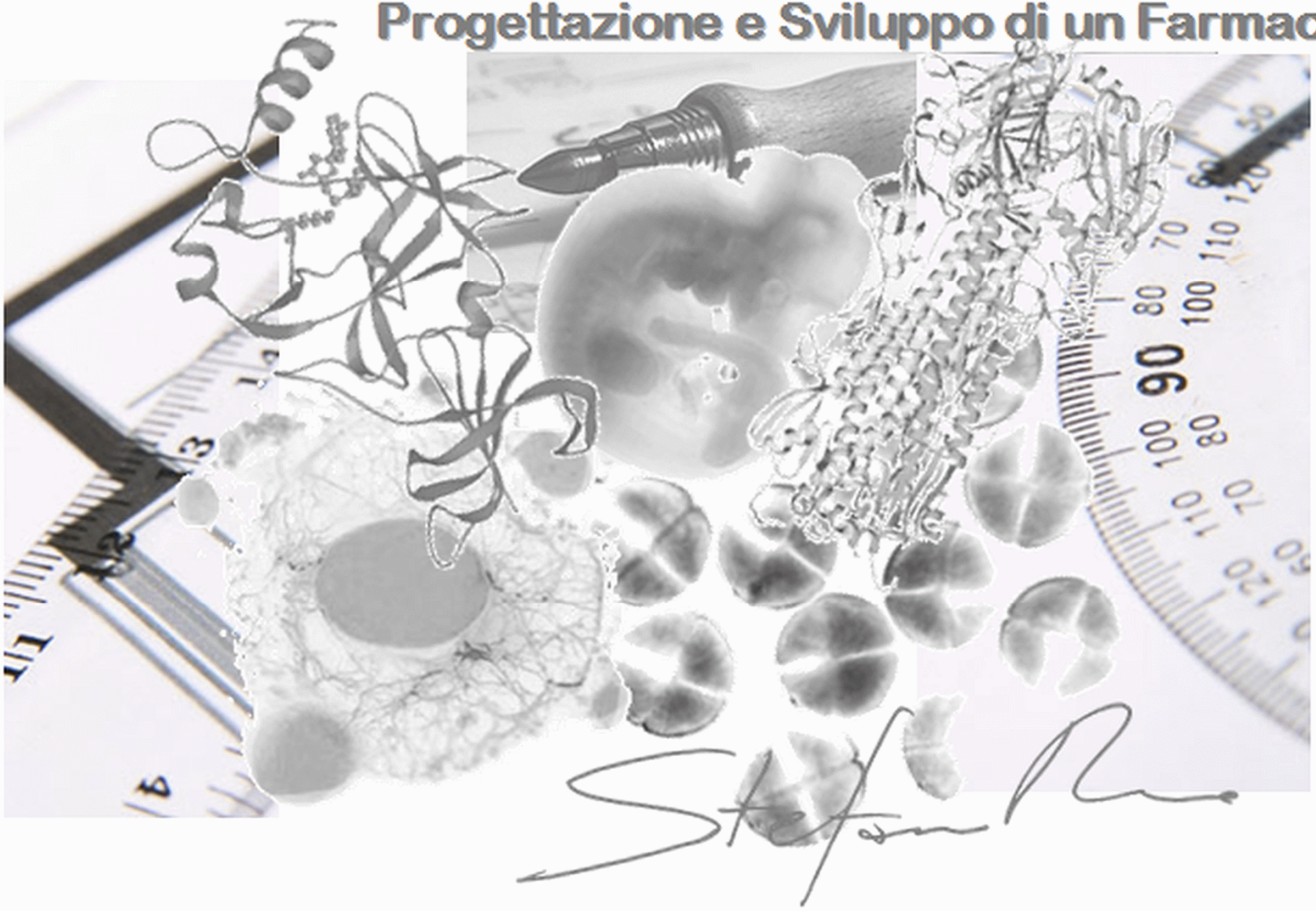
Progettazione e Sviluppo di un Farmaco



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MMS Molecular Modeling Section

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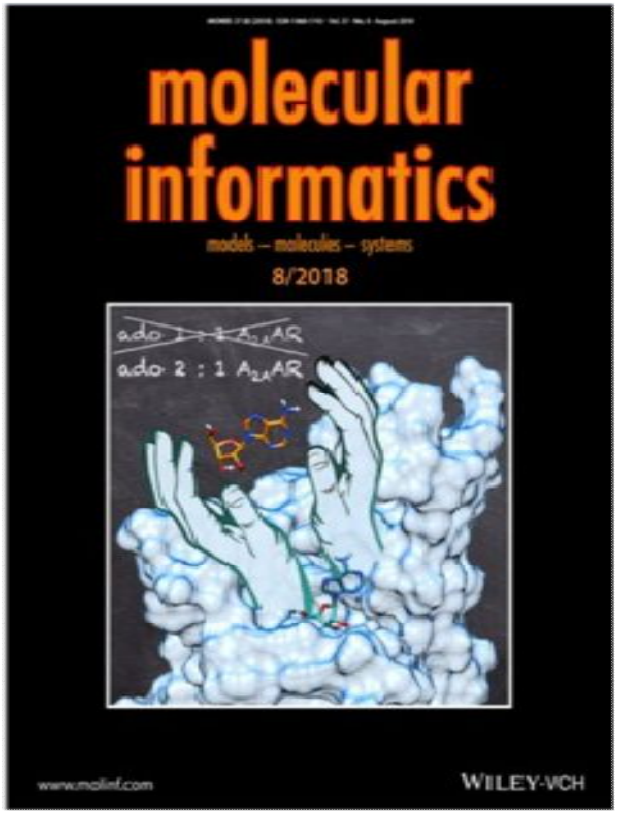

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pril 01. 2016

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March 14-15, 2019

Molecular Dynamics: Today - Bologna... more

MMS: Latest Hot Publication

Bissaro et 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...

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- Chimica Farmaceutica 2 (CTF)
- Progettazione e Sviluppo di un Farmaco (CTF)
- Biomodeling (BT
- Chemoinformat (ISF)
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- Master, PhD Courses

ockBenck tool. more...

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vents

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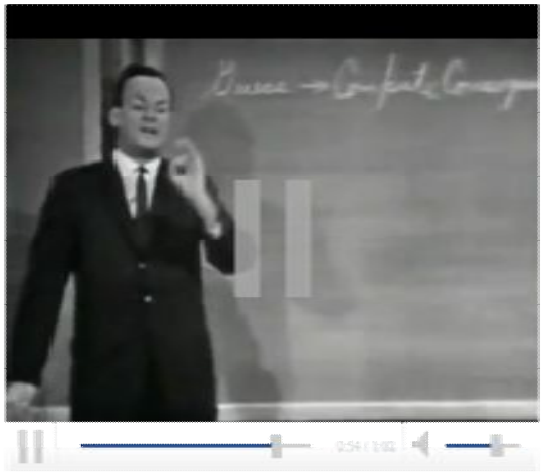
Obbiettivi del percorso formativo:

Il Corso si propone di fornire allo studente le conoscenze di base sulle moderne metodologie computazionali ed informatiche nel campo della progettazione e dell'ottimizzazione di nuovi farmaci, della caratterizzazione a priori delle loro proprietà chimico-fisiche e farmacologiche, e dello studio a livello molecolare dei loro possibili meccanismi d'azione. Il percorso formativo è di carattere teorico anche se è previsto un percorso di esercitazioni virtuali attraverso una piattaforma web-orientata dove lo studente avrà modo di conoscere alcuni degli strumenti informatico/computazionali maggiormente utilizzati sia in ambito accademico sia nelle varie realtà industriali a carattere farmaceutico e biotecnologico. Tutto il materiale presentato durante le lezioni e le esercitazione è in lingua inglese per consentire allo studente di entrare in contatto con la terminologia scientifica correntemente utilizzata internazionalmente in questo ambito.



1. Introduzione alla progettazione di un farmaco			
2. Ligand-based Drug Design (LBDD)			
	Rappresentazioni Molecolari e Similarità Strutturale		
	Ipotesi Farmacoforiche		
	Superfici e Descrittori Molecolari		
	QSARs : introduzione		
	QSARs: elementi di statistica		
3. Structure-based Drug Design (SBDD)			

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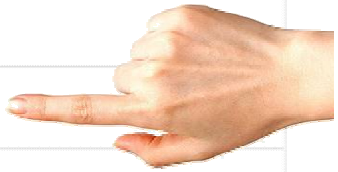

	Analisi Conformazionale		
	Energetica Molecolare		
	Docking & Scoring Virtual Screening		
	Dinamica Molecolare		
	Elementi di Chimica Quantistica		

Per coloro che ancora non si fossero stressati abbastanza, ecco alcuni suggerimenti per procurarsi gratuitamente un "visualizzatore molecolare" per poter continuare a giocare anche in futuro:	
1. Chimera (UCSF)	
2. Pymol (DeLano Scientific LLC):	
3. VMD (UIUC):	
4. Discovery Studio Visualizer (Accelrys):	
5. ICM-Browser (MolSoft):	
6. Molecular Viewer (Molegro):	

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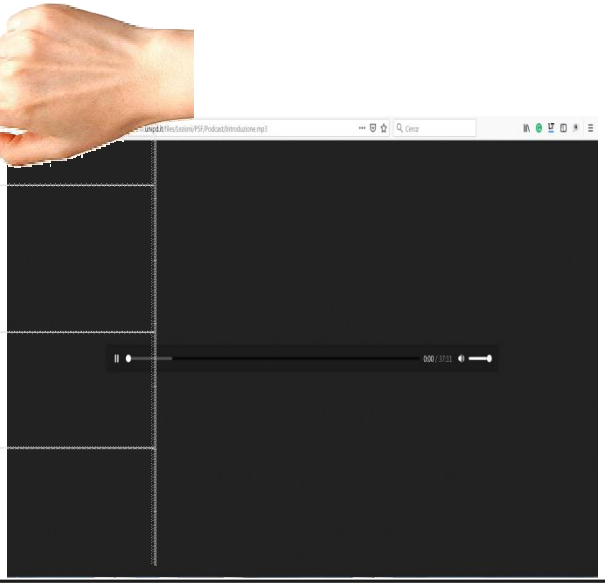
Have a nice listening!

1. Introduzione alla progettazione di un farmaco		Parte 1
2. Ligand-based Drug Design (LBDD)		
	Dal candidato precoce (hit) a quello maturo (lead)	Parte 1 Parte 2 Parte 3 Parte 4
	Rappresentazioni Molecolari	Parte 1 Parte 2 Parte 3
	Similarità Strutturale	Parte 1 Parte 2 Parte 3



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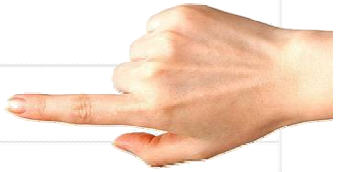

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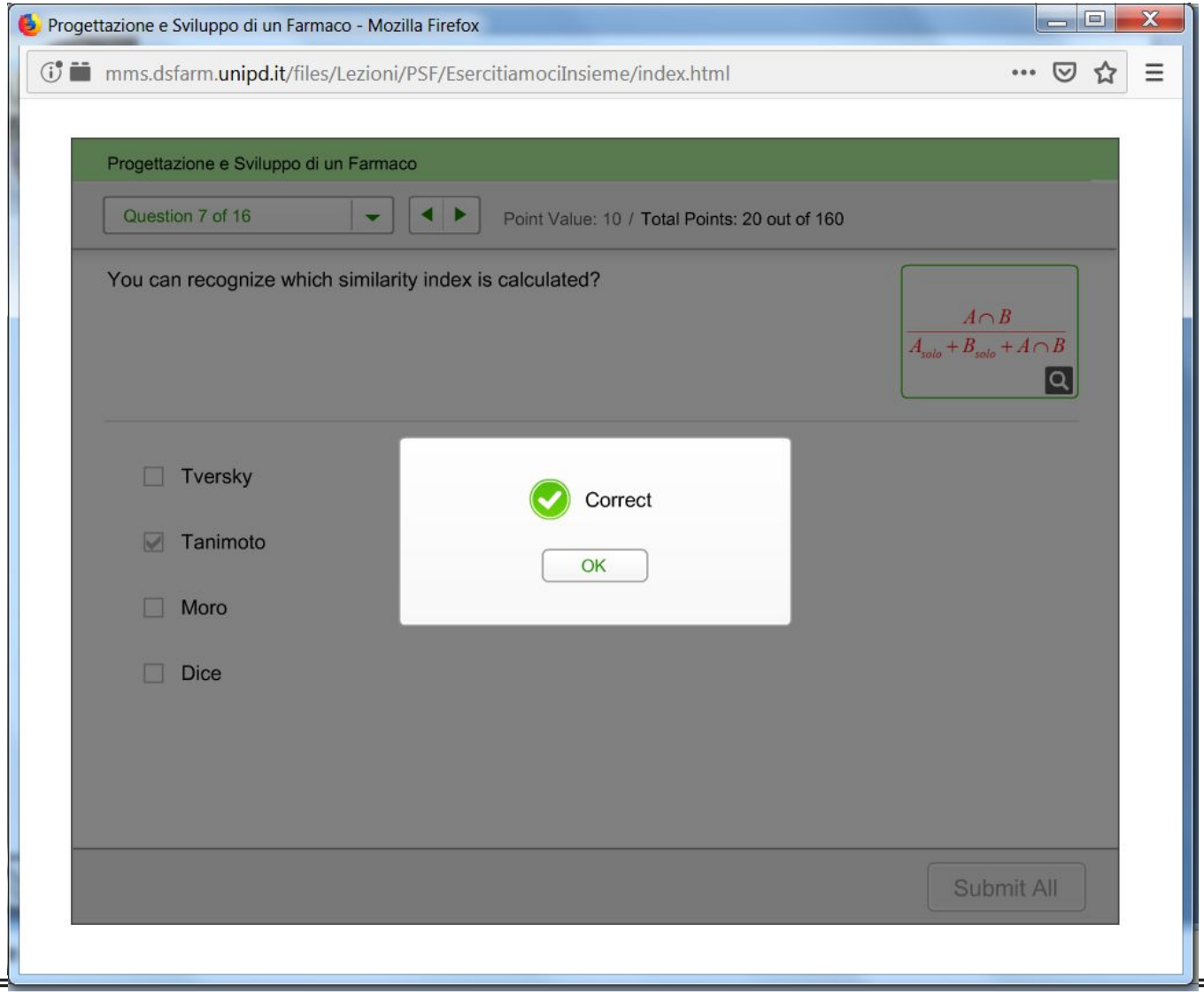

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MMSeLab… broadening perspectives.

@lab MMS

Running Project:	
Project Aims:	
eTools:	
Tutorials:	
References:	

This project was possible thanks to the irreplaceable contributions of Matteo Floris, Davide Sabbadin, , Mattia Sturlese and Andrea Cristiani.

We warmly thank Chemical Computing Group (CCG) for giving access to MOEweb, OpenEye for giving access to OMEGA, Thomas E. Exner for provinding us PLANTS docking tool, Matthias Rarey for ging access to PoseView, and Peter Ertl for its editor.

We are very grateful to the large community of Developers who make possible the use of the following free tools: Ubuntu Linux operating system, Apache web server, PHP scripting language, Jmol - the open source molecular viewer, Jquery - Javascript library, CDK - the chemistry development kit, CACTVS toolkit by Xemistry, Indigo command line utilities by GGA Software Services.

Offline

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ChemDraw Prime

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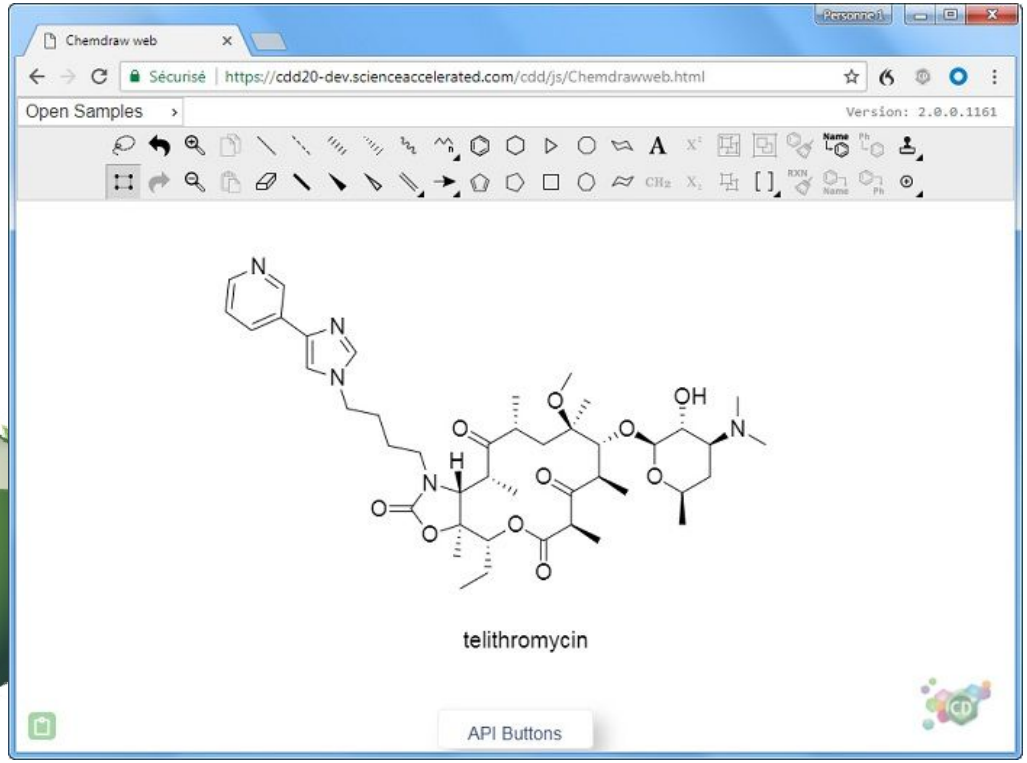

ChemDraw® Prime 17 è un software per il disegno delle strutture molecolari.

Il software è in licenza fino al 31/03/2019.

Può essere utilizzato dagli utenti istituzionali collegandosi al seguente link http://sitesubscription.cambridgesoft.com/

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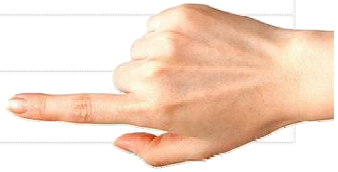

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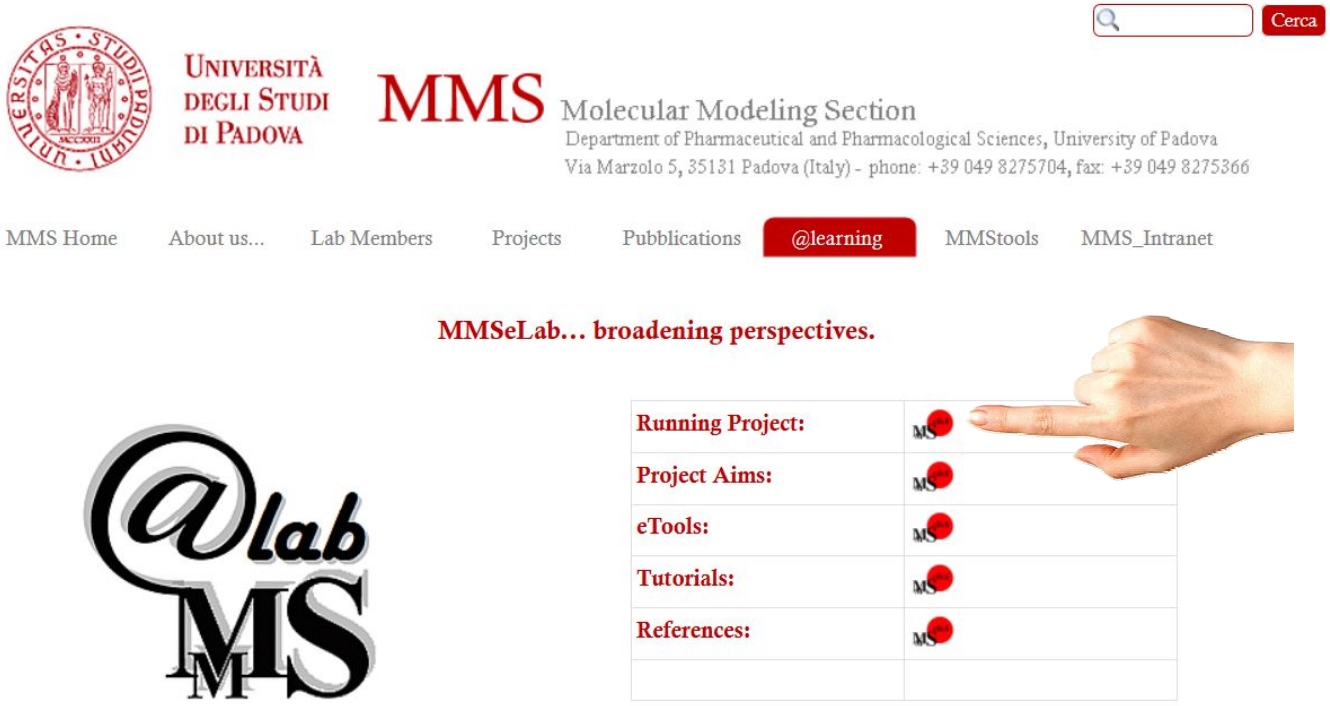
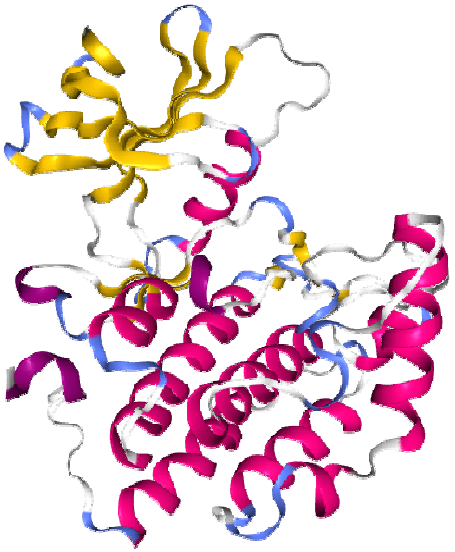
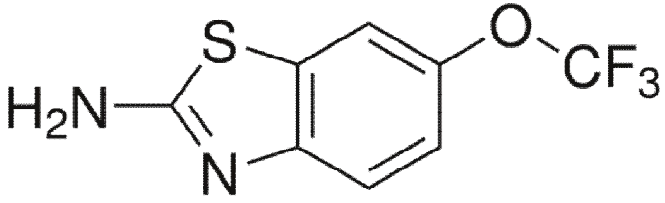


A preview of our PSF 2018/2019 running project!

PDB code: 5LJT



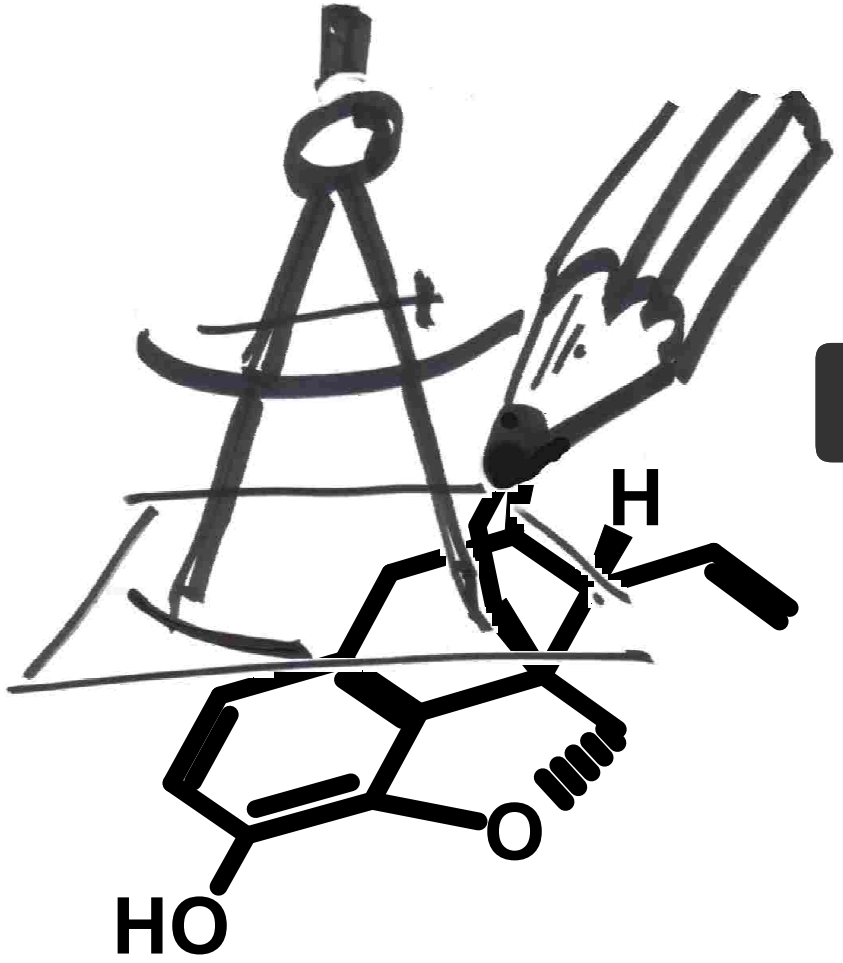


Riluzole

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) in press

Our primary mission will be:

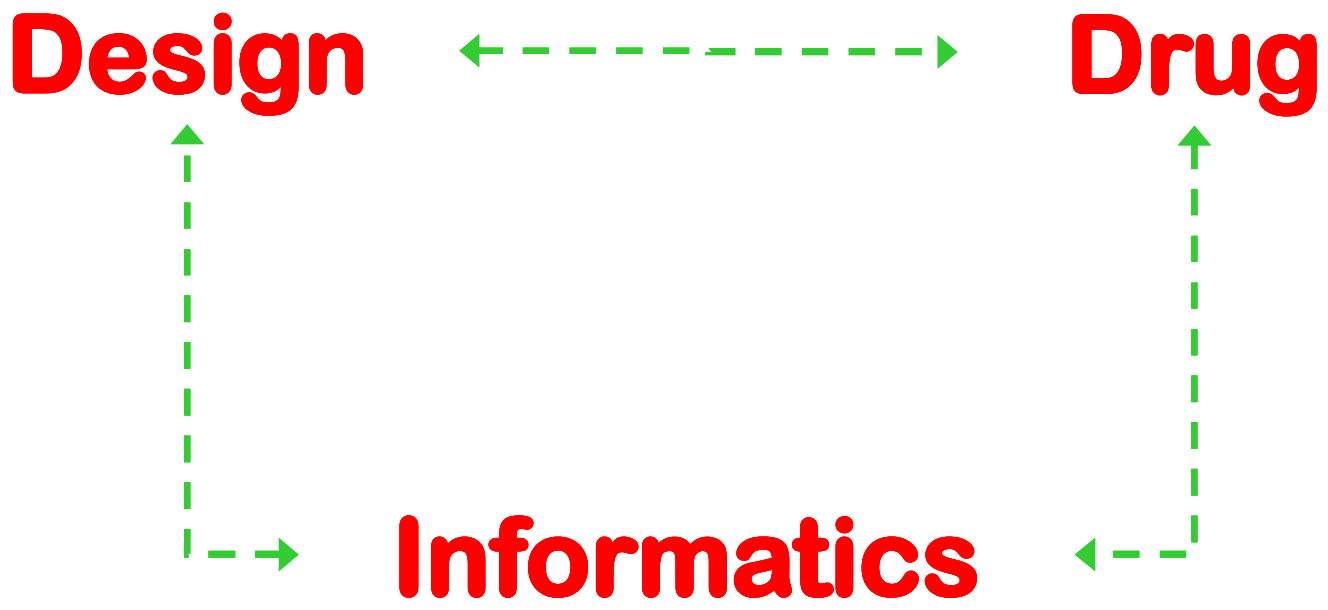


Design!

The most insidious question that you can make me :

Is a drug designable?

Answering to this question needs to find the intimate connection between these three concepts :



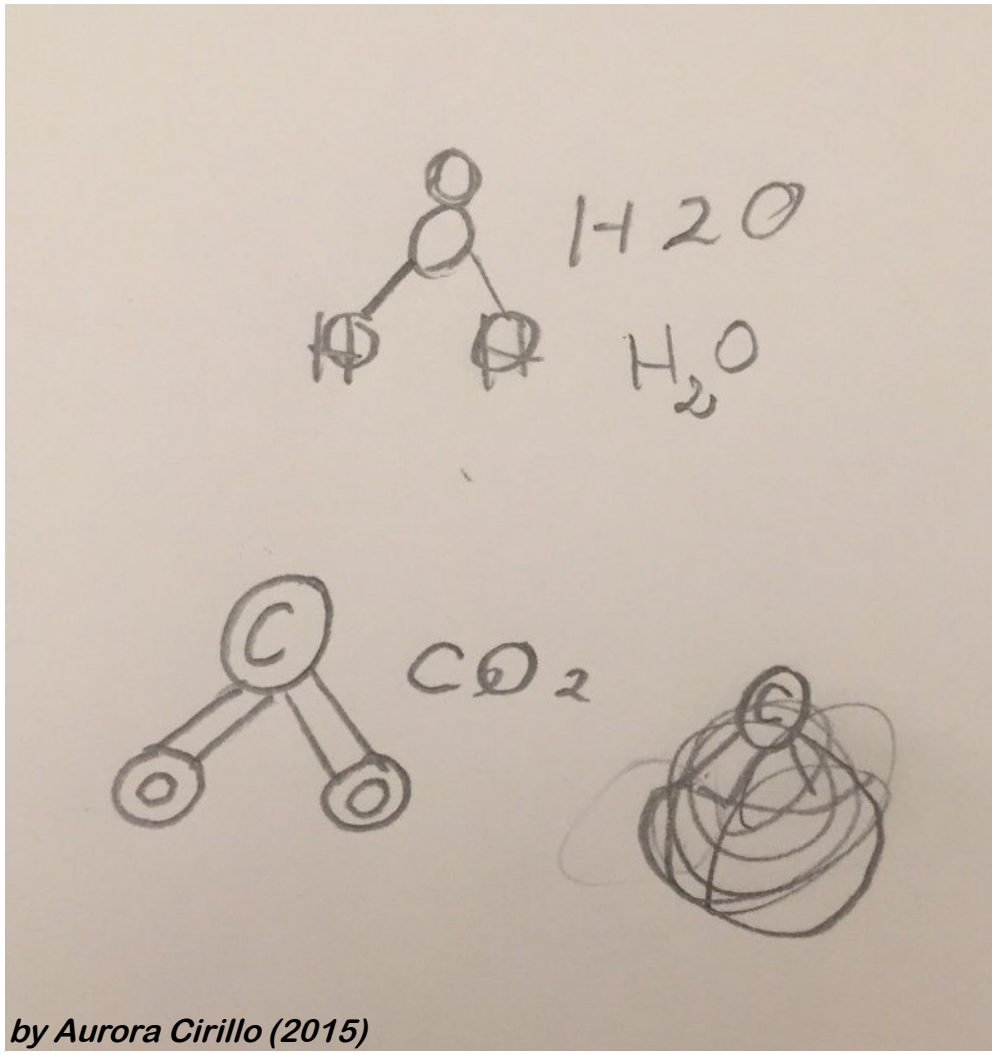
… a bit of:

… be patient:

Design:

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

… there is no doubt that chemists (including medicinal chemists) are of great *drawers* :



by Aurora Cirillo (2015)

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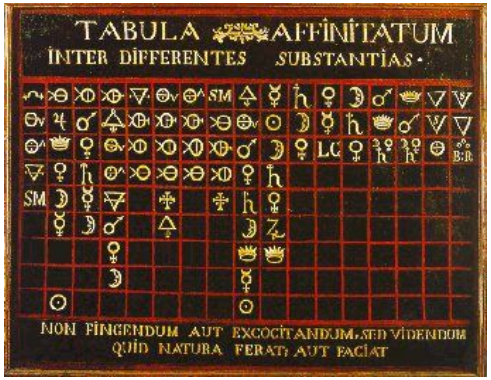
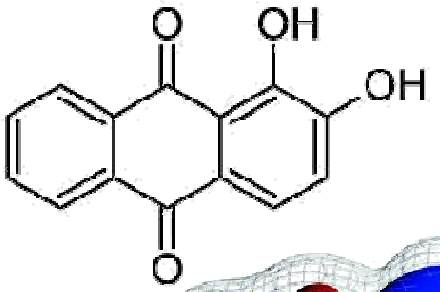
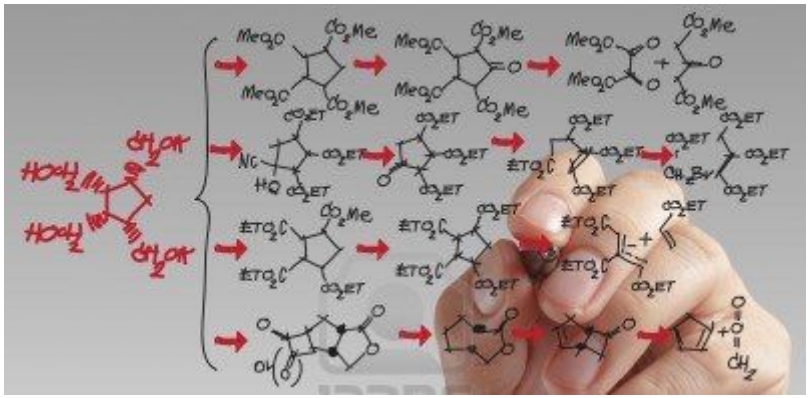
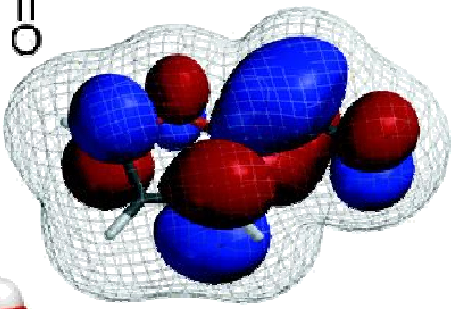
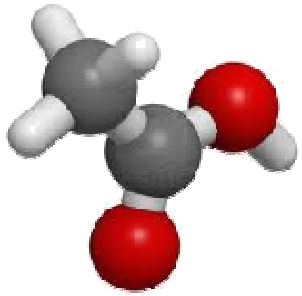
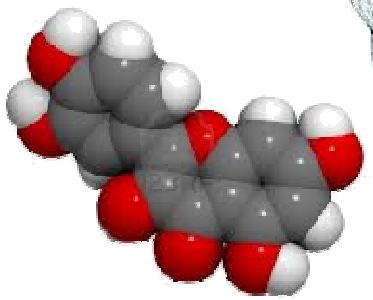


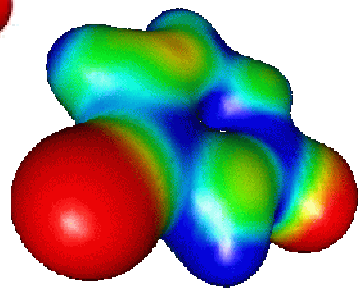










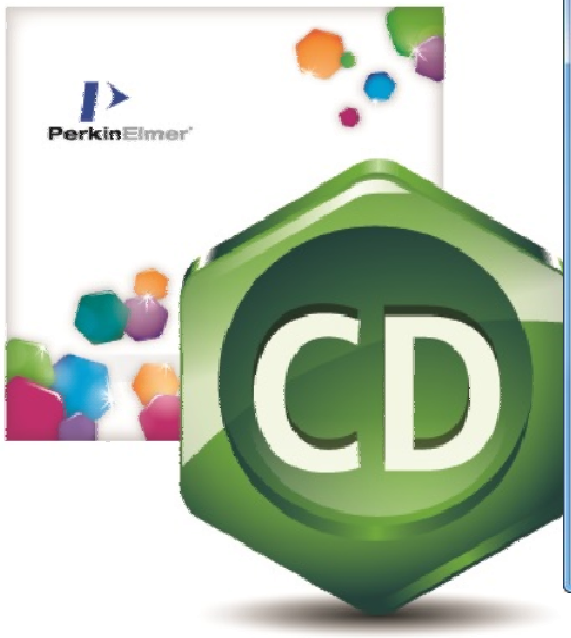


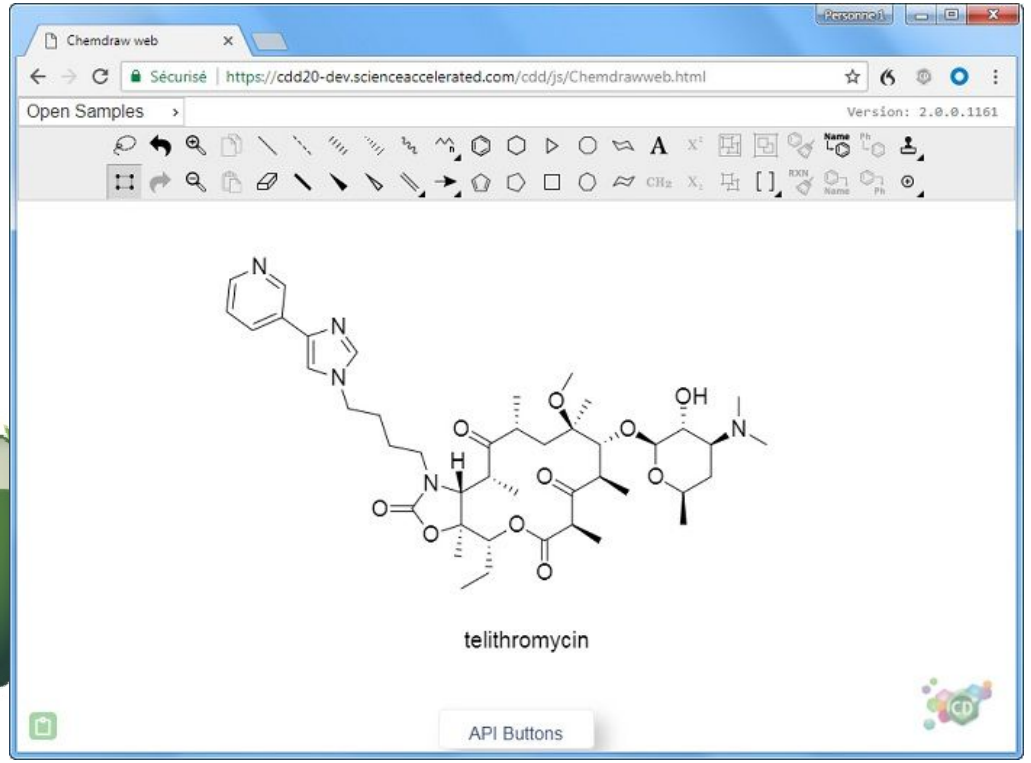
… but what *chemical drawings* are from an informatics point of view?

… please, download ChemDraw!!!

ChemDraw Prime

ultima modifica 05/04/2018 13:40





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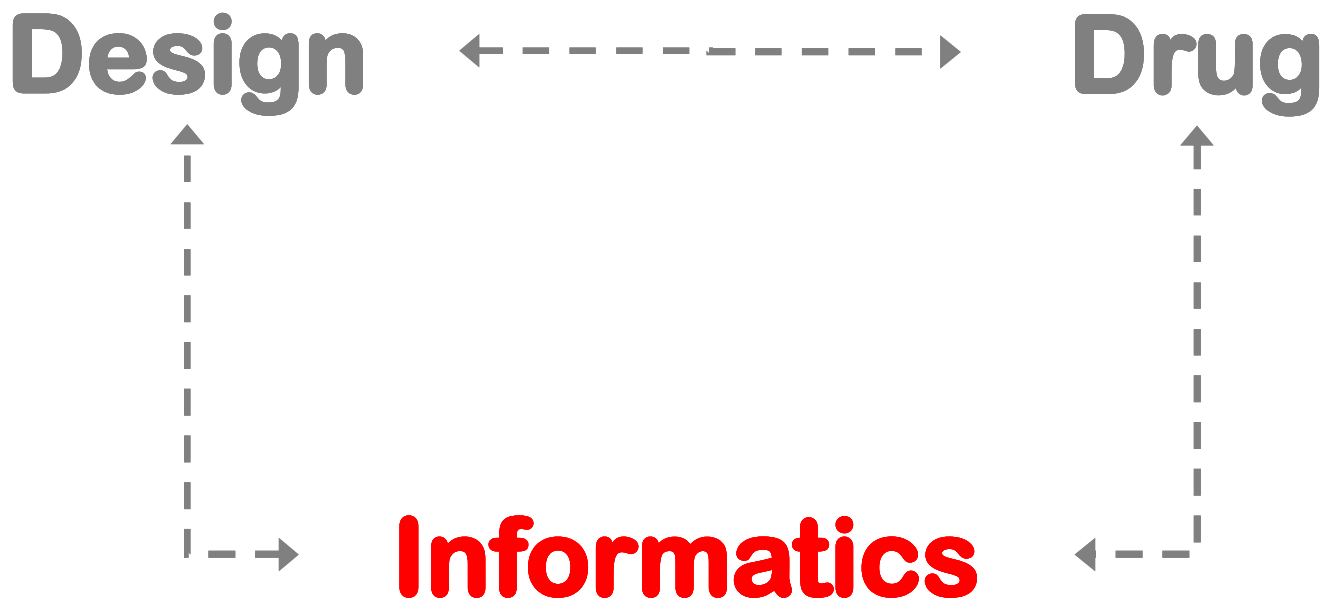
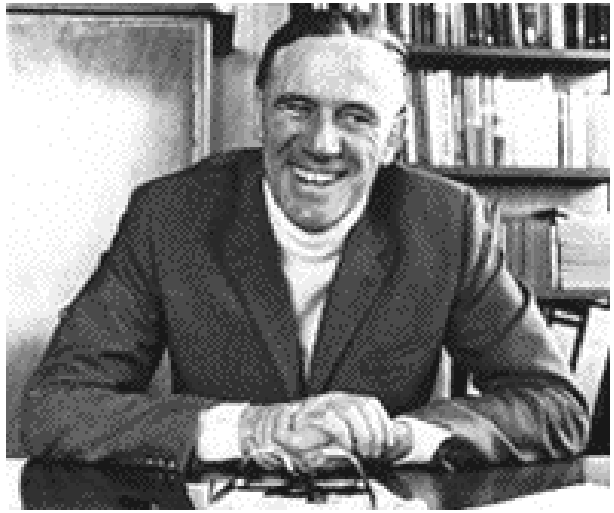
… couple of bits of:



again an egoistic definition of *informatics*:

In 1957 the German computer scientist Karl Steinbuch coined the word *Informatik* by publishing a paper called *"Informatik: Automatische Informationsverarbeitung" (Informatics: Automatic Information Processing).*



It is not sufficient to invent something. You need to recognize, that you have invented something.

Karl Steinbuch

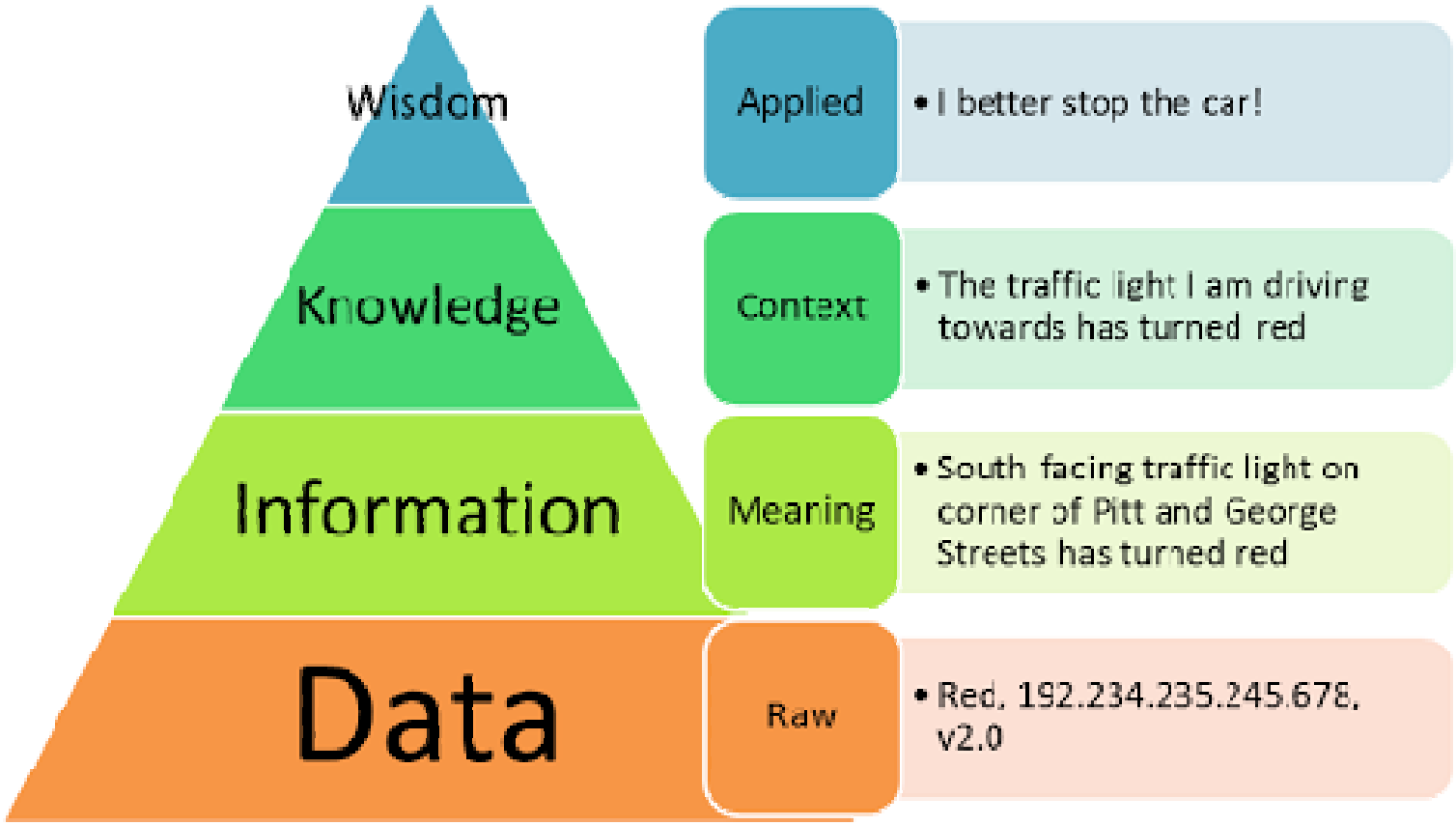
again an egoistic definition of informatics:

Informatics:

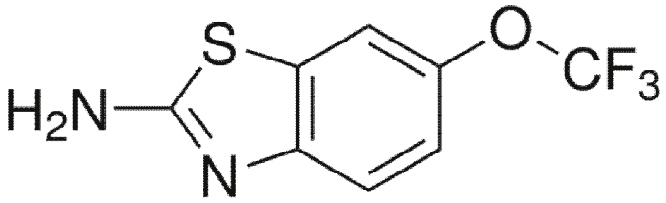
Informatics is, in its most general sense, the *science of information*.

I didn't fond a better representation of this definition that this:

… exciting!



Q: a chemical representation like this, can be considered as a *data* or as an *information*?



A: … visit

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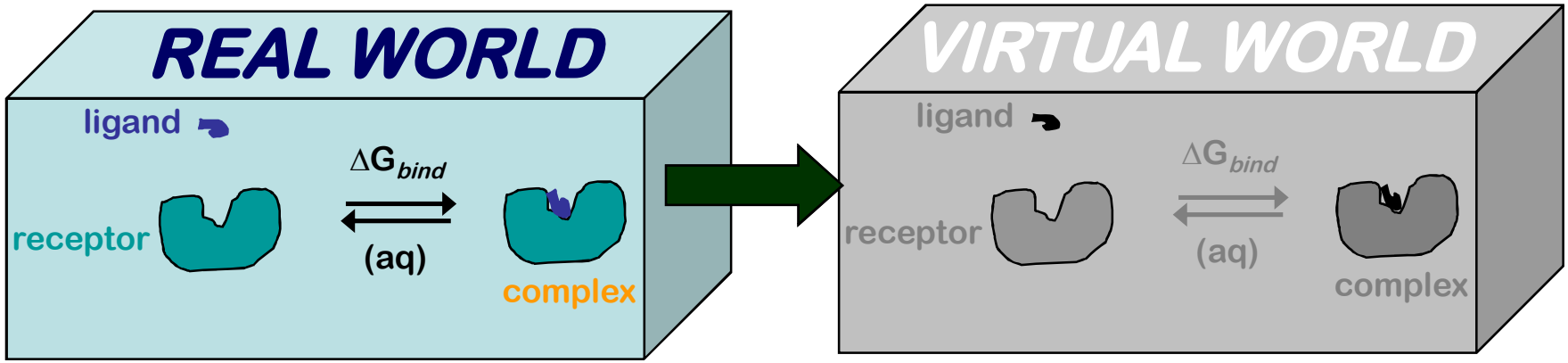
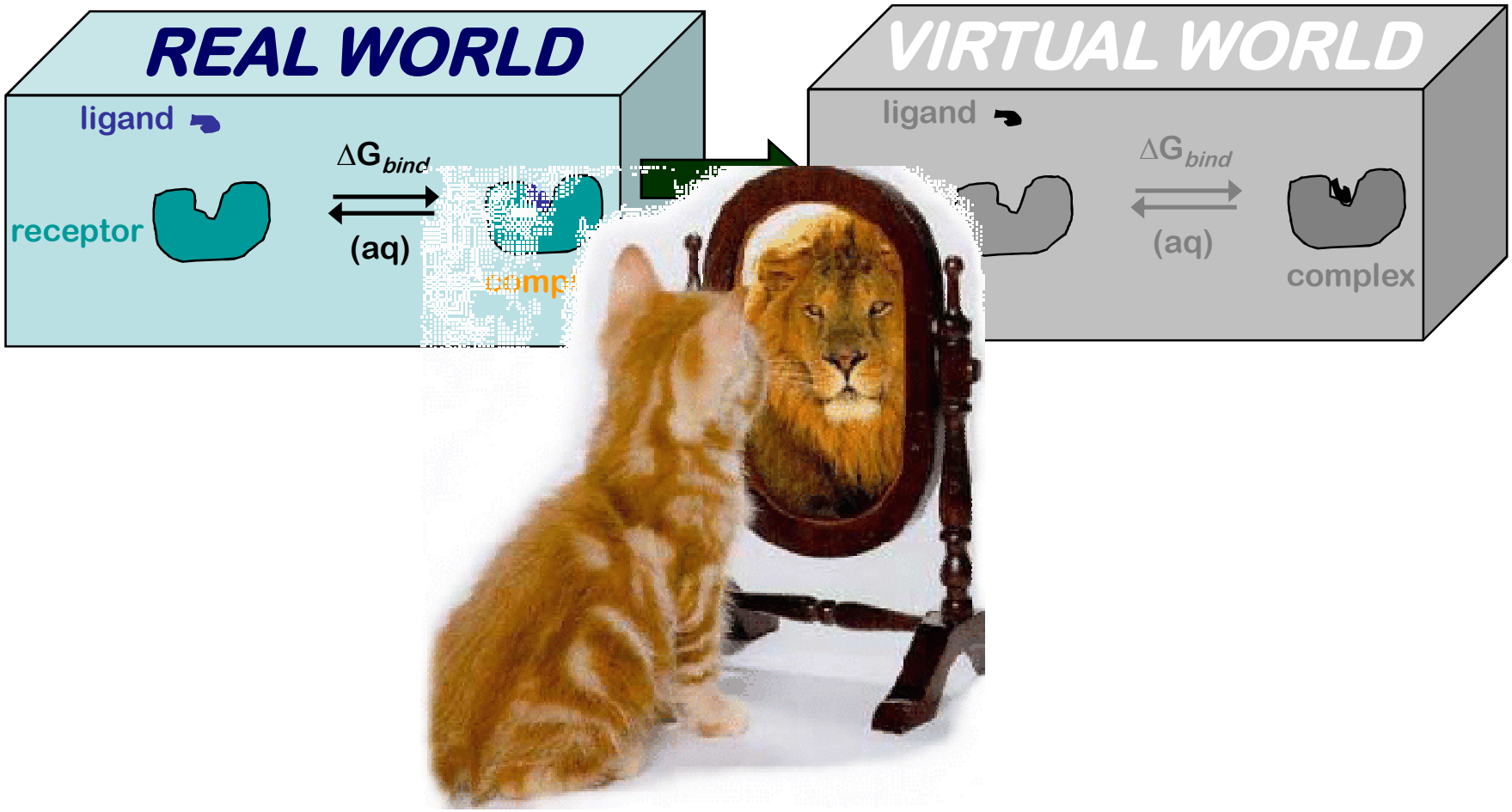
PSF@podcast	
@sertiamoci:	

Informatics is the basic science of any *virtualization* process:

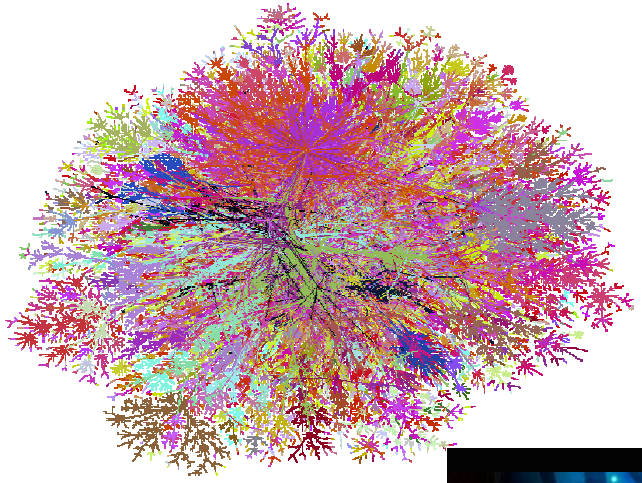
From an informatics point of view, any compu tool is a *virtualization process*: the creation of a virtual version of the real process.

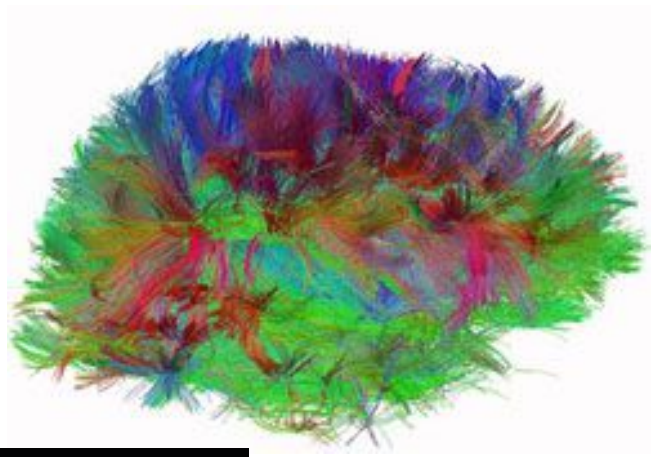


The *accuracy* of this virtualization process is crucial:



the informatics future is the "*virtualization*" of complex systems…

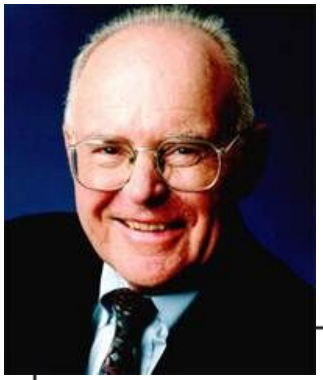




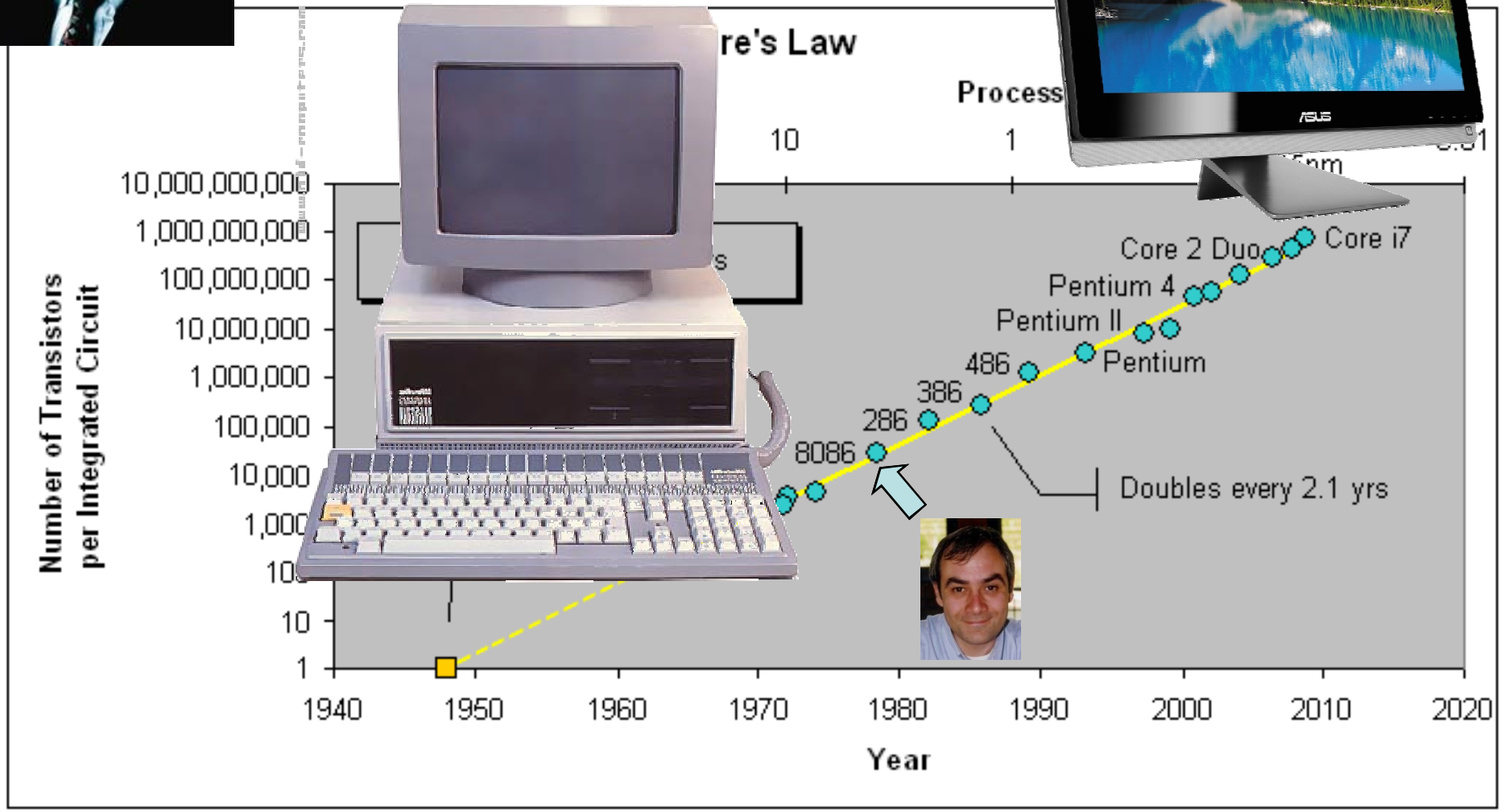
Now, in what informatics has influenced more in our daily life?

Well, we probably summarize the answer in only one word:

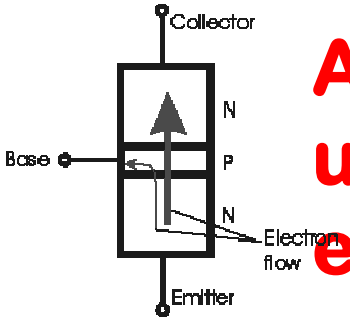
Time



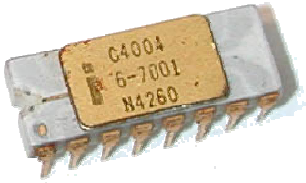
Informatics as synonym[illegible] speed?



just for informatics addicted!



A *transistor* is a semiconductor device used to *amplify* and *switch* (on/off) electronic signals and electrical power.

Processor	Transistor count	Date of introduction	Manufacturer	Process	Area
Intel 4004 	**2,300**	1971	Intel	10 µm	12 mm²
Xbox One Main SoC 	**5,000,000,000**	2013	Microsoft /AMD	28 nm	363 mm²

couple of concrete example..

Informatics helps us to solve simple problems a number of times:

Calculate the molecular weight is trivial thing, calculate 4.5 million ... less!

or solve very complex problems:

Calculate, for example, the binding energy (ΔG_{bind}, kcal x mol) between a ligand and its receptor!

And now back to the future…

ARTIFICIAL INTELLIGENCE (1950's)

The ability of a computer program or a machine to think like humans do.

MACHINE LEARNING (1980's)

Subfield of AI giving machines the skills to learn from examples without being explicitly programmed.

Examples: Fraud detection, marketing personalization, email classification

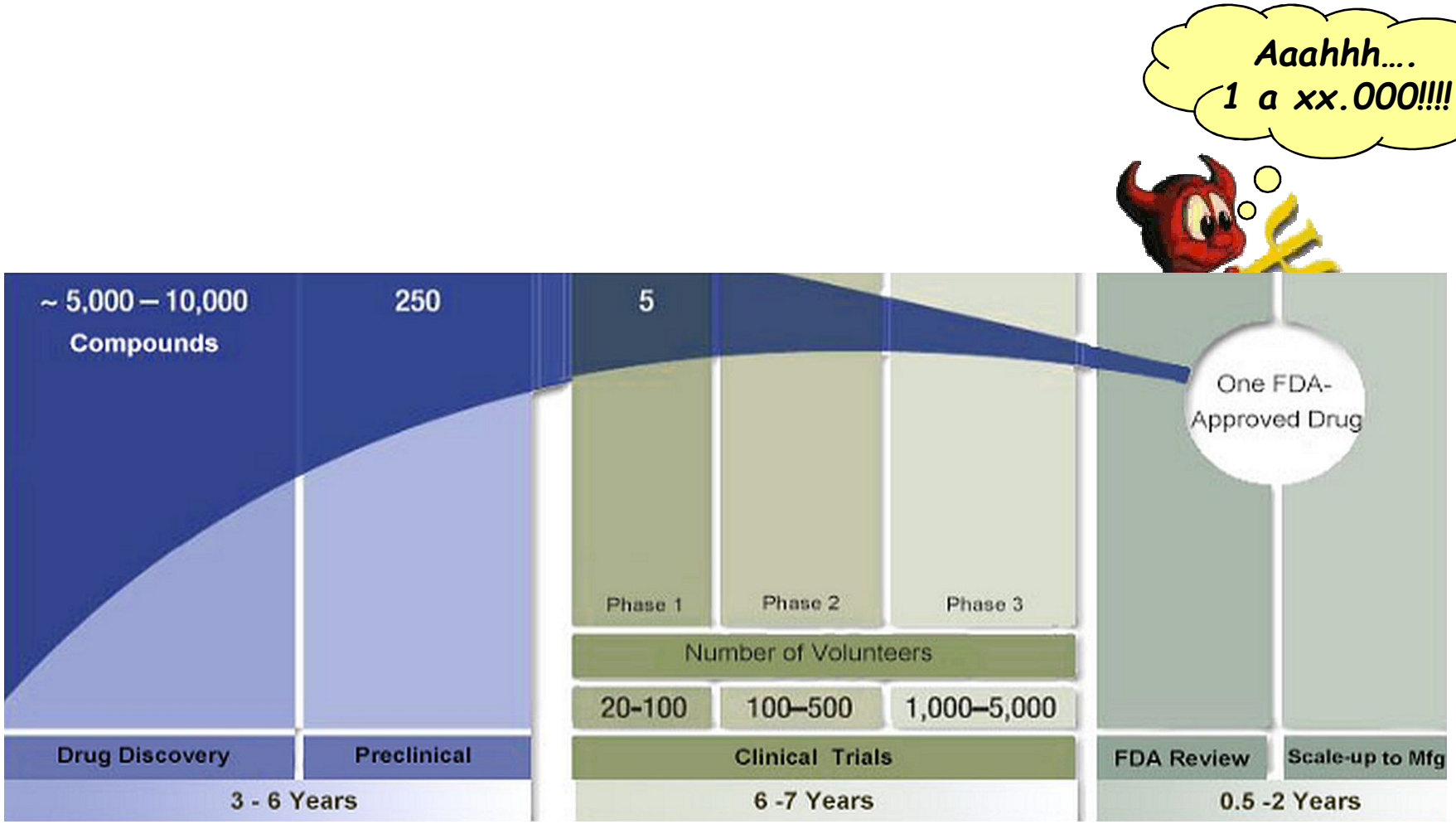
DEEP LEARNING (2010)

Specialized machine learning technique enabling machines to train themselves to perform tasks.

Examples: Image classification, vehicle detection, sentiment analysis

and remember… “Time is money!”

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

A *blockbuster* is a drug with more than $1 billion per year in sales.

Top 10 Drugs by Monthly Prescription

Rank	Drug (Brand Name)	Drug (Active Principle)	Total Prescriptions June 2014 - June 2015
1	Synthroid	Levothyroxine sodium	**21,561,481**
2	Crestor	Rosuvastatin calcium	**21,478,776**
3	Ventolin HFA	Salbutamol sulfate	**18,203,939**
4	Nexium	Esomeprazole magnesium	**15,298,228**
5	Advair Diskus	Fluticasone propionate	**13,776,325**
6	Lantus Solostar	Insulin glargine	**10,939,840**
7	Vyvanse	Lisdexamfetamine	**10,413,999**
8	Lyrica	Pregabalin	**10,022,365**
9	Spiriva Handihaler	Tiotropium bromine	**9,635,935**
10	Januvia	sitagliptin	**9,148,946**

… how many new age drugs do you find in this list?

A *blockbuster* is a drug with more than $1 billion per year in sales.

Top 10 Drugs by Sales

Rank	Drug (Brand Name)	Drug (Active Principle)	Sales Through June 2014
1 (14)	Abilify	Aripiprazolo	$7,240,043,661
2 (63)	Humira	Adalimumab	$6,310,742,887
3	Nexium	Esomeprazole magnesium	$6,303,738,580
4 (2)	Crestor	Rosuvastatin calcium	$5,672,991,435
5 (72)	Enbrel	Etanercept	$5,097,263,350
6 (5)	Advair Diskus	Fluticasone propionate	$5,064,138,456
7 (>100)	Sovaldi	Sofosbuvir (EpaC)	$4,469,558,675
8 (>100)	Remicade	Infliximab	$4,342,356,359
9 (7)	Lantus Solostar	Insulin glargine	$3,829,943,226
10 (>100)	Neulasta	Pegfilgrastim	$3,688,450,342

… and here?

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?

… a bit of:

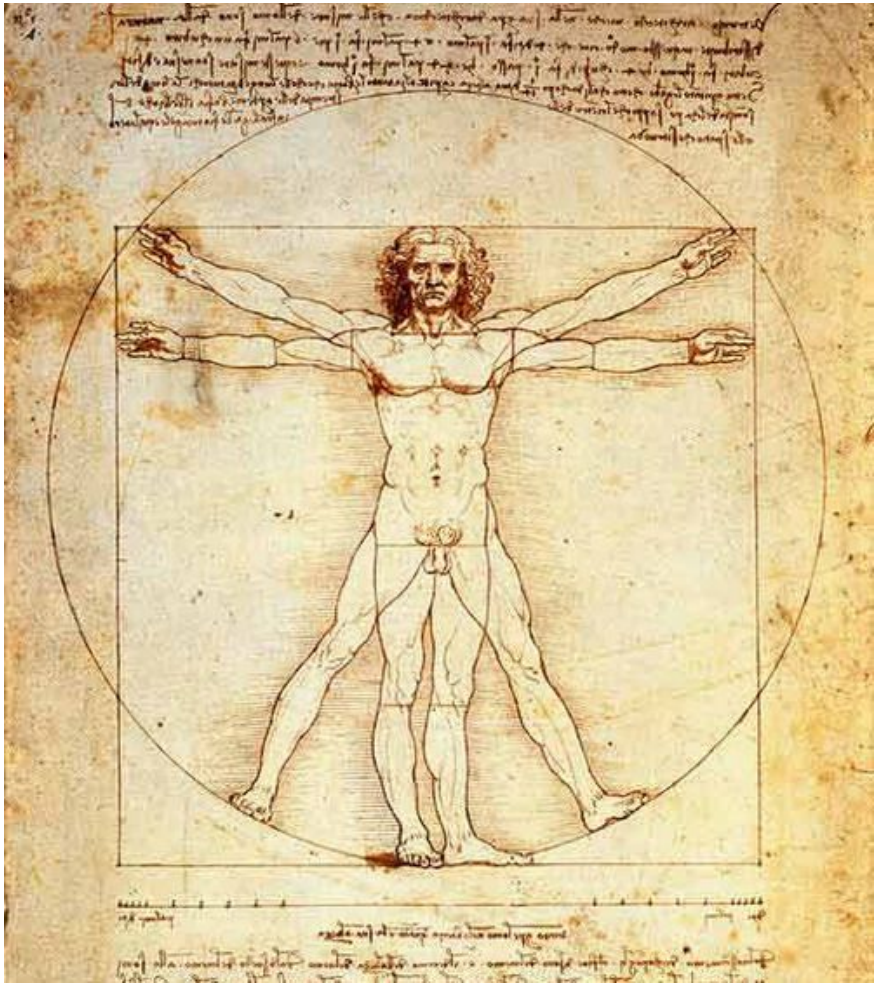
I know very well that you known what drug is… but reconsider its definition in this way:

Drug:

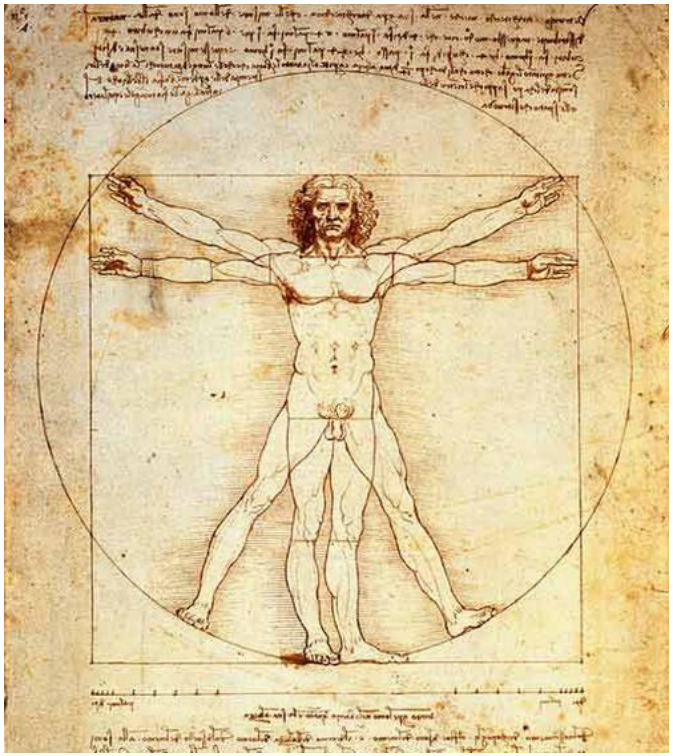
[from gr. φάρμακον] Any substance, organic or inorganic, synthetic or natural, capable of producing in a ***living organism*** *functional modifications, helpful or harmful, by chemical action, physical chemistry or physics.*

Dizionario Treccani

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

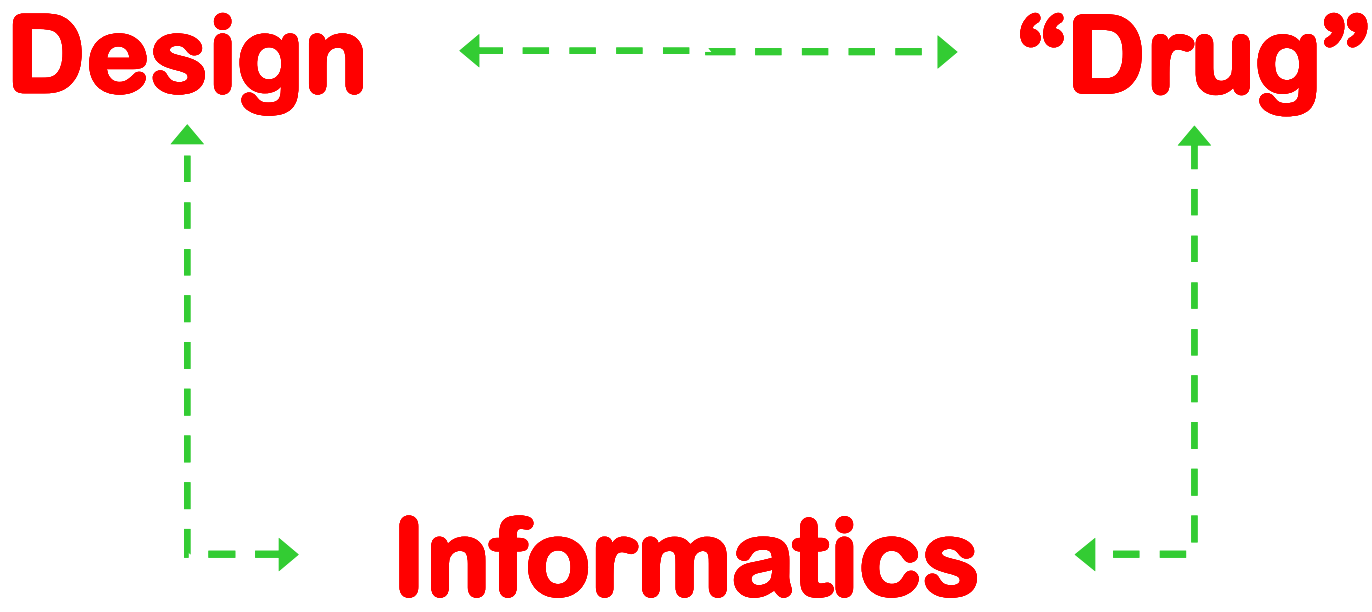


… I suspect that you could have a sensation like this:



We will return later on this concept…

Why we need *"drug" design*?



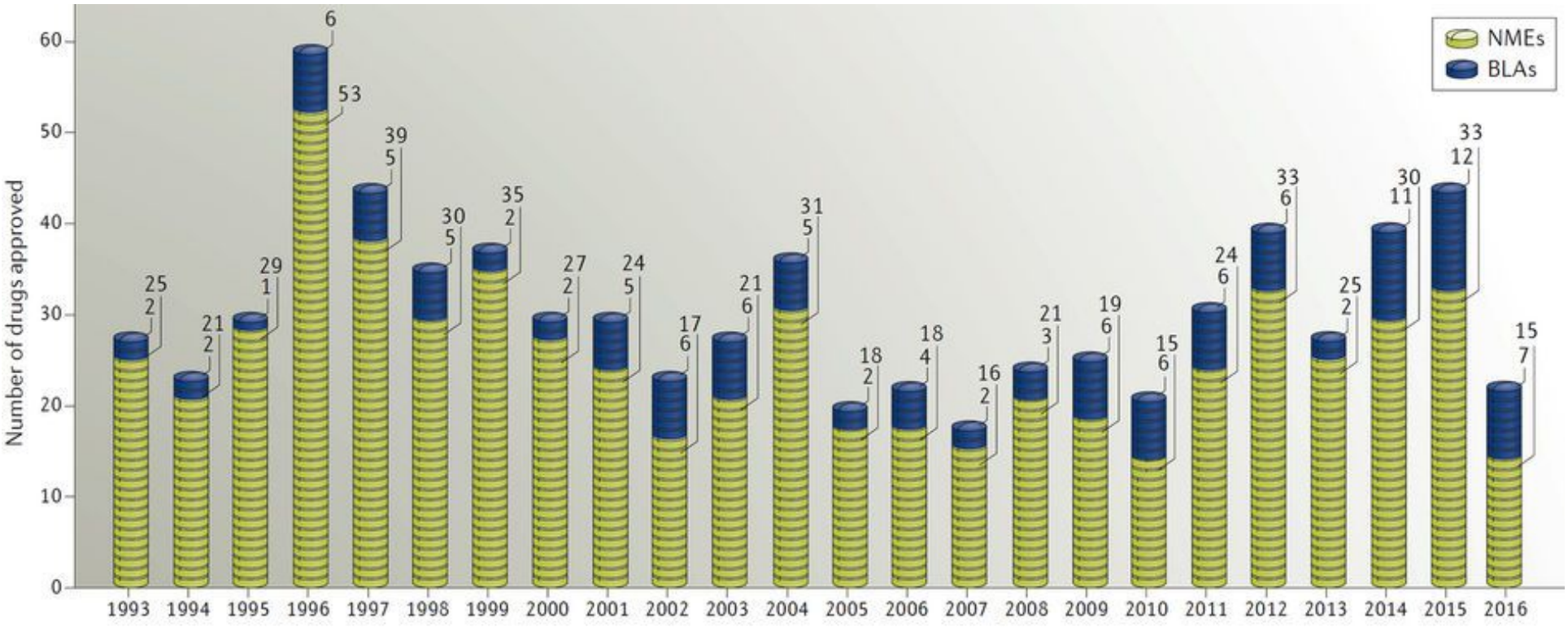
Why we need *"drug" design*?

Drug discovery is a extremely competitive activity!

a.~ 1600 companies;

b. ~ 6000 R&D projects.

Drug discovery statistics:



Nature Reviews | Drug Discovery

http://www.nature.com/nrd/journal/v16/n2/fig_tab/nrd.2017.14_F1.html

First in class:

***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.*

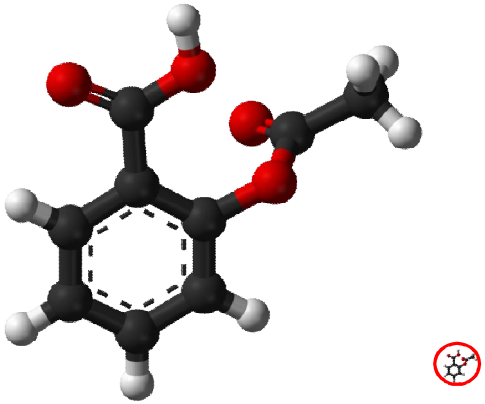
This is distinct from a **First in class** drug which introduces a new mechanism of action for treating a medical condition.

NME versus BLA in one slide…

Vintage drugs

ASPIRINE

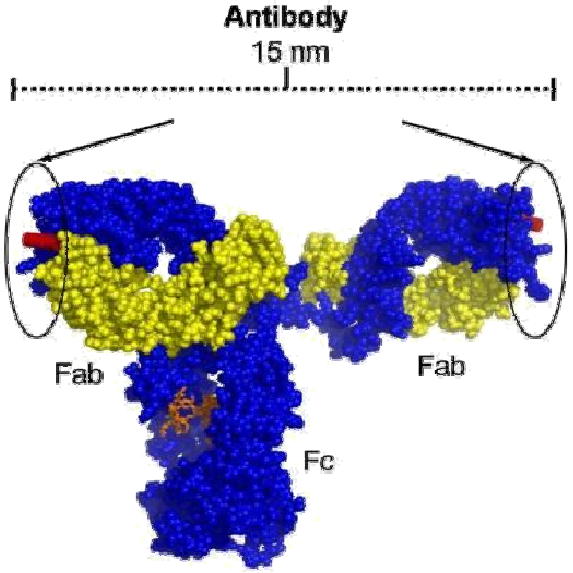
1. small molecule
2. 180 Da
3. 21 atoms
4. usually not immunogenic
5. usually chemically stable



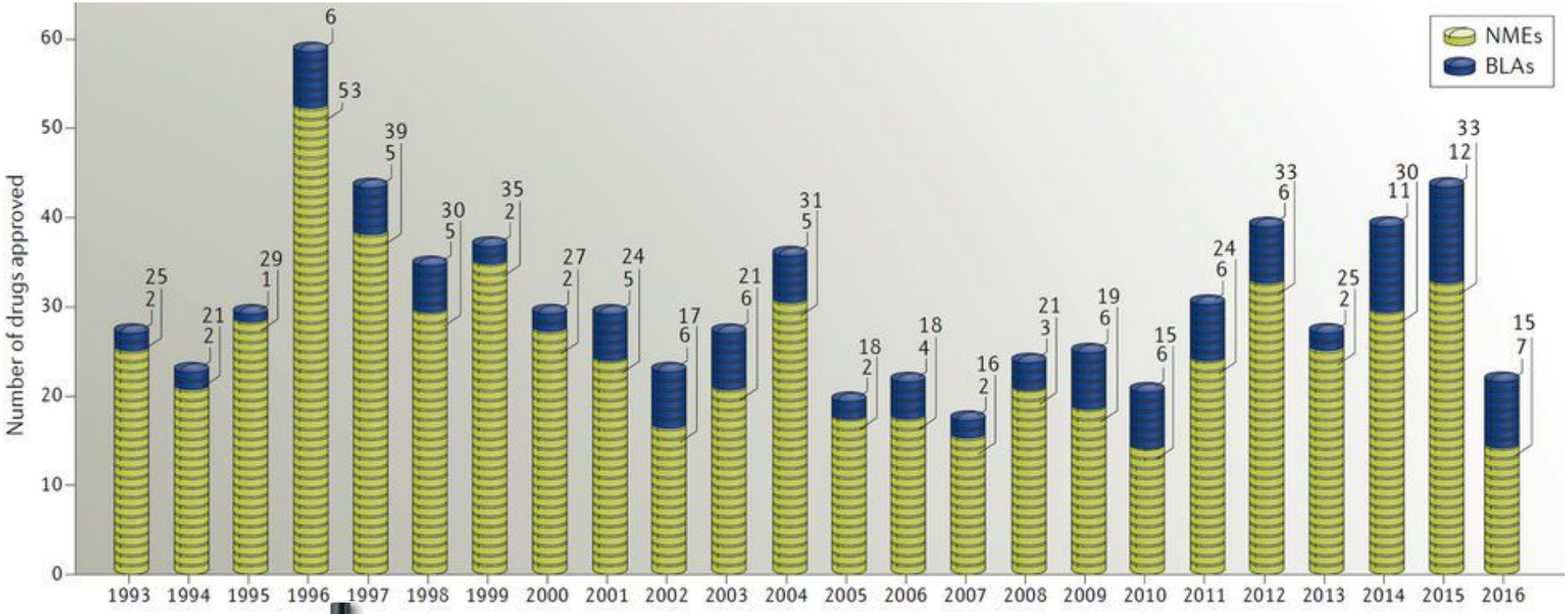
New age (biotech) drugs

MONOCLONAL ANTIBODY (mAb)

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



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



Why we need *"drug" design*?

xx.000 to 1?

Is this ratio really acceptable for a pharma company?

But unfortunately *"drug"* is not designable, yet!

Could we suggest a possible substitute of *"drug"* that is more easily designable?

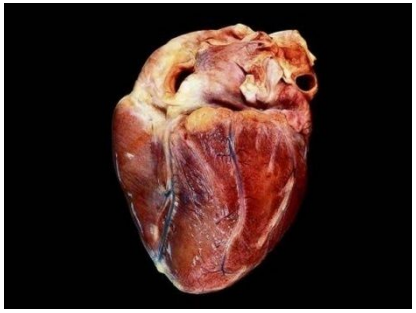
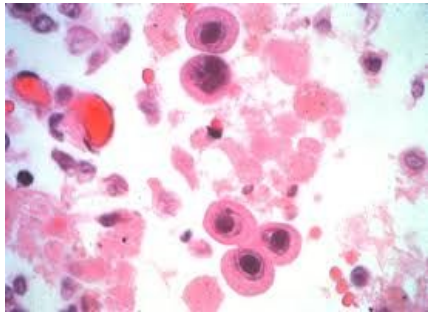
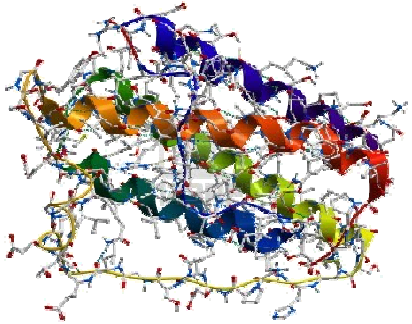
To do this we have to necessarily replace the concept of *living organism* !

An egoistic solution:

drug

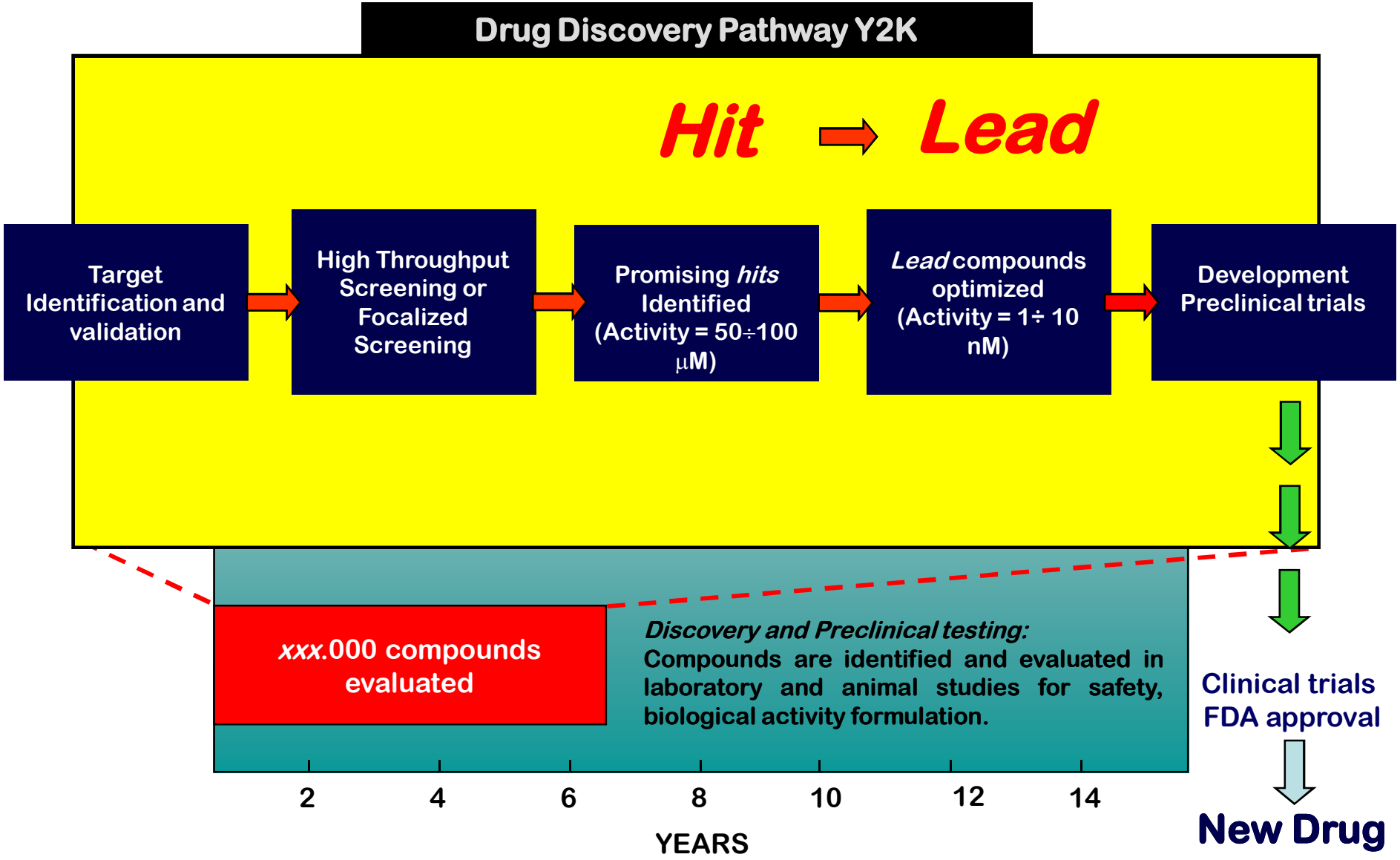




candidate

The “right” road to drug discovery?



Do you remember?

Biological Space

Profiling

Chemical Space

	TargetA	TargetB	TargetC	TargetD	TargetN
Comp.1	$K_1(A)$	$K_1(B)$	$K_1(C)$	$K_1(D)$	$K_1(N)$
Comp.2	$K_2(A)$	$K_2(B)$	$K_2(C)$	$K_2(D)$	$K_2(N)$
Comp.3	$K_3(A)$	$K_3(B)$	$K_3(C)$	$K_3(D)$	$K_3(N)$
Comp.4	$K_4(A)$	$K_4(B)$	$K_4(C)$	$K_4(D)$	$K_4(N)$
Comp.n	$K_n(A)$	$K_n(B)$	$K_n(C)$	$K_n(D)$	$K_n(N)$

Screening Chemical Proteomics

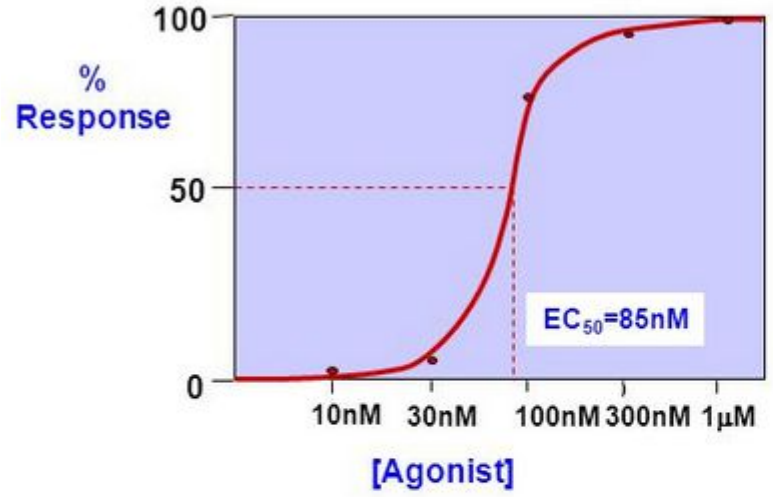
Hit to lead …

- **hits**
  - active in assay
  - defined and confirmed structures
  - drug-like potential

HTS hits from this database typically show micromolar activity with a median "pPotency" of 6. The median molecular mass and lipophilicity (logP) was 359 Da and 3.8, respectively.

when potency is a good potency?

Dose-Response Curves



Enzyme Inhibitors (competitive):

Measure inhibition at differing concentrations of 'drug'.

IC_{50} - The inhibitor concentration that causes a 50% reduction in intrinsic enzyme activity

$pIC_{50} = -\log_{10}(IC_{50})$

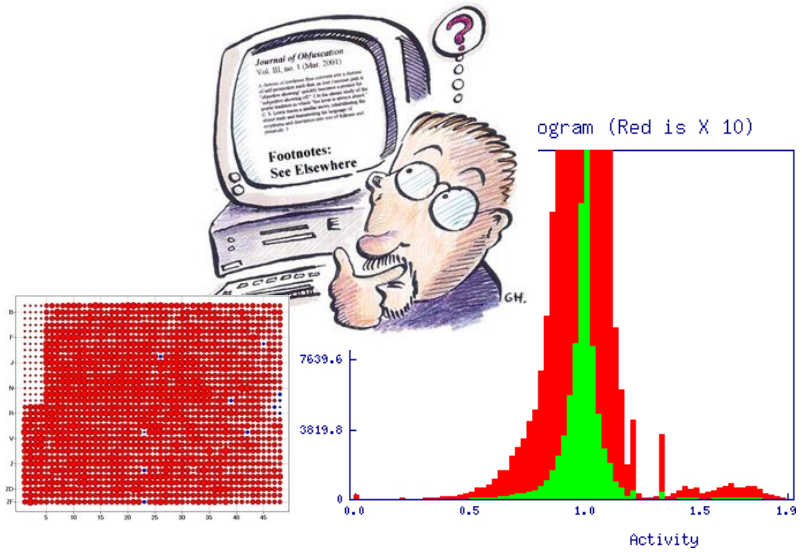
IC_{50} 1μM = pIC_{50} 6.0
IC_{50} 1nM = pIC_{50} 9.0

Agonists: Measure % Response vs Agonist concentration
EC_{50} - The agonist concentration that causes 50% of the maximum response. $pEC_{50} = -\log_{10}(EC_{50})$

Antagonists: Situation more complex. Antagonists displace the agonist dose-response curve rightwards – most accurate measure of potency (pA_2) requires measurement of agonist binding at multiple concentrations of antagonist

For a drug, typically target affinity values of $pIC_{50} \geq 8$ (<10 nM concentration)

the "*hit-to-lead* paradigm": clear the *xxx*.000:1 ratio?



- >1,000,000
- 1,000,000
- 1,000
- 100

- *Initial HTS campaign*
- *Quality control*
- *Primary hit selection*
- *Hit validation*

Bleicher *et al.* (2003) *Nat. Rev. Drug Discov., 2*, 369

Do you remember costs?

Experiment Typical Cost per Compound (€)

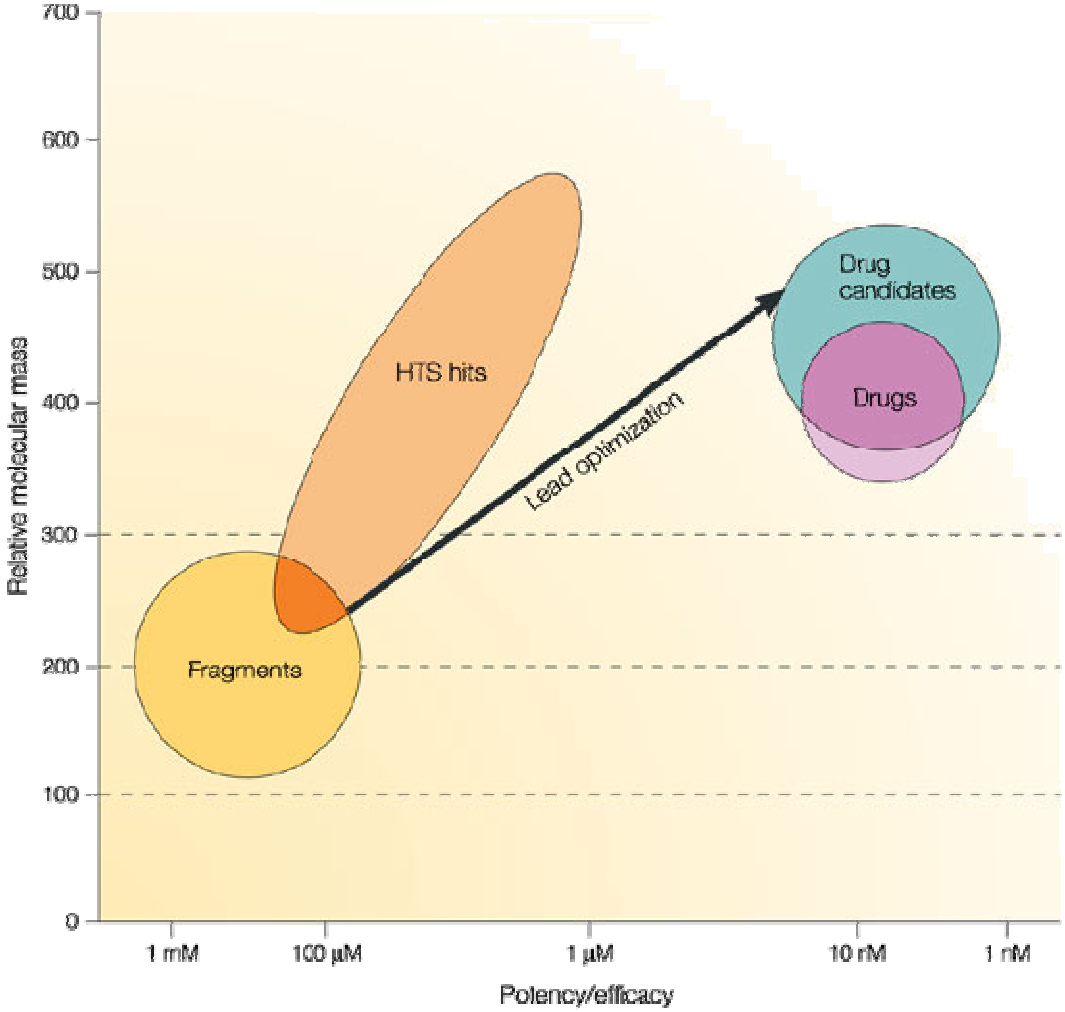
Computer modeling	7
Biochemical assay	270
Cell culture assay	2.700
Rat acute toxicity	8.100
Protein crystal structure	68.000
Animal efficacy trial	200.000
Rat 2-year chronic oral toxicity	550.000
Human clinical trial	3.500.000

… if we could suggest that chemical compounds could be more hits than other !!!

Hit to lead …

- **leads**
  - potency established
  - selectivity/specificity
  - Mechanism of action (MOA) established
  - *in vivo* efficacy
  - ADME/Tox
  - pharmaceutically acceptable

when potency is a good potency?



David C. Rees, Miles Congreve,, Christopher W. Murray & Robin Carr Nature Reviews Drug Discovery 3, 660-672, 2004

Nature Reviews | Drug Discovery

I don't have to add anything !!!

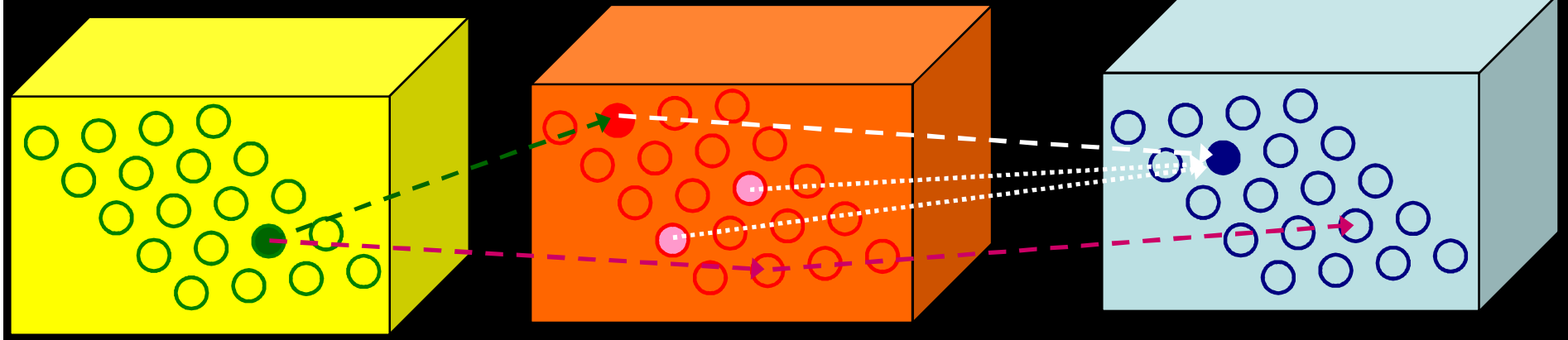
Experiment Typical Cost per Compound (€)

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


TITLE
“Progettazione e Sviluppo di un Farmaco”
DIRECTOR
Stefano Moro
CAMERA
Chimica e Tecnologia Farmaceutiche
DATE
SCENE
TAKE

Possiamo schematizzare questa definizione in modo più farmaceutico?

Farmaco
Interazione Terapeutica
Interazione Collaterale
Target Primario
Target Secondario
Target Collaterale
Patologia



Spazio chimico *Spazio biologico* *Spazio fisio-patologico*

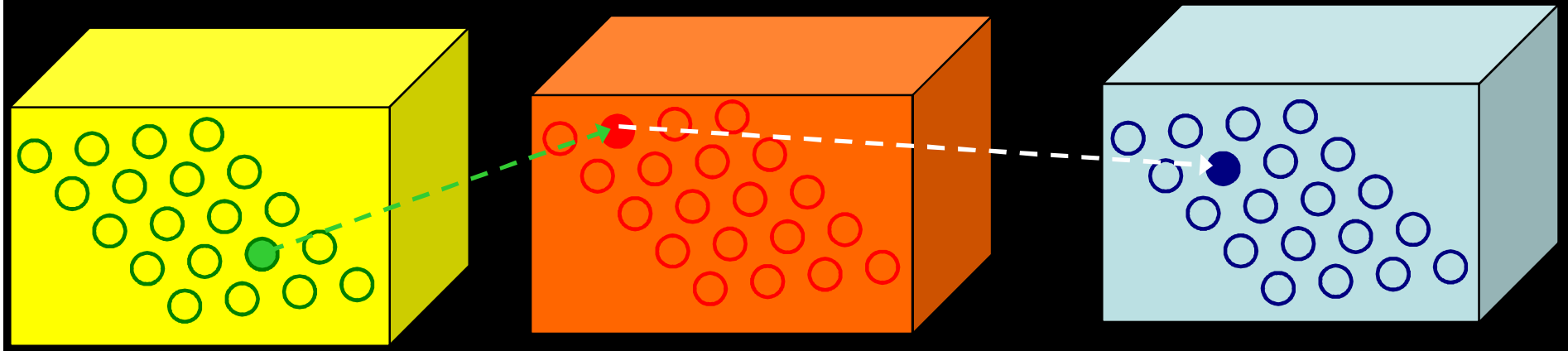
Per molto tempo abbiamo schematizzando troppo descrivendo il tutto attraverso una stechiometria 1 : 1 :1

Farmaco

Interazione Terapeutica

Target Primario

Patologia



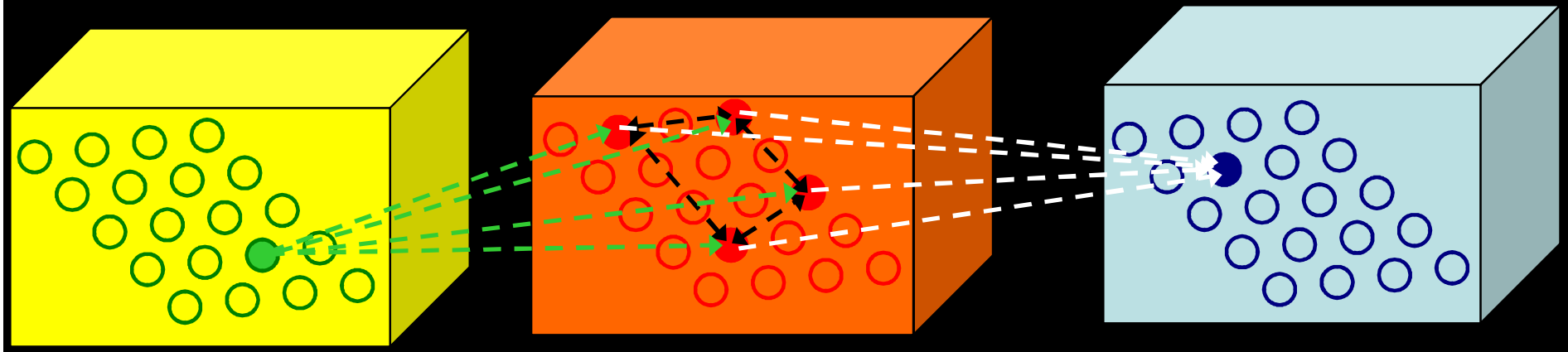
Spazio chimico

Spazio biologico

Spazio fisio-patologico

Ma le cose stanno rapidamente cambiando e oggi si parla sempre di più di farmaci *multi-targets* dove il tutto passa attraverso una stechiometria 1 : N :1

Farmaco
Interazione Terapeutica
Rete di Targets
Patologia

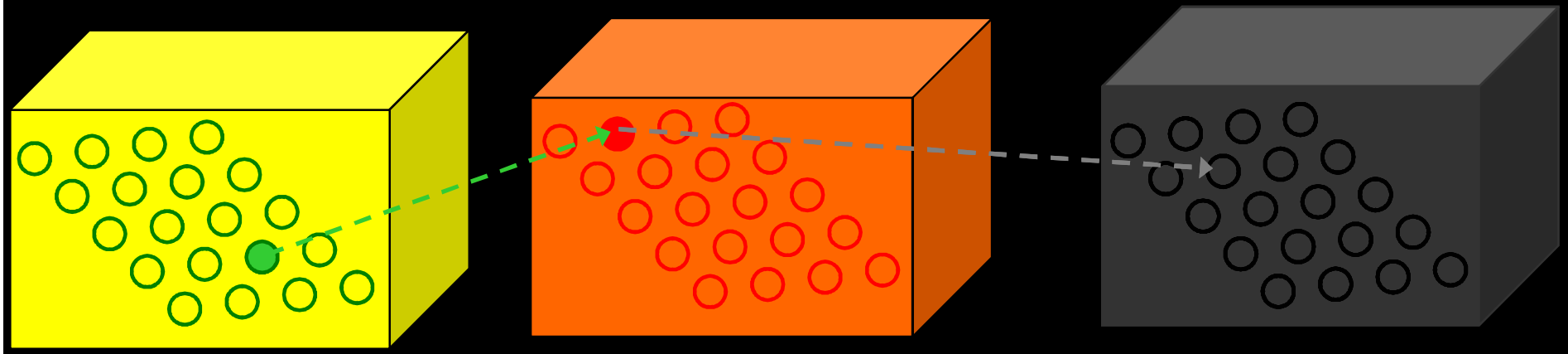


Spazio chimico ***Spazio biologico*** ***Spazio fisio-patologico***

comincia l'era della ***poli-farmacologia***

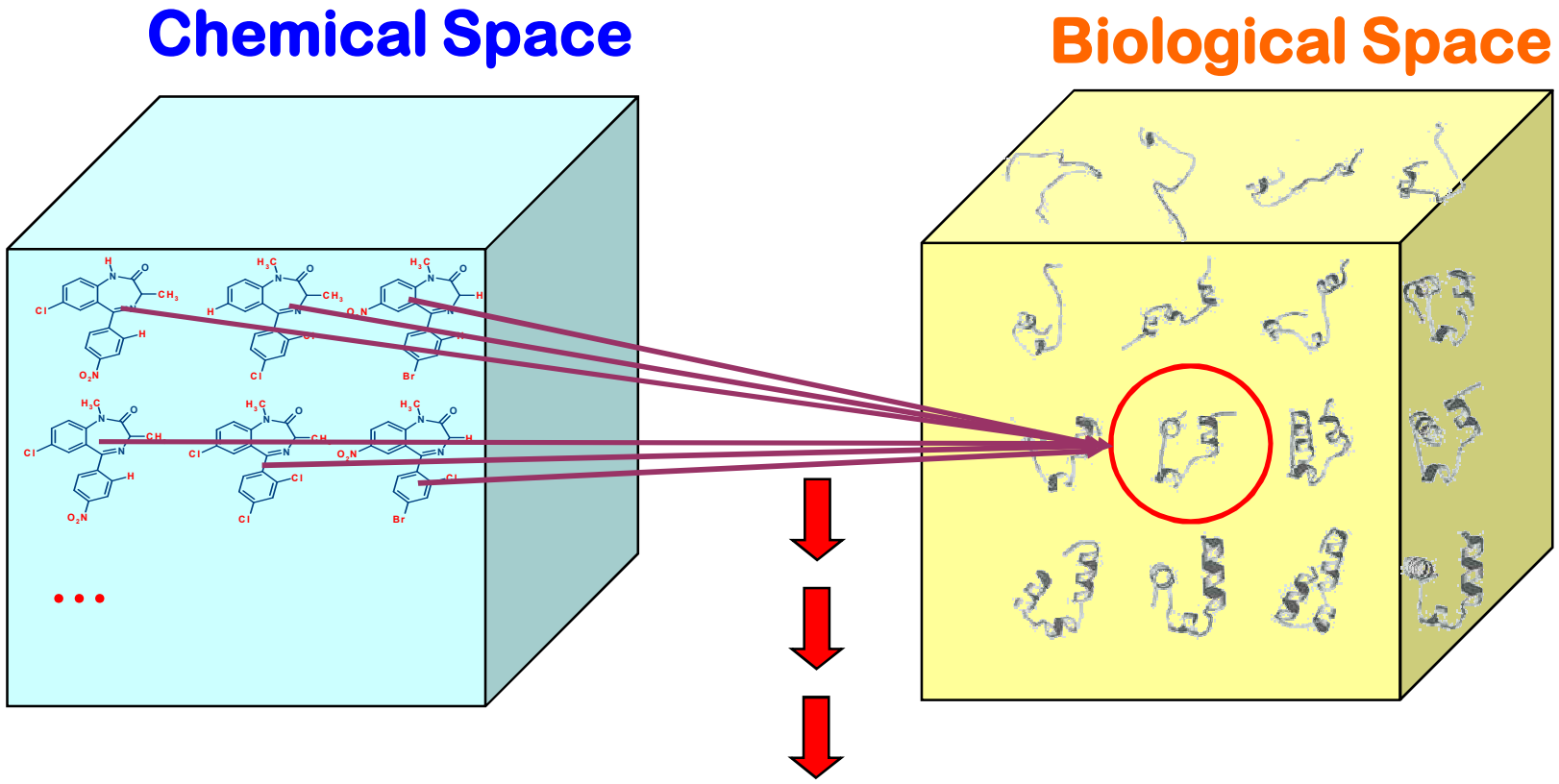
e quindi tendiamo a previlegiare gli spazi dove ci troviamo di più a nostro agio... molto umano!!!

Farmaco
Interazione Terapeutica
Target Primario
Patologia



Spazio chimico *Spazio biologico* *Spazio fisio-patologico*

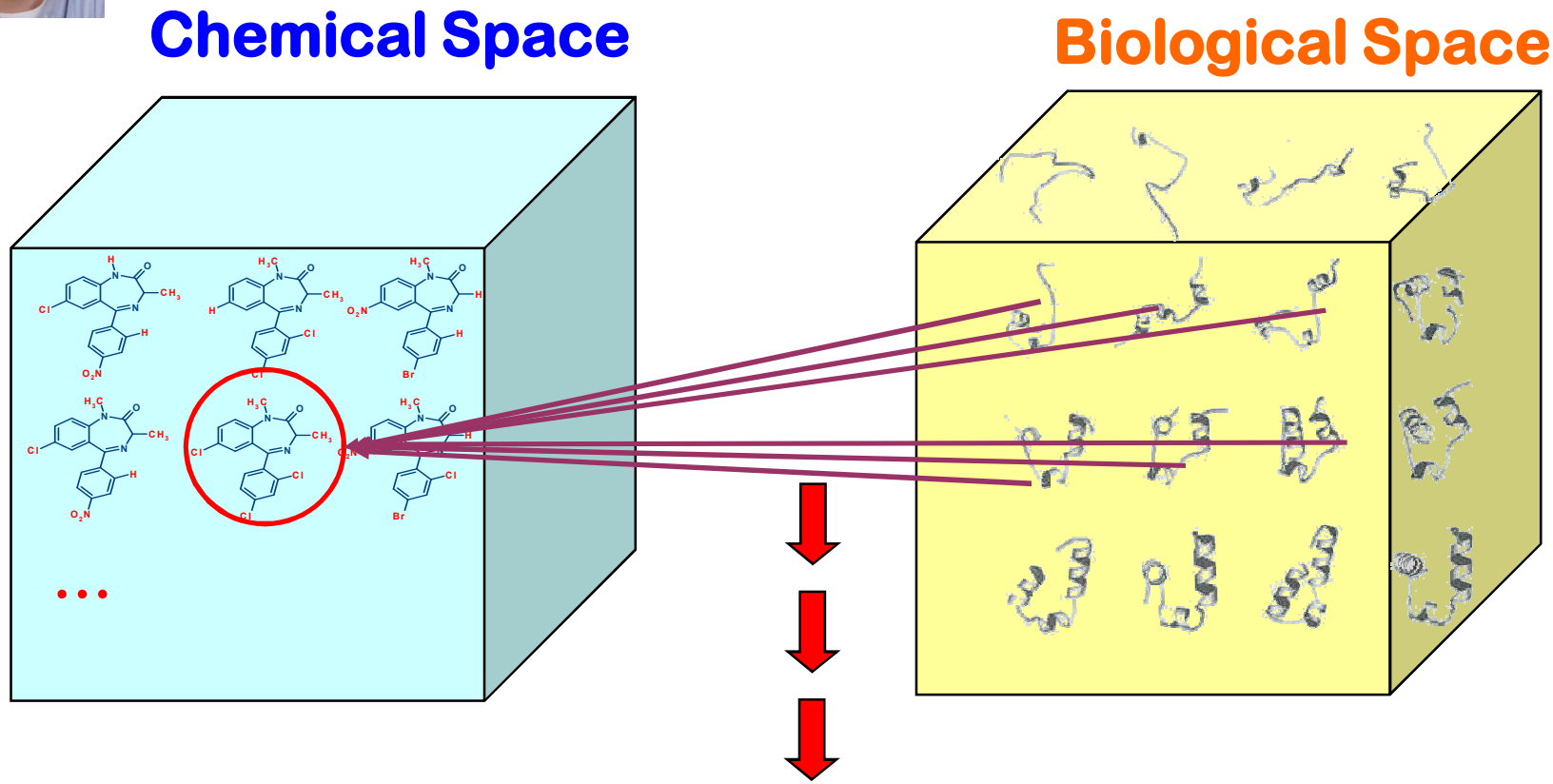
Sicuramente questa è la nostra interfaccia preferita…



SCREENING

Affinità → K_d; EC_{50} …

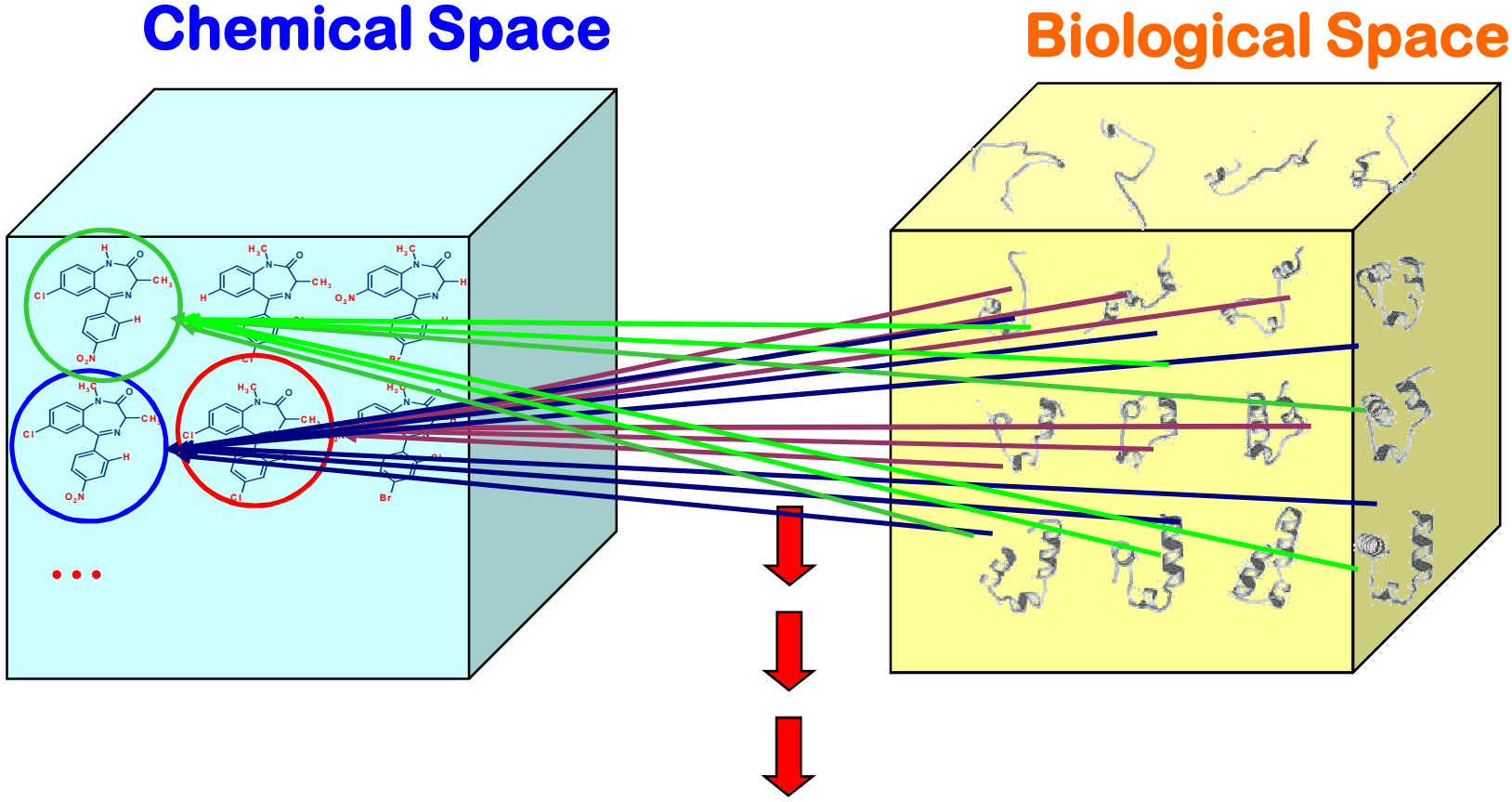
Sicuramente questa è la nostra interfaccia preferita…



PROFILING

Selettività → $K_d(A)/K_d(B)$; $EC_{50}(A)/EC_{50}(B)$ …

ma qui potrebbe allora aprirsi un nuovo scenario...



CHEMICAL GENOMICS/PROTEOMICS