Computational modeling of protein-ligand interactions

O. Taboureau, AC. Camproux, P. Tuffery

UMR-S 973

Molecules Therapeutiques in Silico (MTi) Unit

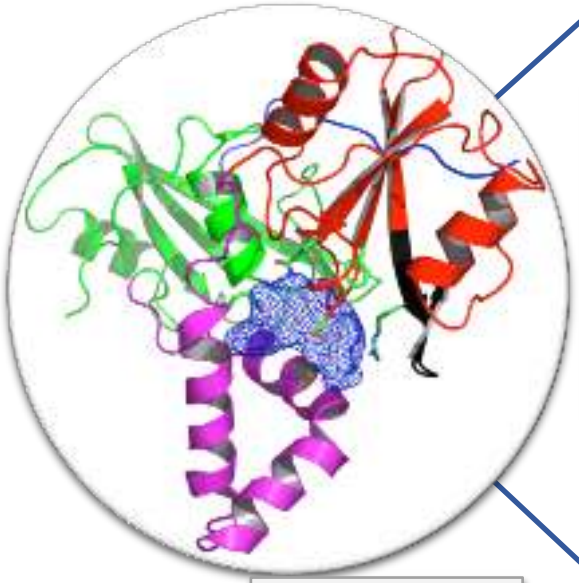
2014-2018

UMR-S 973
(Dir : B. Villoutreix)

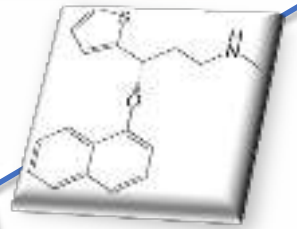
Team 1
P. Tuffery

Peptide design

Team 2
AC. Camproux
O. Taboureau



Profiling

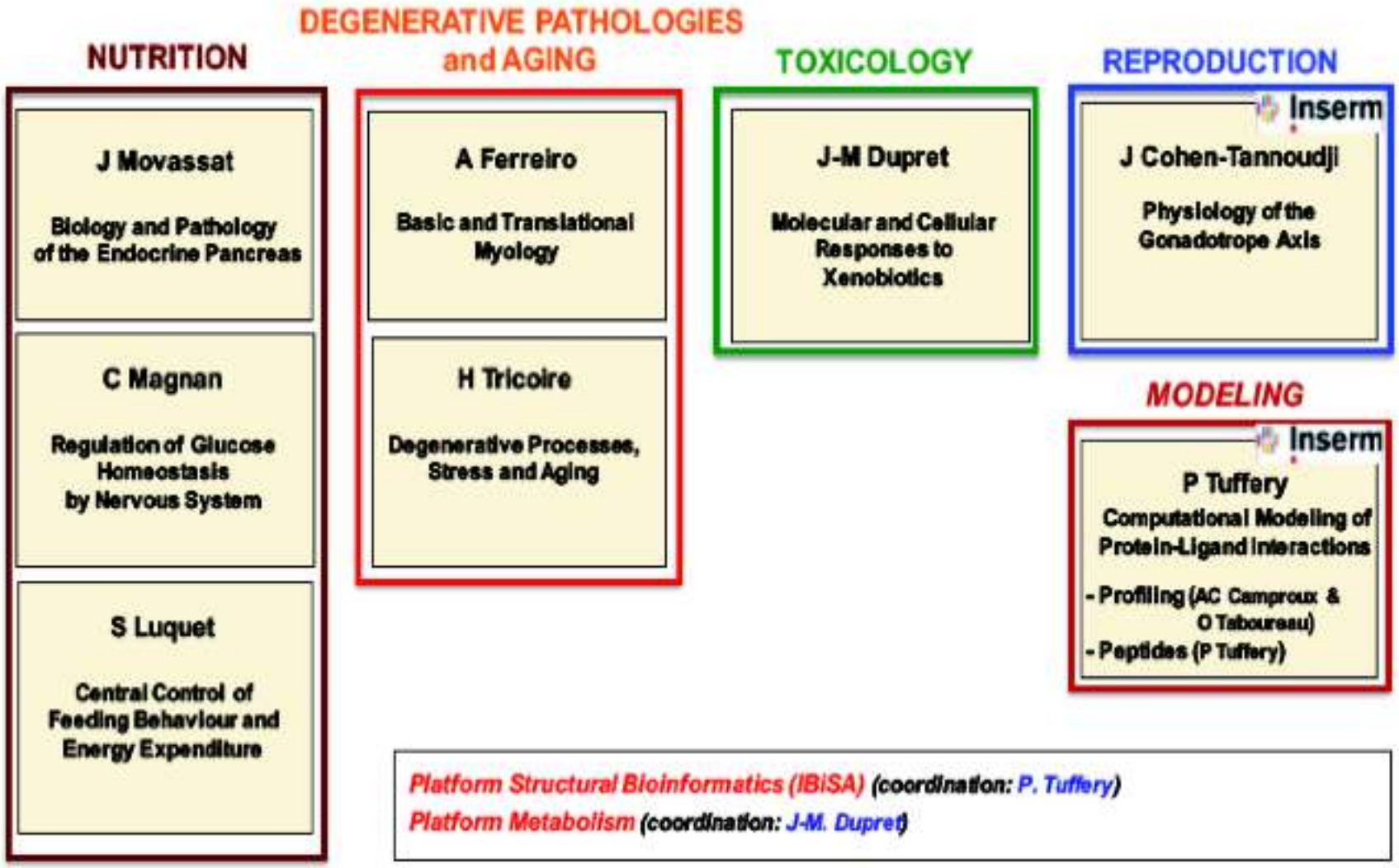


Team 3
M.Miteva
B.Villoutreix

Virtual screening & ADMET

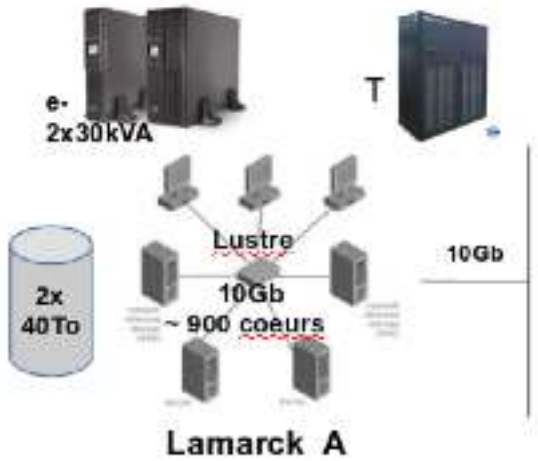
Computational modeling of protein-ligand interactions

2019-2023

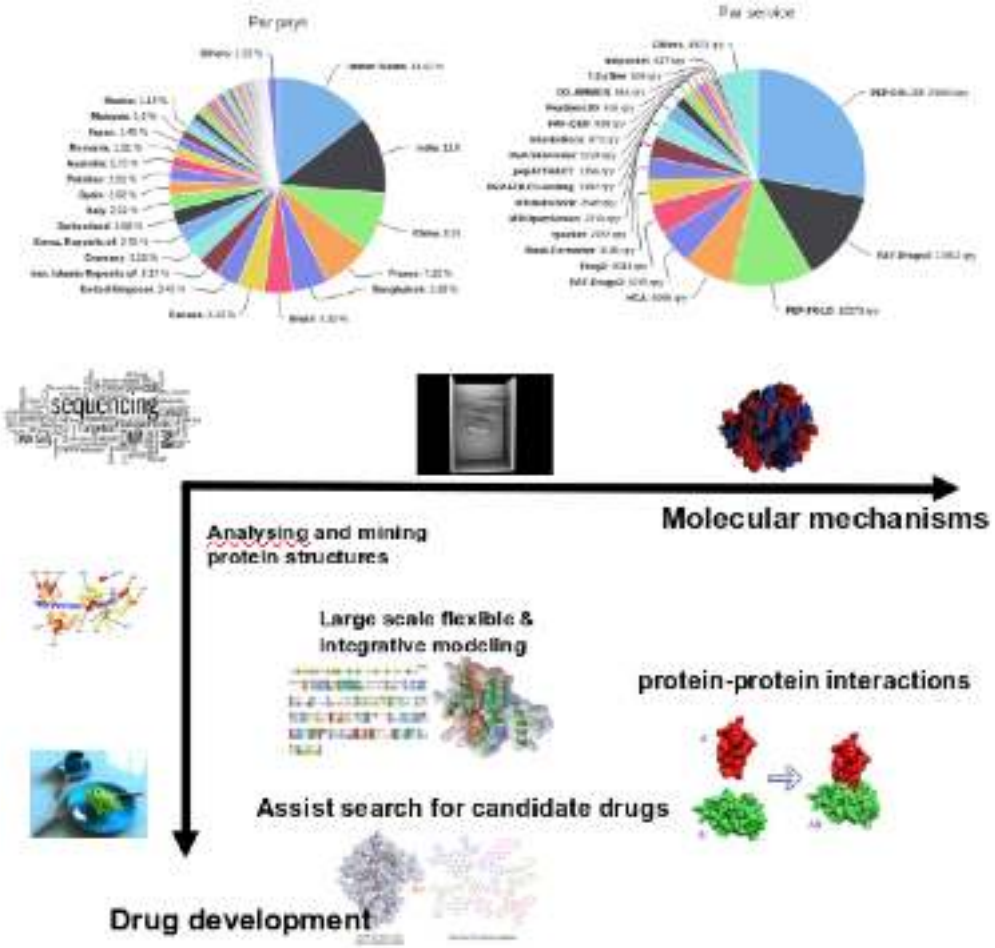


Computational modeling of protein-ligand interactions

Plate-forme RPBS (*IBiSA*) (P. Tufféry, S. De Vries, J. Rey)
(Ressource Parisienne en Bioinformatique Structurale)



PAAS-SdV



http://bioserv.rpbs.univ-paris-diderot.fr/index.html

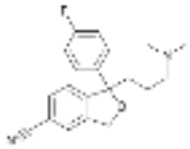
Computational modeling of proteine-ligand interactions

Objectives

Molecules

Small compounds

Peptides



Antibodies

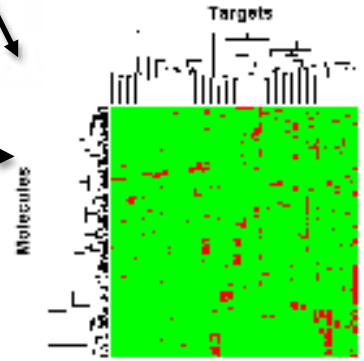
Targets

Proteins

Protein-protein Interactions

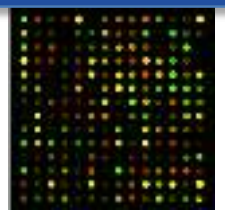
ADN, ARN, ...

Multi targets profiling



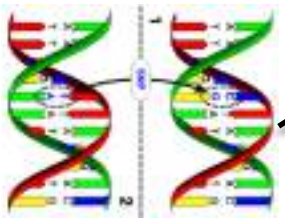
Genomic information

Gene expression and toxicogenomic



Pathway and ppi

Genetic variations



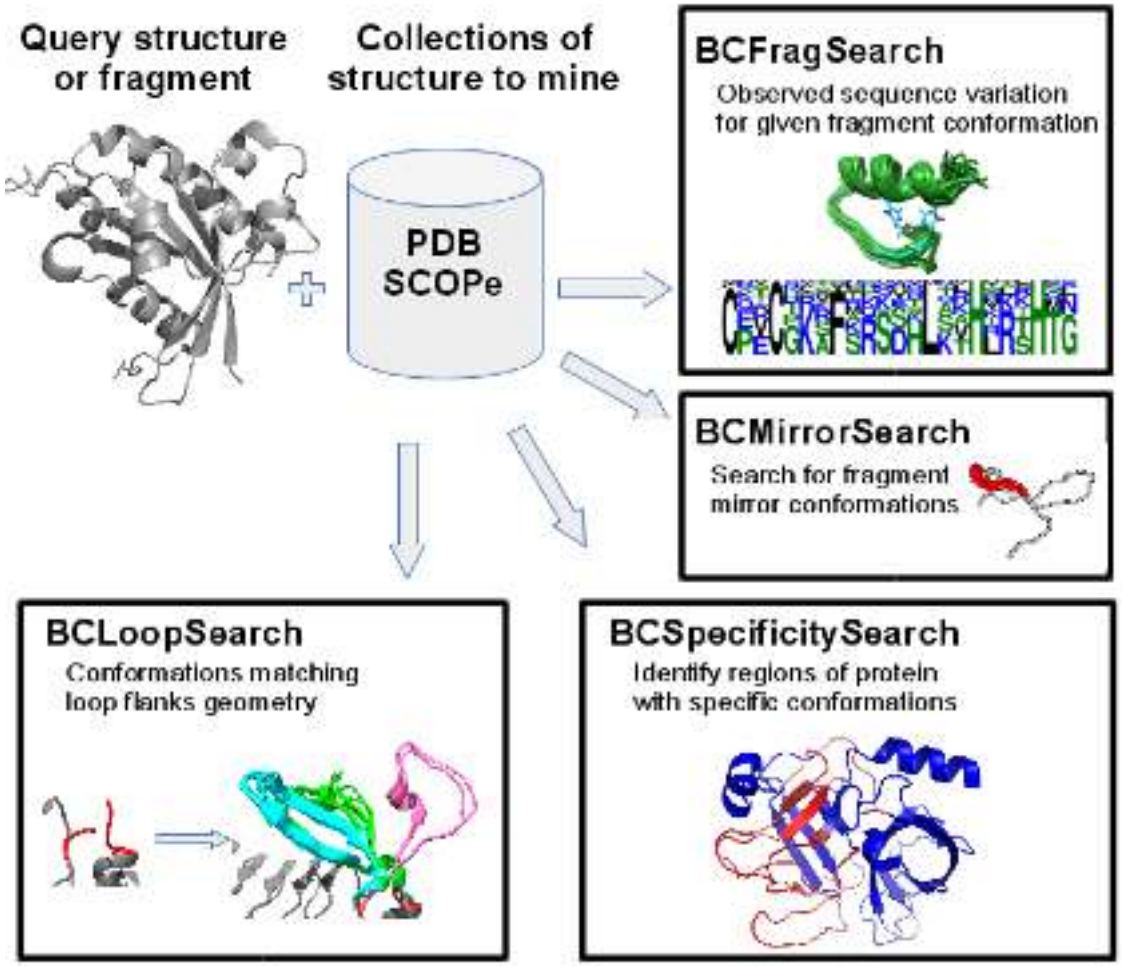
Clinical effects

2 research areas :

- **Pharmacological profiling**
- **Protein-peptide interactions and peptides design**

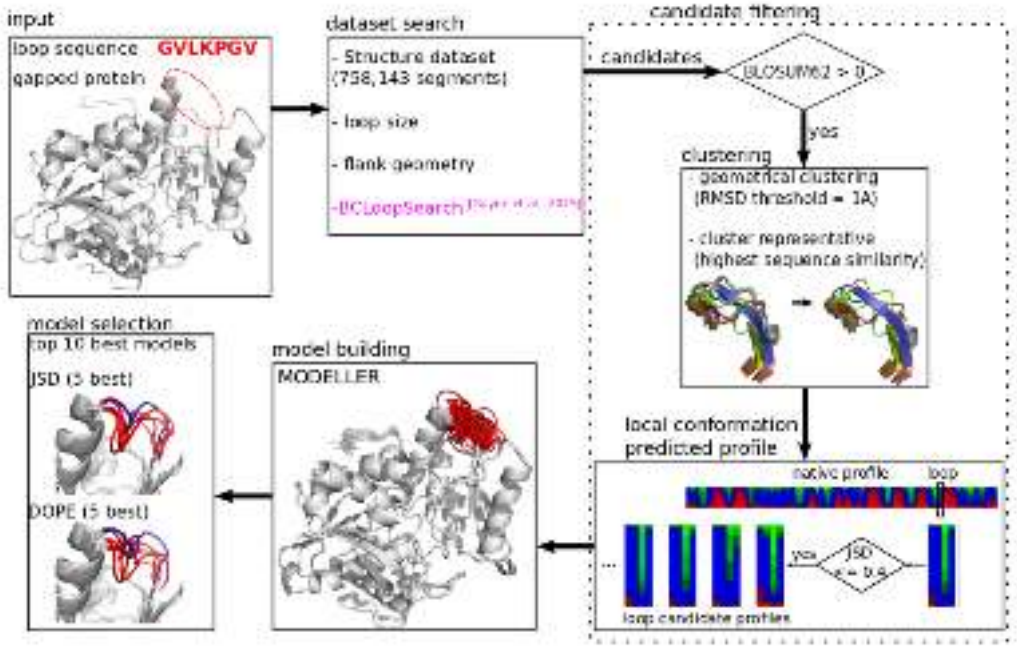
Peptide design: Recognition

Fast geometric search in protein structures



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

Accurate loop modeling



Karami et al., Sci. Rep. 2018

Over 50% of successful loop models are derived from unrelated proteins, indicating that fragments under similar constraints tend to adopt similar structure, beyond mere homology.

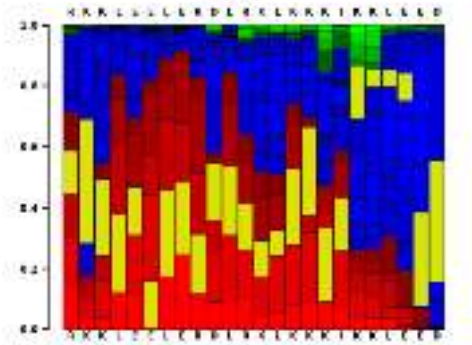
Peptide design: Modeling

Peptide structure modeling

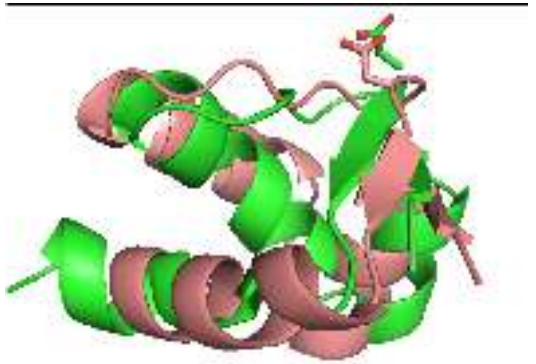
3D encoding of structures
Using Hidden Markov Models

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. NAR, 2016

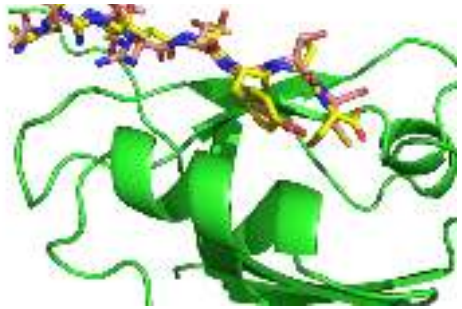
Protein-protein interactions

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, J. Comput Chem., 2016

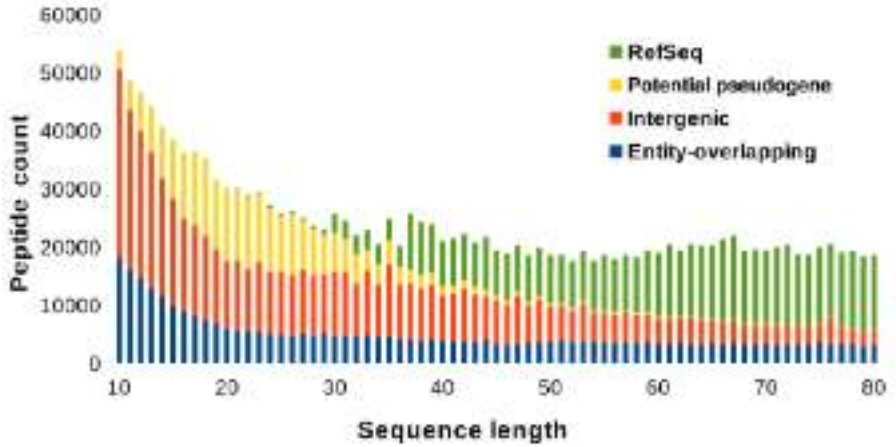
Peptide discovery: BactPepDB: a database of predicted peptides in prokaryotic genomes

BactPepDB

Bacteria Peptide Database

Last production update (15/10/2017) :

- Prokaryotes genomes :
  - ~ 100 orders
  - ~ 200 families
  - ~ 700 genera
  - ~ 1,500 species
  - ~ 2,700 strains
- Total : ~ 2,000,000 peptides
  - ~ 70 % of newcomers
  - ~ 200,000 (~ 20 %) of new intergenic SCSs are conserved to some extent : consistent with genes found in RefSeq

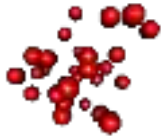


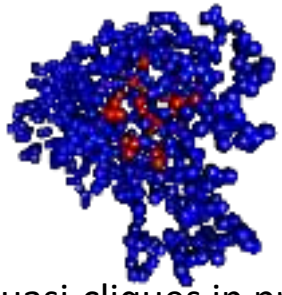
Rey et al., Database, 2015

Peptide design, off-target: Non sequential alignments

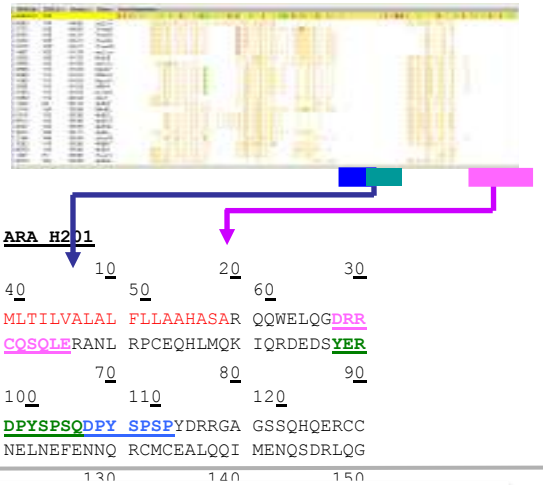
Comparison of atom positions independently of the amino-acid sequence order

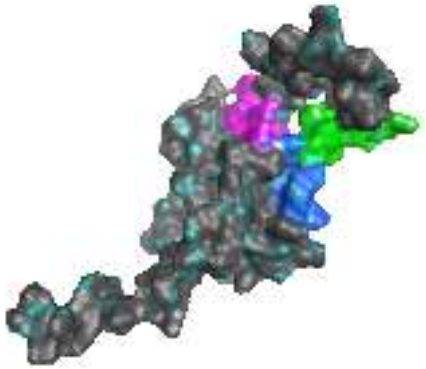
➔Far more difficult problem but useful for protein surface comparisons. atoms involved in a function, : interaction with a drug, interaction with other proteins



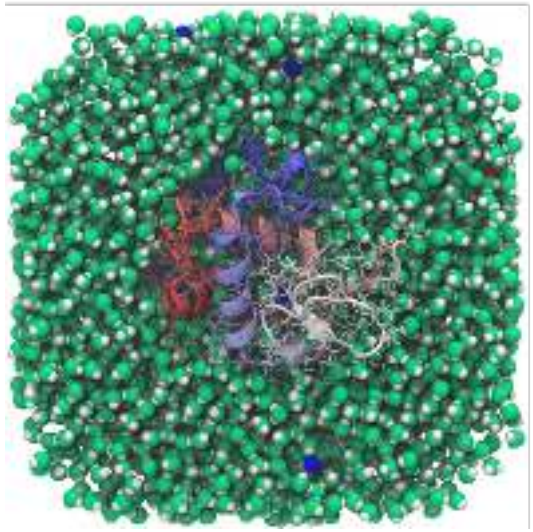


- We use graph theory : search for cliques or quasi-cliques in product graphs
- We developped a similarity measure already used in image analysis for face or object recognition (Binet-Cauchy Kernel)

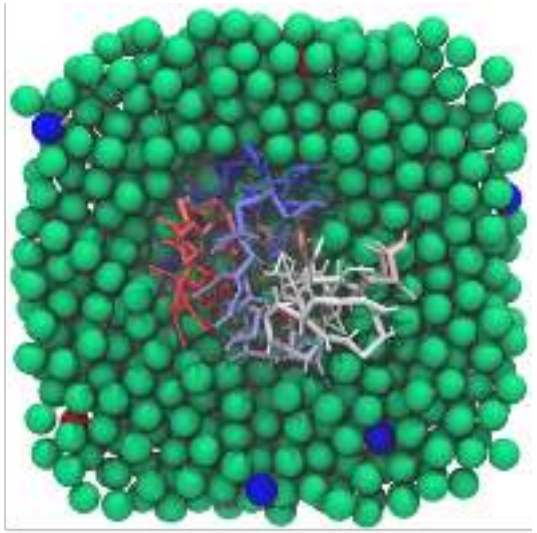




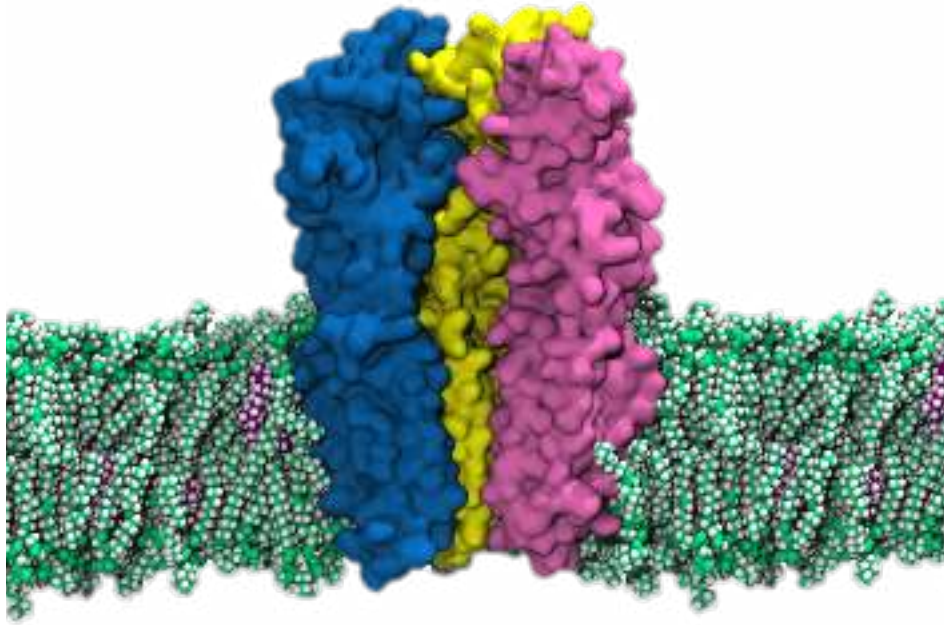
Membrane proteins motions



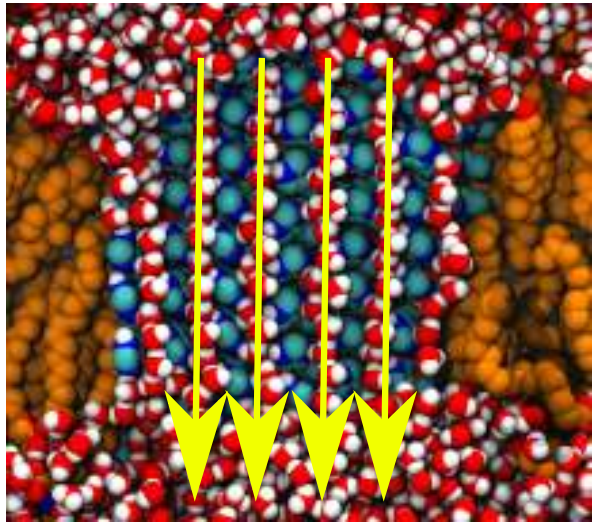
Molecular Dynamic Simutations

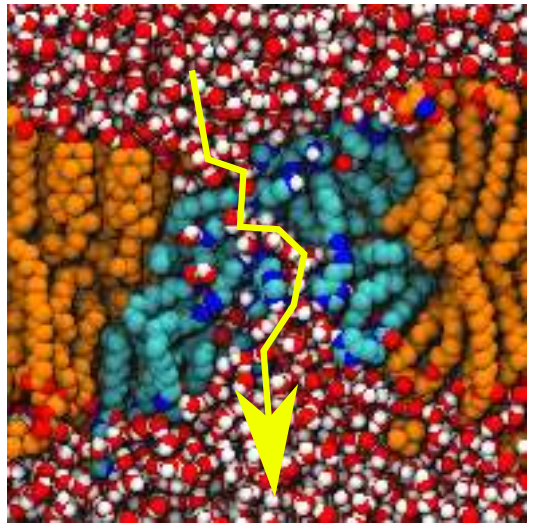


Coarses grain



Synthetic channels





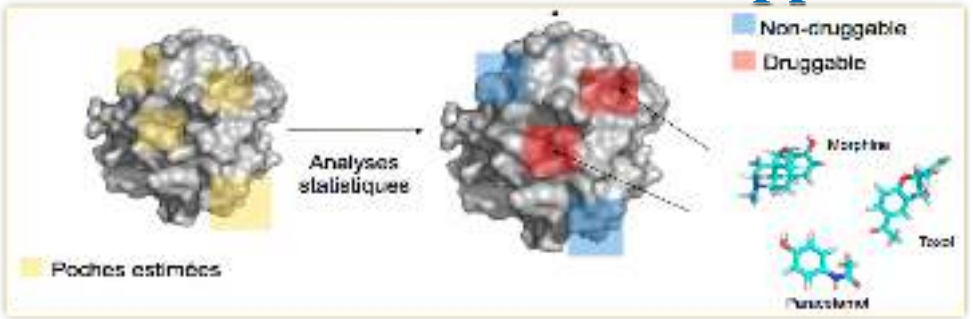
Pharmacological profiling: Target based

Characterization and validation of proteins as therapeutic targets and prediction of drug-target interactions based on statistical & bioinformatics structural approaches

Prediction of druggable targets:

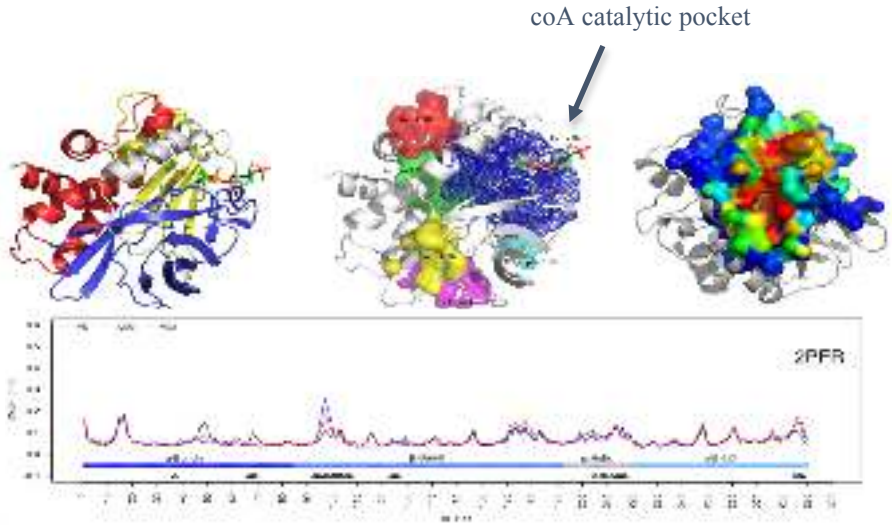
Proteins able to bind drug-like molecules, using statistical approaches: Pockdrug website

Borrel et al, 2015, Hussein et al, 2015



Proteins flexibility and transient pocket analysis

Pockdrug extension using dynamic molecular simulations:

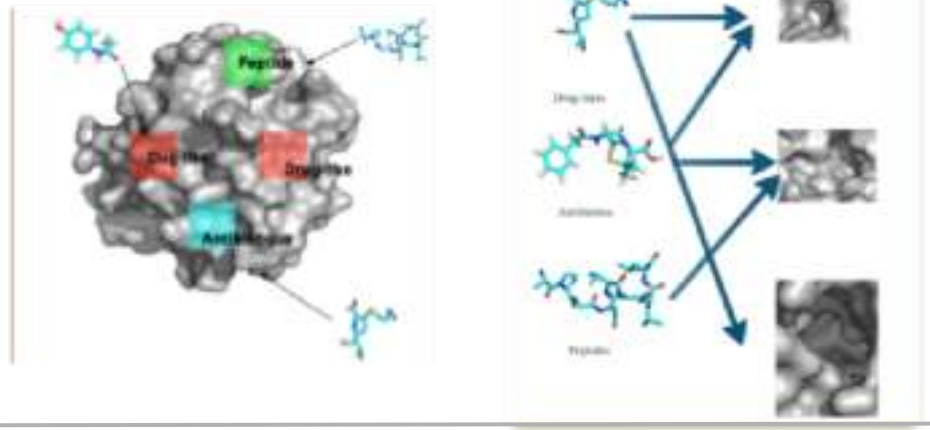


Current applications: NS1 (non structural protein of influenza virus)

Hussein et al, 2017, Regad et al, 2017, Alam et al, 2018

Prediction of ligand profiles using biostatistical approaches

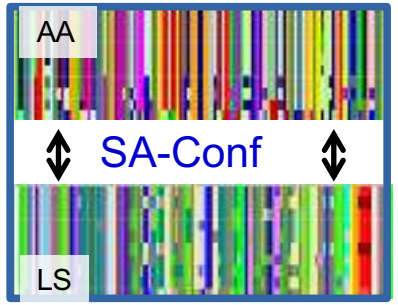
Further deepen the profiling study: propose ligand candidates that can bind with high affinity druggable pockets

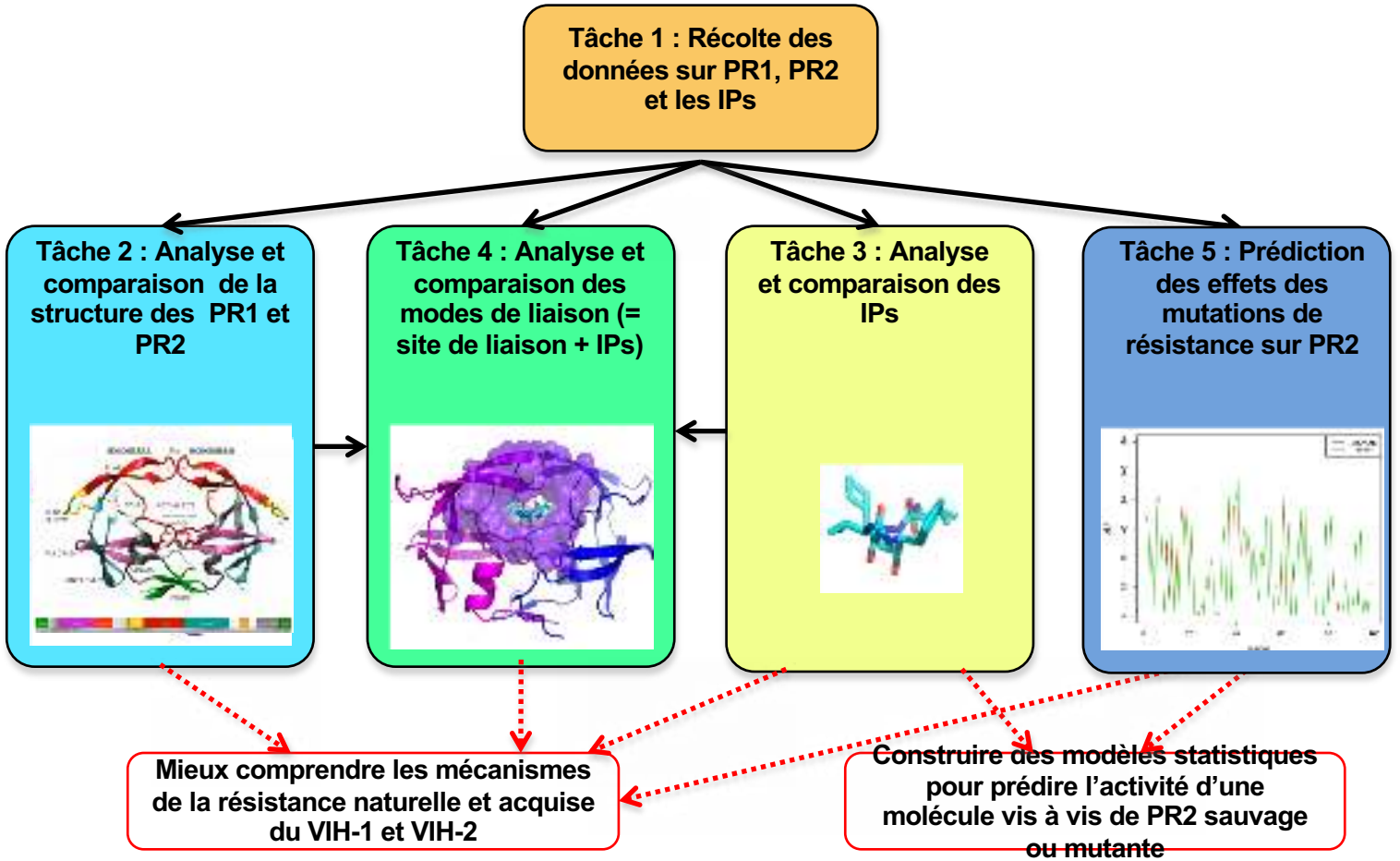


Cerisier et al, 2017a, Cerisier et al, 2017b

Inhibition of HIV-2 protease: study of the resistance mechanism using in silico approaches

3D structures : 15 PR1
13 PR2
unbound, bound forms
(indinavir, darunavir, amprenavir)





Projet VIH2-Bioinfo

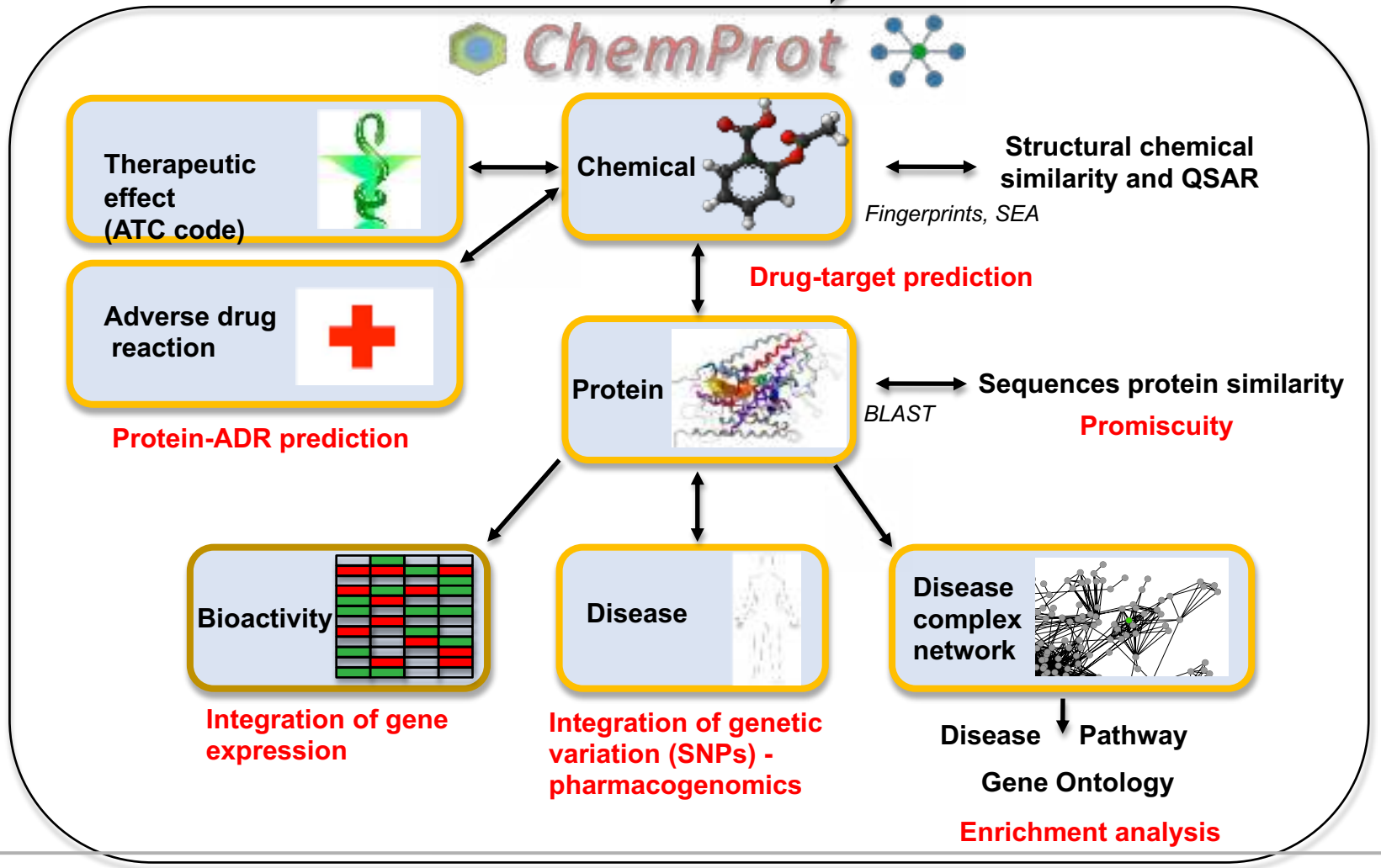
anrs France REcherche Nord & sud Sida hiv Hépatites
Agence autonome de l'Inserm

Triki et al, 2018a, Triki et al, 2018b, Triki et al, 2018c, Triki et al, 2018d accepted

Pharmacological profiling: Data integration

ChemProt: focused on Drug-Target-Biological outcomes profiling

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



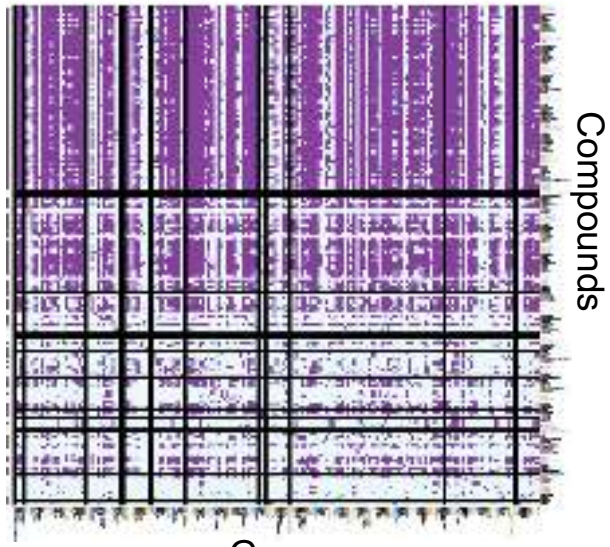
http://potentia.cbs.dtu.dk/ChemProt/

Kringelum J. *Database* 2016

Pharmacological profiling: Systems chemical toxicology

Analysis of large scale microarray data

Toxicogenomics data analysis



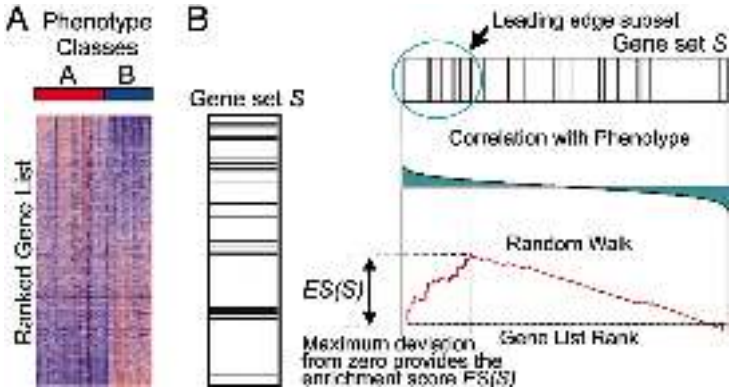
WY-14643

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

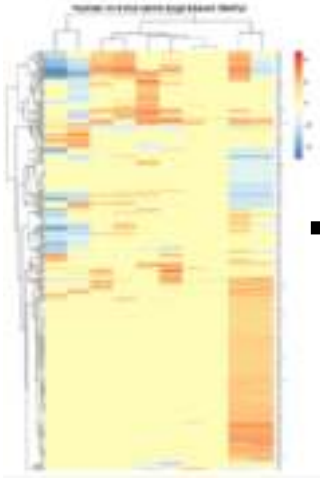
Taboureau O. *J. Pharmacogenom. Pharmacoprot.* 2012

Pharmacological profiling: Example with Steatosis and DILI

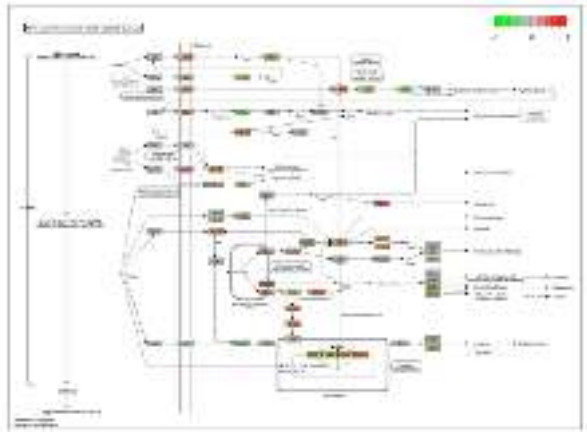
Prediction of DILI compounds and genes associated to steatosis

Ligand-protein interaction

Cell deregulation



Metabolic pathways affected



=

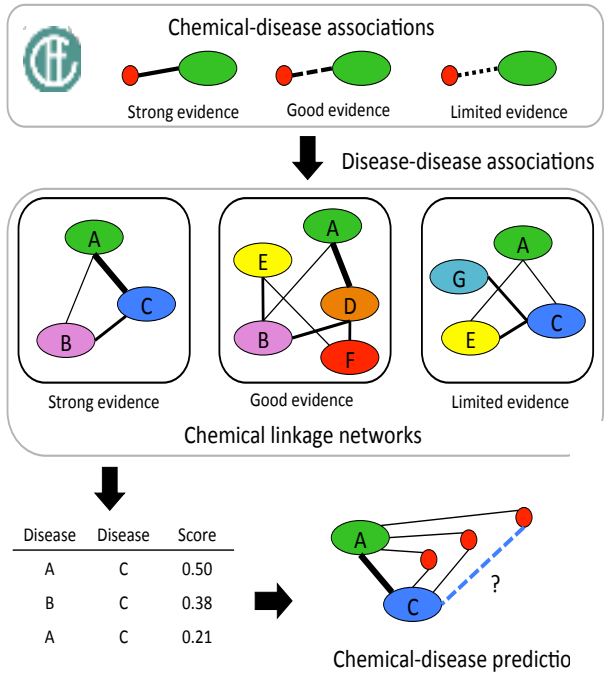
- Suggestion of gene's biomarkers (ALDH7A1, OSBL9 …)
- Suggestion of molecules with a risk.

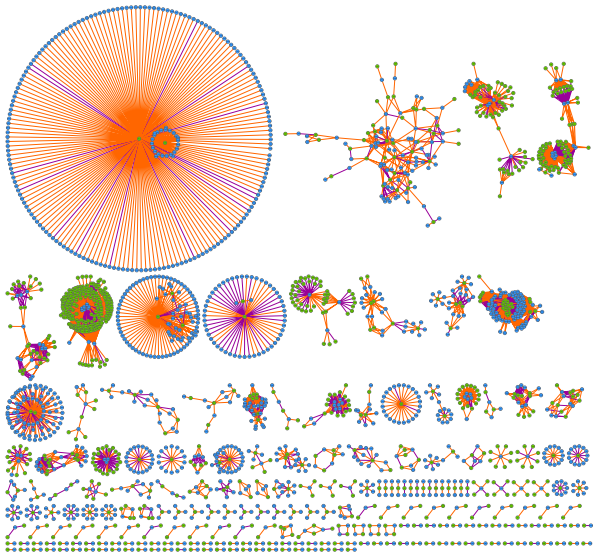
Such analysis can be used for computational phenotypic screen.

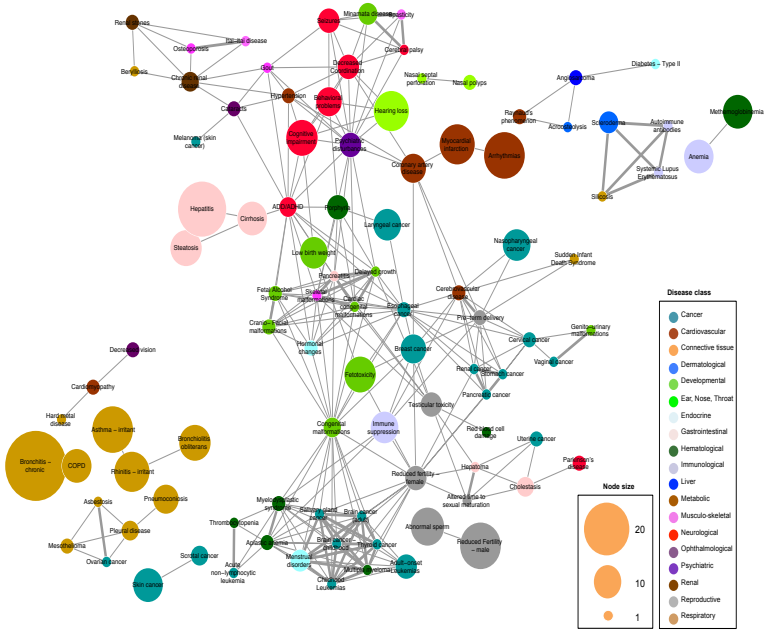
Aguayo-Orozco et al., Front Genet, 2018

Pharmacological profiling: Network-based Analysis

Development of network-based analysis tools to predict chemical-chemical interactions to diseases and other biological outcomes



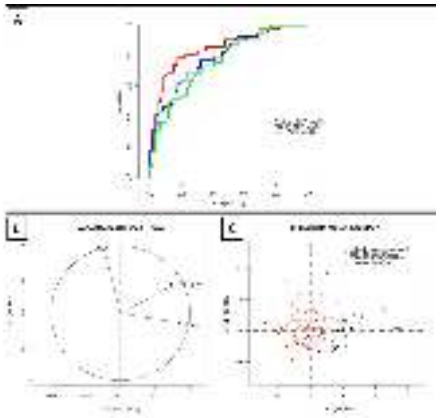




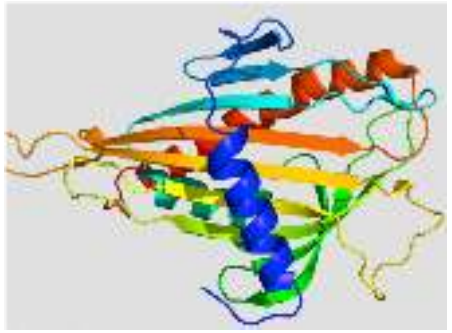
Audouze K et al. PLoS One, 2014; Taboureau et al. ALTEX, 2017

Current collaborations with teams at P7

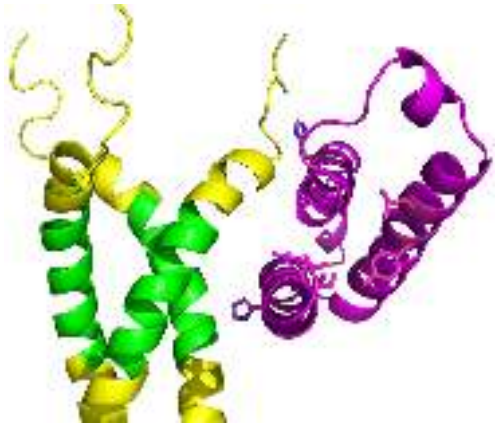
Alzheimer’s disease, DYRK1A, CBS (N. Janel)



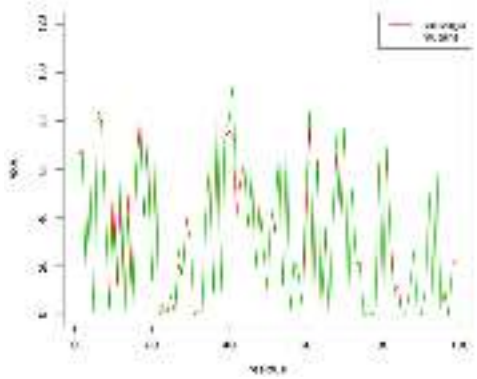
Docking study into the CERT transporter (C. Magnan)



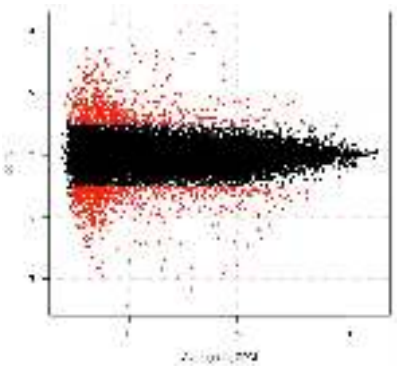
Docking study: HSF2 (A. de Thonel and V. Lallemand-Mezger)

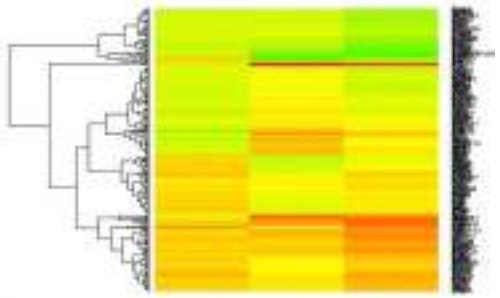


NAT exploration with MD simulation (F. Rodrigues-Lima)



RNAseq study on diabetes. Gut Microbiota peptides (C. Magnan)





Team members

Permanent staff

PR. AC. Camproux

PR. O. Taboureau

CR. M. Petitjean

MCF. A. Badel

MCF. D. Flatters

MCF. L. Regad

Tech. C. Geneix

Post doc and Ph.D in 2018

ATER. V. Leroux
Ph.D N.. Cerisier
PhD. B. Boezio
PhD. P. Laville

Permanent staff

DR. P. Tuffery

MCF. G. Moroy

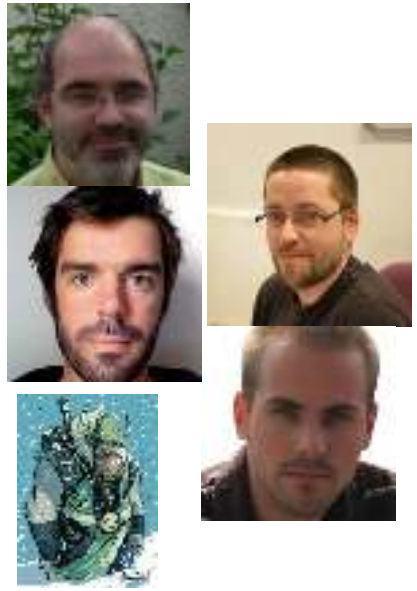
MCF. S. Murail

IG. J. Rey

IG. S. De Vries

Post doc and Ph.D in 2018

Post doc: G. Postic



Thank you