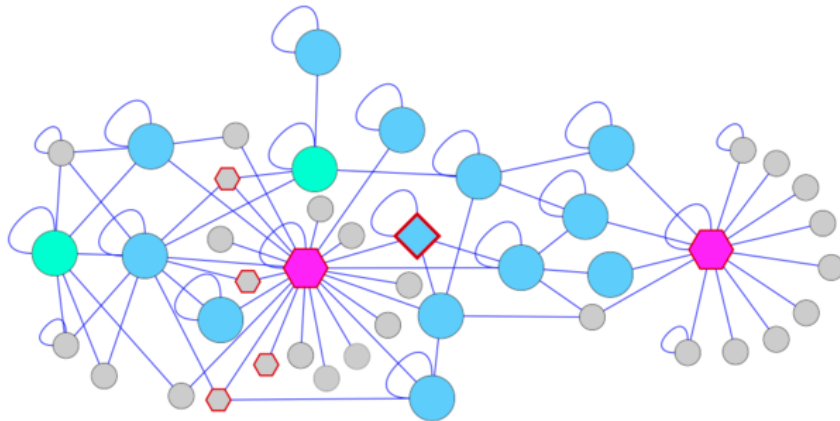


Identification des effets des perturbateurs endocriniens grâce aux études épidémiologiques et aux approches systémiques



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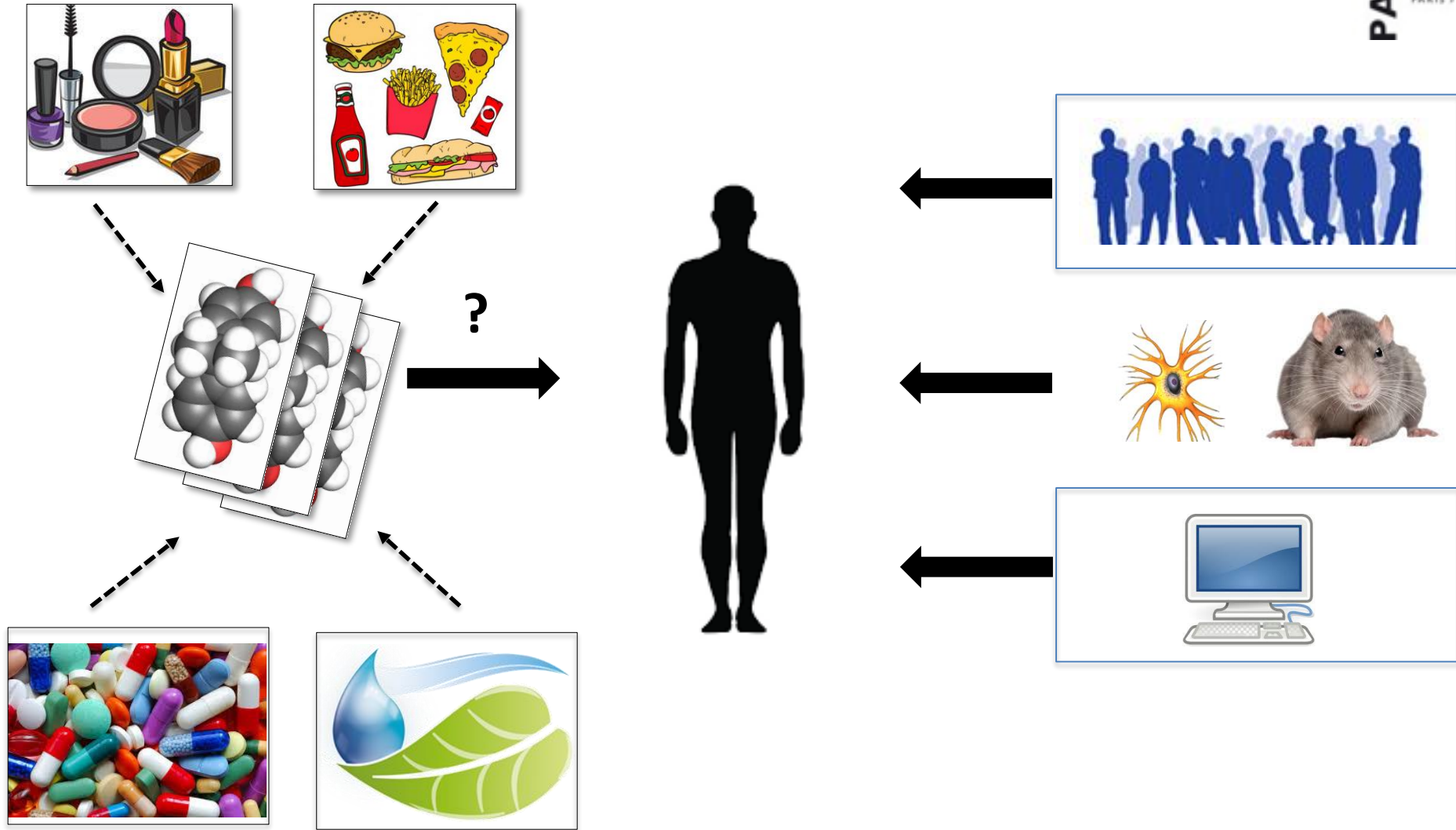
Endocrine disruptors

Selon l'Organisation Mondiale de la Santé (2002):

un « perturbateur endocrinien est une [substance chimique](#) qui altère les fonctions du système endocrinien et de ce fait induit des effets néfastes sur l'organisme d'un individu ou sur ses descendants »



Adverse effects of endocrine disruptors?



Enquête de cohorte



Enquête de cas/témoins



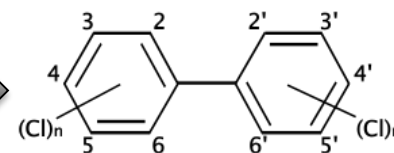
Temps

Présent

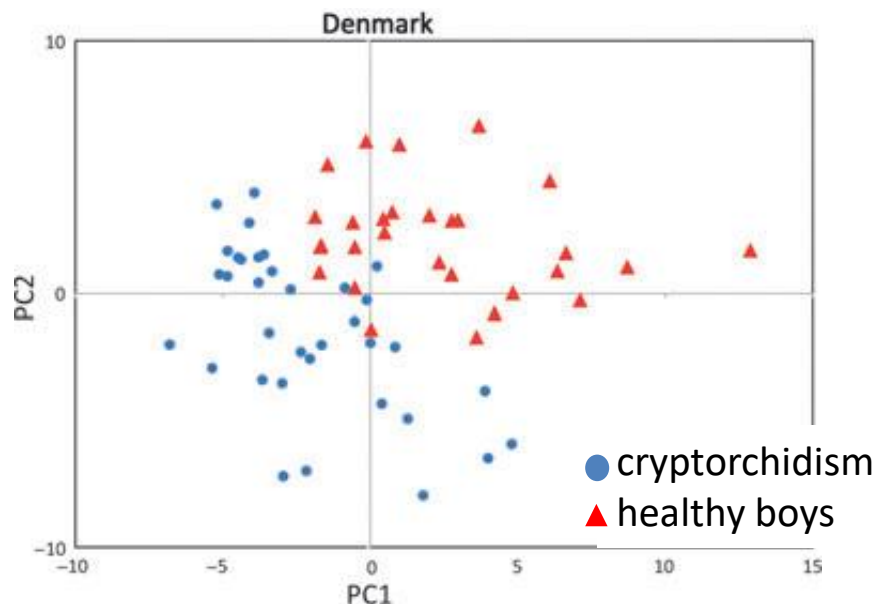
From chemical mixture exposure to cryptorchidism



Cohort: 130 newborn boys
Half of them cryptorchid.

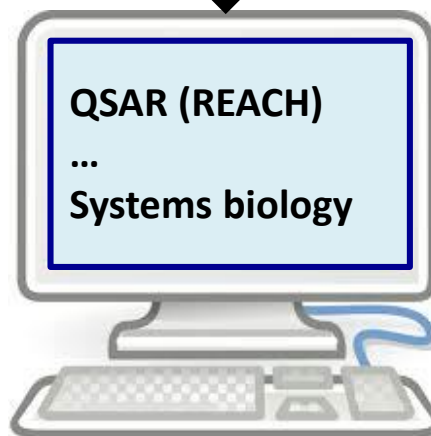
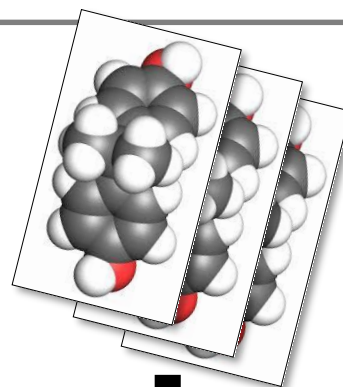


121 environmental chemicals (phthalates, dioxins, PBDEs, PCBs, PBBs...)



Good separation between cases and controls in Danish samples (same with FIN)

The prospect of *in silico* toxicology



Alternative methods
3Rs

Computational methods for
predictive toxicology*

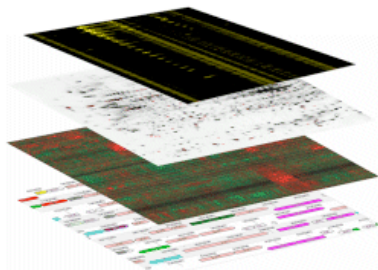
In silico systems chemical biology to explore toxicity hazards

Integration of 2 concepts based on several technologies

Systems biology:

Study of interactions between biological components

- *genes involved in diseases*
- *protein-protein interactions*
- *diseases protein complexes*
- *biological pathways*
- *'omics' (large scale data)*
- *genetic variation (SNP, CNV)*
- *clinical data, patient record, questionnaire*



Chemical biology:

Study of chemical effects

- *chemical-gene associations*
- *chemical-protein interactions*
- *chemical-disease links*
- *chemical-AOP relations*
- *chemical & metabolites, metabolomics*

In silico systems chemical biology to explore toxicity hazards: Application

Systems chemical biology:

Understanding molecular and cellular effects of chemicals in biological systems

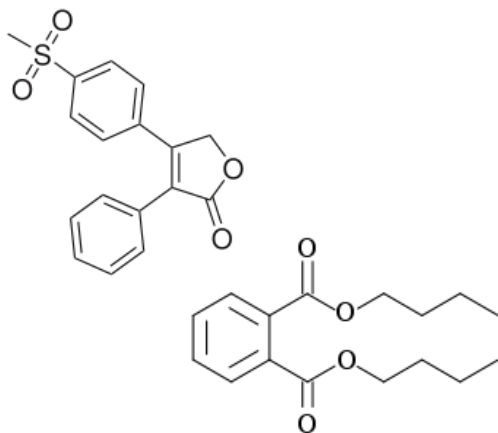
***multidisciplinary
data integration***

Toxicogenomics

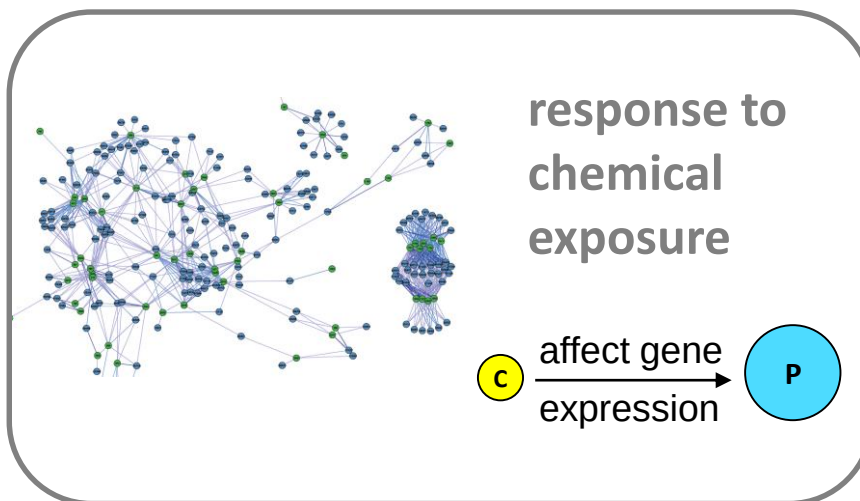
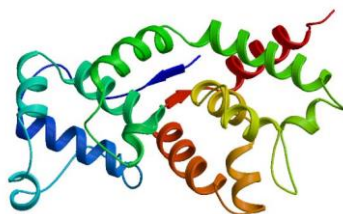
Protein-Protein Association Network:
P-PAN model

P-PAN: Integrative toxicogenomics

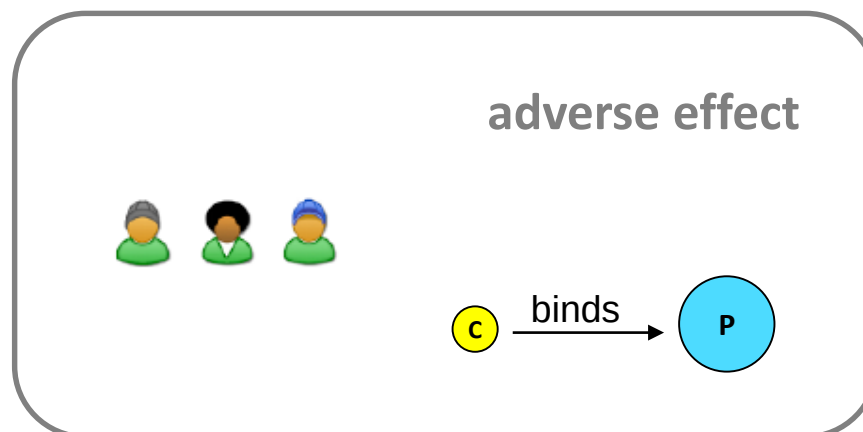
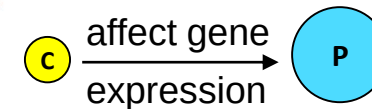
Drugs and
environmental chemicals



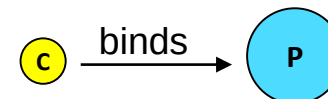
Genes/proteins



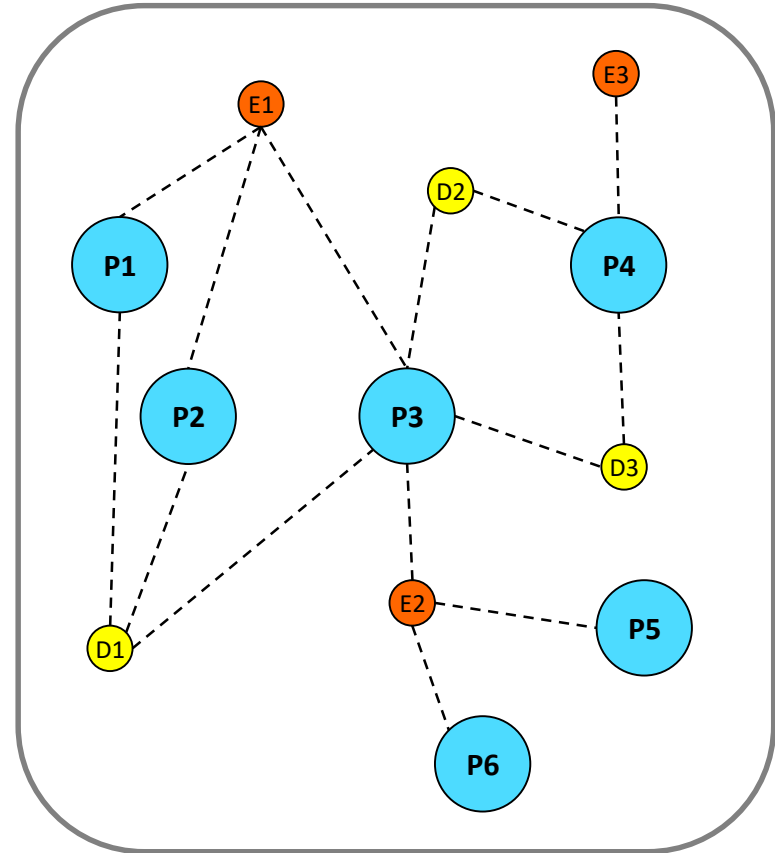
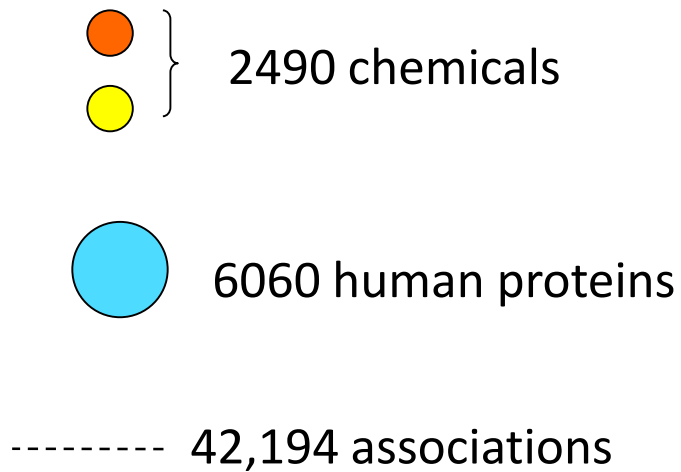
response to
chemical
exposure



adverse effect

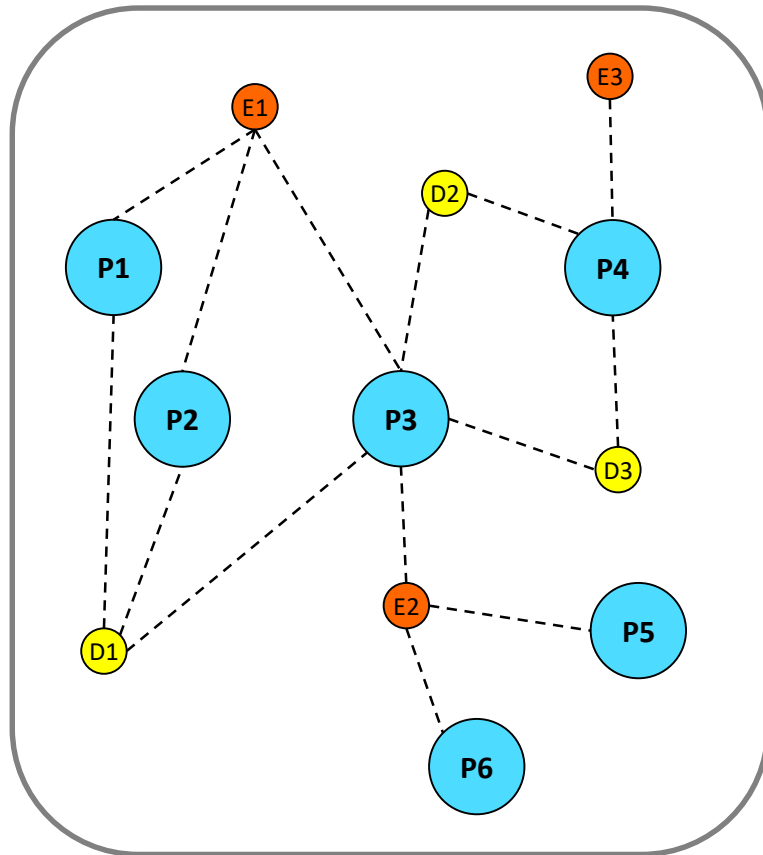


Integrative toxicogenomics



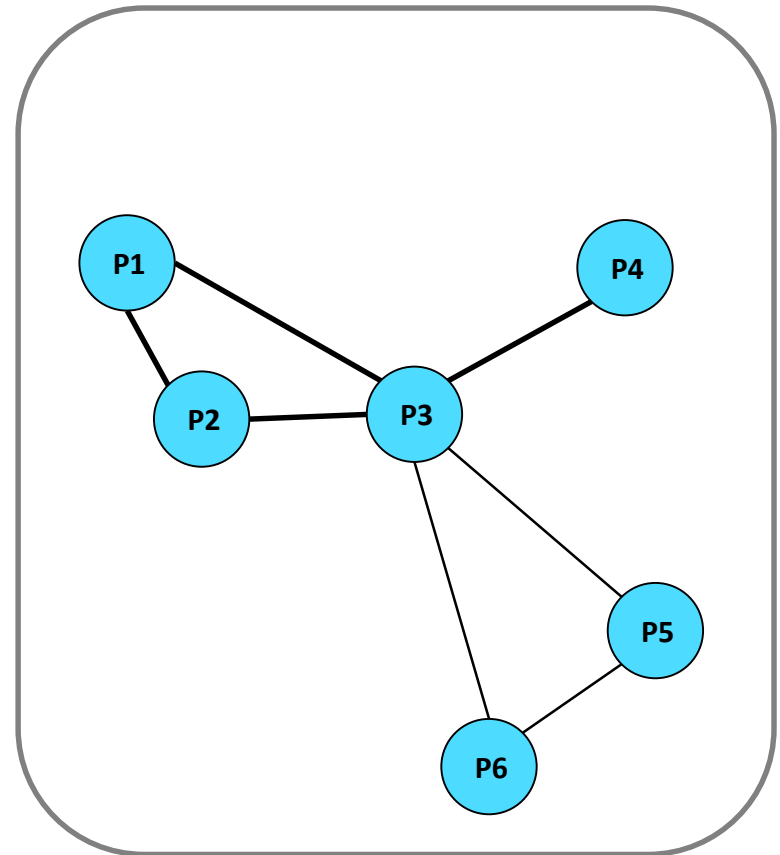
Protein-protein association network

Protein-chemical associations



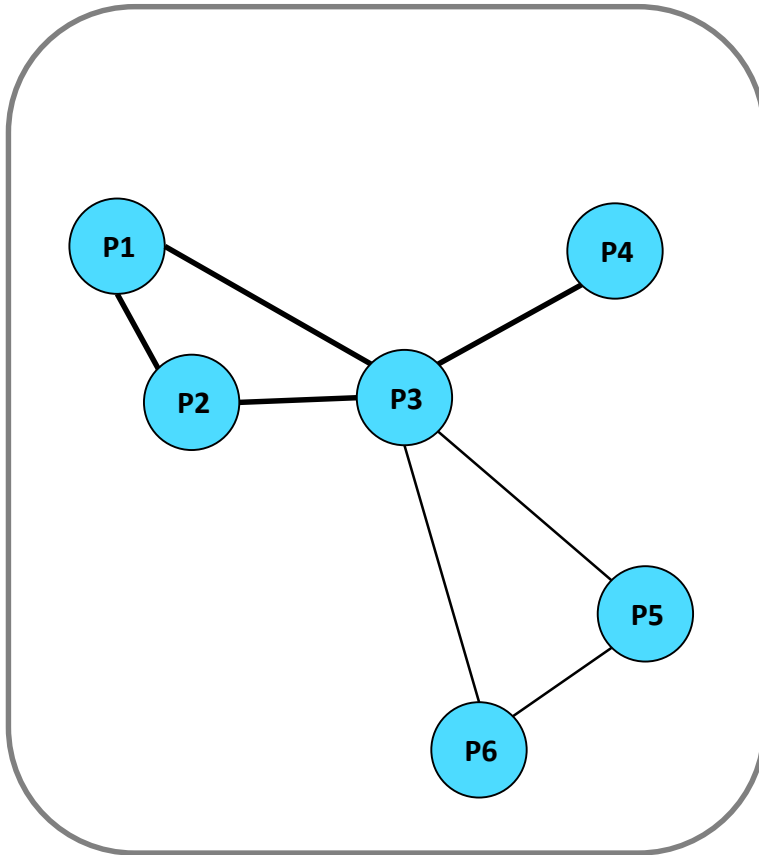
reliability
→
scores

Protein-protein associations



P-PAN: 2M⁰ -> 200,000

Application of *in silico* systems chemical biology: from chemical to biological target

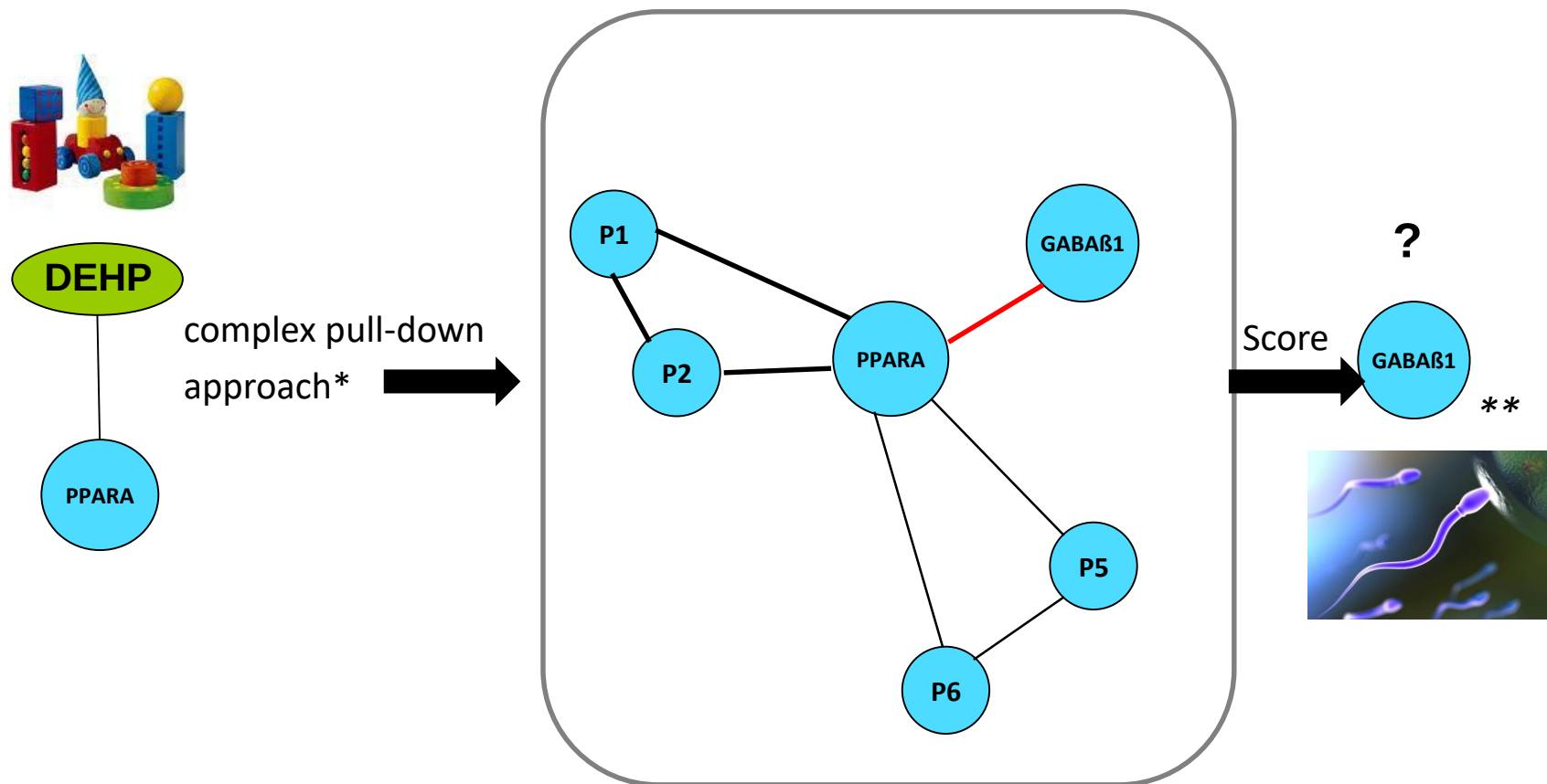


Protein predictions

Protein-Protein Association Network

From chemical to biological target:

1- proteins prediction by biological annotation



DEHP: diethylhexylphthalate

PPARA: peroxisome proliferator-activated receptor alpha

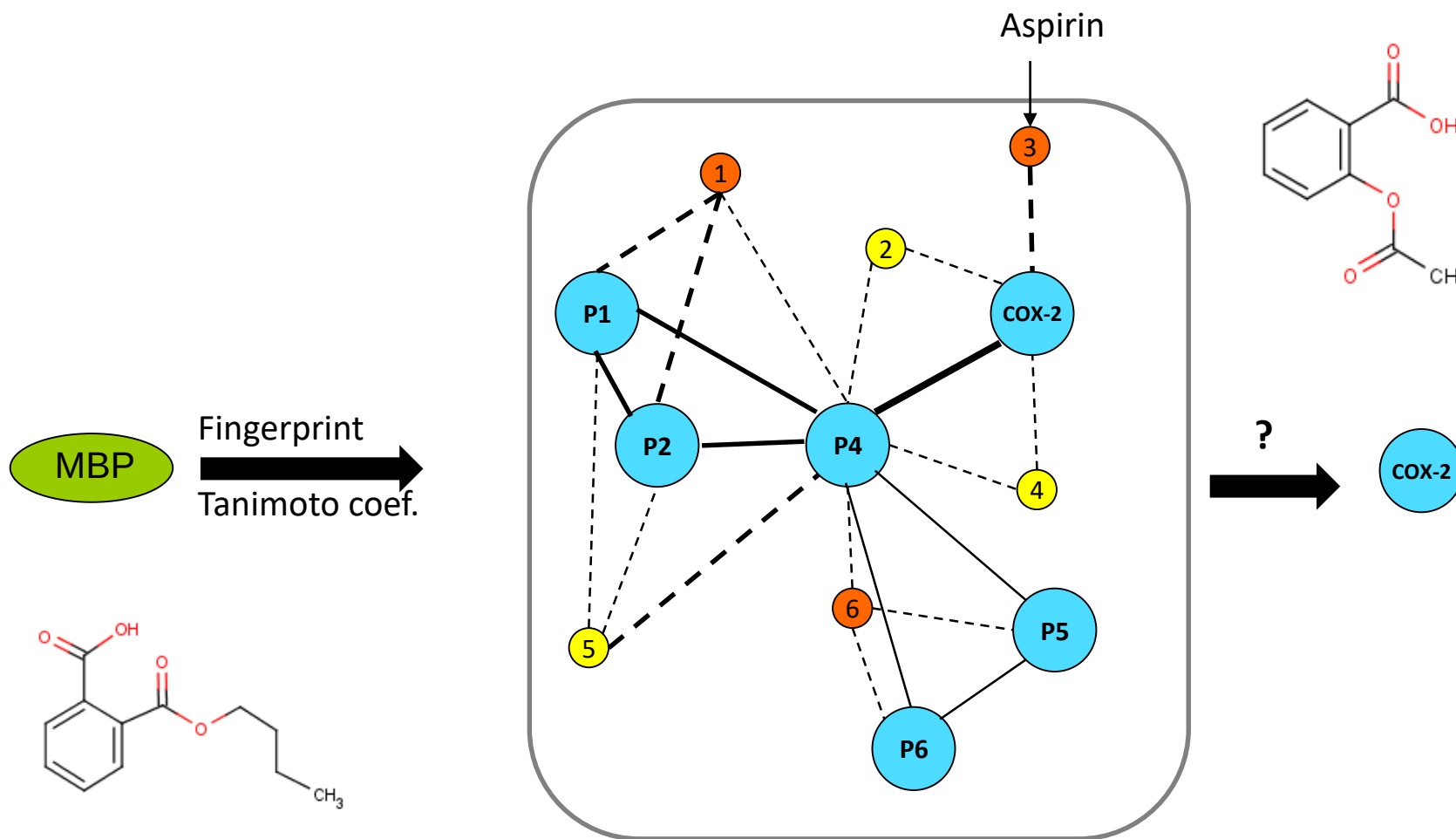
GABAβ1: gamma-aminobutyric acid B receptor 1

*de Lichtenberg et al. **2005** *Science*

** Penatti et al. **2010** *J. Neurosci.*

From chemical to biological target:

2- proteins prediction by chemical similarity



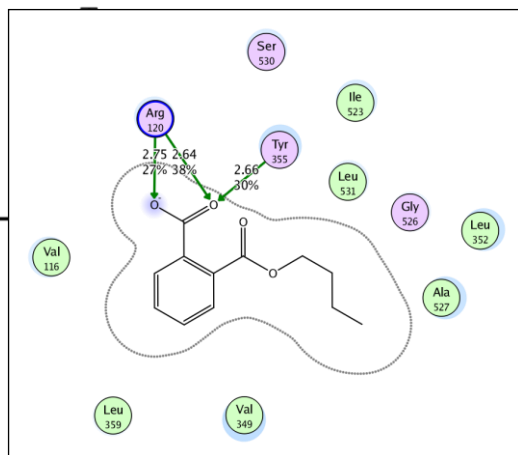
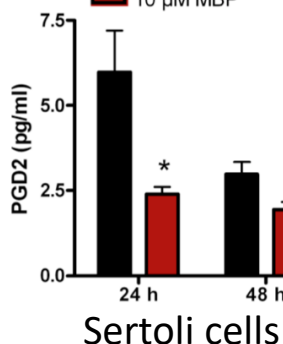
MBP: monobutyl phthalate

COX-2: cyclooxygenase-2; PTGS: prostaglandin-endoperoxide synthase

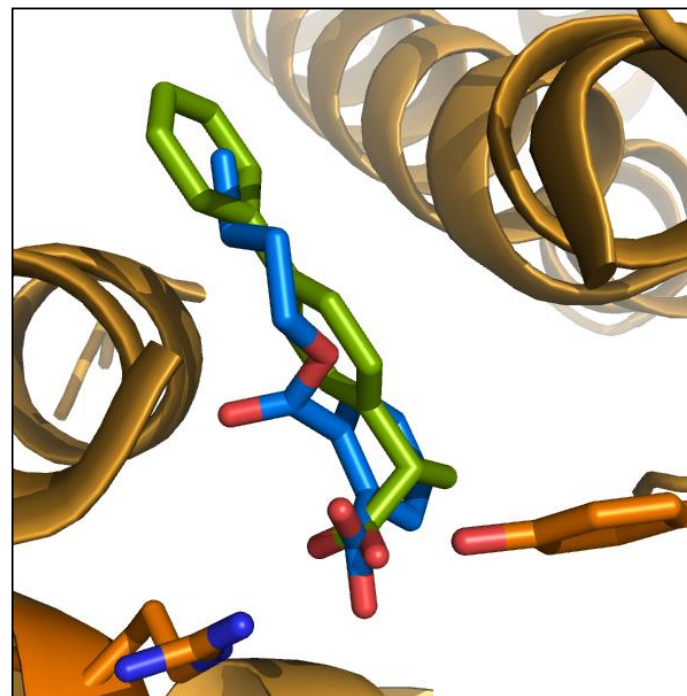
Inhibition of prostaglandin synthesis by EDCs* and 15 widely used pesticides**

a

Control
10 μ M MBP



Protein Database
(1PXX: 2.9Å)



Molecular docking of MBP in COX-2

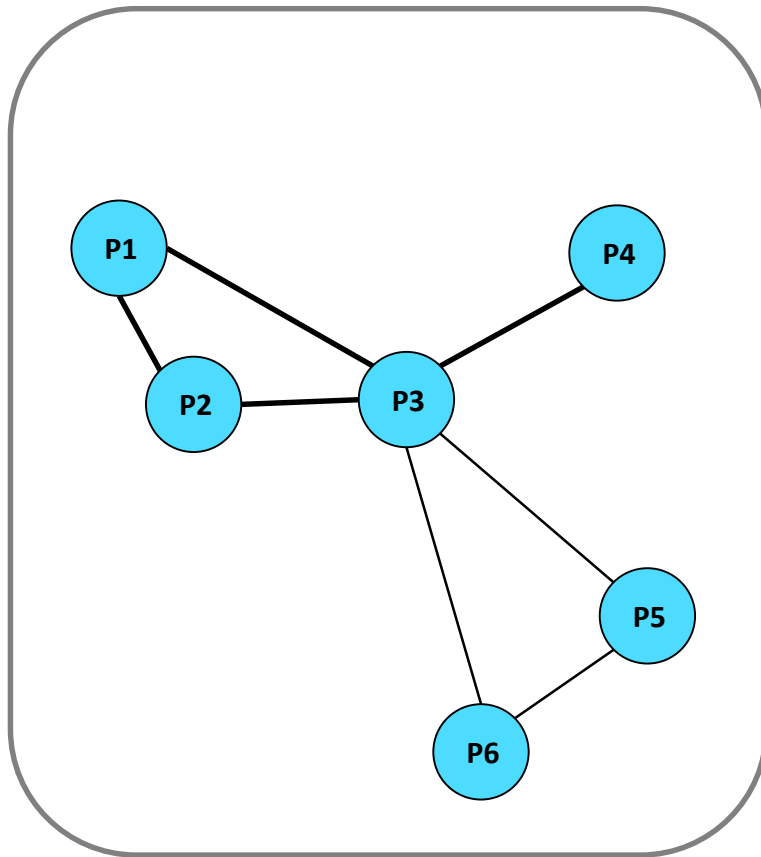
Indomethacine like mode

➡ Novel mode of action by EDCs through inhibition of the prostaglandine pathway - suggest new avenues to investigate the increase in reproductive disorders

* Kristensen et al. **2011** *Environ Health Perspect.*

Kugathas et al. **2015 *Environ Health Perspect.*

Application of *in silico* systems chemical biology: from chemical to disease

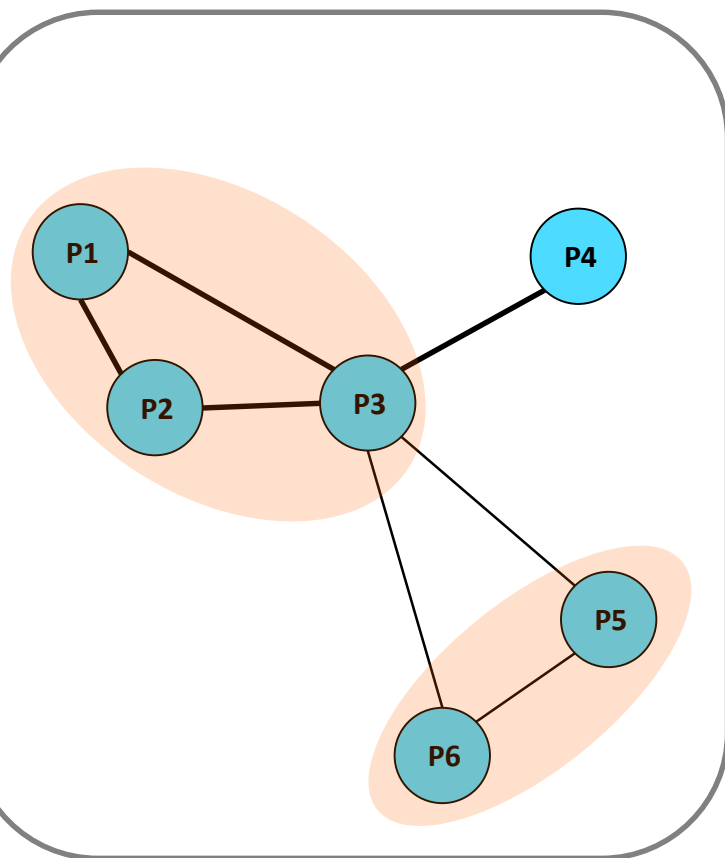


➔ Disease predictions

Protein-Protein Association Network

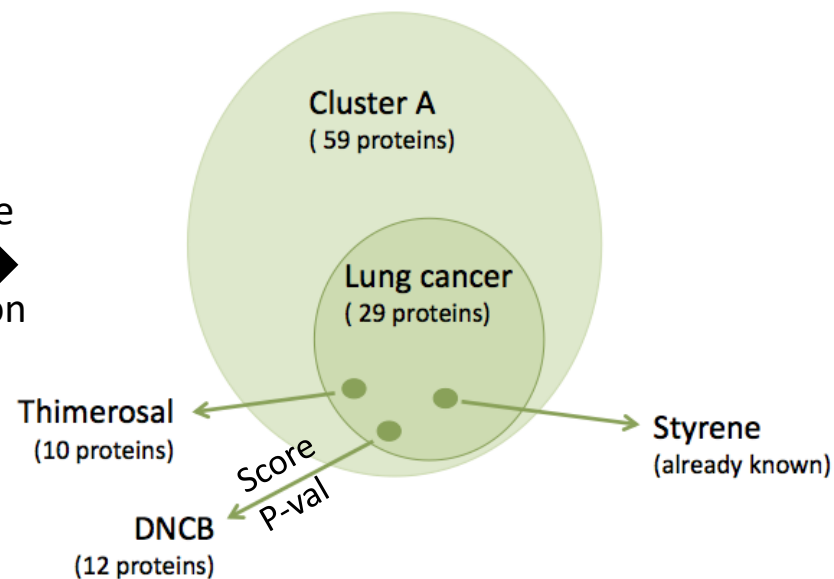
From chemical to disease: Disease prediction

Markov clustering: graph clustering



Protein-disease
Data integration

Biological enrichment: biostatistics



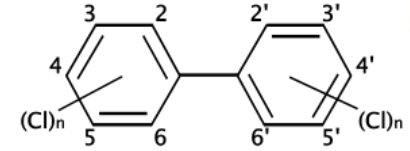
p, p' DDT $\longrightarrow$ hypospadias, cryptorchidism

Audouze & Grandjean **2011** *Environ Health Perspect.*

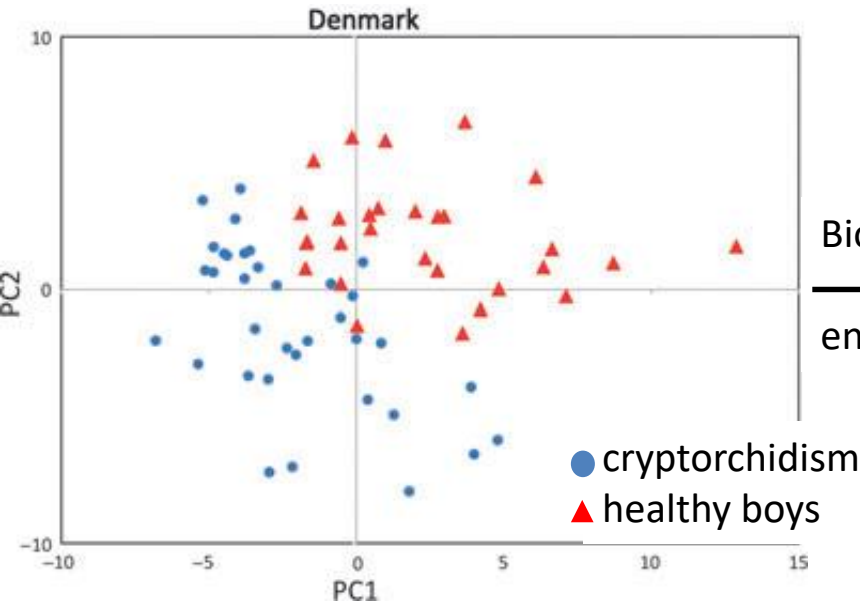
From chemical mixture exposure to cryptorchidism



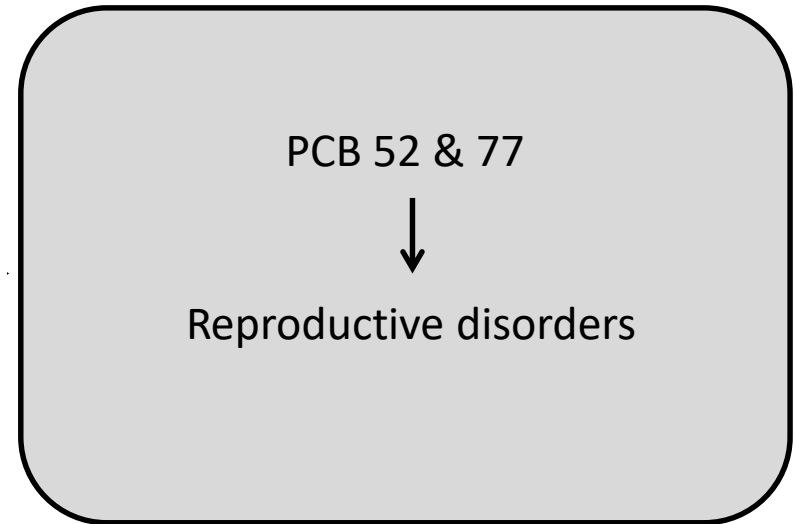
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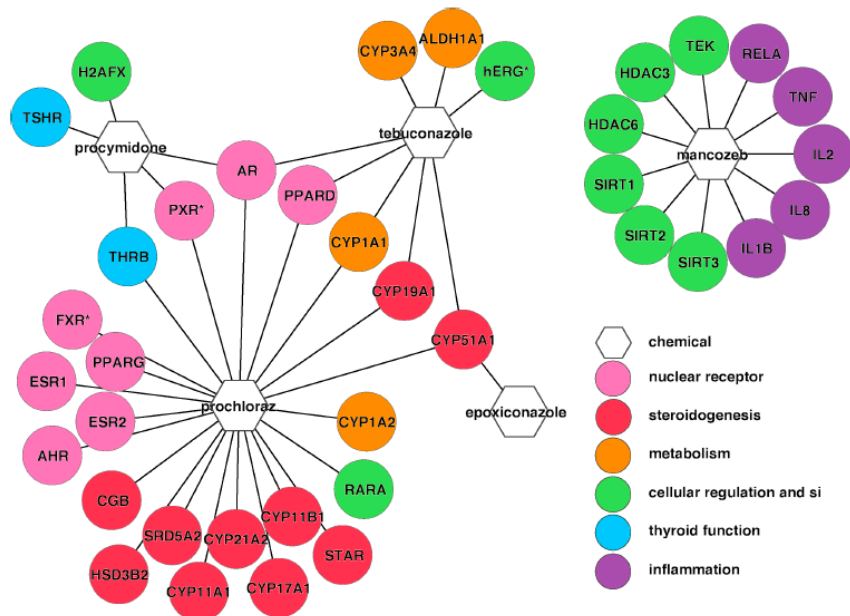


Biological
enrichment



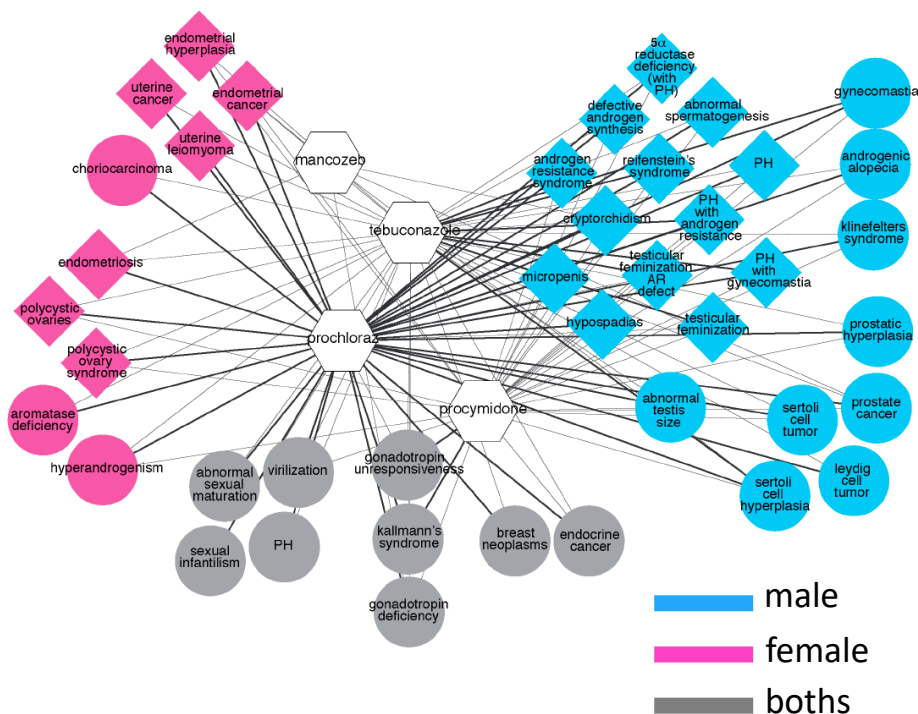
Mixture of endocrine disruptors may contribute to observed adverse trends in male reproductive health

From chemical mixture to disease: ex. with 5 pesticides



Adrenal diseases

Reproductive disorders



Mixture of EDCs



147
EDCs

ToxCast™



9000
cpds

ToxCast™

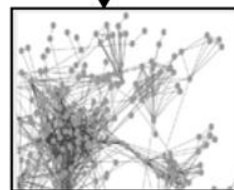
76
EDCs

5000
act.
cpds

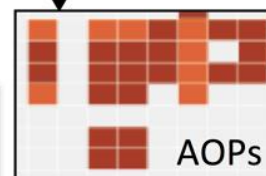
A
dverse
O
utcome
P
athway
WIKI

220 unique
human genes

38 unique
genes



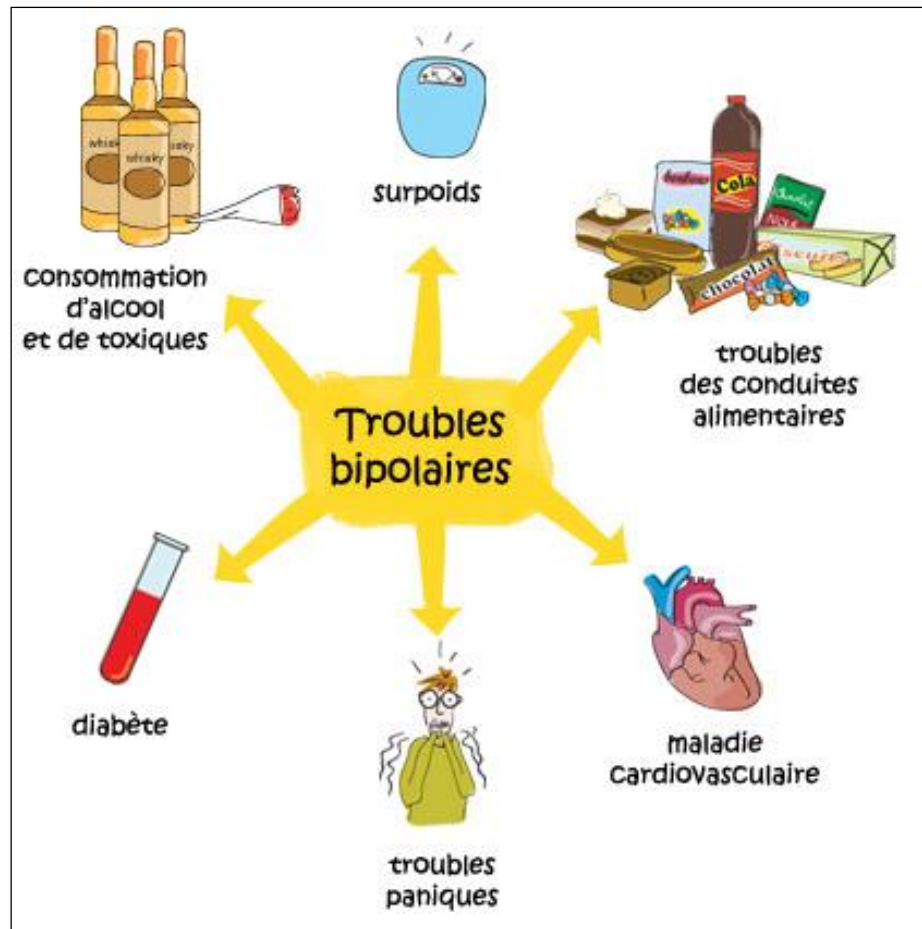
Pathways/Diseases



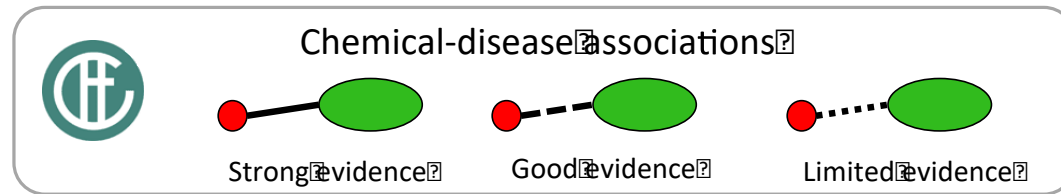
AOPs

SYSTEMS BIOLOGY

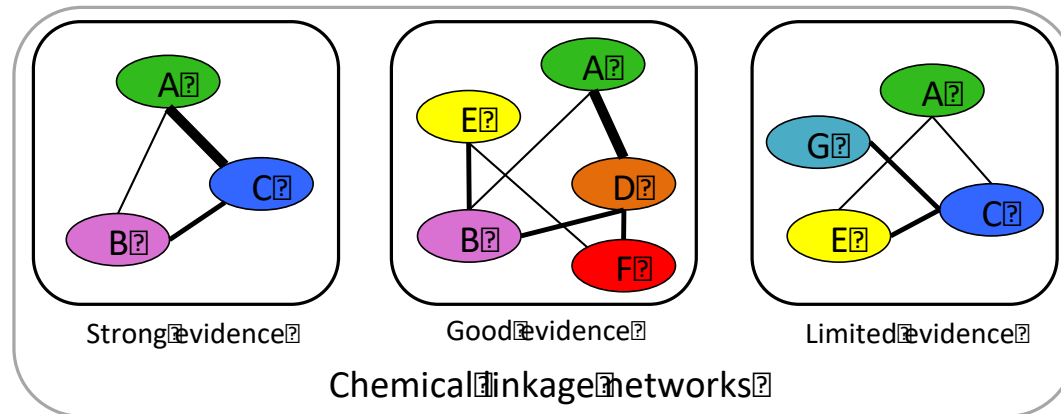
From chemicals to disease comorbidities



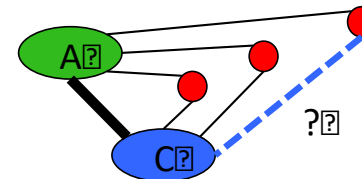
From chemicals to disease comorbidities



Disease-disease associations

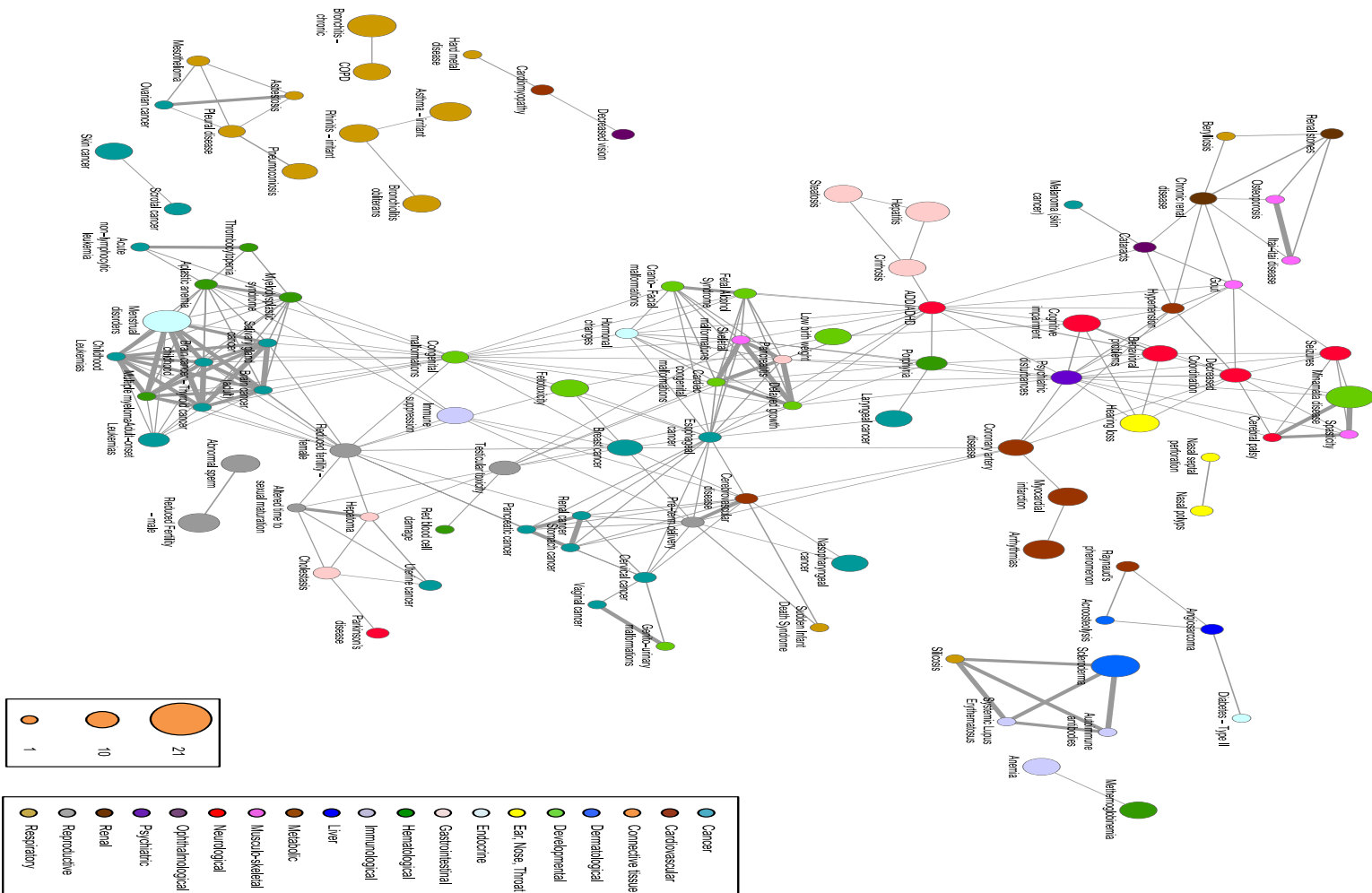


Disease	Disease	Score
A	C	0.50
B	C	0.38
A	C	0.21

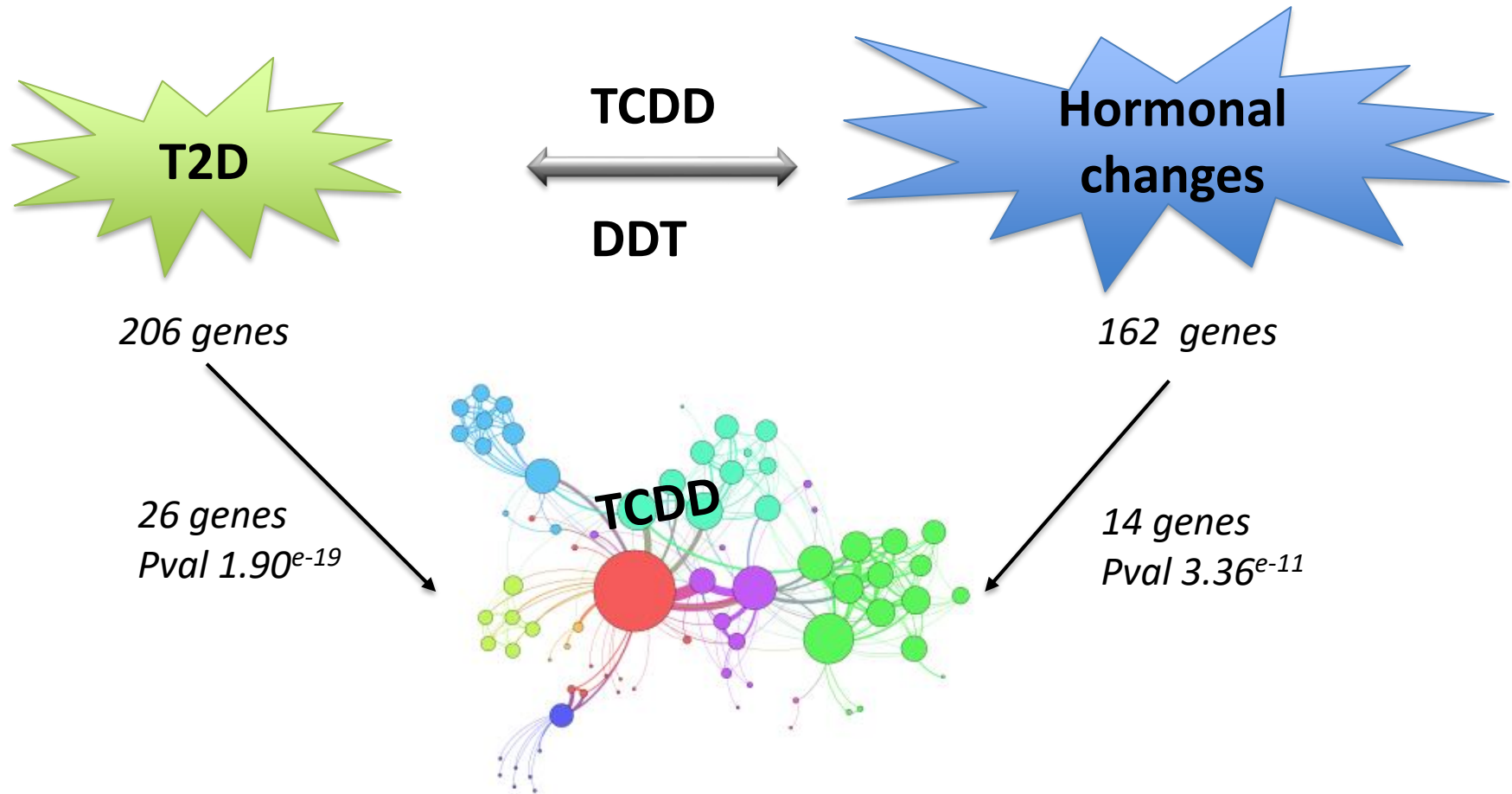


Chemical-disease prediction

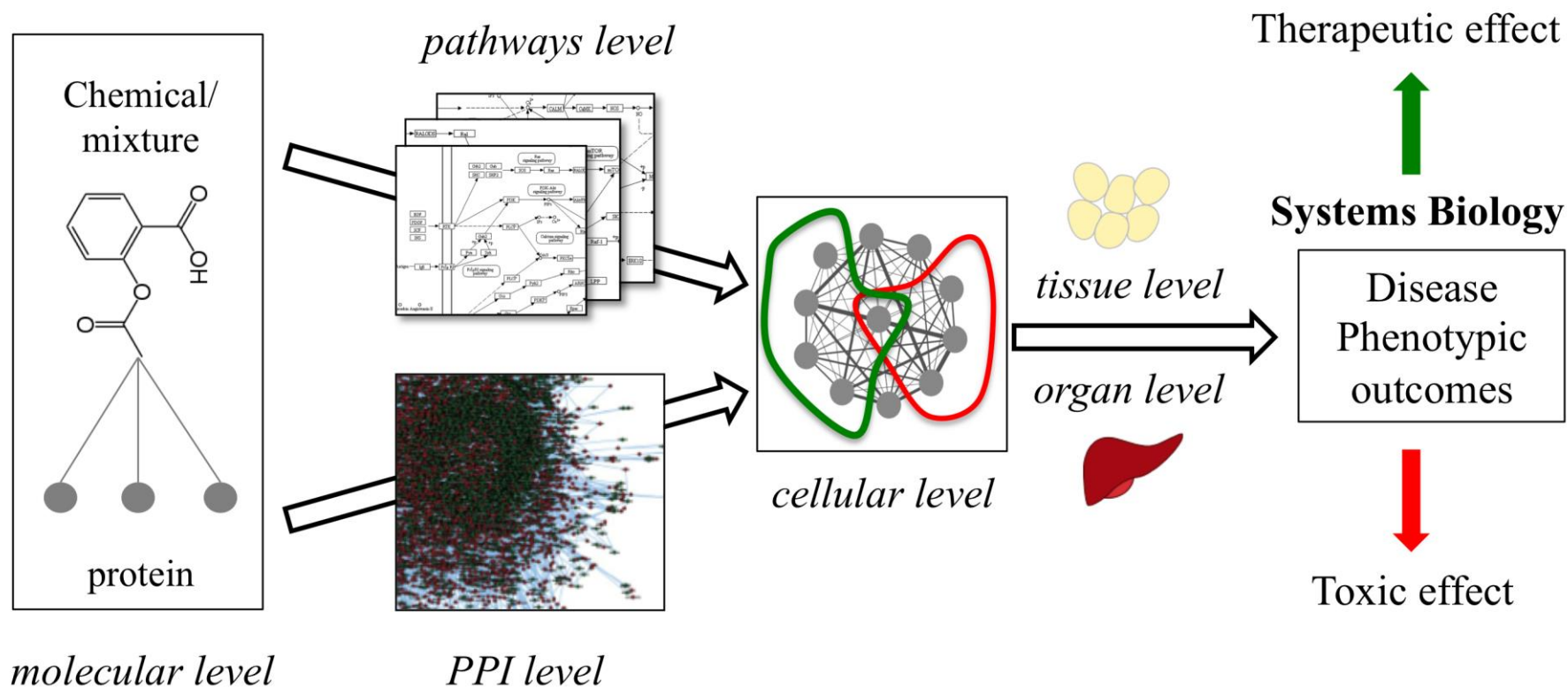
From chemicals to disease comorbidities



From chemicals to disease comorbidities



From systems biology to predictive toxicology: Identifying effects of EDCs



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Prof. J. Toppari



Prof. O. Taboureau



Prof. B. Jégou



and the PhDs and Post-docs



and **THANK YOU** for your attention!