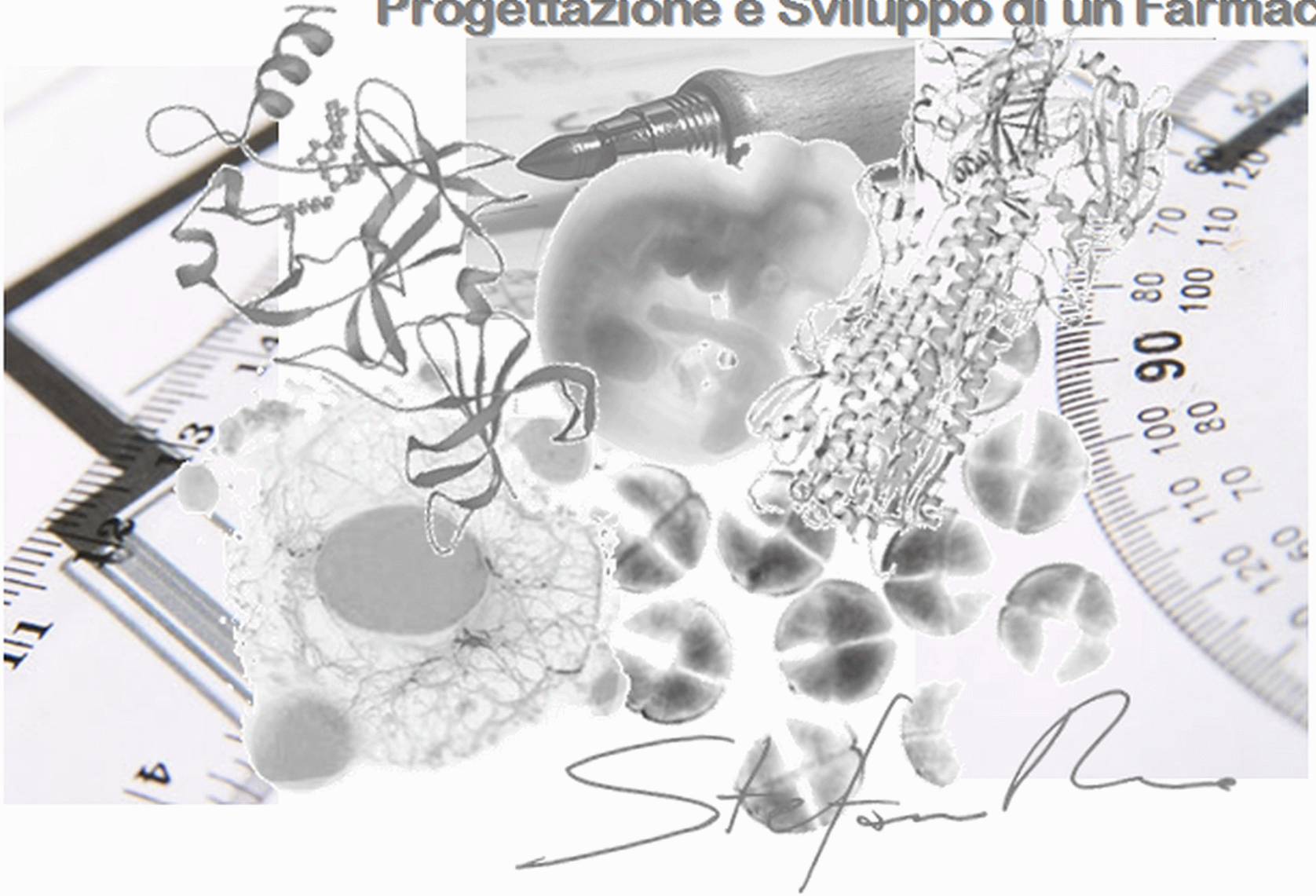
# Progettazione e Sviluppo di un Farmaco



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UNIVERSITÀ DEGLI STUDI DI PADOVA

MMS Molecular Modeling Section

Department of Pharmaceutical and Pharmacological Sciences, University of Padova

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### News & Updates

…y 01, 2023

…gins collaboration with Cresset. *more...*

### MMS: Events

**September, 2024**

XXVIII EFMC International Symposium on Medicinal Chemistry... *more*

### MMS: Latest Hot Publication

**Gianferrara T et al.** "Are Two Riboses Better Than One? The Case of the Recognition and Activation of Adenosine Receptors" ChemMedChem (2023) *more...*

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- Chimica Farmaceutica 2 (CTF)
- Progettazione e Sviluppo di un Farmaco
- Biomodel
- Chimica I
- Chemoin
- Tossicolo ale
- (Master F School)
- Master, P Courses


**September, 2022**
**XXVII National Meeting in Medicinal Chemistry...** *more*

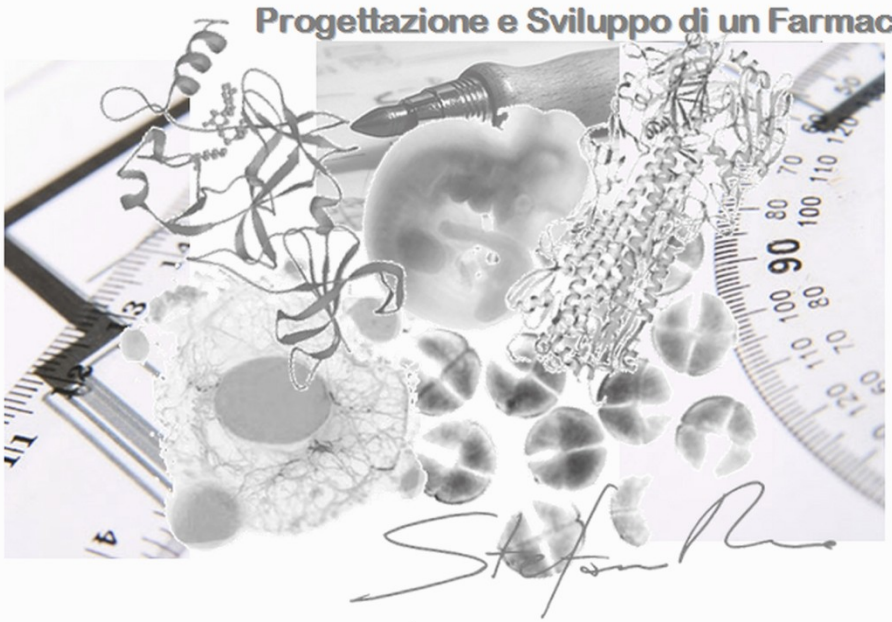
## MMS: Latest Hot Publication

**Heilmann E et al.** "SARS-CoV-2 3CL$^{pro}$ mutations selected in a VSV-based system confer resistance to nirmatrelvir, ensitrelvir, and GC376" Sci Transl Med. (2022) *more...*.

Presentazione di PowerPoint - DrugDiscovery_Y2K.pdf – Mozilla Firefox

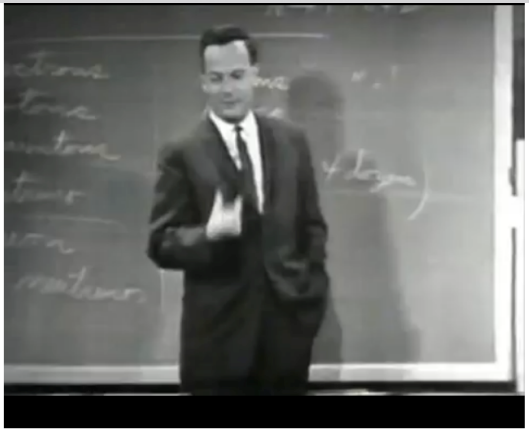
mms.dsfarm.unipd.it/files/Lezioni/PSF/PDF/DrugDiscovery_Y2K.pdf

1 di 90 Zoom automatico









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lications | @learning | MMStools | MMS_Intranet

e metodologie computazionali ed informatiche nel campo della progettazione e
rietà chimico-fisiche e farmacologiche, e dello studio a livello molecolare dei loro
e è previsto un percorso di esercitazioni virtuali attraverso una piattaforma web-
tico/computazionali maggiormente utilizzati sia in ambito accademico sia nelle
resentato durante le lezioni e le esercitazione è in lingua inglese per consentire allo
a internazionalmente in questo ambito.

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

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| **@sertiamoci:** | |
| | |
| **Great Memories:** | |

| | | |
|---|---|---|
| | Analisi Conformazionale | |
| | Energetica Molecolare | |
| | Docking & Scoring<br>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) | |
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| 5. ICM-Browser (MolSoft): | |
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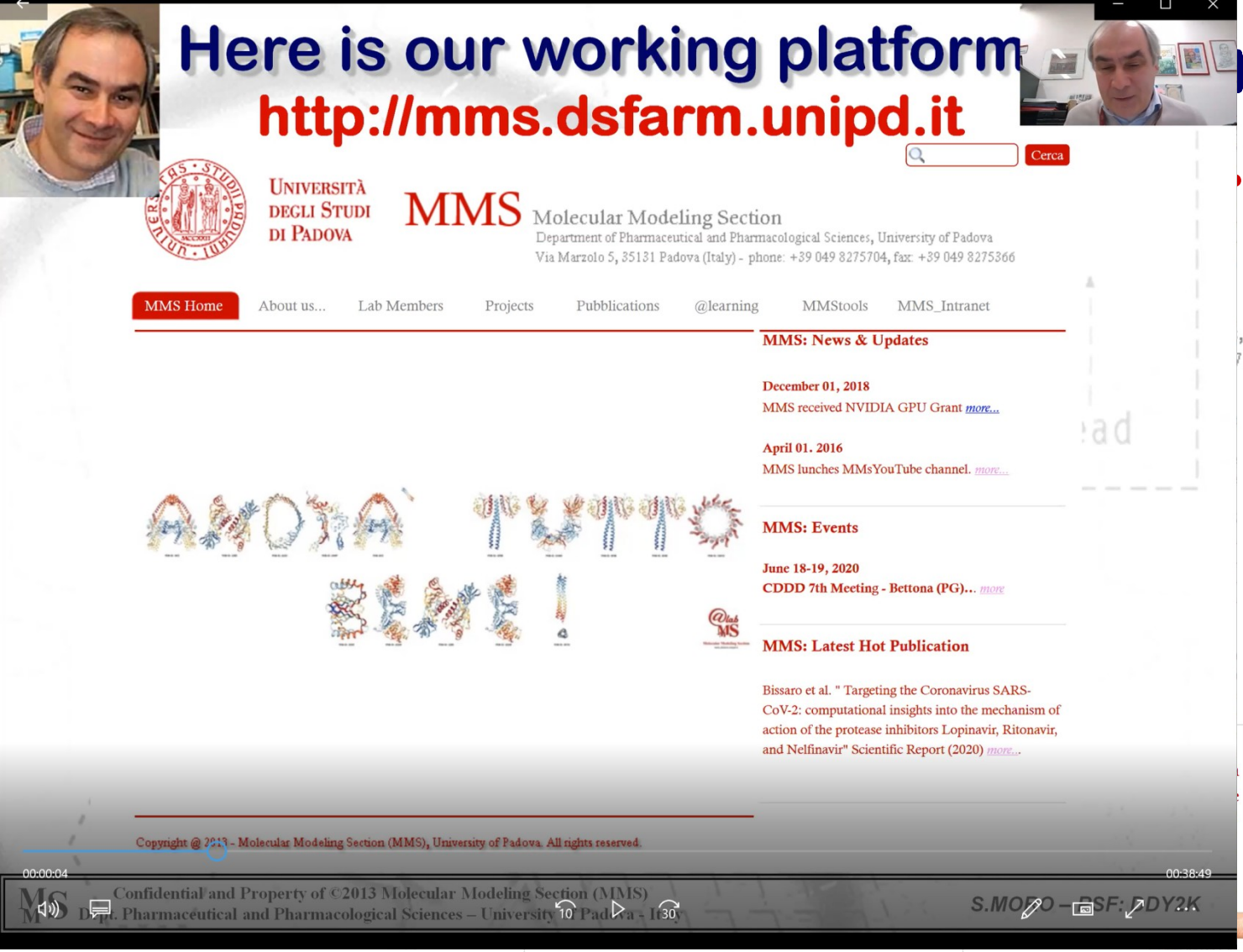


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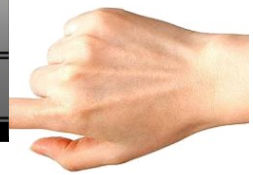

| | | |
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| **2. Ligand-based Drug Design (LBDD)** | | |
| | Rappresentazioni Molecolari e Similarità Strutturale | Parte 1 |

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**MMSeLab… broadening perspectives.**

@lab MMS

| | |
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| **Running Project:** | |
| **Project Aims:** | |
| **eTools:** | |
| **Tutorials:** | |
| **References:** | |
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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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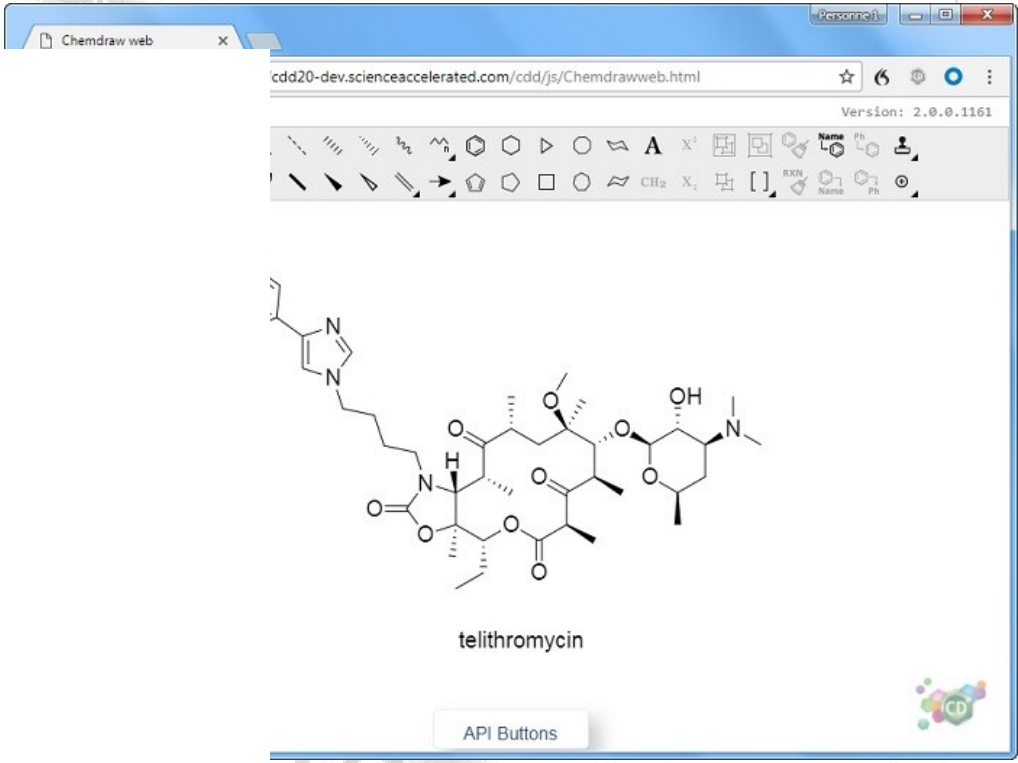
ultima modifica 09/03/2022 09:59




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

Licenza sw rinnovata con contratto triennale: 09.03.2022 – 08.03.2025

Può essere utilizzato dagli utenti istituzionali collegandosi al seguente link https://informatics.perkinelmer.com/sitesubscription/

Requisiti sw e hw e consigli per l'installazione

*http://bibliotecachimica.cab.unipd.it/documenti-download/chemdraw-prime*

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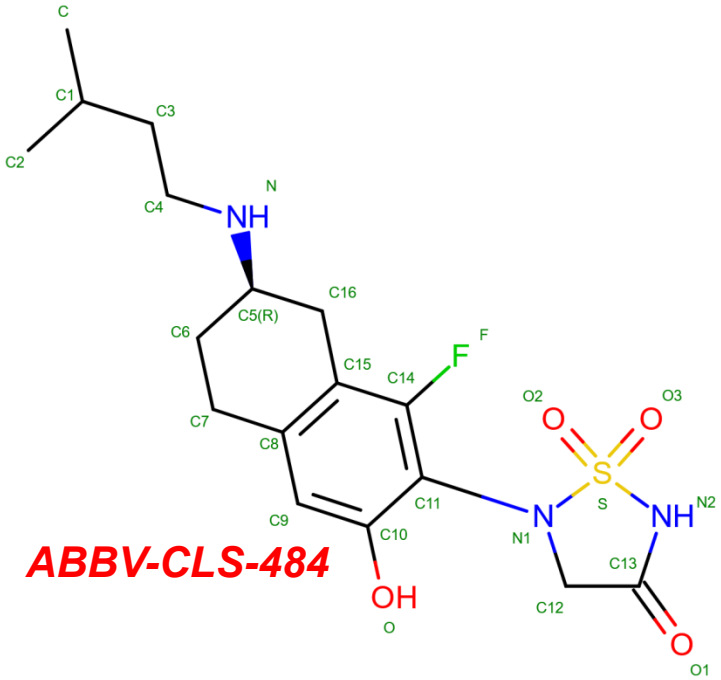
Offline

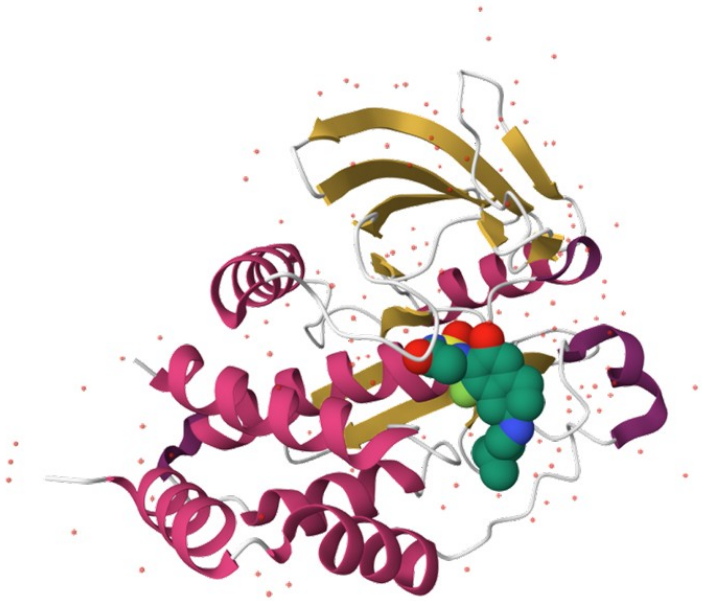
# A preview of our PSF 2023/2024 running project!

```
                                                                                                                    
                9        19        29        39        49        59        69        79        89        99       109
MAMPTTIEREFEELDTQRRWQPLYLEIRNESHDYPHRVAKFPENRNRNRYRDVSPYDHSRVKLQNAENDYINASLVDIEEAQRSYILTQGPLPNTCCHFWLMVWQQKTKAVVML
       119       129       139       149       159       169       179       189       199       209       219
NRIVEKESVKCAQYWPTDDQEMLFKETGFSVKLLSEDVKSYYTVHLLQLENINSGETRTISHFHYTTWPDFGVPESPASFLNFLFKVRESGSLNPDHGPAVIHCSAGIGRSGTF
  229       239       249       259       269
SLVDTCLVLMEKGDDINIKQVLLNMRKYRMGLIQTPDQLRFSYMAIIEGAKCIKGDSSIQKRWKELSKEDLSPAFDHSPNKIMTEKYNHHHHHHHH
```




***ABBV-CLS-484***

**PDB code: 7UAD**

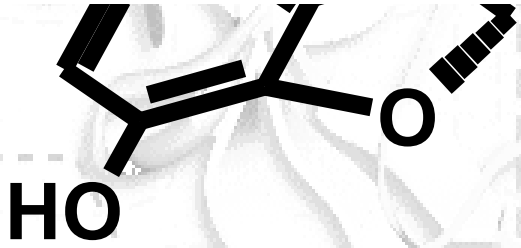


## The PTPN2/PTPN1 inhibitor ABBV-CLS-484 unleashes potent anti-tumour immunity.

Baumgartner CK, *et al* .The PTPN2/PTPN1 inhibitor ABBV-CLS-484 unleashes potent anti-tumour immunity. Nature. 2023 Oct;622(7984):850-862. doi: 10.1038/s41586-023-06575-7. Epub 2023 Oct 4.

# Our primary mission will be:

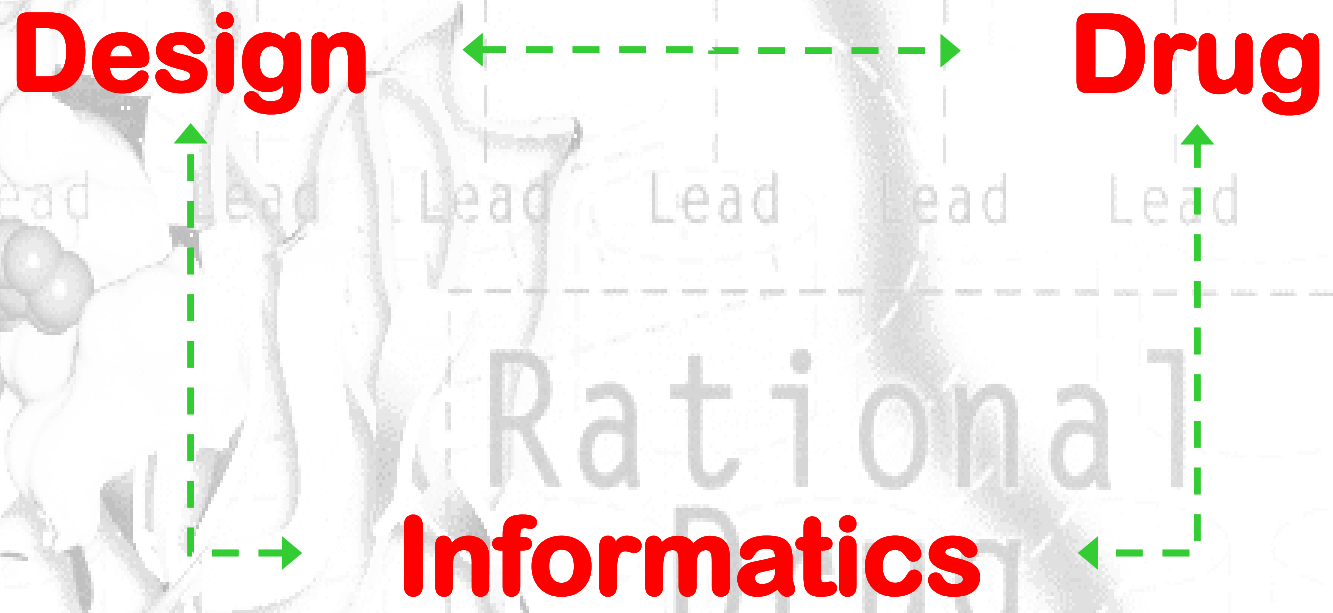
## Design!



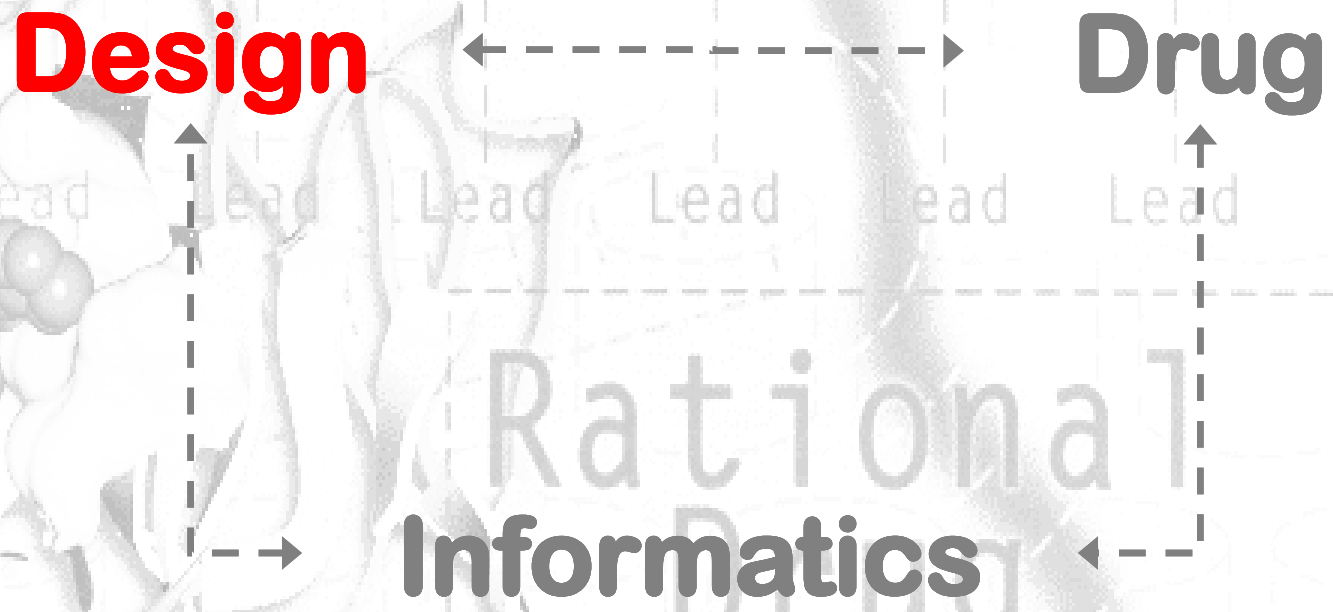
# The most insidious question that you can make me :

## 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.

...

# Design

**we will have to think carefully about the relationship between *drawing* and *reality***

# … 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 …

The average adult male has around *36 trillion cells* in their body, while average adult females have *28 trillion*, researchers have found. Unexpectedly, the mass of small cells in our bodies, such as blood cells, is roughly the same as that of large ones such as muscle cells – a finding that has puzzled researchers (by *Ian Hatton at the Max Planck Institute for Mathematics in the Sciences in Leipzig, Germany*)

How many million protein molecules are there in a single cell? *42*! (by *Douglas Adams. University of Toronto in Canada*)

According to an estimate made by engineers at Washington University, there are around $10^{14}$ atoms in a typical human cell. Another way of looking at it is that this is 100,000,000,000,000 or 100 trillion atoms. Interestingly, the number of cells in the human body is estimated to be about the same as the number of atoms in a human cell.

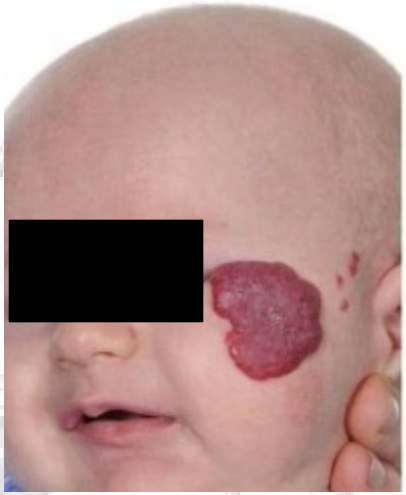
# … the complexity is not much different to deal with this problem.

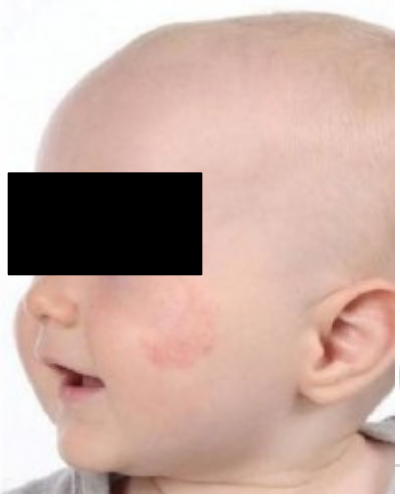
**How many planets are there really in the universe?**

**Erik Zackrisson, an astrophysicist at Uppsala University in Sweden, crunched the numbers on a computer model that simulated the evolution of the universe since the Big Bang.**

**He found that — given our current understanding of the universe and the laws of physics — there should be 7 times $10^{20}$ planets in the universe. That's 7 followed by 20 zeroes or 70 quintillion.**

# and I don't have a better example to describe a drug:

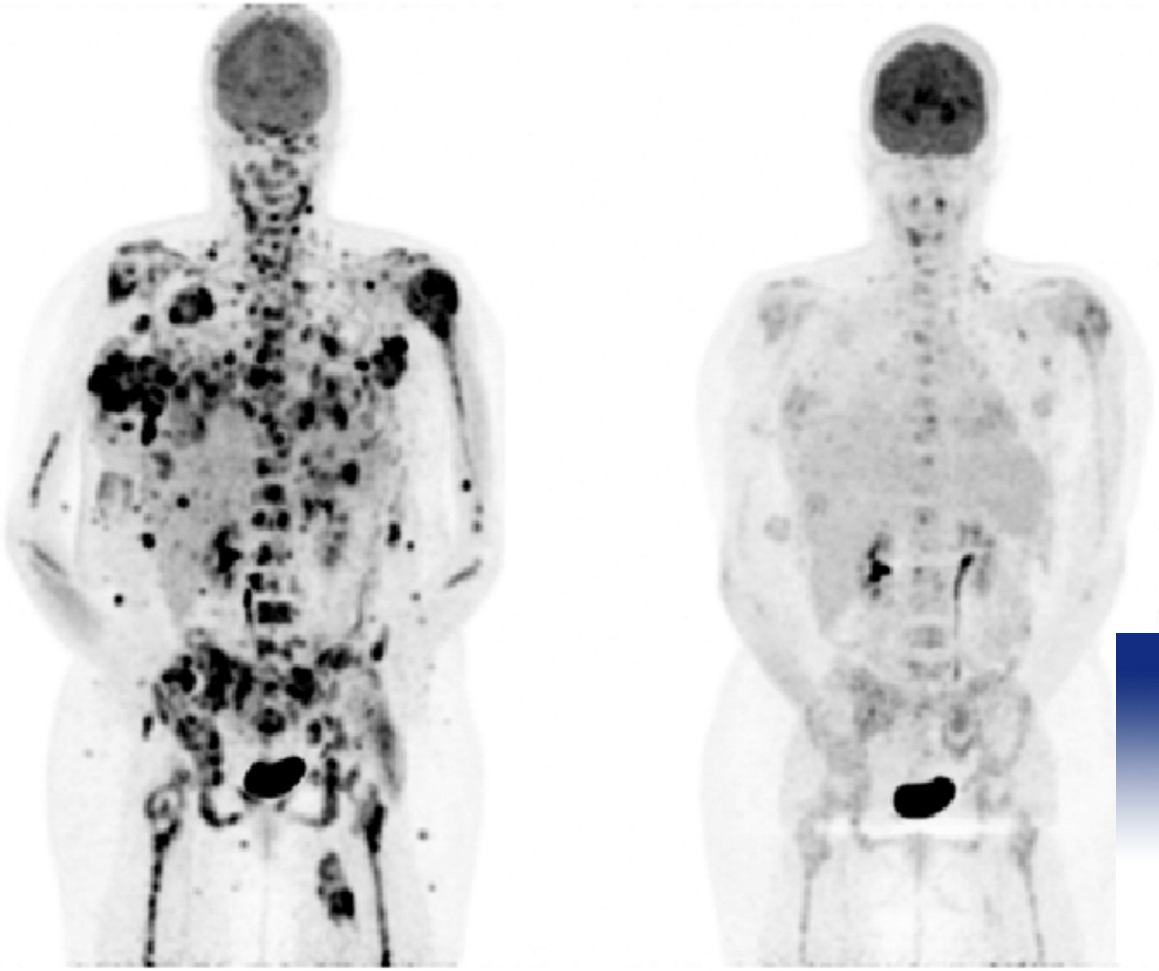




*Infantile Hemangioma*


*Propranolol*

# or this:

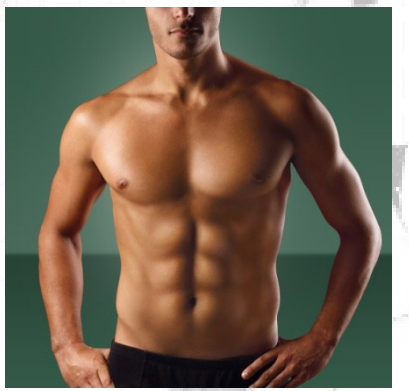


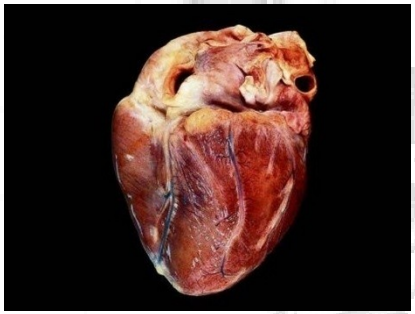

FDG-PET scan images of a patient with metastatic melanoma before (*left*) and after (*right*) treatment with BRAF inhibitor. Therapy consisted of 15 days treatment with 960mg of the BRAFV600E inhibitor, **Vemurafenib , PLX4032**, given orally twice daily as a single agent. (*with permission from the Molecular Imaging Department of the Peter MacCallum Cancer Centre, Melbourne*).

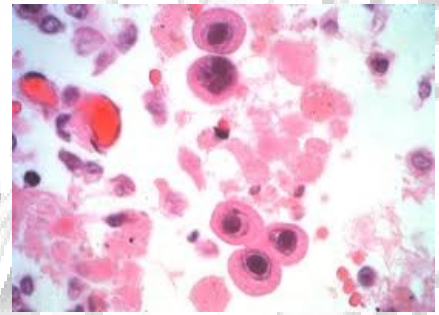
# try to respond with intellectual honesty:

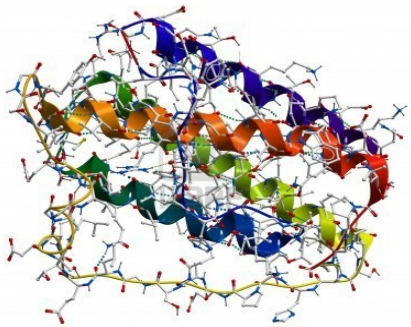
## Is this designable?

# Choose the best solution:









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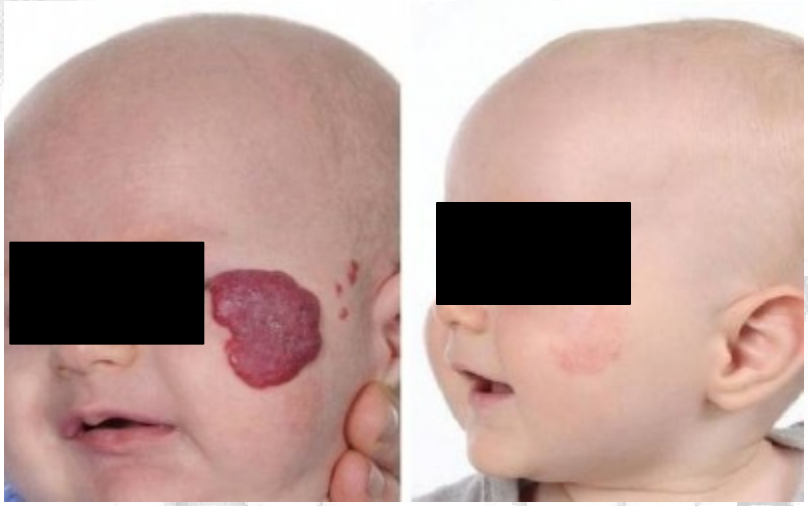
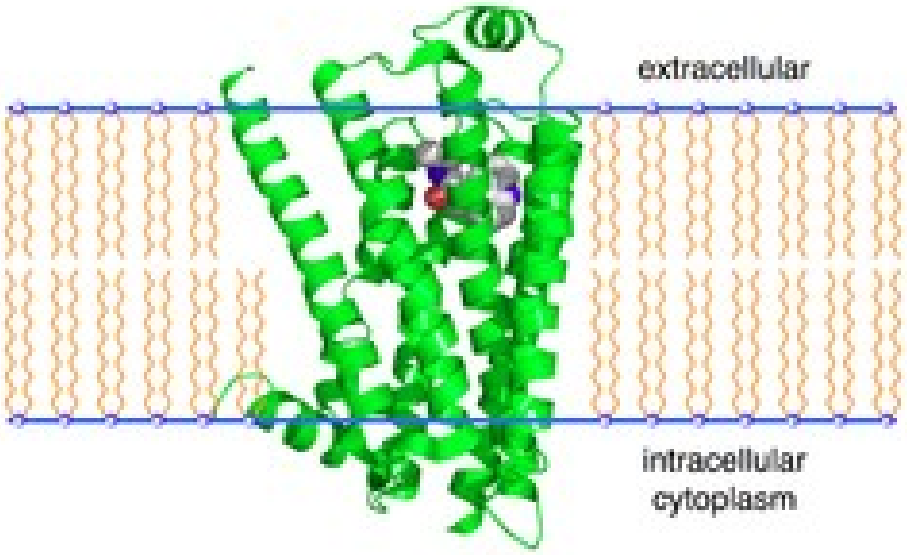
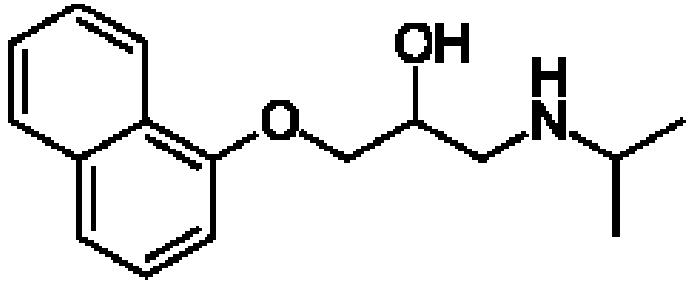


*Infantile Hemangioma*




*Beta adrenergic receptors*

*$10^n$ events ➡ 1 event*




*Propranolol*

# Do you remember?

Farmaco

Interazione Terapeutica

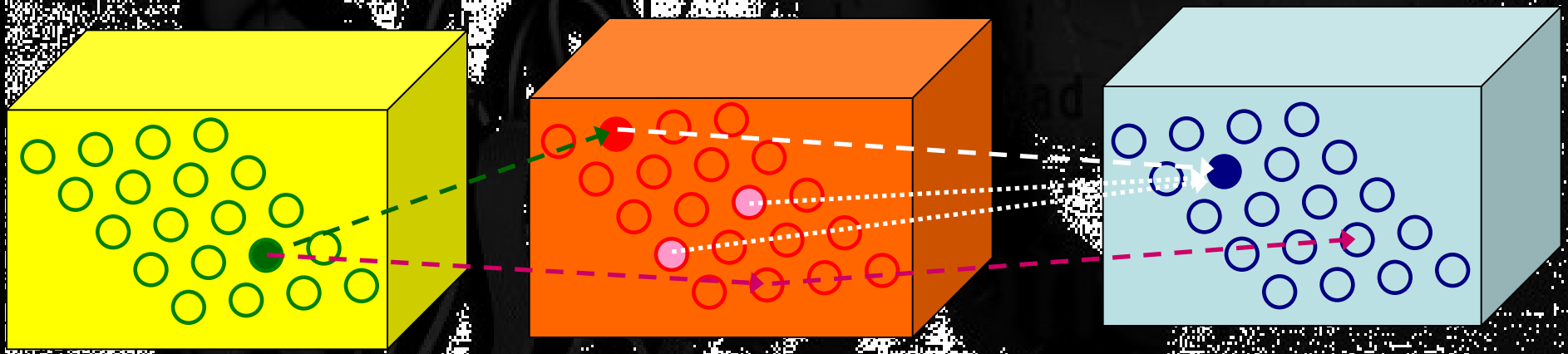
Interazione Collaterale

Target Primario

Target Secondario

Target Collaterale

Patologia



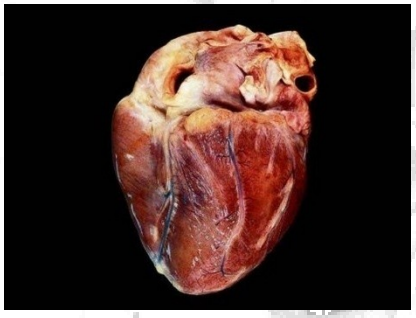
*Spazio chimico*

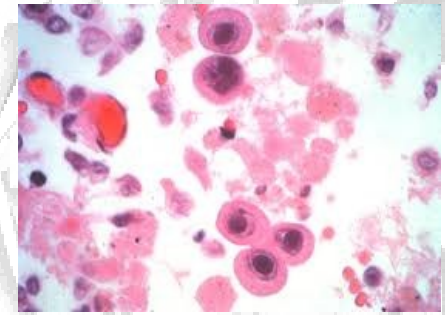
*Spazio biologico*

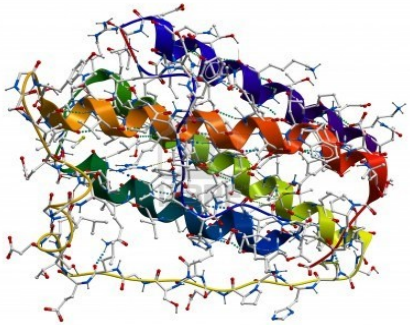
*Spazio fisio-patologico*

# Choose the best solution: the redutionistic approach

***Drug***







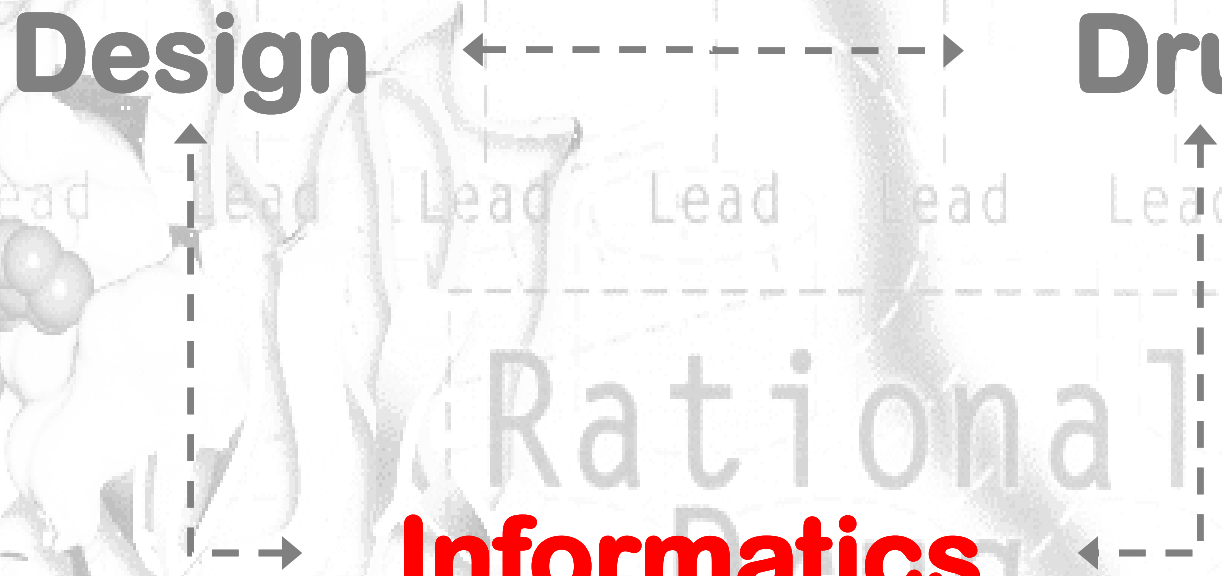
***Candidate***

# Again, try to respond with the same intellectual honesty:

## Is a drug candidate designable?

We will return later on this concept…

# … 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***

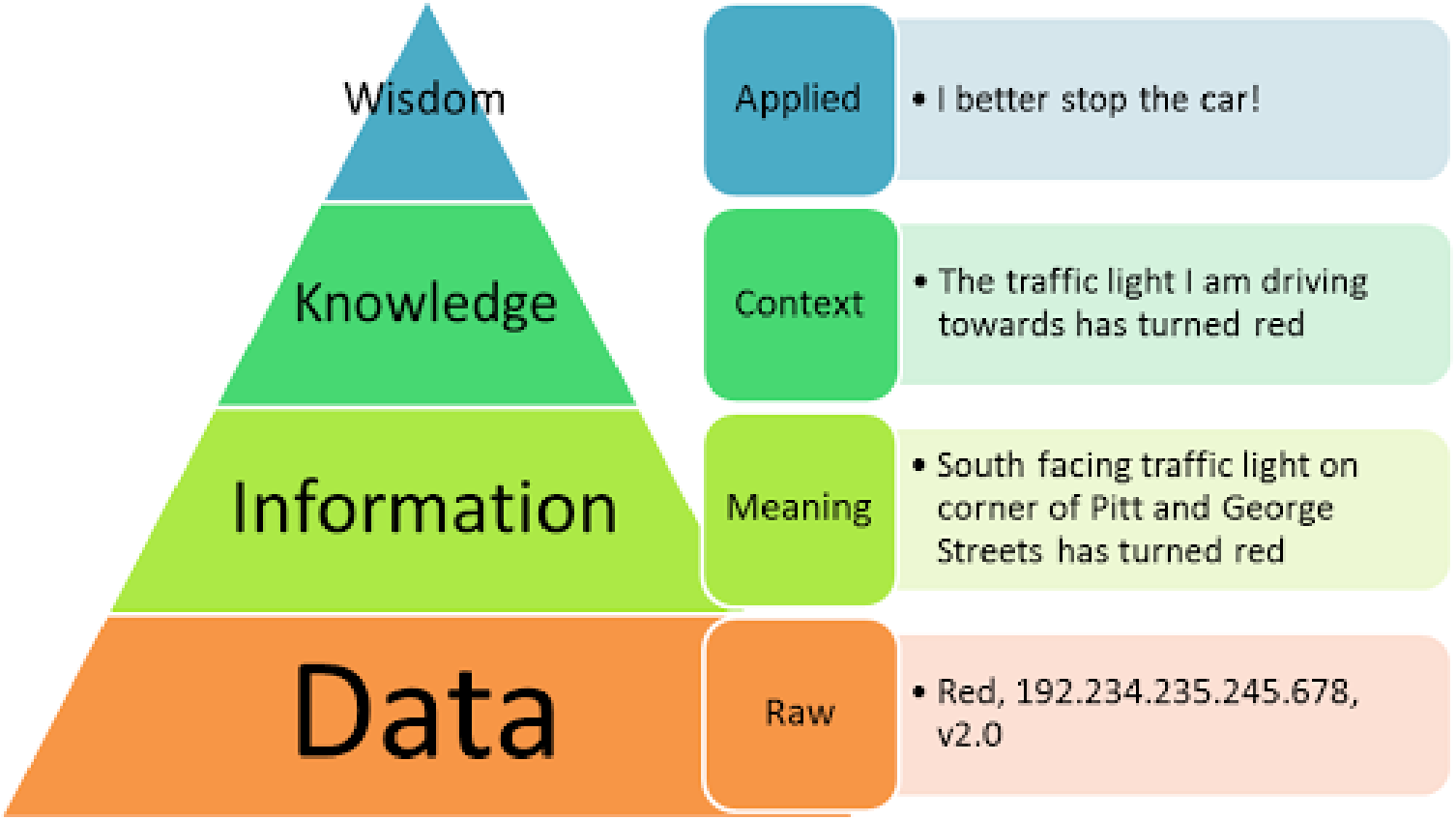
# again an egoistic definition of informatics:

## Informatics:

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

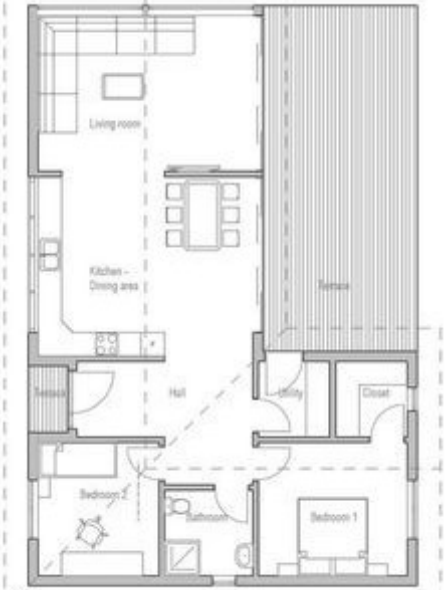
I didn't fond a better representation of this definition that this:

# … exciting!



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

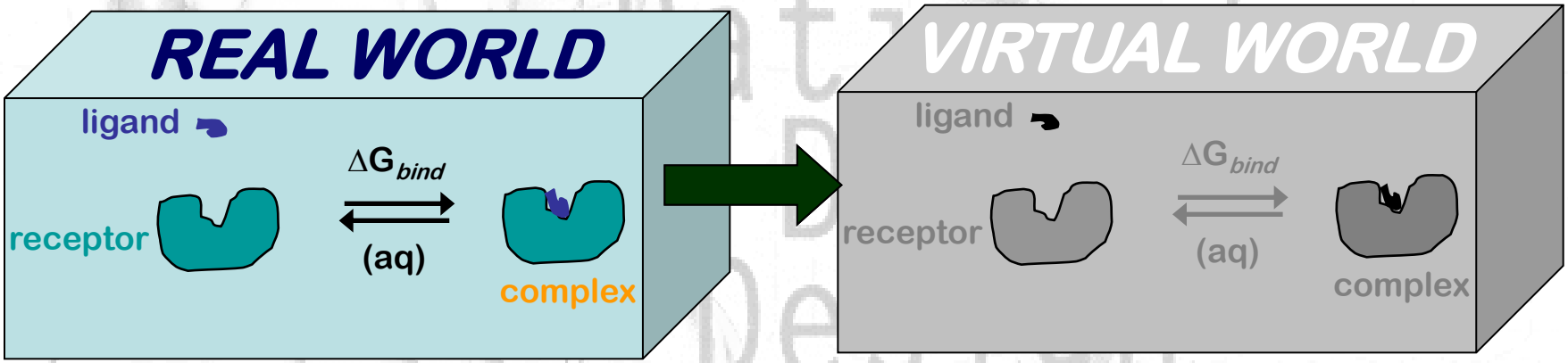
**REAL WORLD**



**VIRTUAL WORLD**

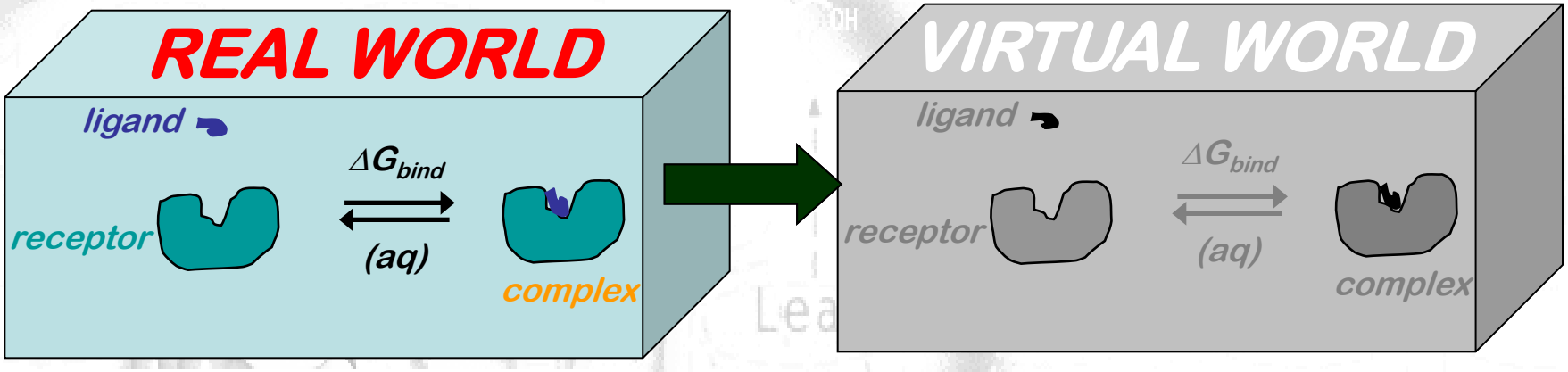
# Informatics is the basic science of any *virtualization* process:

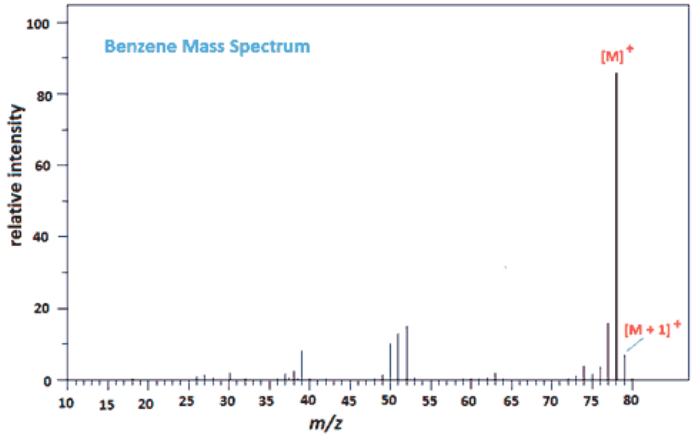
**From an informatics point of view, any compu tool is a *virtualization process*: the creation of a virtual version of the real process.**



# The *accuracy* of this virtualization process is crucial:


# My favorite example:




**Q: determine the molecular weight of benzene?**
**A:**

*C6H6*
*Hydrogen (H) 1.00794 atomic mass*
*Carbon (C) 12.0107 atomic mass*

*Molecular weight calculation:*
*12.0107*6 + 1.00794*6*

*= 78.11184 g/mol*

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

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

# Time

# couple of concrete example…

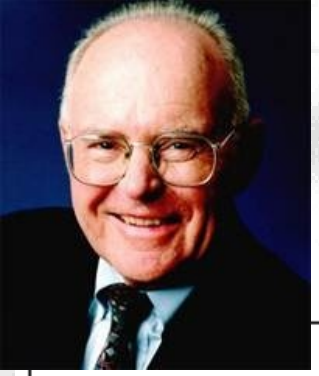
**Informatics helps us to solve simple problems a number of times:**

**Calculate the molecular weight is trivial thing, calculate 10 millions … less!**

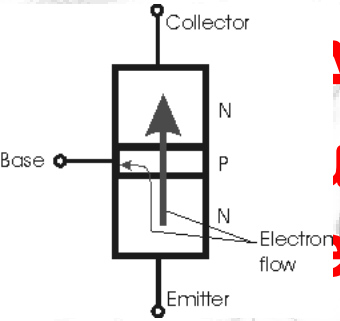
**or solve very complex problems:**

**Calculate, for example, the binding energy ($\Delta G_{bind}$, kcal x mol) between a ligand and its receptor is not trial at all!**

# Informatics as synonymous of speed?

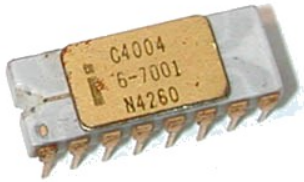


# just for informatics addicted!

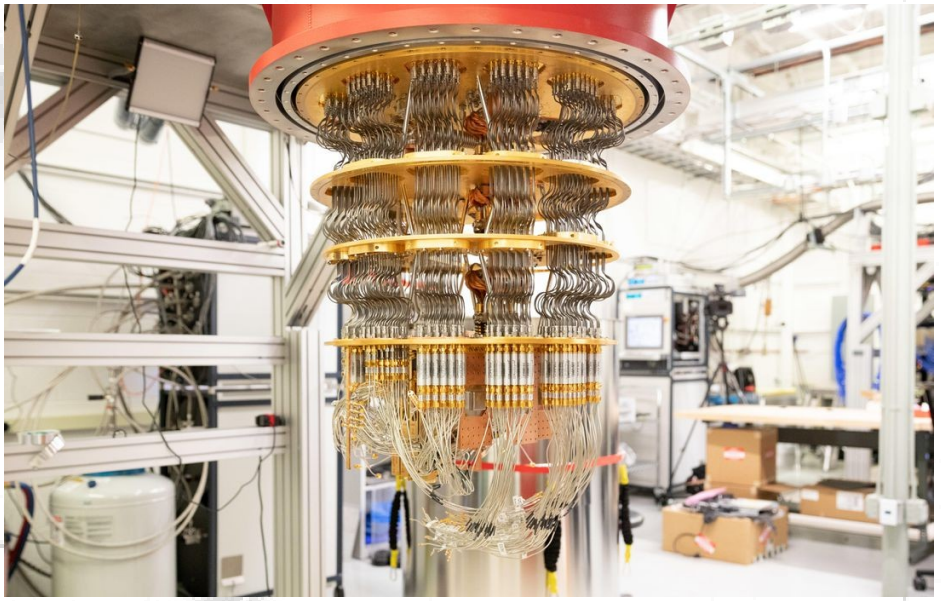



A *transistor* is a semiconductor device used to *amplify* and *switch* (on/off) electronic signals and electrical power.

| 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 |




# just for informatics addicted!



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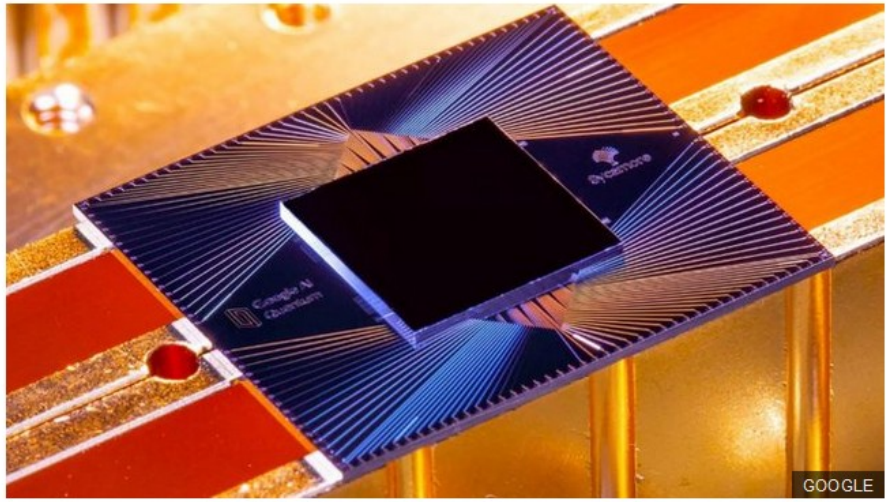
Science & Environment

## Google claims 'quantum supremacy' for computer

By Paul Rincon
Science editor, BBC News website

23 October 2019 | Share




**The technology giant's Sycamore quantum processor was able to perform a specific task in 200 seconds that would take the world's best supercomputer 10,000 years to complete.**

# 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)

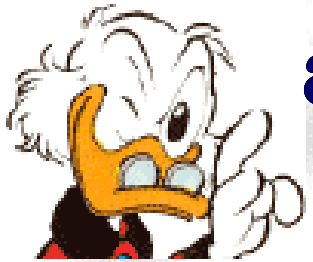
*Subfield of AI giving machines the skills to learn from examples without being explicitly programmed.*

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



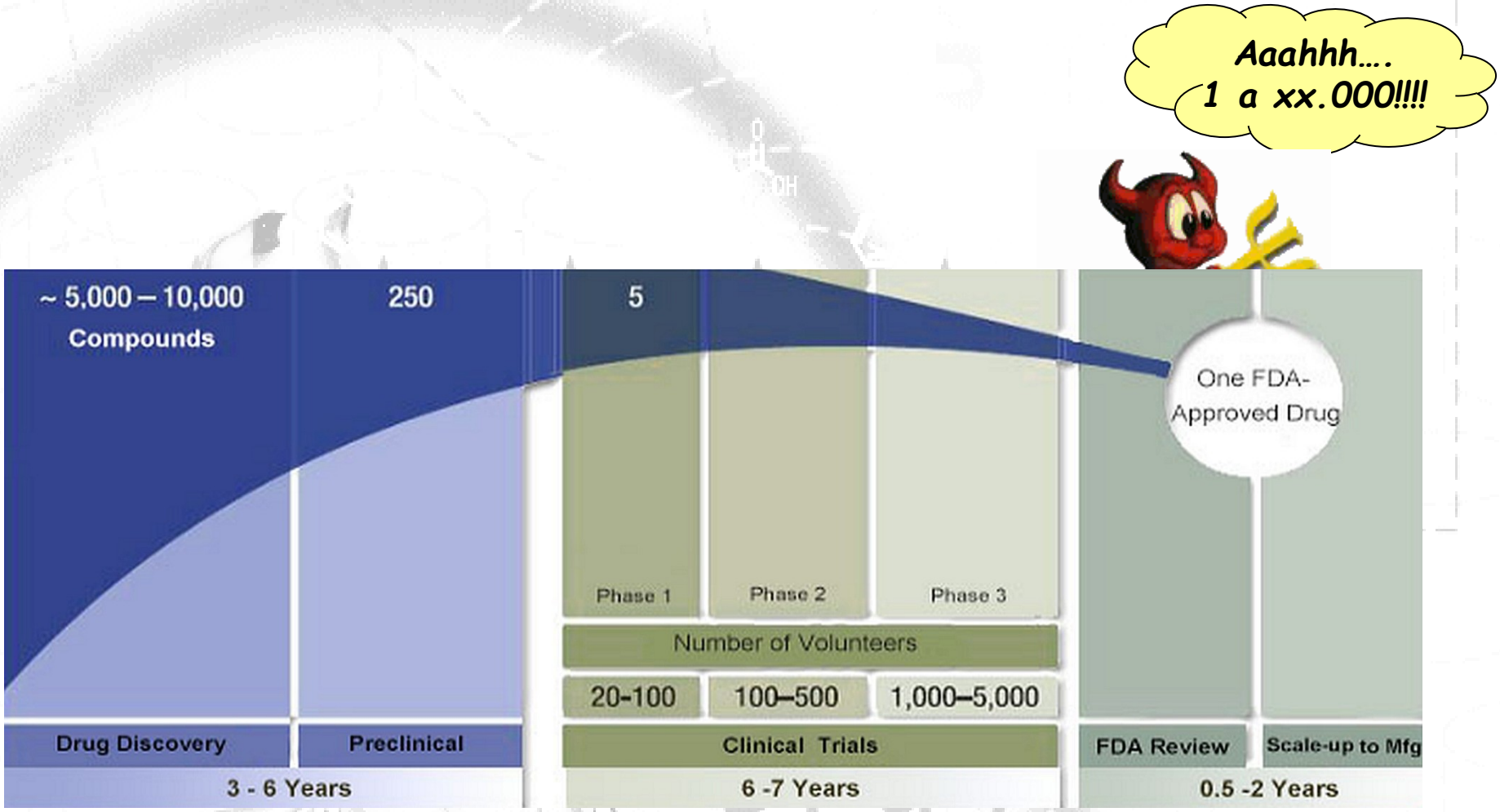
# and remember… “Time is money!”

# Why we need *"drug" design*?

**Design** ⟷ **"Drug"**

**Informatics**

# 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 $1000 million (even more!!!)**

# 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*?

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

**a.~ 1600 companies;**

**b. ~ 6000 R&D projects.**

# Drug discovery statistics:

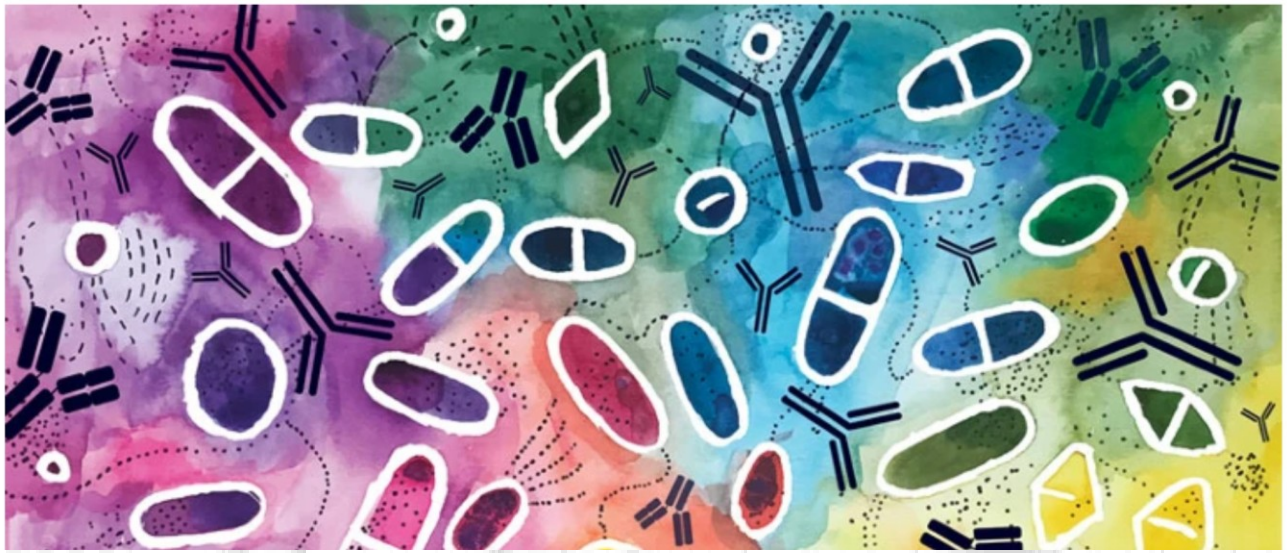
*credits: https://www.nature.com/articles/d41573-023-00001-3*

NEWS | 03 January 2023 | Update 16 January 2023

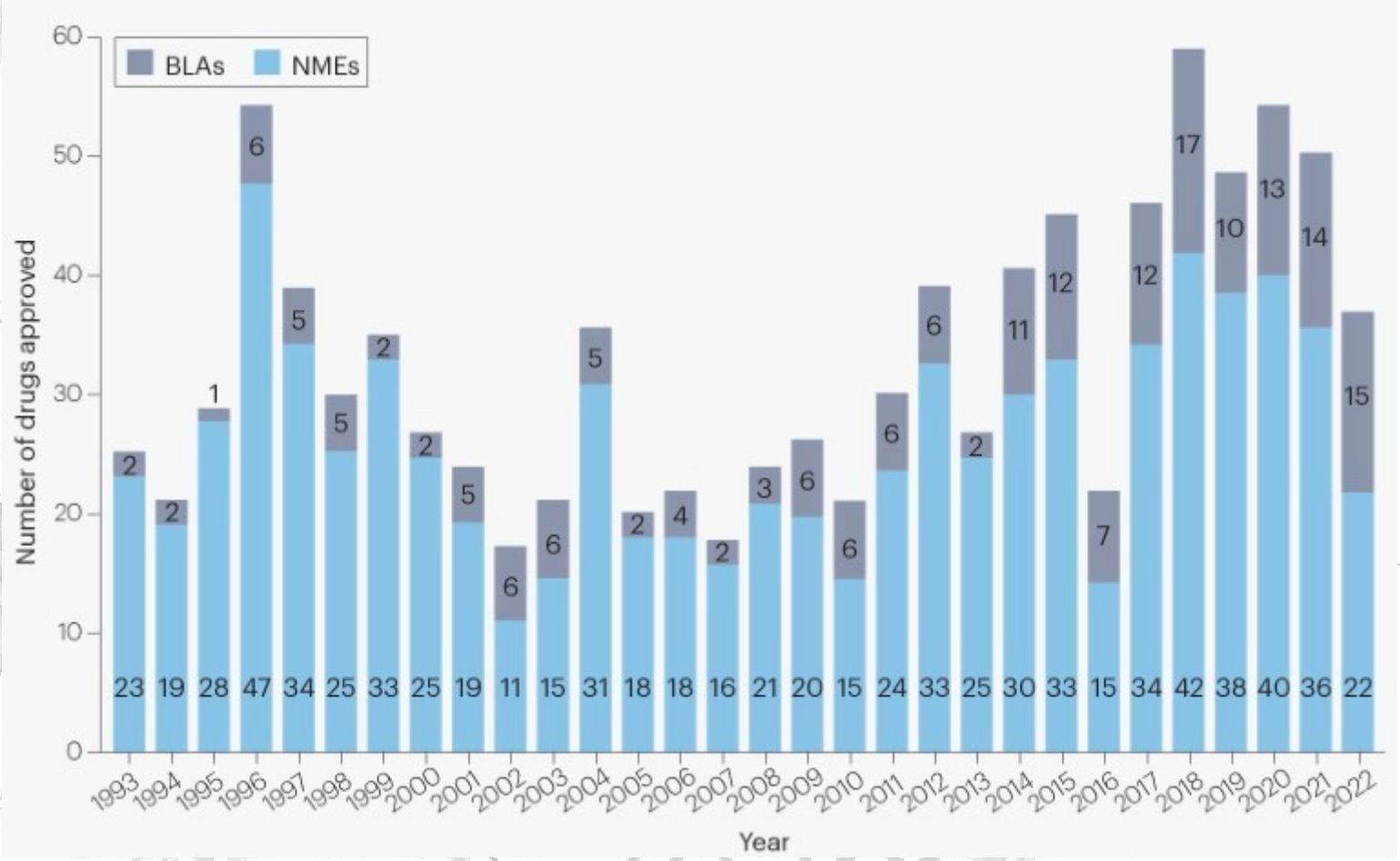
## 2022 FDA approvals

**The FDA approved 37 novel drugs in 2022, the fewest to pass regulatory scrutiny since 2016.**

Asher Mullard



# Houston, we've had a problem here!

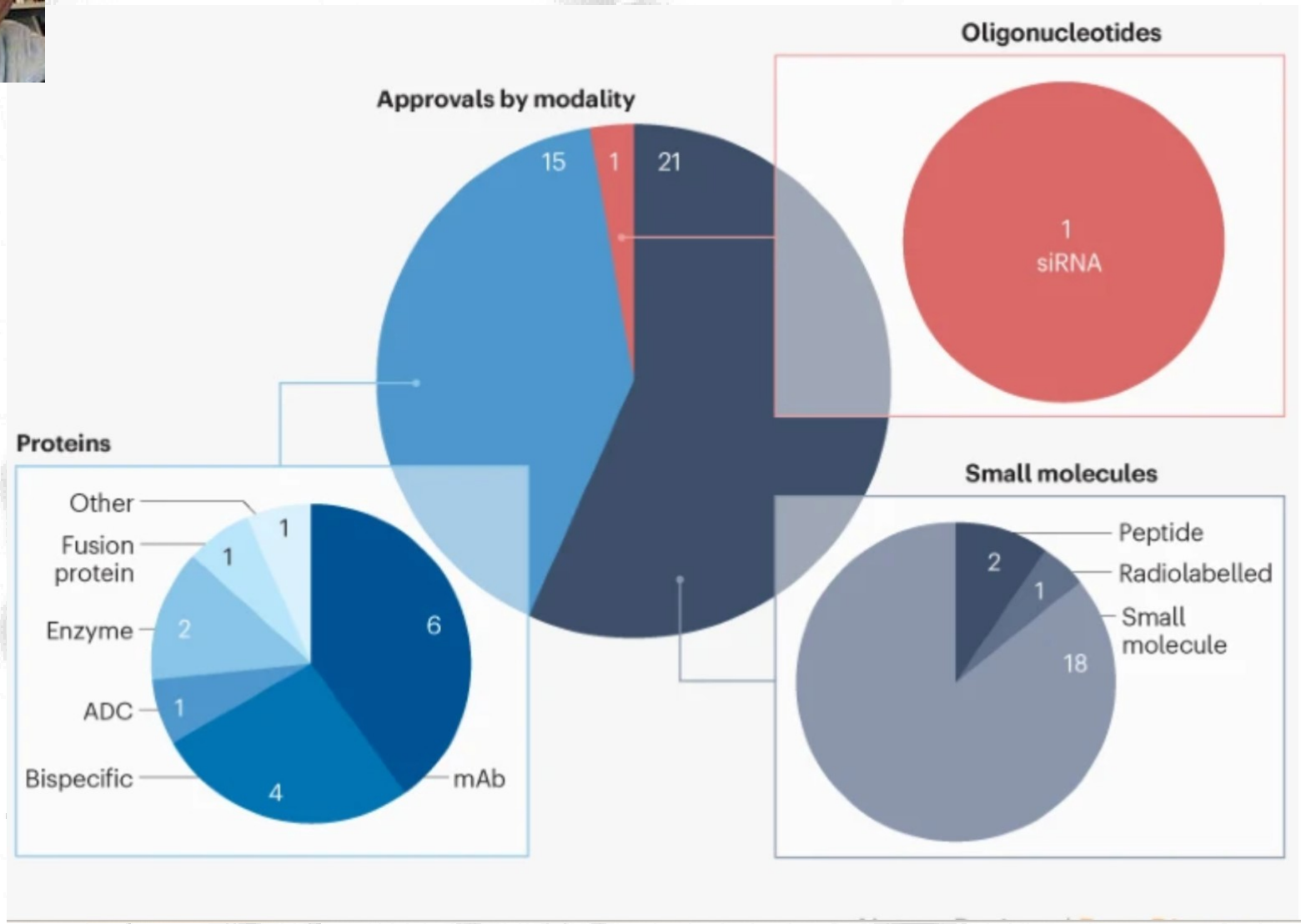



**Novel FDA approvals since 1993. Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's CDER. See Table 1 for new approvals in 2022. Products approved by CBER, including vaccines and gene therapies, are not included in this drug count (Table 2). Source: FDA.**

***credits: https://www.nature.com/articles/d41573-023-00001-3***

# Drug discovery statistics:

*credits: https://www.nature.com/articles/d41573-023-00001-3*

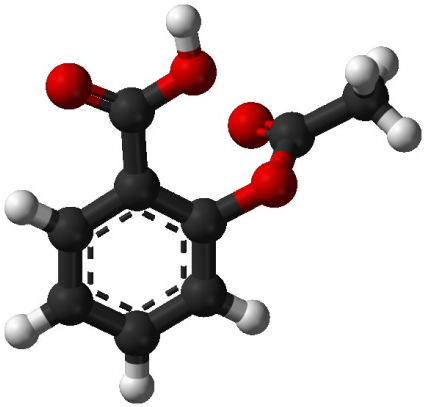


# A very general introduction:

## Vintage drugs

**ASPIRINE**

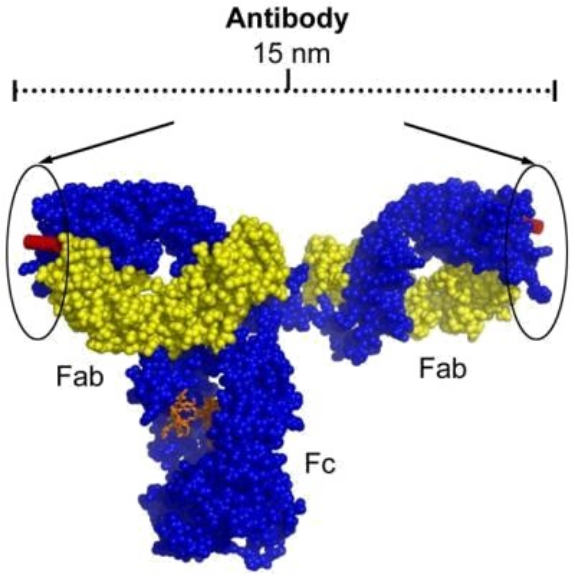
1. small molecule
2. 180 Da
3. 21 atoms
4. usually not immunogenic
5. usually chemically stable



## New age (biotech) drugs

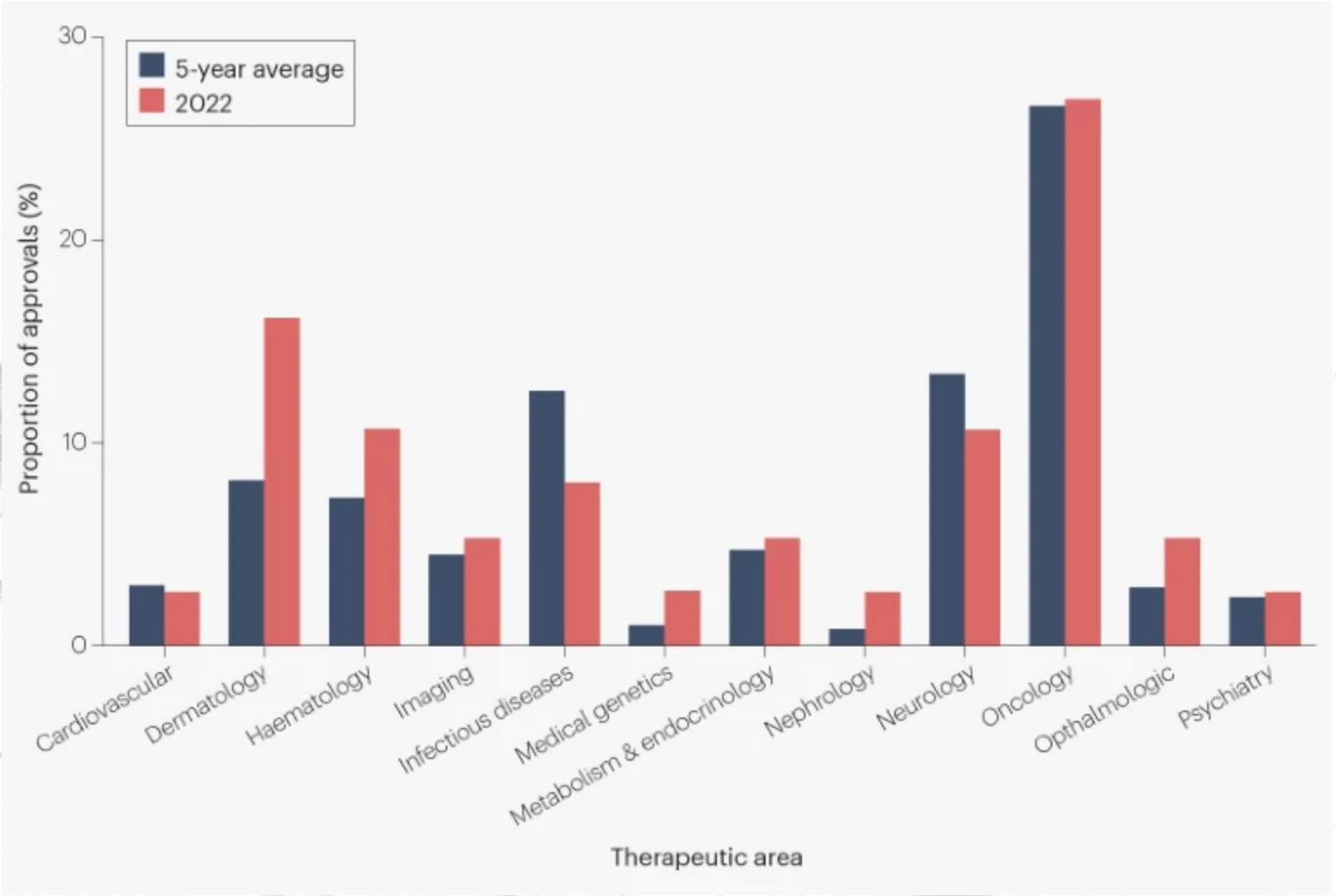
**MONOCLONAL ANTIBODY (mAb)**

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

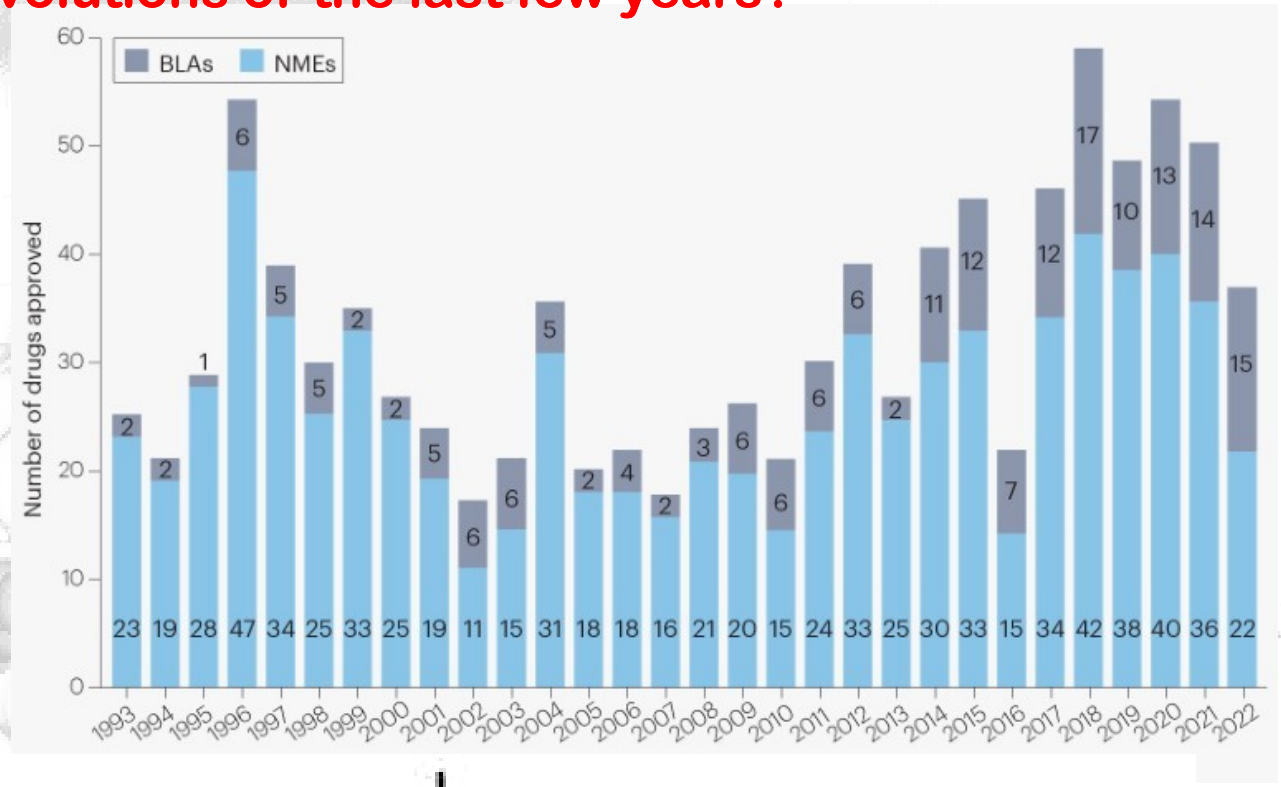


# Drug discovery statistics:

***credits: https://www.nature.com/articles/d41573-023-00001-3***



# 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?

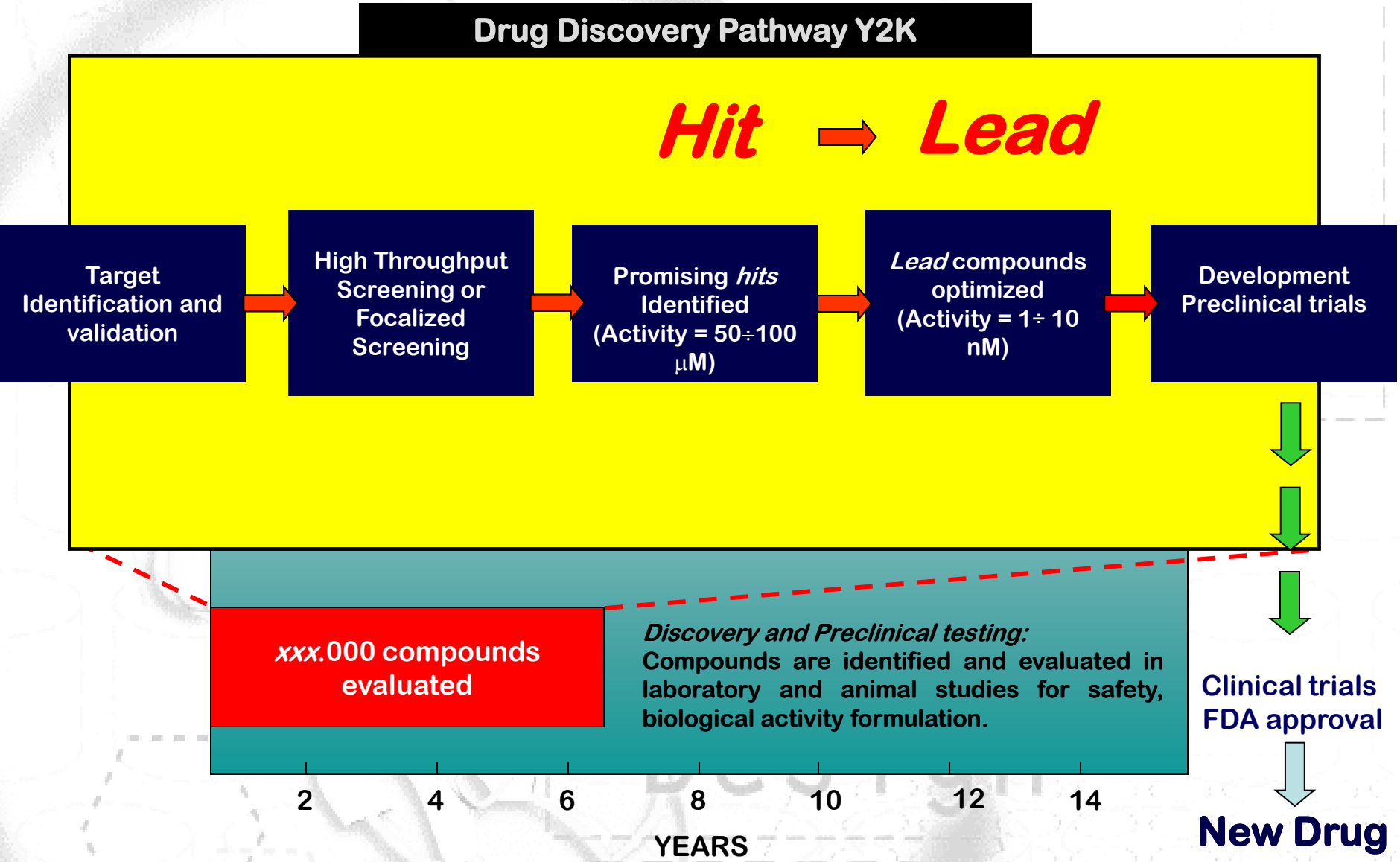
## Is this ratio really acceptable for a pharma company?

# 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* !**

# The “right” road to drug discovery?



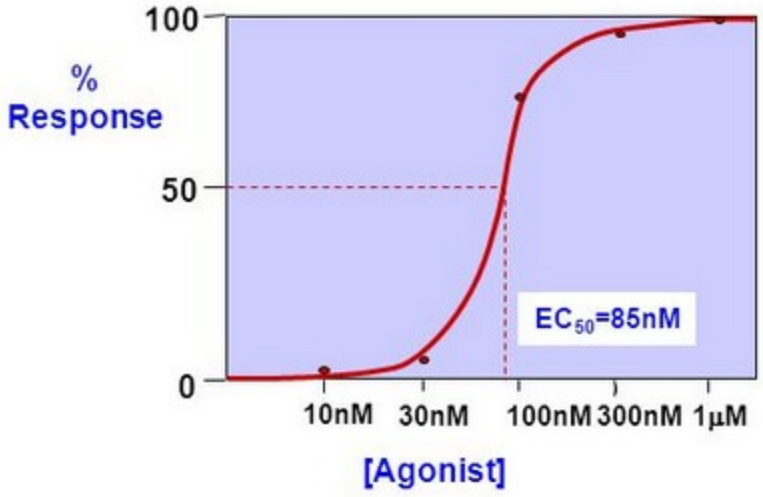
# Hit to lead …

- **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

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

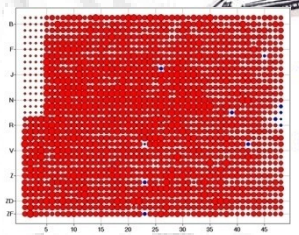
$IC_{50}$ 1μM = $pIC_{50}$ 6.0
$IC_{50}$ 1nM = $pIC_{50}$ 9.0

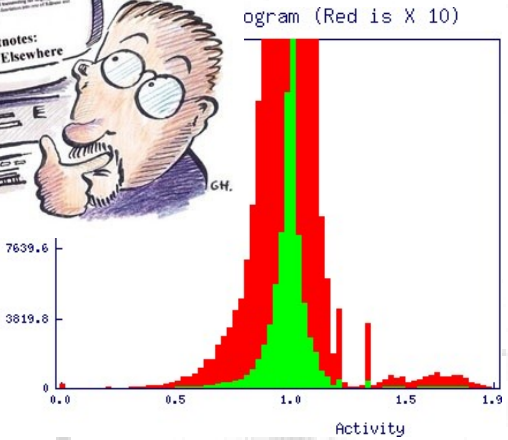
Agonists: Measure % Response vs Agonist concentration
$EC_{50}$ - The agonist concentration that causes 50% of the maximum response. $pEC_{50} = -\log_{10}(EC_{50})$

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?

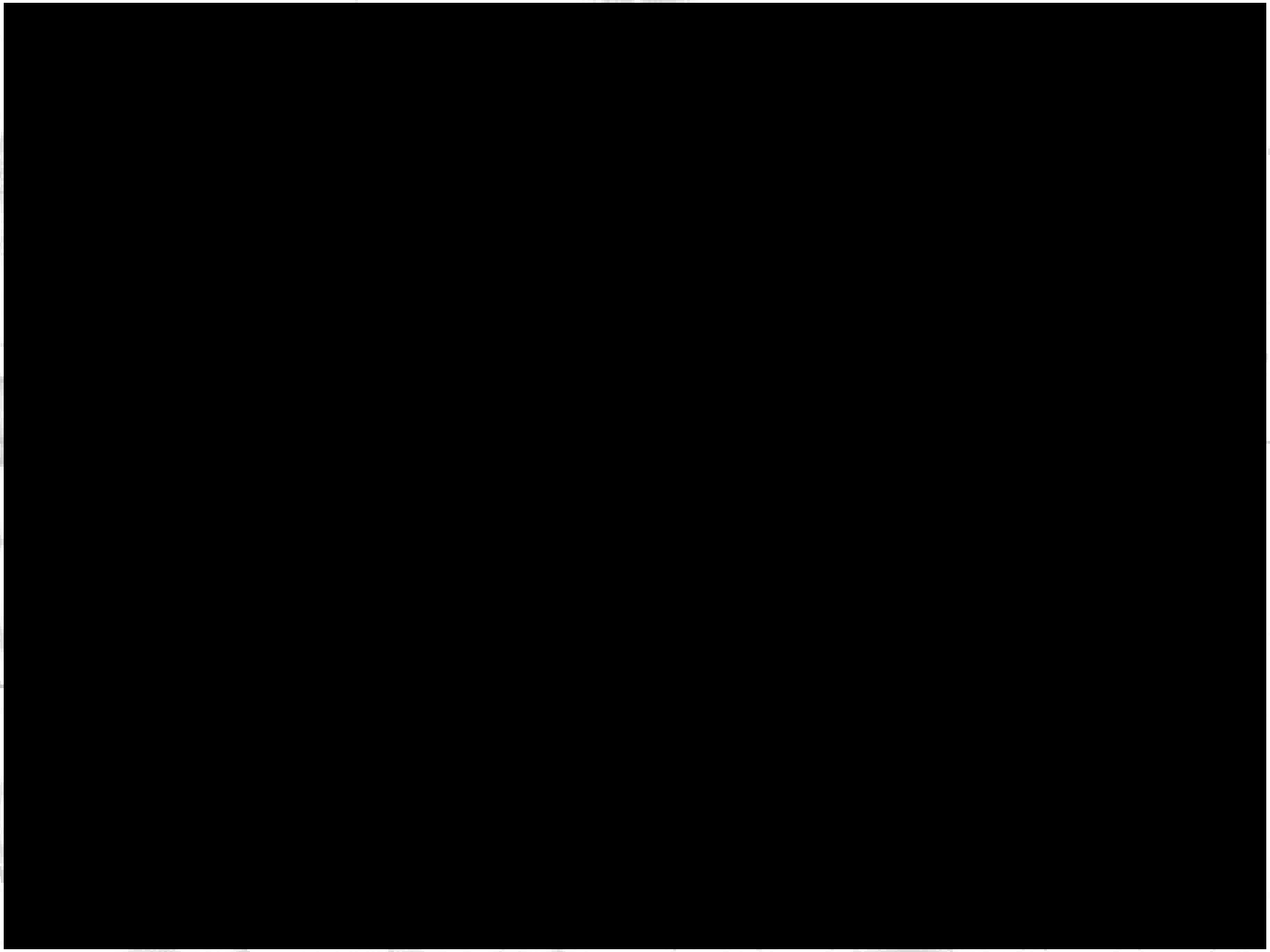



- >1,000,000
- 1,000,000
- 1,000
- 100

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

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

# Screening automatization @DSF



# 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 !!!**

# Back to the insidious question that you can make me :

## Is a hit designable?

# Hit2Lead

# Hit to lead …

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

# 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 |
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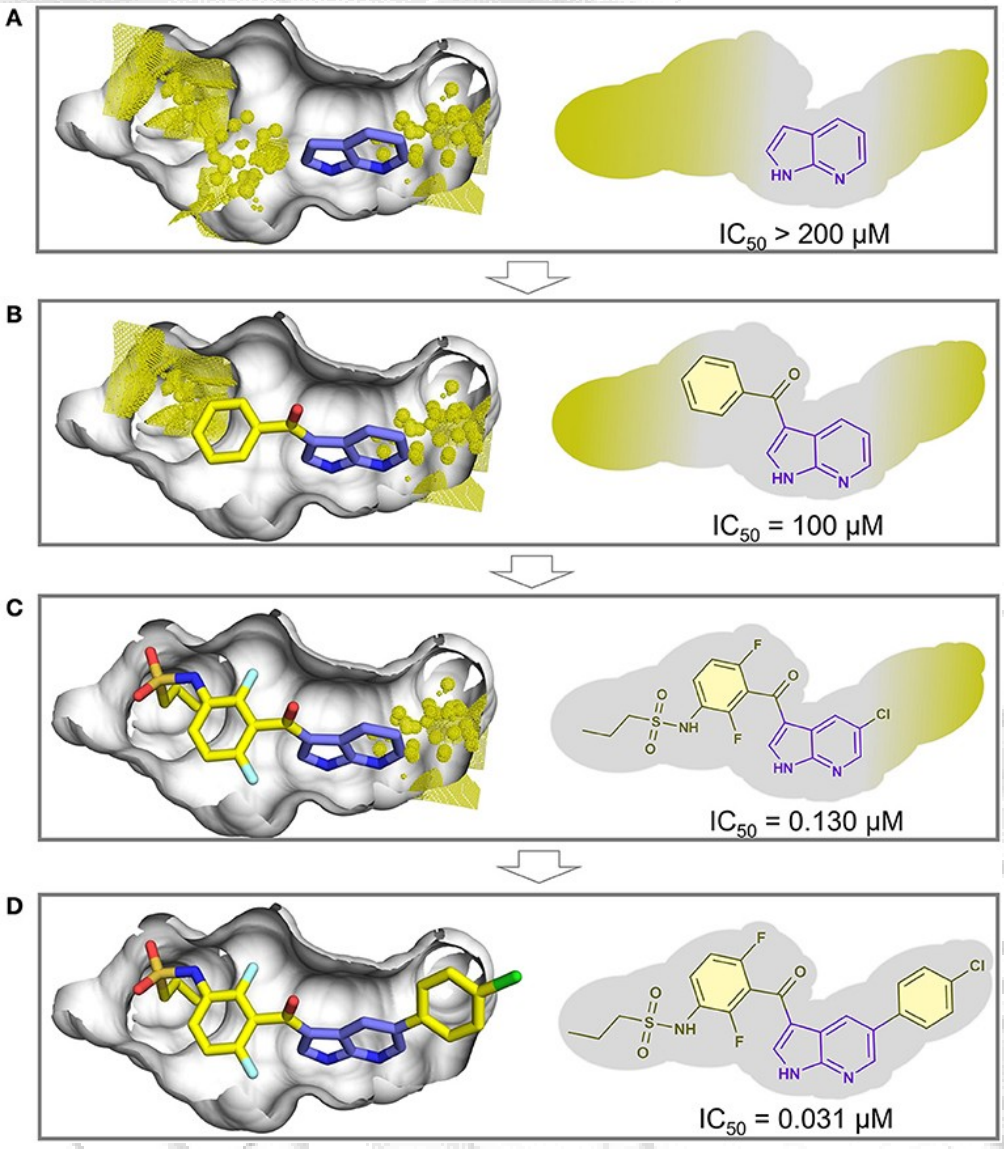
| Human clinical trial | 3.500.000 |

# Hit2Lead

# Hit2Lead… a pragmatic view:




PM = 118.14; logP = 1.56

PM = 222.25; logP = 2.79

PM = 413.83; logP = 3.88

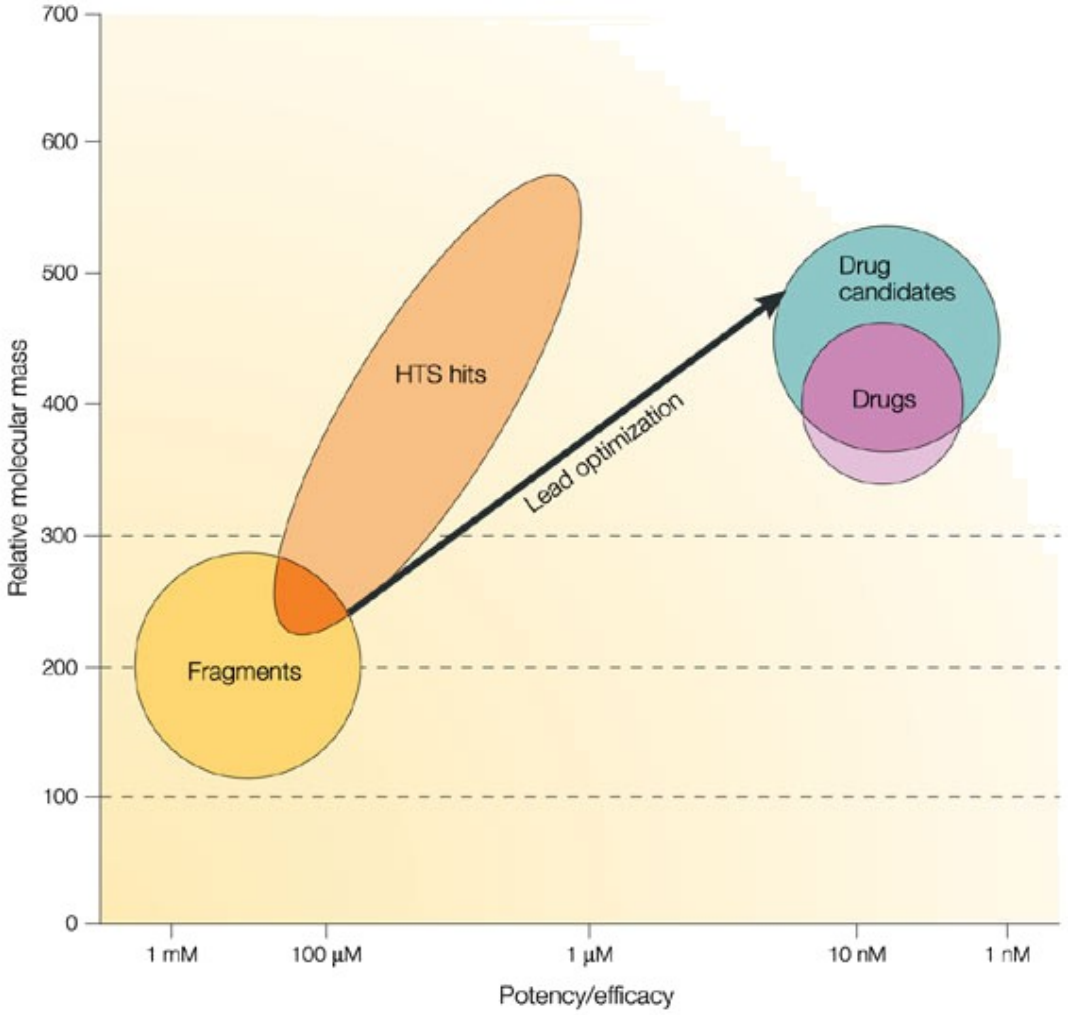
PM = 489.93; logP = 5.54

Front. Chem., 18 February 2020 | https://doi.org/10.3389/fchem.2020.00093

# And back again to the insidious question that you can make me :

## Is a lead designable?

# Remember this graph…




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

Nature Reviews | Drug Discovery