Approches computationelles pour la recherche d'effecteurs moléculaires

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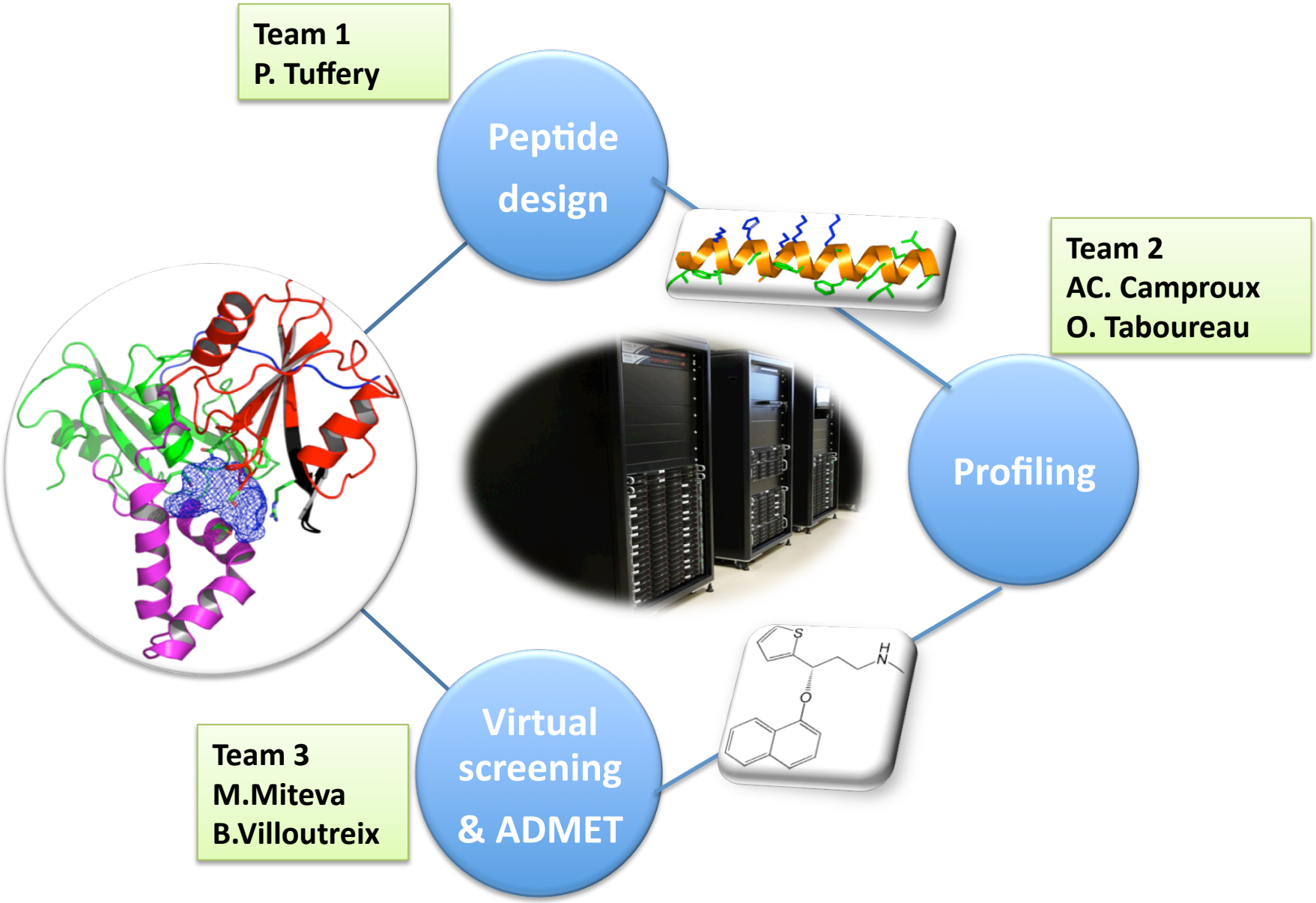
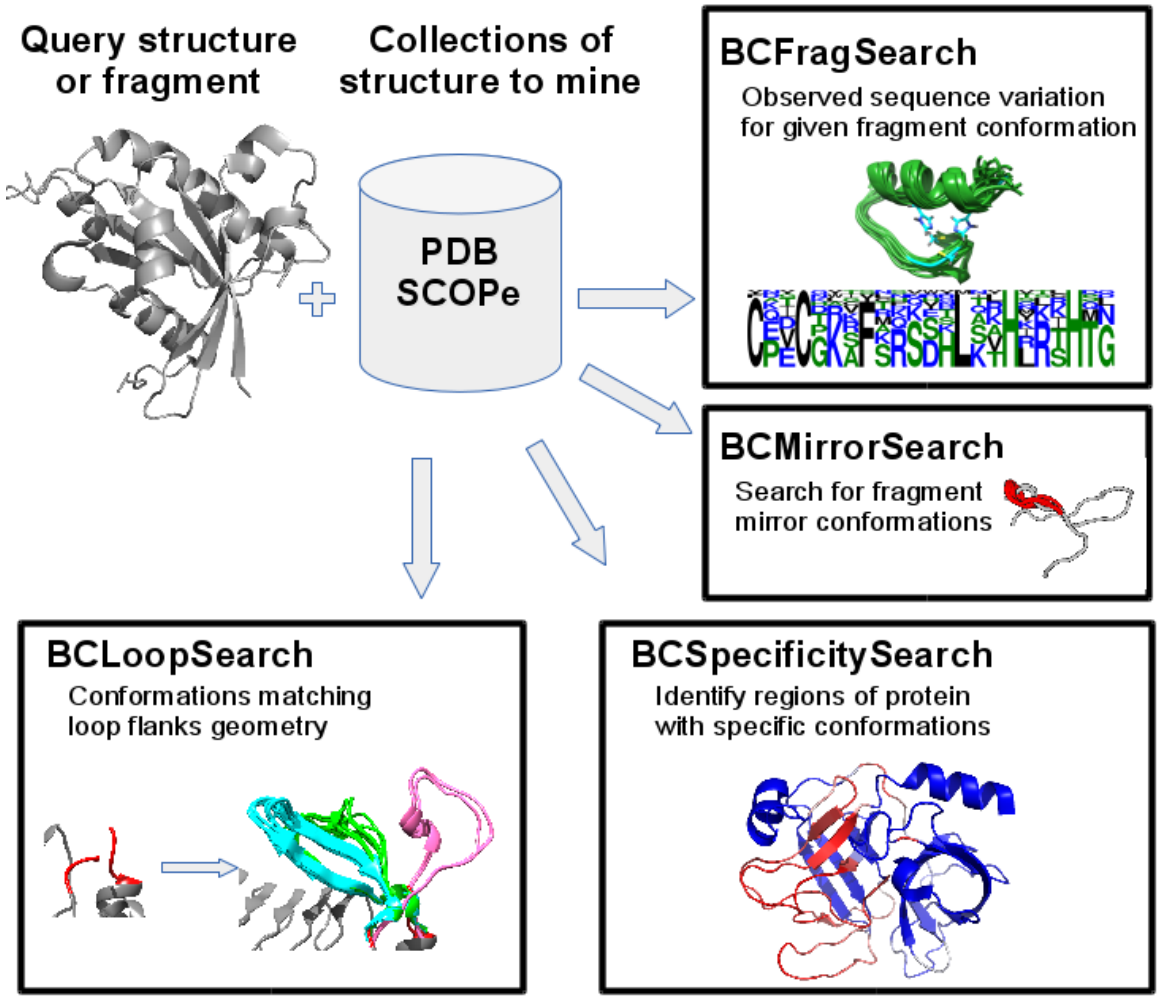
Molecules Therapeutiques in Silico (MTi) Unit - Goal



Peptide design: Recognition

Fast geometric search in protein structures



Input: gapped amino acid sequence
Output: 3D fragments matching flanks & size 3D

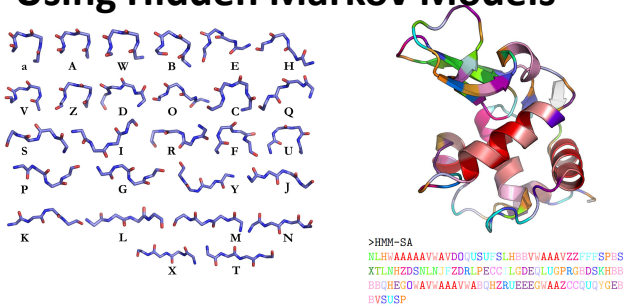
Guyon et al., Bioinformatics 2014; NAR 2015

Peptide design: Modeling

Team 1

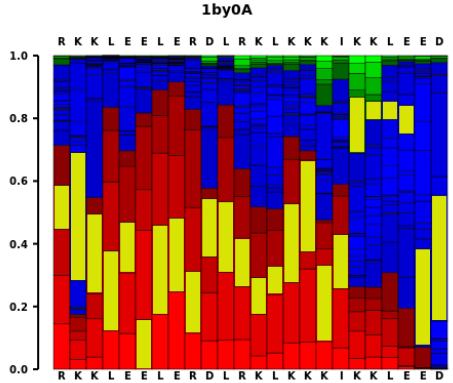
Peptide structure modeling

3D encoding of structures Using Hidden Markov Models

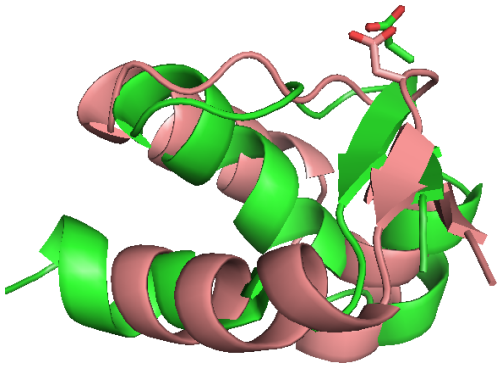


Camproux et al. J. Mol. Biol., 2004

Forward-backtrack, K-best, Taboo sampling



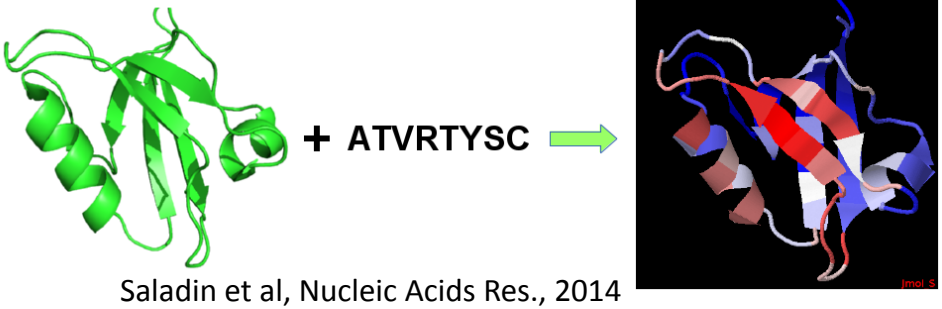
Maupetit et al., NAR, 2009
Thevenet et al., NAR, 2012



Shen et al., J. Chem. Theor. Comput., 2014
Lamiable et al. submitted

Protein-protein interactions

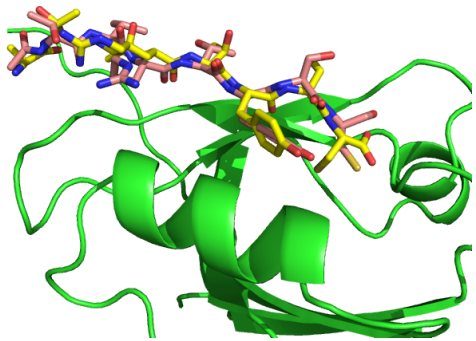
Protein binding site identification



Saladin et al, Nucleic Acids Res., 2014

http://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-SiteFinder/
http://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD/
http://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD3/

Folding peptide at Protein binding site



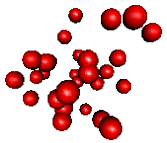
Lamiable et al, submitted

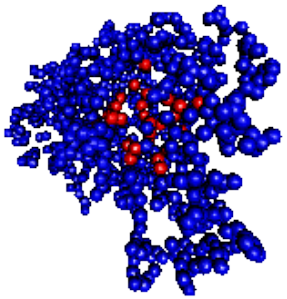
Peptide design: Non sequential alignments

Team 1

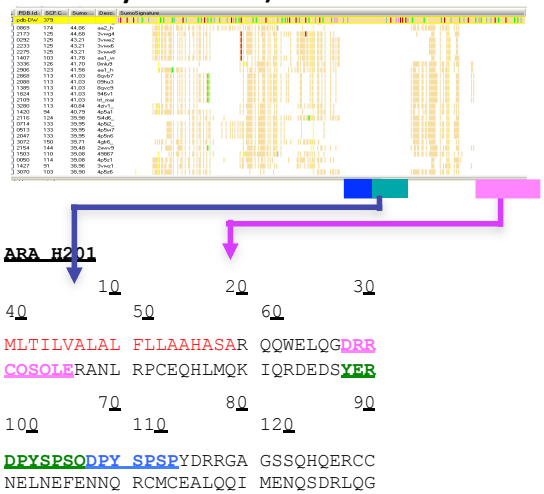
Comparison of atom positions independently of the amino-acid sequence order

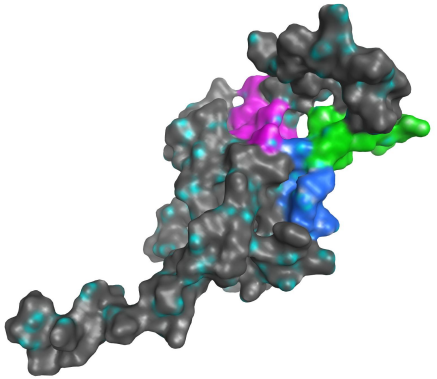
➔Far more difficult problem but useful for protein surface comparisons. atoms involved in a function, : interaction with other proteins





- We use graph theory : search for cliques or quasi-cliques in product graphs
- We developped a similarity measure already used in image analysis for face or object recognition (Binet-Cauchy Kernel)



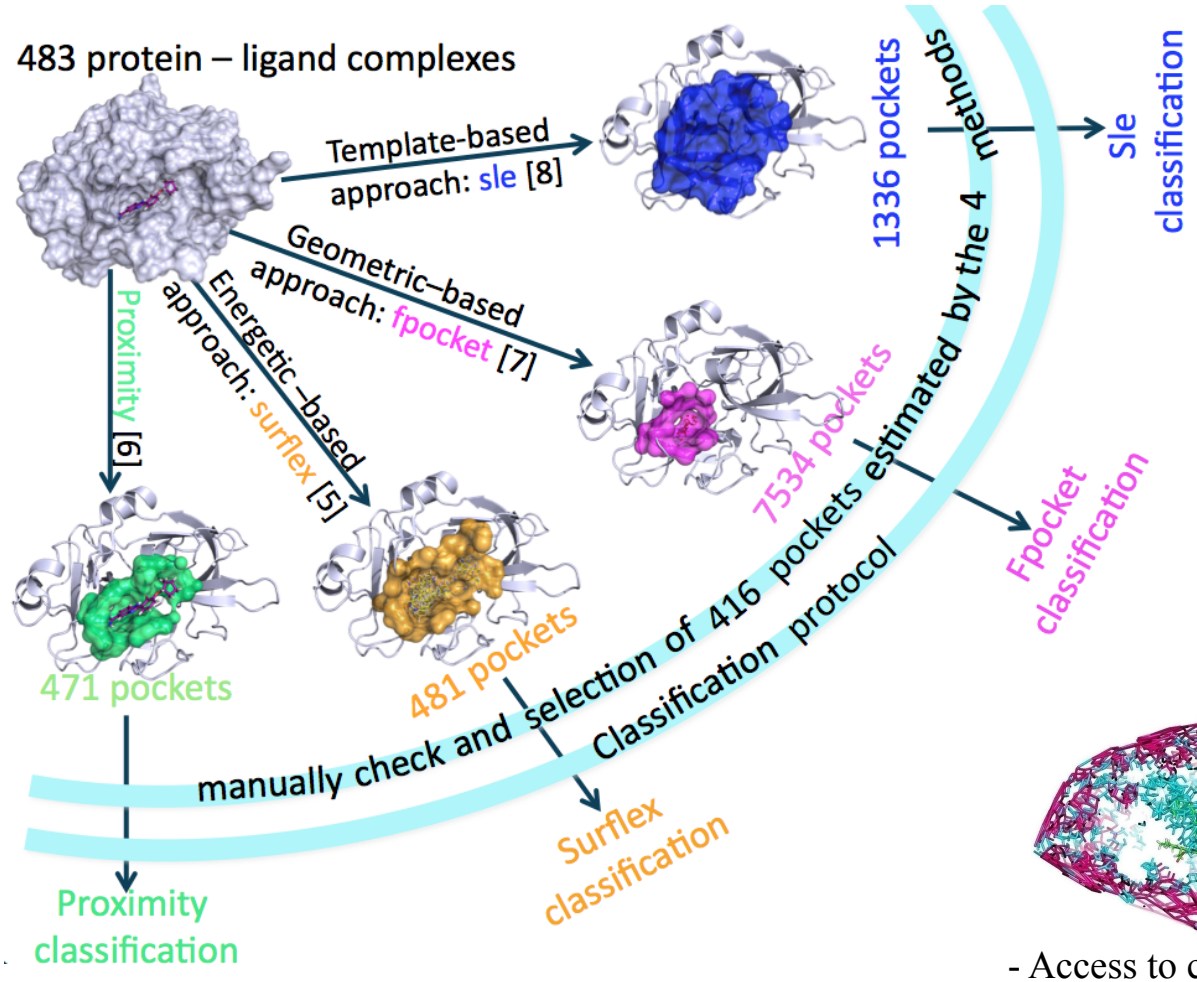


Rasolohery I., Moroy G. and Guyon F. PatchSearch: a fast method for protein binding site recognition (*In preparation*)

Pharmacological profiling: Target (Pocket) characterization

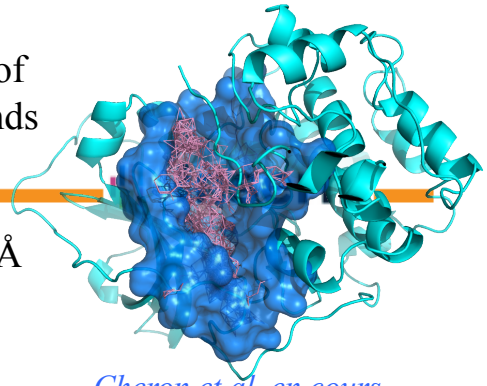
Team 2

Pocket estimation uncertainties



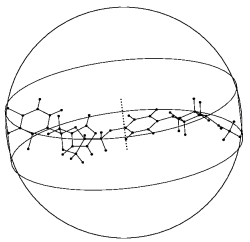
SLE pocket = the largest region binding at least one ligand atom

- Superimposition of homologous ligands → superligand
- Target atoms 4.5Å



Cheron et al, en cours

CCCPP: Estimation of pocket and channel



- Access to channel
- Take in consideration the form and size of ligand.

Benkaidali and al., Bioinformatics, 2013; Borel and al. J.Chem.Inf Mod. 2015; Hussein HA and al. NAR 2015

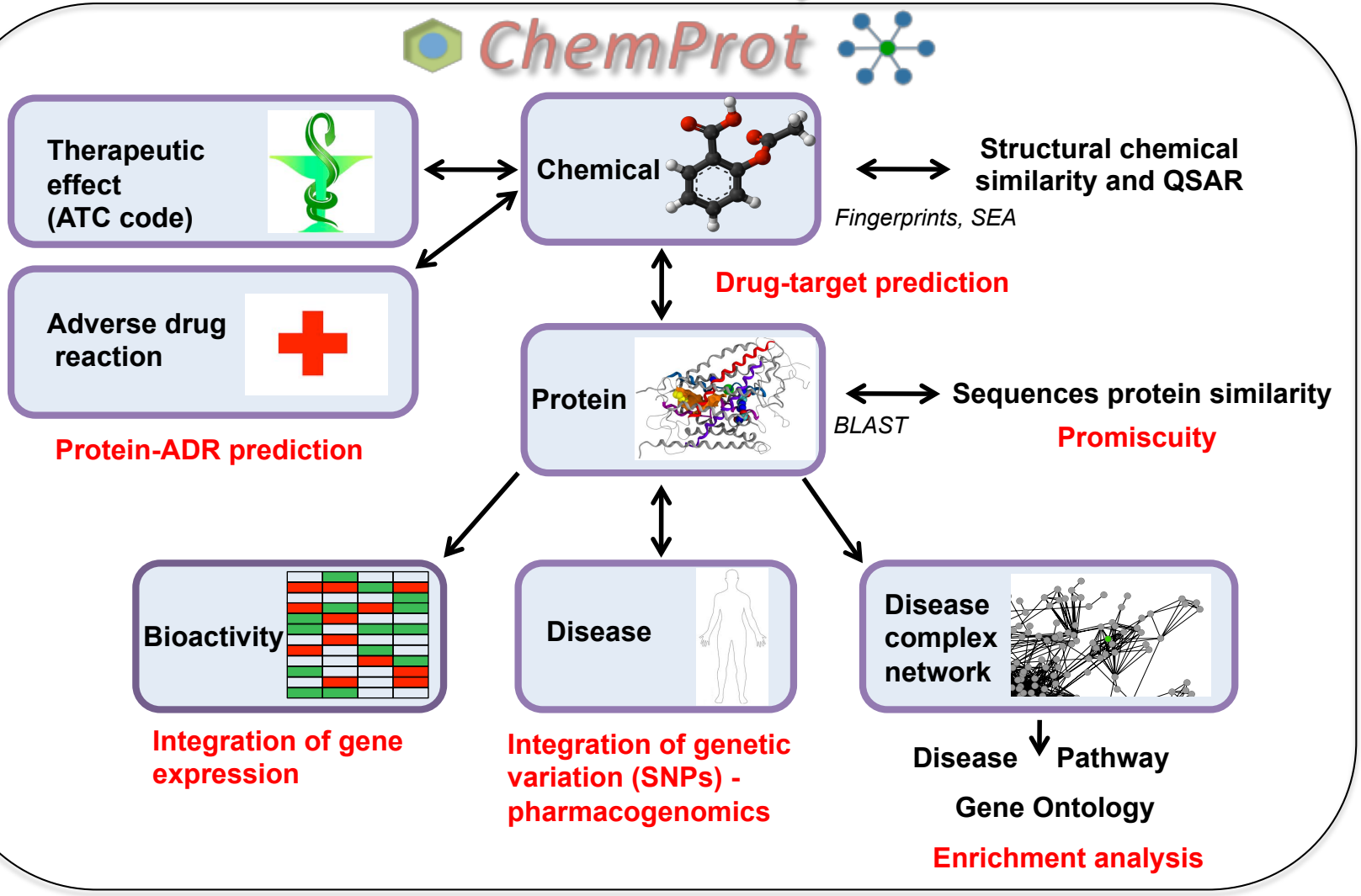
Pharmacological profiling: Data integration

Team 2

ChemProt: focused on Drug-Target-Biological outcomes profiling

Many data not always linked together → **Need of data integration**

ChemProt



http://potentia.cbs.dtu.dk/ChemProt/

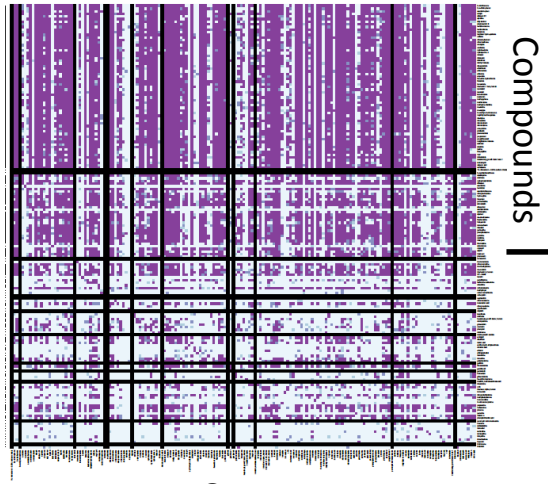
Kringelum J. *Database* 2016

How to explain the mechanism of chemical toxicity?

Analysis of large scale microarray data

More than 10000 samples

Toxicogenomics data analysis



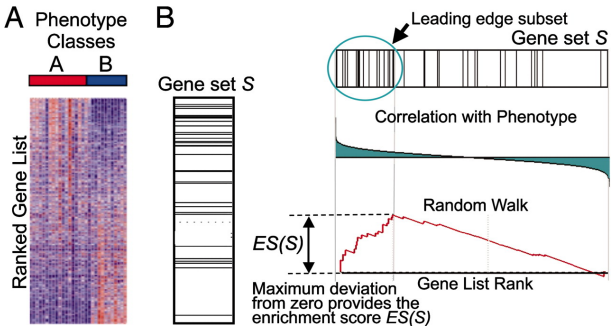
WY-14643

Gene	pvalNom(invitro)	pvalNom(invivo)
Acot1	4.45e-04	6.74e-08
Aig1	2.82e-04	2.14e-06
Ehhadh	4.43e-05	3.18e-06
Acox1	5.31e-04	4.97e-06
Cpt1b	1.53e-03	5.95e-06
Cpt2	2.09e-03	6.82e-06
Slc27a2	6.04e-04	1.04e-05

Lipid metabolism

Fatty acid transporter

Gene Set Enrichment Analysis approach (GSEA)

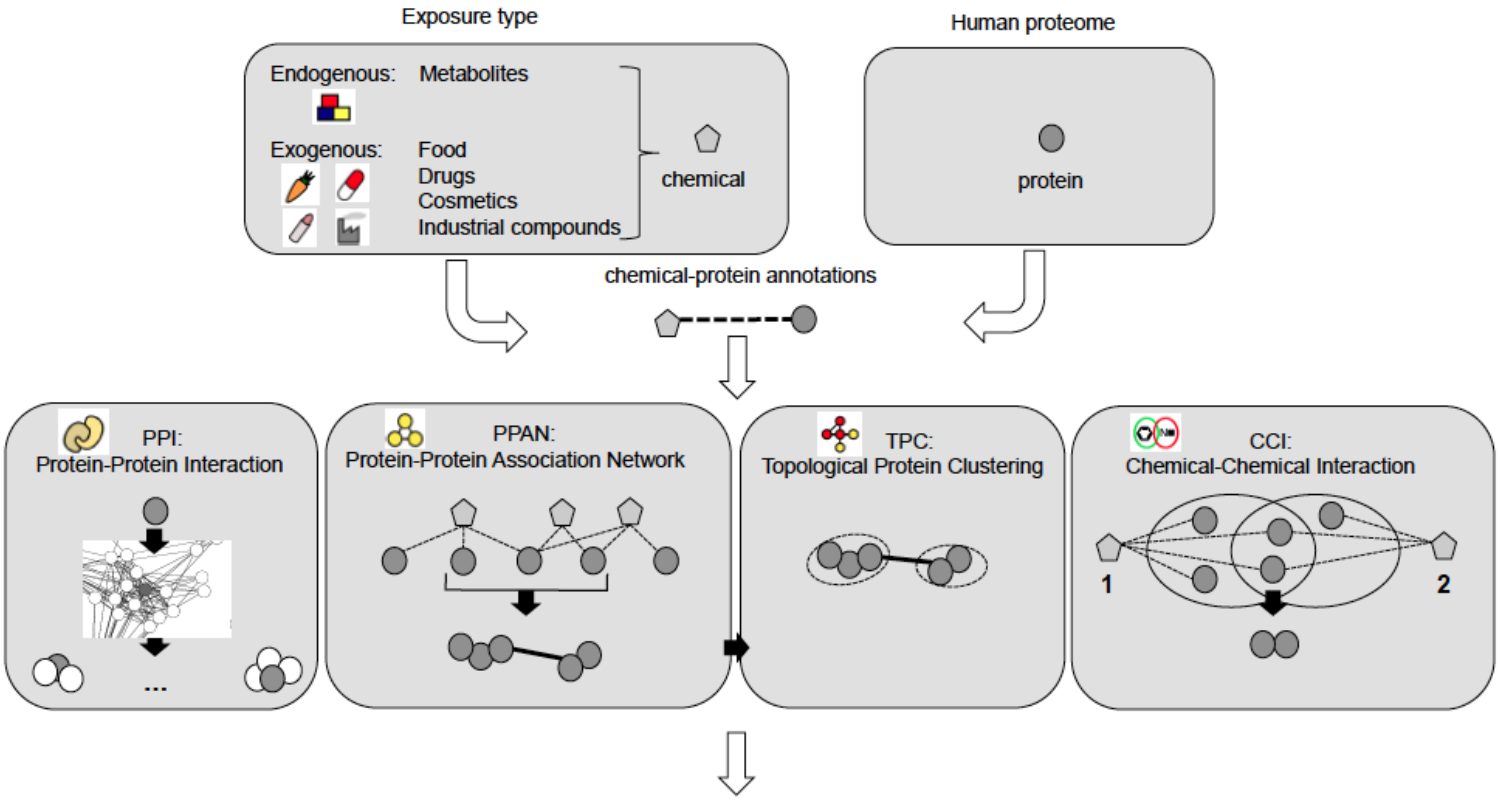


Acetaminophen

Rat, in vitro, Liver High_24hr		
	pVal	adj. pVal
Renal Necrosis	2.20E-89	6.59E-88
arrayV3_LivNecr	1.83E-70	5.31E-69
Xenobiotic Metabolism Signaling	9.96E-59	2.79E-57
HepTox_LivNecr	1.17E-58	3.15E-57
arrayV3_LivProl	3.07E-57	7.99E-56
Liver Necrosis	1.82E-56	4.56E-55
arrayV3_HepCholest	3.55E-50	8.53E-49
HepTox_LivProl	7.88E-46	1.81E-44
Liver Proliferation	8.78E-43	1.93E-41
Cardiac Necrosis	1.60E-41	3.36E-40
Apoptosis	3.05E-39	6.09E-38
NRF2-mediated Oxidative Stress Response	4.11E-39	7.81E-38
Oxidative Stress	4.11E-39	7.81E-38
HepTox_HepCholest	1.76E-38	2.99E-37
PPAR-RXR Activation	1.88E-38	3.00E-37
Hepatic Cholestasis	4.34E-35	6.51E-34
Molecular toxicity pathway	3.16E-28	4.43E-27
AHR Signaling	2.30E-27	2.98E-26
LXR-RXR Activation	1.30E-24	1.56E-23
FXR-RXR Activation	1.18E-19	1.30E-18
Hepatotox_humArray_v3	1.06E-17	1.06E-16
Hepatotox_humArray_v2	5.18E-10	4.67E-09
Hepatotox_humArray_v1	4.42E-09	3.54E-08
Stress and toxicity pathway	1.33E-08	9.32E-08
CAR-RXR Activation	3.52E-07	2.11E-06
Human cardiotoxicity	3.86E-07	2.11E-06
Neurotoxicity	5.15E-07	2.11E-06
Human Nephrotoxicity	6.63E-07	2.11E-06
Hepatotoxicity	9.85E-06	1.97E-05
Hepatotox_reliable	8.94E-05	8.94E-05

Chemicals exposure impact to human health

Development of network-based analysis tools to predict chemical-chemical interactions to diseases

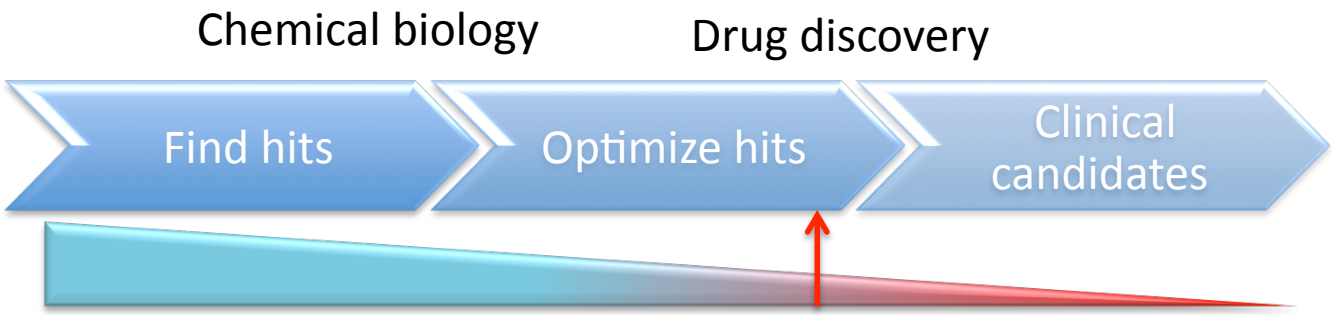


Disease/ Pathway/ GO	Proteins	P-val
Disease X	●●○●	1.8e-5
Disease Y	●●	0.003
Pathway A	●○●	1.2e-4
Pathway B	●●	0.05

Taboureau et al. (2013) Bioinformatics

Team 3

Virtual screening and rational design of protein-protein interaction (PPI) modulators with balanced ADME-Tox properties



1. Finding hits

Virtual screening & PPI characterization

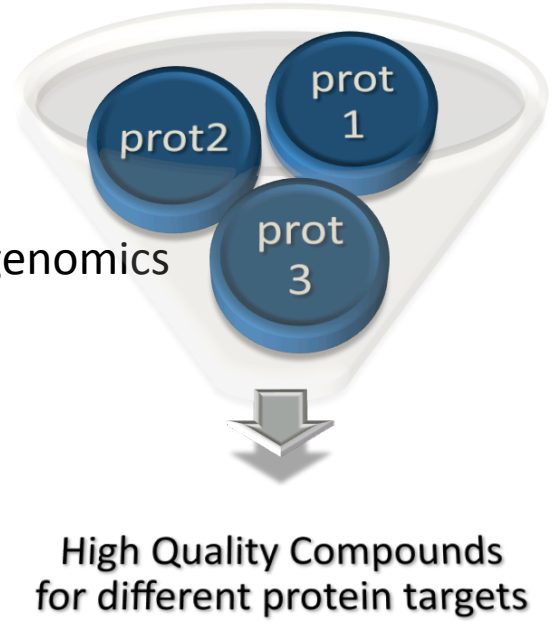
2. Optimizing hits

Multi-parameter optimization including ADME-Tox & pharmacogenomics

3. Applications on different protein targets

cancer, cardiovassular diseases, rare diseases

Nicolaes et al. Blood 2014; Zhang et al. Plos One 2014



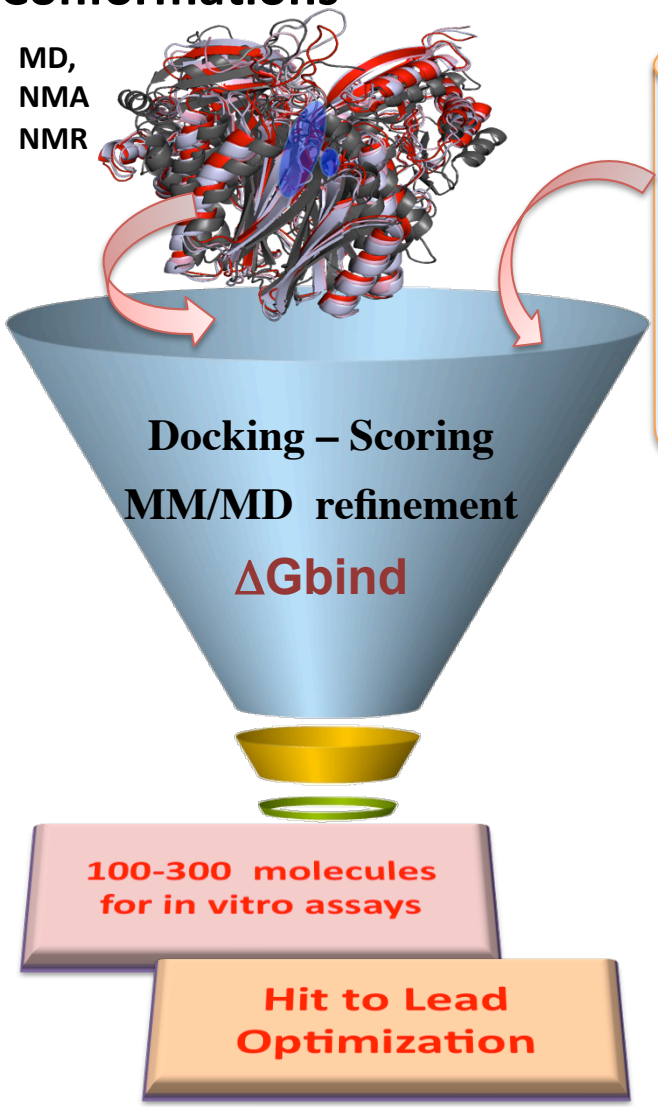
High Quality Compounds
for different protein targets

Team 3

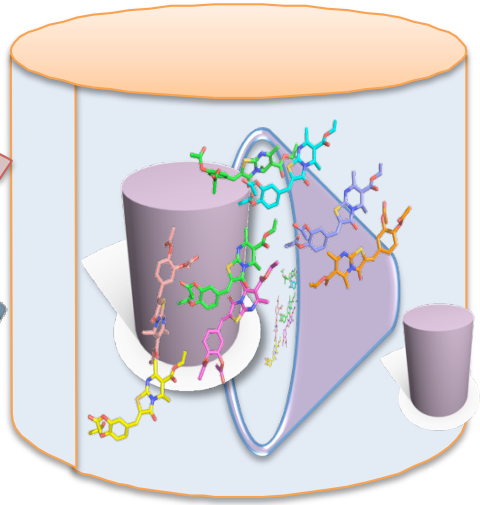
Virtual screening and receptor flexibility

Multiple Receptor Conformations

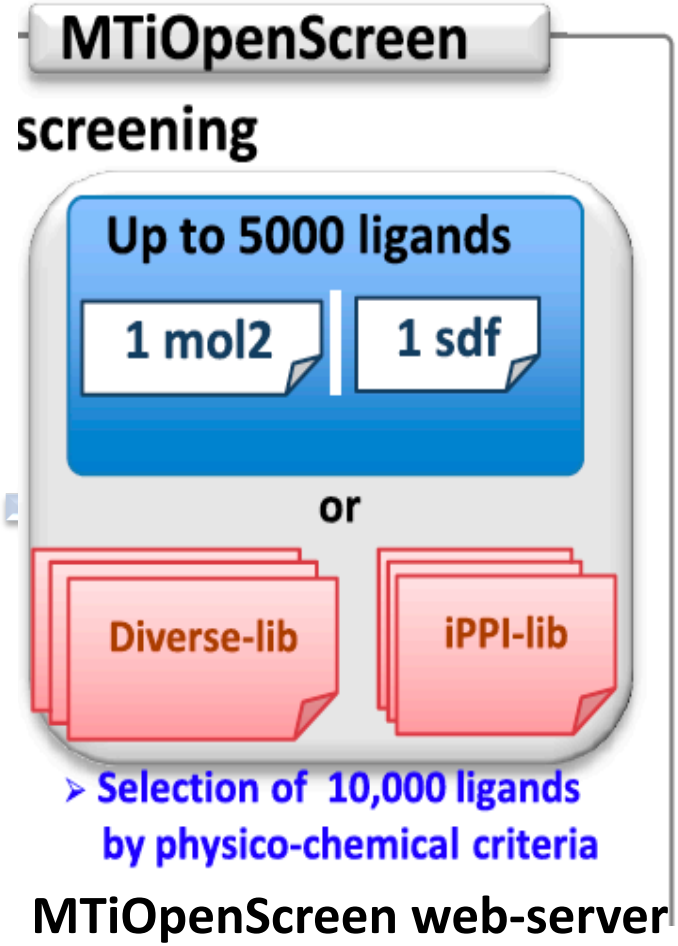
MD,
NMA
NMR



Compound Collection



FAF-Drugs3 web-server
i-PPI filters
2D->3D



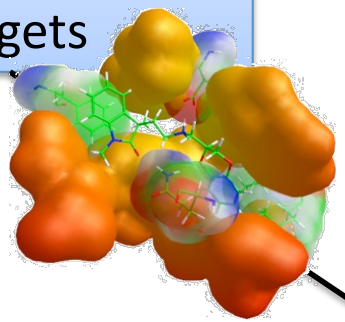
MTiOpenScreen web-server

Labbe et al. NAR 2015, Moroy et al. Future Med. Chem. 2015

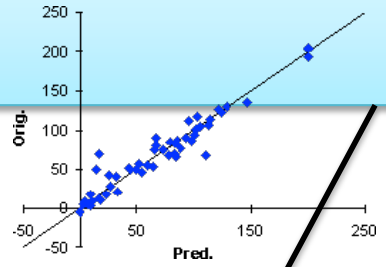
Team 3

Virtual screening and integrated ADME-Tox prediction

Structural and docking analysis on ADME-Tox off-targets

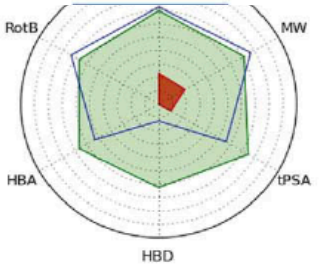


QSAR models

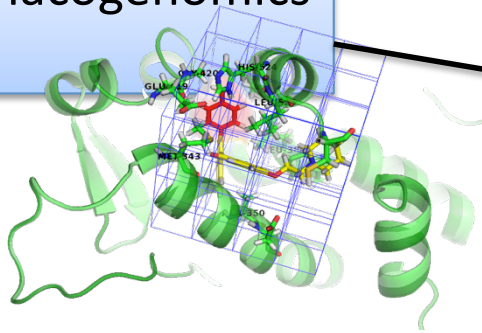


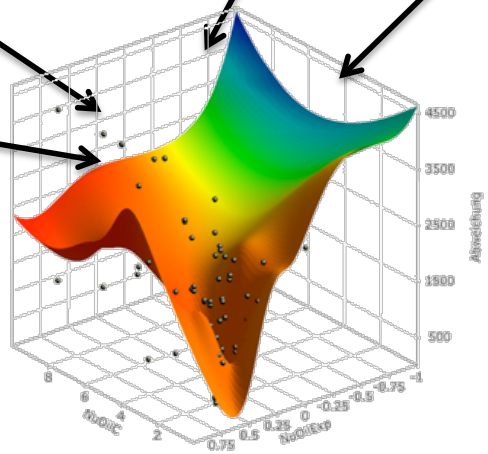
PhysChem properties & filtering

FAF-Drugs3



Pharmacogenomics





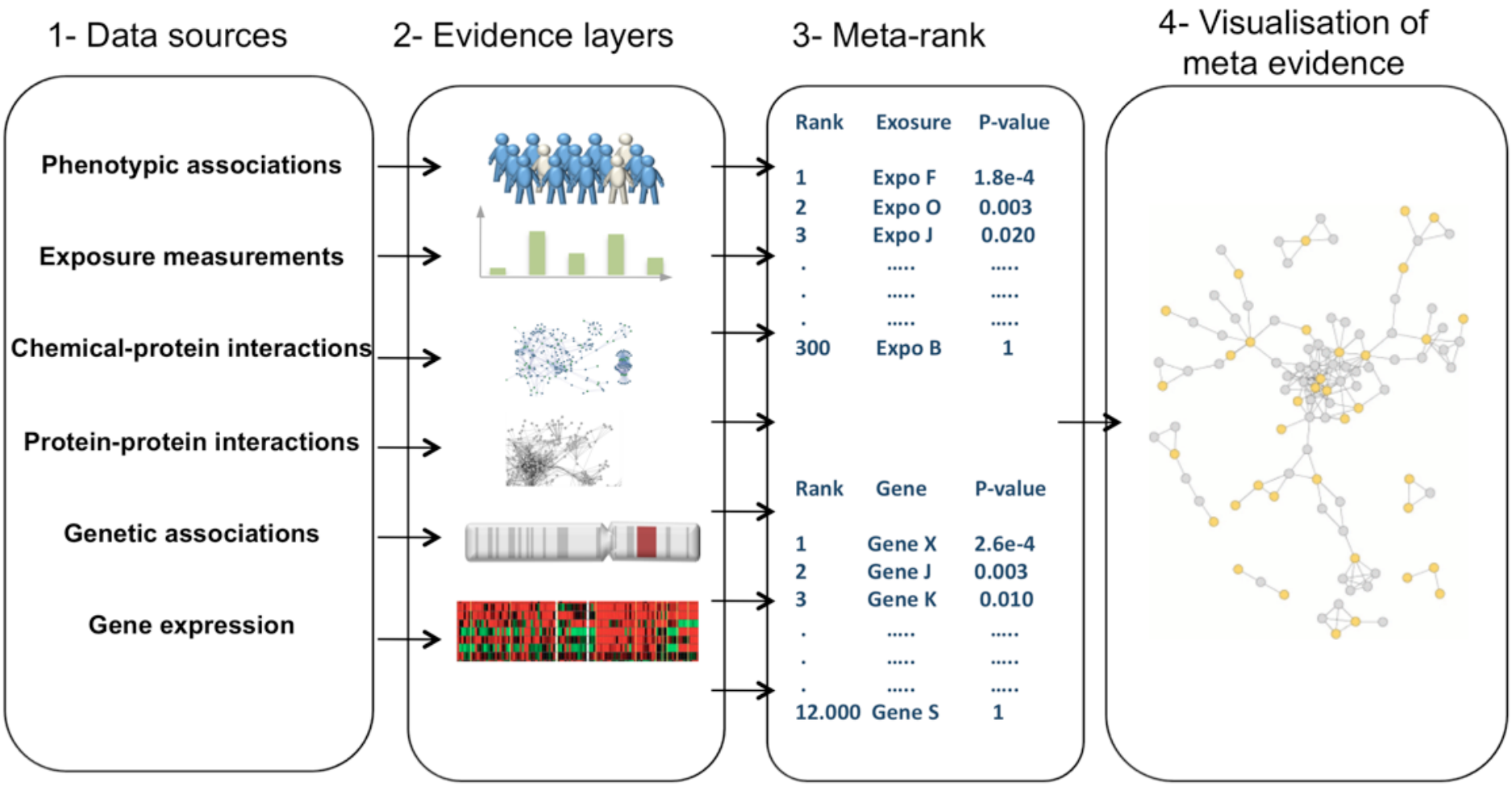
- PhysChem rules
- Toxic groups
- Pan Assay Interference Cmps.

Multidimensional in silico ADME-Tox prediction

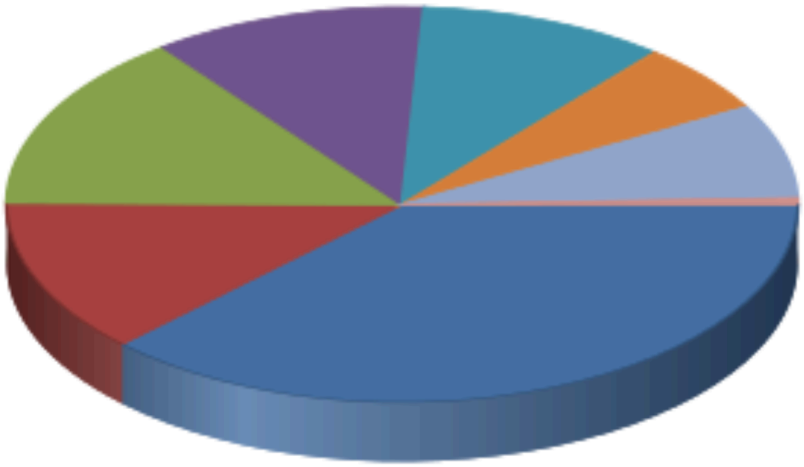
Lagorce et al. NAR 2015, Martiny et al. Bioinformatics 2015

Perspective-1: Integrative systems

Objective: Development of computational tools to understand the relationship between molecular effectors (environmental chemicals, drugs, natural products, peptides) and disease susceptibility genes at different layers of complexity.



Perspective-2: Molecular effectors



Small Molecules
Drug Delivery
Antibodies
Biologics
Stem Cells
Other
Biomarkers
Vaccines

http://isddteach.sdv.univ-paris-diderot.fr/fr/accueil.html