About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

In silico screening to discover inhibitors of protein-protein interactions targeting angiogenesis

Maria A. Miteva

Molécules Thérapeutiques *in silico* (MTi)
Inserm U973 – University Paris Diderot
Team "VLS, PPI & ADMET in silico"

Valencia, August 25, 2015

Modulate PPIs by low MW compounds

- Estimated 150.000 to 650.000 PPIs insufficiently exploited

  (Stumpf et al PNAS 2008)

- Many PPI associated to specific diseases *(Wells & McClendon Nature 2007)*

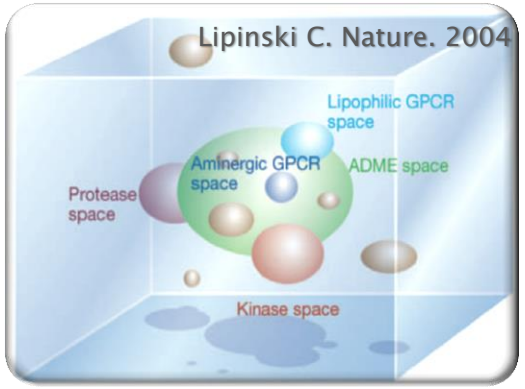
  Growing interest of industry to low MW PPI modulators

  20 LMW PPI cmpds are in phase I to III clinical trials;
  Expected sales worldwide of over $800 million/year within 4 years

  (Mullard Nature Rev Drug Discov 2012)

- It is difficult to modulate PPI with a small molecule:
  - ✓ PPI interfaces: flat, large, flexible
  - ✓ no sufficient data on chemical space to modulate PPI

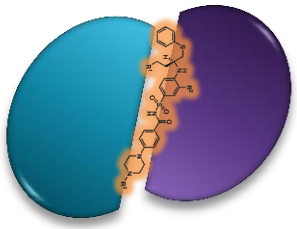
NO SUFFICIENT KNOWLEDGE ON KEY PHYSICO-CHEMICAL CHARACTERISTICS OF LOW MW PPI MODULATORS COMPARED TO OTHER PROTEIN FAMILIES !



Modulation of PPIs

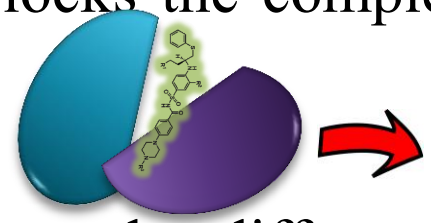
Examples of modulation

- **Orthosteric inhibition:**

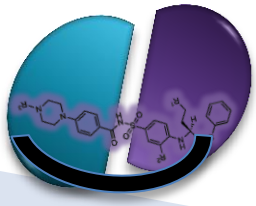


- **Allosteric inhibition**: (conformation, dynamics)

- **Interfacial binders**: the ligand binds to a pocket that is transiently formed and locks the complex in a nonproductive conformation



- **Stabilization** of PPIs (here also different mechanisms)



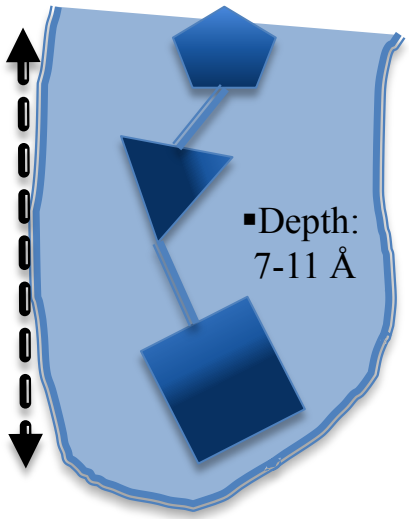
•*Jin et al. Annual Rev Pharmaco Toxico, 2014*

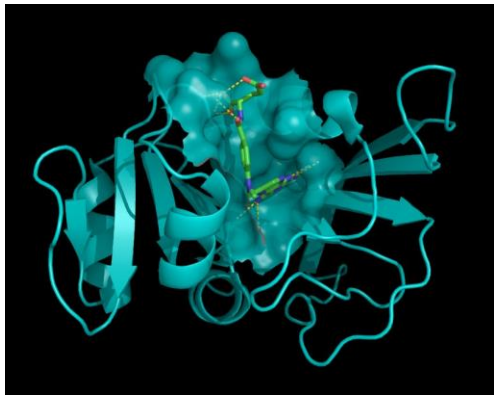
•*Ottmann et al. Angew. Chem. Int. Ed. 51, 2012*

•*Zhang et al. Plos One 2014 9:e110884*

Small-molecule (LMW) binding pockets

Cmpds have been essentially developed for regular pockets

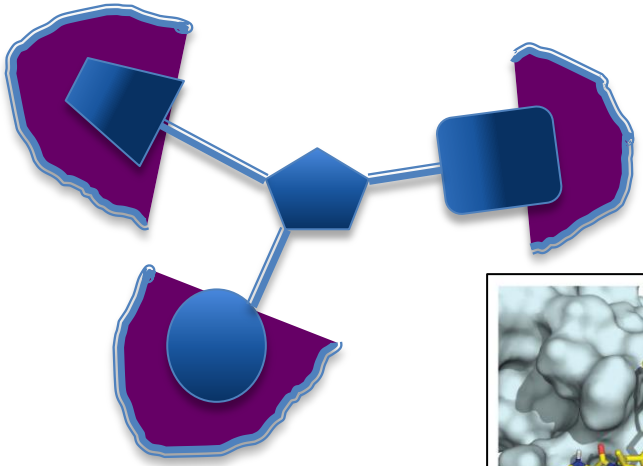


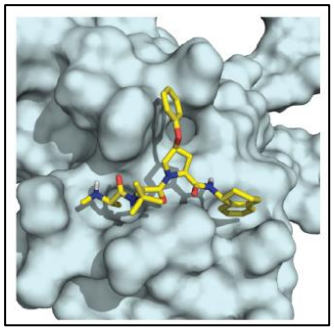


Dihydrofolate reductase methotrexate

Enzyme pockets

- Hydrophobicity: 60 to 80 %
- Surface area: 300-600Å^2
- Volume (smaller for allosteric): ~500 Å^3





1TFT: Xiap-caspase 9

"PPI pockets"

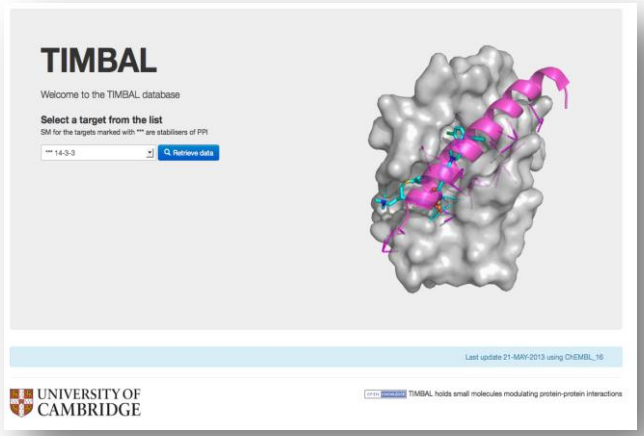
- In general 3 to 5 subpockets, each ~ 50 Å^3
- Transient pockets
- Interface regions likely to be ligandable are more predisposed to surface pocket formation

Perot et al. Drug Discov Today 2010
Li et al, J Mol Graphics & Model, 2013
Gao & Skolnick, Plos Comput Biol, Oct 2013

Fuller et al., Jackson, DDT 2009
Eyrisch & Helms, 2007
Karanicolas et al, Plos Comput Biol, 2013

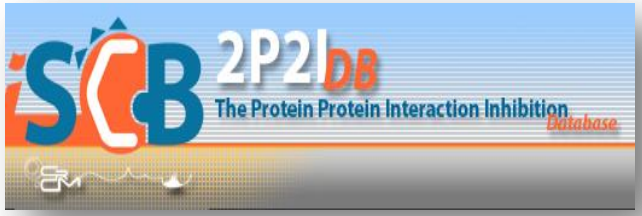
LMW Modulators of PPI :Databases

Need data to learn :



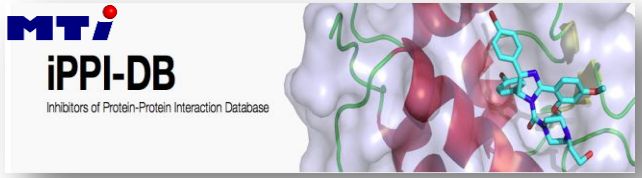
TIMBAL : small molecules that modulate PPI
created in 2008, by manually curating information;
Now automated searches on the ChEMBL database (about 8000 cmpds)

Higueruelo et al, 2009
Blundell Lab, Chem Biol & Drug Design



$2P2I_{DB}$ **:** structures of PPI complexes with known small molecule inhibitors; ~200 small molecule inhibitors (**hand-curated)**

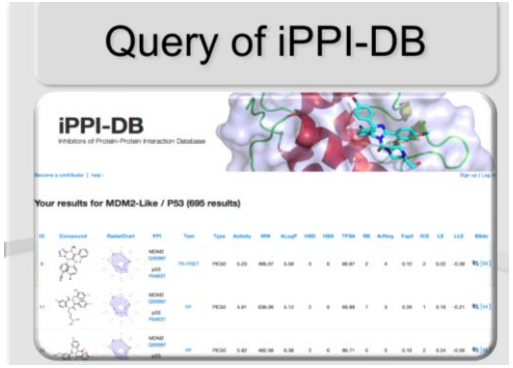
Basse et al, NAR, 2013
Bourgeas et al, PlosOne 2010, (Morelli's lab)



iPPI-DB : 1650 (soon ~2000) non-peptidic inhibitors across 13 families of PPI (**hand-curated**)

Labbé et al. Drug Discov Today 2013
Villoutreix et al. Mol Inform 2014

iPPI-DB: A Unique Database of small-molecule modulators of PPI



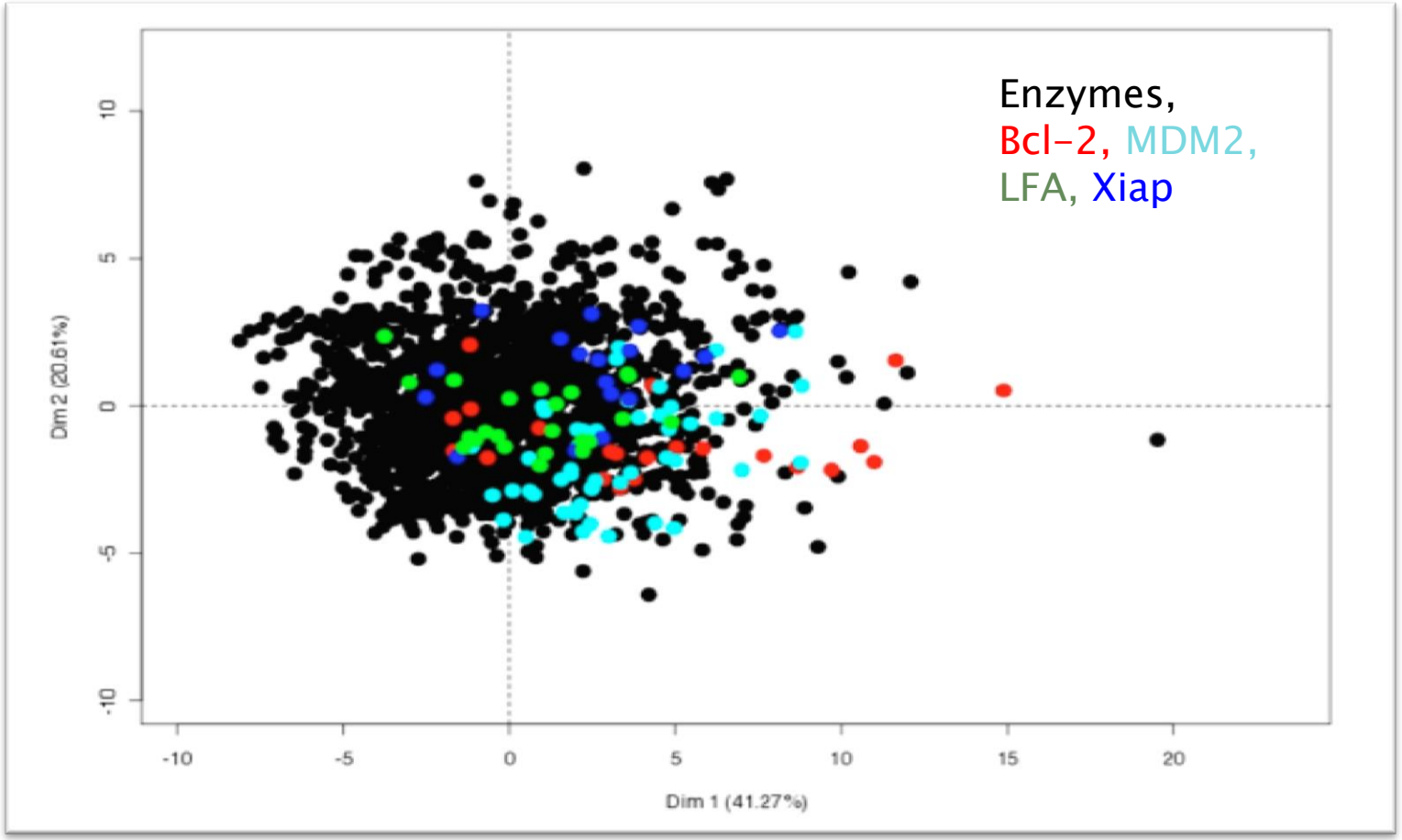
- **Source**
  - Litterature (PubMed), world patents
  - Manually curated by a medicinal chemist
- **Criteria**
  - Activity : IC50, Ki, Kd, EC50 --> < 30 µM
  - Absence of reactive or promiscuous groups
  - Rule out peptides (Absence of 3 continuous peptide bonds) & macrocycles

Labbé et al. Drug Discov Today 2013

Nb of iPPI	Nb of assay data	Nb of PPI	Nb of References	
1650	2435	31	117	84 articles
				33 world patents

http://www.ippidb.cdithem.fr

Chemical Space of i-PPI



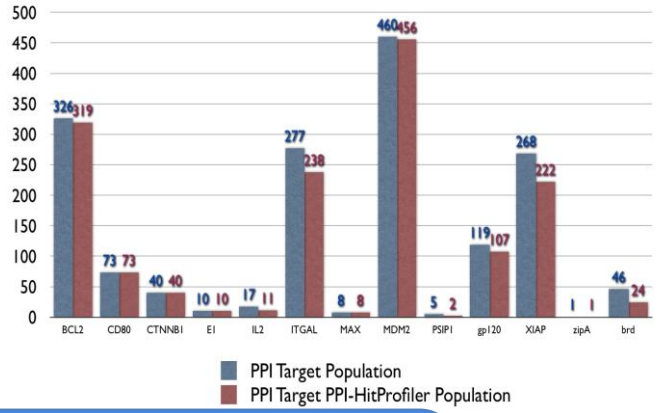
- PPI modulators do not cover the chemical space of enzyme inhibitors:
  ? Need of new PPI modulators

Sperandio et al. Plos Comput Biol 2010
Villoutreix et al. Mol Informat 2014

iPPI-Focused collections

Original Filter: PPI-HitProfiler

- Specific molecular shape
- Multiple bonds and aromatic rings
- Validated on the experimental binding data of 500,000 cmpds from PubChem BioAssay and 11 PPI targets



iPPI-lib HitProfiler
http://www.cdithem.fr/getPPIHitProfiler.php or via FAFDrugs3
Sperandio et al. Plos Comput Biol 2010

iPPI-lib

3 mln PubChem cmps → FAF-Drugs3 → PPI-HitProfiler → FCFP_4 Tanimoto 0.3

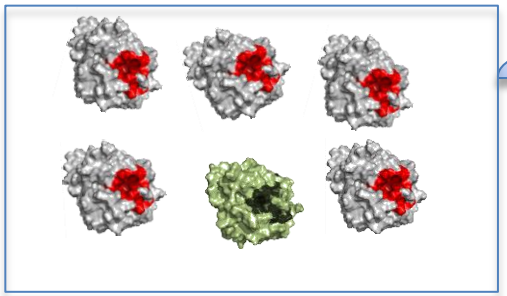
50,000 drug-like i-PPI like molecules

iPPI-lib & MTiOpenScreen web-server
http://bioserv.rpbs.univ-paris-diderot.fr/services/MTiOpenScreen/

Labbe et al. NAR 2015

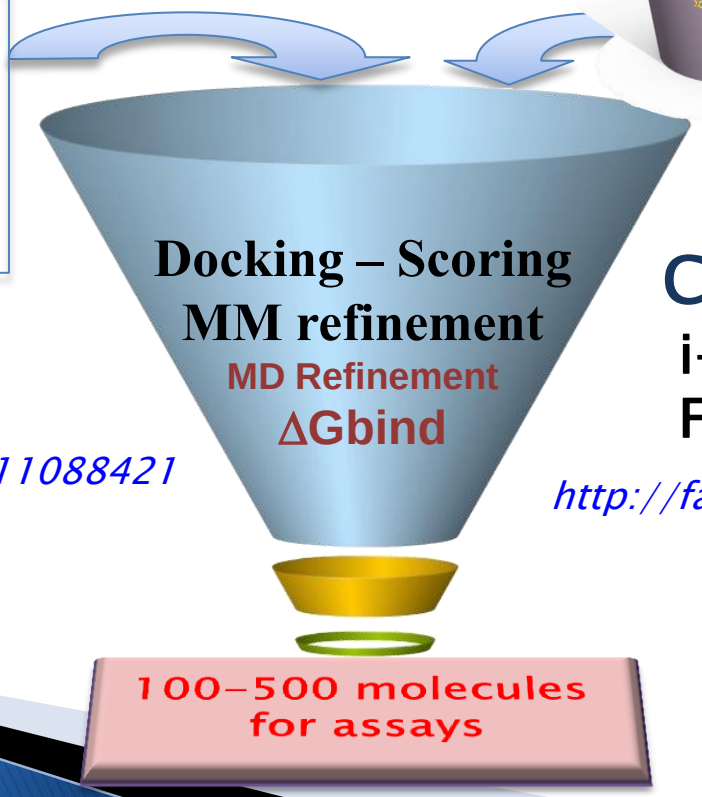
Our Structure-based VS approach

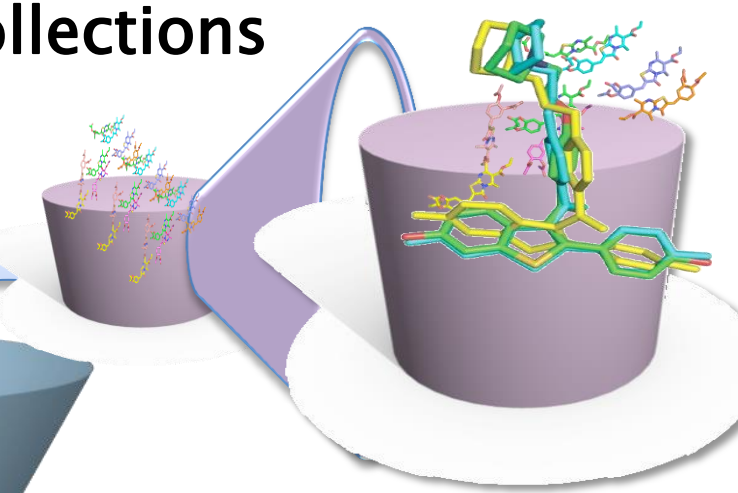
- ✓ Protein receptor flexibility
- ✓ ADME-Tox filtering
- ✓ Focused i-PPI compound collections



Multiple Protein Conformations

Zhe et al. Plos One 2014 , 9:e11088421





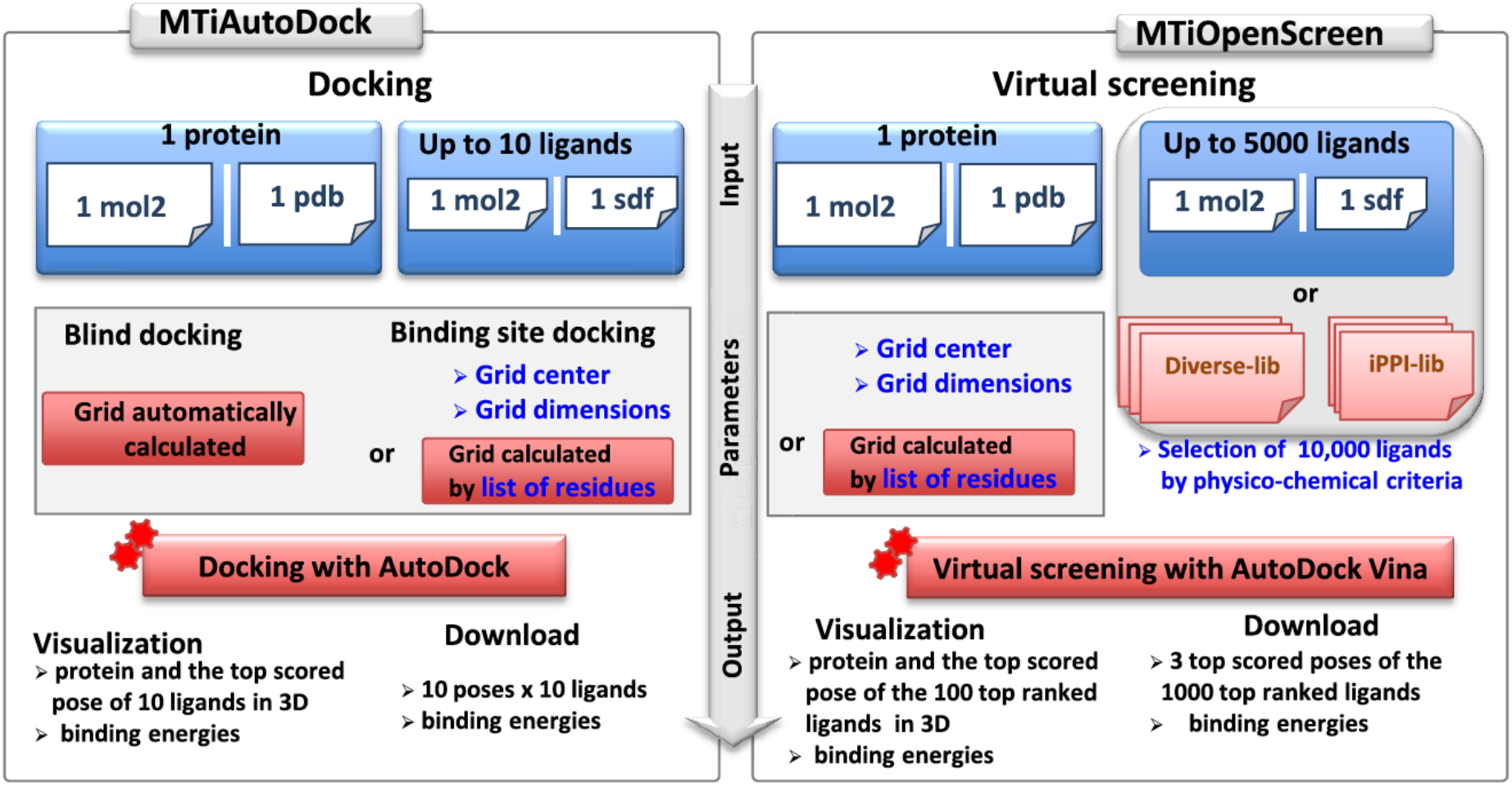
Compound collection

i-PPI filters, ADME-Tox: FAFDrugs3

http://fafdrugs3.mti.univ-paris-diderot.fr

Lagorce et al. NAR 2015

MTiOpenScreen web-server



http://bioserv.rpbs.univ-paris-diderot.fr/services/MTiOpenScreen/

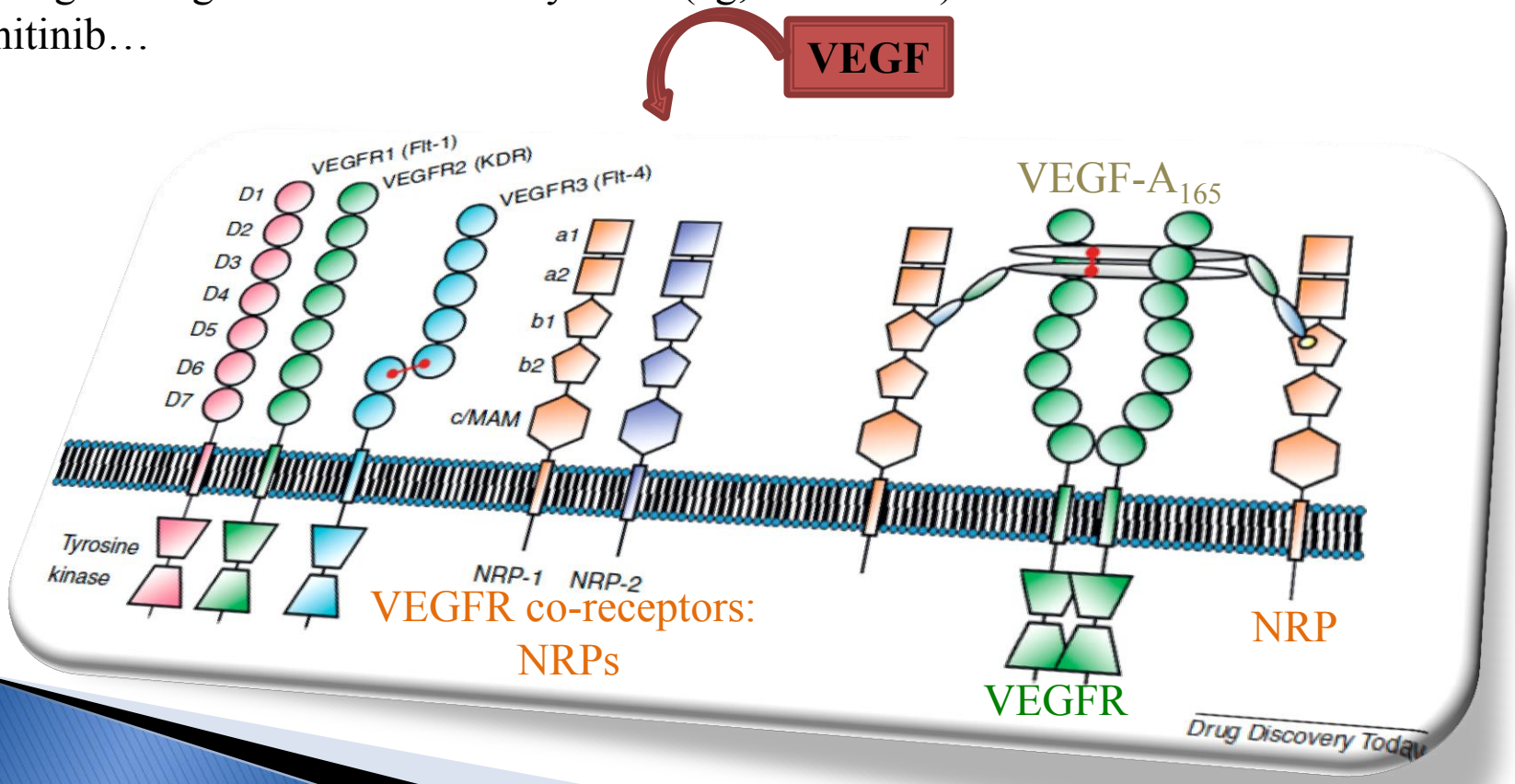
Labbe et al. NAR 2015

Inhibiting protein-protein interactions in angiogenesis

✓Targeting angiogenesis could be of interest to complement chemotherapeutic approaches to treat cancer

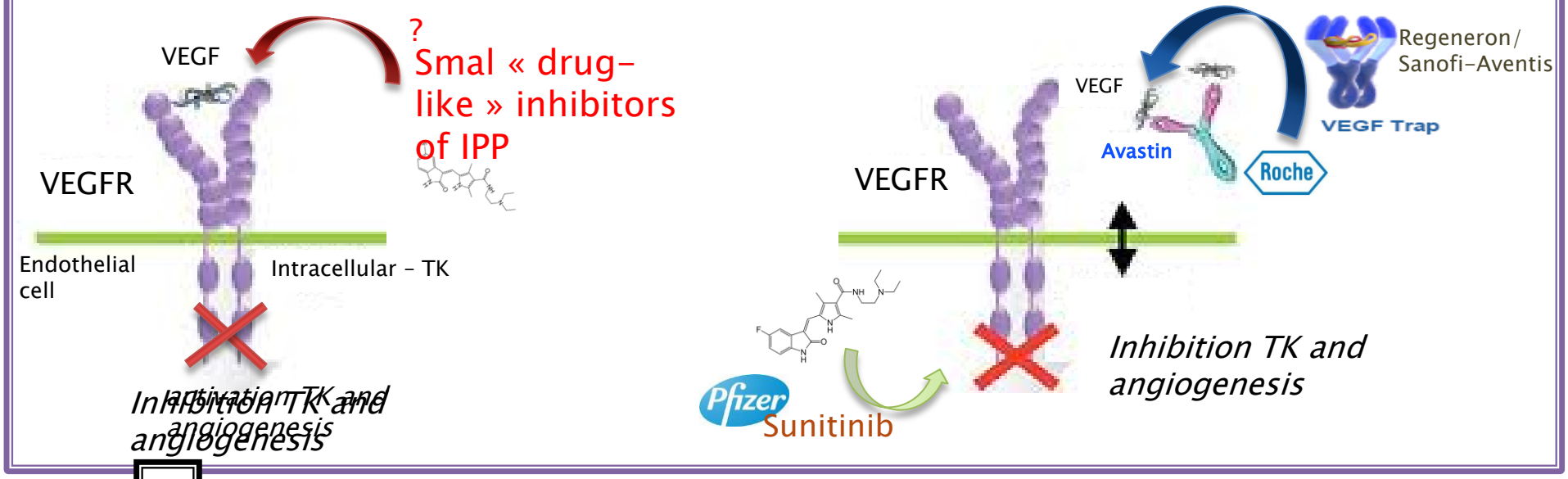
✓A pivotal pro-angiogenic signalling molecule is VEGF-A, which promotes proliferation, survival, migration…

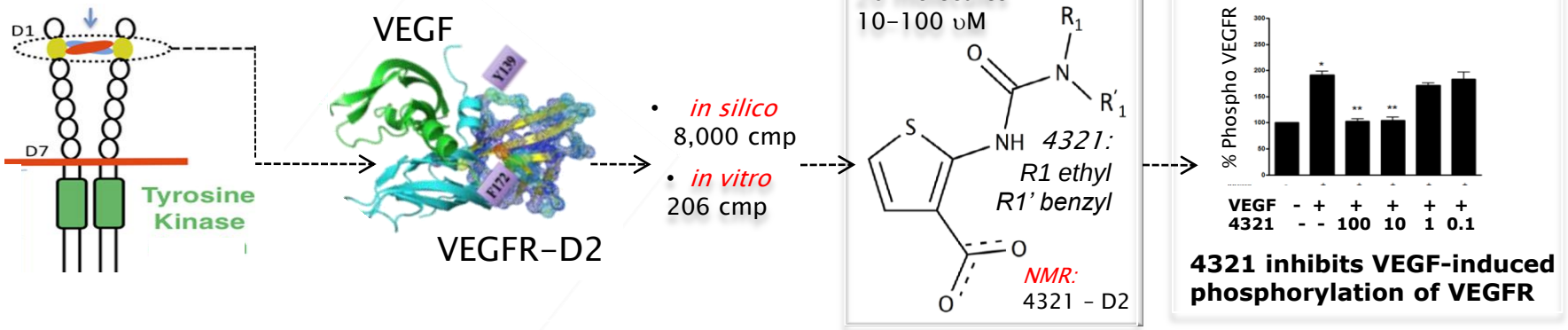
✓Drugs acting here are essentially mAb (eg, Avastin…) and kinase inhibitors: sorafenib, sunitinib…



Djordjevic and Driscoll, DDT 2013

Anti-angiogenic drug-like molecules blocking VEGF-VEGFR





Gautier et al. Chem Biol 2011

Anti-angiogenic drug-like molecules blocking VEGF-NRP

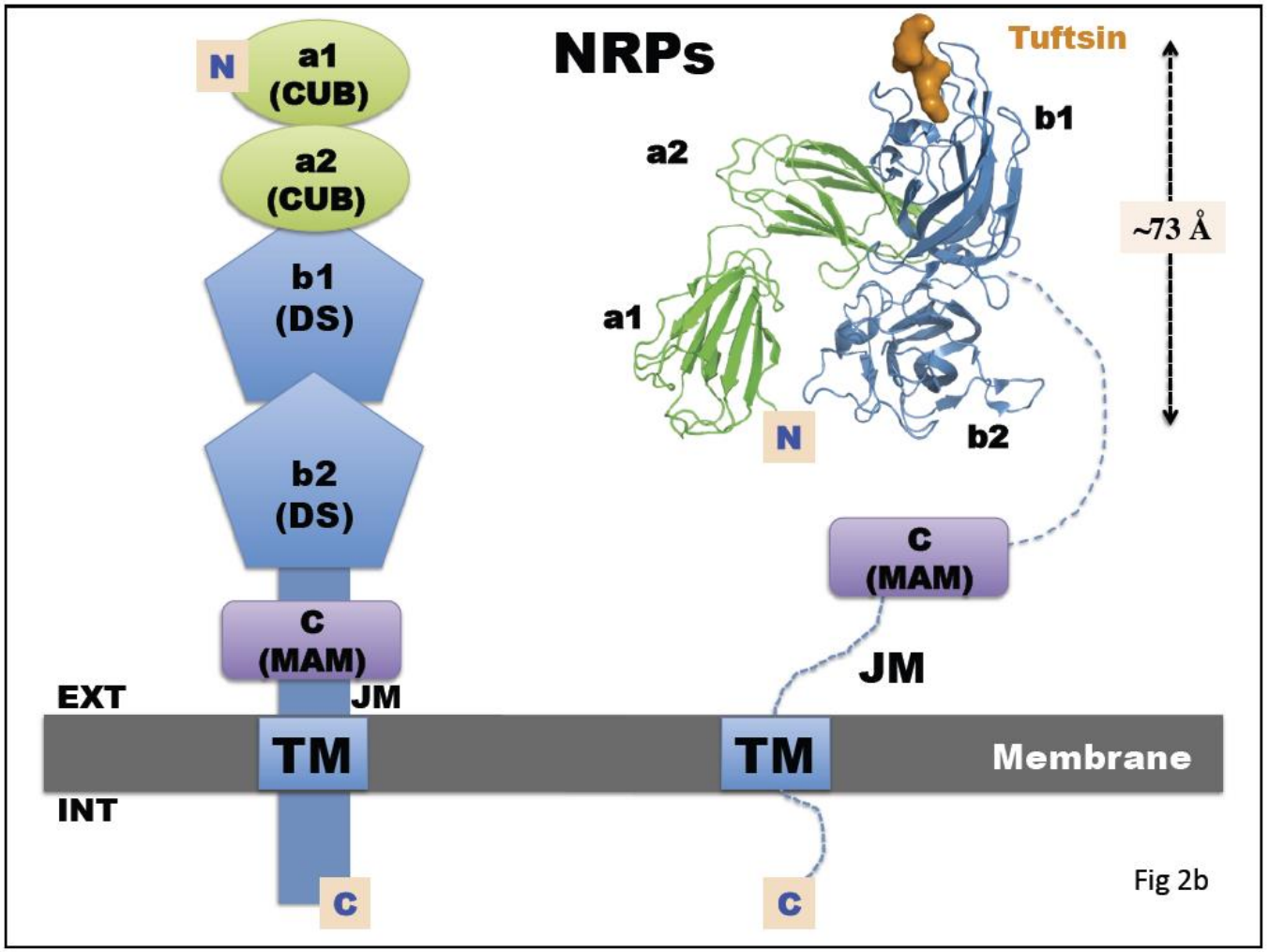
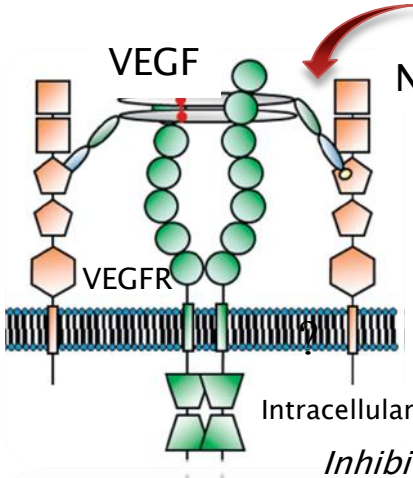
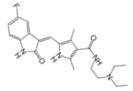


Fig 2b

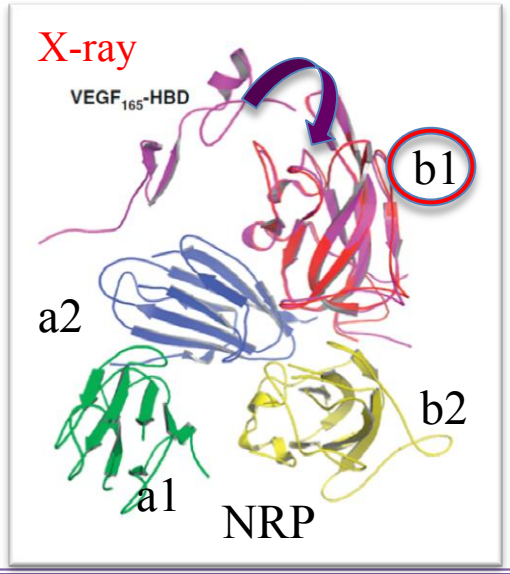
Anti-angiogenic drug-like molecules blocking VEGF-NRP

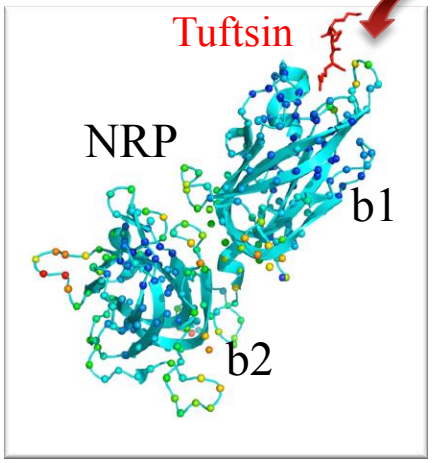


? Smal « drug-like » inhibitors of IPP

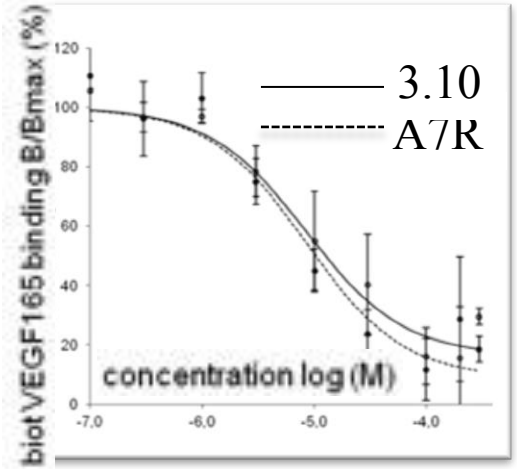


Inhibition of VEGFR dimerization and angiogenesis

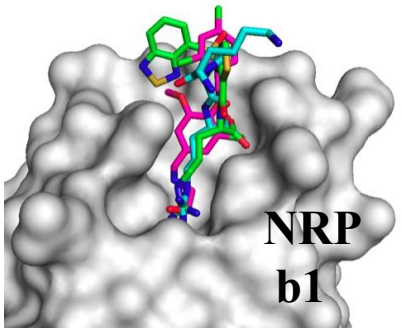




- SBVS
  MS-DOCK, SF
  500,000 cmp
- *in vitro*
  508 cmp
- *Ligand Info*
  70 cmp
- *in vitro*
  133 cmp



EG00229 (X-ray)
Tuftsin (X-ray)
Our cmp 3.10 (docking)



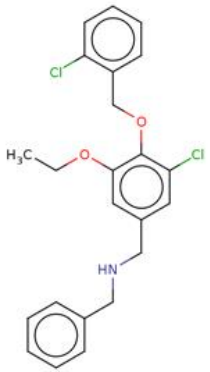
New scaffold: 4 cmpds with <4 microM affinity to NRP

Starzec et al. Bioorg Med Chem. 2014

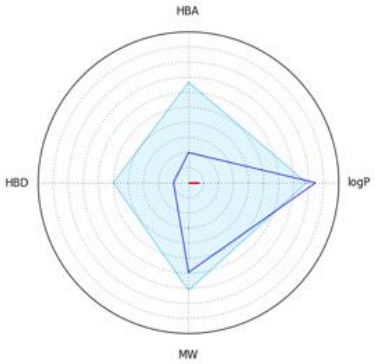
Anti-angiogenic drug-like molecules blocking VEGF-NRP

K_i: 11 micro-M; log P: 5.9; MW: 453; LE: 0.2, PPI-hit-Profiler: yes (FAF-Drugs3 server)
Some other cmpds have better physchem properties…For the time being, proof of concept studies

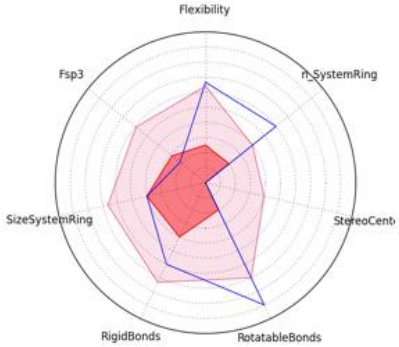
2D Structure



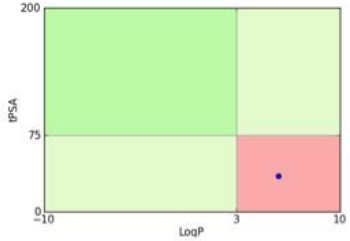
PhysChem Filter Positioning



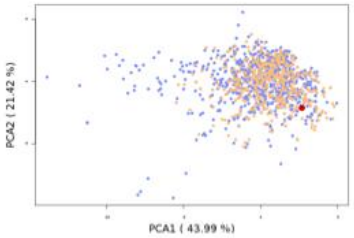
Compound Complexicity



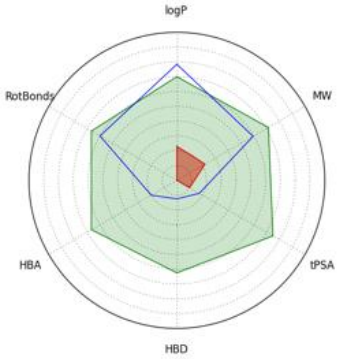
Pfizer 3/75 Rule Positioning



Oral Property Space



Oral Absorption Estimation



Oral Bioavailability

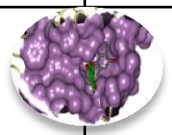
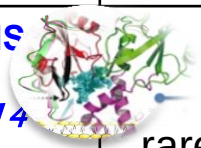
- Lipinski RO5
- Veber Rule
- Egan Rule
- Bayer Oral Physchem Score

Drug Safety Profiling

- GSK 4/400 Rule
- Pfizer 3/75 Rule
- Phospholipidosis Non Inducer
- Lilly MedChem Rules : PASS

http://fafdrugs3.mti.univ-paris-diderot.fr

Success stories are growing rapidly !

Drug Target	Diseases	Docking software	Drugs / hits
HIV integrase ***McCammon group, J Med Chem, 2004***	AIDS	AutoDock MRC Relaxed scheme	**Isentres (Merck)**
Mycobacterium tuberculosis HisG ATP transferase ***Cho et al. J Med Chem 2008***	tuberculosis	GOLD, FlexX	**IC50=4 uM**
Insulin-like Growth Factor-1 Receptor (RTK) ***Liu et al. J Med Chem 2010***	cancer	Receptor-based pharmacophore, Glide XP	**IC50=0.05 uM**
Factor V/VIII – membrane interactions ***Segers et al. PNAS 2007*** 	coagulation system, thrombosis	FRED, Surflex, LigandFit	**IC50=3.5 uM**
Enzymes: CDC25, proteasome,.. ***Montes et al. J Chem Inf Model 2008*** ***Maréchal et al. Curr Med Chem 2013 …*** 	cancer	FRED, Surflex, LigandFit	**IC50=13 uM**
PPI: SYK kinase, VEGFR, NRP, SMS ***Starzec et al. Bioorg Med Chem. 2014*** ***Zhang et al. Plos One 2014 …*** 	allergies, cancer, rare diseases	MS-DOCK, MD Surflex, Vina	**IC50= 4 uM**

Conclusions

- Structure-based VS methods are well established to identify new hits
- Importance of ADME-Tox filtering of compound collections
- PPI modulators focused compound collections
- Protein flexibility consideration

Acknowledgements

Team "Virtual screening, PPI modulators – ADMET"

- Dr. Olivier Sperandio
- Dr. David Lagorce
- Céline Labbé (Engineer)
- Isabella Guedes (*PhD student*)
- Mélaine Kuenemann (*PhD student*)
- Dr. Zhe Zhang (*former PhD student*)
- Dr. Virginie Martiny *(former PhD student)*
-
- Dr. Pierre Tuffery (team Peptide design)
- Dr. Bruno Villoutreix (Dir. MTi)

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- Pr. C. Garbay (Univ. Paris Descartes)
- Dr. A. Starzec (Univ. Paris 13)
- Pr. G. Perret (Univ. Paris 13)
- Dr. D. Perahia (ENS Cachan)

- Pr. E. Alexov (Univ. Clemson, US)
- Dr. Ikeguchi (Josay Univ., Japon)
- Pr. P. Carbonell (Univ. Manchester)
- Pr. J. Baell (Univ. Melbourne)
- Dr. T. Pencheva (Bulg Acad Sci)
- Pr. I. Pajeva (Bulg Acad Sci)
- Pr. A. Isvoran (West Univ. Timisoara)

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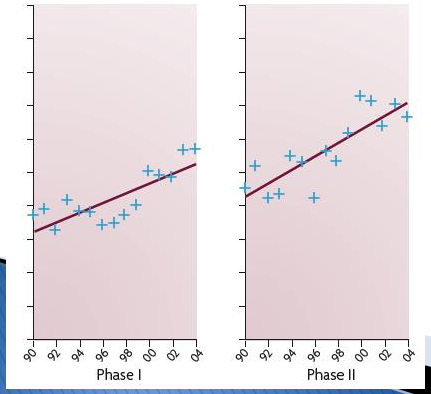
Chercheur en santé depuis 1964
Health research since 1964

THANK YOU

Conclusions

- Today about 20 LMW PPI cmpds are in phase I to III clinical trials. **Expected sales worldwide (to start with) of over $800 million/each year within 4 years**
- In **phase I**, latest generation of PPI modulators (developed between 2005-2012) seem to have **82% probability of making it to the next phase** compared to 54% for all NMEs, and for **phase II**, the probability of success seems to be **57%** for PPI modulators **compared to 34%** for all NMEs (Phase III can not be evaluated at present due to small sample size)

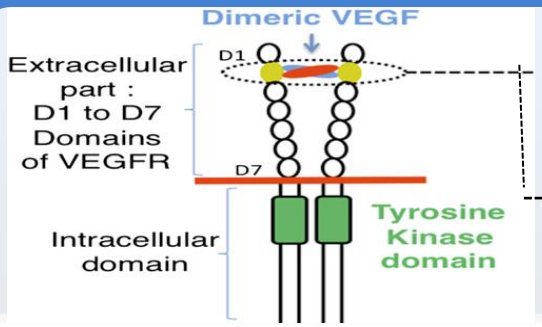


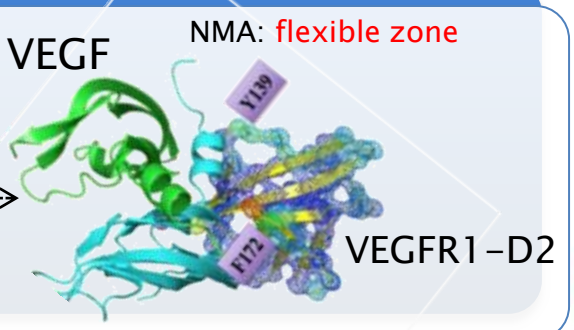
Trends in attrition rates of drug development projects. Data are for projects started between 1990 and 2004 in the United States, Europe and Japan

Some hope with PPI modulators ? Some PPI targets seem much more promising than some of the ~500 regular targets currently investigated…with over 300,000 PPIs in human, there is a lot to do !

- *Meier et al DDT 2013*
- *Nat Rev Drug Discovery, June 2011, Vol 10*

We discovered the first anti-angiogenic drug-like molecules blocking VEGF-VEGFR

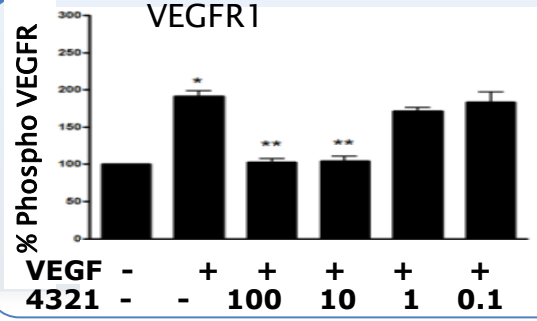




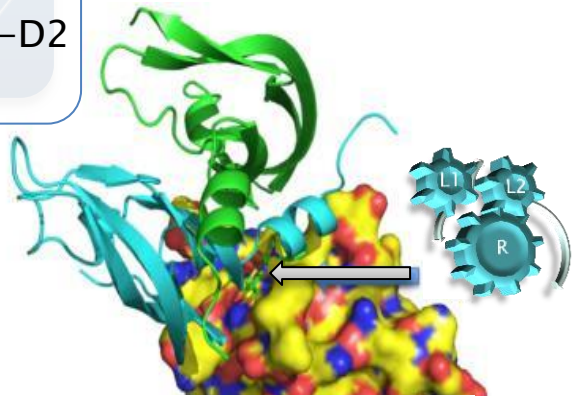
8,000 mols National Chemical library CERMN docking Surflex

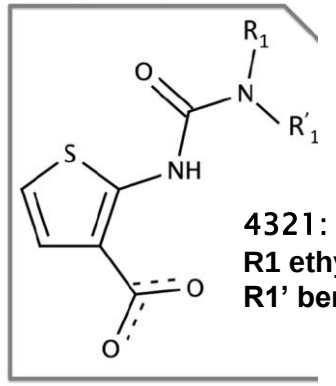
206 mols *in vitro* displacement of VEGFR

20 actives IC50 < 100 μM
10 actives IC50 ~10-20 μM



4321 inhibits VEGF-induced phosphorylation of VEGFR
HUVEC,WT blot





4321:
R1 ethyl
R1' benzyl

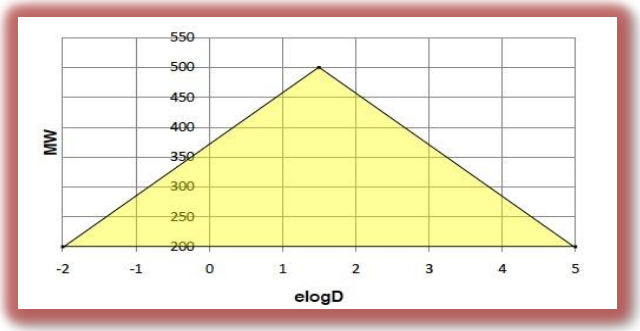
Binding of 4231 into D2 domain was validated by NMR experiments

Gautier, Miteva et al. Chem Biol 2011

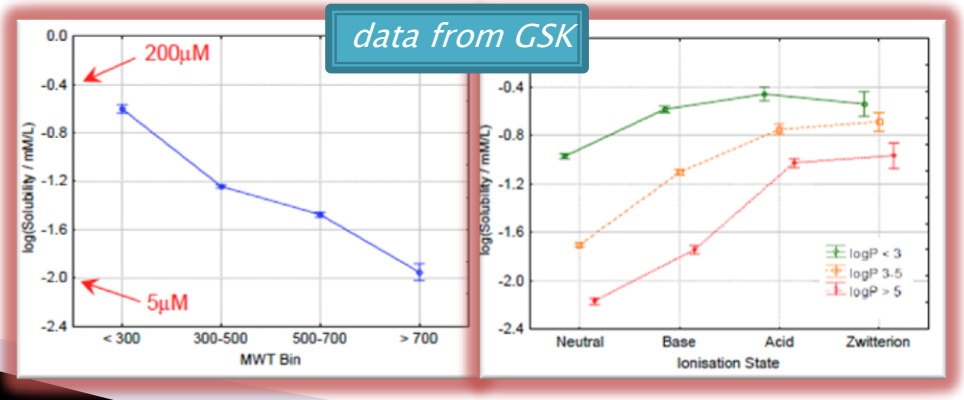
ADME-Tox Prediction

- **Lipinski's rule of 5** for oral absorption (1997), but new rules are also for toxicity
- **Veber's rule** (2002) for oral absorption: nb of rotatable bonds, TPSA, …
- **GSK rule of 4** (2009): MW < 400 and clog P < 4 to reduce ADMET problems
- **Pfizer 3/75** (2008): significant reduction of toxicity *in vivo* when clogP <3 and TPSA >75 Å^2 (toxicity, off-target, CYP, hERG)

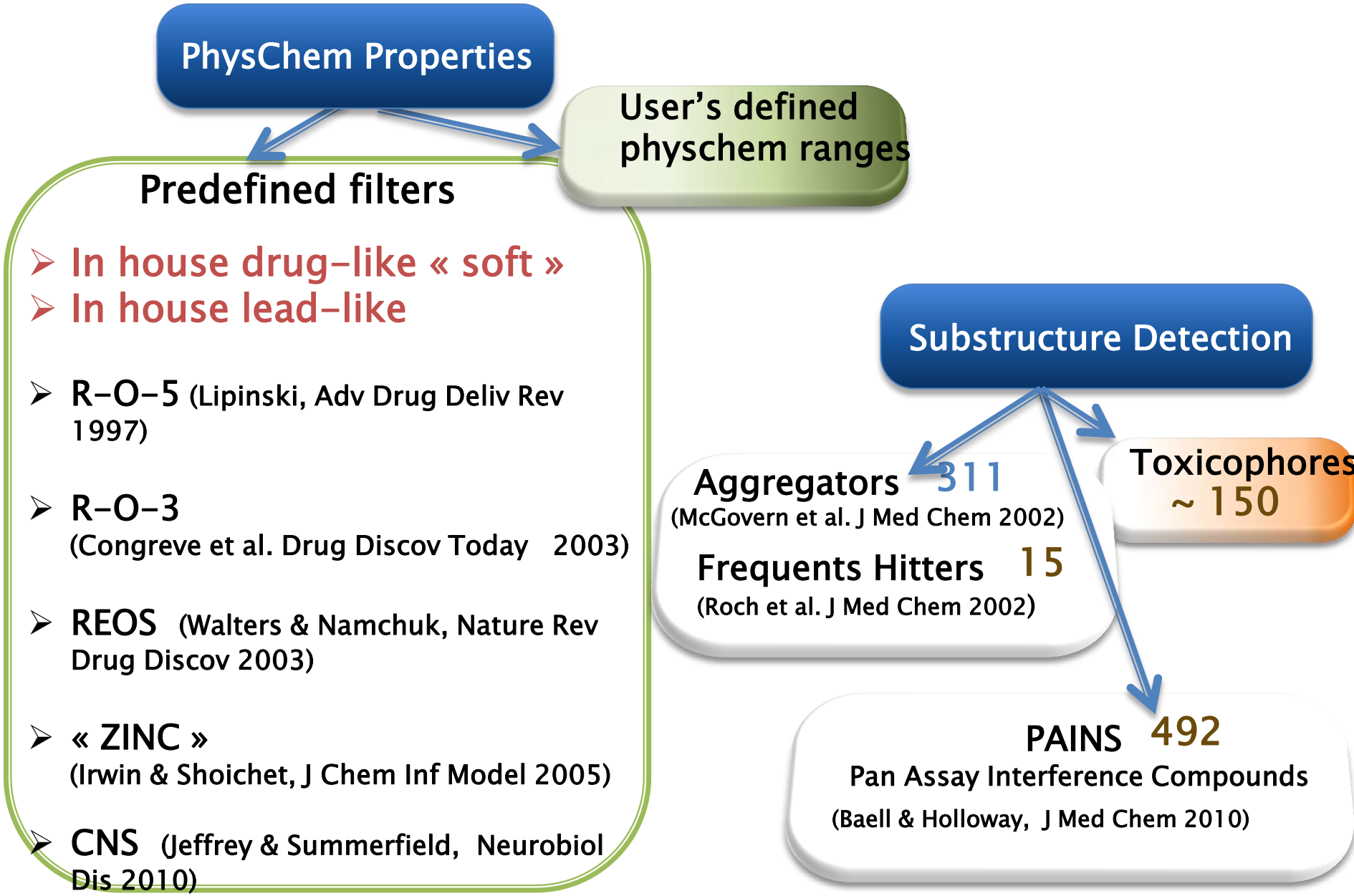
- **Golden triangle** (Pfizer 2009):
  the yellow region is found to have a higher chance for permeability and metabolic stability



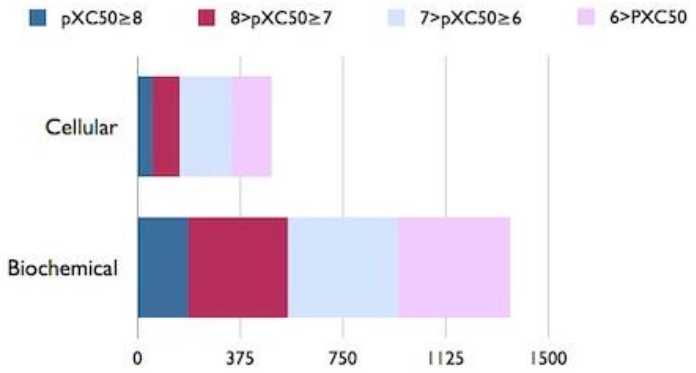
- **Solubility**
  - ↓ with ↑ size and clogP
  - ↑ with ↑ ionisation

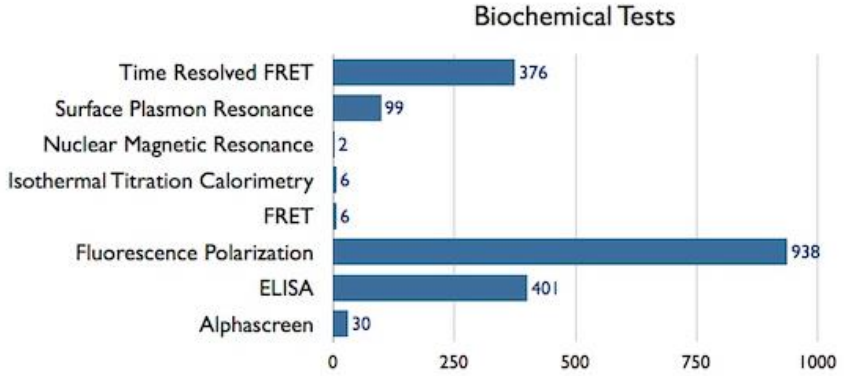


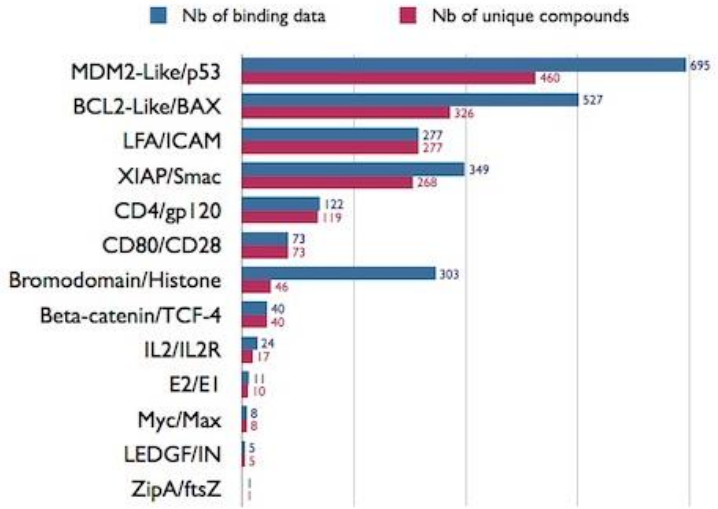
Filtering and Substructure Detection in FAFDrugs2

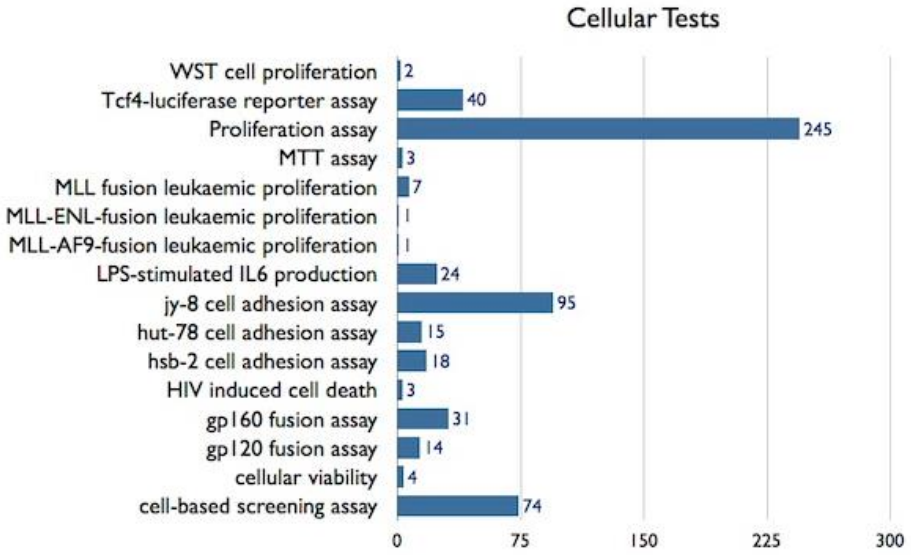


iPPI-DB Stats



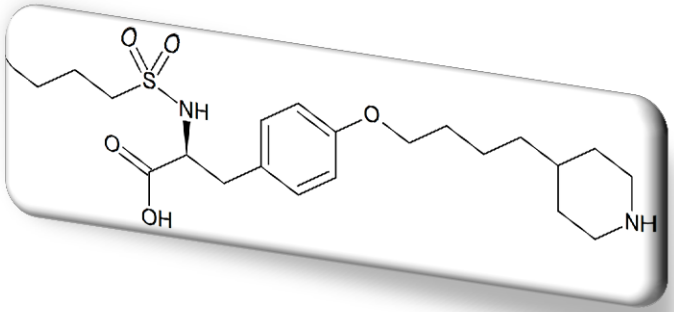






Drugs discovered using VS

Aggrastat : fibrinogen receptor antagonist (Merck) (optimized by LBVS)
anticoagulant and platelet aggregation inhibitor
modulates a protein-protein interaction (between Integrin glycoprotein Alpha IIb and Beta II and Fibrinogen receptors on platelets)

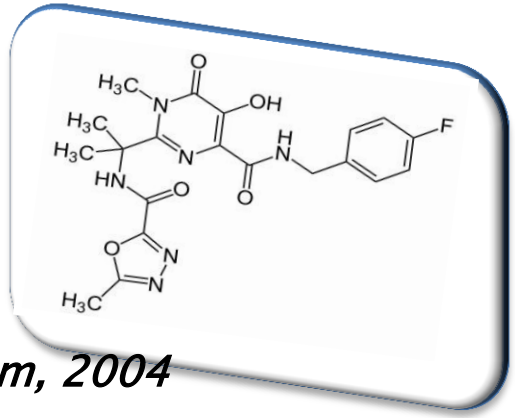


PRX-00023 (Phase IIb) antidepressant, 5-HT 1A receptor agonist (SBVS)

SC12267 (Phase IIa) immunosuppressant, inhibitor of dihydroorotate dehydrogenase (SBVS)

DE Clark. Expert Opinion on Drug Discovery 2008

Isentres : AIDS, HIV integrase inhibitor (Merck), SBVS
docking - AutoDock
Flexibility receptor by MD - MRC Relaxed Complex Method

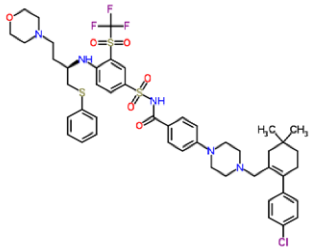


McCammon group, J Med Chem, 2004

PPI modulators

PPI inhibitors

Drugs: ***Navitoclax*** (ABT-263), Phase II
(Bcl-2 ,cancer, Abbott)

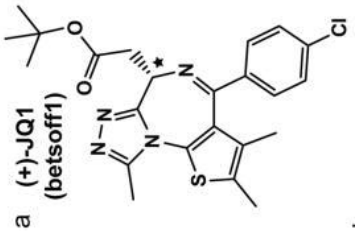


RG7112 (Phase Ib)
(MDM2, cancer, Roche)

Mullard A. Nature Rev Drug Discov. 2012

Lead

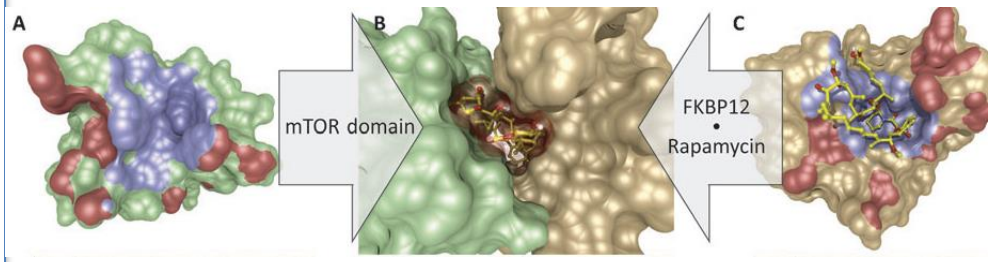
BRD4 epigenetic reader recognizing acetyl-histones ; cancer
Tensha Therapeut, GSK interested;



Bradner et al. Nature 2010

PPI stabilizers

Drugs: ***Rapamycin,*** immunosuppressant



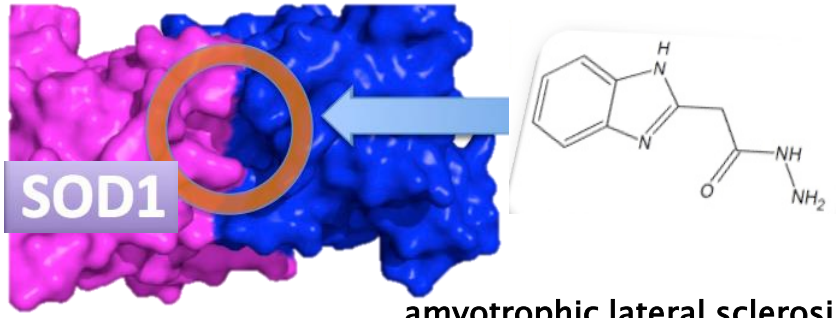
the protein kinase mTOR

immunosuppressant FK506

Paclitaxel

cell-cycle arrest by modulating microtubules structures, cancer Thiel et al. Angew. Chem.Int.Ed 2012, 51:2

Lead



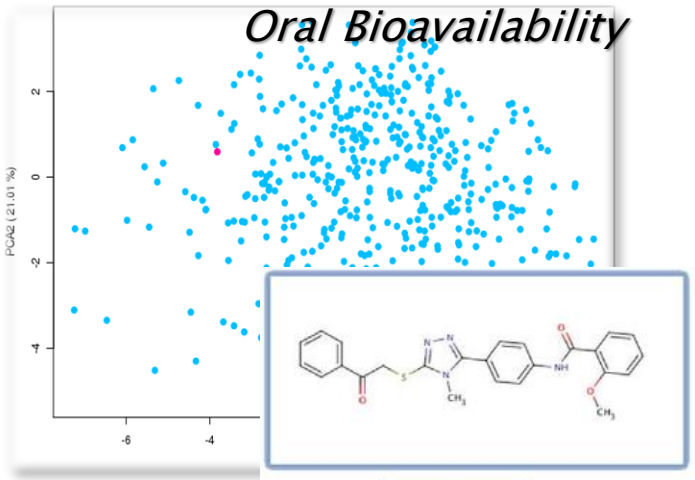
amyotrophic lateral sclerosis

SBVS: Ray et al. PNAS 2005, 102: 3639
H2L: Chen et al. J Med Chem 2012,55: 515

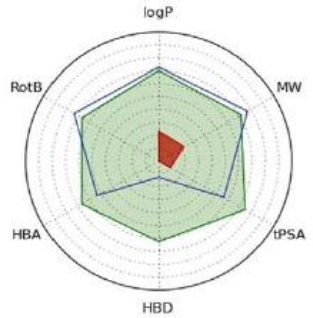
FAFDrugs3 : Free ADME-Tox Filtering of chemical compounds

- Simple PhysChem rules for oral bioavailability
  drug/lead/fragment-like cmps filters
  - **Lipinski rules**: HBD, HBA, MW, log P
  - **Oprea rules**: number of rings, rotatable bonds
- Toxic atoms/groups ~150
- Frequent hitters & Pan Assay Interference Compounds (PAINS) ~500

Lagorce et al. NAR 2015

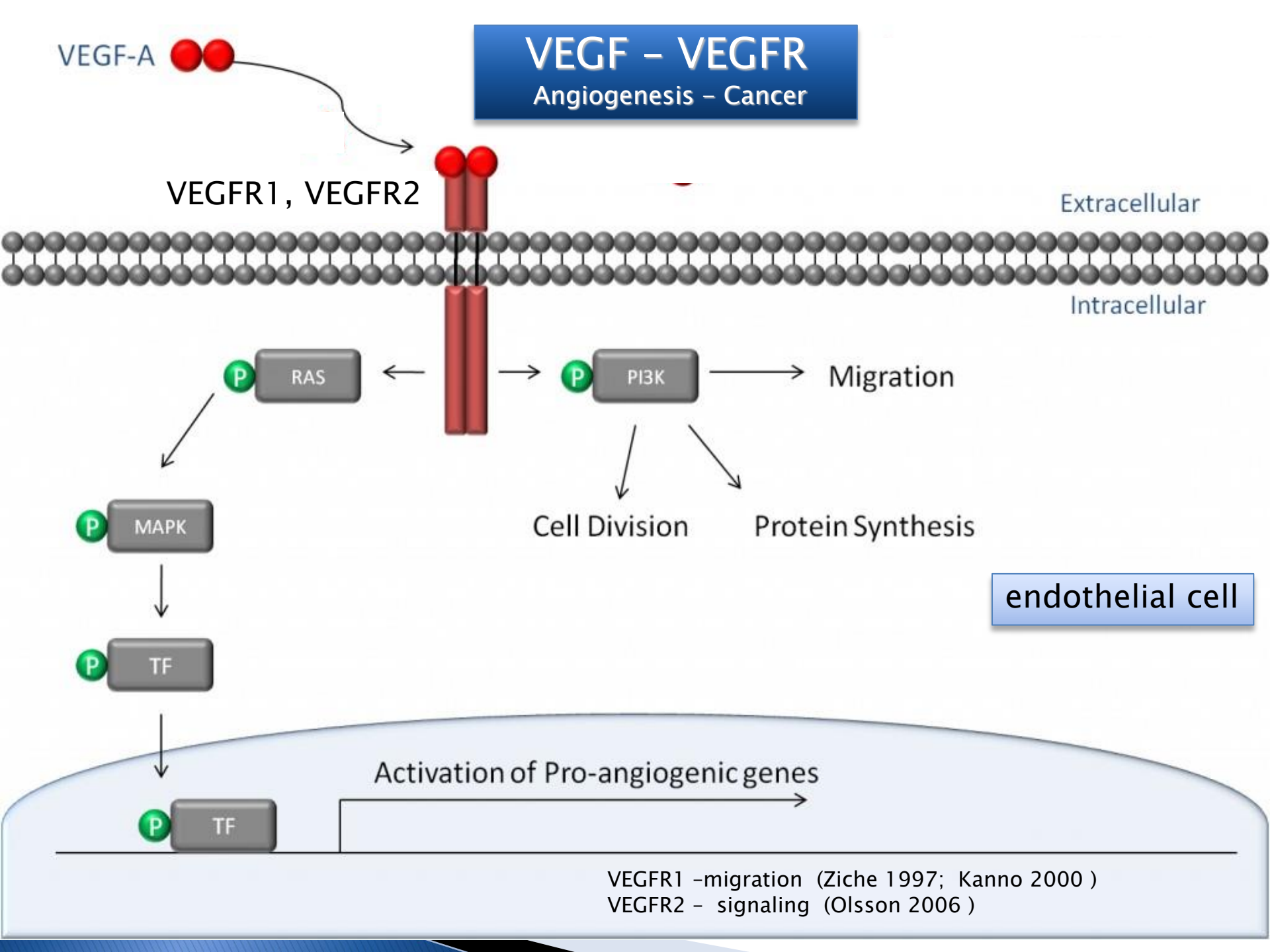


Simple PhysChem



FAFDrugs3 web-server:

http://fafdrugs3.mti.univ-paris-diderot.fr


VEGF-A
VEGF – VEGFR
Angiogenesis – Cancer
VEGFR1, VEGFR2
Extracellular
Intracellular
P
RAS
P
PI3K
Migration
P
MAPK
Cell Division
Protein Synthesis
endothelial cell
P
TF
Activation of Pro-angiogenic genes
P
TF
VEGFR1 –migration (Ziche 1997; Kanno 2000)
VEGFR2 – signaling (Olsson 2006)

Let us meet again..

We welcome you all to our future conferences of OMICS International

4th Annual Conference on European Pharma Congress

June 18-20,2016, Berlin, Germany.

http://europe.pharmaceuticalconferences.com/