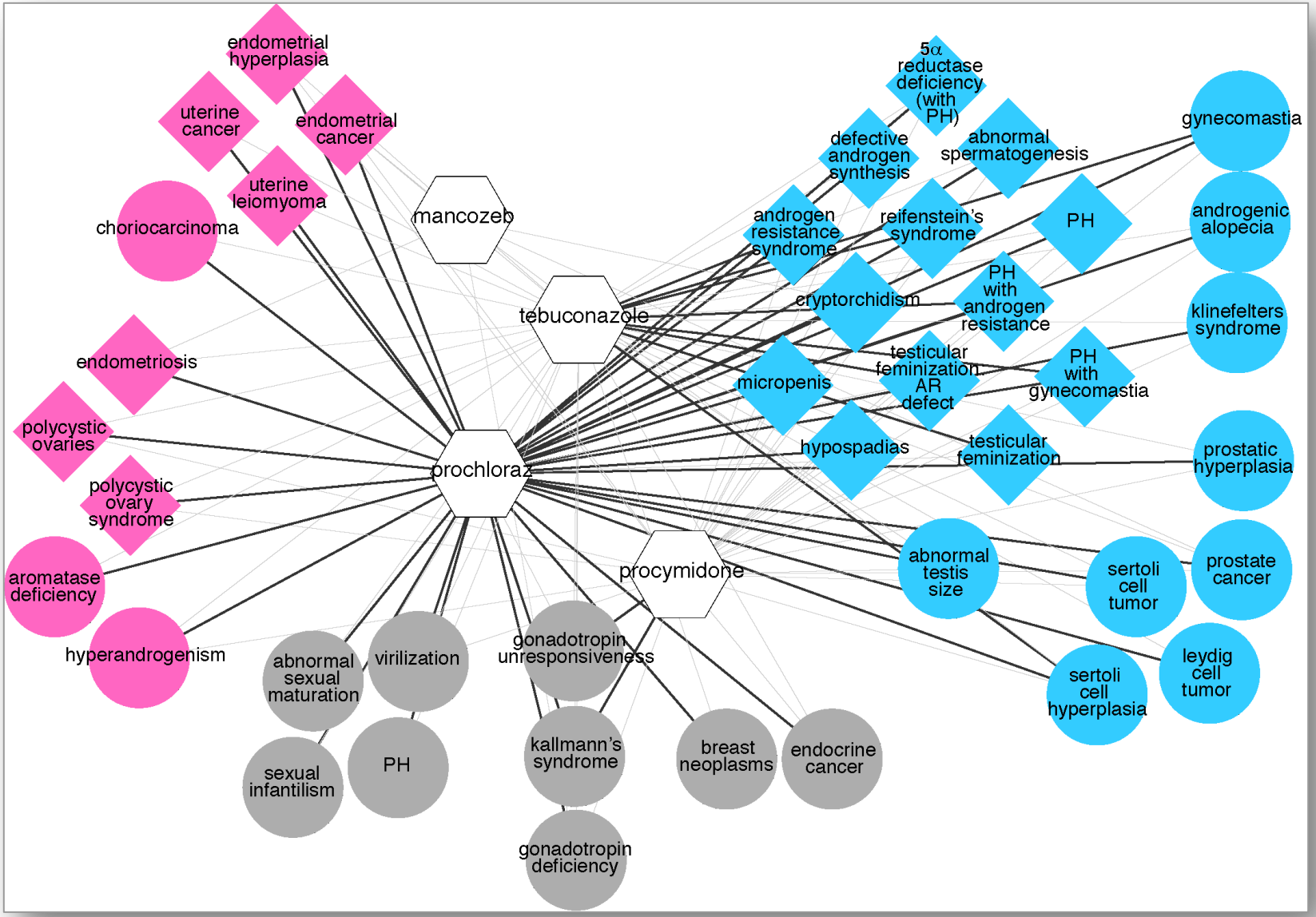
Integrative systems biology (cont'd)



Integrative systems biology (cont'd)



Integrative systems biology (cont'd)

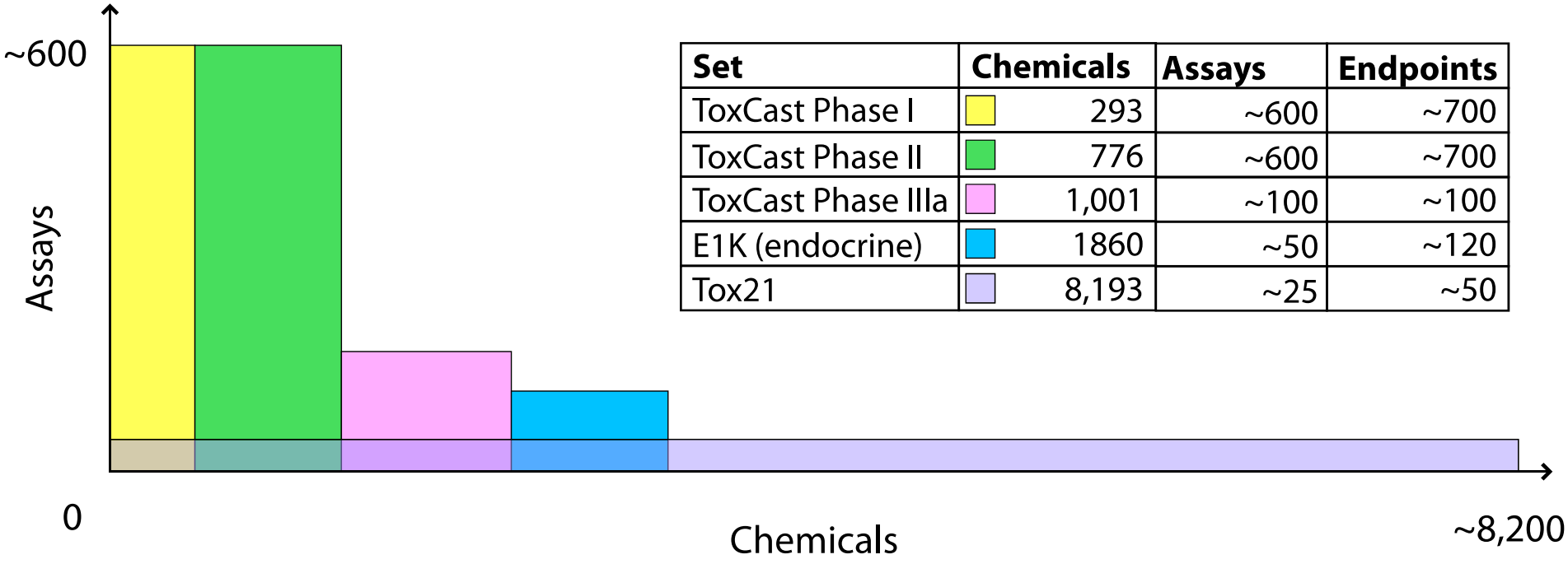


Strengths and Limitations

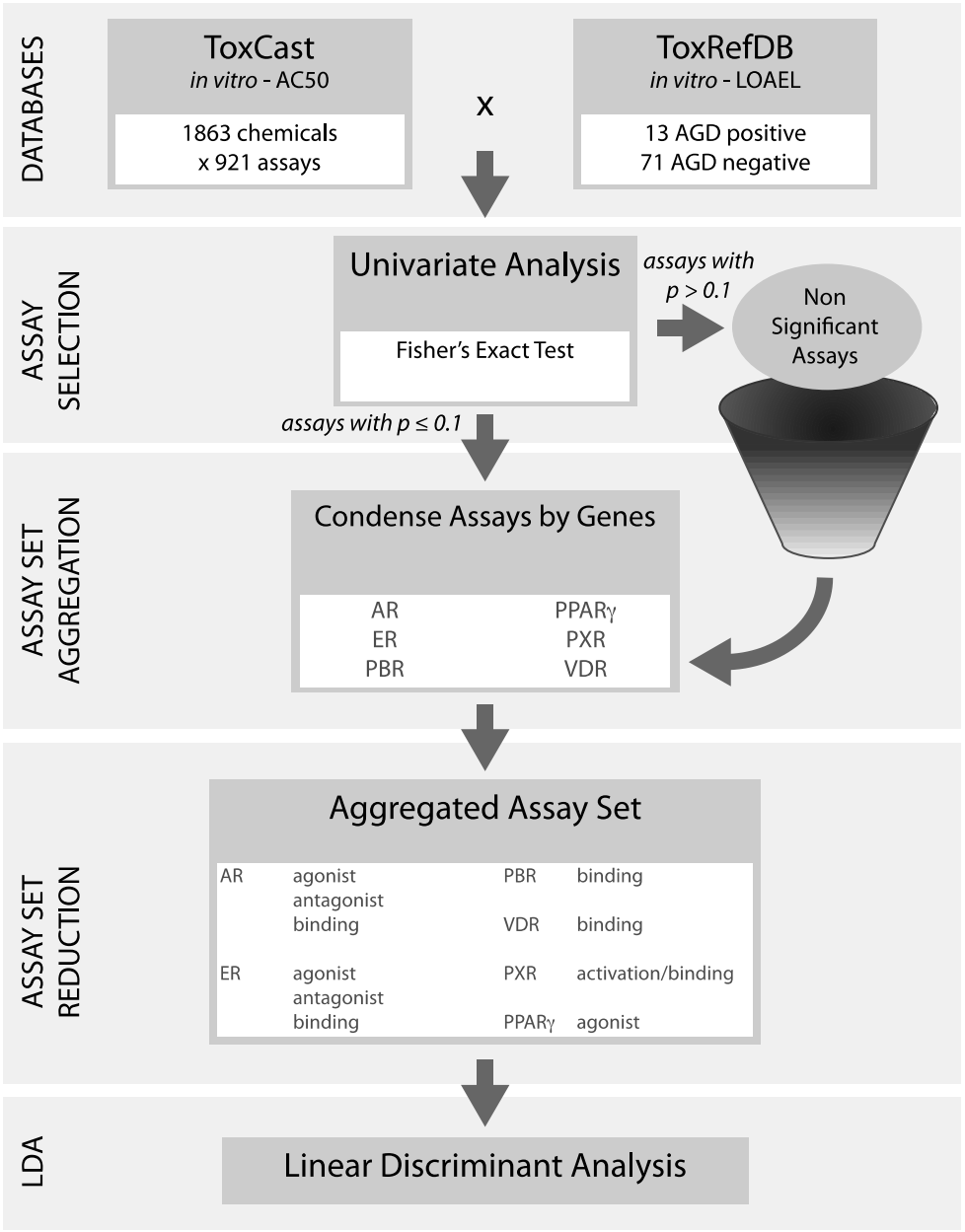
- Quick and “dirty”
- Overview of available data
- Predictions of potential pathway or disease associations
- Human predictions
- Grouping of chemicals for mixture predictions

- Dependence on the amount and quality of experimental evidence
- Backtracking data source
- The type of association

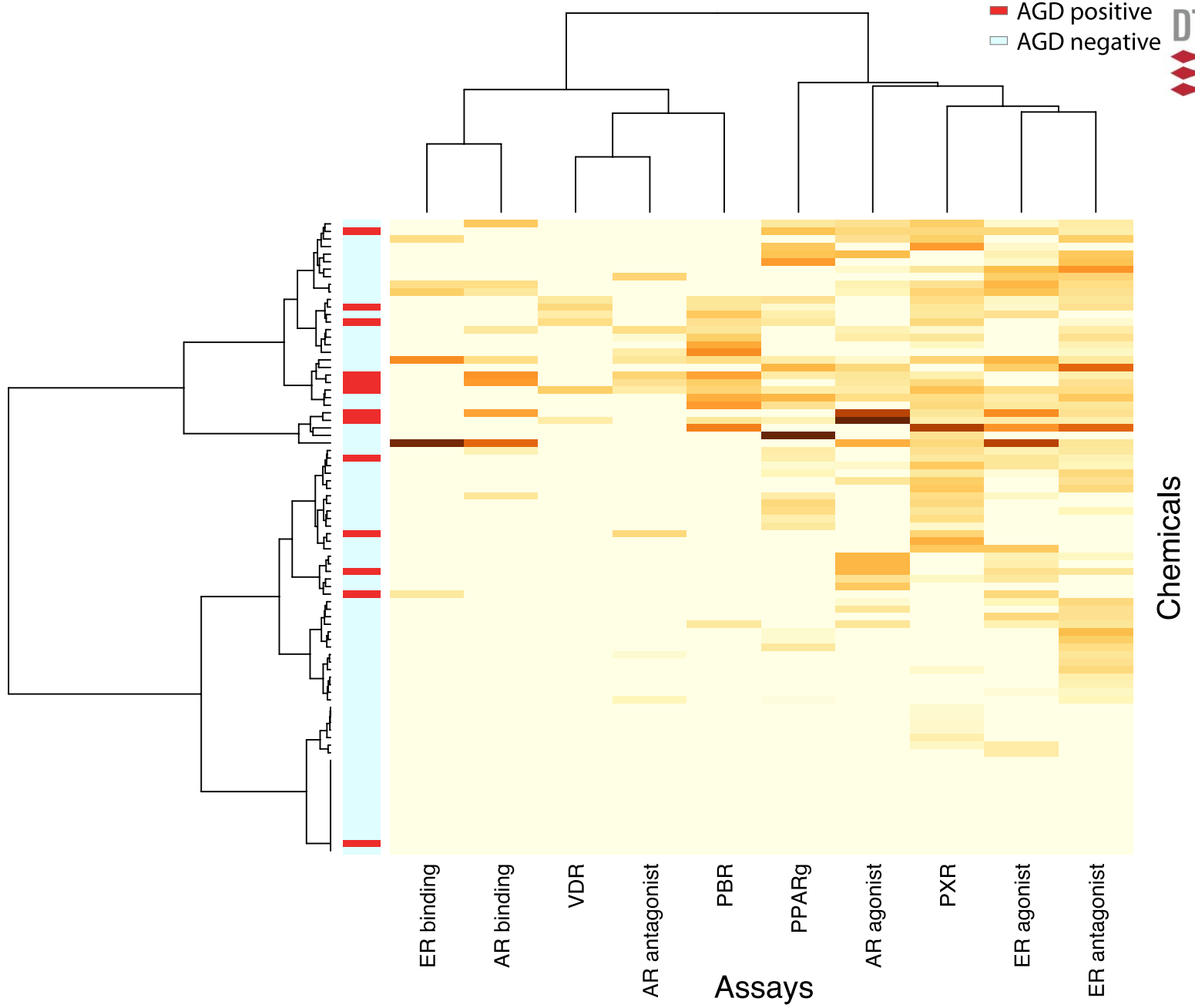
Modeling ToxCast™



Set	Chemicals	Assays	Endpoints
ToxCast Phase I	293	~600	~700
ToxCast Phase II	776	~600	~700
ToxCast Phase IIIa	1,001	~100	~100
E1K (endocrine)	1860	~50	~120
Tox21	8,193	~25	~50



Adapted from [Martin et al. 2011, Sipes et al. 2011]


AGD positive
AGD negative
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Chemicals
ER binding
AR binding
VDR
AR antagonist
PBR
PPARg
AR agonist
PXR
ER agonist
ER antagonist
Assays

External validation

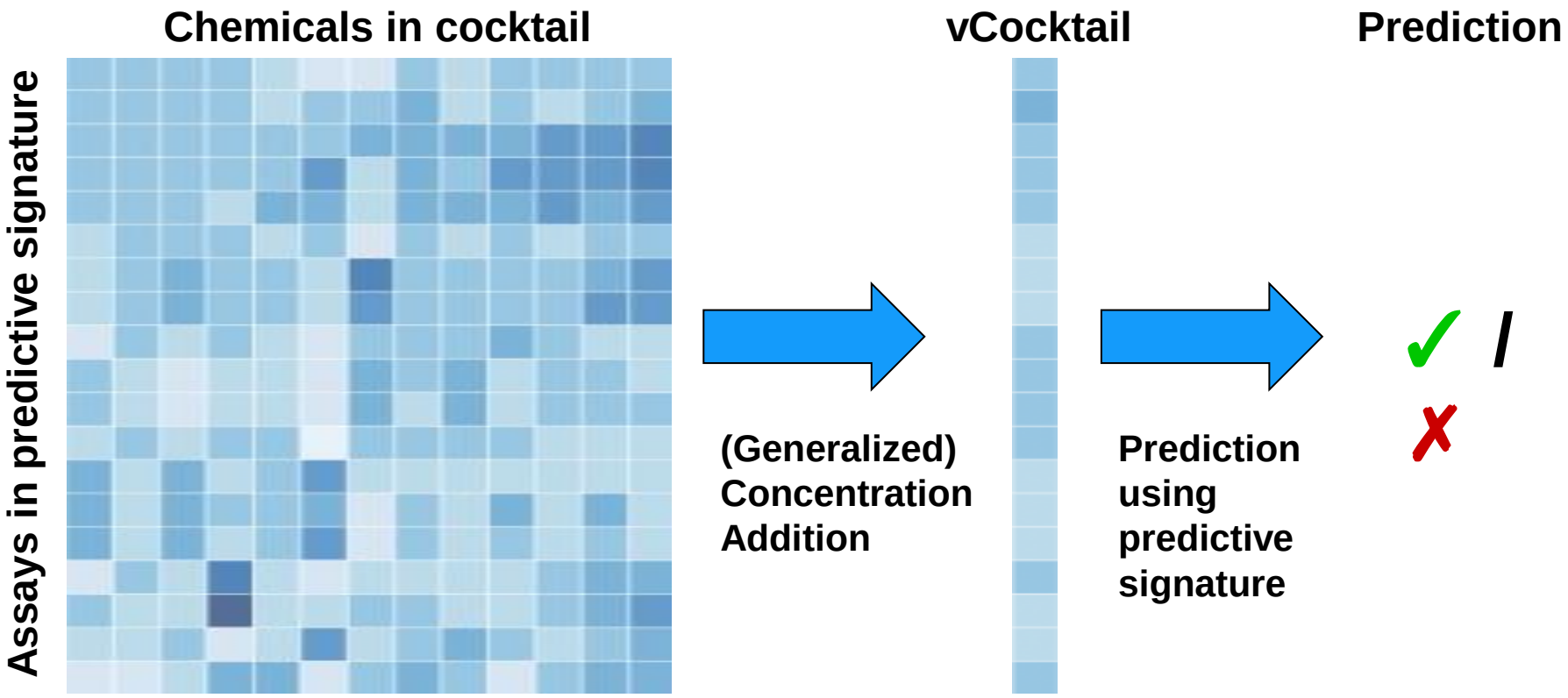
Chemical name	LOAEL	Evidence of reproductive toxicity	Predicted reproductive toxicant
Epoxiconazole	15 mg/kg/day	Yes	No
Ketoconazole	50 mg/kg/day	Yes	Yes
Genistein	5 ppm	Yes	No
Linuron	75 mg/kg/day	Yes	Yes
Prochloraz	50 mg/kg/day	Yes	No
Paracetamol	150 mg/kg/day	Yes	No
Propiconazole	2500 ppm	No	Yes
Tebuconazole	NA	No	Yes
Di-n-octyl phthalate	NA	No	No
Ethylparaben	NA	No	No
Heptachlor	NA	No	No
Lindane	NA	No	Yes
Octamethylcyclotetrasiloxane	NA	No	No
Dimethyl phthalate	NA	No	No

External validation

	Model statistics	
	Full model	Validation
Sensitivity	62 %	33 %
Specificity	94 %	63 %
Balanced accuracy	78 %	48 %
Accuracy	89 %	50 %
Precision	67 %	40 %
p-value	1×10^{-6}	NS

NS: Not significant

Virtual cocktail



Computational toxicology – Major findings

- Different methods contributes differently
- Integrative systems biology allows grouping according to effects in humans
- Modeling ToxCast can help prioritize chemicals for further testing
- Input to mode of action
- Input to hypothesis generation

Thanks ☺

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