“Drug Design today … between myth and reality. ”

Stefano Moro

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Bibliometric indexes:	R Google Scopus ORCID
CV:	
Biblio Sketch:	I consider myself a molecular psychologist. A molecular psychologist is a scientist who studies psychology of molecules, the systematic investigation of the molecular life, including molecular behavior and molecular cognition.
	Marta & Stefano best chemical experiment... MS

Here is our working platform...

http://mms.dsfarm.unipd.it

Cerca

UNIVERSITÀ DEGLI STUDI DI PADOVA

MMS Molecular Modeling Section

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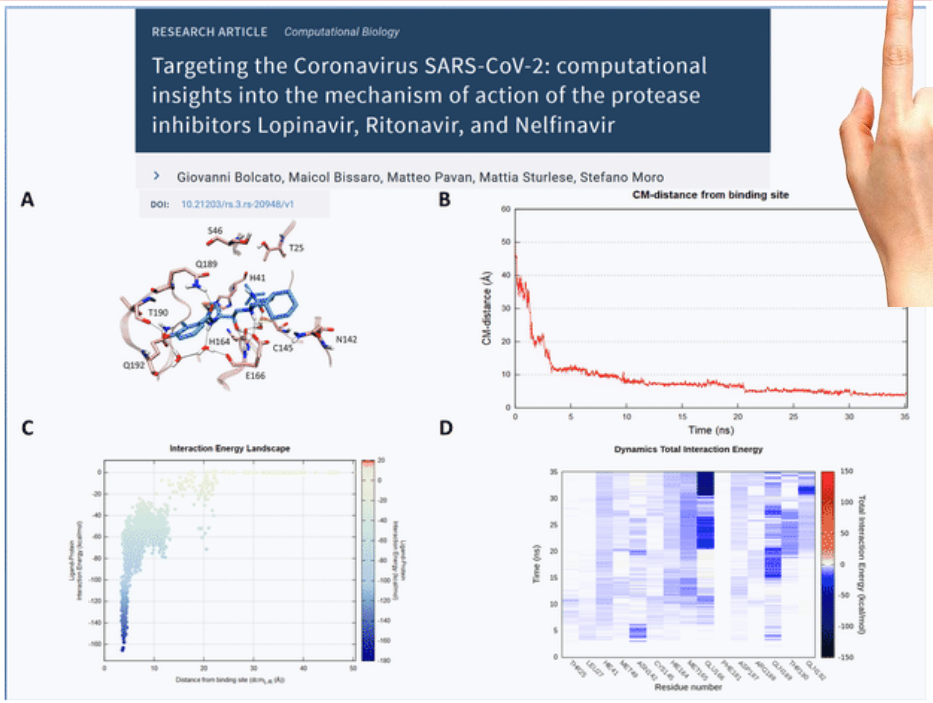

: News & Updates

ember 01, 2018

MS: Events

June 18-19, 2020
CDDD 7th Meeting - Bettona (PG)... more

MMS: Latest Hot Publication

Bissaro et al. " Targeting the Coronavirus SARS-CoV-2: computational insights into the mechanism of action of the protease inhibitors Lopinavir, Ritonavir, and Nelfinavir" Scientific Report (2020) more...

Here is our working platform...

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- Chimica Farmaceutica 2 (CTF)
- Progettazione e Sviluppo di un Farnarco (CTF)
- Biomodeling (BTF)
- Chemoinformatica (ISF)
- Tossicologia Computazionale (Master REACH, Speciality School)
- Master, PhD and Advance Courses

...uTube channel. more...

...ockBenck tool. more...

...MS: Events

...14-15, 2019

...Dynamics: Today - Bologna... more

...atest Hot Publication

...al. " Targeting protein kinase CK1δ with Riluzole: could it be one of the possible missing bricks to interpret its effect in the treatment of ALS from a molecular point of view?" ChemMedChem. (2018) more...

Here is our working platform…

Cerca

Cerca

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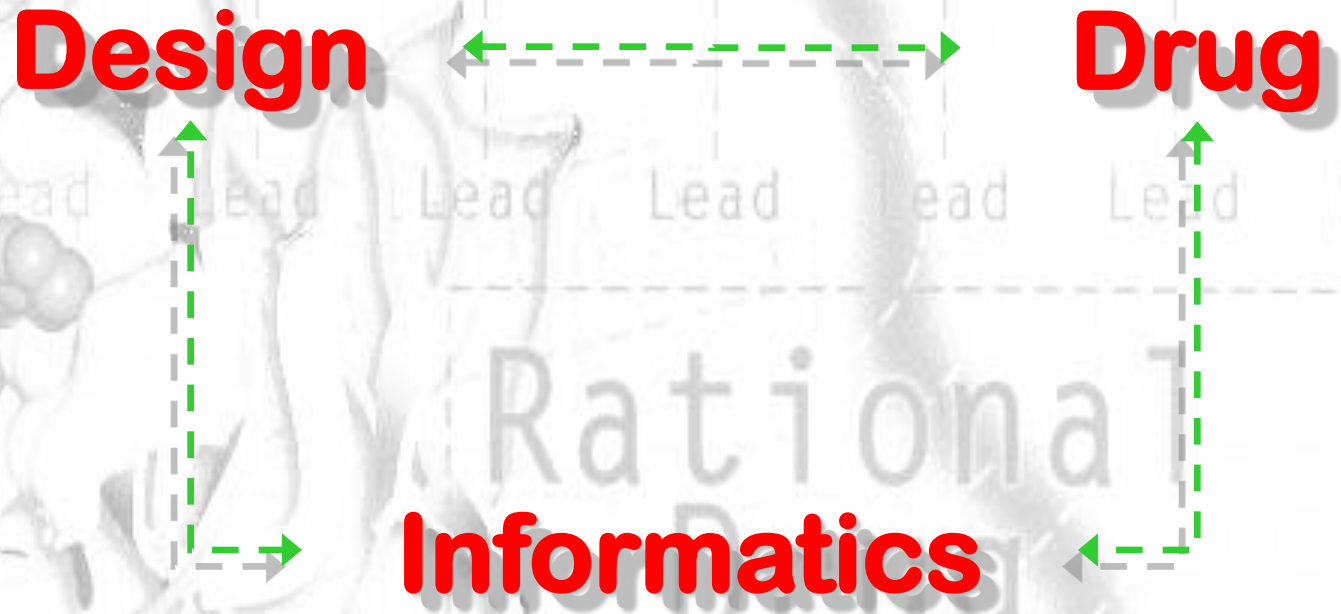
hospital pharmacy

Lecture 1	
Lecture 2	

Why we are here today… to find the intimate connection between these three concepts :



Drug discovery statistics:

https://www.nature.com/articles/d41573-020-00001-7

NEWS · 08 JANUARY 2020

2019 FDA drug approvals

The FDA approved 48 new drugs last year, keeping up the momentum of recent years.

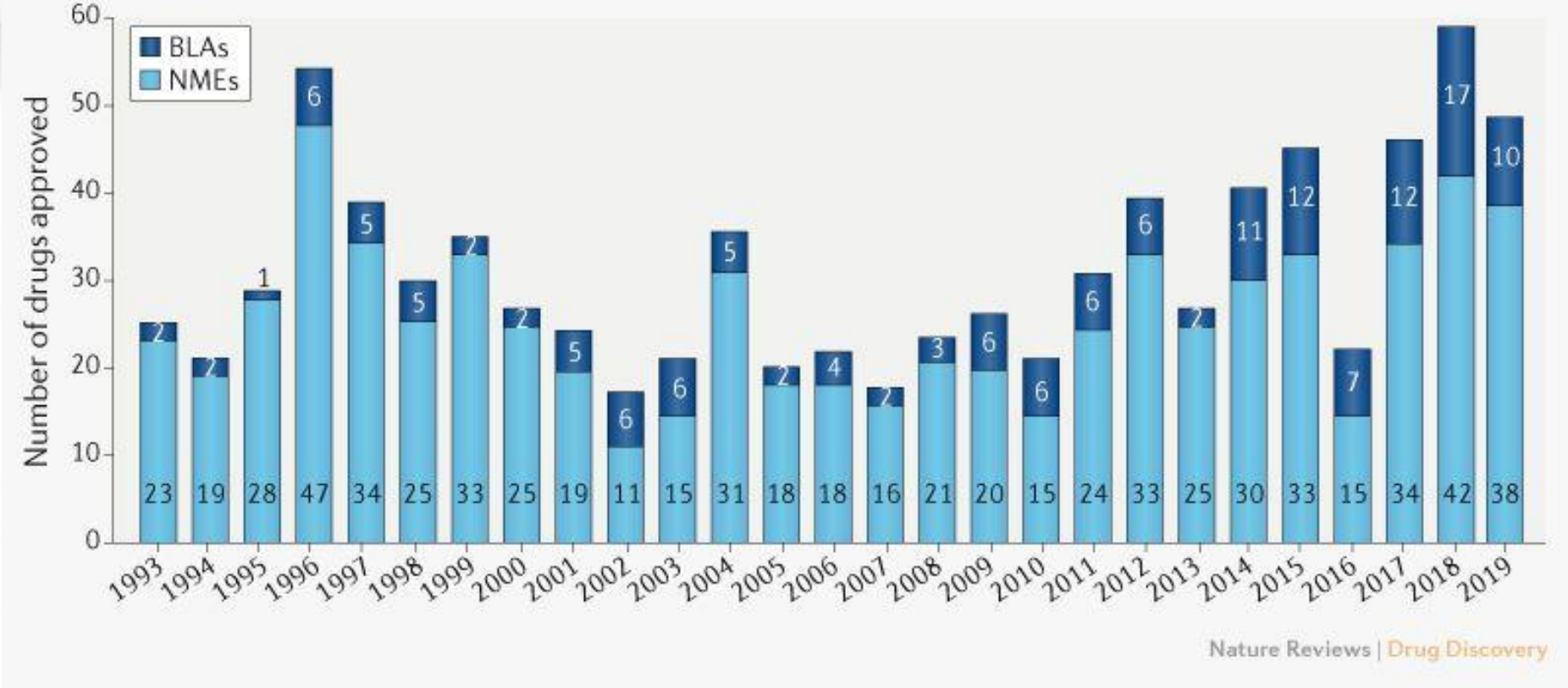
Asher Mullard

The FDA's Center for Drug Evaluation and Research (CDER) approved 48 novel drugs in 2019 (Table 1). Although this approval count falls short of CDER's record 59 approvals of 2018, it still comes in as the third biggest approval class in the past 25 years (Fig. 1).

PDF version

Drug discovery statistics:

https://www.nature.com/articles/d41573-020-00001-7



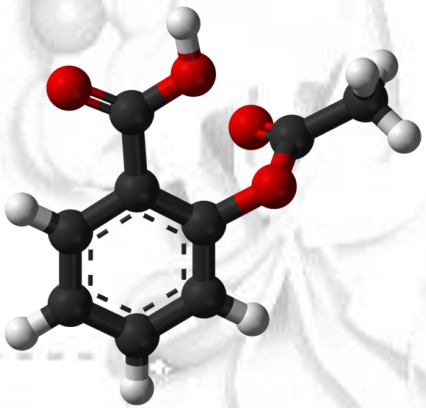
A ***Novel Drug*** or a ***New Molecular Entity (NME)*** is an active compound, complex, molecule that previously has not been approved by the FDA/EMA.

A very general introduction:

Vintage drugs

ASPIRINE

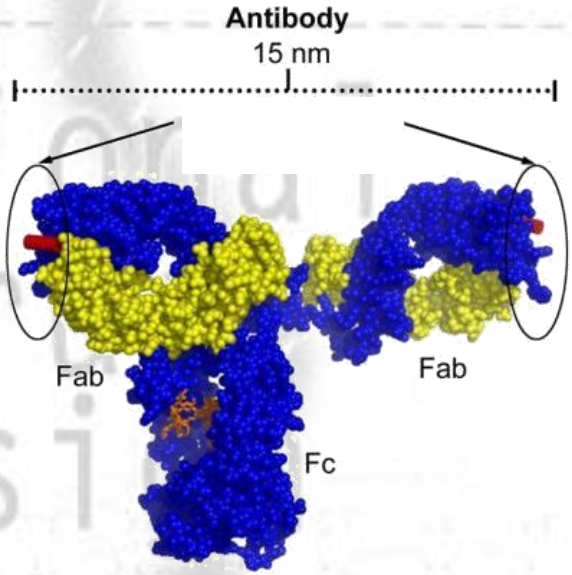
1. small molecule
2. 180 Da
3. 21 atoms
4. usually not immunogenic
5. usually chemically stable



New age (biotech) drugs

MONOCLONAL ANTIBODY (mAb)

1. macromolecule
2. 150˙000 Da
3. 20˙000 atoms
4. usually immunogenic
5. usually chemically instable



Drug discovery statistics:

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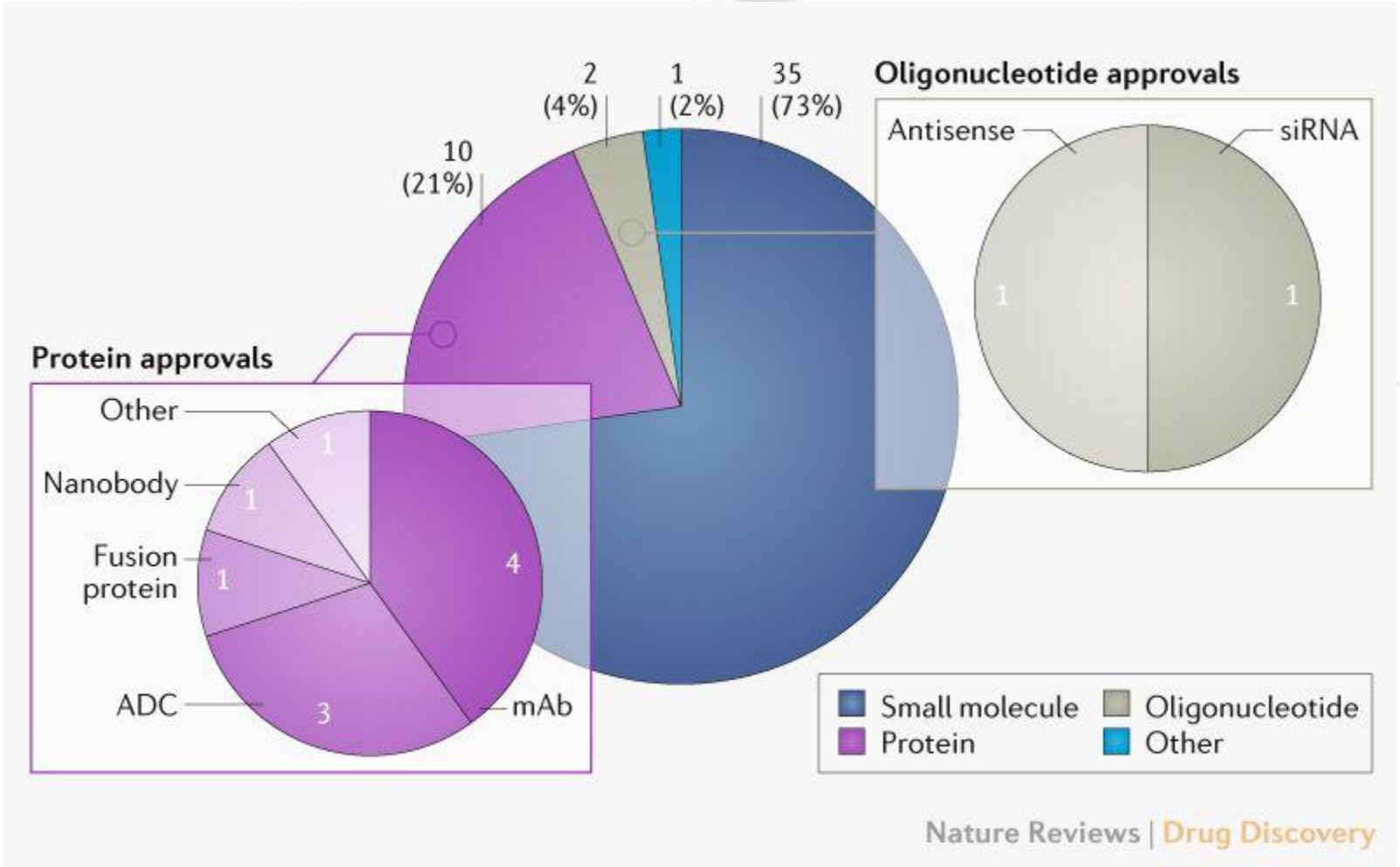

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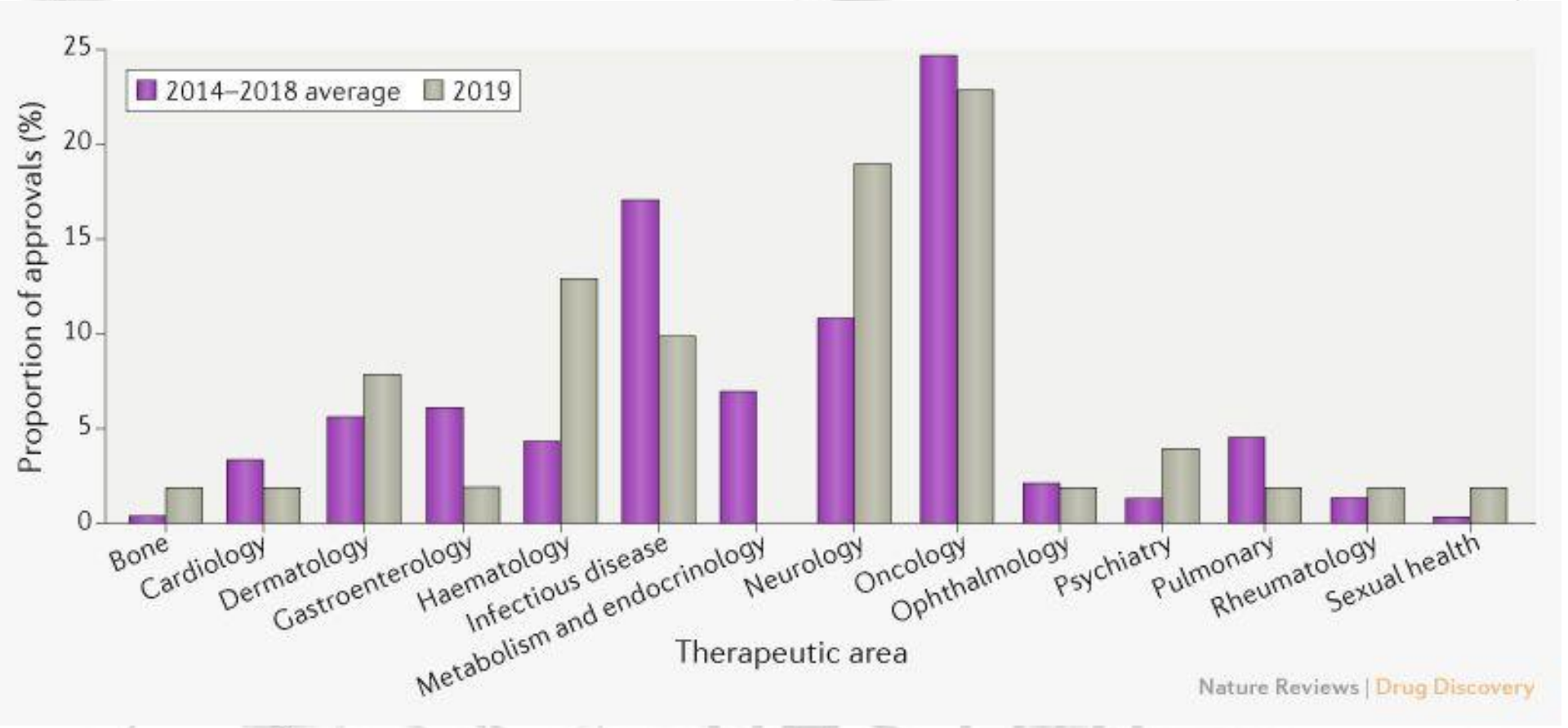
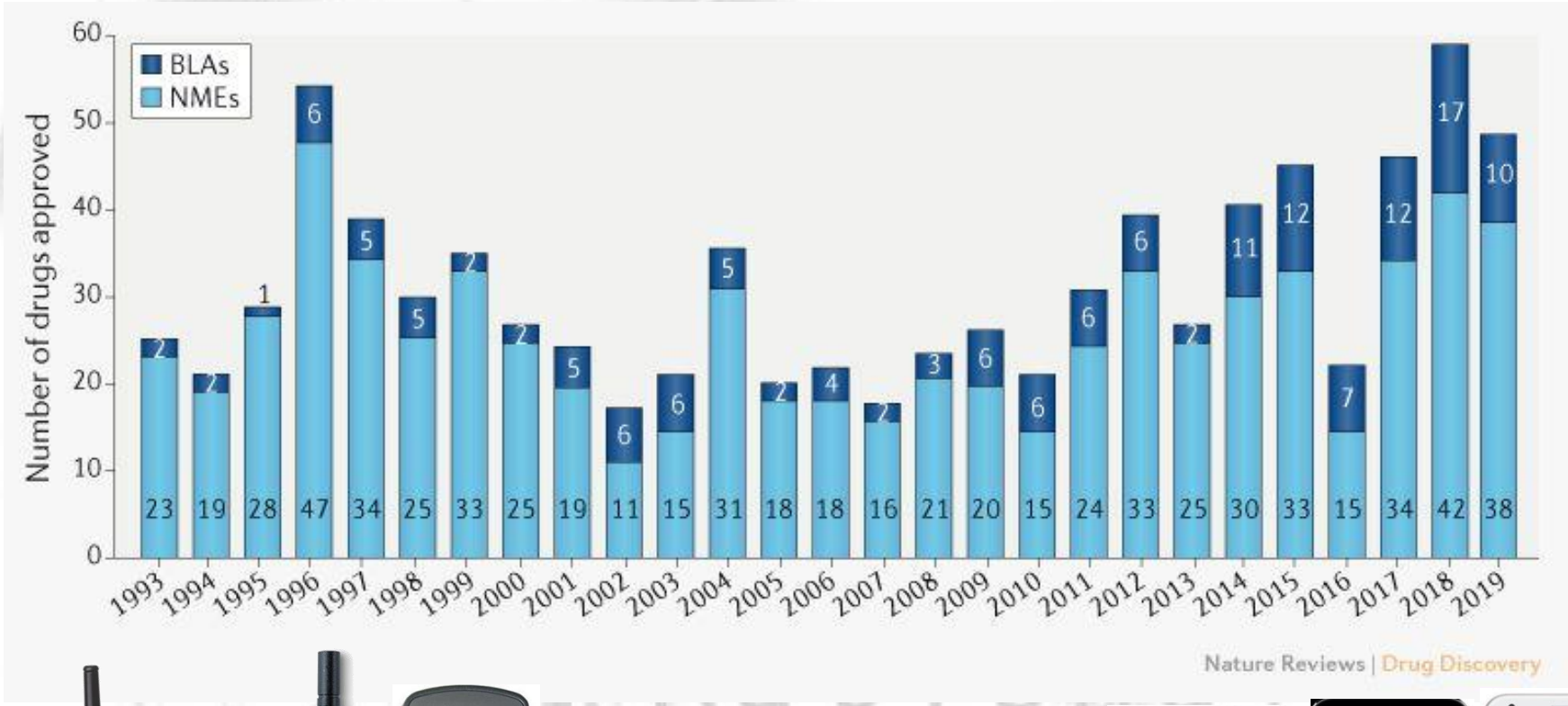


Why has the pharmaceutical industry apparently not benefited from the sci/tech revolutions of the last few years?



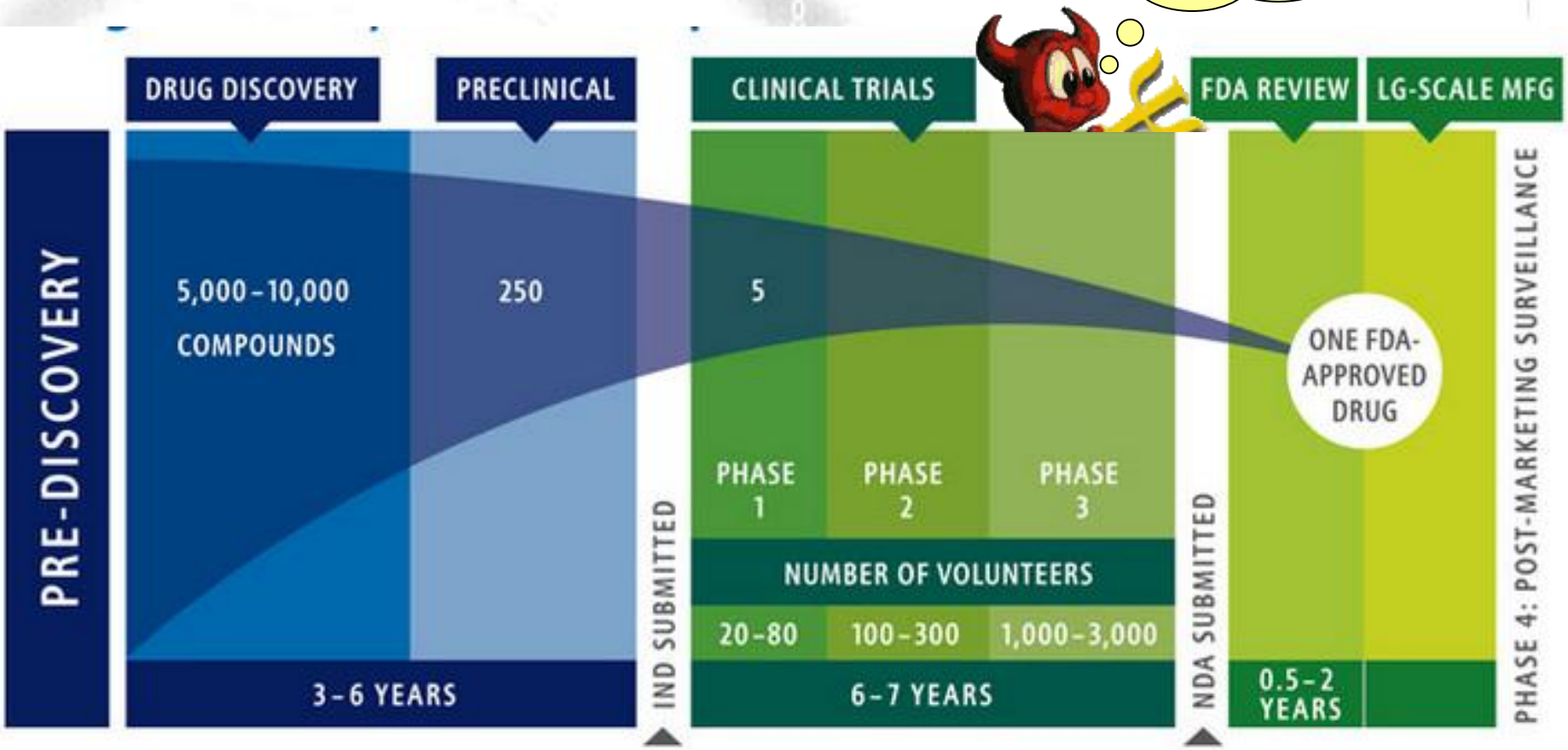
Why we need *"drug" design*?

Drug discovery is a extremely competitive activity!

a.~ 1600 companies;

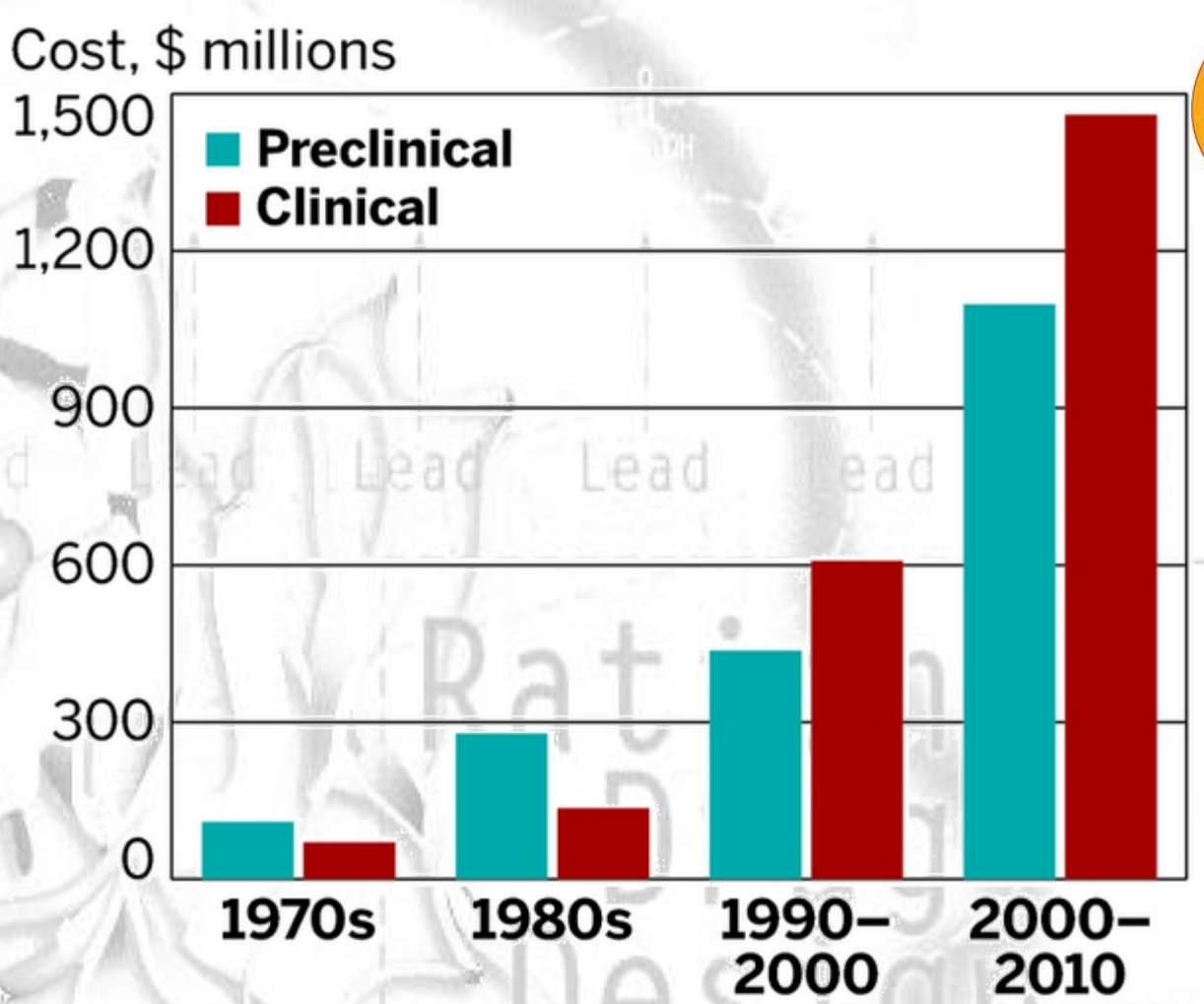
b. ~ 6000 R&D projects.

but *time* is the worse enemy in drug discovery…



Bringing a new drug to market can take 8-14 years and costs between $400 and $900 million… or even more!!

Some details about costs:



The cost of developing a new drug has skyrocketed since the 1970s. *Source: Tufts Center for the Study of Drug Development.*

Some details about costs:

this is something nobody says!!!

The easiest way to see the cost of this time is to examine the opportunity investors lose by committing their money into the pharmaceutical research process as opposed to other possible investments. The alternative investment opportunity could be putting their money in a start-up internet company; perhaps the alternative investment opportunity is putting their money in a less risky asset such as an electric utility; or, perhaps both. If we use the broader market as the potential alternative investment opportunity, then it is possible to quantify the lost investment opportunity that potential investors forgo by investing their money in the risky pharmaceutical research process. *Between 1964 and 2013 the average annual return of the S&P 500 was 9.9 percent.* Investors, consequently, can earn a return of 9.9 percent on their money if they just invest in the market instead of investing their savings into the pharmaceutical research process.

Initial Investment	**$100.00**
Annual growth in investment over R&D timeframe	
Year 1	$109.89
Year 2	$120.76
Year 3	$132.71
Year 4	$145.84
Year 5	$160.27
Year 6	$176.12
Year 7	$193.55
Year 8	$212.69
Year 9	$233.73
Year 10	$256.86
Year 11	$282.27
Year 12	$310.19
Year 13	$340.88
Year 14	$374.60
Year 15	$411.65

Some details about costs:

Experiment Typical Cost per Compound (€)

Computer modeling	7
Biochemical assay	270
Cell culture assay	2.700
Rat acute toxicity	8.100
Protein crystal structure	68.000
Animal efficacy trial	200.000
Rat 2-year chronic oral toxicity	550.000
Human clinical trial	3.500.000

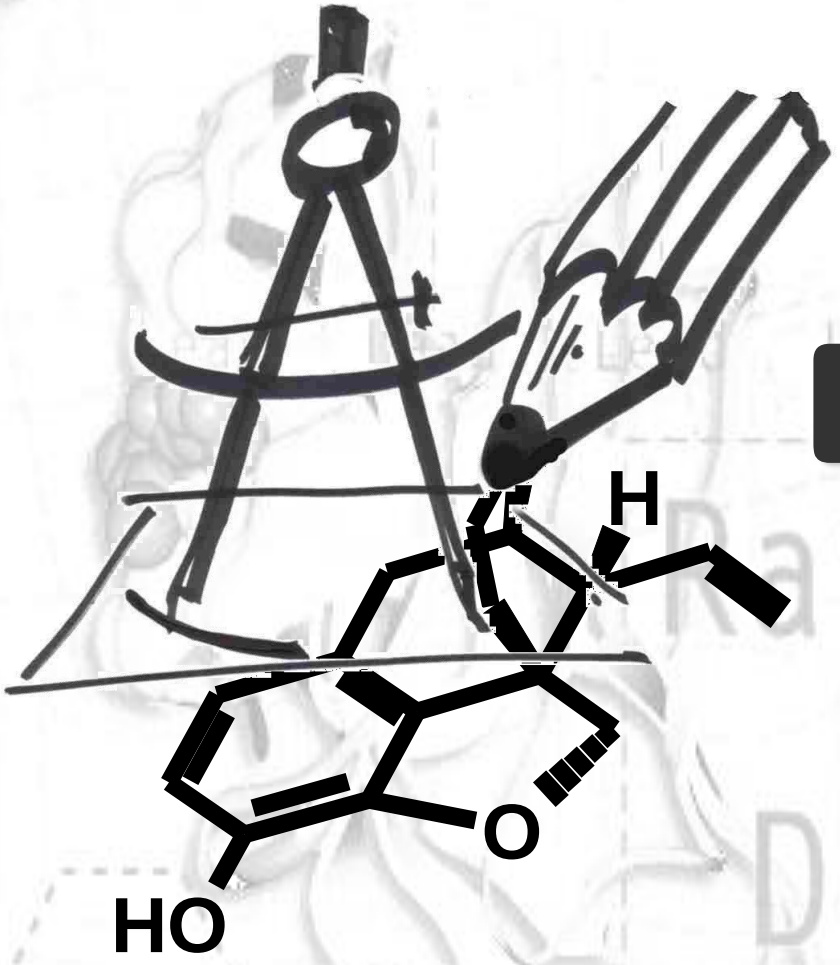
You understand why it is so attractive to the pharmaceutical industry?

Why we need *"drug" design*?

xx.000 to 1?

Is this ratio really acceptable for a pharma company?

Our primary mission will be:



Design!

The most insidious question that you can make me :

Is a drug designable?

… a bit of:

… be patient:

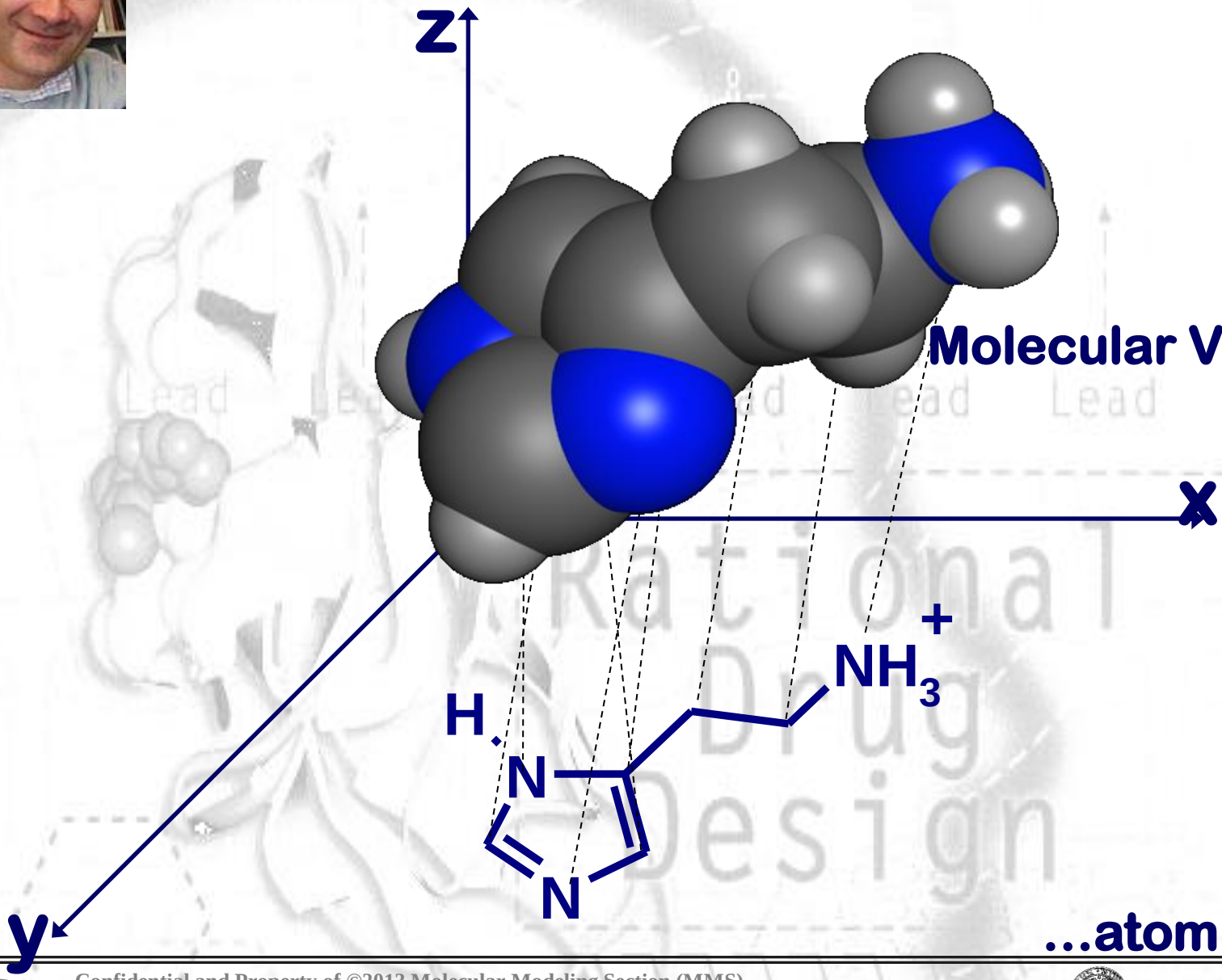
Design:

set up a project of a work by making **drawings** and **calculations** necessary for its realization.

… be patient:

Design:

the shadow of the reality:



…atom is $4/3\pi r^3$?

At this point measure the molecular size is easy…

Verloop A., Hoogenstraaten W., Tipker J. "Development and application of new steric substituent parameters in drug design." In Drug Design (Ed. Ariëns), vol.7, pp.165-207 (1976), New York: Academic Press.

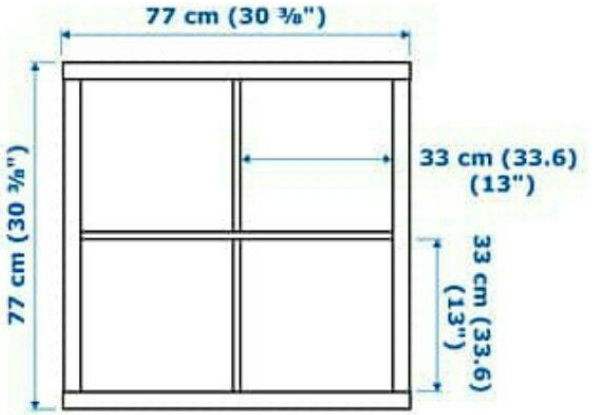
My favorite example:

IKEA

CERCA UN PRODOTTO O UN SERVIZIO

NOVITÀ | OFFERTE | PRODOTTI | AMBIENTI | IDEE | RISTORANTE E BOTTEGA | DOVE SIAMO

Home / Soggiorno / Scaffali



Credits: https://www.ikea.com/it/it/catalog/products/20275814/

… and now, it's your turn!

Again, is a drug designable?

… a bit of:

Design ⟷ Drug

Informatics

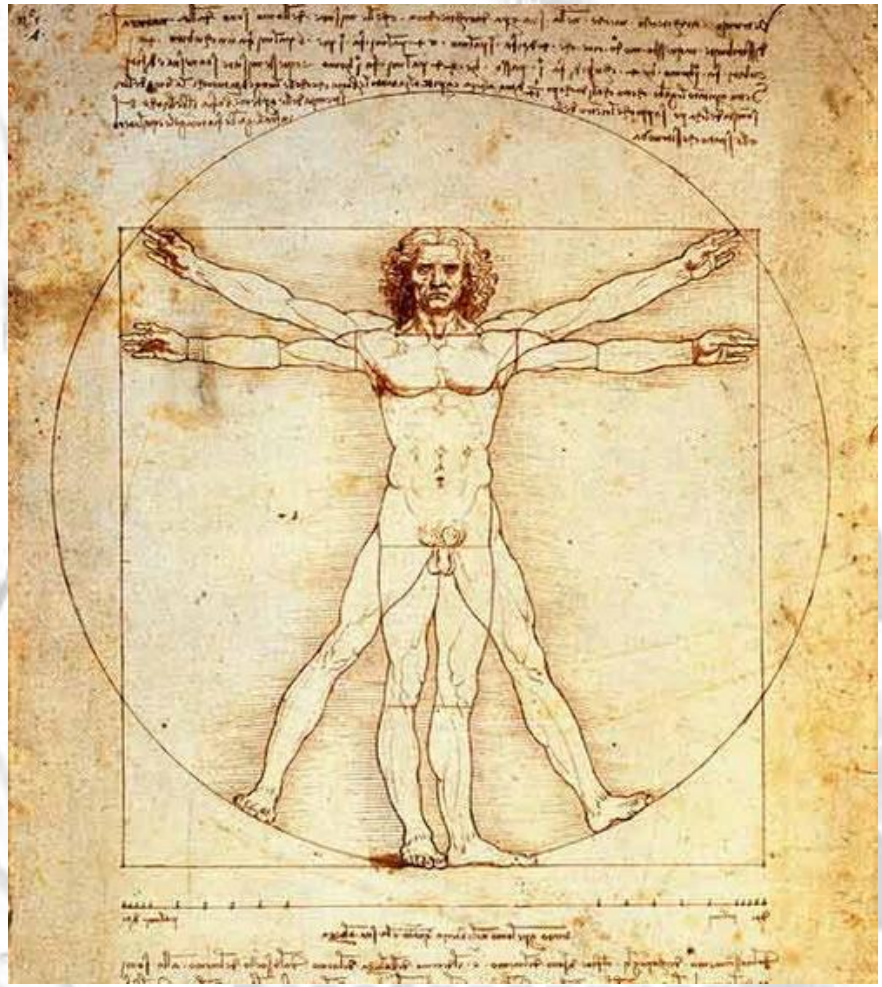
I know very well that you known what drug is... but reconsider its definition in terms of his designability:

Drug:

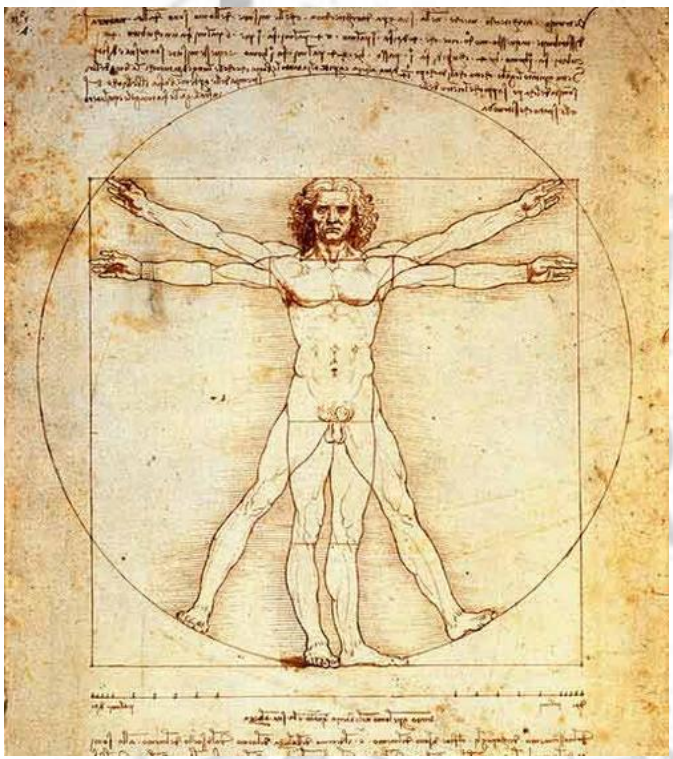
[from gr. φάρμακον] Any substance, organic or inorganic, synthetic or natural, capable of producing in a **living organism** functional modifications, helpful or harmful, by chemical action, physical chemistry or physics.

Dizionario Treccani

… and a 'living organism' is difficult to accommodate in a design process (drawing and calculations), though …

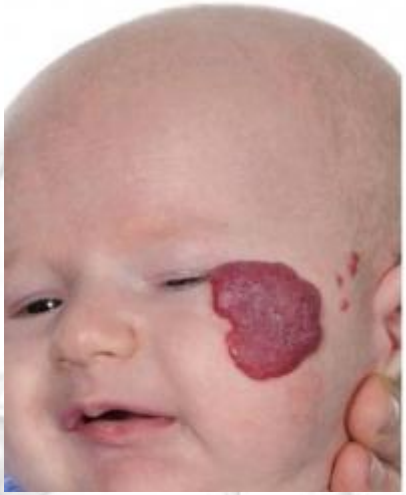


… I suspect that you could have a sensation like this:



We will return later on this concept…

I don’t have a better example:



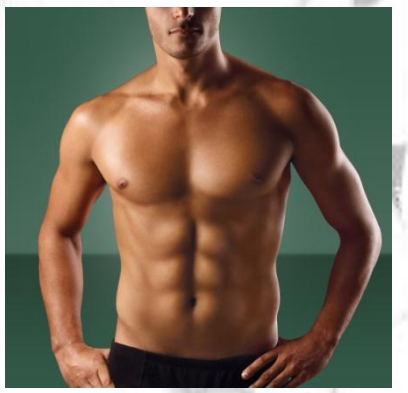
Infantile Hemangioma

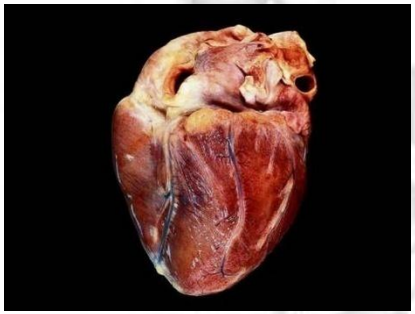
Propranolol

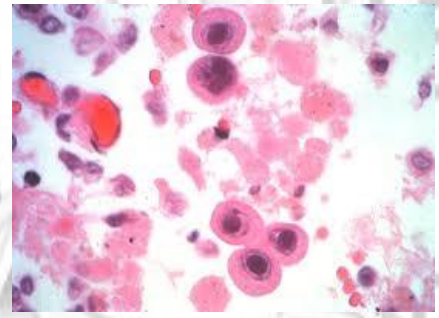
try to respond with intellectual honesty:

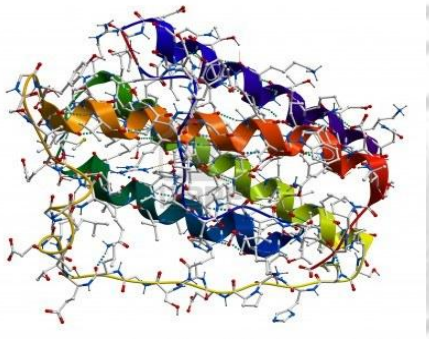
Is this designable?

Choose the best solution:

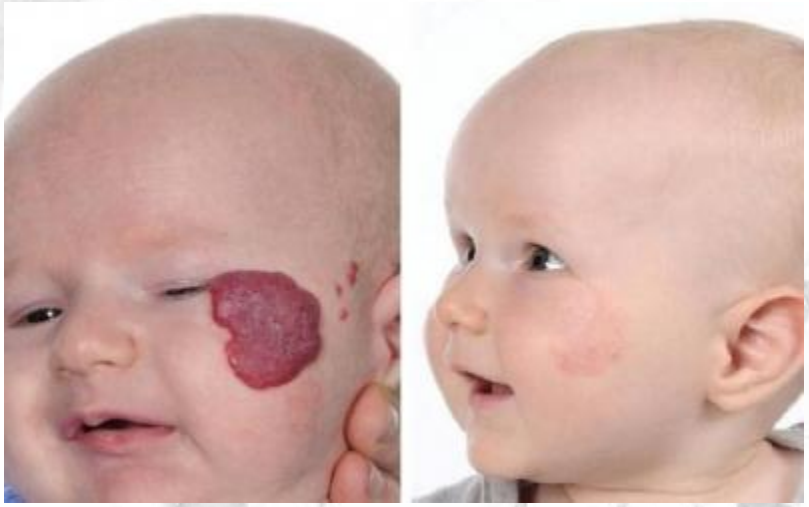




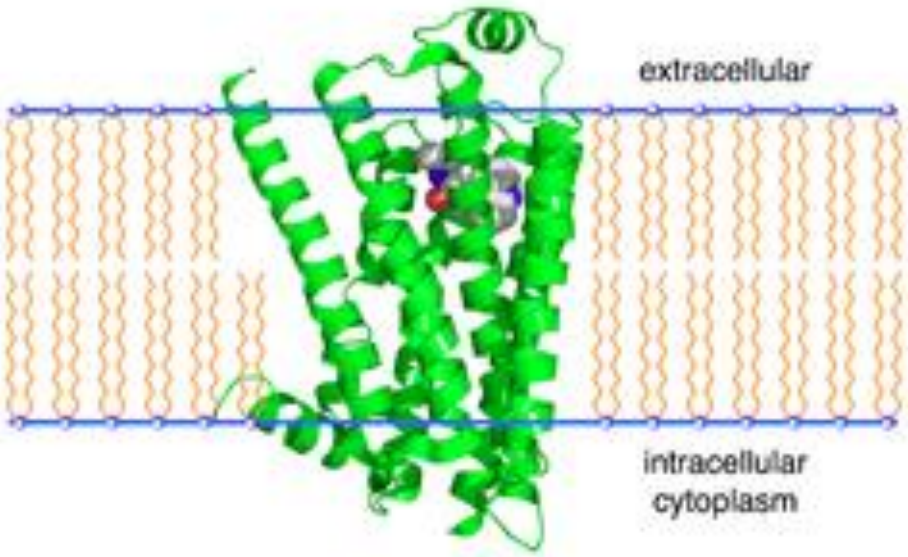




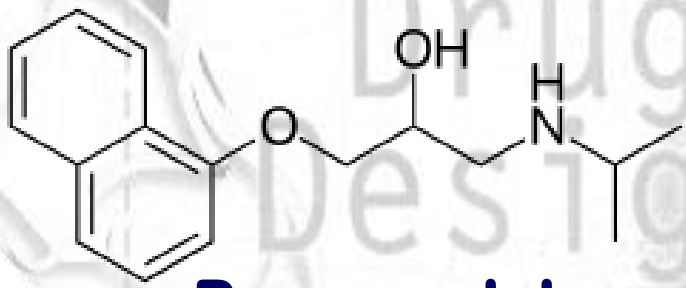
Choose the best solution:



Infantile Hemangioma



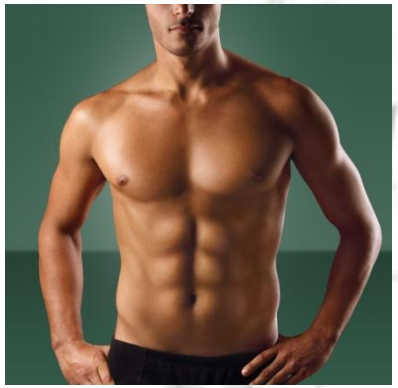
Beta adrenergic receptors

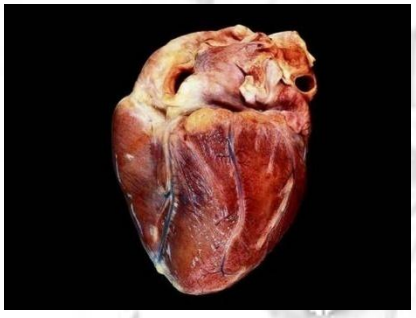


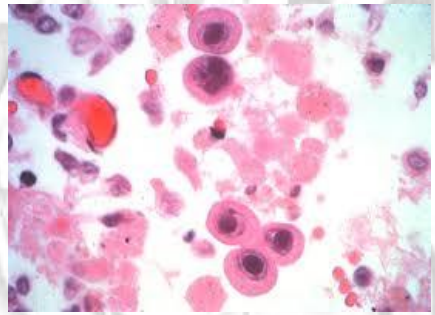
Propranolol

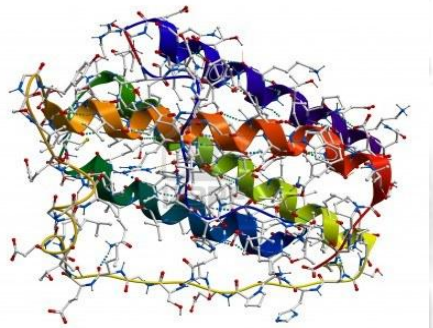
Choose the best solution:

Drug



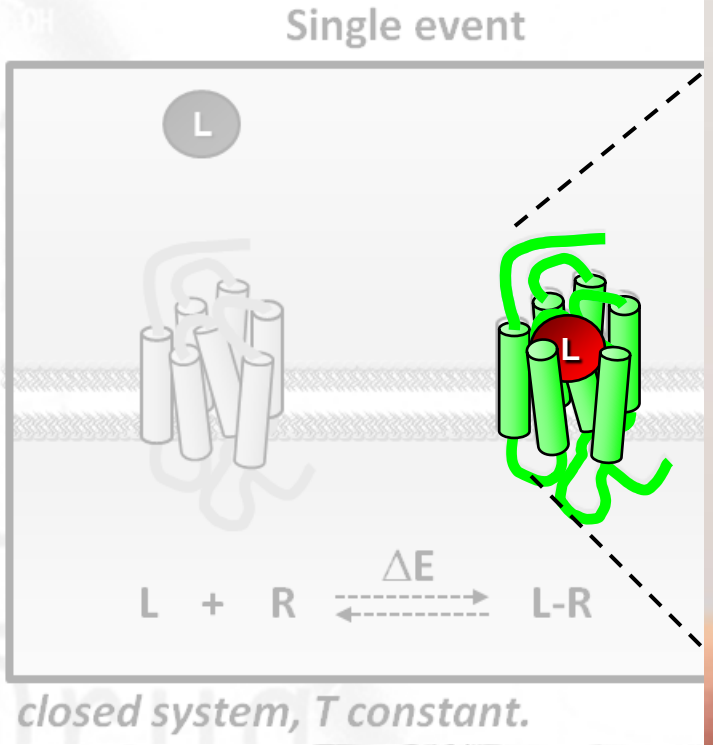


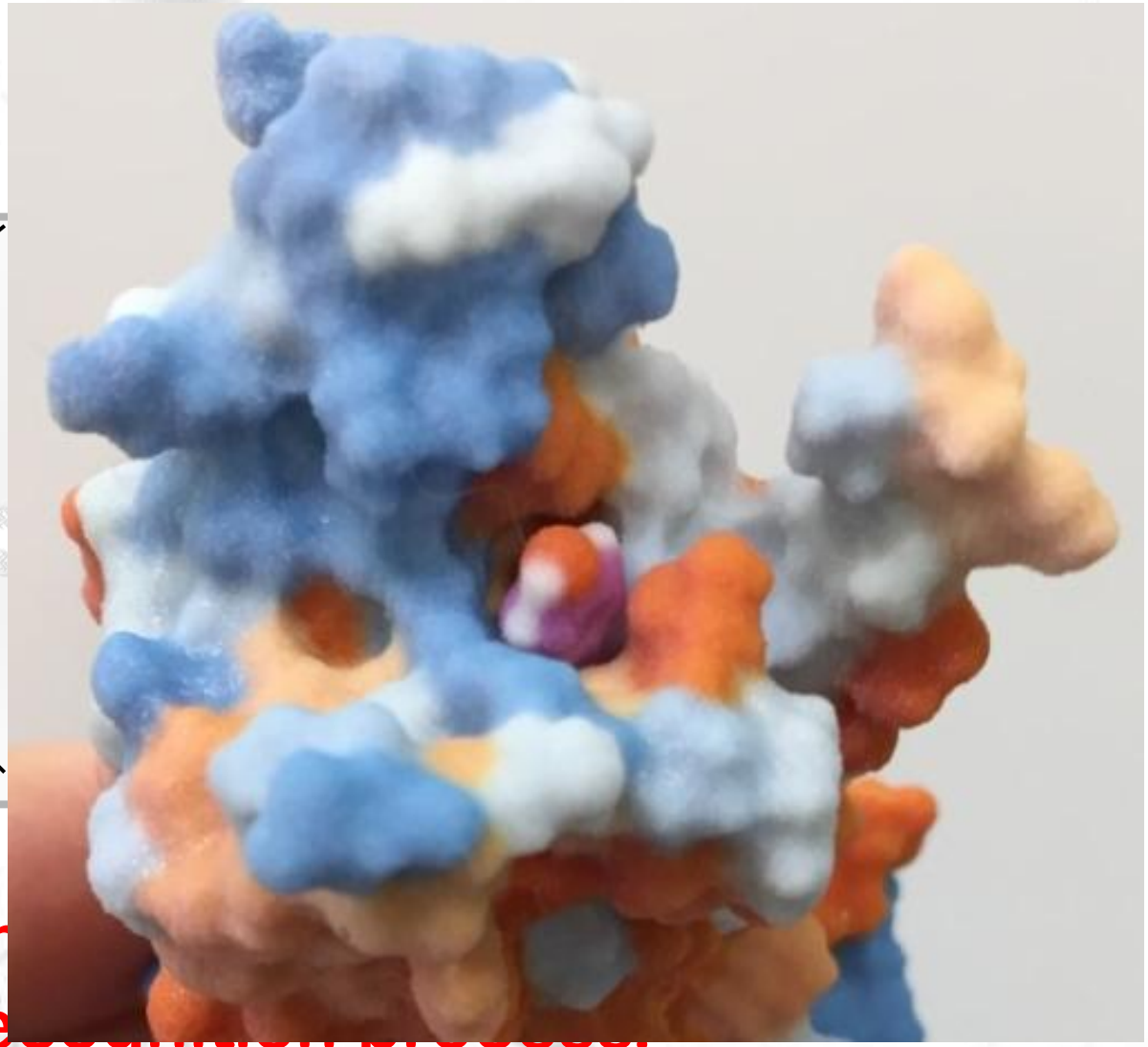




Candidate

Why we consider the 3D structures are exciting?

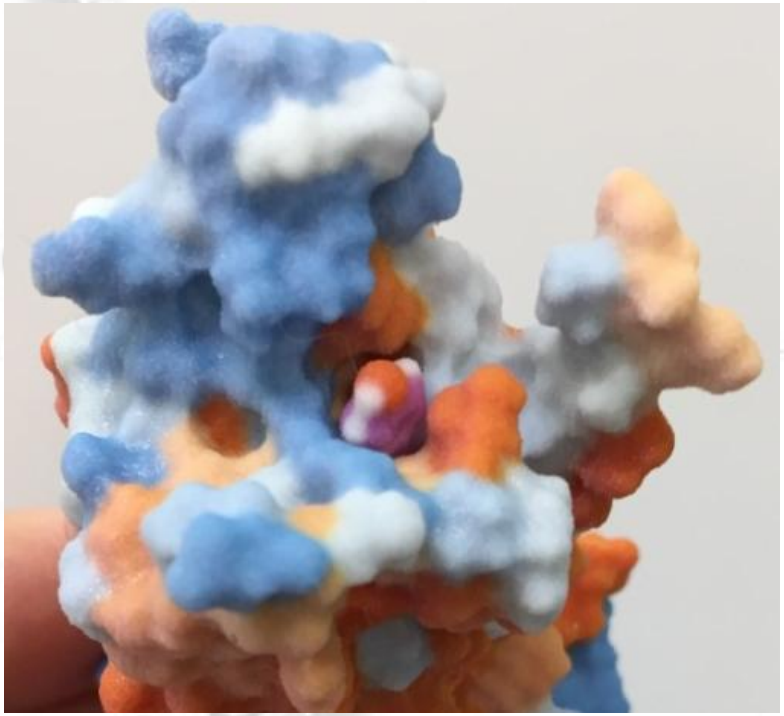




The natural link with
a ligand-receptor re

MMS Lab (2015): 3D printed model of the human A2A adenosine receptor co-crystallized its antagonist ZM 241385 (PDB entry: 4EIY)

How is it possible to create a realisting protein (molecule) 3D printing?



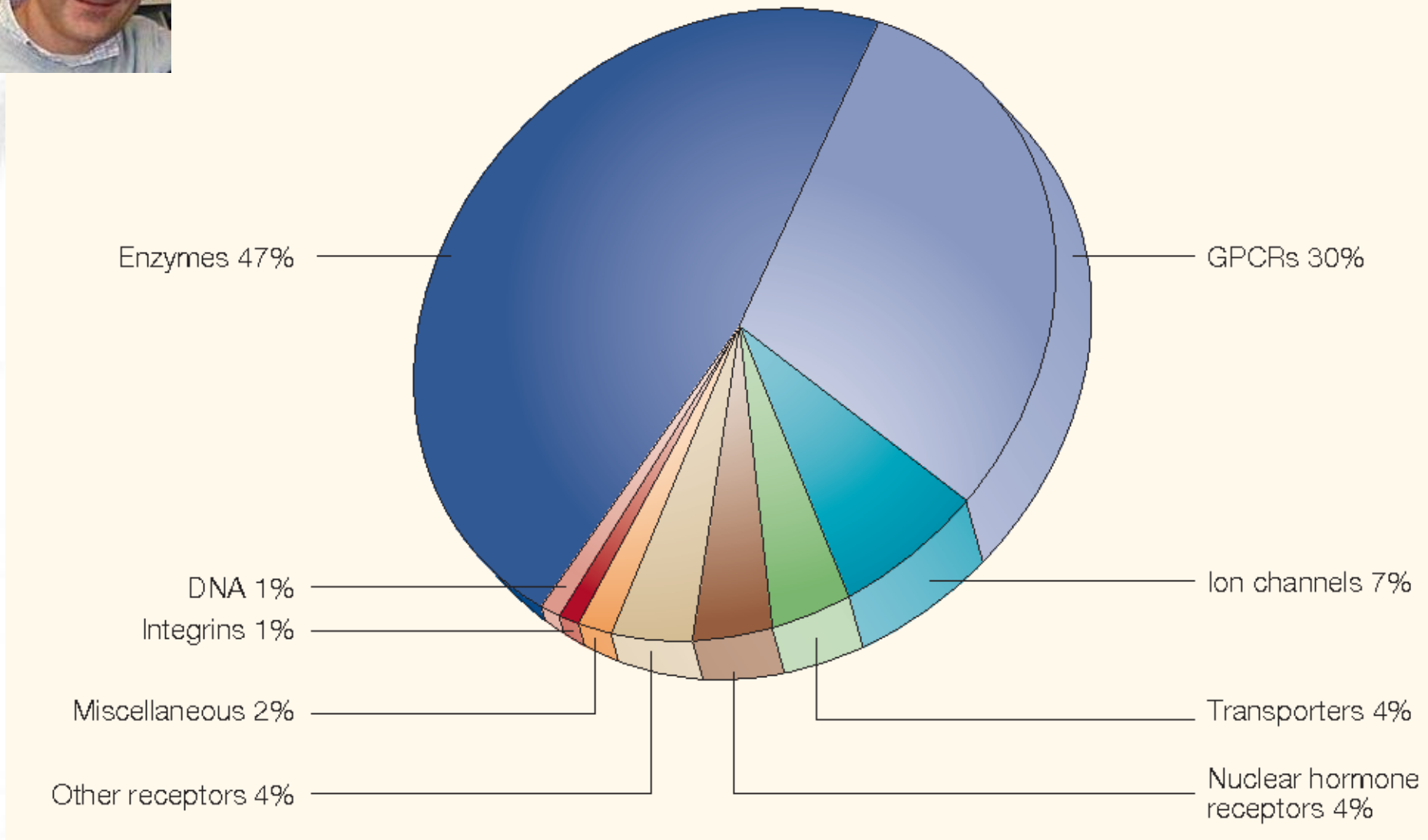
Some details about costs:

Experiment Typical Cost per Compound (€)

Computer modeling	7
Biochemical assay	270
Cell culture assay	2.700
Rat acute toxicity	8.100
Protein crystal structure	68.000
Animal efficacy trial	200.000
Rat 2-year chronic oral toxicity	550.000
Human clinical trial	3.500.000

You understand why it is so attractive to the pharmaceutical industry?

Druggable targets…



credits: https://www.semanticscholar.org/paper/The-druggable-genome-Hopkins-Groom/648a2ef46c4f7b335741111c445ee26adf2f0644/

I would like to start from here!

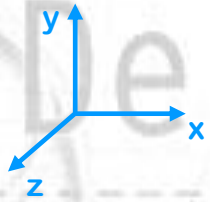
NMR
Spectroscopy

X-Ray
Crystallography


```
N 10.801 -12.147  -5.180
C 11.124 -13.382  -4.414
C 11.769 -12.878  -3.130
O 11.175 -12.047  -2.441
C 12.075 -14.259  -5.228
C 11.564 -14.543  -6.638
C 12.414 -15.556  -7.397
O 12.439 -16.745  -6.995
O 13.043 -15.163  -8.409
N 12.965 -13.355  -2.800
C 13.656 -12.864  -1.611
C 14.518 -11.718  -2.102
```

Compu Methods

3D



… and this is our favorite hunting place!

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A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

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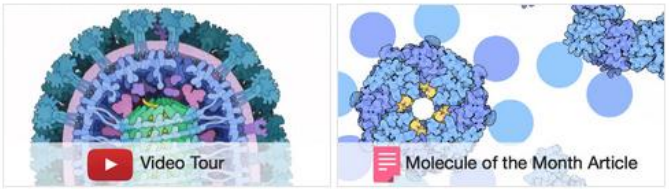
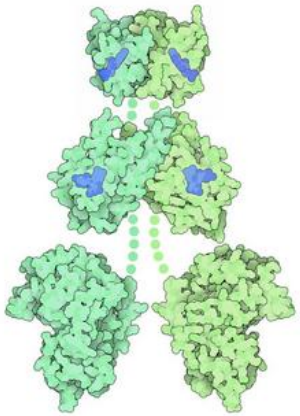
Structure and Health Focus: Ebola Virus Proteins



March Molecule of the Month



Phototropin

PDB… in numbers:

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Other Statistics

PDB Data Distribution by Experimental Method and Molecular Type

Copy | CSV

Experimental Method	Proteins	Nucleic Acids	Protein/NA Complex	Other	Total
X-Ray	126880	2012	6547	8	135447
NMR	11062	1279	259	8	12608
Electron Microscopy	2277	31	800	0	3108
Other	256	4	6	13	279
Multi Method	129	5	2	1	137
Total	140604	3331	7614	30	151579

125334 structures in the PDB have a structure factor file.
9949 structures in the PDB have an NMR restraint file.
3701 structures in the PDB have a chemical shifts file.
3167 structures in the PDB have a 3DEM map file.

Data cellected: May 2019

PDB… in numbers:

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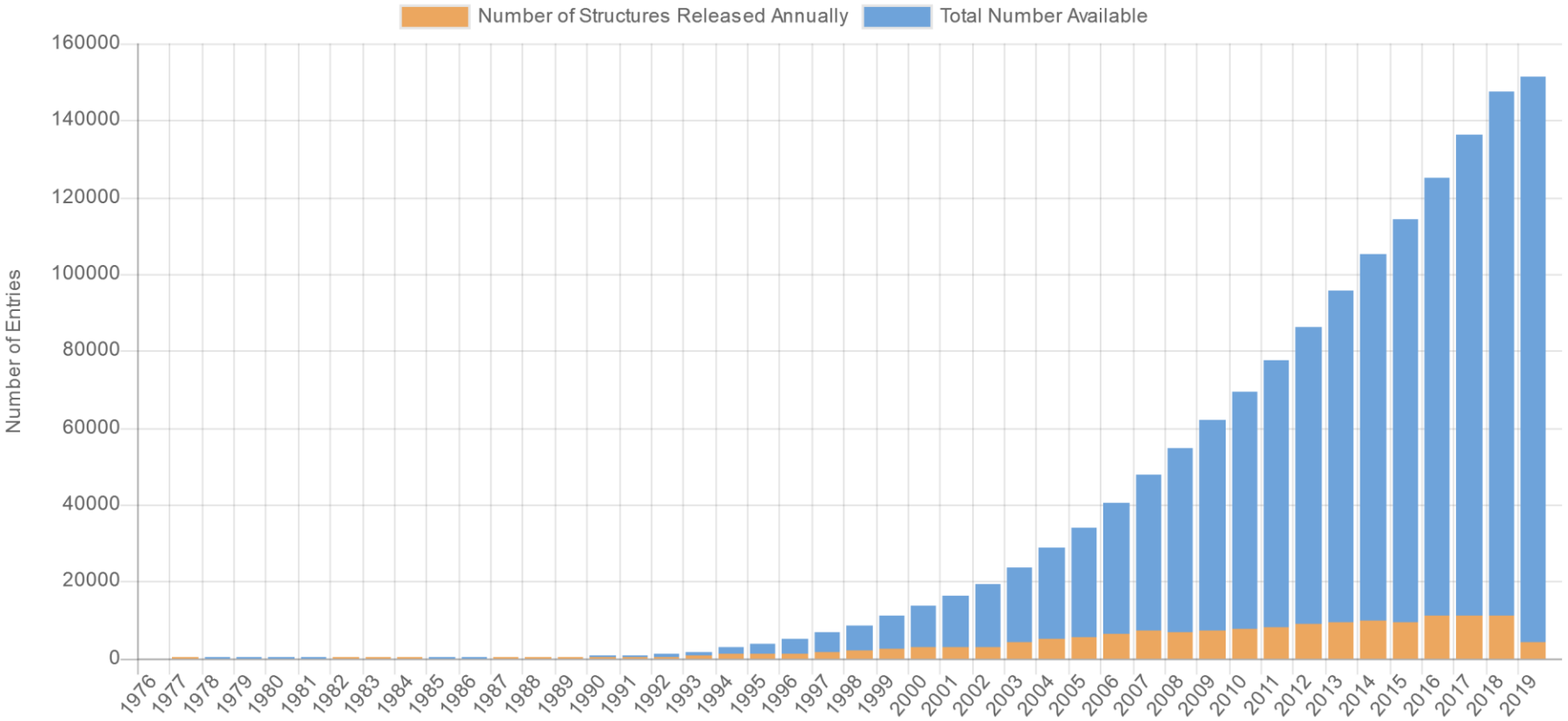


Data collected: May 2019

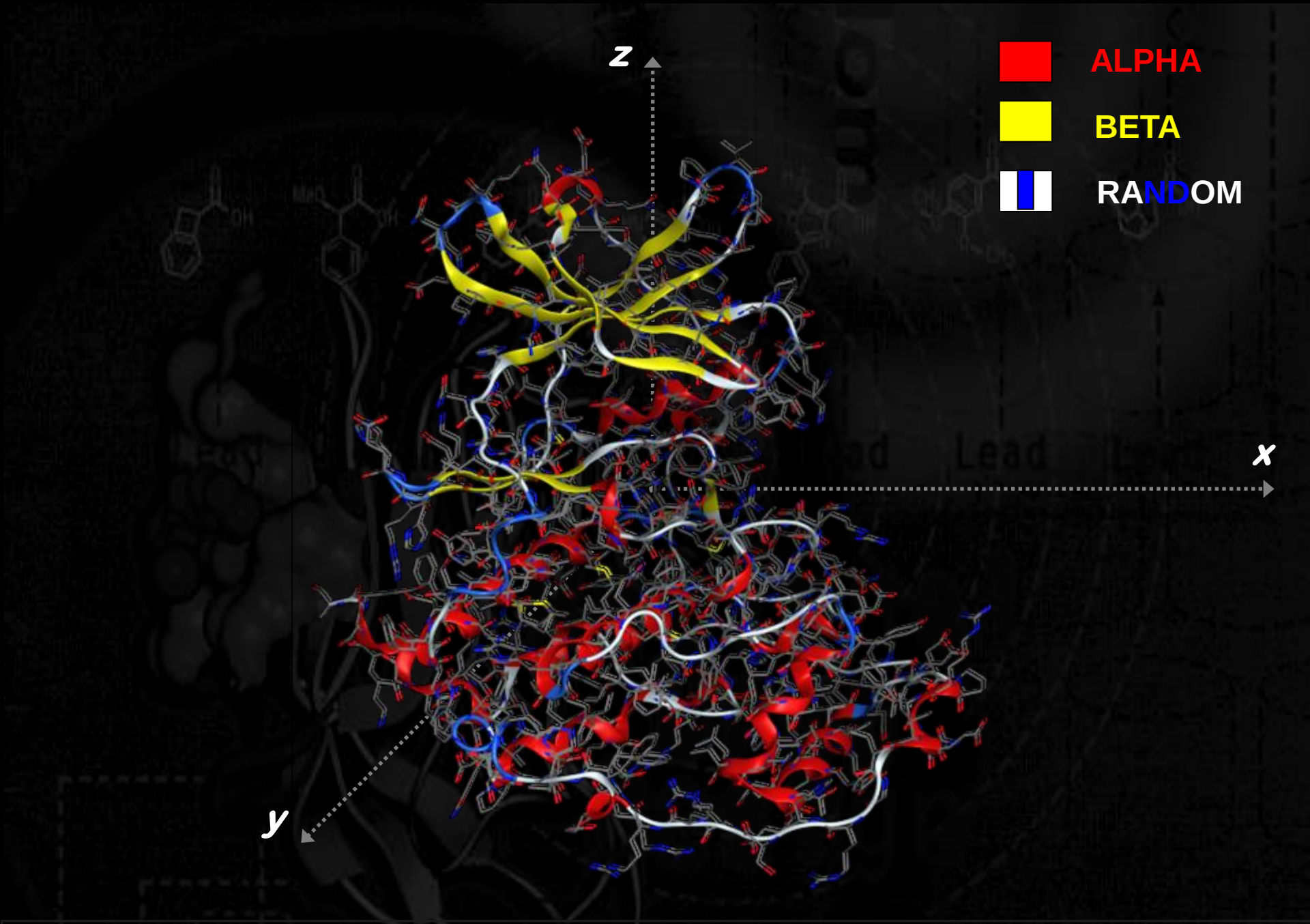
From small molecule to its biological target…

z

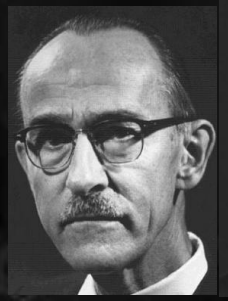
C (x, y, z)

x

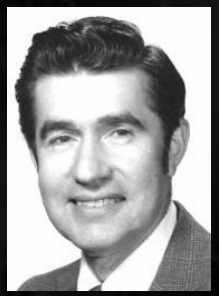
y



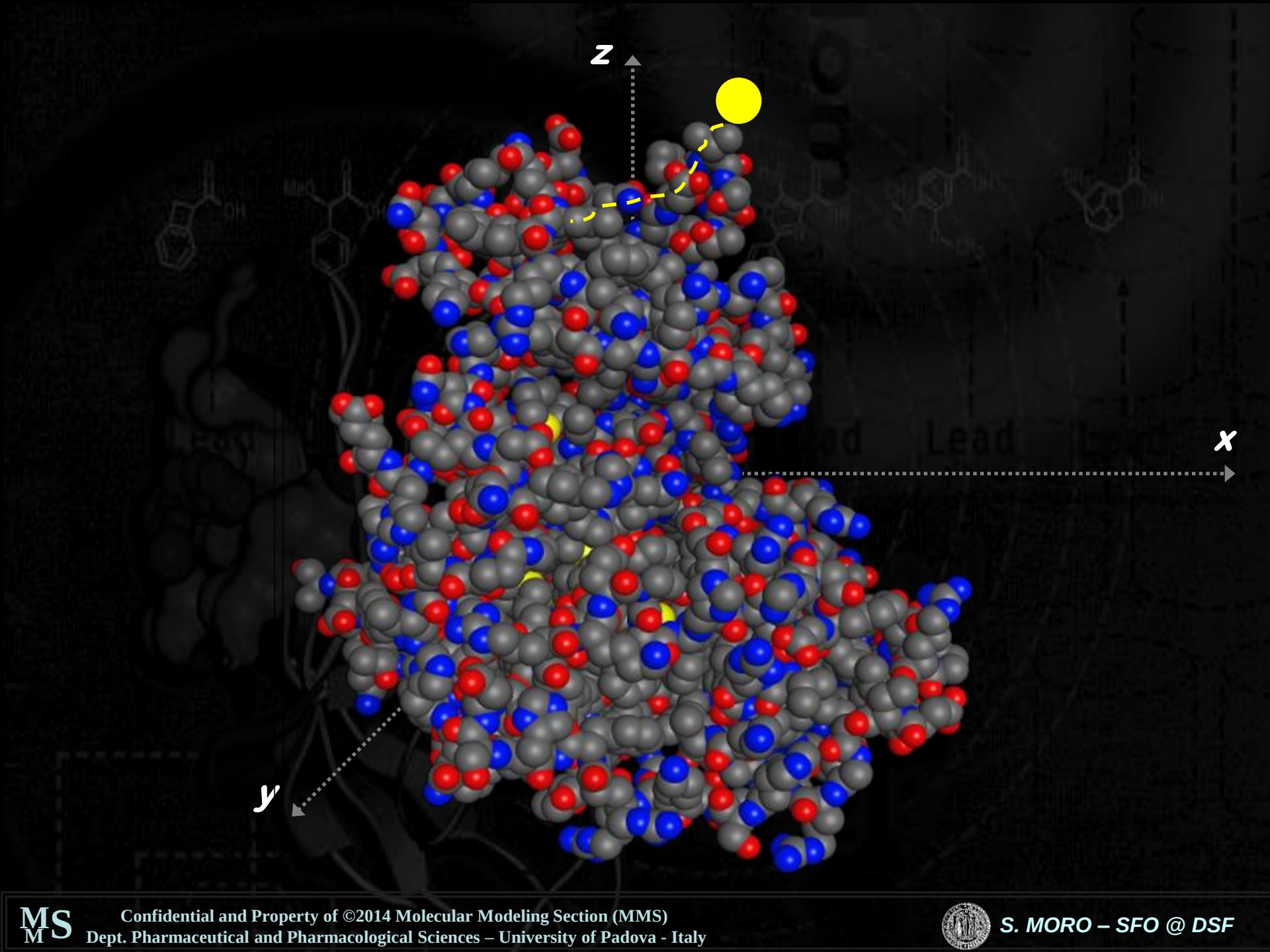
CPK model:

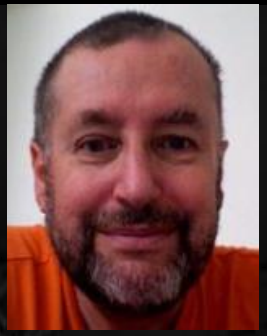


Robert Corey Linus Pauling



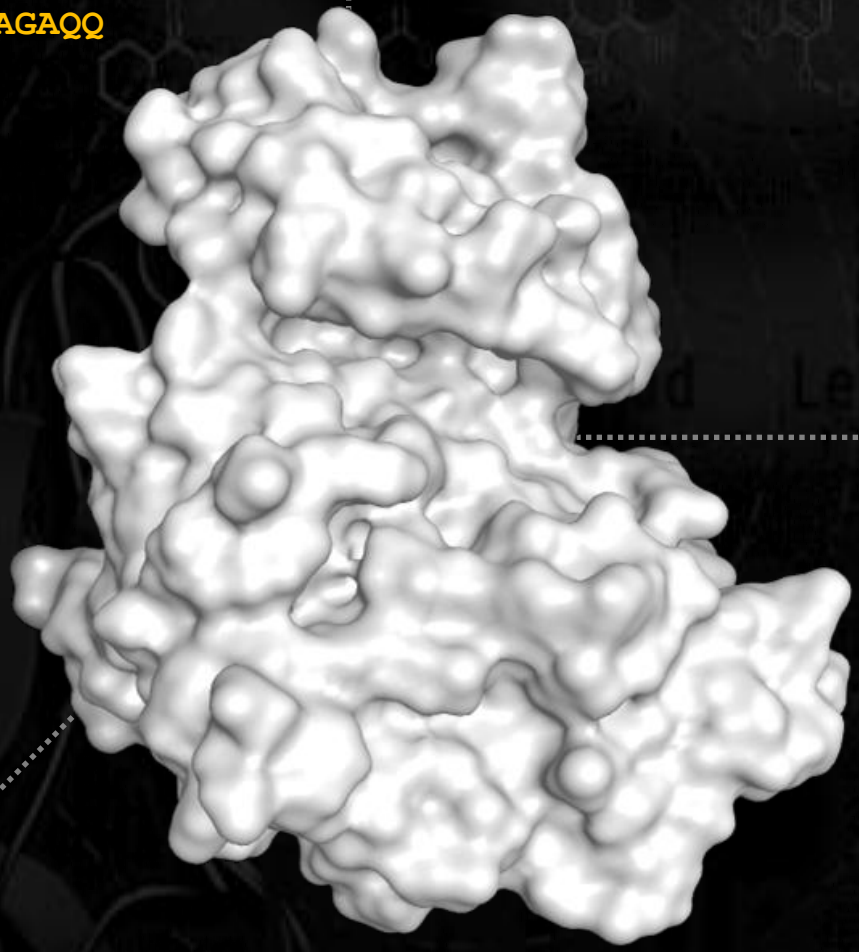
Walter Koltun





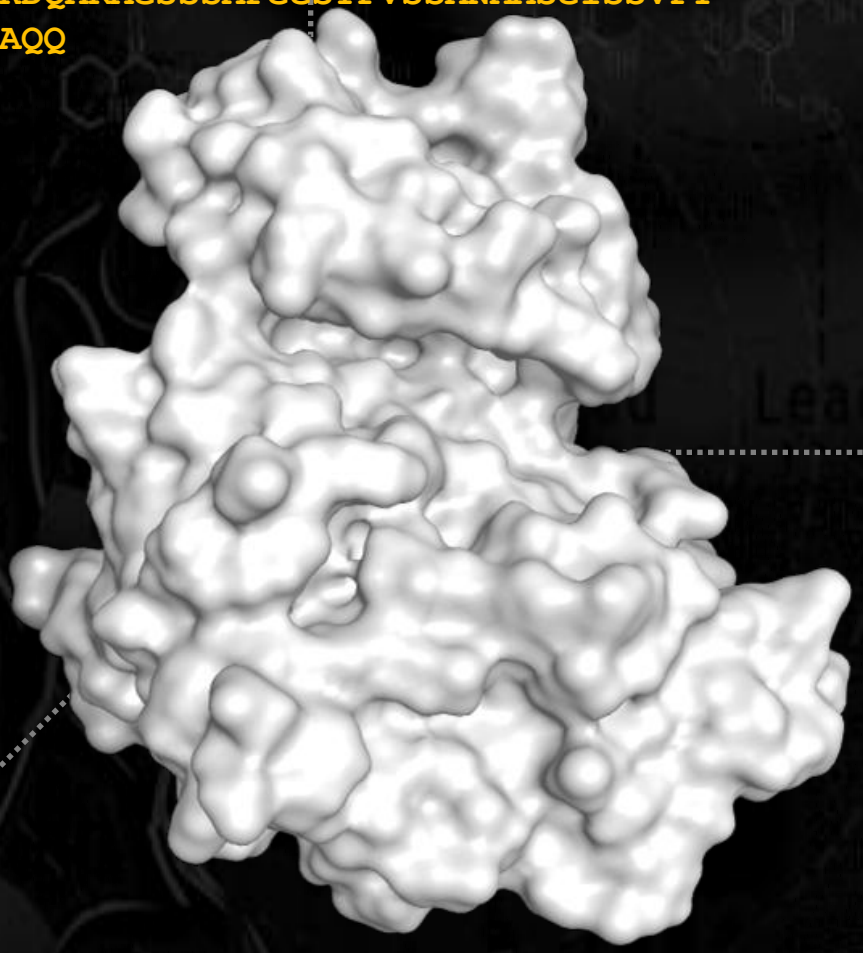
Michael Connolly

MSGPVPSRARVYTDVNTHRPREYWDYESHVVEWGNQDDYQLVRKLGRGKYSEVFEAINIT
NNEKVVVKILKPVKKKKIKREIKILENLRGGPNIITLADIVKDPVSRTPALVFEHVNNTD
FKQLYQTLTDYDIRFYMYEILKALDYCHSMGIMHRDVKPHNVMIDHEHRKLRLIDWGLAE
FYHPGQEYNVRVASRYFKGPELLVDYQMYDYSLDMWSLGCMLASMIFRKEPFFHGHDNYD
QLVRIAKVLGTEDLYDYIDKYNIELDPRFNDILGRHSRKRWERFVHSENQHLVSPEALDF
LDKLLRYDHQSRLTAREAMEHPYFYTVVKDQARMGSSSMPGGSTPVSSANMMSGISSVPT
PSPLGPLAGSPVIAAANPLGMPVPAAAGAQQ



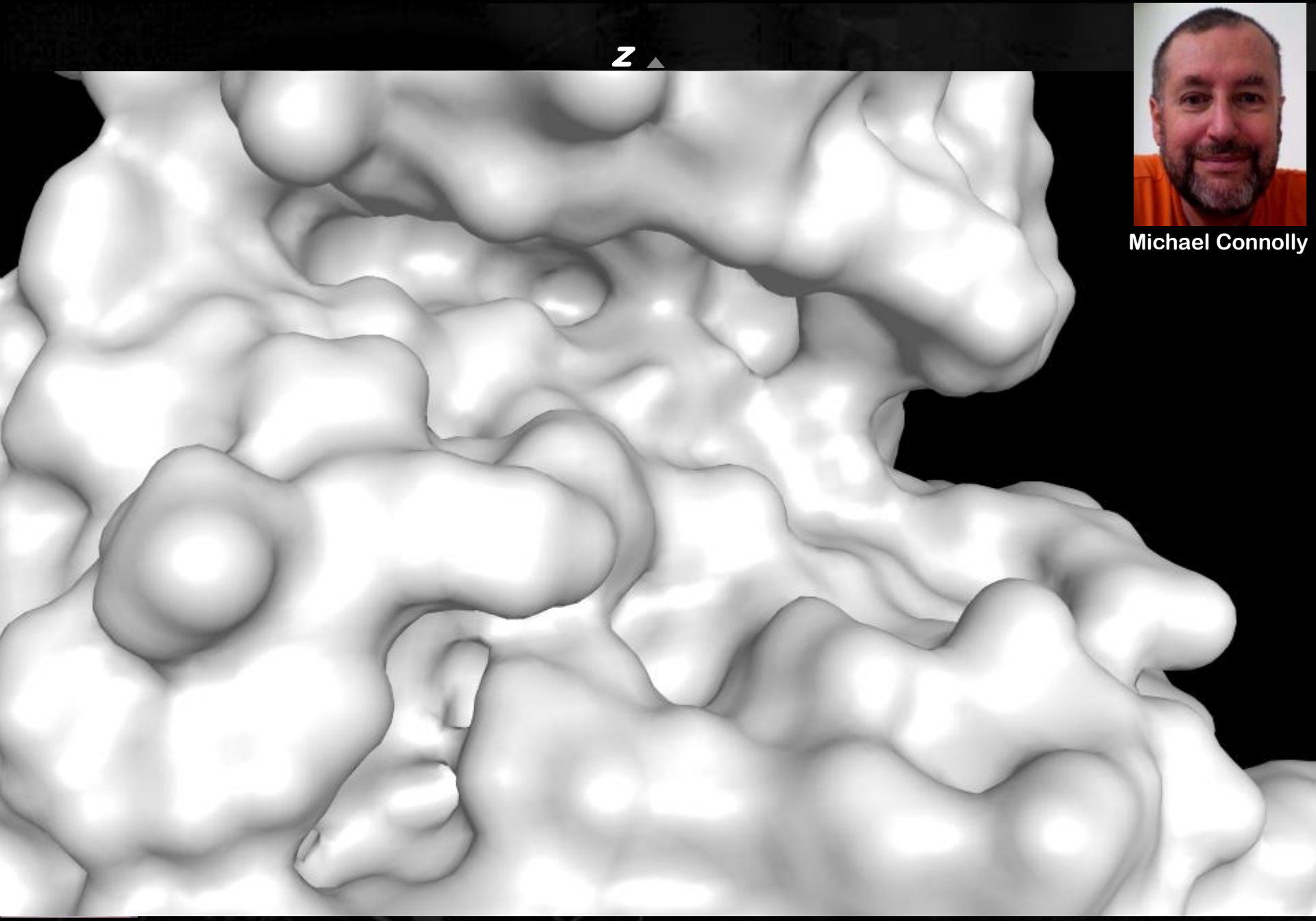
From sequence to topology... from topology to function

MSGPVPSRARVYTDVNTHRPREYWDYESHVVEWGNQDDYQLVRKLGRGKYSEVFEAINIT
NNEKVVVKILKPVKKKKIKREIKILENLRGGPNIITLADIVKDPVSRTPALVFEHVNNTD
FKQLYQTLTDYDIRFYMYEILKALDYCHSMGIMHRDVKPHNVMIDHEHRKLRLIDWGLAE
FYHPGQEYNVRVASRYFKGPELLVDYQMYDYSLDMWSLGCMLASMIFRKEPFFHGHDNYD
QLVRIAKVLGTEDLYDYIDKYNIELDPRFNDILGRHSRKRWERFVHSENQHLVSPEALDF
LDKLLRYDHQSRLTAREAMEHPYFYTVVKDQARMGSSSMPGGSTPVSSANMMSGISSVPT
PSPLGPLAGSPVIAAANPLGMPVPAAAGAQQ

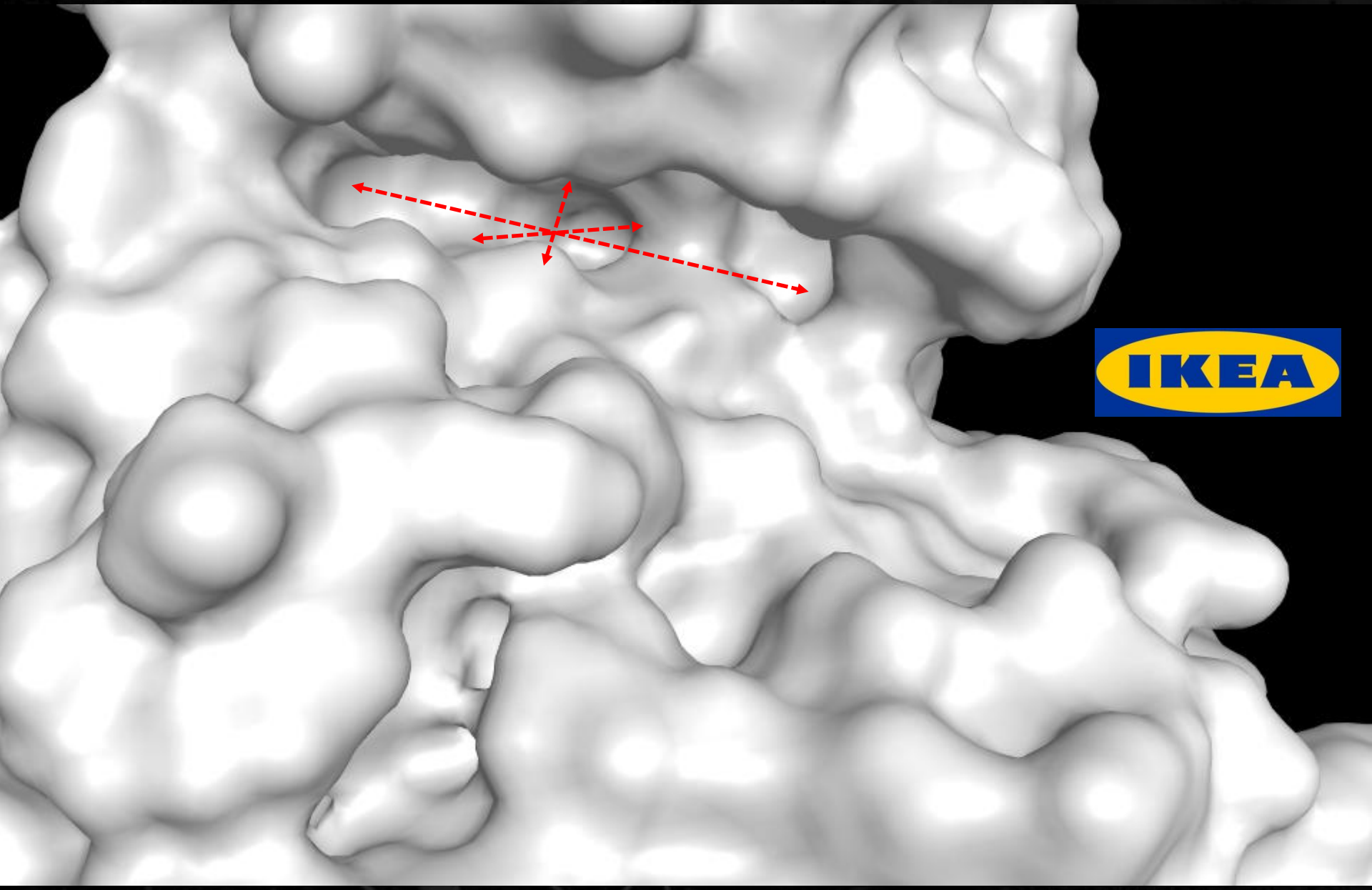


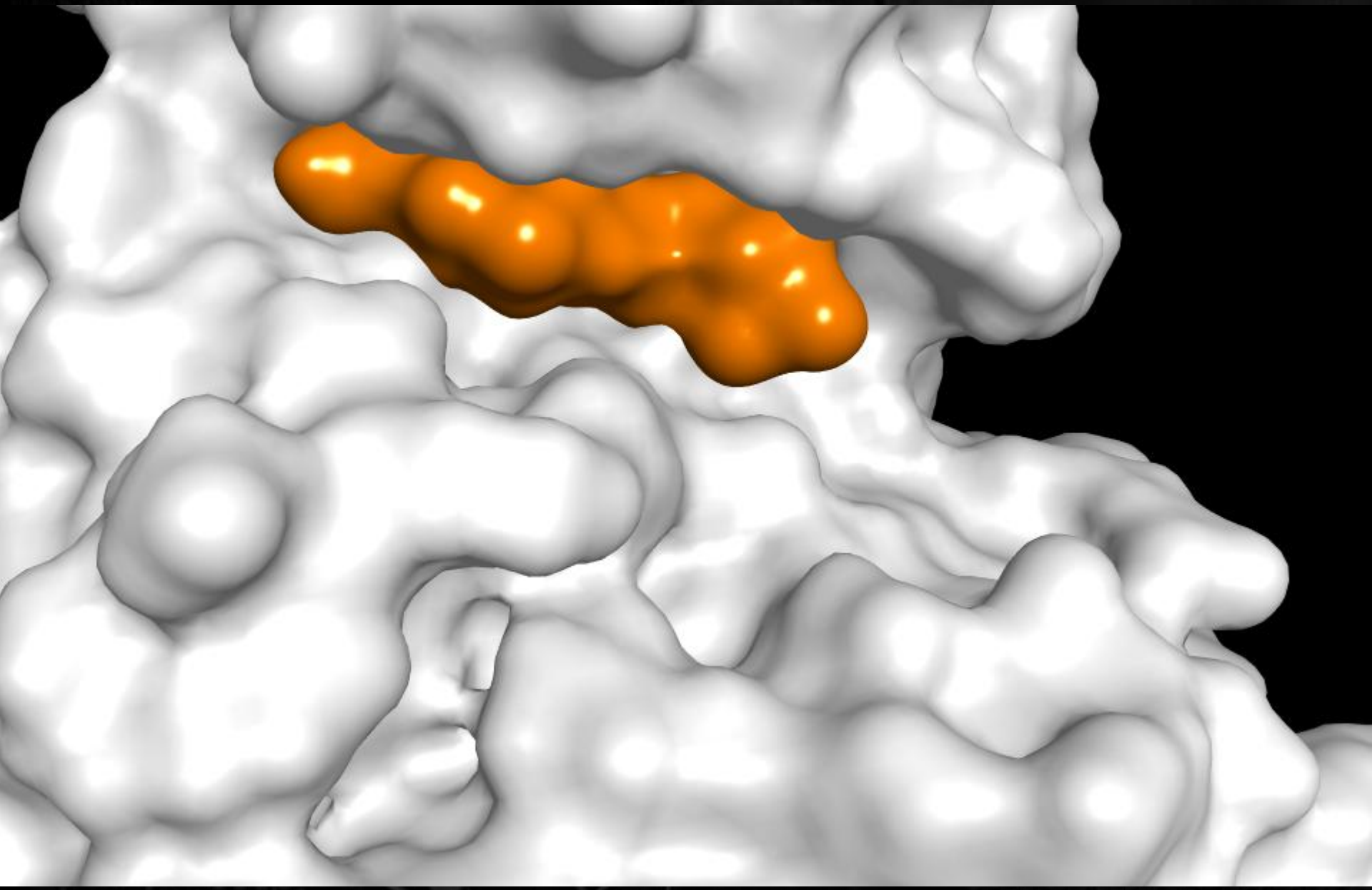
1. where?
2. how?
3. how long?

From sequence to topology... from topology to recognition

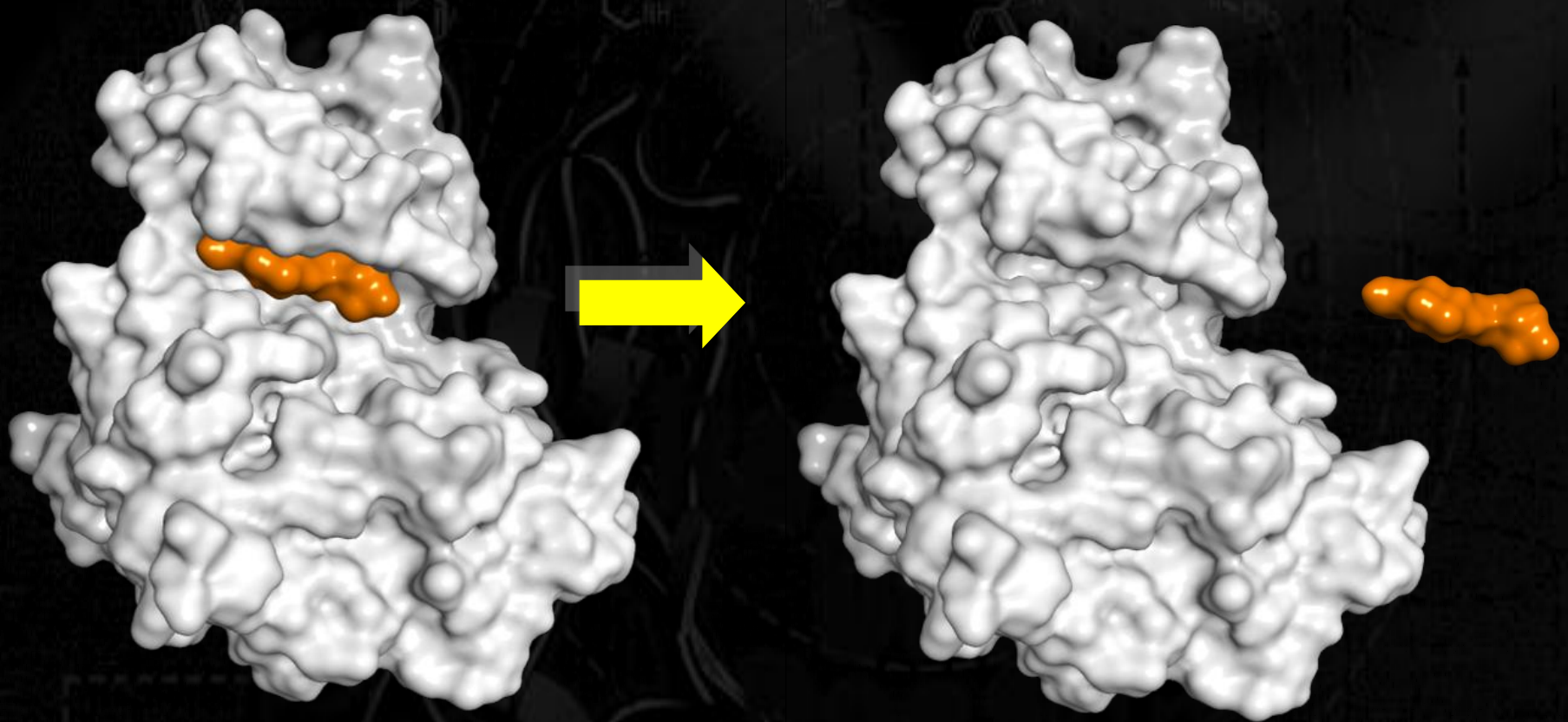


Michael Connolly

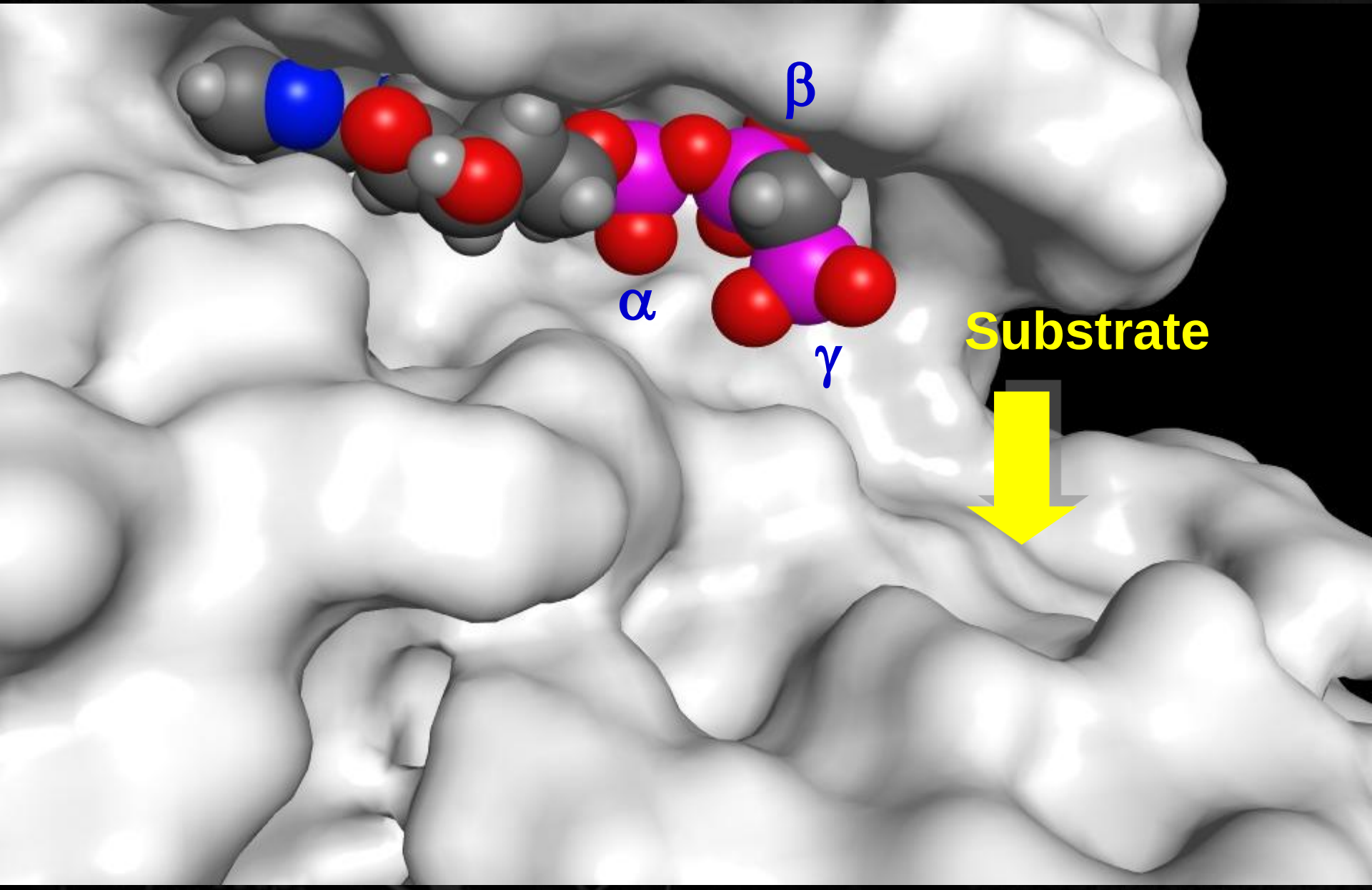


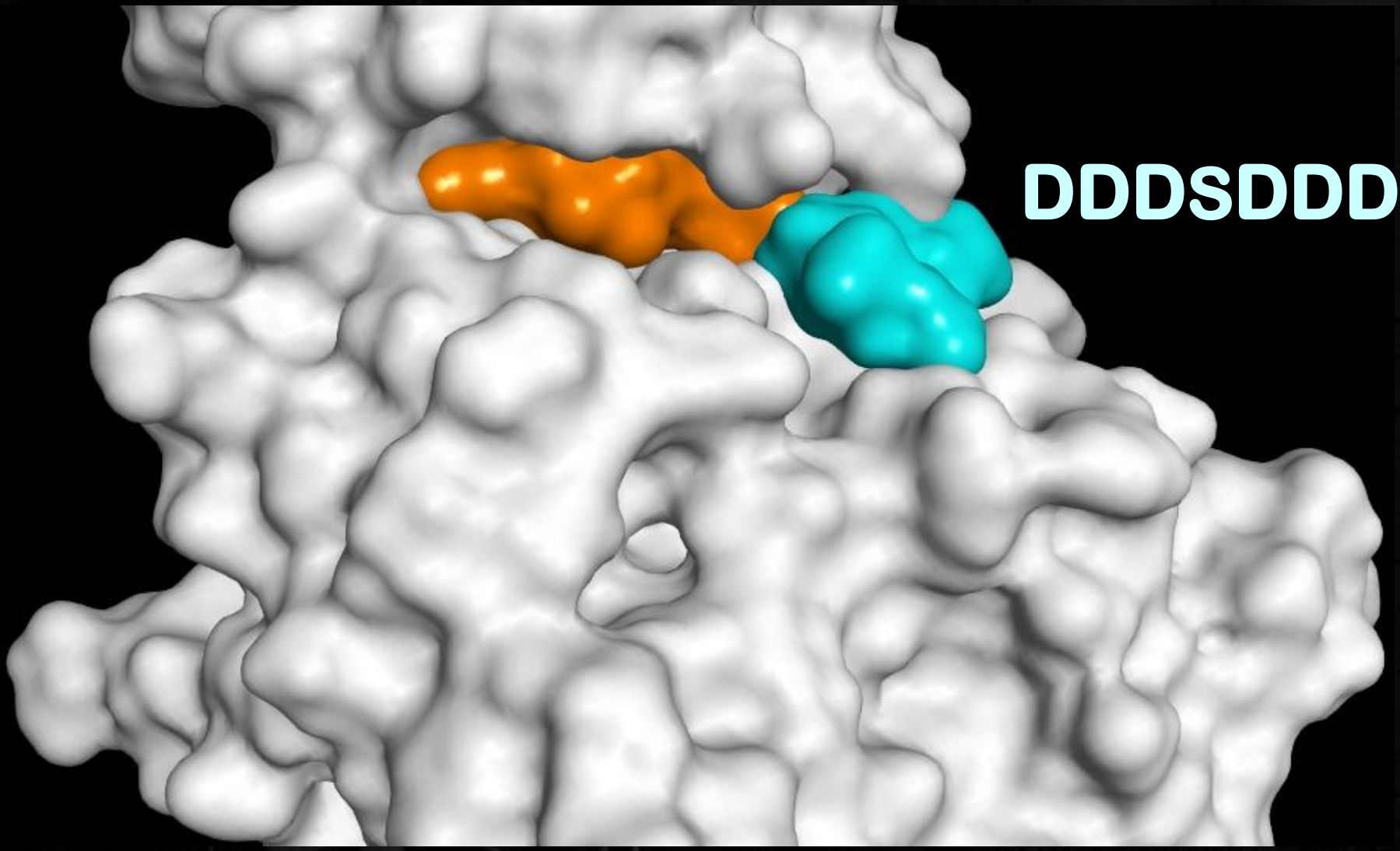


You have now a wonderful tool to estimate the topological complementarity between a cavity and its ligand:

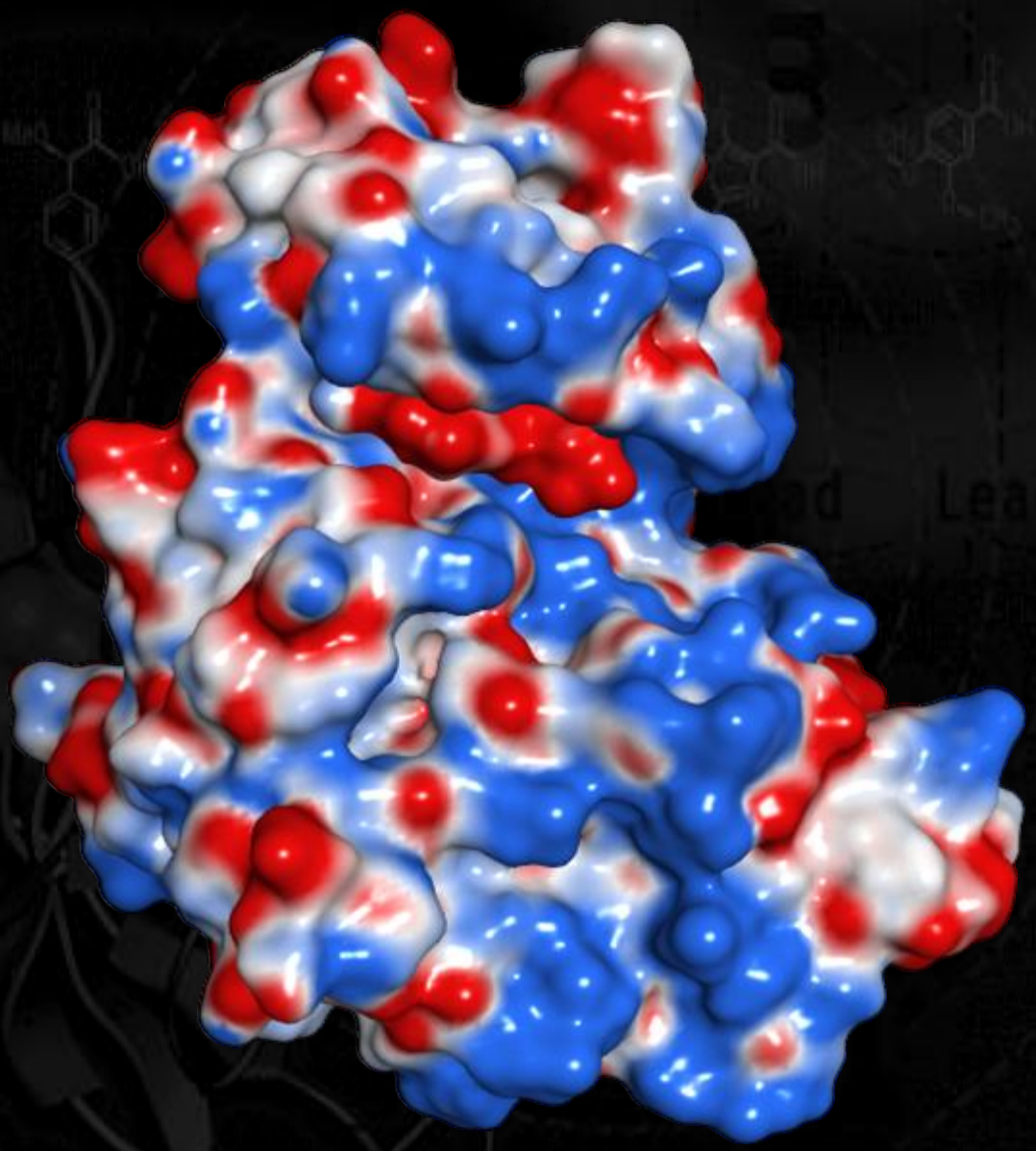


$$\text{Complementarity} \propto \text{Vol}_{\text{cavity}} - \text{Vol}_{\text{ligand}}$$





... very charming!



$V_{el} < 0$

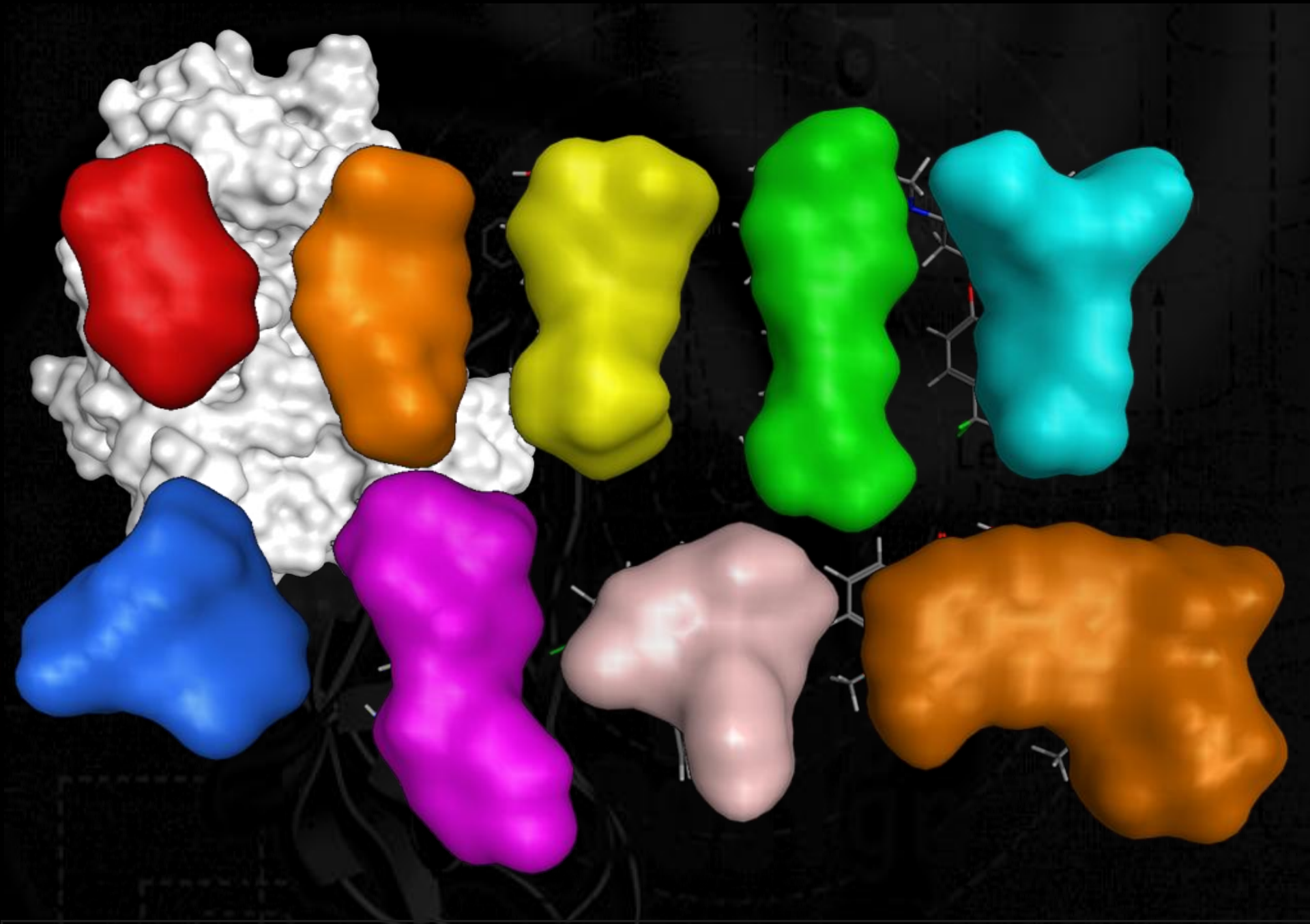
$V_{el} = 0$

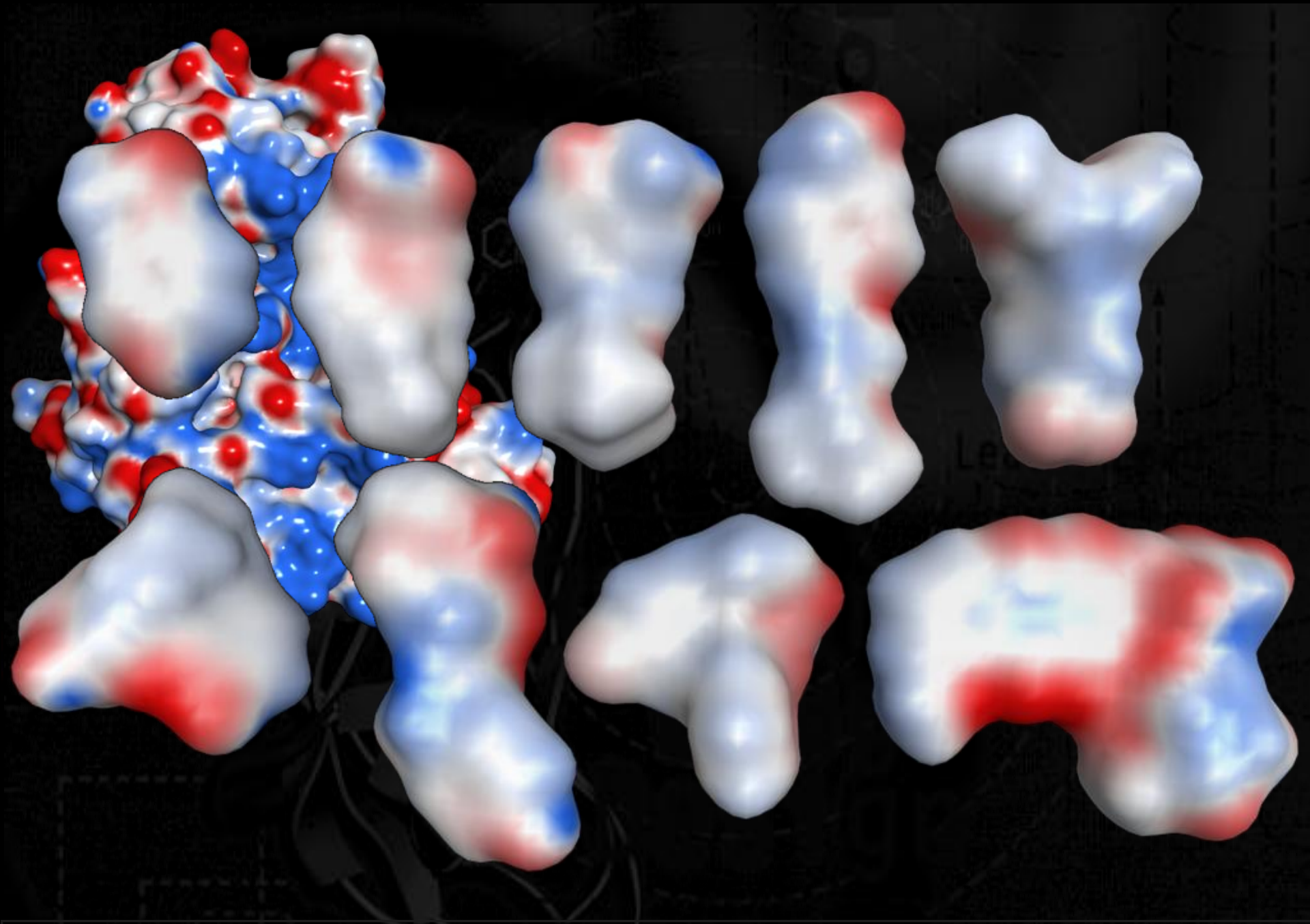
$V_{el} > 0$

Again, try to respond with the same intellectual honesty:

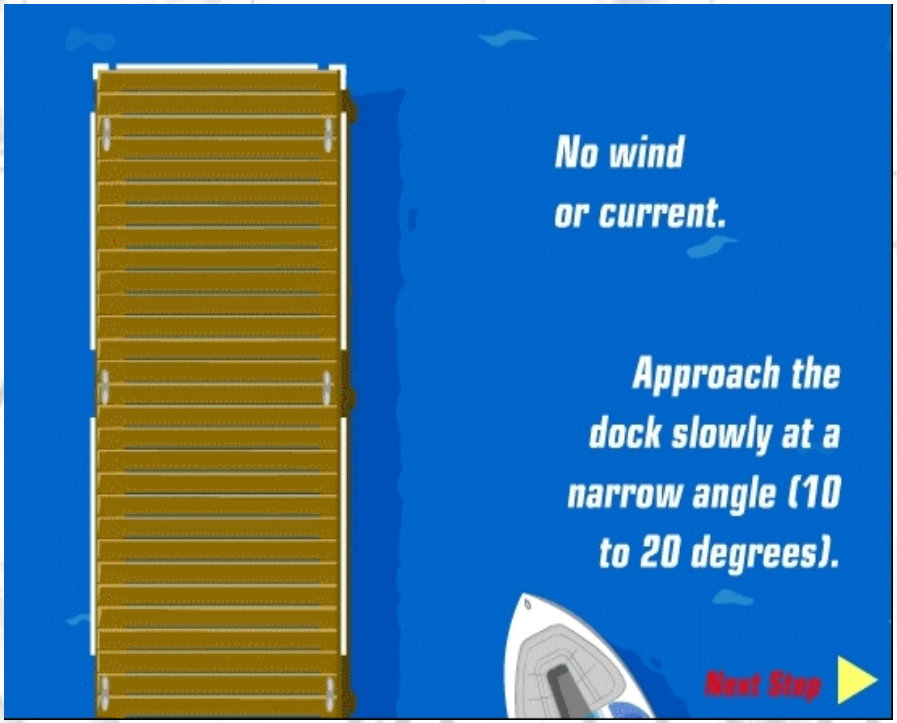
Is a drug candidate designable?

We will return later on this concept…



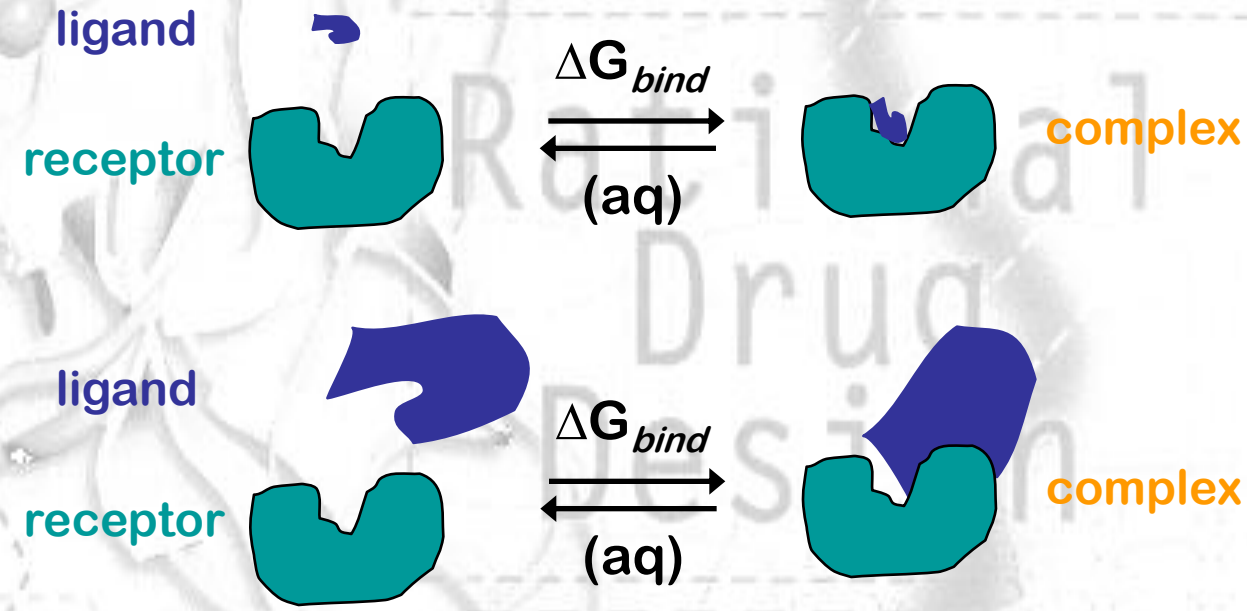


Docking & Scoring

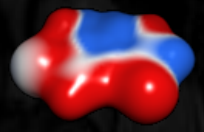


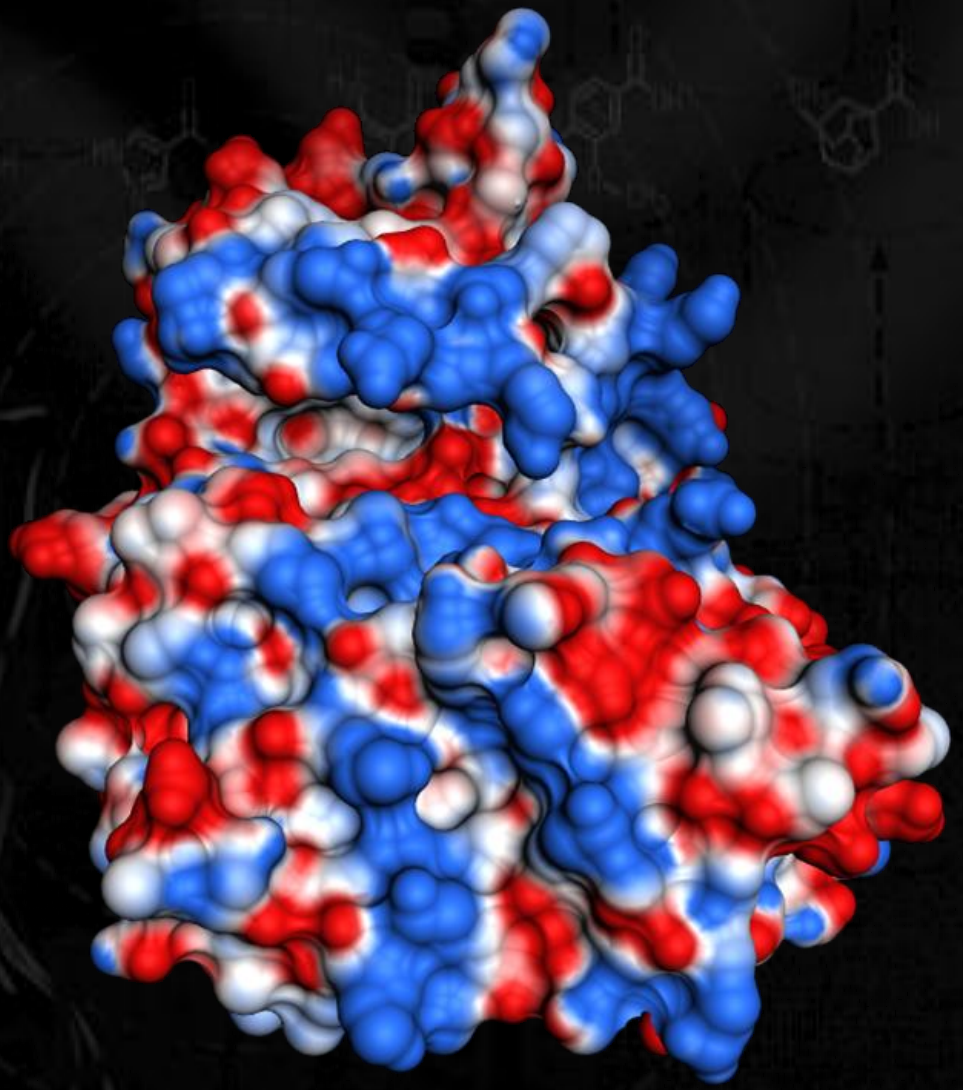
What does it mean Docking?

Generally speaking, any computational strategy that use 3D information about the "receptor" to predict *binding modes* and *affinities* for different ligands.



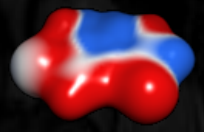
Here is the problem...

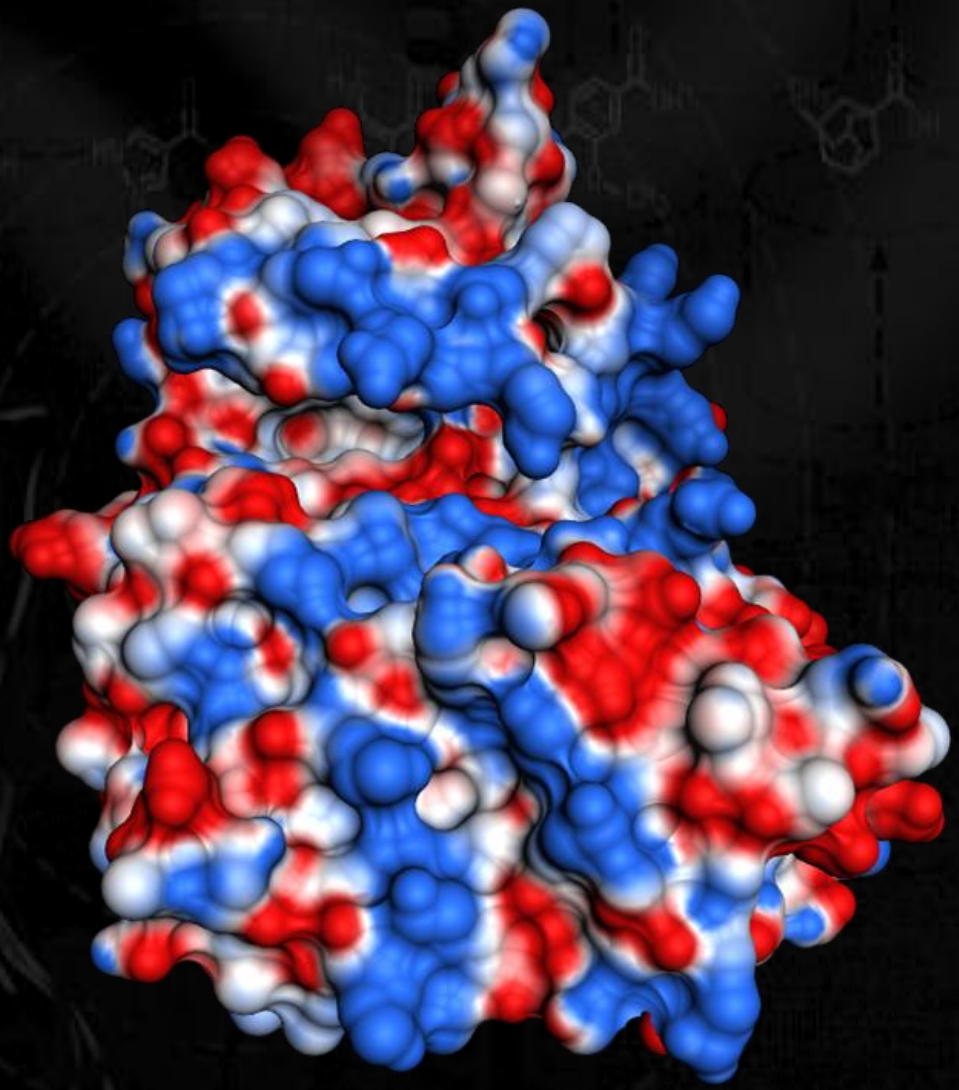




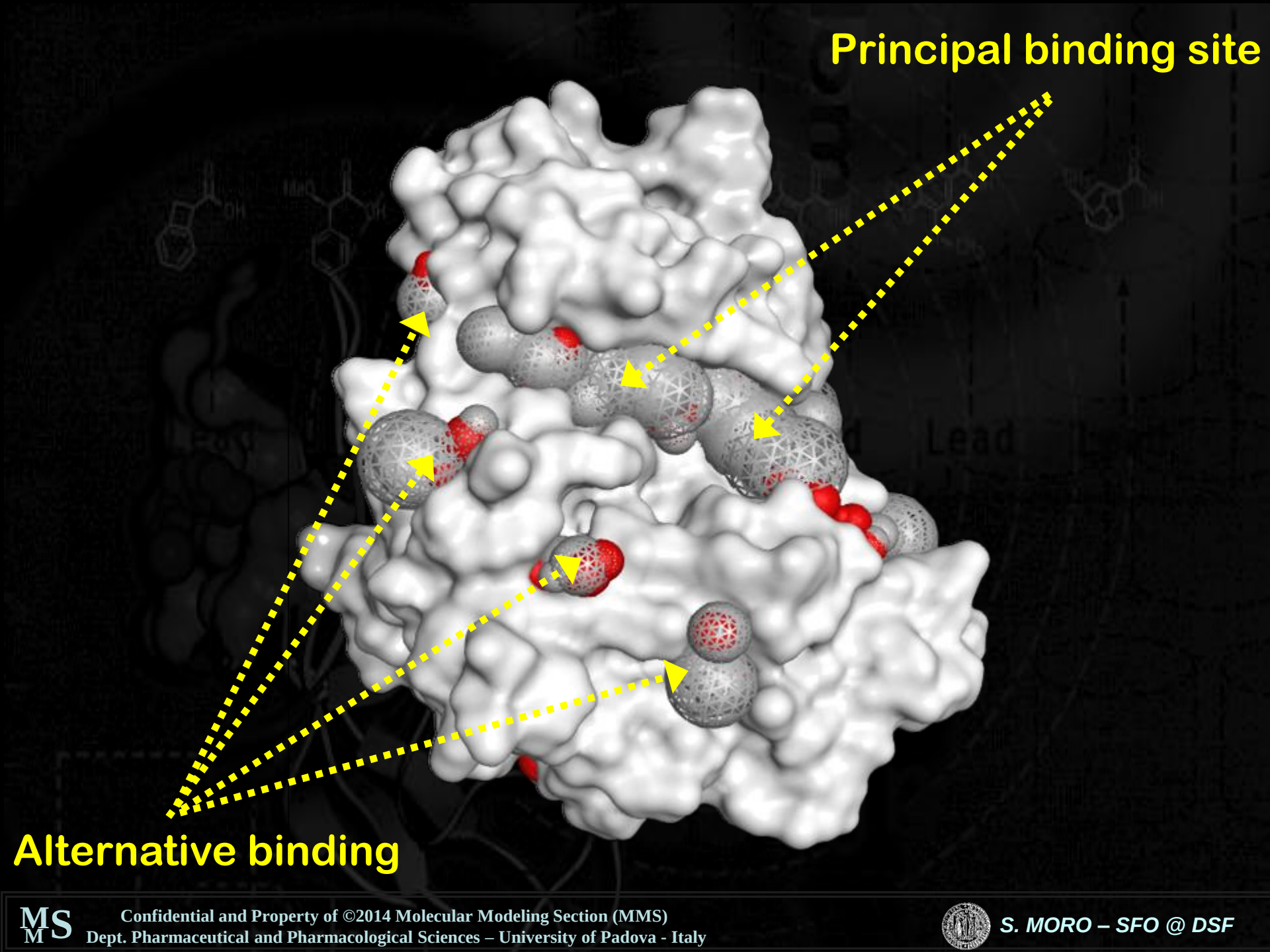
1. where?
2. how?
3. how long?

Virtualize docking and scoring...

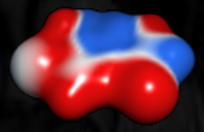


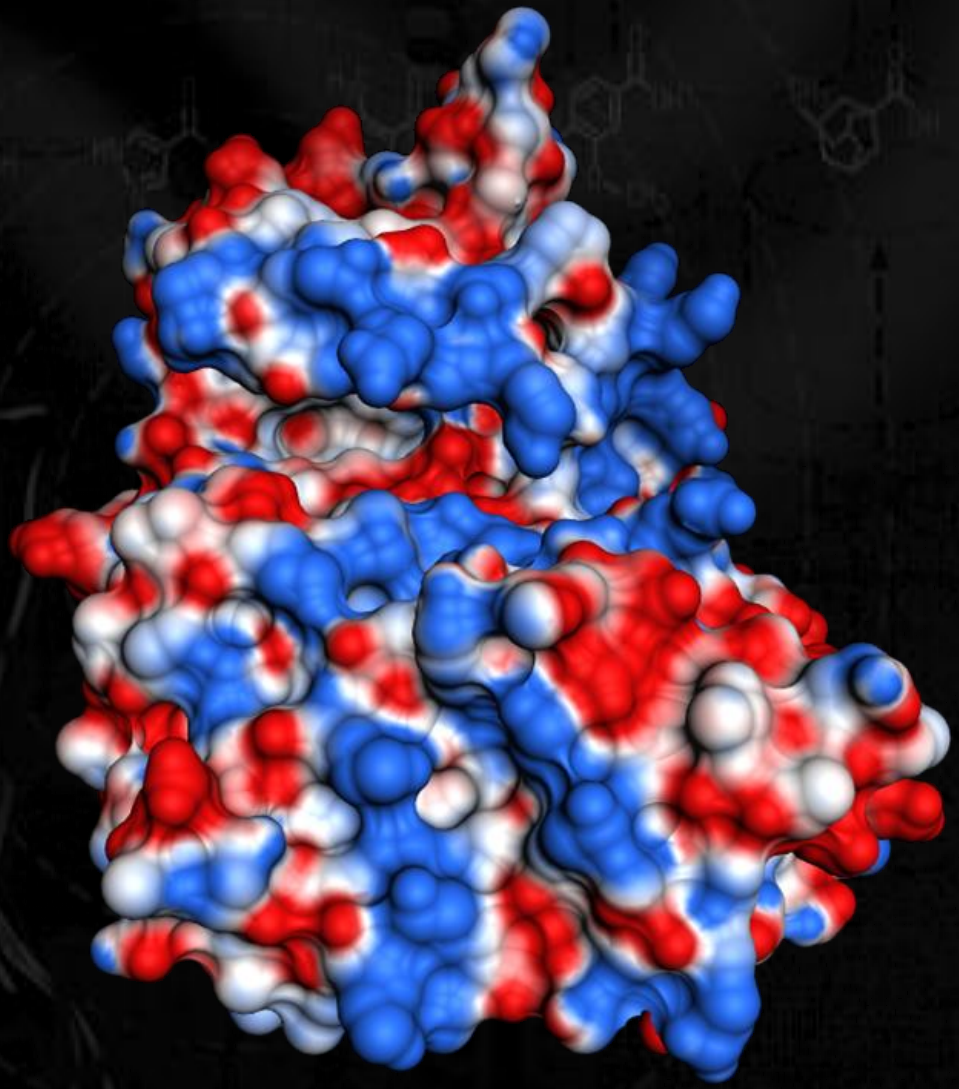


1. where?



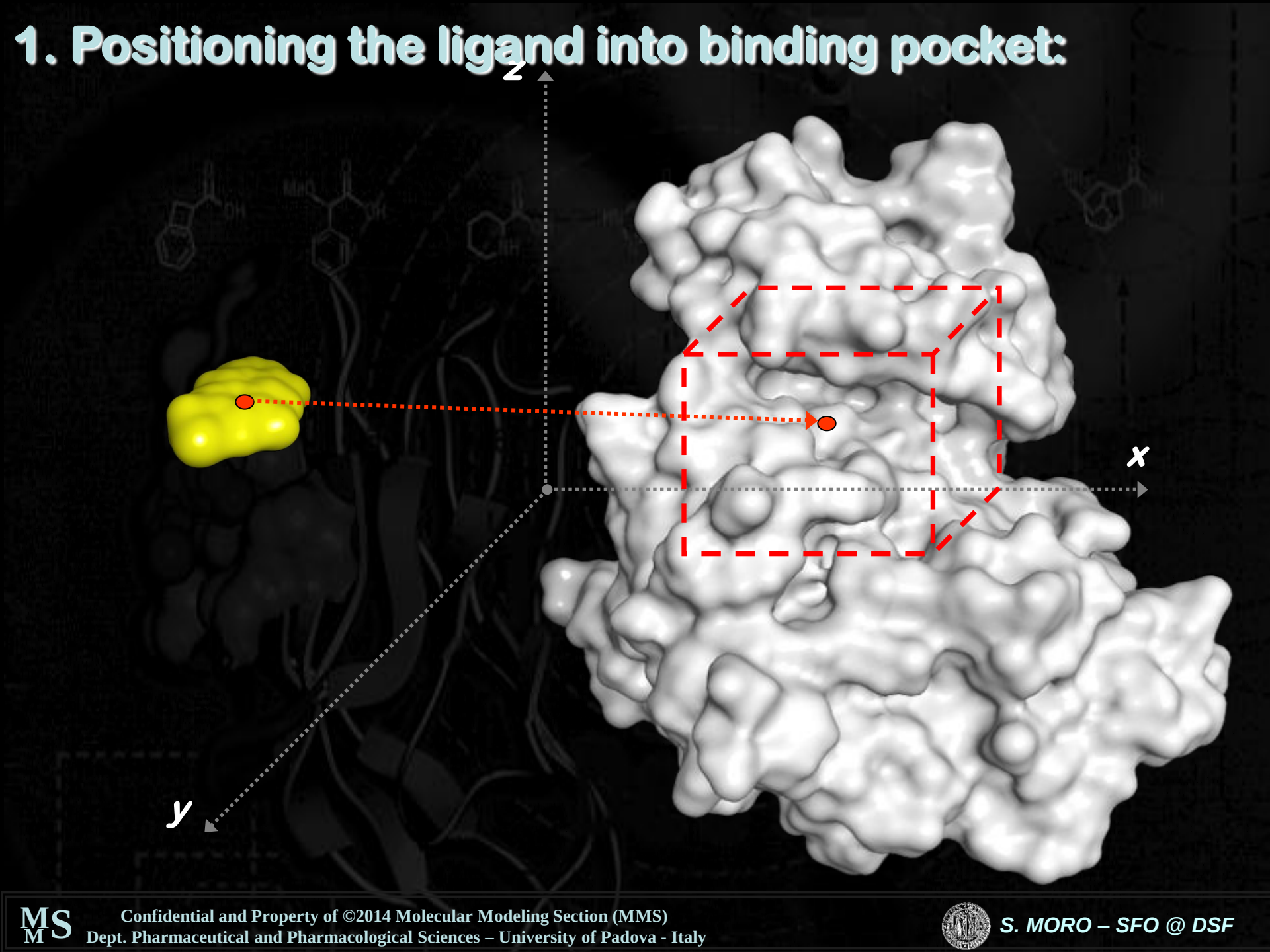
Virtualize docking and scoring…



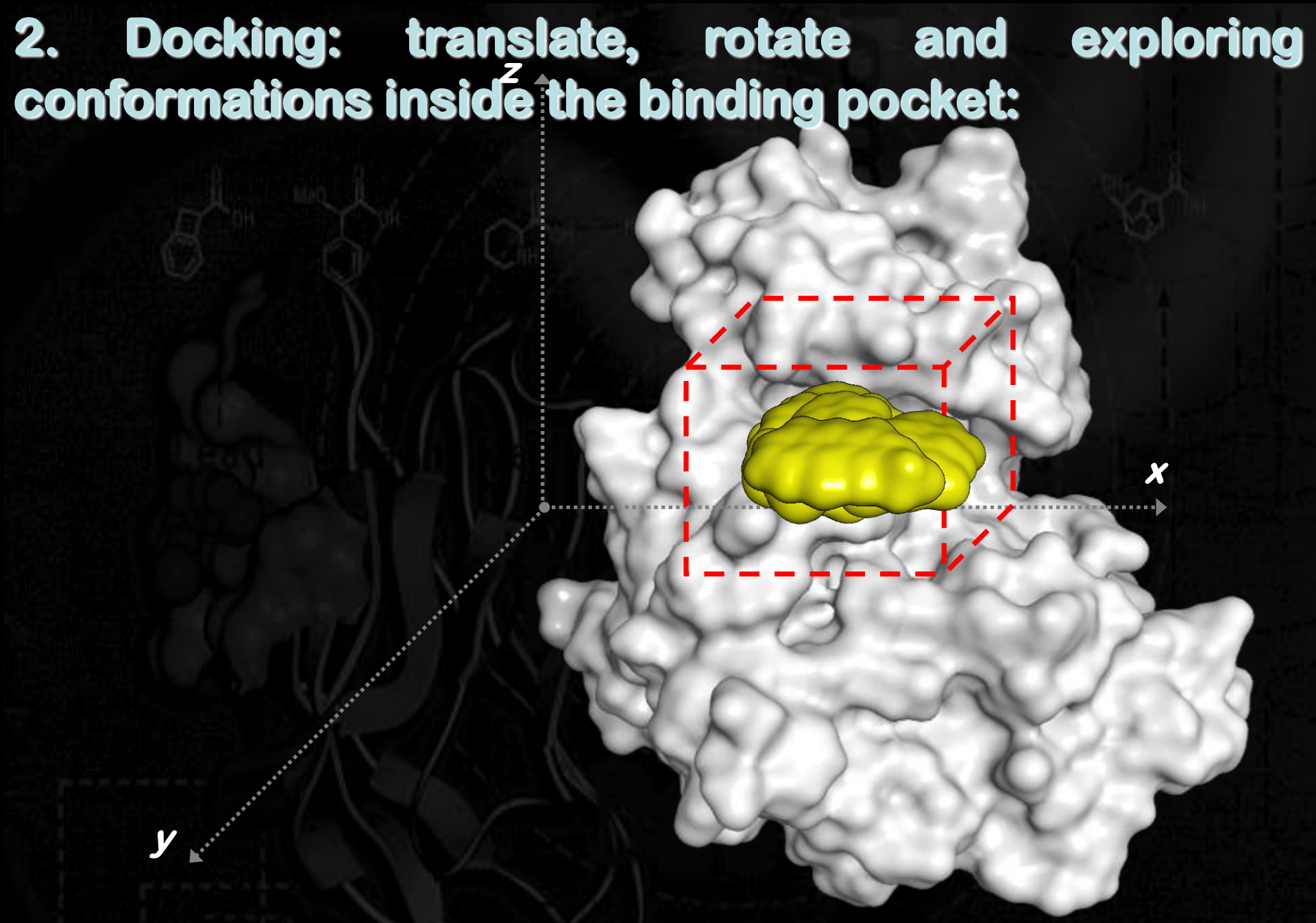


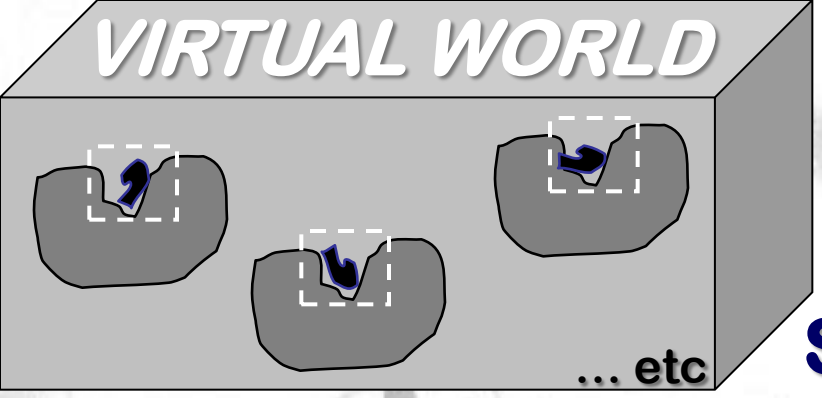
1. where?
2. how?

1. Positioning the ligand into binding pocket:



2. Docking: translate, rotate and exploring conformations inside the binding pocket:





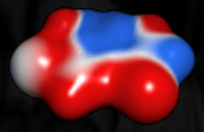
Some definitions:

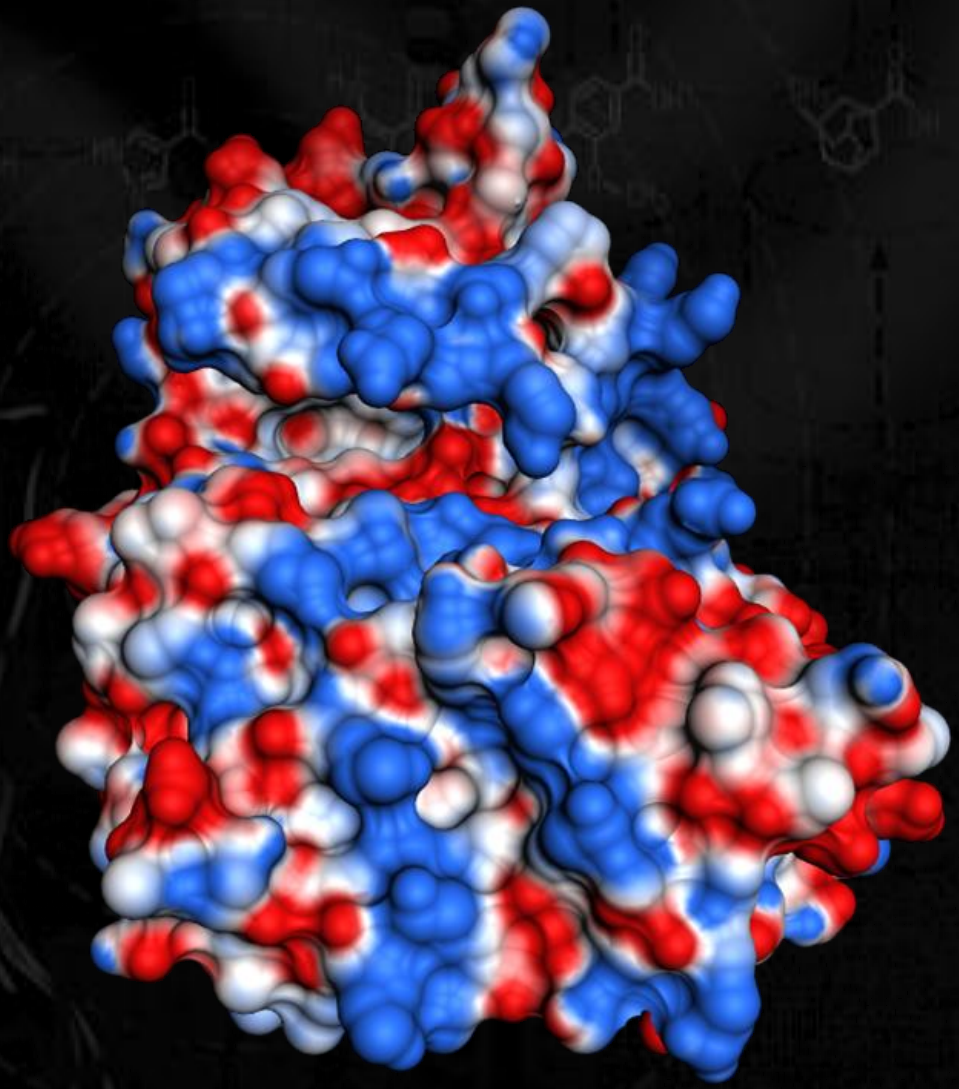
We define as POSE:

a. **the respective orientation of the ligand *vs* protein;**

b. **the bound conformation of the ligand.**

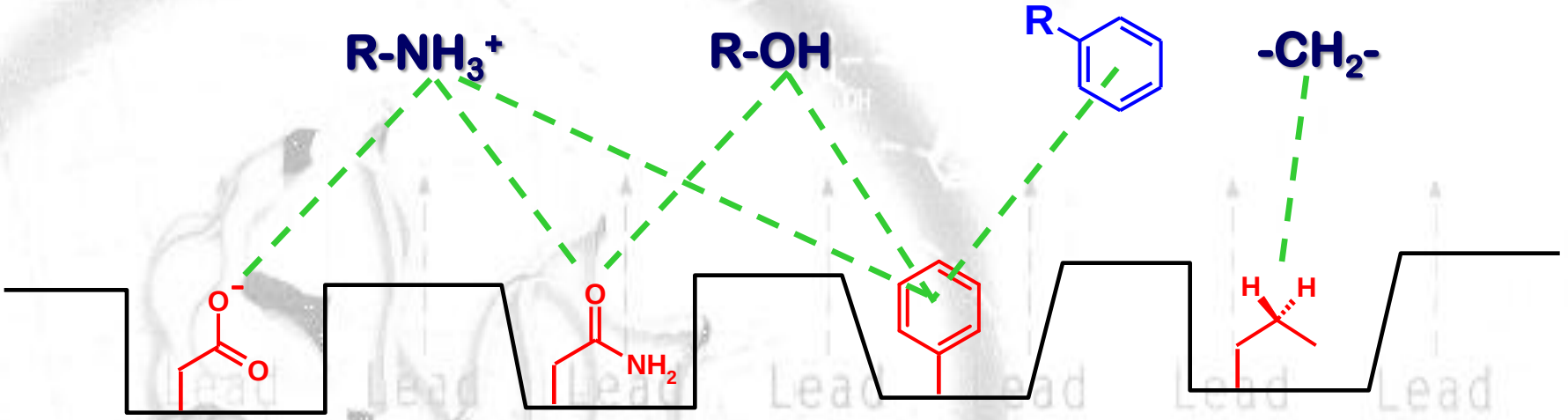
Virtualize docking and scoring…





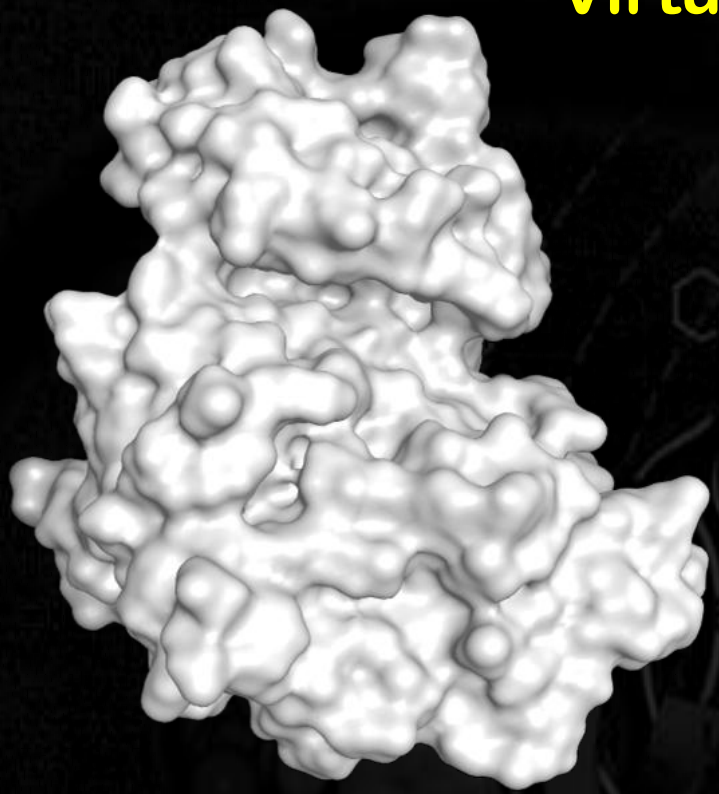
1. where?
2. how?
3. how long?

Empirical Scoring Functions

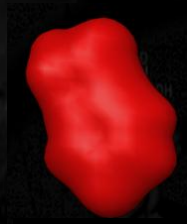


		(kcal/mol)
charge-charge interaction (*ionic bond*):	$-\Delta G^0 \cong$	5 ÷ 10
charge-dipole interaction:	$-\Delta G^0 \cong$	1 ÷ 7
charge-π interaction:	$-\Delta G^0 \cong$	8 ÷ 10
hydrogen bond:	$-\Delta G^0 \cong$	1 ÷ 7
charge transfer interaction:	$-\Delta G^0 \cong$	1 ÷ 6
π-π interaction:	$-\Delta G^0 \cong$	1 ÷ 2
dipole-dipole interaction (van der Waals):	$-\Delta G^0 \cong$	0.5 ÷ 1

Virtual screening by molecular docking



Scoring:



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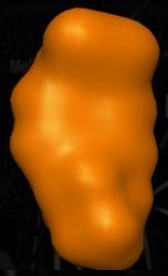
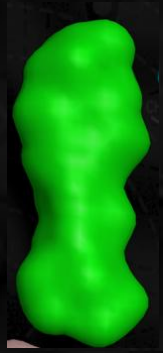


43

37

Scoring:



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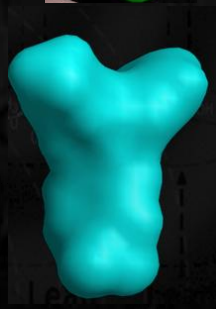

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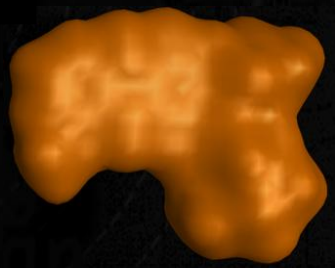

3

GRAZIE
PER LA PAZIENZA