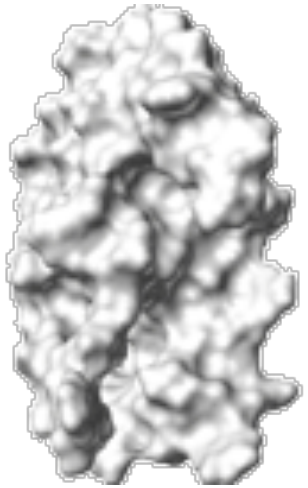
An Example of A Challenging Chemical Space: Protein-Protein Interfaces…



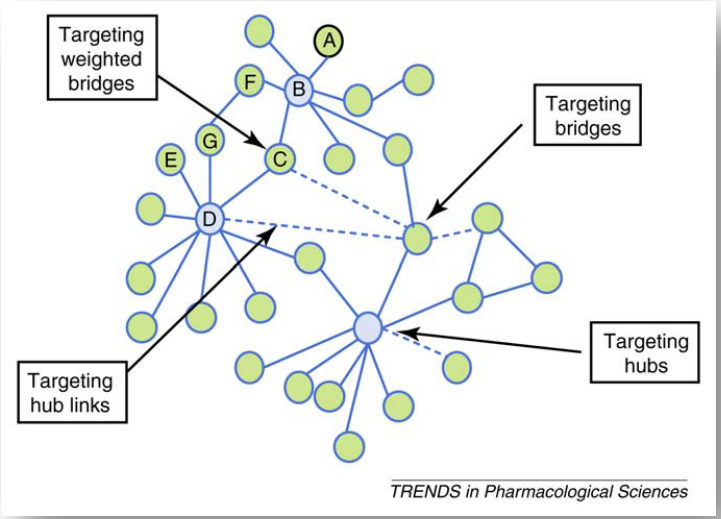
Laboratory 'integrative Structural & Chemical Biology (iSCB)'
Cancer Research Center of Marseille (CRCM)
CNRS-UMR7258 ; INSERM U 1268 ; Aix-Marseille University

Institut Paoli-Calmettes
27 Boulevard Leï Roure BP30059
13273 Marseille Cedex 9
France

Some Definitions: PPIs and Networks

- **PPI Networks control pathways involved in normal and pathological actions**

⇒ **In protein-protein interaction networks, the nodes represent proteins and the edges represent the detected protein–protein interactions (PPIs).**



'**Nodes**'=Discrete molecules (transcripts, proteins, metabolites…)

'**Edges**' = Functional connection between nodes

'**Hubs**' = Nodes possessing a higher number of functional connections (k) within the network

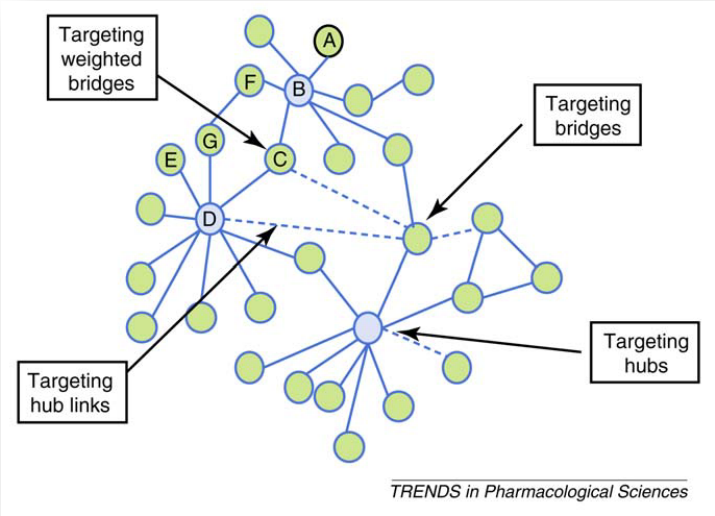
'**Network**'= Scale Free system (their degree distribution follow a power of law) in which most nodes have few links and a few of the nodes are hubs => provide network stability.

1- FLIRI A. *et al* (2009) Cause-effect relationships in medicine: a protein network perspective. *TRENDS in Pharm. Sci.* **31(11)** 547-55.

Hub Targeting vs. 'Edgetic' concept

Targeting a Hub affect the entire network !

For antibiotics, fungicides, pesticides and anticancer compounds development : Hub targets and multi-target approaches are of interest because network damage corresponds to the desired drug action !

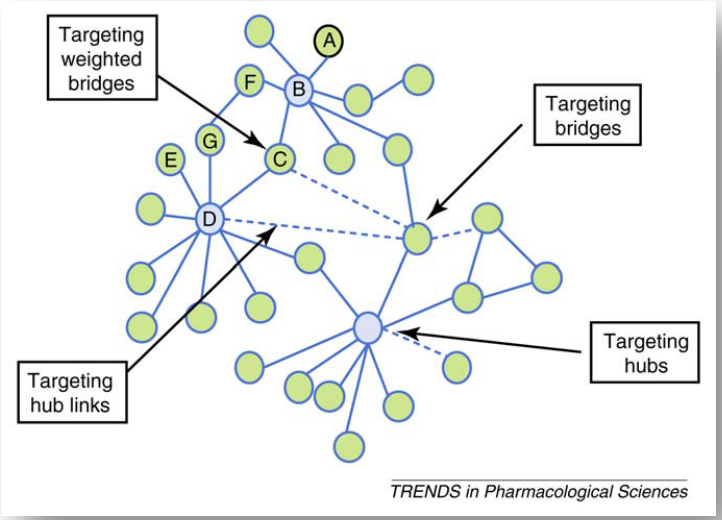


« …Edge-specific genetic perturbations confer distinct functional consequences from node removal[1]… »

One can disrupt information flow between functional modules by targeting bridges !

⇒ Bridging nodes should also be considered as attractive targets for human disease

1- Zhong Q. *et al.* 2009 – Edgetic perturbation models of human inherited disorders Mol. Syst. Biol. 5 321

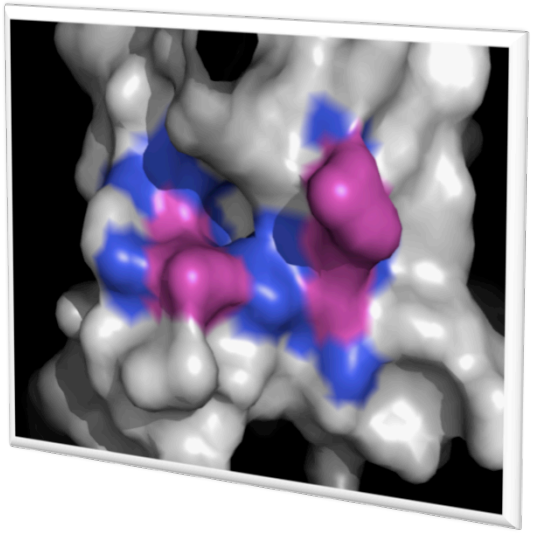


With our efforts targting Hubs or Bridges, Modulators of PPIs (PPIMs) are the next innovative drugs that will reach the market in the next decade

Can we learn from Success Stories to Accelerate this Goal ?

Modulators of Protein-Protein Interaction (PPIMs)

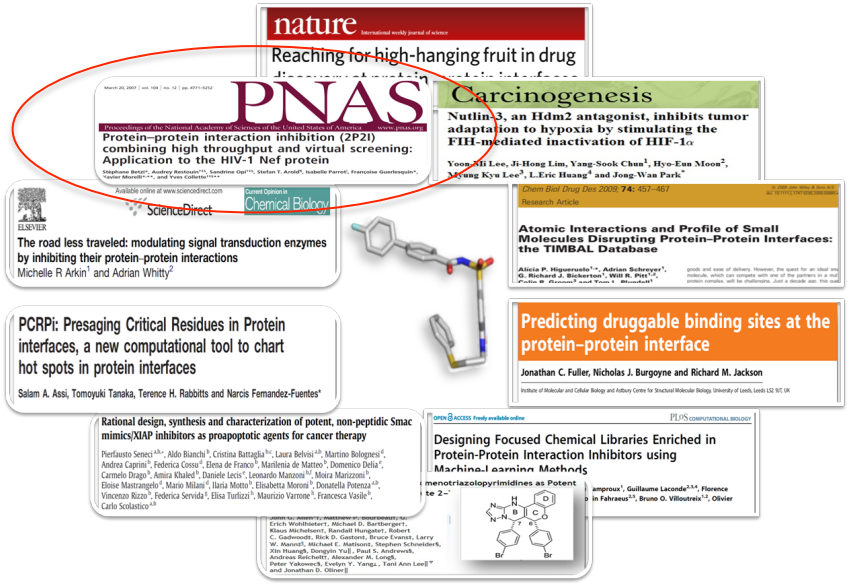
Looking for the Holy Grail…



Hot Spot Residues

Binding energy can be ascribed to a small set of residues

Clackson, T., and J. A. Wells. 1995. Science ***267:***383-386.



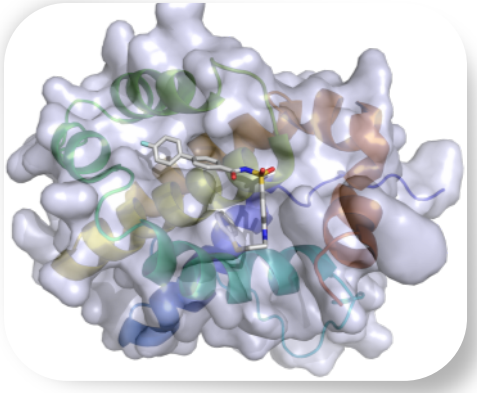
Success Stories

hundreds molecules identified as PPIMs for ~40 targets

1- Betzi *et al* (2007) Protein-Protein Interaction Inhibition (2P2I) combining highthroughput & virtual screening: Application to the Nef HIV-1 Protein. ***PNAS***

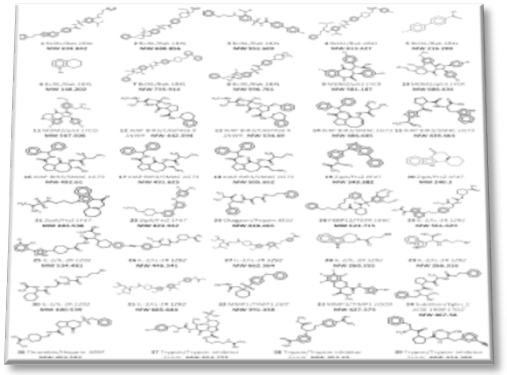
YES ! But…

"Despite these recent successes, chemoinformatics approaches targeting PPIs still face two main daunting challenges"…



Target Selection:

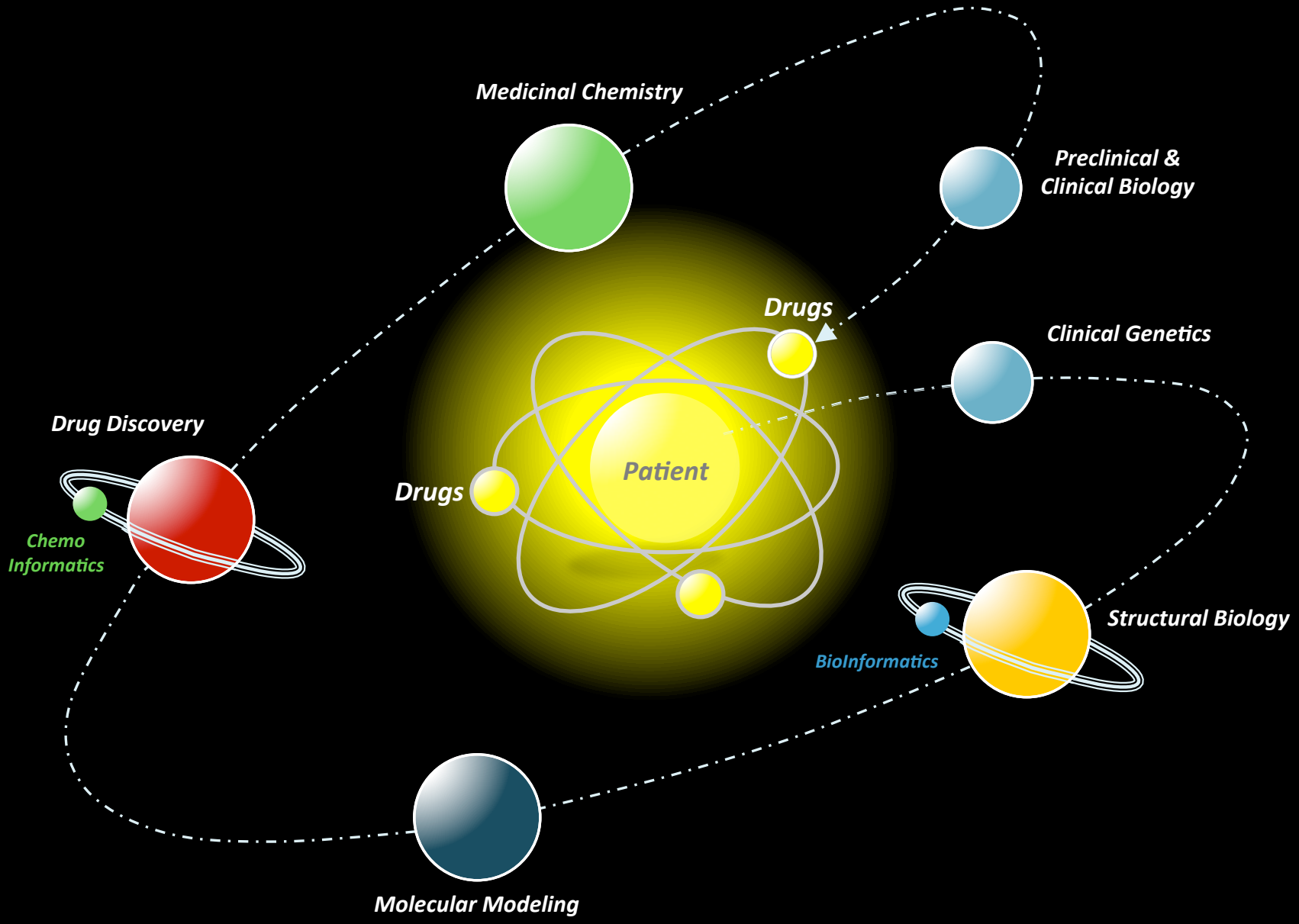
Can we predict 'Druggable PPInterfaces'



Compounds Selection:

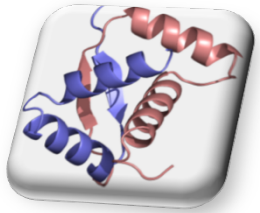
Can we design focused libraries dedicated to PPIs ?

What makes a Protein-Protein Interface (PPI) different from any Enzyme ?



Biophysical & Geometrical Properties of PPIs

Homo-oligomer particularities:

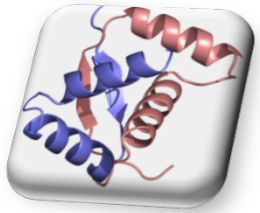


- Obligate complexes most of the time (denaturation is often necessary)
- Structure and amino-acid composition: Optimized for this oligomeric state
- Interacting zone between two monomers:
  - ✓ Never in contact with solvent
  - ✓ Possesses a hydrophobic profile

Each monomer does not posses a peripherical surface hydrophylic and a hydrophobic core but the global oligomer rather adopts this profile

Nooren & Thornton, 2003, EMBO J., 22(14), 3486-92

Biophysical & Geometrical Properties of PPIs



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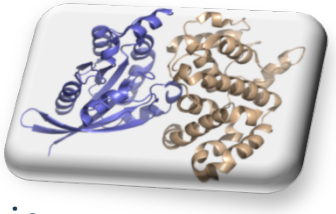
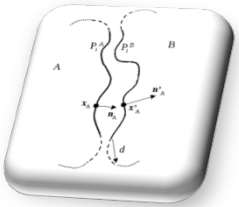


Hetero-oligomer particularities:

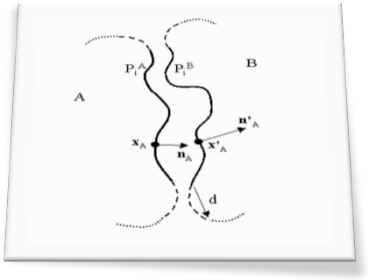
- Most of the time, **transient complexes**
- Existence of monomeric state and multimeric state implies many restraints in term of structure and composition in amino acids.
  - ✓ Statistically contact surfaces are **less hydrophobic** and **more planar** compare to homodimers

Transient complexes are great targets for biomedical research since their roles are most often in regulation processes of the cell

Nooren & Thornton, 2003, EMBO J., 22(14), 3486-92



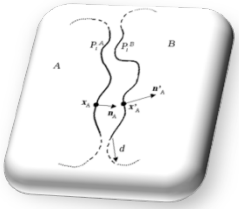
Biophysical & Geometrical Properties of PPIs



Interface Size (SASA = Solvant Accessible Surface Area):

$$IS = SASA_{subunit\ A} + SASA_{subunit\ B} - SASA_{complex\ A/B}$$

Type of Complex	Homodimers	Heterodimers		Non specific
Average Interacting Surface	3 880 Å²	Transient 'strong' 2304 Å²	Transient 'weak' 1386 Å²	1 510 Å²
		Transient 'Average' 1910 Å²		



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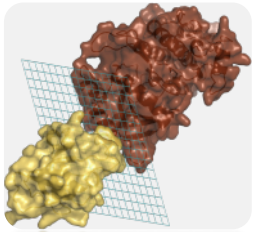
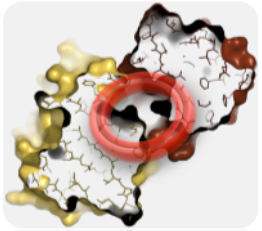
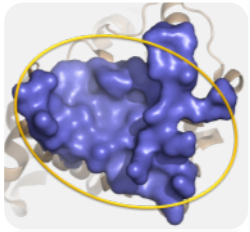


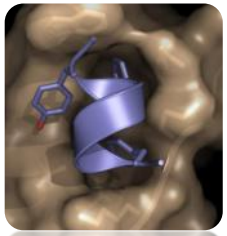
Planarity



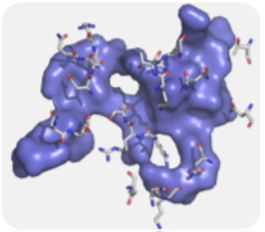
Gap Volume



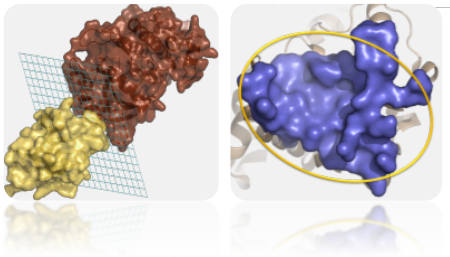
Eccentricity



Pockets



Type of Residues



Biophysical & Geometrical Properties of PPIs

Planarity :

- **Planarity = Root Mean Square Deviation of all the interface atoms from the least square plane through the atoms (minimum =0)**

  - ✓ Average value for Homodimers = 3.5+/- 1.7A
  - ✓ Average value for Heterocomplexes = 2.8 +/- 0.9A

⇒ **Protein-Protein Interfaces are generally flat in shape**

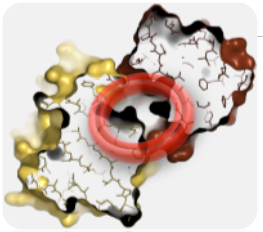
Eccentricity:

- **Circularity = Length's Ratio of the principal axes of the least squares plane through the atoms in the interface (ratio=1 means the atoms at the interface are circular)**

  - ✓ Average value for Homodimers = 0.71 +/- 0.17
  - ✓ Average value for Heterocomplexes = 0.73 +/- 0.05

⇒ **Protein-Protein Interfaces are generally circular**

Jones and Thornton (1996). *Principles of protein-protein interactions.* Proc. Natl. Acad. Sci. USA, 93(1), 13-20

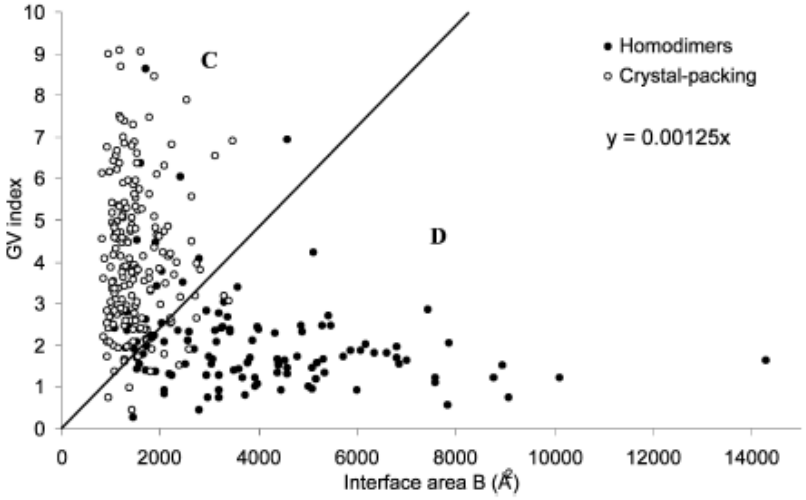


Biophysical & Geometrical Properties of PPIs

Shape Complementarity – Laskowski -:

GV(A) = GV between mol (A^3)/ Interface area (A^2) (per complex)

- Average value (Homodimer/Heterodimer): 2.1 +/-1A^3
- Average value (Non Specific complexes): 4.4 +/-1.9A^3



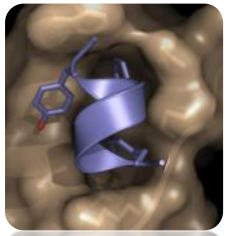
Local Density – Bahadur, 2004 –

•The Local Density (LD) is the mean number of interface atoms that are within 12A of another interface atom. The Global Density (GD) measures the atomic density at the interface atoms normalized to the dimensions of the interface

- Average Value of LD = 42-45 for the specific interfaces and 30% lower for crystal packing

=> Gap Volume + LD + GD is a good index to differentiate specific to non specific complexes

Bahadur and Zacharias. *Dissecting subunit interfaces in homodimeric proteins*. Cell. Mol. Life Sci. 65 (2008) 1059-1072



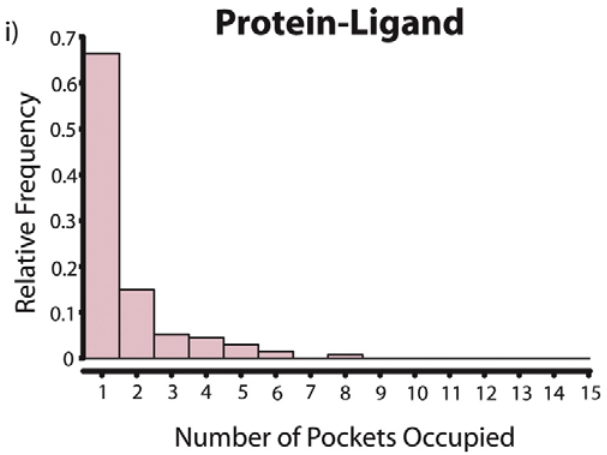
Biophysical & Geometrical Properties of PPIs

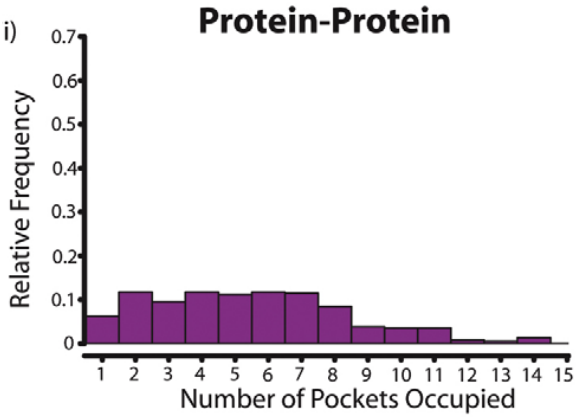
Pockets at interface :

- PLIs tend to occur in one or two disproportionately large pockets (average volume 260 Å^3).

- PPIs tend to occur in several average-sized pockets (6±3) that have a similar active volume to that of the average surface pocket (Average volume 55 Å^3).

=> PLIs have large and deep pocket (evolved in that sense) – Not the case of heterodimeric PPIs





Fuller, JC *et al.* (2009). Predicting druggable binding sites at the protein-protein interface. Drug Disc. Today *14*, 155-161.

Biophysical & Geometrical Properties of PPIs

Protein-Protein Interfaces & Water Molecules:

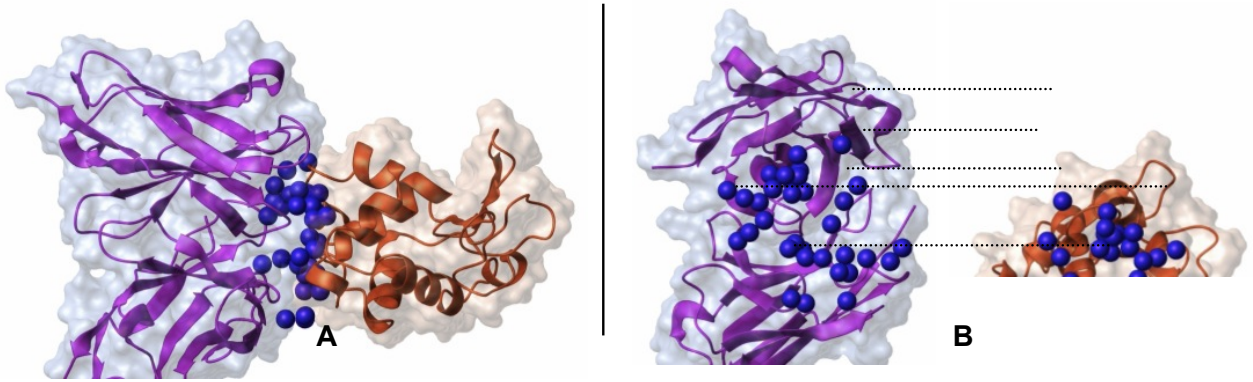
- **Excluded solvent molecules always occur during complex formation**

⇒ Favorable hydrophobic effect suggesting that water molecules should be excluded from interaction interfaces to permit complex formation.

- High resolution complexes permit to observe water molecules at the interface:

⇒ Supplementary network of polar interactions

1.5 Å resolution X-ray structure of mouse D1.3 monoclonal antibody fragment Fv in violet complexed to the chicken egg lysozyme in orange (code PDB : 1A2Y, (Dall'Acqua et al. 1998)

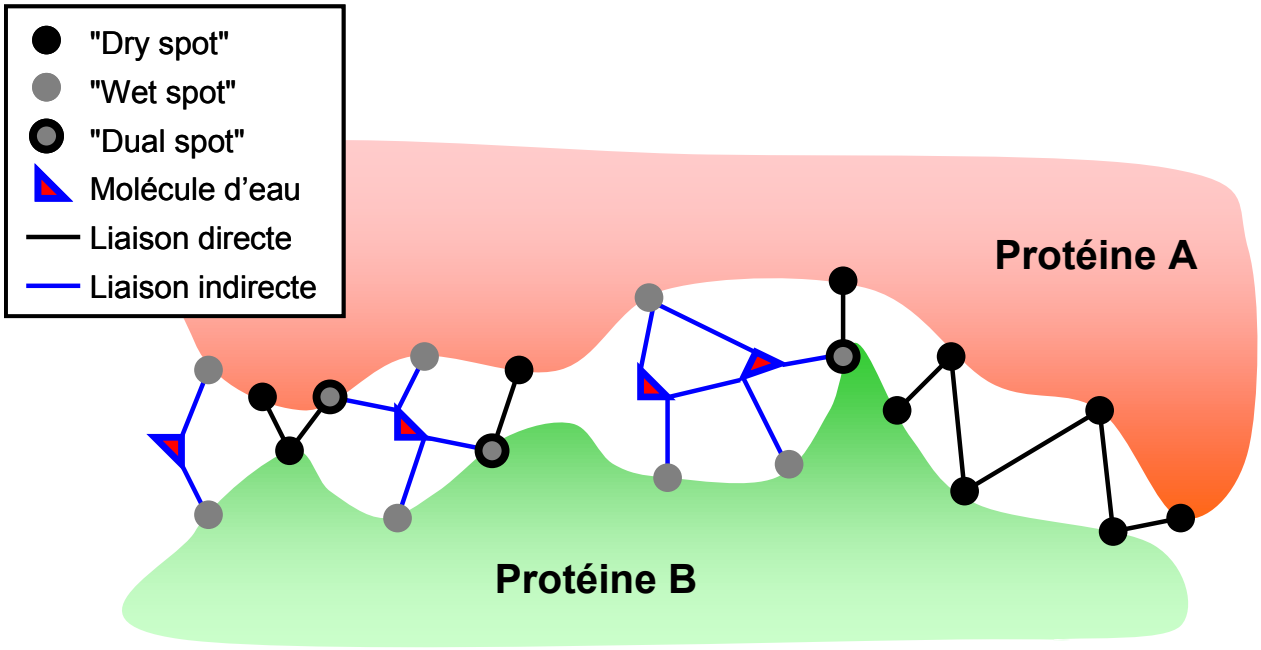


Biophysical & Geometrical Properties of PPIs

⇒ The residues interacting through these molecules are called « wet spots »

⇒ The one interacting directly are called « dry spots »

⇒ The one interacting both directly and indirectly are called « dual spots »



Biophysical & Geometrical Properties of PPIs

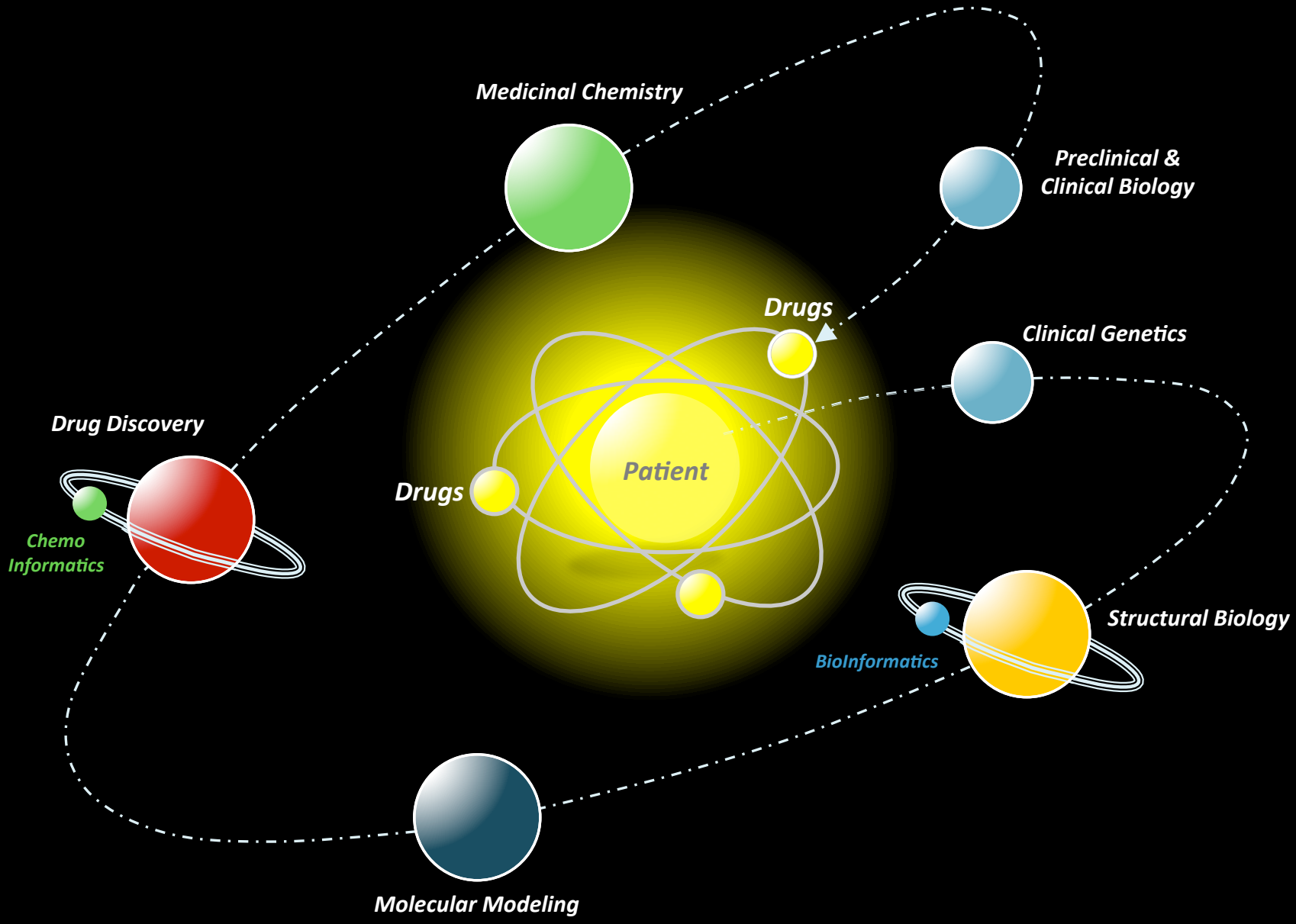
- Average water molecules at 'specific' protein-protein interface
  - **1 water molecule every 100 A^2**
- Average water molecules at 'non specific' protein-protein interface
  - **1 water molecule every 65 A^2**

⇒ Bahadur & Zacharias proposed that interaction through water molecules are more common than direct hydrogen bond in PPIs.

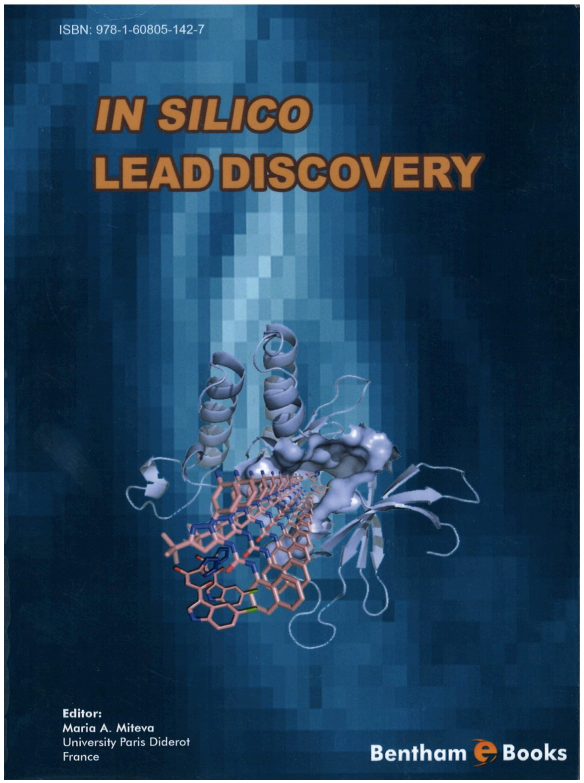
⇒ **Be careful in "In Silico Drug Discovery" research projects…** ☹☹☹

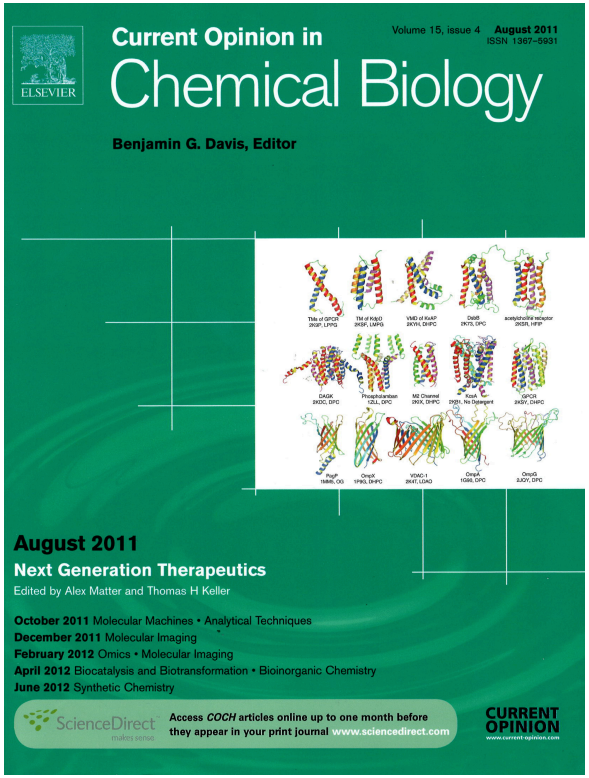
Bahadur and Zacharias. *Dissecting subunit interfaces in homodimeric proteins*. Cell. Mol. Life Sci. 65 (2008) 1059-1072

What makes a PPI a good Target for Drug Discovery ?



Some References...





118 *In Silico Lead Discovery*, 2011, 118-143

CHAPTER 7

Protein-Protein Interaction Inhibition (2P2I): Mixed Methodologies for the Acceleration of Lead Discovery

Philippe Roche and Xavier Morelli

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ScienceDirect

Current Opinion in Chemical Biology

Chemical and structural lessons from recent successes in protein–protein interaction inhibition (2P2I)

Xavier Morelli, Raphaël Bourgeas and Philippe Roche

'Druggability' Assessment: Pockets Finders

Evolutionary algorithms or Structure-Based algorithms (Geometry & Energy based)		
PocketPicker	Software	http://gecco.org.chemie.uni-frankfurt.de/pocketpicker/index.html
Q-SiteFinder	Web Server	http://www.modelling.leeds.ac.uk/qsitefinder/
LIGSITE	Web Server	http://projects.biotec.tu-dresden.de/pocket/
Surfnet	Software	http://www.biochem.ucl.ac.uk/~roman/surfnet/surfnet.html
CASTp	Web Server	http://sts.bioengr.uic.edu/castp/
AVP	Software	http://www.bioinf.org.uk/software/avp/
AutoLigand	Software	http://autodock.scripps.edu/resources/autoligand
fpocket	Software	http://fpocket.sourceforge.net/
SiteMap	Software	http://www.schrodinger.com/products/14/20/
Molecular Dynamics Simulations – based Software		
MDpocket	Software	http://fpocket.sourceforge.net/
MetaMethods		
Metapocket	Web Server	http://metapocket.eml.org/
Metapocket2.0	Web Server	http://sysbio.zju.edu.cn/metapocket/

Adapted from Roche & Morelli, . *In: Miteva M, editor. In silico lead discovery: Bentham. Chapter 7, p167-200 and from Marabotti & Milanesi WRJPP, 2012*

'Druggability' Assessment: Other Tools

PPI Analysis		
PROTORP	**Webserver**	**http://bioinformatics.sussex.ac.uk/protorp/**
PDBePISA	Web Server	http://www.ebi.ac.uk/msd-srv/prot_int/pistart.html
PIC	Web Server	http://pic.mbu.iisc.ernet.in/
$2P2I_{INSPECTOR}$	**Webserver**	**http://2P2Idb.cnrs-mrs.fr**

Mathematical Models to Assess Druggability based on physico-chemical properties

✓ **Cheng A.C., et al. (*Nat. Biotechnol., 2007):***

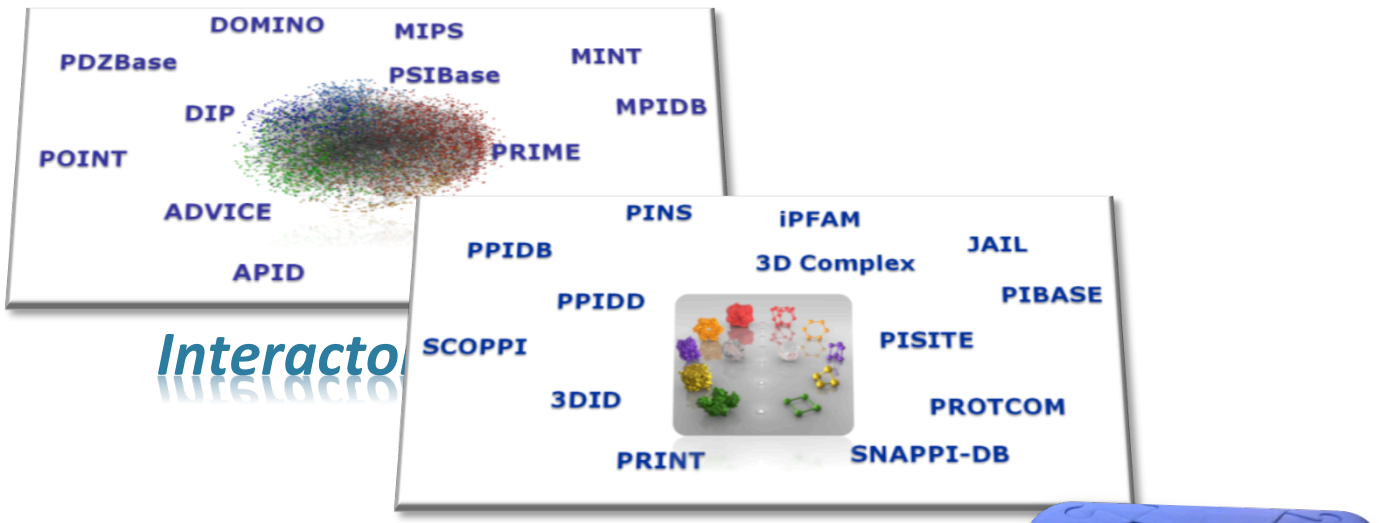
27 Target binding sites - Decision tree –

Presence of cavities, hydrophobicity and size, the shape complementarity between the two interacting subunits within the cavity

⇒ **Good discrimination was achieved between non druggable and 'easily druggable' protein-protein interfaces**

⇒ **What about Success Stories with STRUCTURALLY validated PPIMs ?**

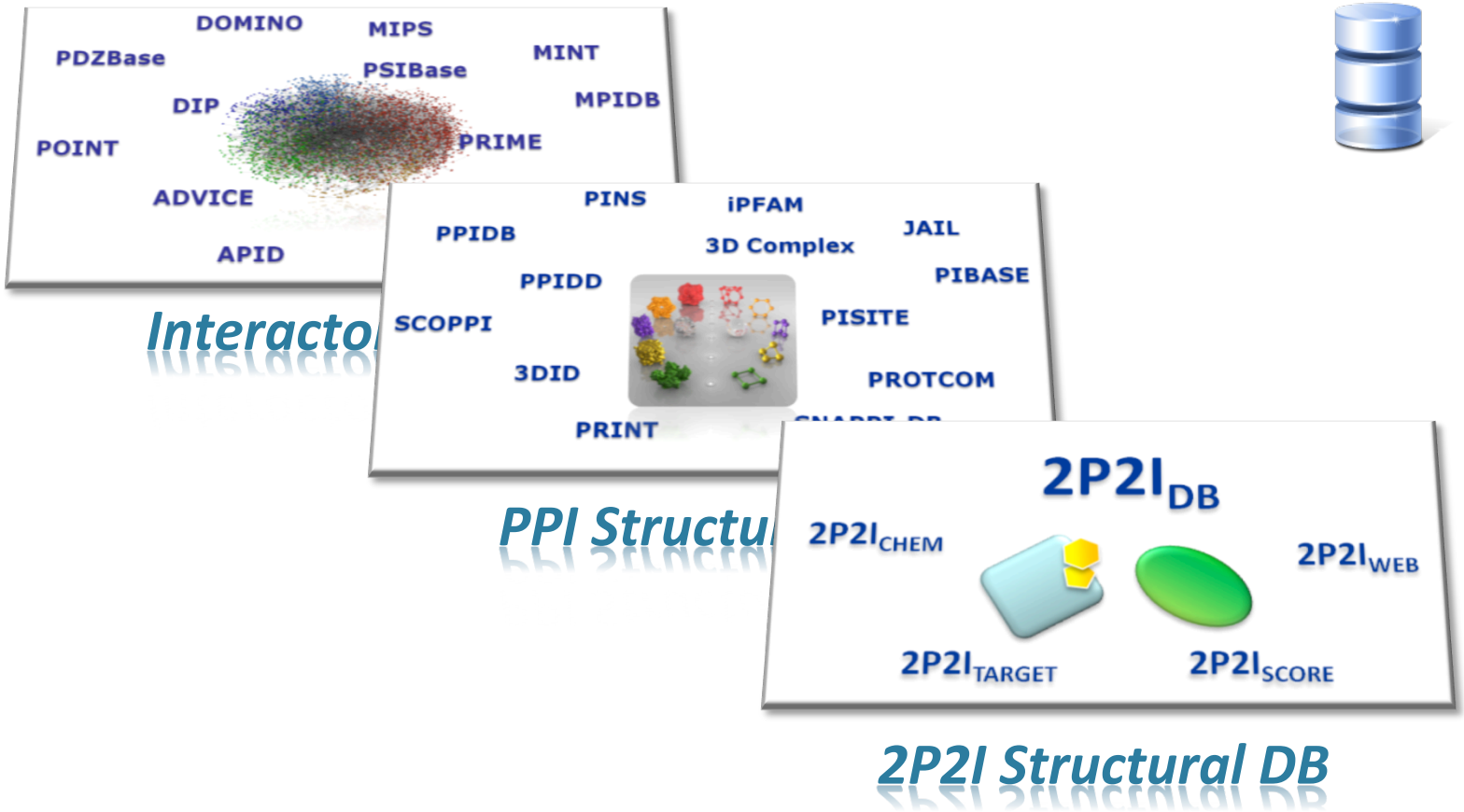
'Druggability' based on Success Stories



Missing Tools

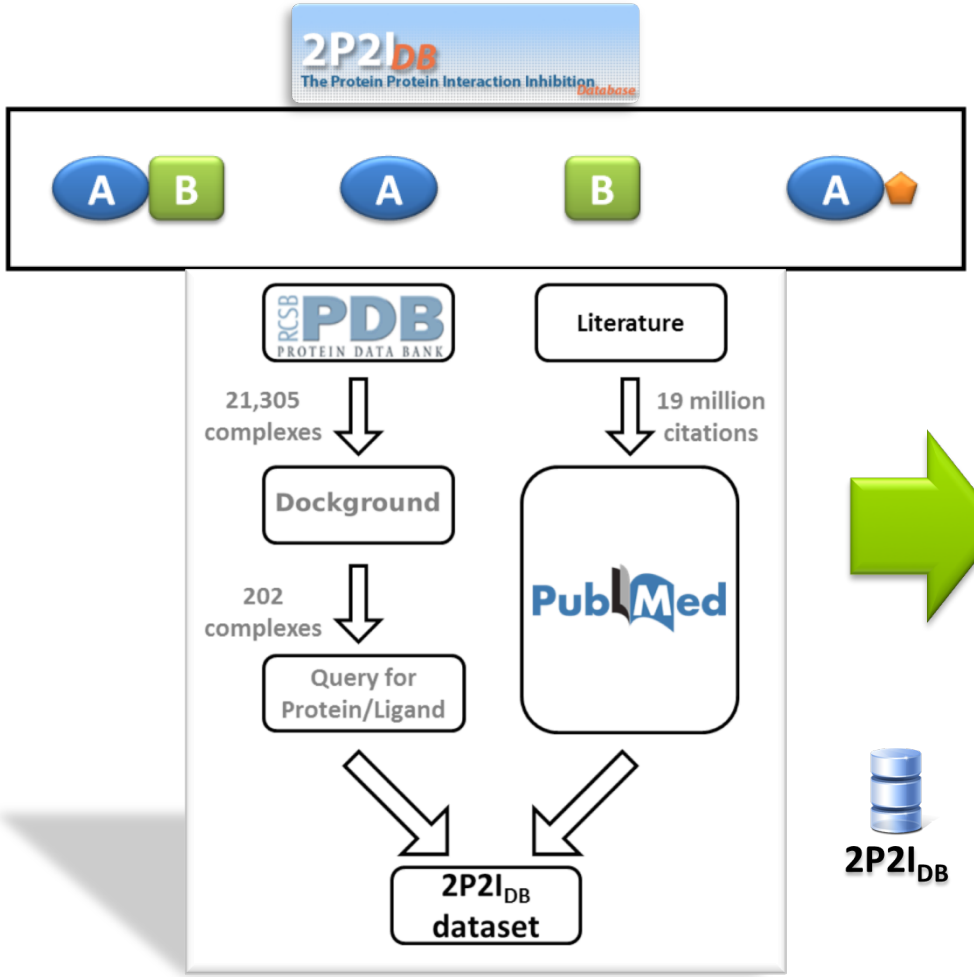
Roche & Morelli (2010) Protein-Protein Interaction Inhibition (2P2I): Mixed Methodologies for the Acceleration of Lead Discovery. In: Miteva M, editor. In silico lead discovery: Bentham. Chapter 7, p167-200.

'Druggability' based on Success Stories

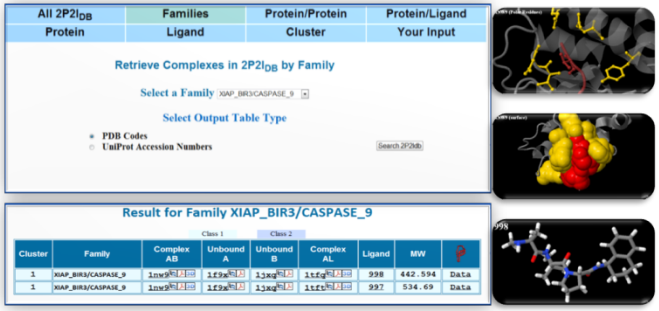


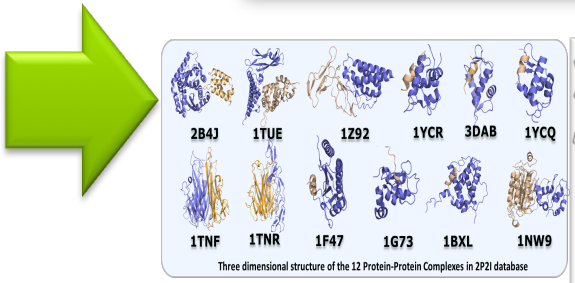
*Roche & Morelli (2010) **Protein-Protein Interaction Inhibition (2P2I)**: Mixed Methodologies for the Acceleration of Lead Discovery. In: Miteva M, editor. In silico lead discovery: Bentham. Chapter 7, p167-200.*

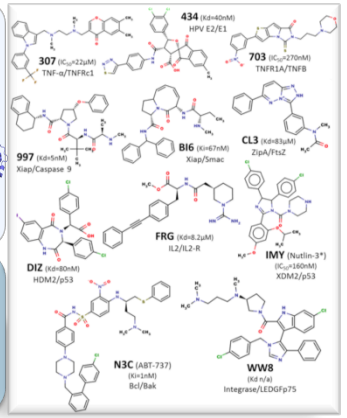
'Druggability' based on Success Stories



http://2p2idb.cnrs-mrs.fr/





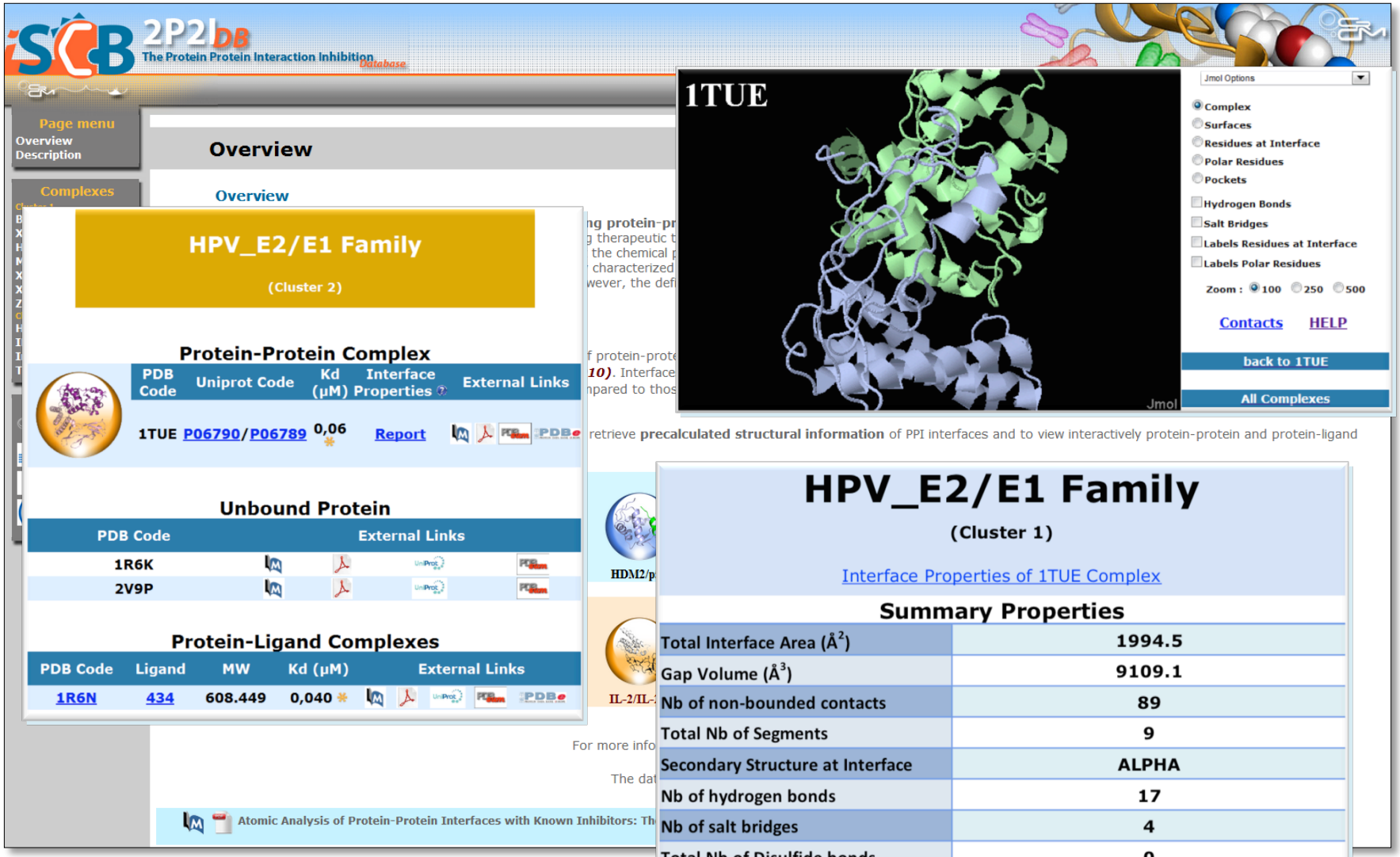


2P2I DB

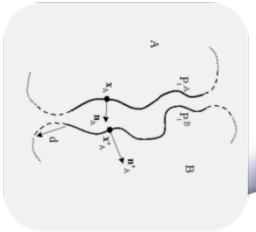
39 Inhibitors

Bourgeas R. Basse MJ. Morelli X. & Roche P. (2010) Atomic Analysis of PPIs with known inhibitors… *PLoS ONE 5 e9598*

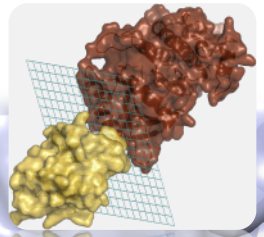
2P2I$_{WEB}$: http://2p2idb.cnrs-mrs.fr



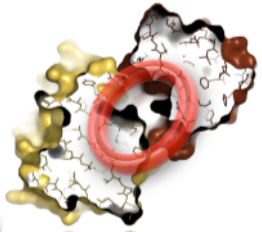
'Druggability' assessment: 2P2I INSPECTOR



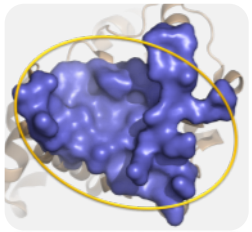
SASA



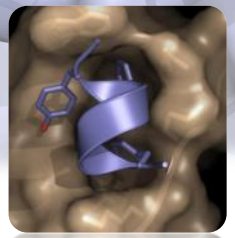
Planarity



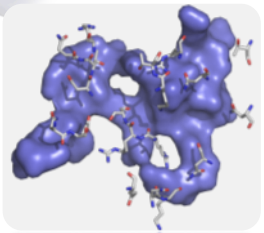
Gap Volume



Eccentricity



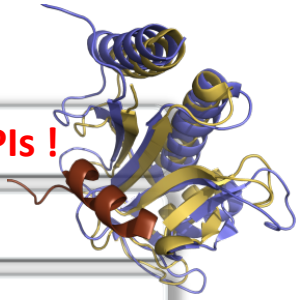
Pockets



Type of Residues

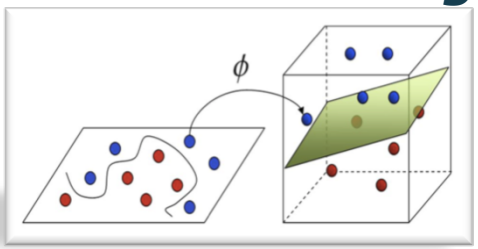
Bourgeas R. Basse MJ. Morelli X. & Roche P. (2010) Atomic Analysis of PPIs with known inhibitors: **The 2P2I Database** *PLoS ONE* ***5*** *e9598*

'Druggability' assessment: 2P2I$_{INSPECTOR}$

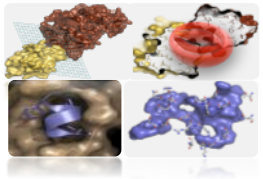


Size	• Smaller and more hydrophobic Interface than standard PPIs !
Shape	• Same shape (planarity and eccentricity)
Dynamics	• No major conformational changes (rmsd < 2Å)
Pockets	• Few pockets at the interface (150 Å^3 for 1.8 ±0.7 pockets)
Charged	• Less charged residues and less salt bridges
Non polar	• More non polar atoms
HBonds	• On average more hydrogen bonds than typical PPIs
Composition	• More aromatic and large residues

Machine Learning



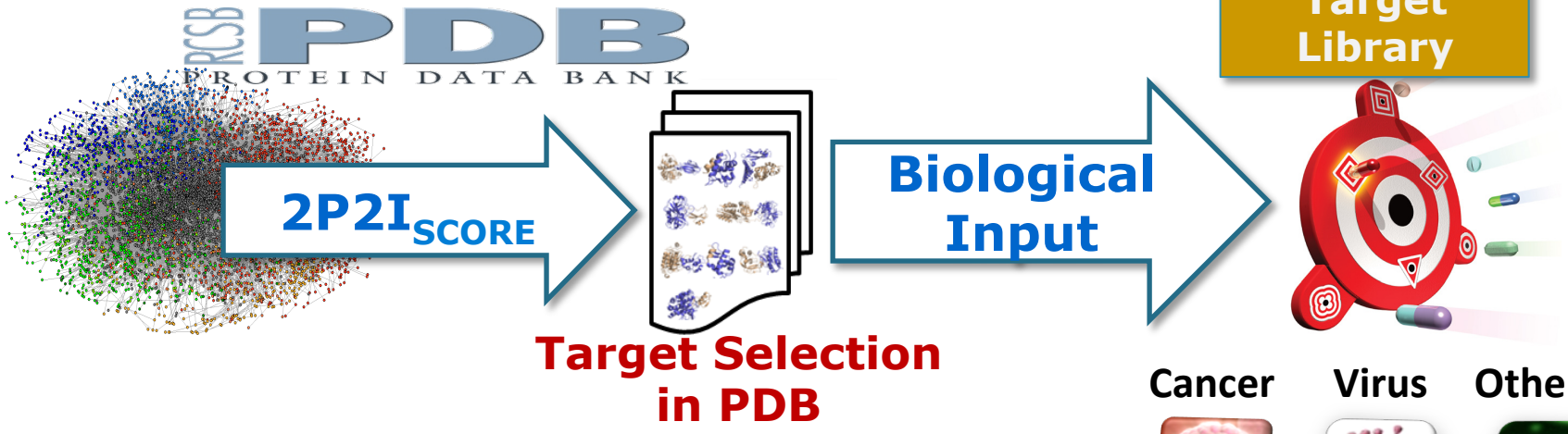
Targetability Assessment

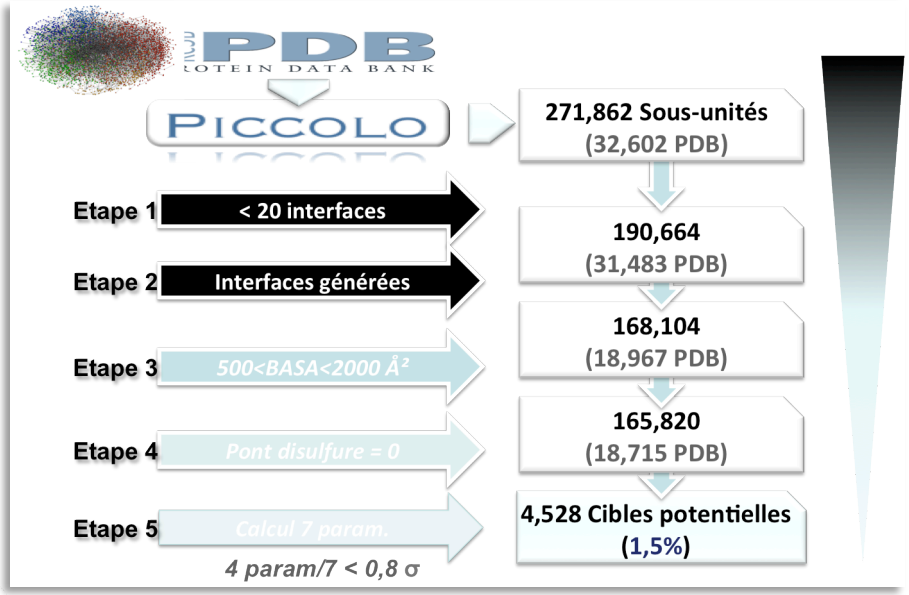


2P2I$_{INSPECTOR}$ + 2P2I$_{SCORE}$

Bourgeas et al (2010) Atomic Analysis of PPIs with known inhibitors: The 2P2I Database PLoS ONE 5 e9598

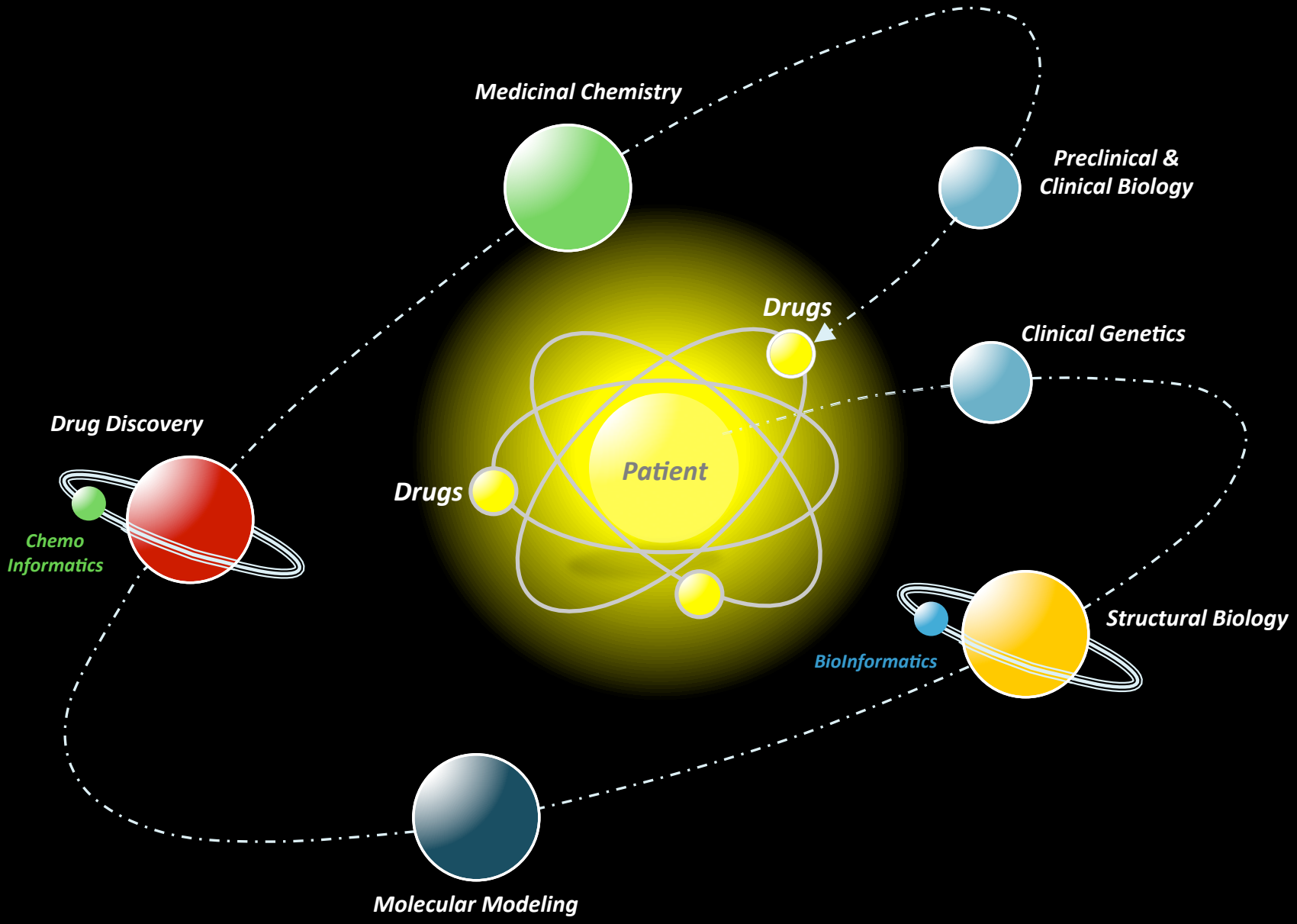
2P2I$_{INSPECTOR}$ & 2P2I$_{SCORE}$: UNDER GOING EFFORTS…





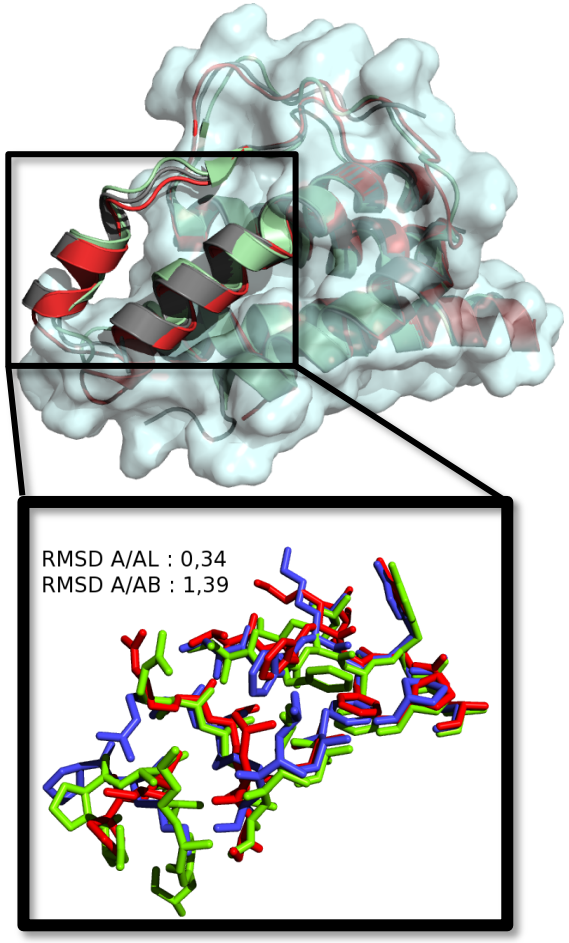
4,528 Potential Targets That are being Clustered Based on Their Metabolism Pathway (Hubs, Bridges, other) …

Are the dynamics at the interface important for Drug Discovery ?

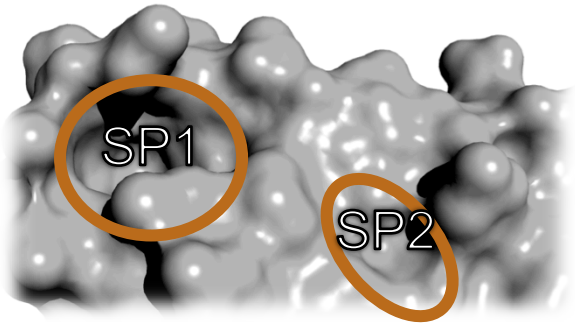


Importance of MDS in the Drug Discovery Process

Example of IL-2 (1M47)/ IL-2R (1Z92)

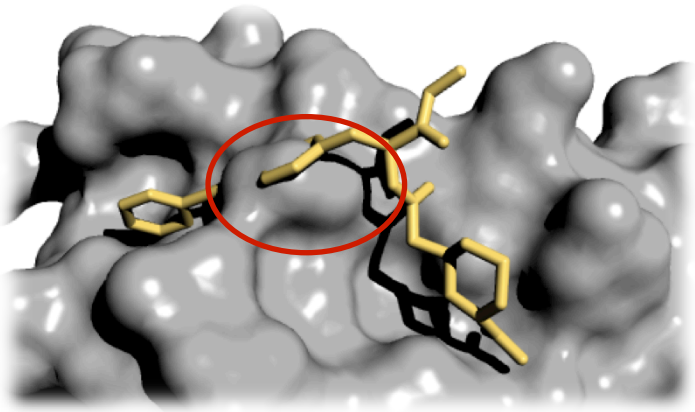


2 Pockets Identified

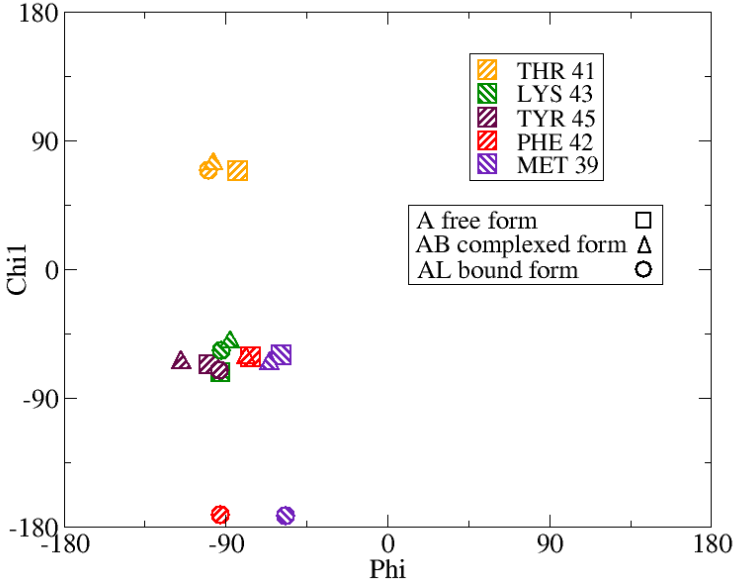


Importance of MDS in the Drug Discovery Process

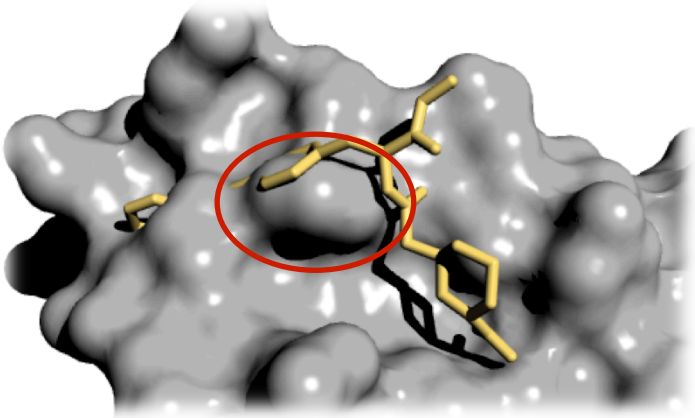
Example of IL-2 (1M47)/ IL-2R (1Z92)



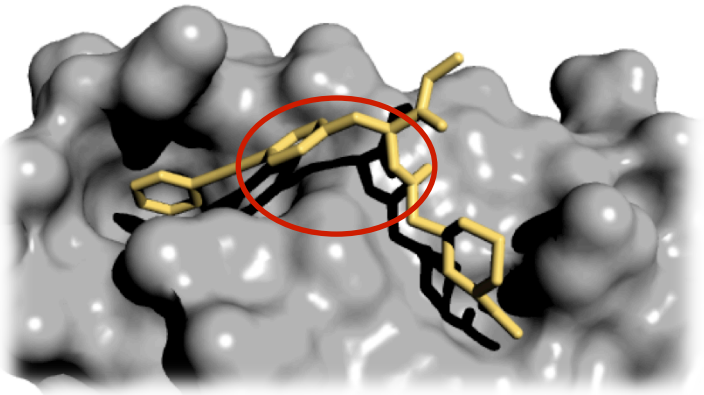
1M47 + FRG (form ‘A’)



‘Cryptic’ pocket



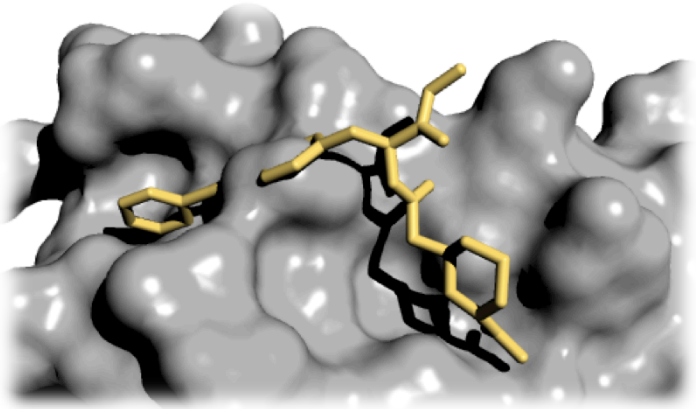
1Z92 + FRG (form ‘AB’)



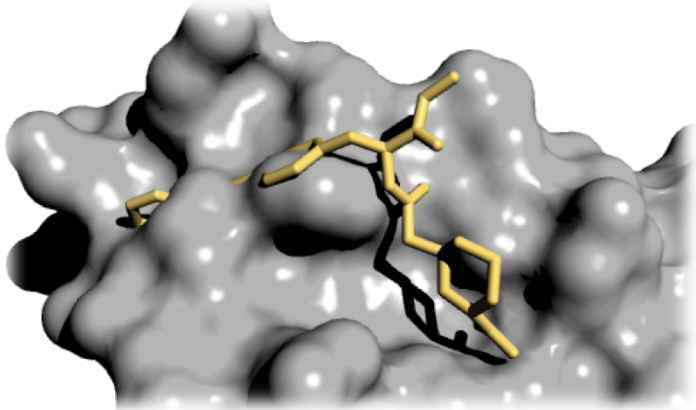
1M48 + FRG (form ‘AL’)

Importance of MDS in the Drug Discovery Process

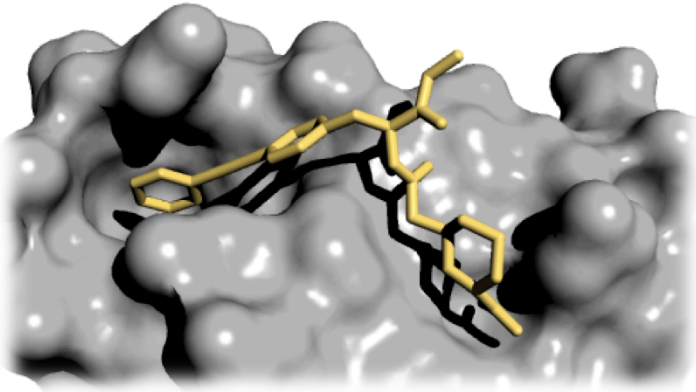
Example of IL-2 (1M47)/ IL-2R (1Z92)



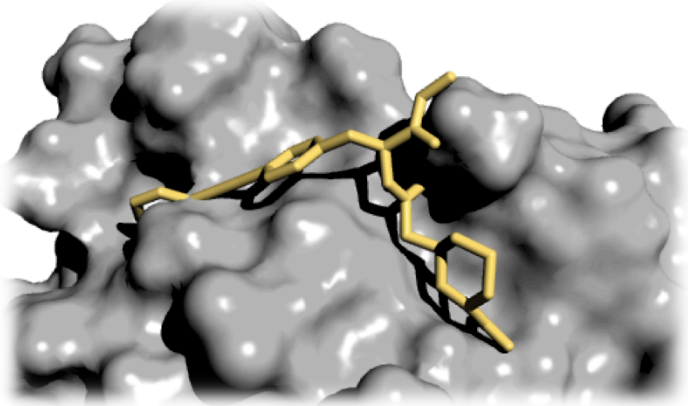
1M47 + FRG (form ‘A’)



1Z92 + FRG (form ‘AB’)



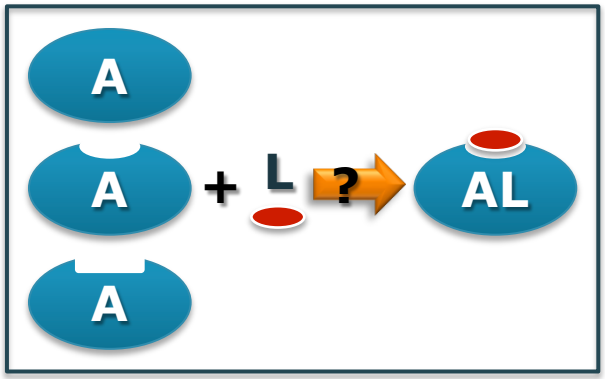
1M48 + FRG (form ‘AL’)



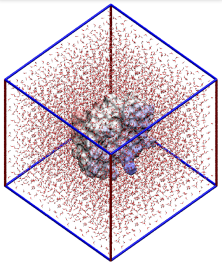
1M47 MDS frame + FRG

Application to Transient Pockets at the Interface

Detection of Interfacial Ligand Pockets in The Free Form

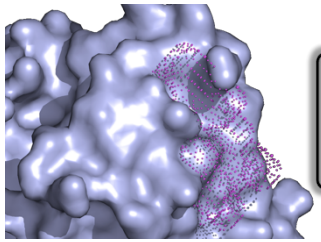


Molecular Dynamics

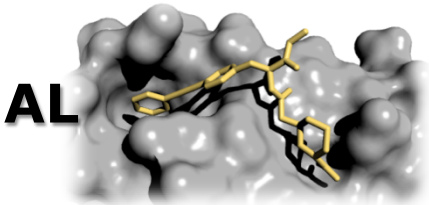


200-500ns

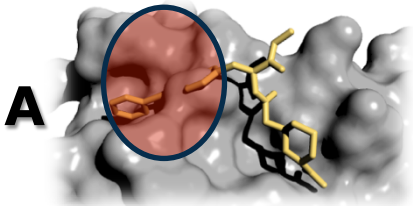
fpocket



Interfacial Pockets

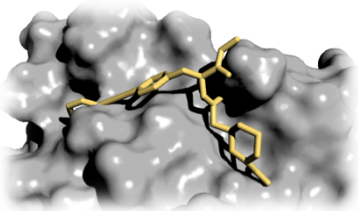


IL-2 Protein/Inhibitor (FRG)



Free IL-2 Protein
(Clash with FRG)

MD

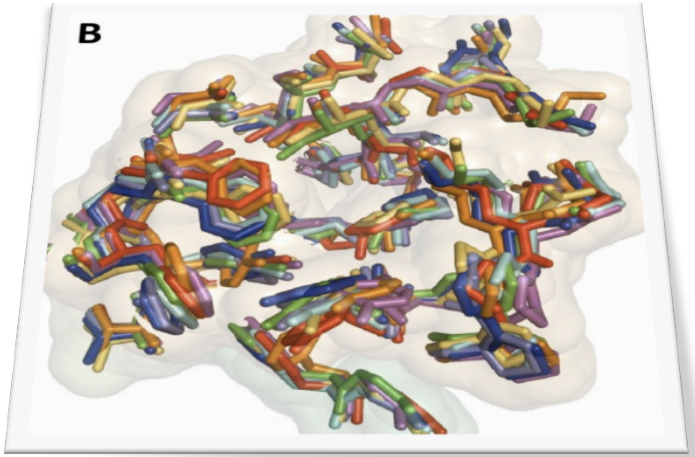


Free IL-2 Protein
(MD frame)

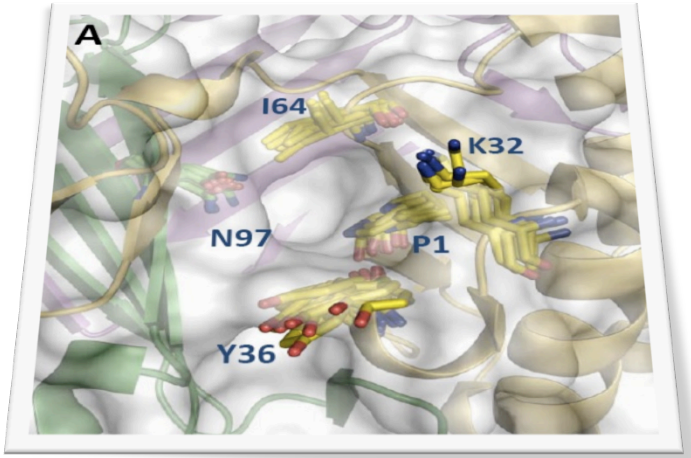
15% conformations
Vol>200 Å³

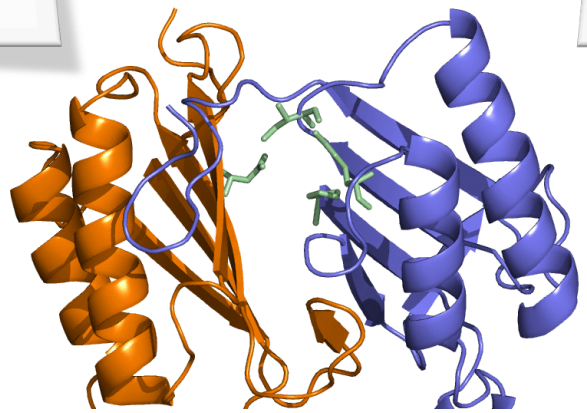
2P2I$_{DB}$ complexes
200,000 hours.cpu
CRIHAN super calculator

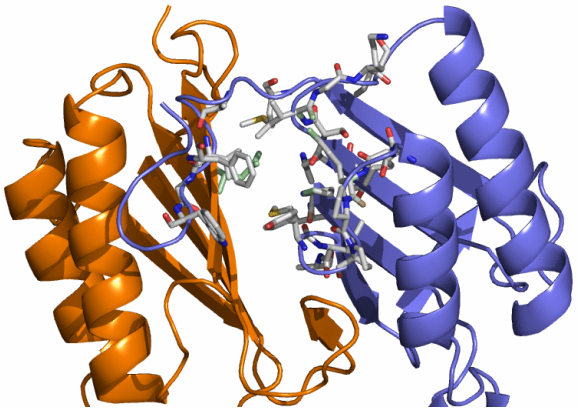
Importance of MDS to the Drug Discovery Process

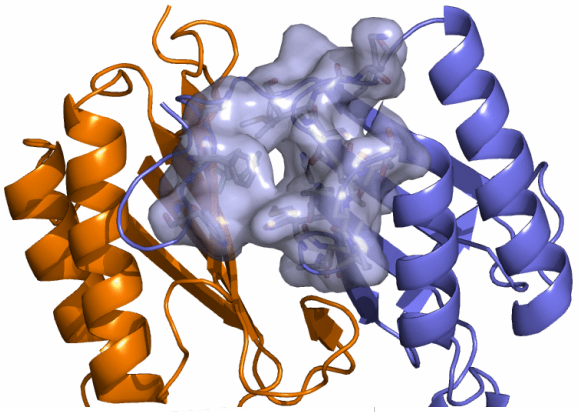


Enrichment Factor >20



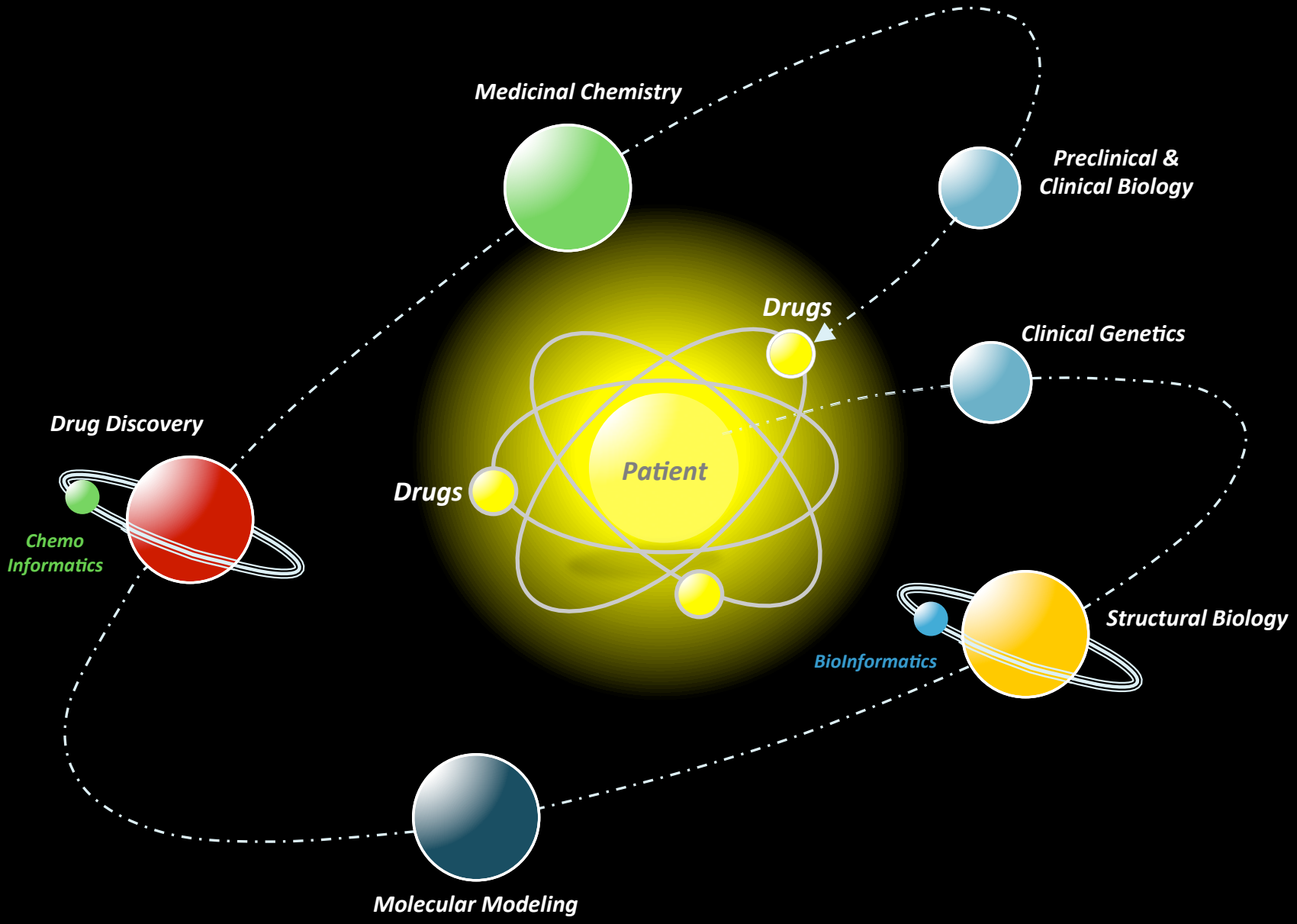






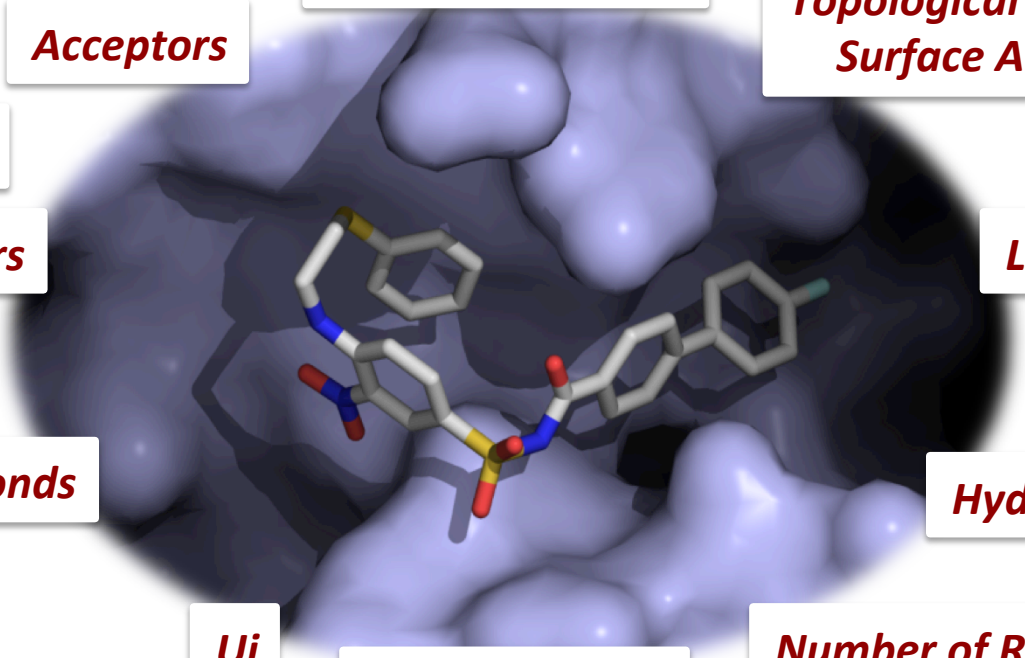
El Turk *et al.*,
Bioorg. Med. Chem., 2010

Are the actual libraries appropriate to search for PPI Modulators ?



Chemical Compounds as Modulators of PPIs

Molecular Descriptors



Chemical Compounds as Modulators of PPIs

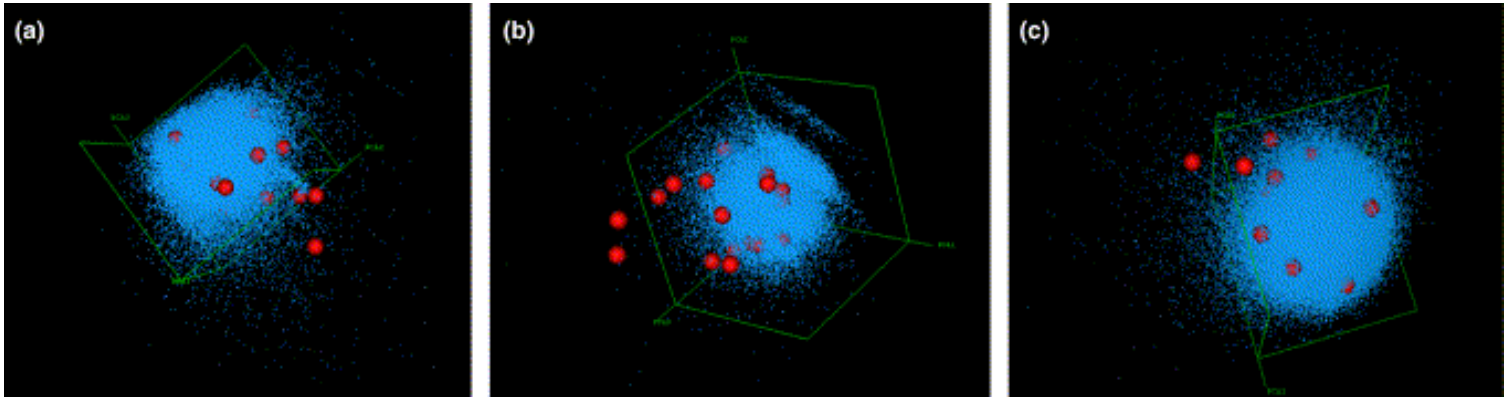


Figure 4. 3D plot of a principal component analysis (PCA) of three vendor databases (library compounds in blue) compared to 19 published SMPPIIs (in red). The calculations and views were performed using MOE, and in all cases the first three components represent 55% of the information. ***(a)*** *Projection of the Chemical Diversity database (119 475 compounds).* ***(b)*** *Projection of the Maybridge database (59 223 compounds).* ***(c)*** *Projection of the Asinex database (321 867 compounds).*

- **In 2004, Pagliaro *et al.* study 19 known PPI's Inhibitors**

⇒ 'Lipinski' standards are not valuable for PPI's Inhibition (molecular weight, polar surface & SlogP mainly)

⇒ Necessity to abolish preliminary filters for PPI's

Pagliaro et al. (2004). *Emerging classes of protein-protein interaction inhibitors …* Curr. Opin. Chem. Biol. 8(4), 442-9

Success depends on the Input…

"The readings look good, but just in case, when was the last time the system was checked for bugs?"

Need to Design Focused Libraries Dedicated to PPIs

Chemical Compounds as Modulators of PPIs

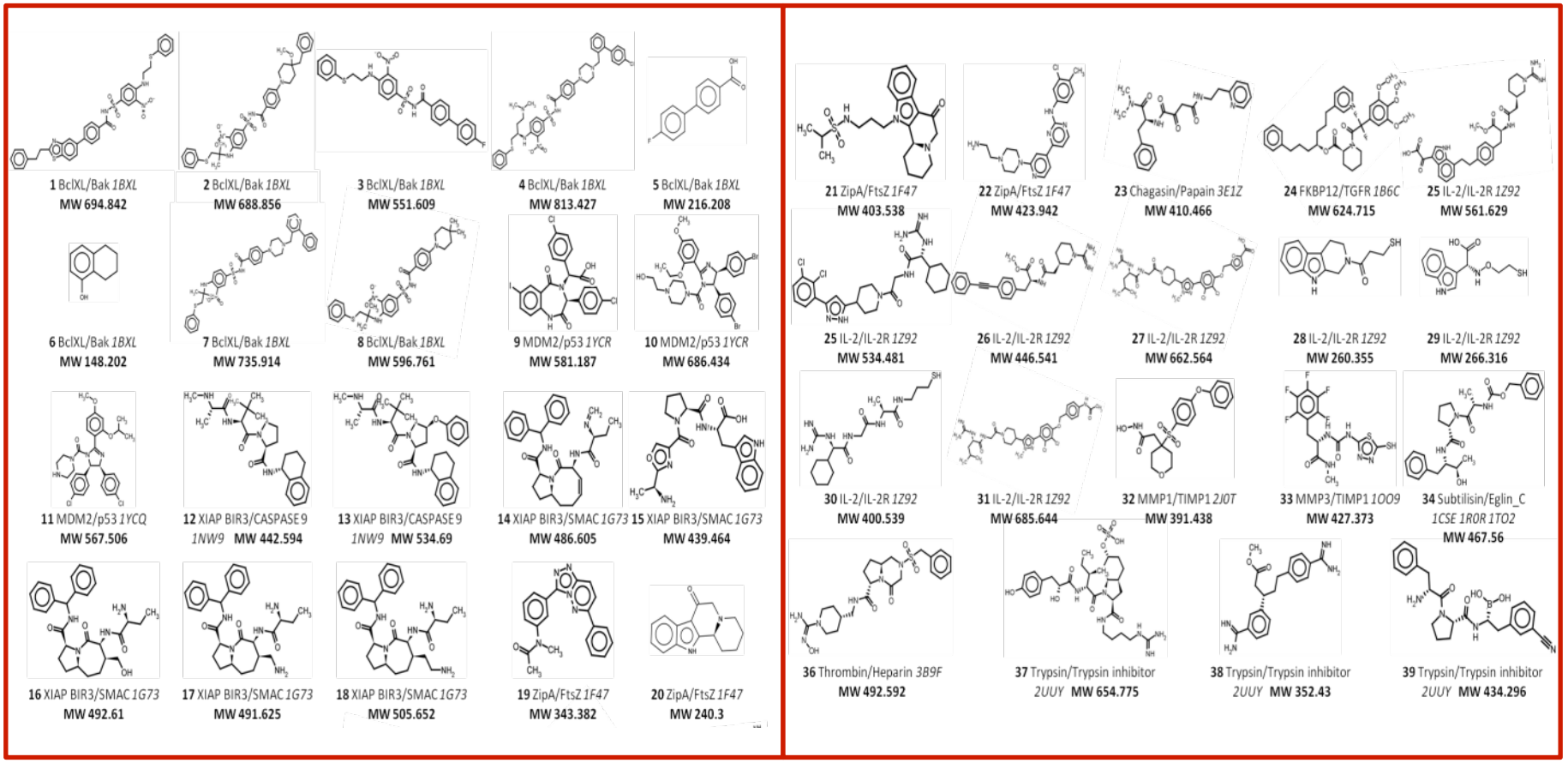
✓ **Neugebaueur - Klein (*J. Med. Chem. 2007*):**
25 compounds - Decision tree - 3 descriptors (Dragon, Talete)
Molecular Shape ; Presence of Ester function ; 3D structure of the molecule

✓ **Higueruelo / Blundell (*Chem. Biol. Drug Design, 2009*)**
104 molecules disrupting 17 PPIs, retrieved from 40 papers.
⇒ Timbal database: http://www-cryst.bioc.cam.ac.uk/timbal

✓ **Reynes – Sperandio - Villoutreix (*PLoS Comp. Biol. 2010*):**
66 diverse i-PPIs *vs.* 557 traditional drugs – Decision tree
Molecular Shape ; Multiplicity (multiple or aromatic bond)
⇒ Hit Profiler: http://www.cdithem.fr/ppiHitProfiler.php?lg=en

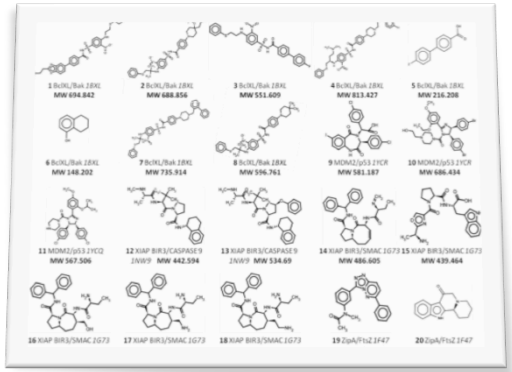
⇒ What about Success Stories with STRUCTURALLY validated PPIMs ?

Chemical Compounds as Modulators of PPIs



***Roche & Morelli (2010) Protein-Protein Interaction Inhibition** (2P2I): Mixed Methodologies for the Acceleration of Lead Discovery. In: Miteva M, editor. In silico lead discovery: Bentham. Chapter 7, p167-200.*

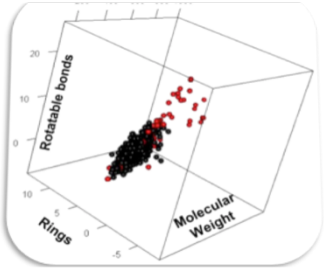
Chemical Compounds as Modulators of PPIs



39 confirmed Inhibitors

Comparison with a Set of Compounds From Several Libraries

Dragon molecular descriptors



PPI Modulators …

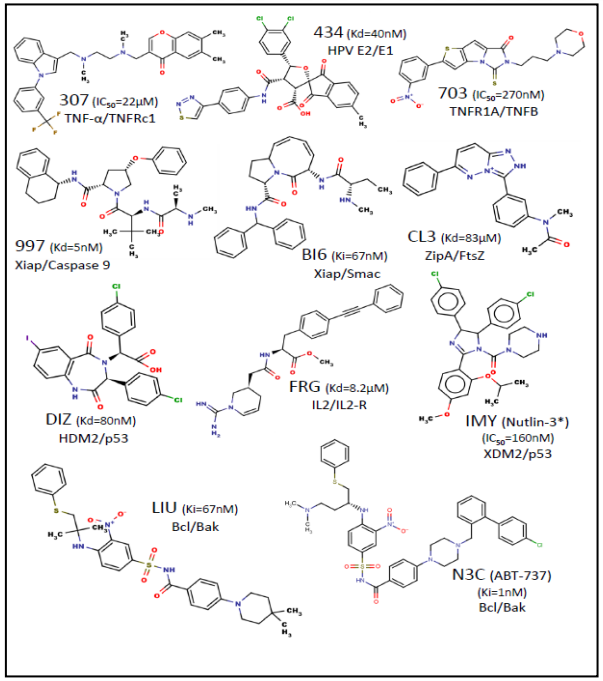
- Bigger (average Molecular Weight > 400 Da)
- More Hydrophobic (average alogP ~4)
- More Rings (~4 in average)
- More than 4 Hydrogen Bond Acceptors

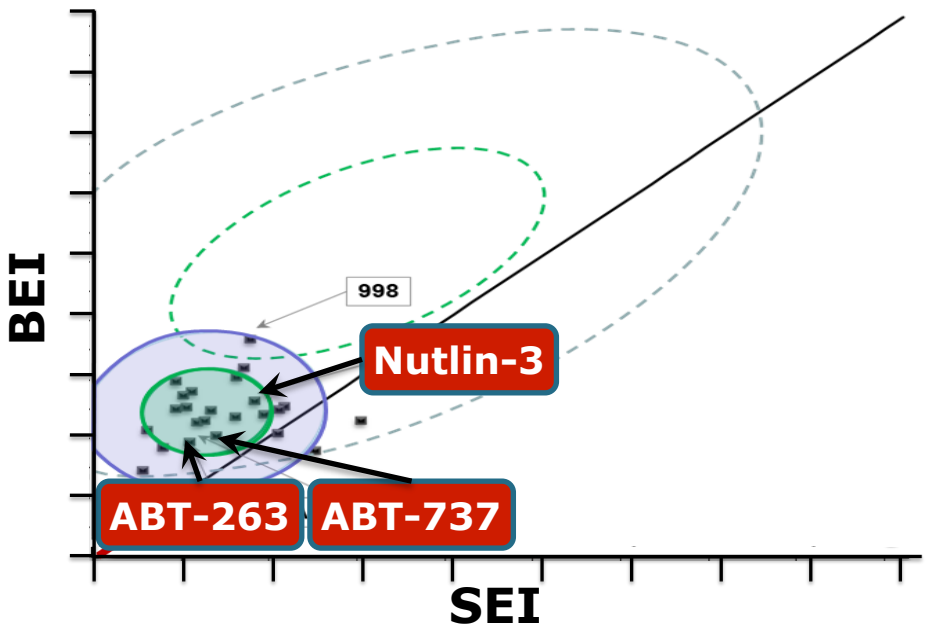
'Rule of 4' as a Guideline for PPI Inhibitors

>50% follow Lipinski Ro5

Morelli, X., Bourgeas, R., and Roche, P. (2011). Chemical and Structural Lessons from recent successes in Protein-Protein Interaction Inhibition (2P2I). ***Current Opinion Chemical Biology 15, 475-481.***

PPI Modulators: "Drug-like" Compounds ?





Abad-Zapatero & Metz JT 2005 *Drug Discov Today* **10**:464-469.
Ligand efficiency indices as guideposts for drug discovery.

$$BEI = \frac{\mathrm{pK_i\ or\ pK_d\ or\ pIC_{50}}}{\mathrm{MW}}$$

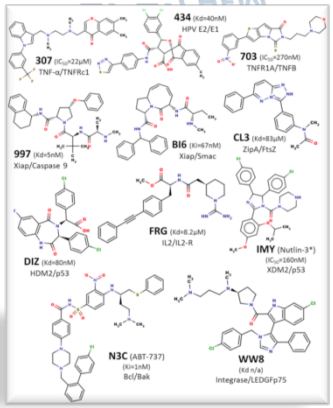
$$SEI = \frac{\mathrm{pK_i\ or\ pK_d\ or\ pIC_{50}}}{\mathrm{PSA}}$$

PPI Inhibitors Should not be Rejected for Their 'Low Probability to be Developed as Drugs'.

Morelli, X., Bourgeas, R., and Roche, P. (2011). *Chemical and Structural Lessons from recent successes in Protein-Protein Interaction Inhibition (2P2I).* ***Current Opinion Chemical Biology 15, 475-481.***

A Dedicated Tool to filter libraries: 2P2I$_{HUNTER}$

2P2I$_{CHEM}$



Tanimoto 0.8

Training set

Positive set
32 compounds

Negative set
1018 compounds

Dragon
11 molecular descriptors

Tanimoto 0.8

NCI Diversity

Support Vector Machine

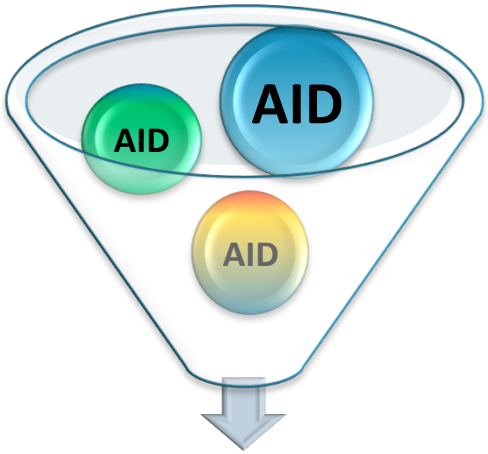
-Classification
-RBN Kernel
-5fold cross-validation
-30 repeats

Selection of External Validation Datasets

Available public source

PubChem BioAssay

600,000 AIDs



- Query "Protein-protein…"
- Secondary screening
- In *vitro* test
- No redundancy

2 high quality validation datasets

- AID 1496/*1438*
- AID 1531/*1896-1897*

Validation Bioassays

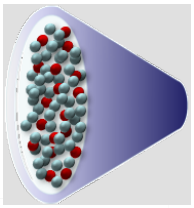
Inhibiting the binding between the RUNX1 Runt domain and Core Binding Factor β Subunit

AID	Tested	Active	Hit Rate	Assay
1496	215676	993	0.46	Primary Screen (FRET)
1438	**2224**	**45**	**2.02**	**Dose Response Confirmation**

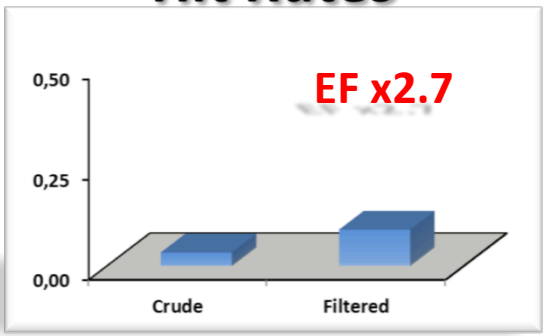
MEKK2-MEK5 interaction

AID	Tested	Active	Hit Rate	Assay
1531	289475	3276	1.13	Primary Screen
1892	5940	144	2.42	Single Concentration Confirmation Screen
1897	**185**	**93**	**50.27**	**Dose Response Confirmation**

AID 1531/1897: MEKK2-MEK5 Interaction

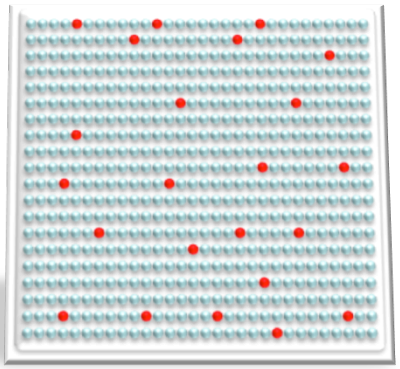


$2P2I_{RO4}$

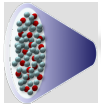


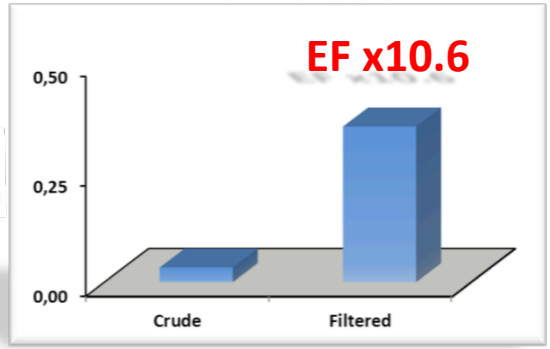
20% selected

AID1531



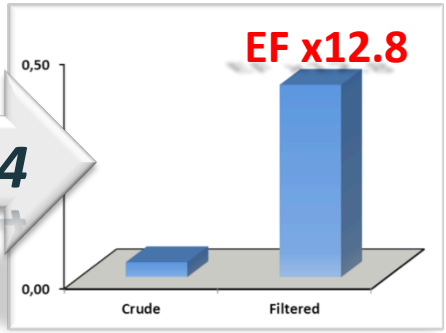
$2P2I_{HUNTER}$





3% selected

$2P2I_{HUNTER}$+Ro4

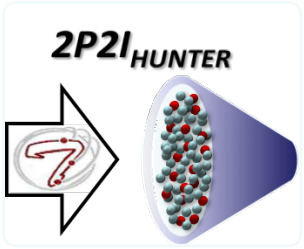


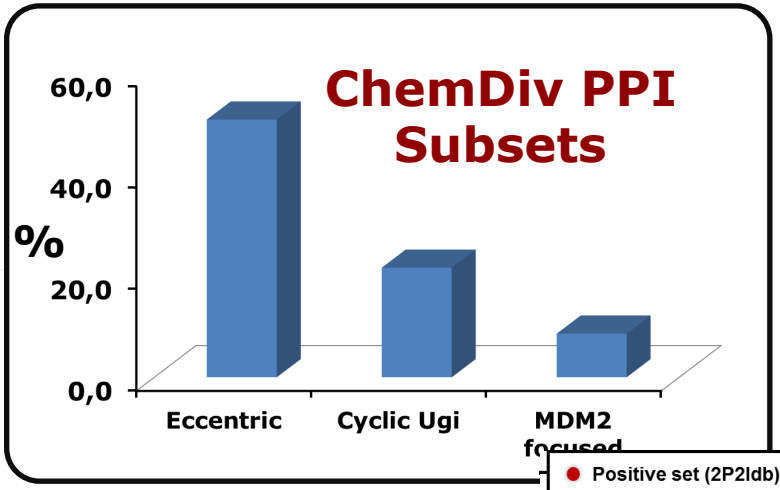
~2% selected

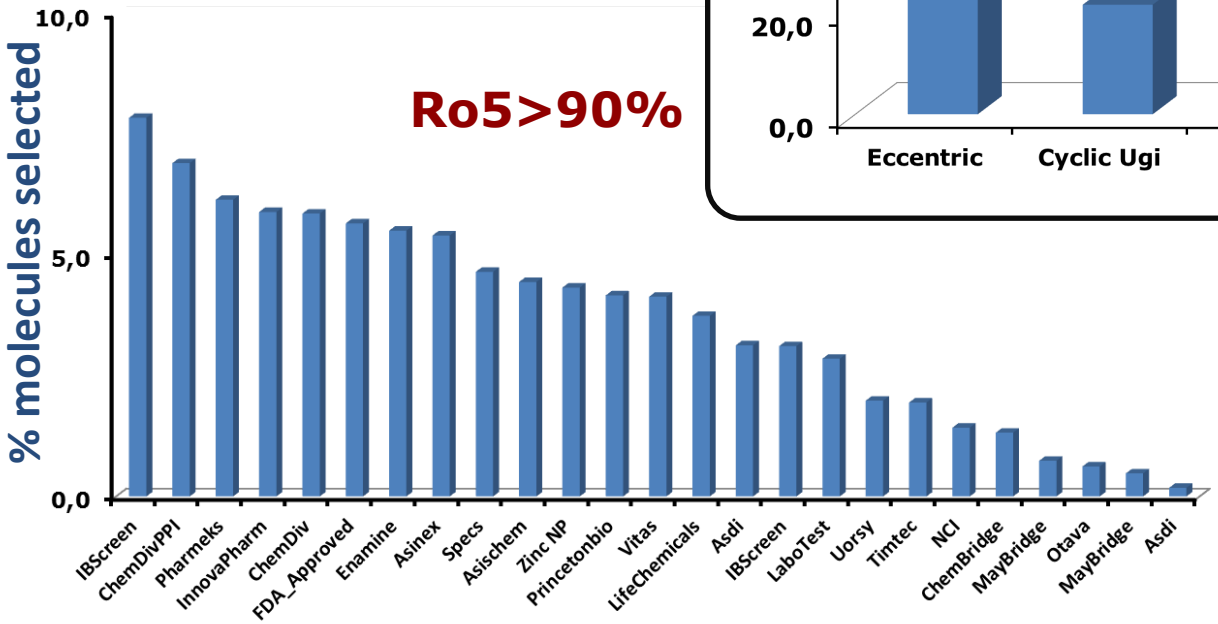
Example of a focused library dedicated to PPIs: 2P2I$_{DIV}$

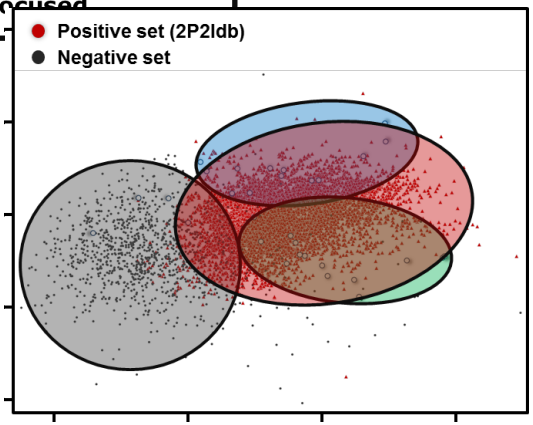
8 Millions cpds

Application to 25 Commercial Libraries





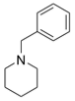
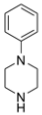
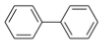


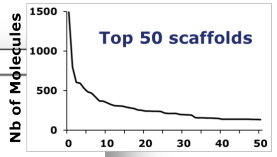


Example of a focused library dedicated to PPIs: 2P2I$_{DIV}$

In House Chemical Library 2P2I$_{CHEM}$
➢ 5-10,000 Compounds

- 233,727 compounds
- 141,088 unique compounds
- 42,100 scaffolds
- >22,000 with 'privileged structures'

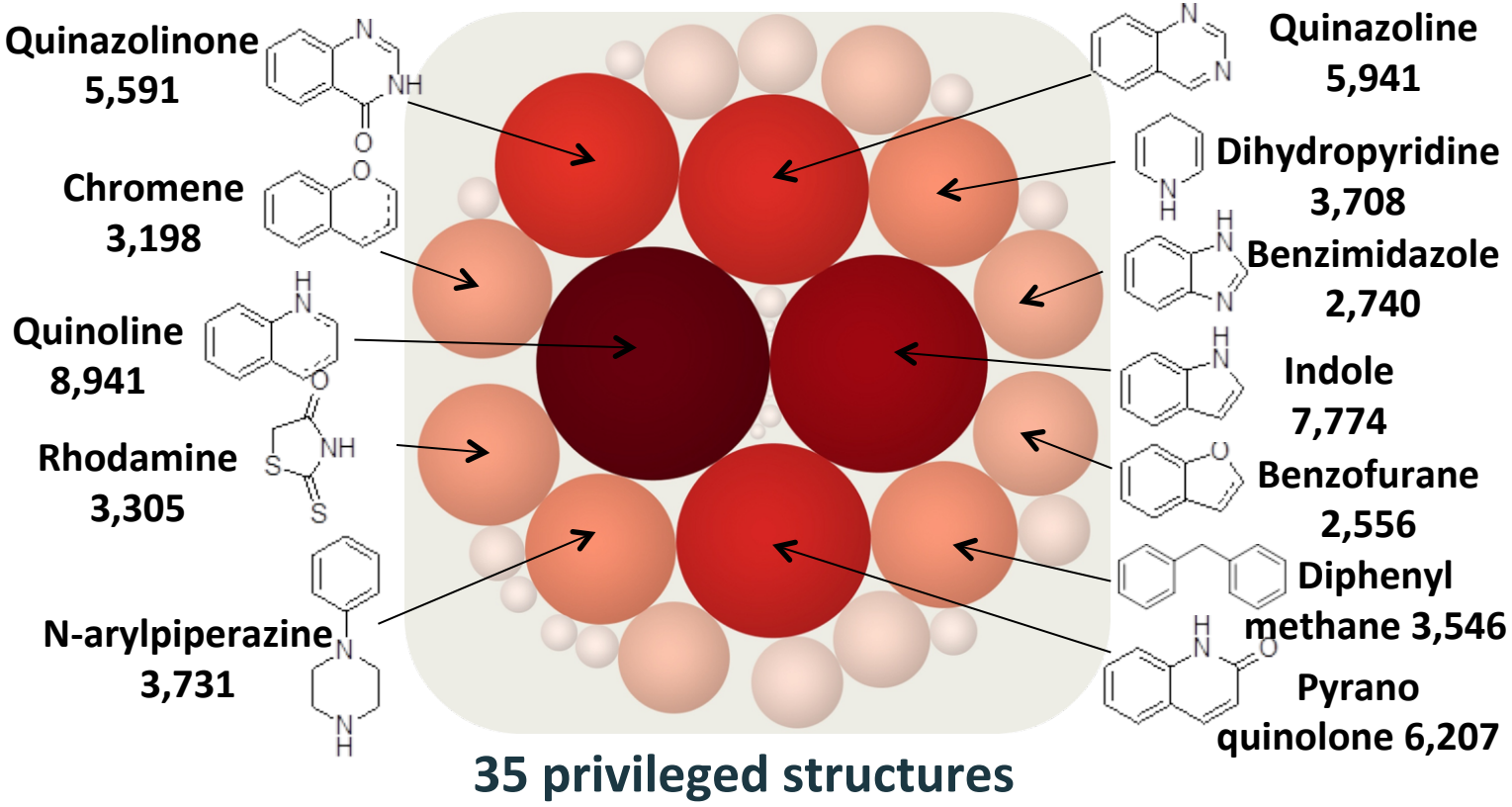
Privileged Structures	Structure	Nbre molécules	%
Quinazoline		110	0,08
Quinazolinone		3491	2,47
Quinoxaline		171	0,12
Indoline		4391	3,11
Benzofuran		2053	1,46
Chromone		882	0,63
Coumarine		1697	1,20
Benzylpiperidine		389	0,28
Arylpiperidine		280	0,20
Arylpiperazine		1313	0,93
Benzimidazole		310	0,22
Biphenyl		767	0,54
Quinoline		1515	1,07
Benzothiophene		99	0,07
Pyranoquinolone		5128	3,64



Privileged structures:
« a single molecular framework able to provide ligands for diverse receptors.
Evans *et al., J.Med.Chem., 1988 (Merck)*

Rules from Smythe (Chem. Rev. 2003) & Welsch (Curr. Opin. Chem. Biol. 2010)

Example of a focused library dedicated to PPIs: $2P2I_{DIV}$



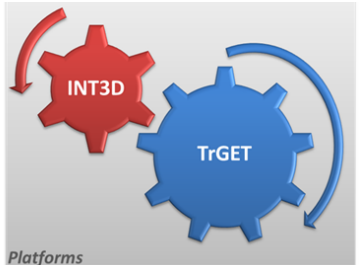
35 privileged structures

=> 8,000 compounds : $2P2I_{DIV}$

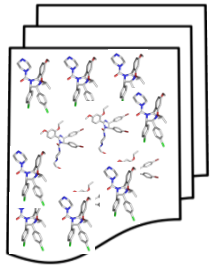
=> 1731 with Fsp3 > 0.4 (average = 0.5): $2P2I_{3D}$

Perspectives / Example with Workflow

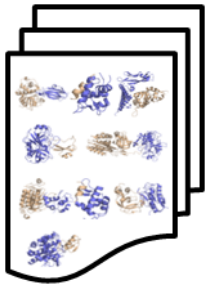
2P2I$_{DIV}$



2P2I$_{TARGET}$



2P2I
In silico



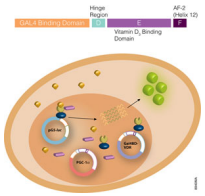
Focused Library of PPI inhibitors

~8000 compounds

Hit Compounds Selection

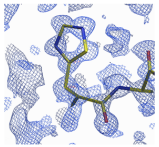
10 "Druggable" PPI Targets Selected from Cancer Center

Validation, Characterization

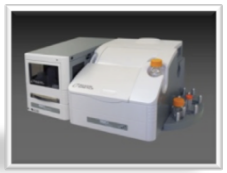


BRET / HTRF

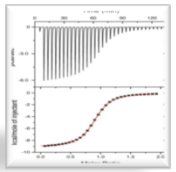
NMR



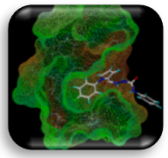
X-ray



Interferometry



ITC

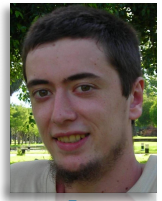


Hit2Lead

Special Thanks to ...

MJ Basse
Database Management

PostDoc
V Hamon



PhD
R Bourgeas

S Bouzidi

G Gyurik
Undergraduates

P Roche
Molecular Modeling
Chemoinformatics

S Combes & JM Brunel
Organic Chemistry

S Betzi
Structural Biochemistry
(X-Rays, NMR, ITC)

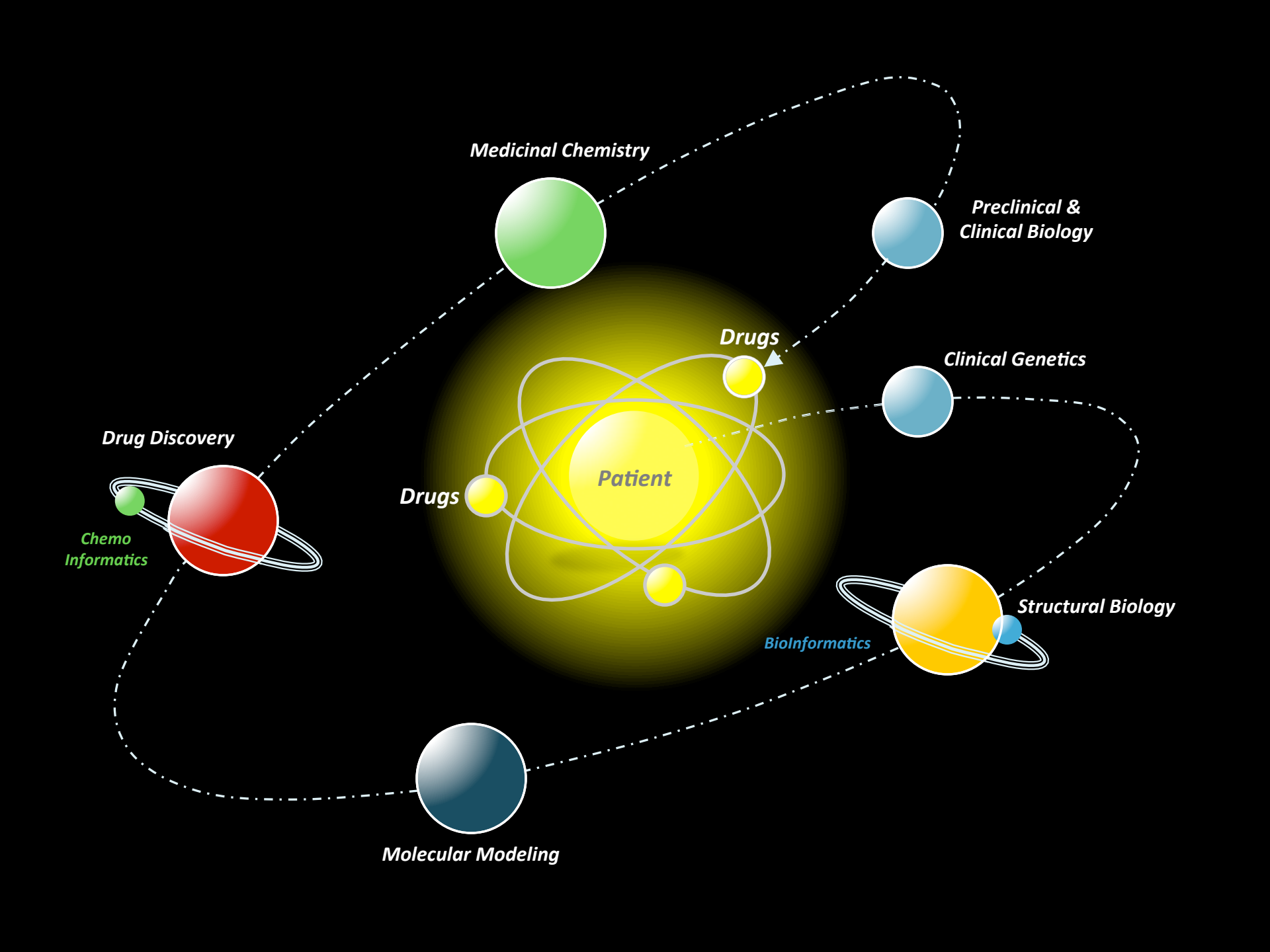
Laboratory integrative Structural & Chemical Biology

Directors: Xavier Morelli & Yves Collette

" Innovative approaches to tackle the refractory space of Protein-Protein Interactions (PPIs) and their implication in Cancer Cell Signaling and Epigenetic processes"

http://iscb.cnrs-mrs.fr/

THANK YOU !!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