

**“Drug Design today ... between myth  
and reality.”**

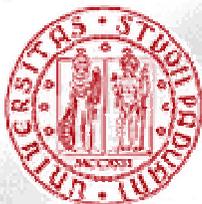
**Stefano Moro**

**Molecular Modeling Section (MMS)**

**Department of Pharmaceutical and Pharmacological Sciences**

**University of Padova**

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**MMS**

Molecular Modeling Section

Department of Pharmaceutical and Pharmacological Sciences, University of Padua

Via Marzolo 5, 35131 Padova (Italy) - phone: +39 049 8275704, fax: +39 049 8275366

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**Stefano Moro, Ph.D.**

Professor of Medicinal Chemistry

Molecular Modeling Section (MMS)

Via Marzolo 5 - 35131 Padova (Italy)

phone: +39 049 827 5704; fax: +39 049 827 5366

email: [stefano.moro@unipd.it](mailto:stefano.moro@unipd.it); Skype user: smoro65

**Bibliometric indexes:**



Google

Scopus

ORCID

**CV:**



**Biblio Sketch:**

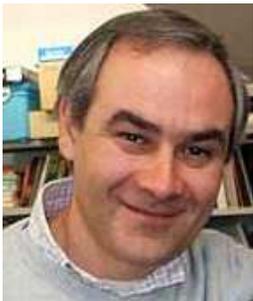
I consider myself a molecular psychologist. A molecular psychologist is a scientist who studies psychology of molecules, the systematic investigation of the molecular life, including molecular behavior and molecular cognition.

Marta & Stefano best chemical experiment... MS

MS

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S. MORO – SGSS – 2018



# Here is our working platform...

<http://mms.dsfarm.unipd.it>



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April 01, 2016

MMS launches MMSYouTube channel. [more...](#)

October 01, 2015

MMS launches the DockBench tool. [more...](#)

January 24, 2014

MMS launches the Supervised Molecular Dynamics

#### MMS: Events

November 16-17, 2017

5th CDD Meeting in Milan... [more](#)

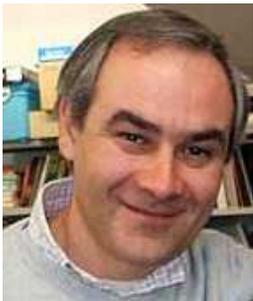
#### MMS: Latest Hot Publication

Salmasso et al. "Exploring Protein-Peptide Recognition Pathways Using a Supervised Molecular Dynamics Approach." *Structure* (2017) [more...](#)

MS  
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Dipartimento di Farmacologia e Farmacologia Clinica, Università di Padova  
Via Marzotto 5, 35131 Padova, Italy | phone: +39 049 8077704, fax: +39 049 8077704

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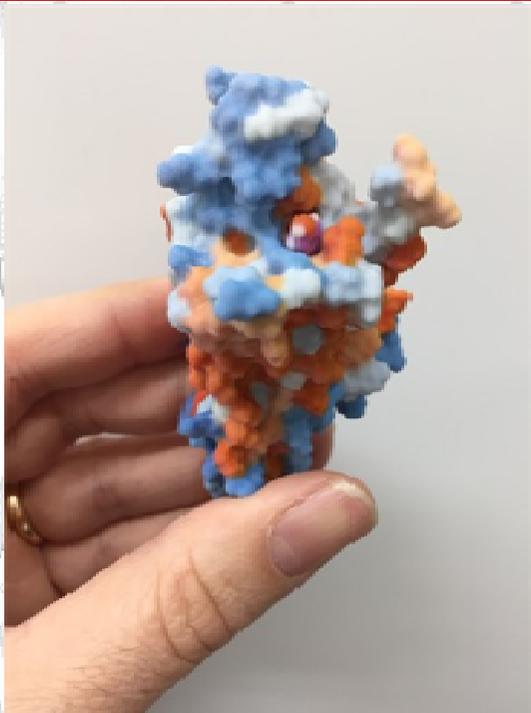
**MMS: Events**

**January 24-28, 2016**  
 Keystone Symposia - Pivotal Signaling  
 Fairmont Hotel Vancouver - Vancouver, British  
 Columbia, Canada... [more...](#)

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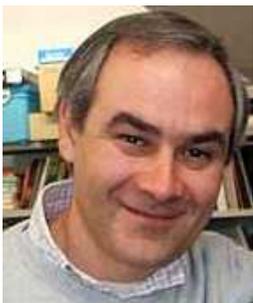
**MMS: Latest Hot Publication**

Sabbadin D. et al. "Exploring the recognition pathway at the human A2A adenosine receptor of the endogenous agonist adenosine using supervised molecular dynamics simulations." *MedChemComm* (2015) [more...](#)



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### Ph.D. Courses

April 2017	<a href="#">Training course Elixir-ITA, Padova</a>	
April 2014	<a href="#">PhD Spring School, Padova (Italy)</a>	
June 2012	<a href="#">PhD Summer School, Vigo (Spain)</a>	

### Hospital Pharmacy

September 2017	Padova (Italy)	
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### Scuola Galileiana di Studi Superiori

May 2018	Padova (Italy)	
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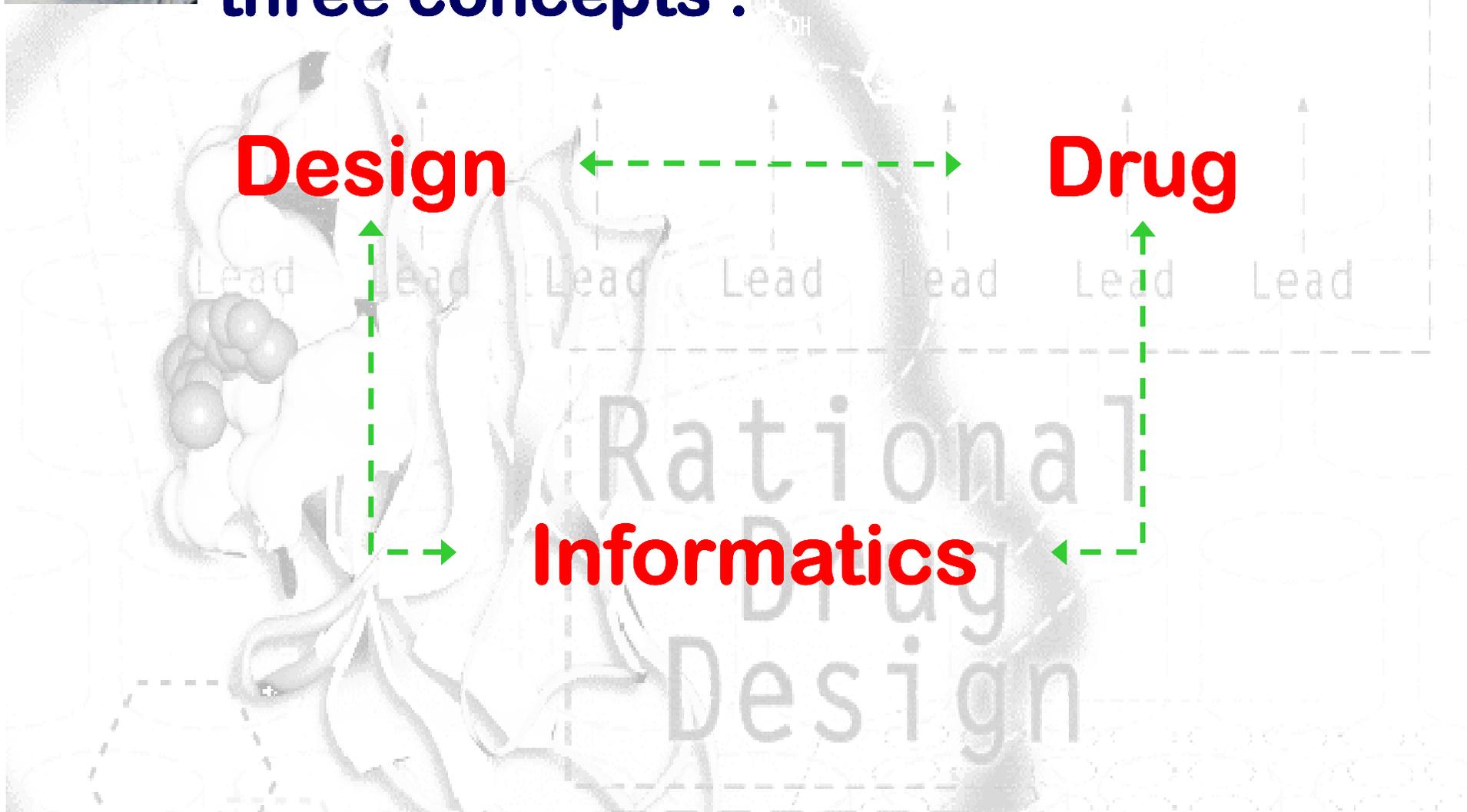
MS

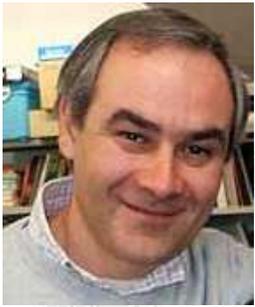
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S. MORO – SGSS – 2018

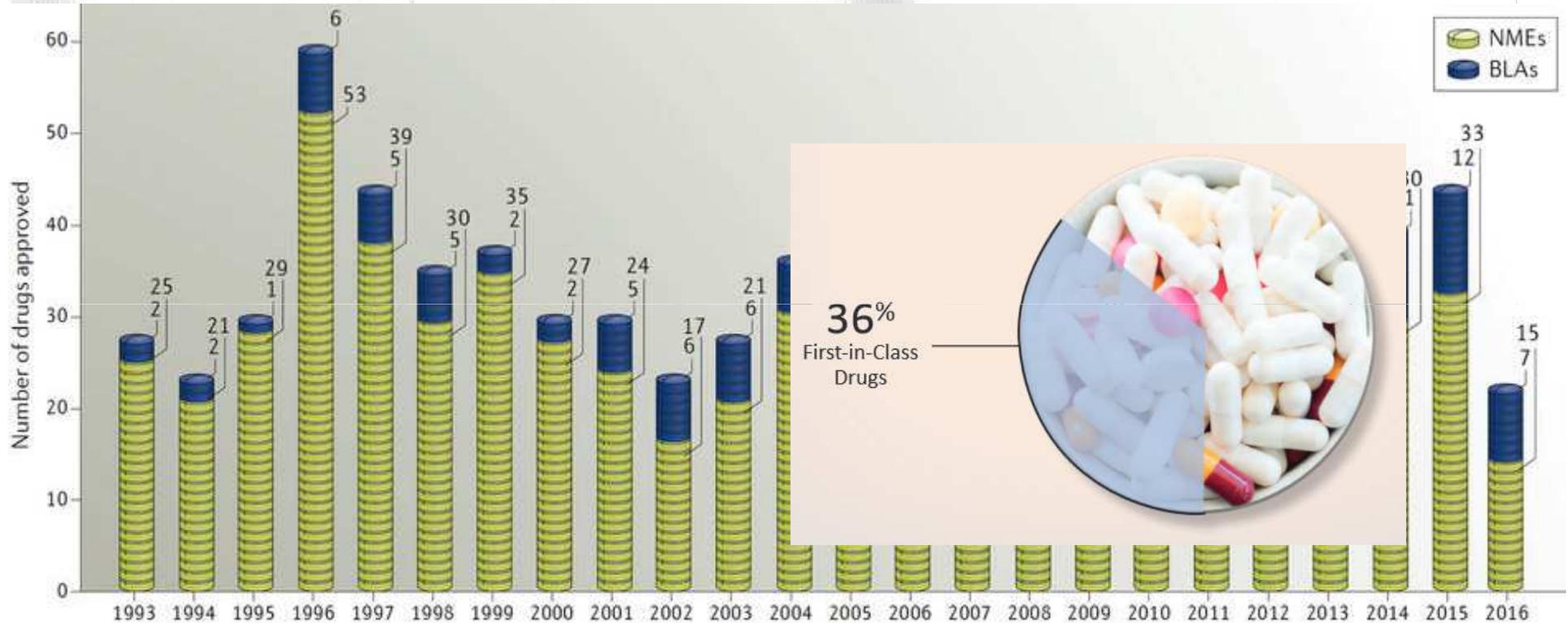


Why we are here today... to find the intimate connection between these three concepts :

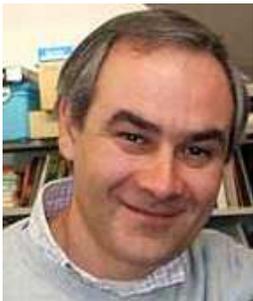




# Houston, we've had a problem here!



**We define first in class a drug which introduces a new mechanism of action for treating a medical condition.**

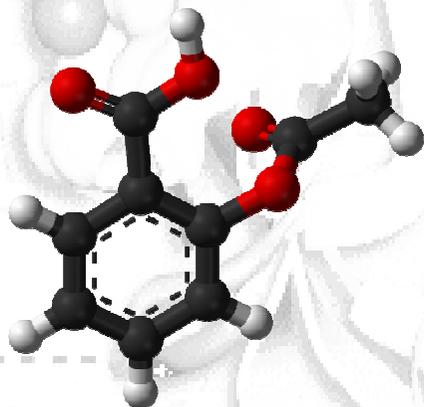


# NME *versus* BLA in one slide...

## Vintage drugs

### *ASPIRINE*

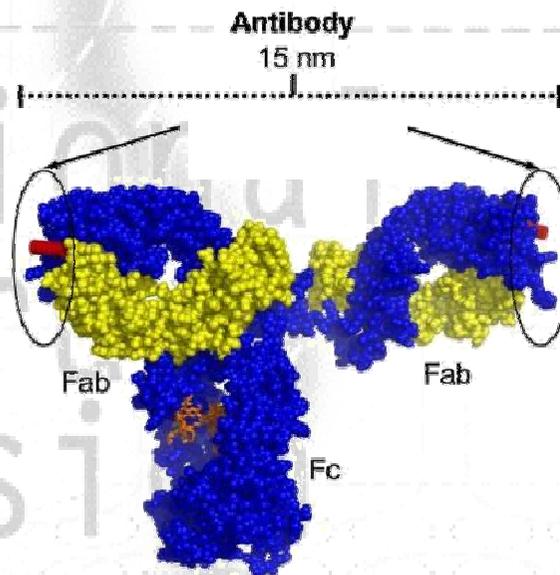
1. small molecule
2. 180 Da
3. 21 atoms
4. usually not immunogenic
5. usually chemically stable



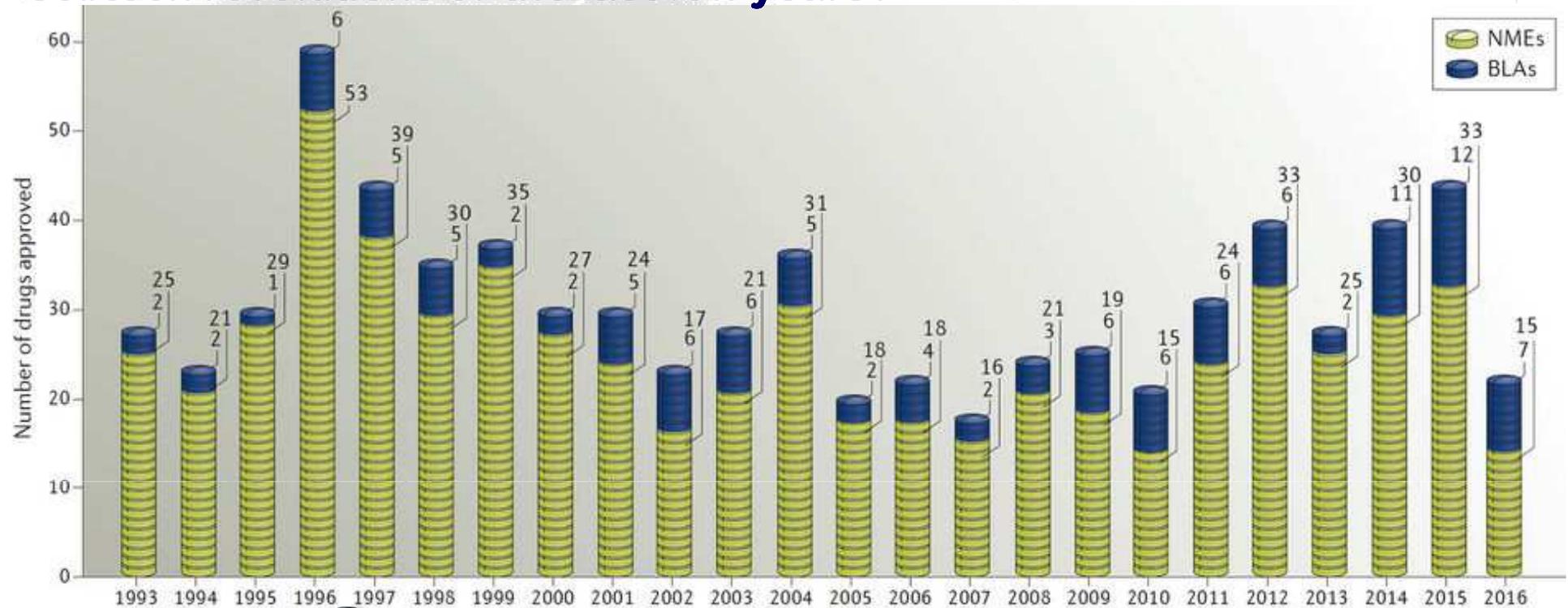
## New age (biotech) drugs

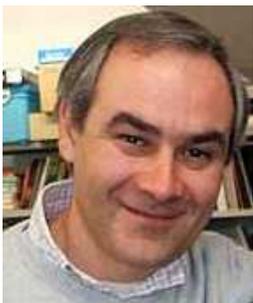
### *MONOCLONAL ANTIBODY (mAb)*

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?





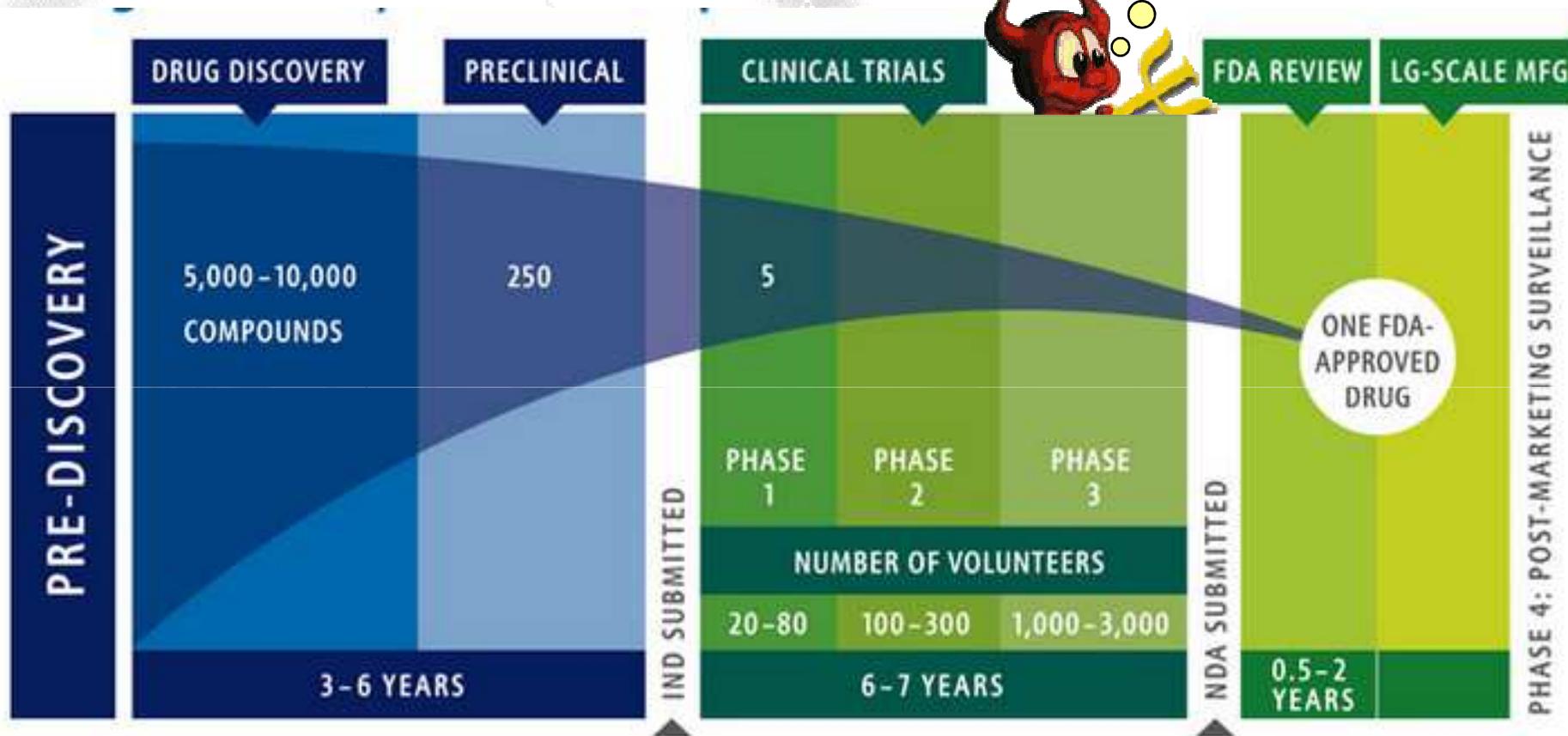
## Why we need “drug” design?

**Drug discovery is an extremely competitive activity!**

- a. ~ 1600 companies;
- b. ~ 6000 R&D projects.

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

Aaahhh...  
1 a xxx.000!!!!

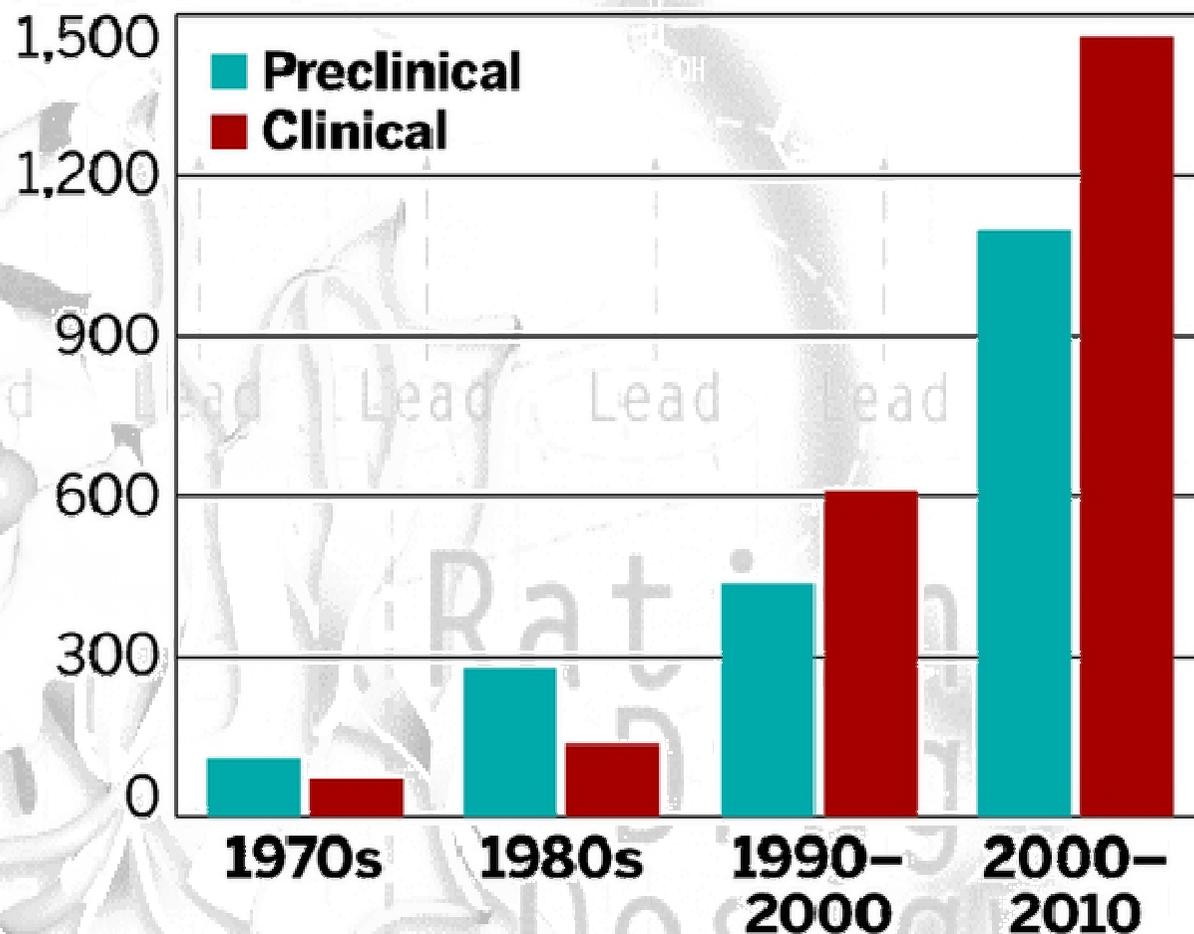


**Bringing a new drug to market can take 8-14 years and costs between \$400 and \$900 million... or even more!!**

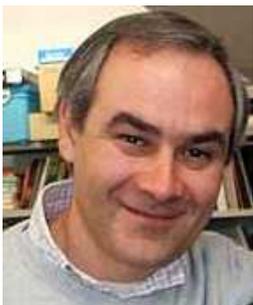


## Some details about costs:

Cost, \$ millions



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

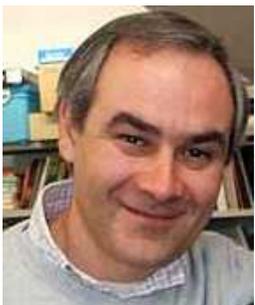


## Some details about costs:

### *Experiment Typical Cost per Compound (€)*

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

**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?**

The worthwhile “pharma” goal (dream):

## *From Lead to Drug in Five Years*

*International Drug Discovery and Development Summit – December 2-5, 2011,  
Honolulu, Hi, USA*

### **Priorities:**

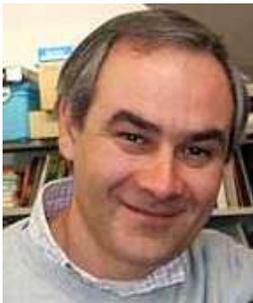
**Lead selection using virtual screening;**

*In vitro* screening for drug toxicity;

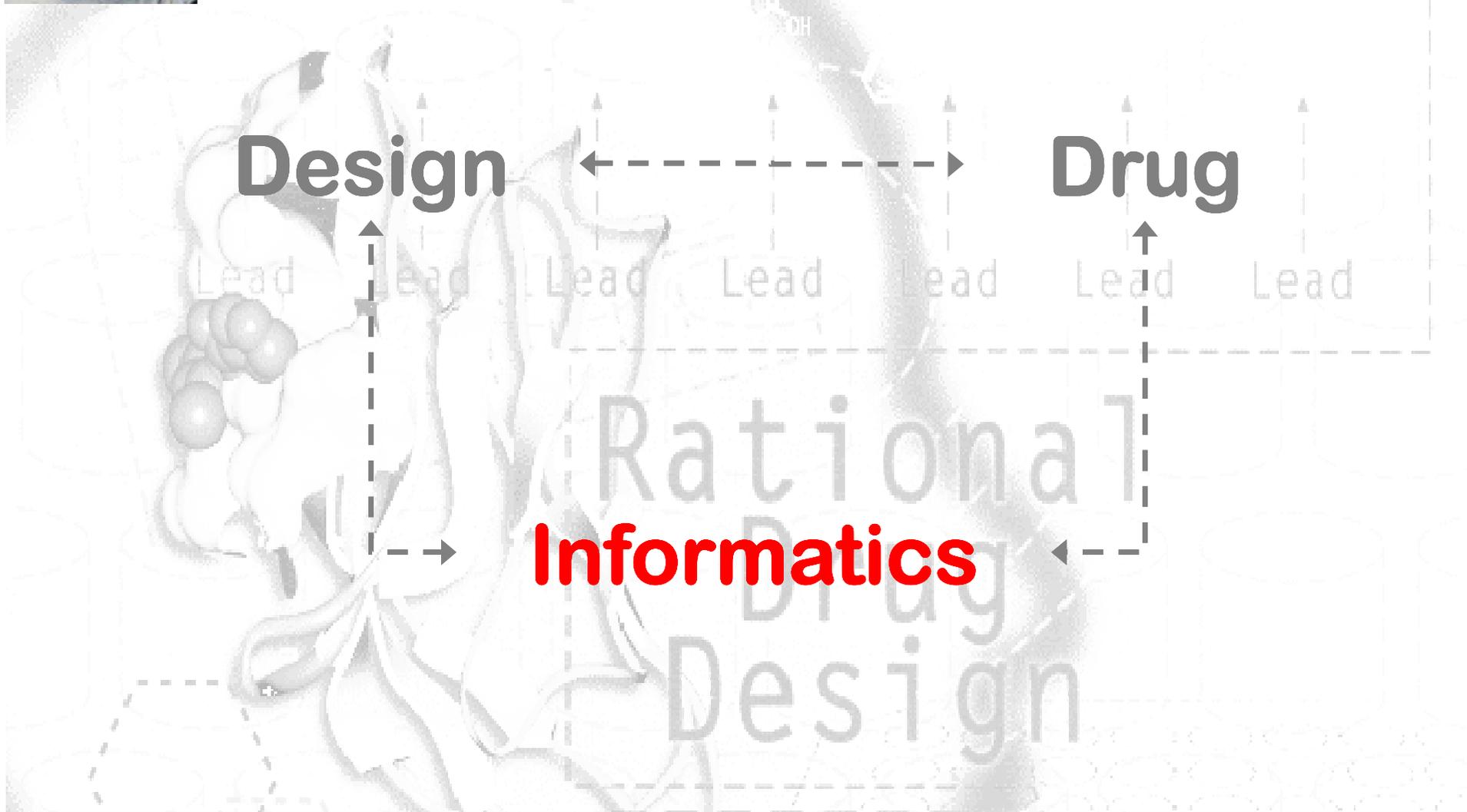
Solubility and bioavailability;

Animal models: accelerating discovery;

Accelerating clinical studies.



... couple of bits of:





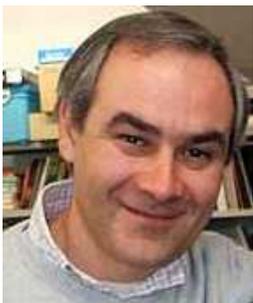
again an egoistic definition of informatics:

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

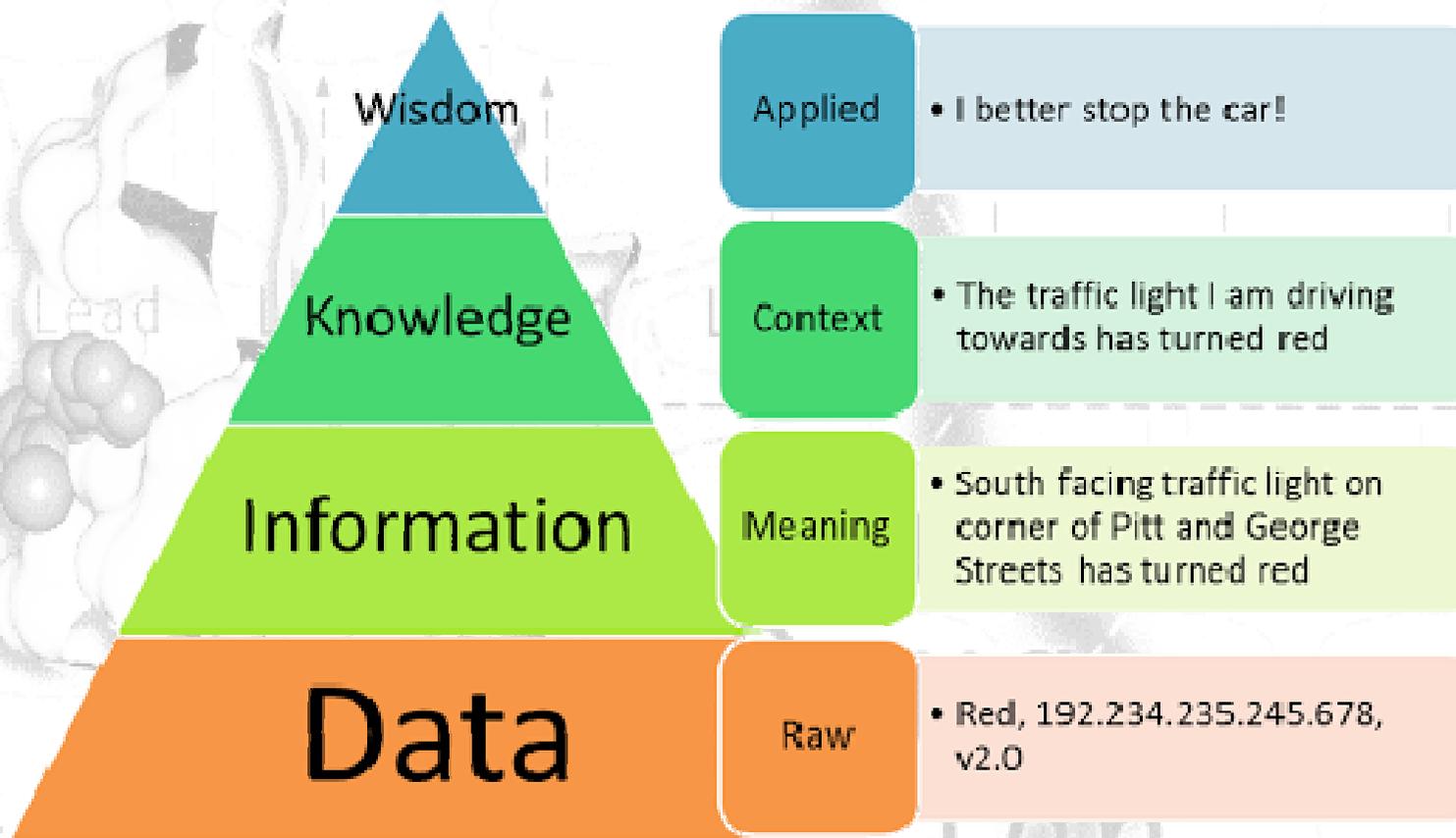


It is not sufficient to invent something. You need to recognize, that you have invented something.

*Karl Steinbuch*



... exciting!



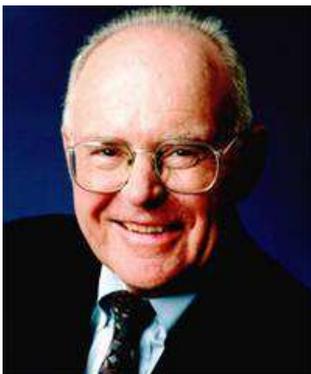
© 2011 Angus McDonald



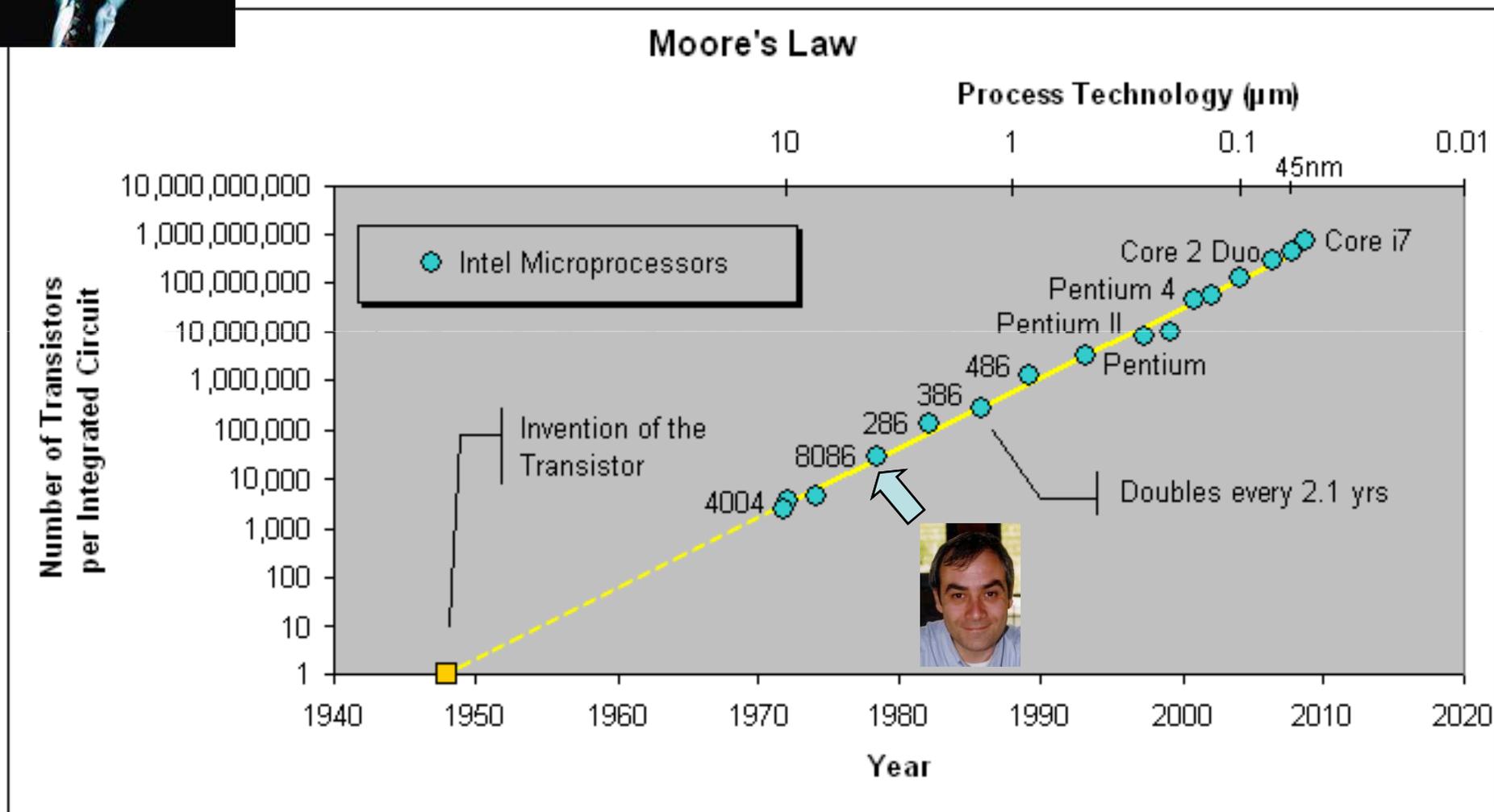
Now, in what informatics has influenced more in our daily life?

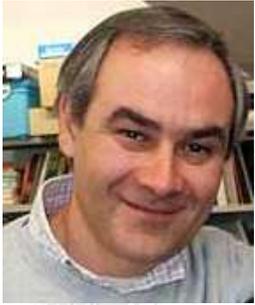
Well, we probably summarize the answer in only one word:

**Time**



# Informatics as synonymous of speed?





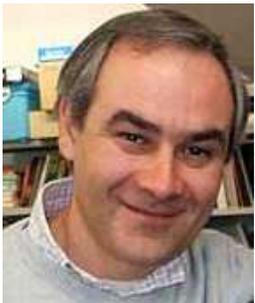
## **couple of concrete example..**

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

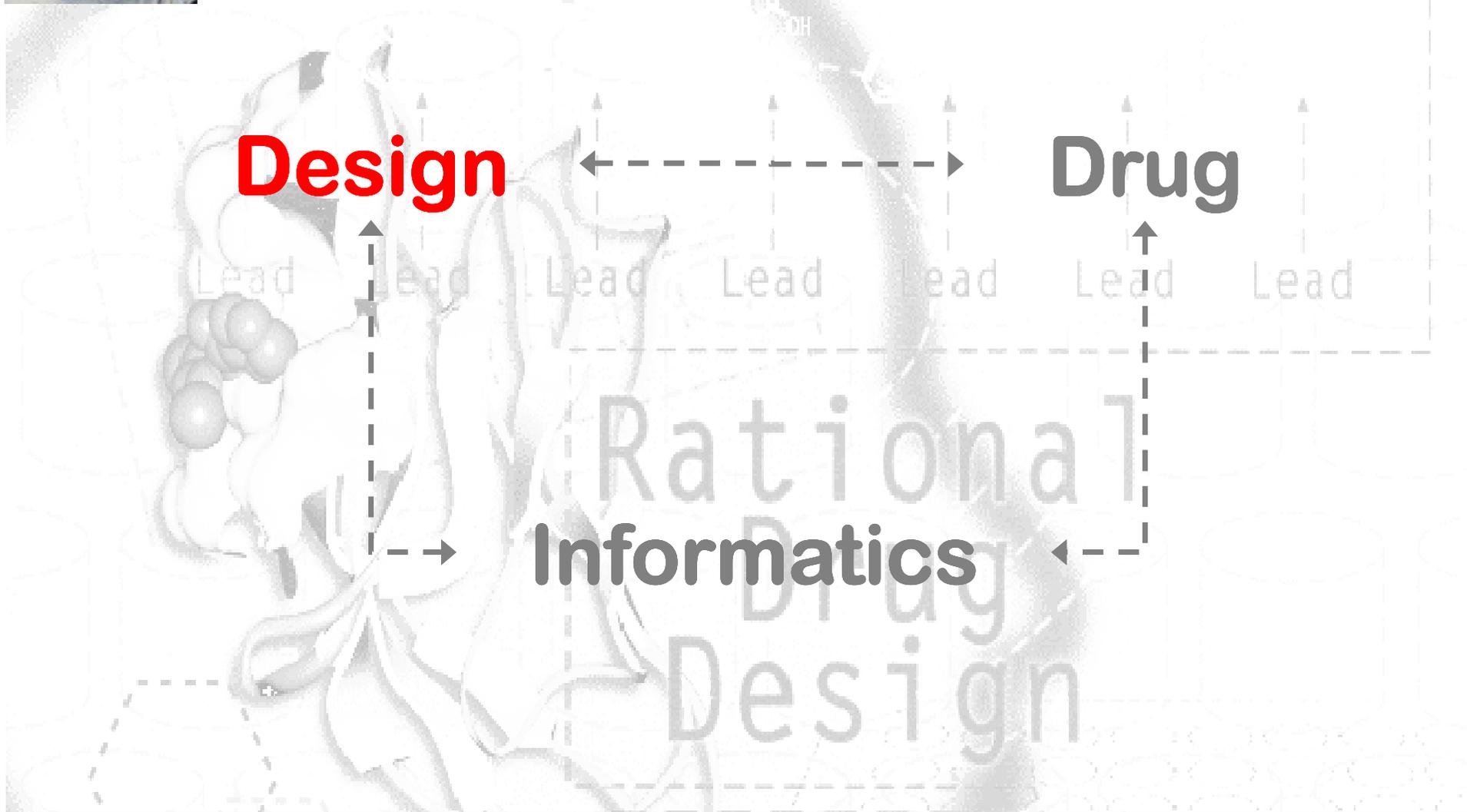
**Calculate the molecular weight is trivial thing, calculate 4.5 million ... less!**

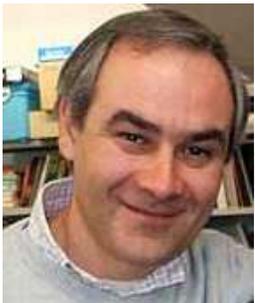
**or solve very complex problems:**

**Calculate, for example, the binding energy ( $\Delta G_{\text{bind}}$ , kcal x mol) between a ligand and its receptor!**



... a bit of:





... be patient:

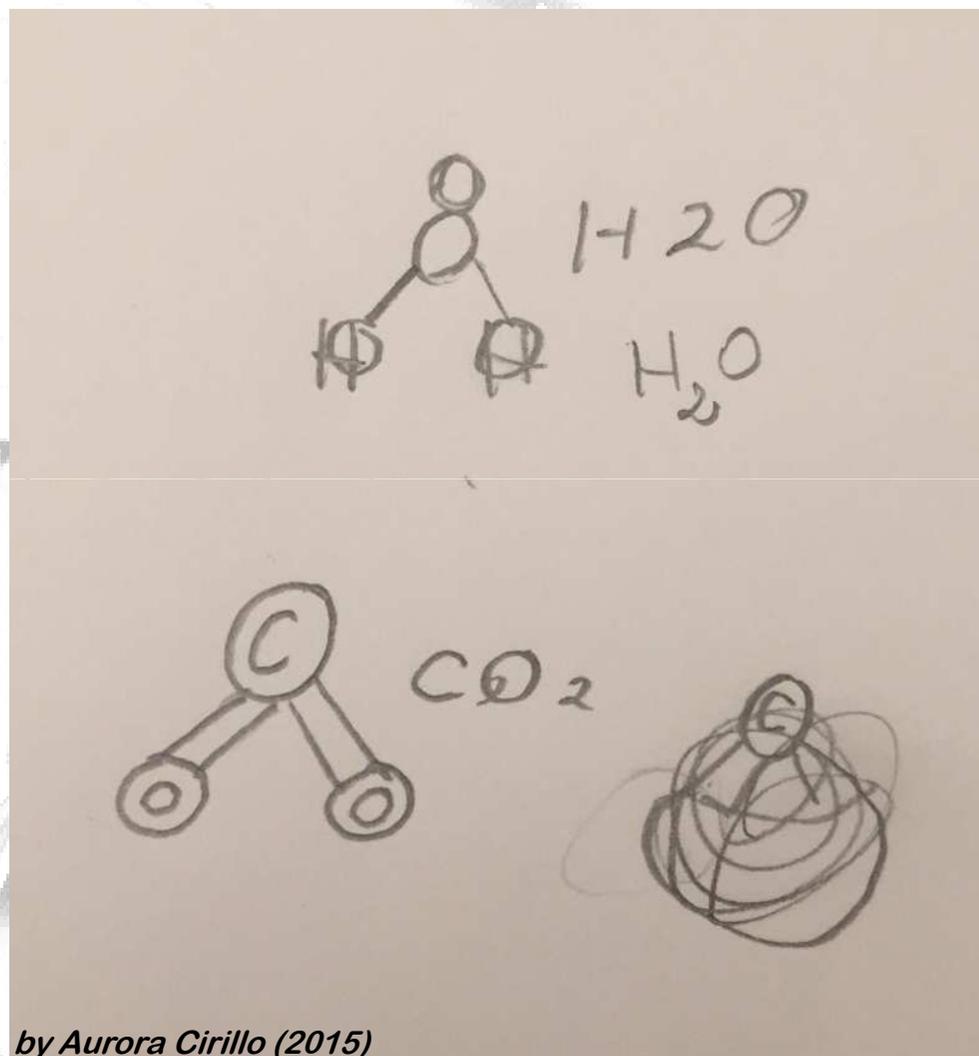
## Design:

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

Rational  
Drug  
Design

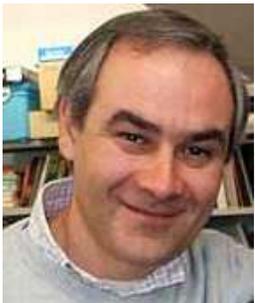


... there is no doubt that chemists (including medicinal chemists) are of great *drawers*:



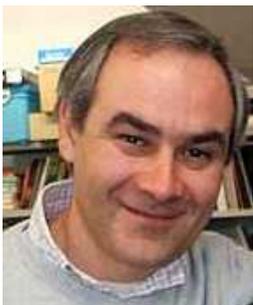
by Aurora Cirillo (2015)





... a bit of:



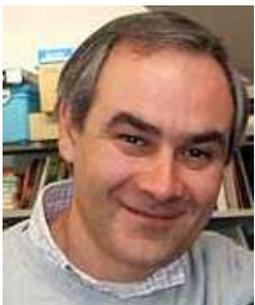


I know very well that you know what drug is... but reconsider its definition in this way:

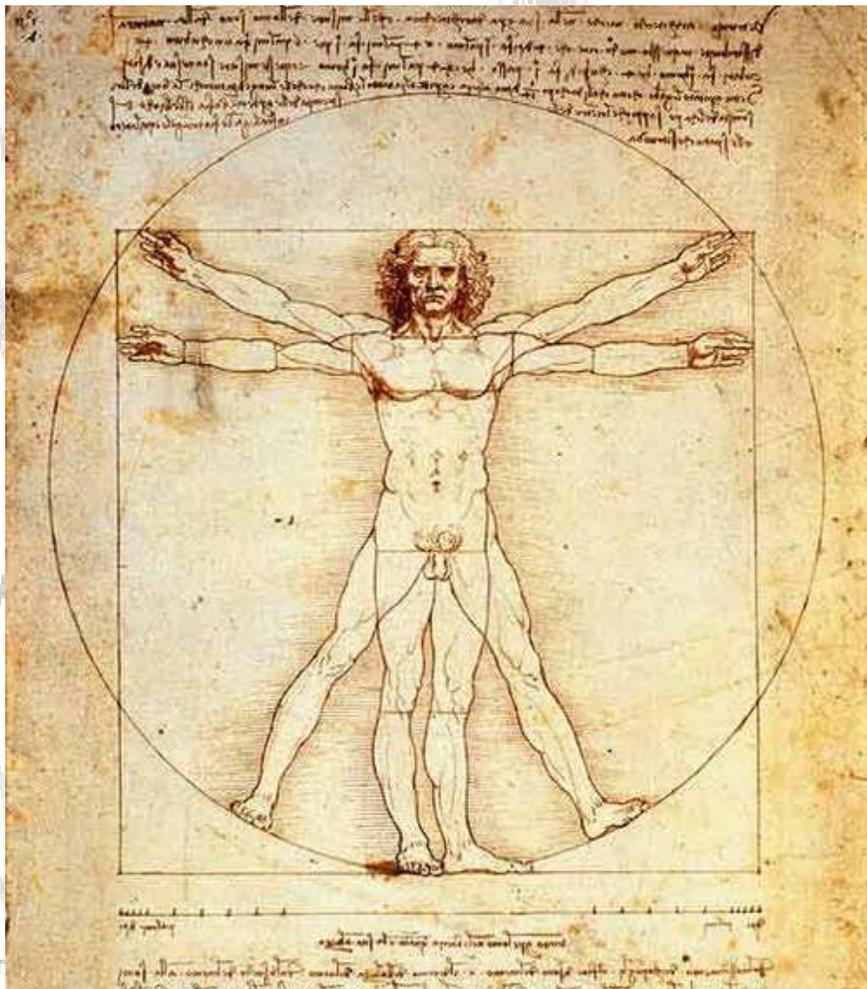
## Drug:

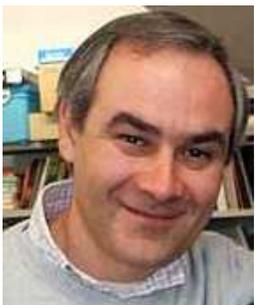
[from gr. φάρμακον] *Any substance, organic or inorganic, synthetic or natural, capable of producing in a **living organism** functional modifications, helpful or harmful, by chemical action, physical chemistry or physics.*

*Dizionario Treccani*

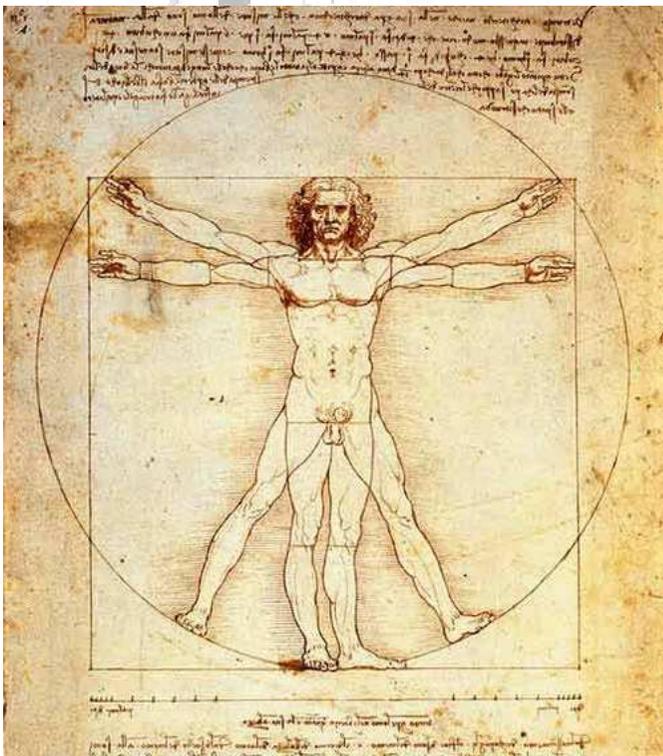


... and a '*living organism*' is difficult to accommodate in a design process (drawing and calculations), though ...

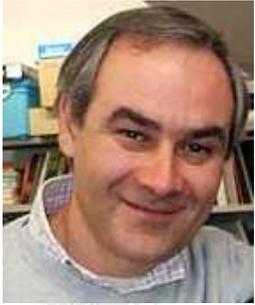




... I suspect that you could have a sensation like this:



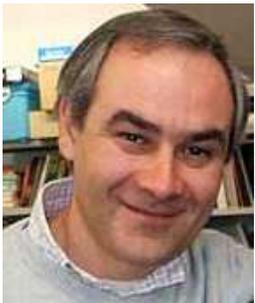
**We will return later on this concept...**



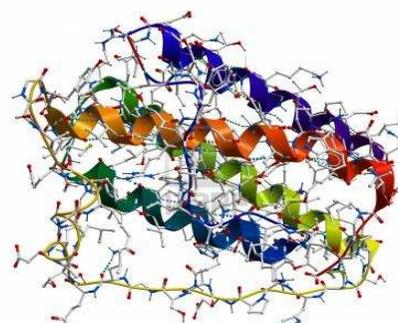
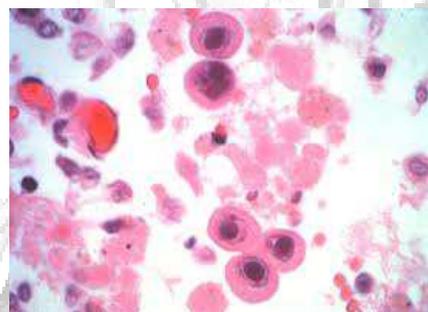
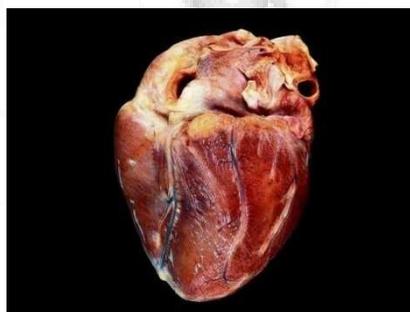
**Last but not least, we never forget the three milestone aspects of being a drug:**

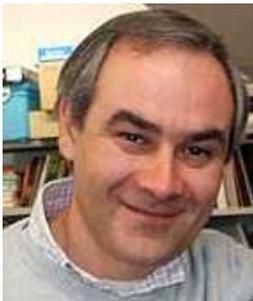
- 1. Pharmacodynamics;**
- 2. Pharmacokinetics;**
- 3. Formulation.**

Rational  
Drug  
Design



# Choose the best solution:

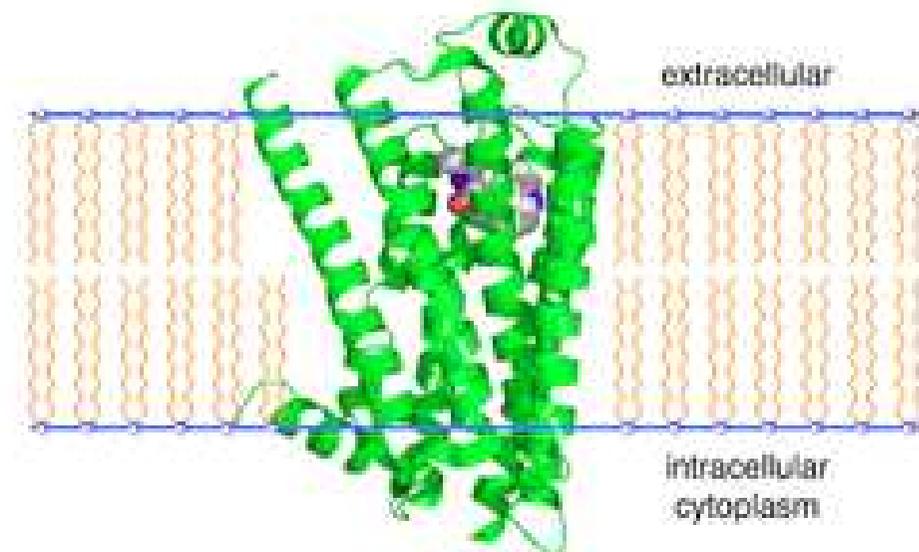




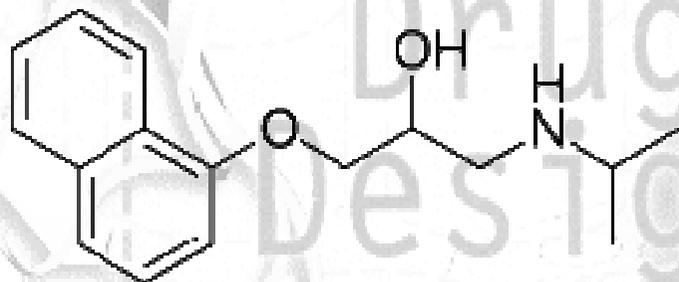
# Choose the best solution:



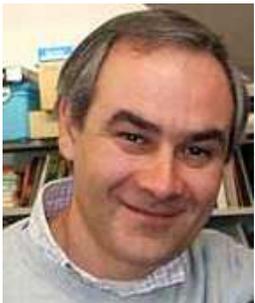
**Infantile Hemangioma**



**Beta adrenergic receptors**

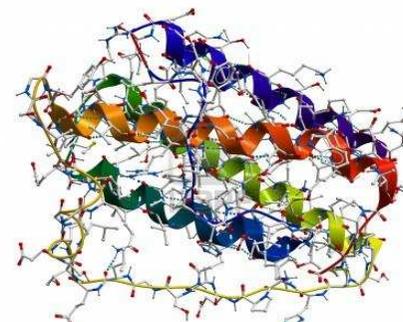
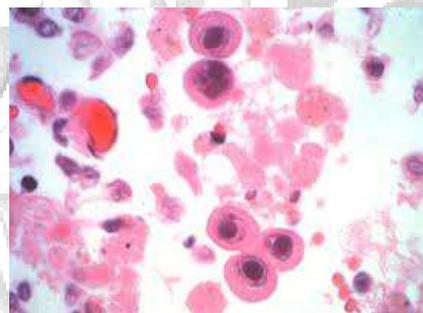
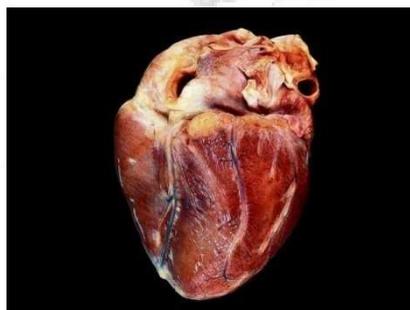
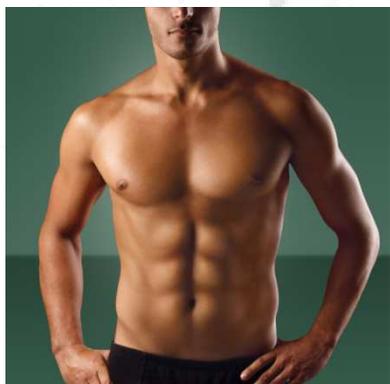


**Propranolol**

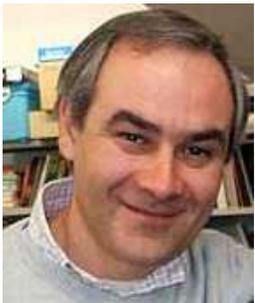


# Choose the best solution:

**Drug**



**Candidate**



# Stretching time!

