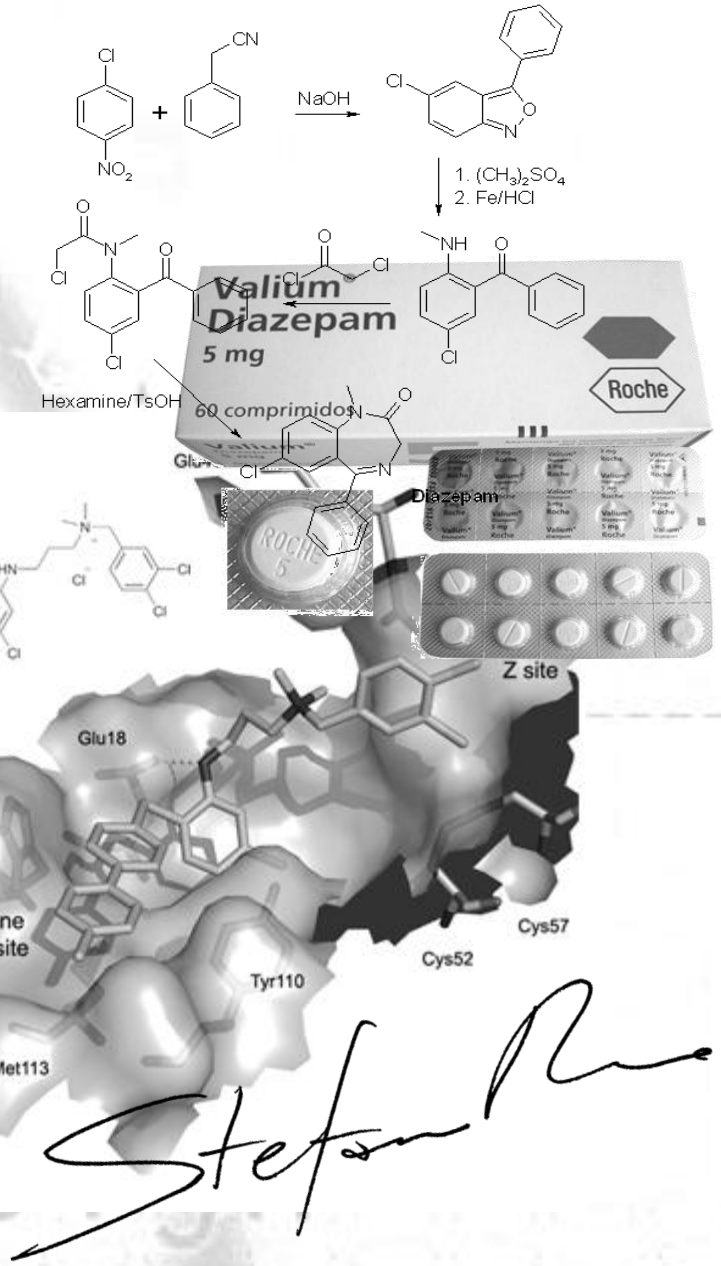
Chimica Farmaceutica



Ecco come organizzeremo il nostro viaggio…

http://mms.dsfarm.unipd.it

Cerca

UNIVERSITÀ DEGLI STUDI DI PADOVA

MMS Molecular Modeling Section

Department of Pharmaceutical and Pharmacological Sciences, University of Padova
Via Marzolo 5, 35131 Padova (Italy) - phone: +39 049 8275704, fax: +39 049 8275366

MMS Home | About us... | Lab Members | Projects | Pubblications | @learning | MMStools | MMS_Intranet

: News & Updates

ember 01, 2018

MMS: 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...*.

http://mms.dsfarm.unipd.it

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- Chimica Farmaceutica 2 (CTF)
- Progettazione e Sviluppo di un Farnarco (CTF)
- Biomodeling (BTF)
- Chimica Farmaceutica (CI)
- Chemoinformatica (...)
- Tossicologia Computazionale (Master REACH ... School)
- Master, PhD and ...ses

MMS: Events

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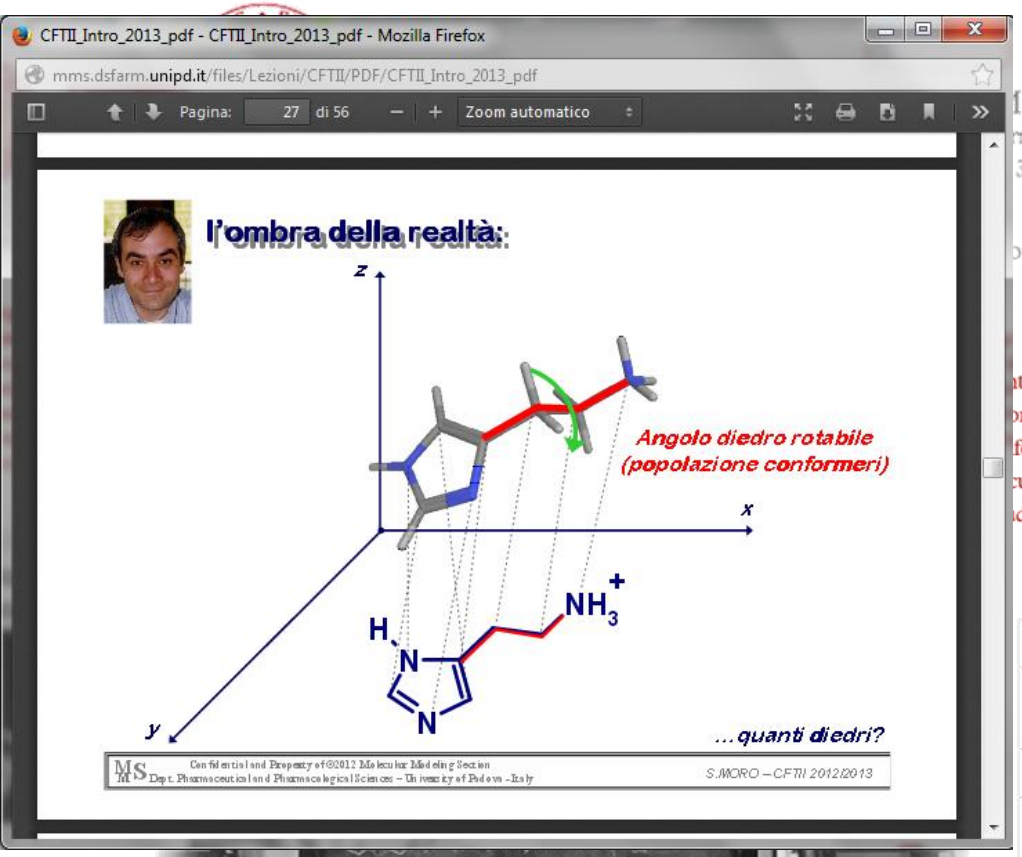

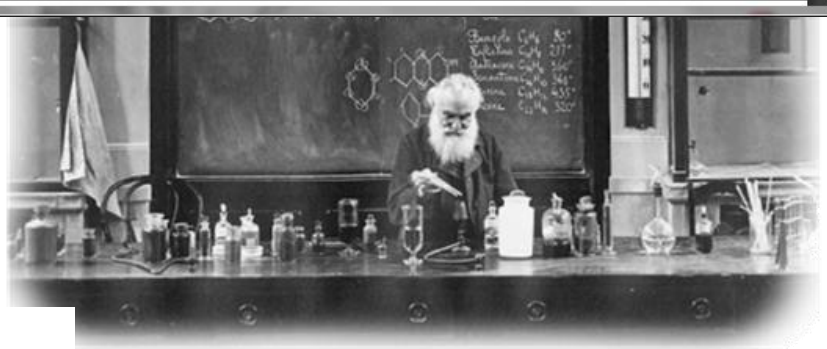

Cerca

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31 Padova (Italy) - phone: +39 049 8275704, fax: +39 049 8275366

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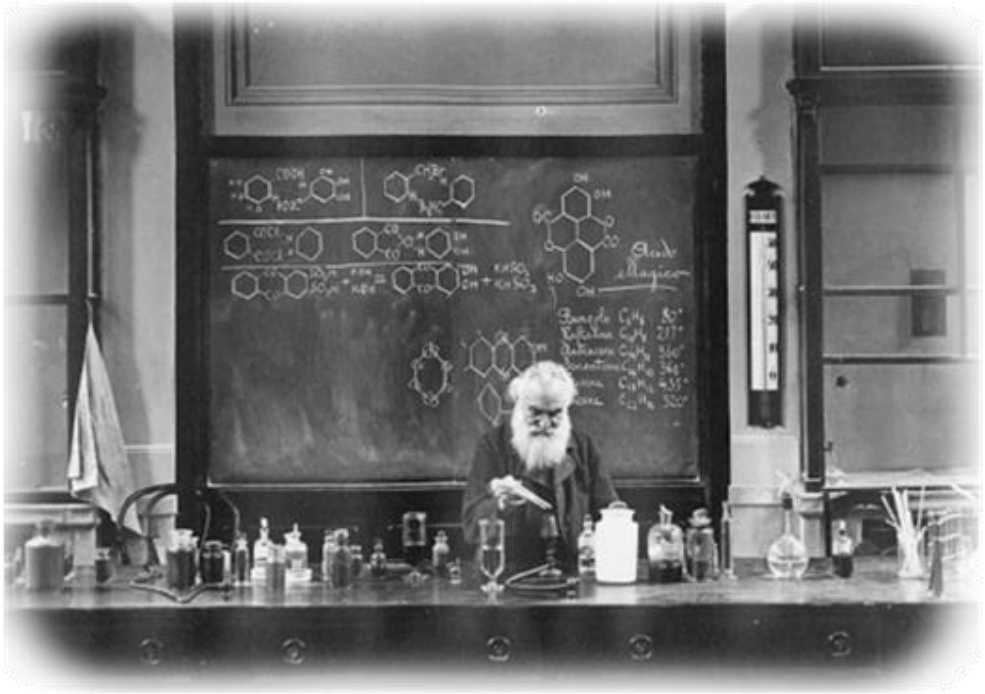
tali riguardanti le strategie generali di progettazione, la sintesi, lo studio dei
oni fra struttura chimica e attività biologica di alcune classi di farmaci. In
ferici. Si prevede che lo studente acquisisca la conoscenza dei concetti
cutere i meccanismi d'azione e le relazioni struttura-attività di farmaci sulla
dente acquisisca gli elementi indispensabili per progettare farmaci su basi

1. Parte generale	
Introzione al corso: Farmaco e dintorni	
2. Casi di Studio	

http://mms.dsfarm.unipd.it

Obbiettivi del percorso formativo:

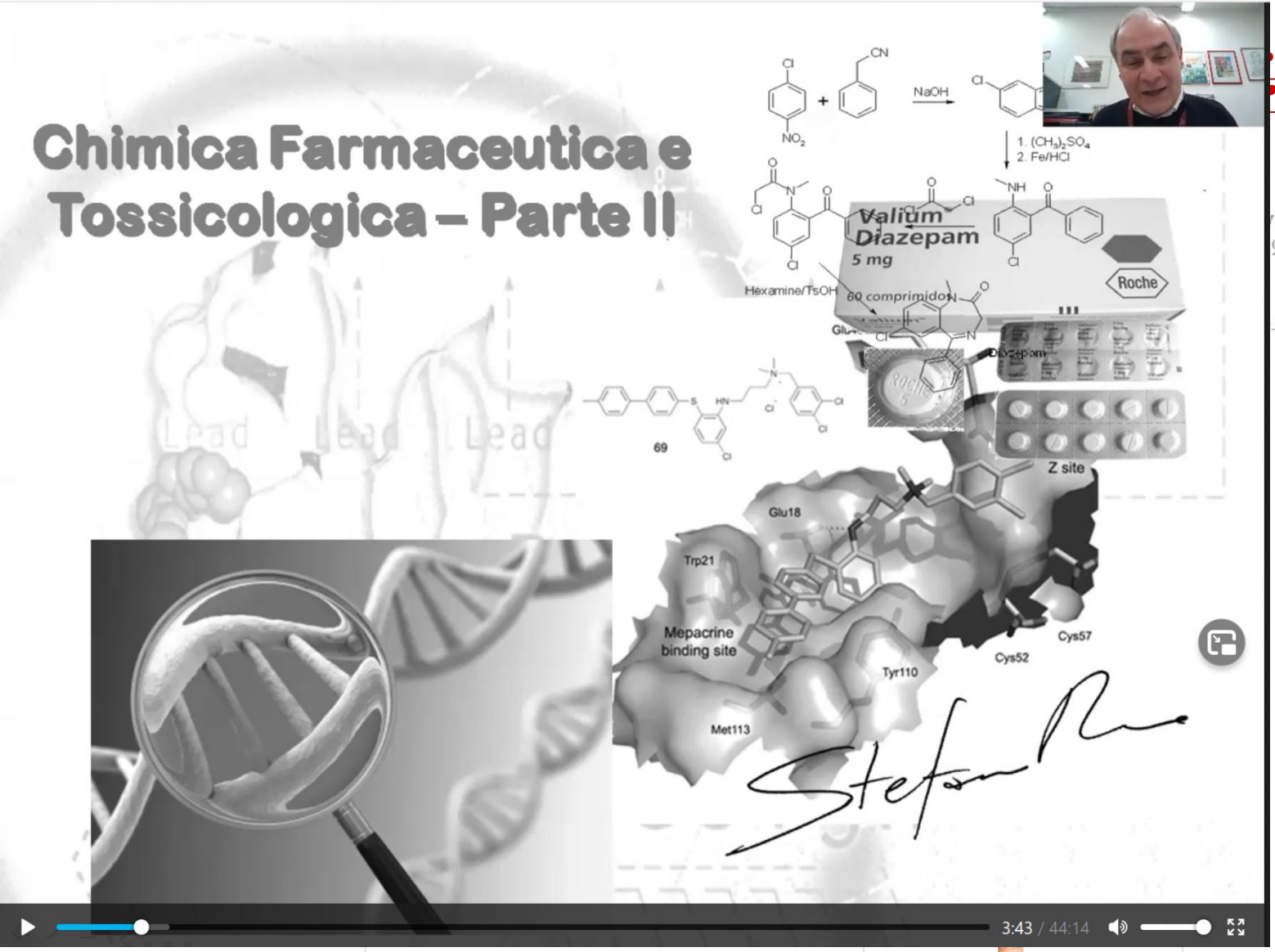
Gli obiettivi dell'insegnamento sono quelli di fornire allo studente le conoscenze fondamentali riguardanti le strategie generali di progettazione, la sintesi, lo studio dei meccanismi d'azione a livello molecolare e degli aspetti chimico-tossicologici e le relazioni fra struttura chimica e attività biologica di alcune classi di farmaci. In particolare saranno studiati i farmaci che agiscono sui sistemi nervosi centrali e periferici. Si prevede che lo studente acquisisca la conoscenza dei concetti fondamentali relativi allo studio chimico-molecolare dei farmaci e che sia in grado di discutere i meccanismi d'azione e le relazioni struttura-attività di farmaci sulla base delle caratteristiche chimiche delle molecole coinvolte. Si prevede inoltre che lo studente acquisisca gli elementi indispensabili per progettare farmaci su basi razionali.



1. Parte generale			
Introzione al corso: Farmaco e dintorni			
2. Casi di Studio			

CF@zoomcast:

Chimica Farmaceutica e Tossicologica – Parte II



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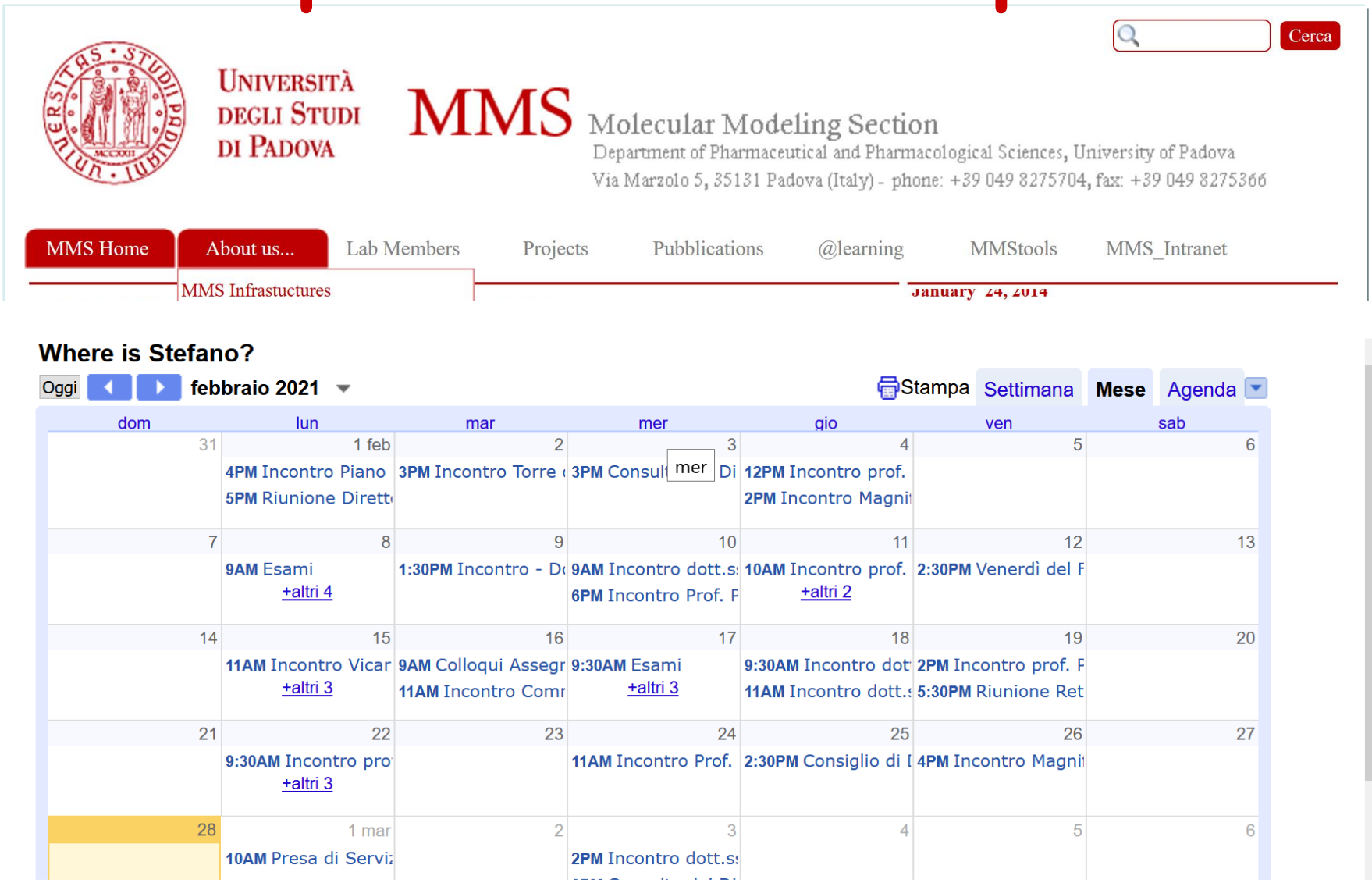


Menù (turistico) del *trimestre* di CF

✔Parte prima: generale

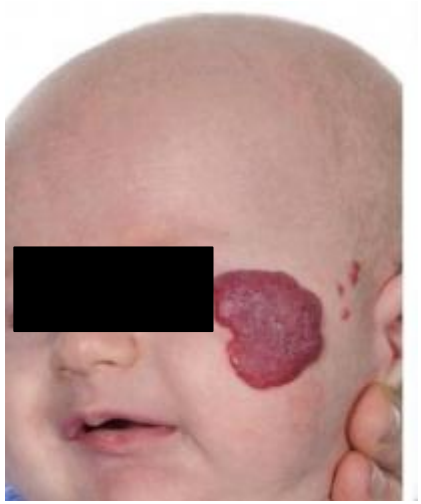
Farmaco e dintorni: dal concetto di entità chimica a quello di farmaco

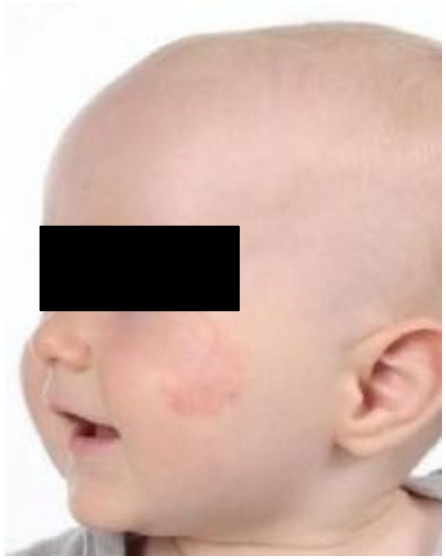
Parte seconda: casi di studio

Are you ready to start?


BABBO, COSA PENSI DELL'8 MARZO?
CHE PER NOI MASCHI, PRIMA ERA UN DOVERE. OGGI È UNA SPERANZA.

how can we define a drug?



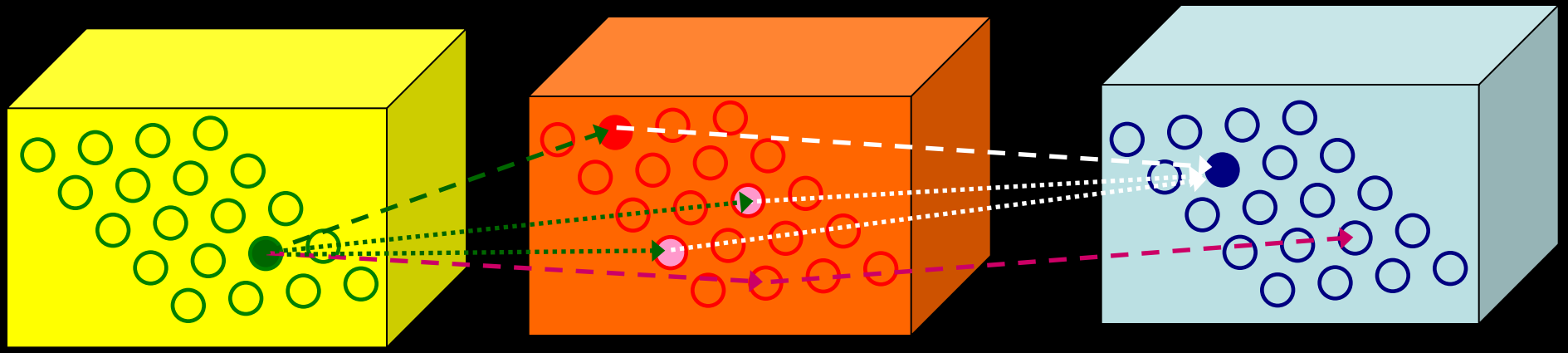


Infantile Hemangioma

Propranolol

How we can schematize our definition?

Drug
Therapeutic Interaction
Collateral Interaction
Biological or "On" Target
Secondary On Target
Anti or "Off" Target
Pathology



Chemical Space

Biological Space

Physio-Pathological Space

Summarizing:

Biological or “On” Target:

is a receptor, enzyme, or other cellular target that, when affected by a drug, causes the desired theraputical effect.

Anti or “Off” Target:

is a receptor, enzyme, or other cellular target that, when affected by a drug, causes undesirable side-effects.

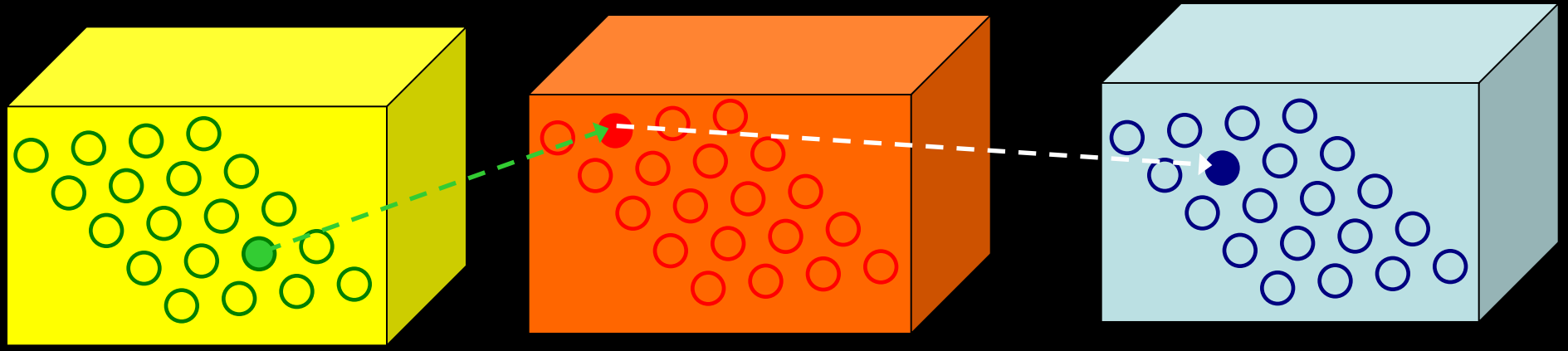
For a long long time we have considered as true this egoistic stoichiometry… 1 : 1 : 1

Biological or "On" Target

Drug

Therapeutic Interaction

Pathology

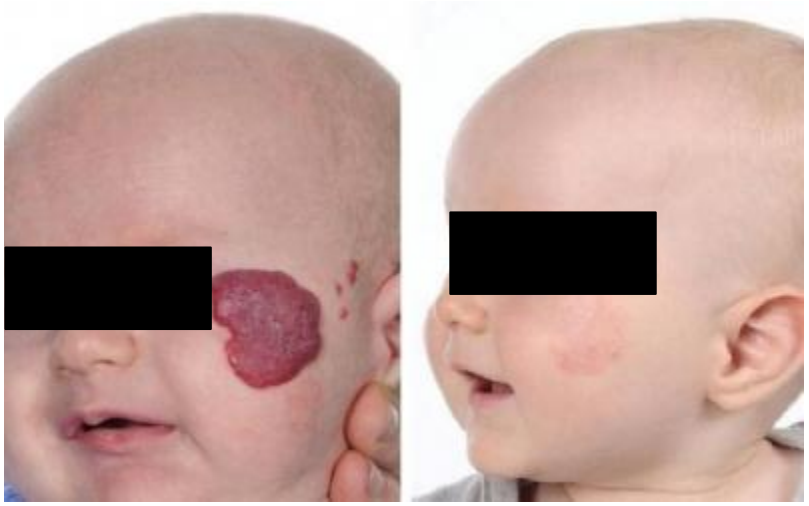


Chemical Space

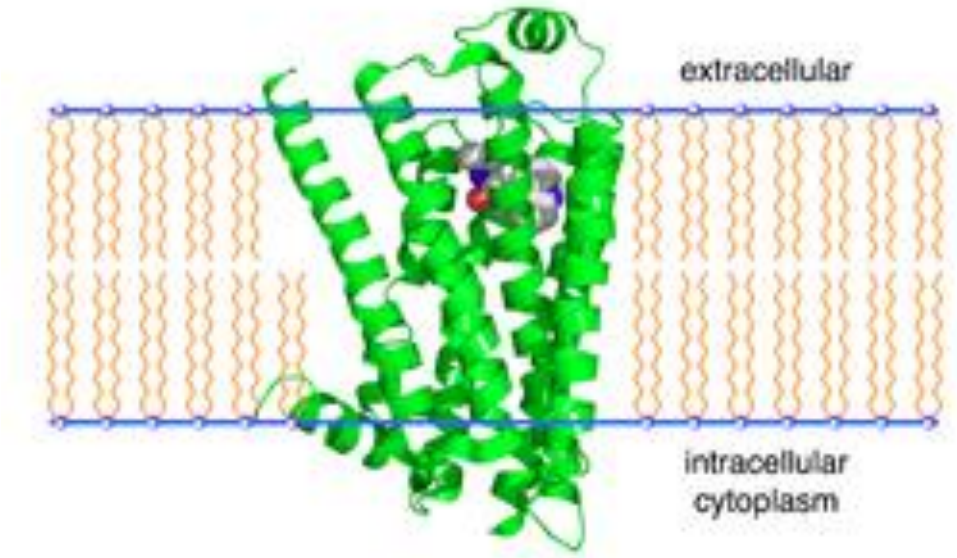
Biological Space

Physio-Pathological Space

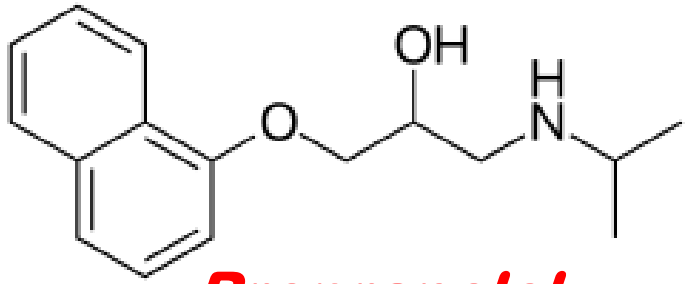
Choose the best solution:



Infantile Hemangioma



Beta adrenergic receptors



Propranolol

Now we have to change our mind: from *single-target* to *multi-targets* changing the stoichiometry to 1 : N : 1

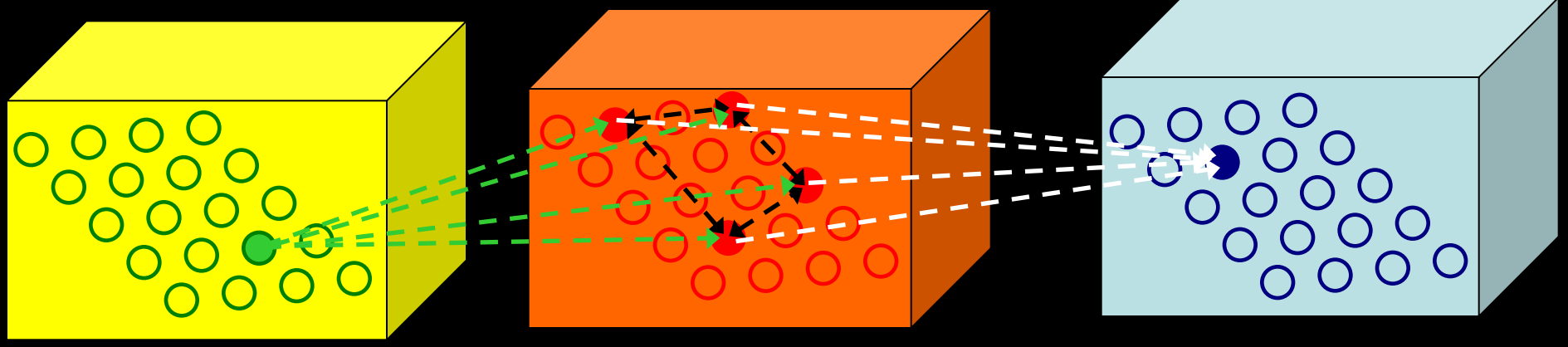
Biological or "On" Target

Secondary On Target

Drug

Therapeutic Interaction

Pathology



Chemical Space

Biological Space

Physio-Pathological Space

This is the era of *multi -target pharmacology*

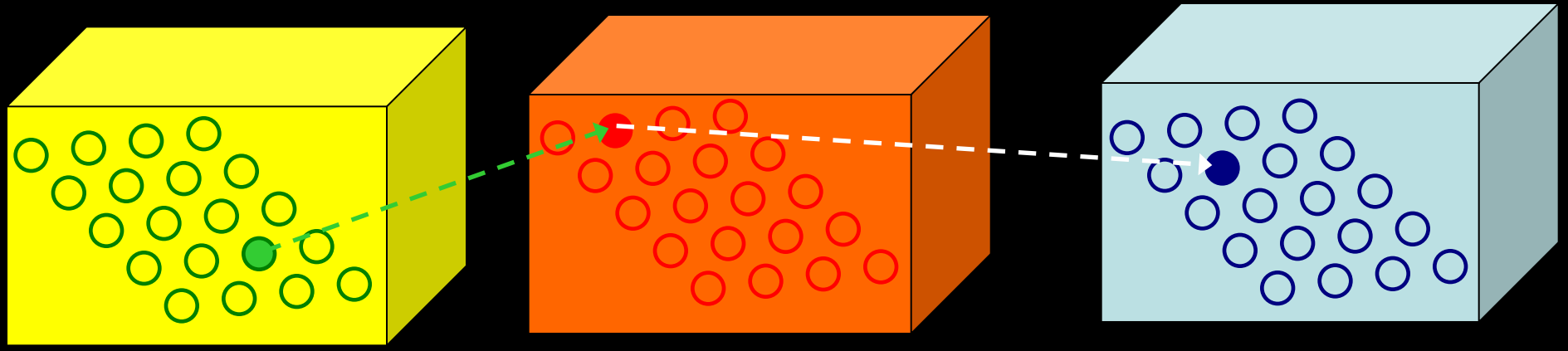
As medicinal chemists we often reduce the complexity of drug's concept in this way:

Biological or "On" Target

Drug

Therapeutic Interaction

Pathology



Chemical Space

Biological Space

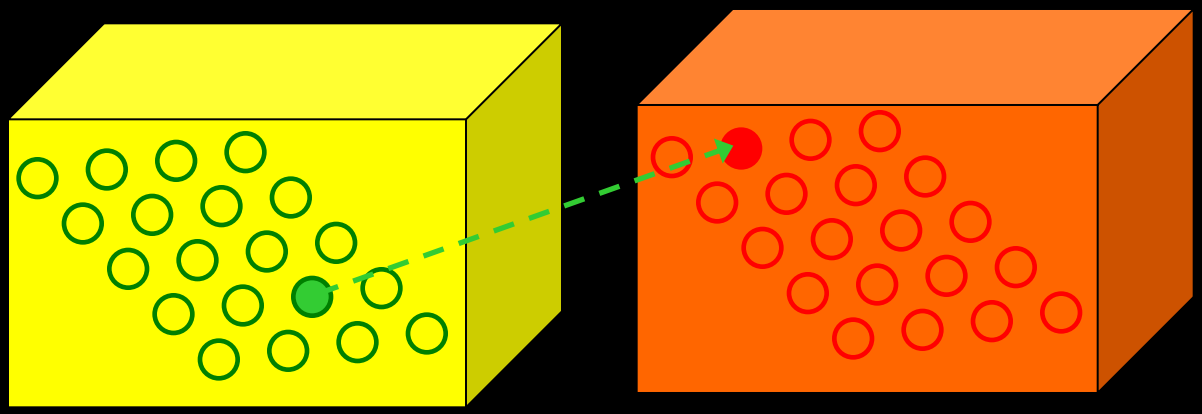
Physio-Pathological Space

And very very often as medicinal chemists we pretend to oversimplify the complexity of drug's concept in this way:

Biological or "On" Target

Drug

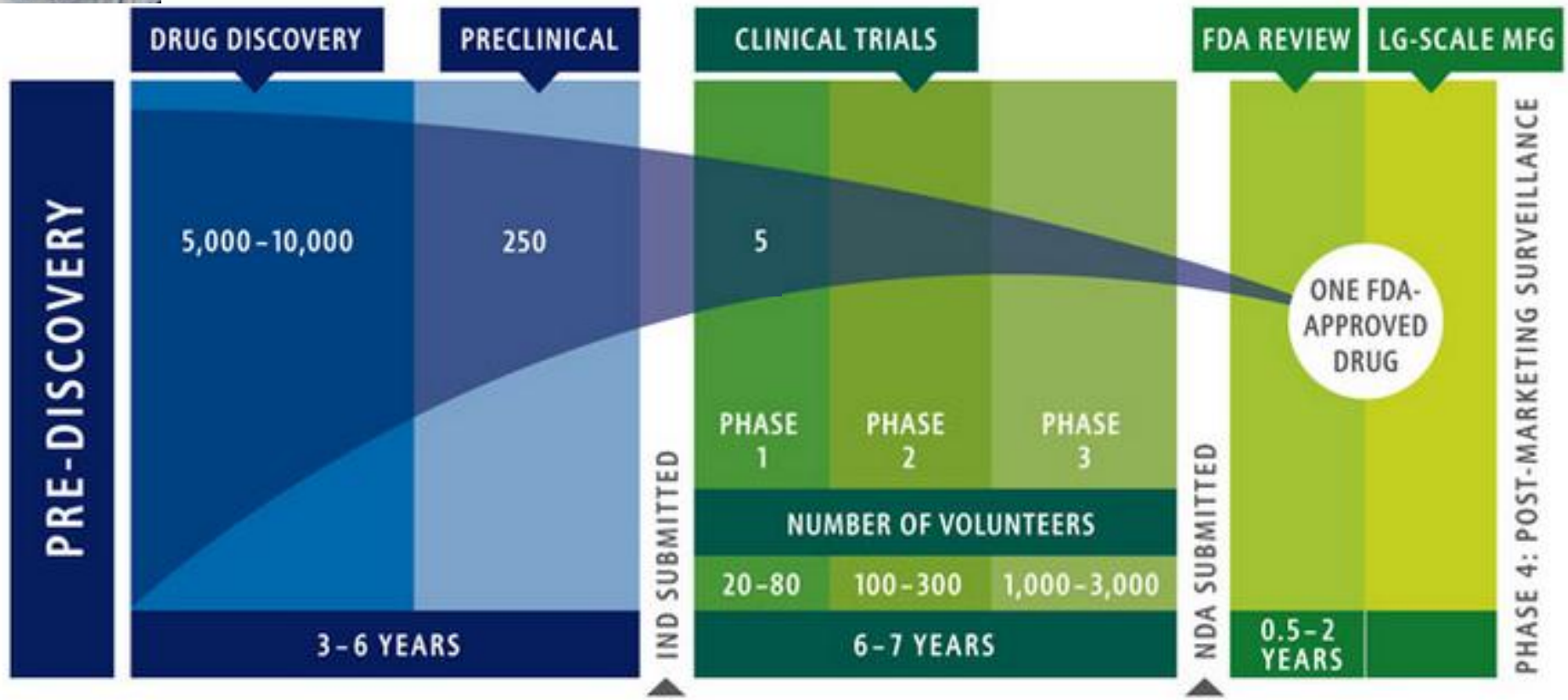
Therapeutic Interaction



Chemical Space

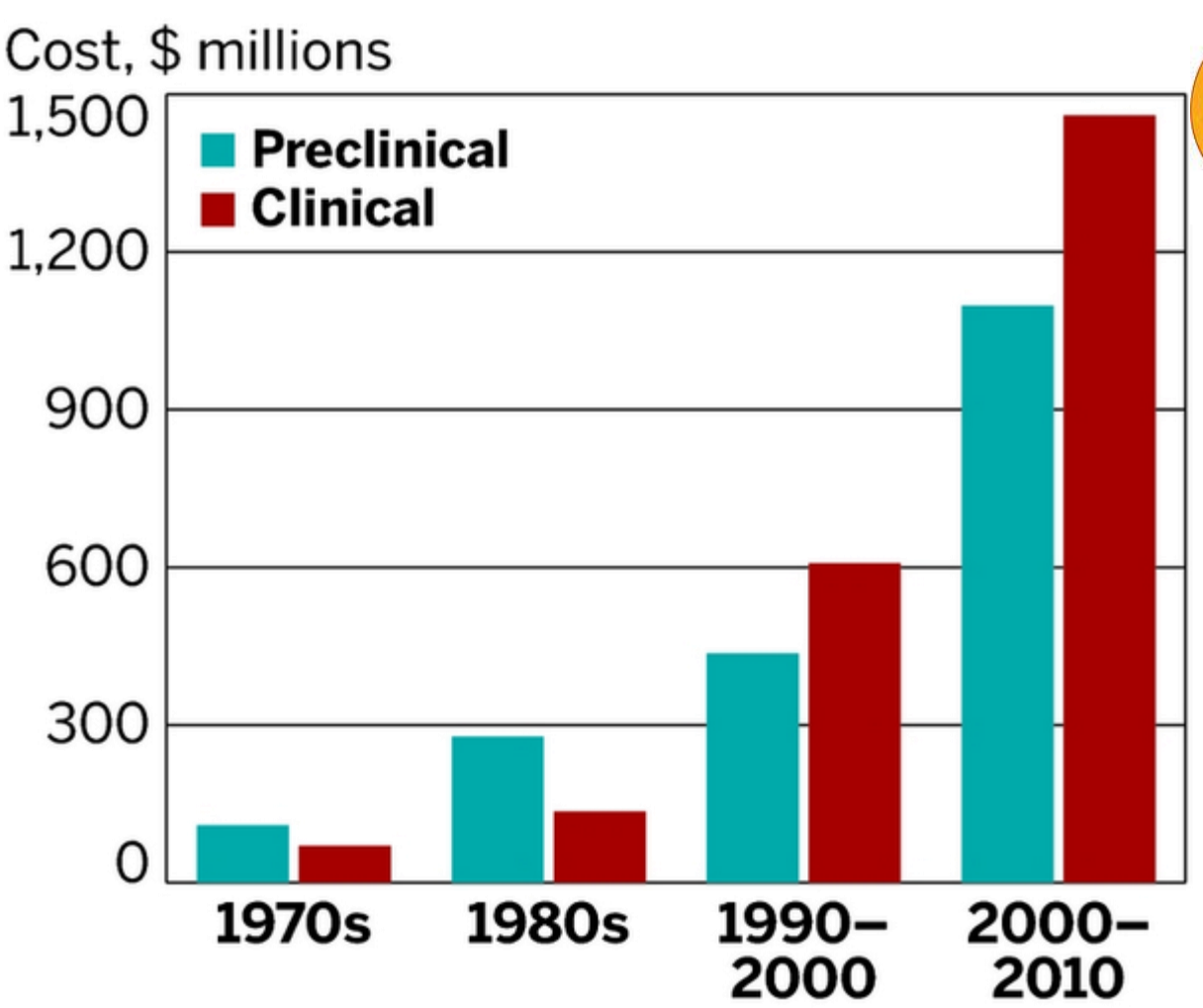
Biological Space

the long history of the birth of a drug…



Bringing a new drug to market can take 8-14 years and costs between $500 and $1000 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:

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?

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

Drug discovery statistics:

https://www.nature.com/articles/d41573-021-00002-0

NEWS · 05 JANUARY 2021 · UPDATE 18 JANUARY 2021

2020 FDA drug approvals

The FDA approved 53 novel drugs in 2020, the second highest count in over 20 years.

Asher Mullard

Despite the disruptions caused by COVID-19, the FDA's Center for Drug Evaluation and Research (CDER) approved 53 novel therapeutics in 2020. This is the second highest total ever, falling just short of 2018's all-time high of 59, and tying with the 1996 approval cohort (Fig. 1).

PDF version

Houston, we've had a problem here!

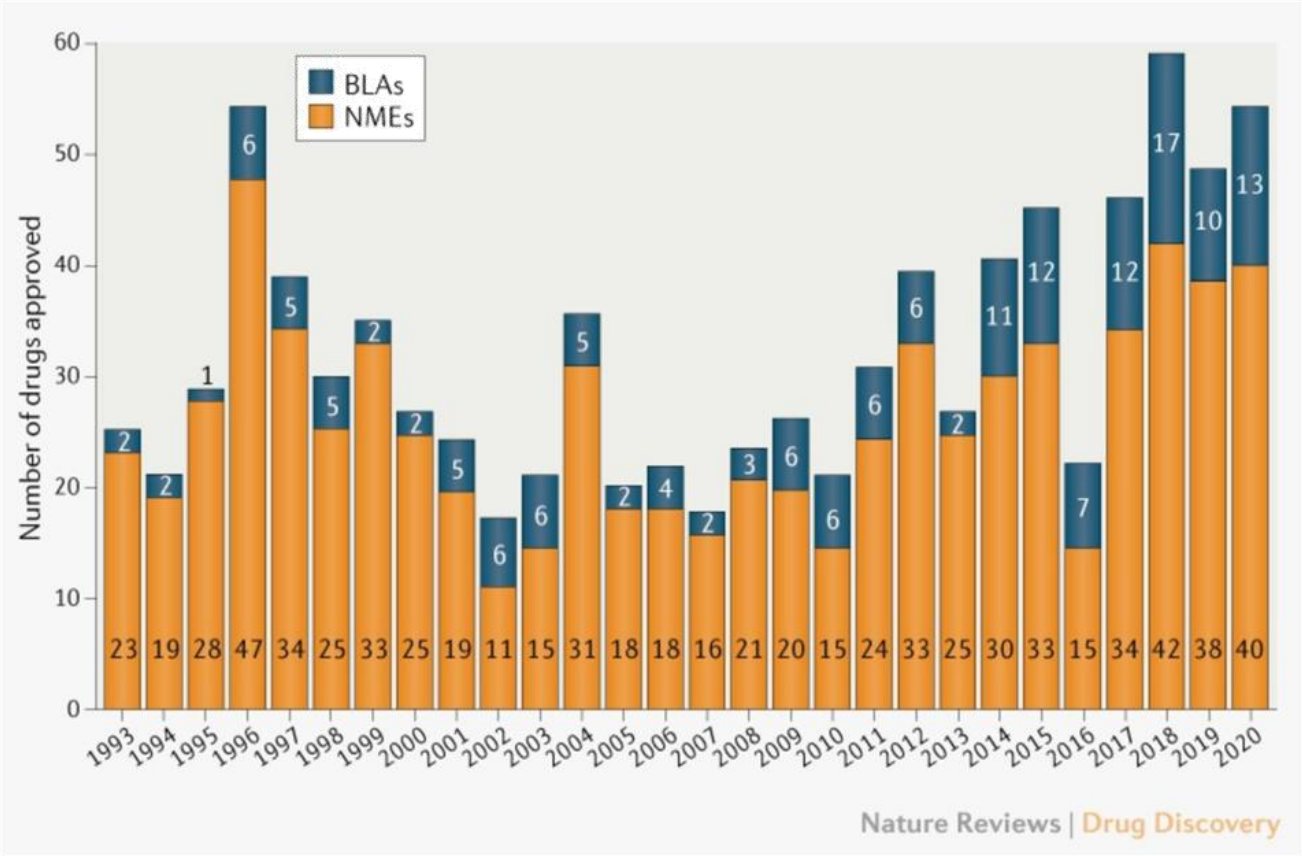
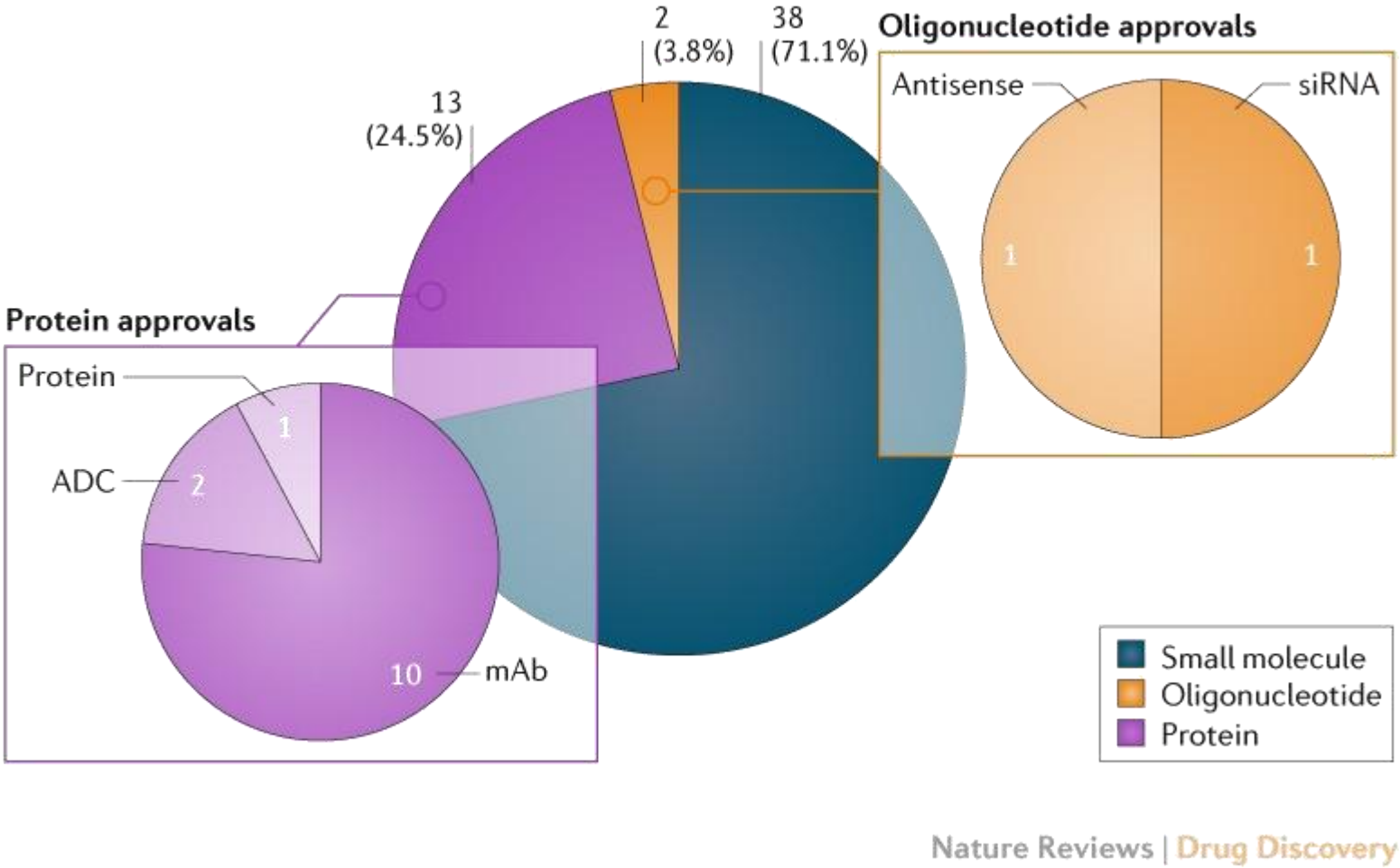


Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2020. Approvals by the Center for Biologics Evaluation and Research (CBER), for products such as vaccines and gene therapies, are not included in this drug count (see Table 2). Source: FDA.

credits: https://www.nature.com/articles/d41573-021-00002-0

Drug discovery statistics:

https://www.nature.com/articles/d41573-021-00002-0

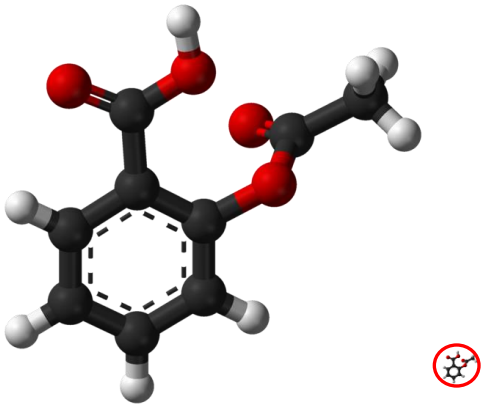


A very general introduction:

Vintage drugs

ASPIRINE

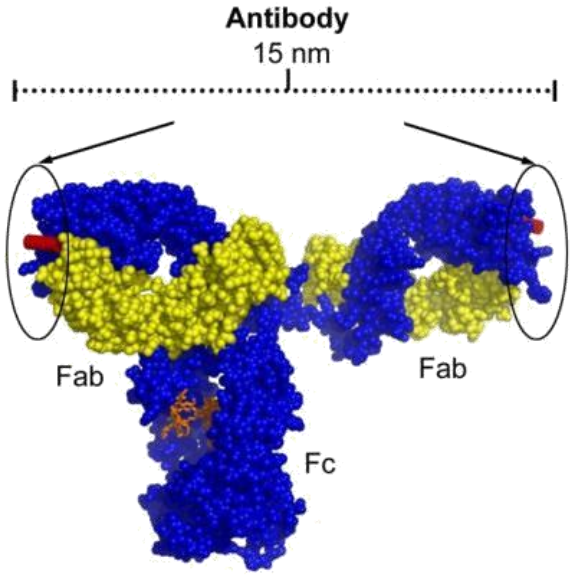
1. small molecule
2. 180 Da
3. 21 atoms
4. usually not immunogenic
5. usually chemically stable



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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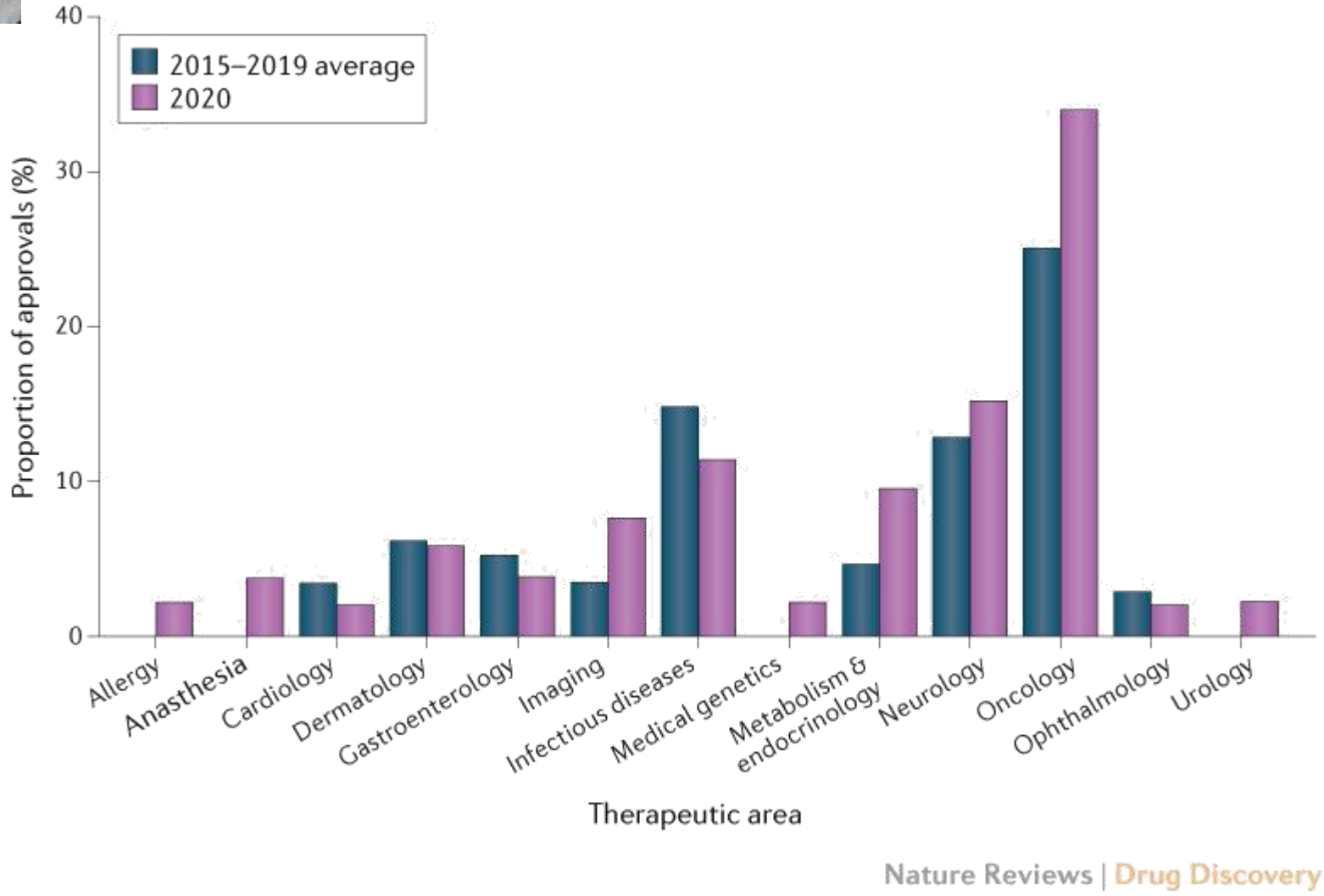
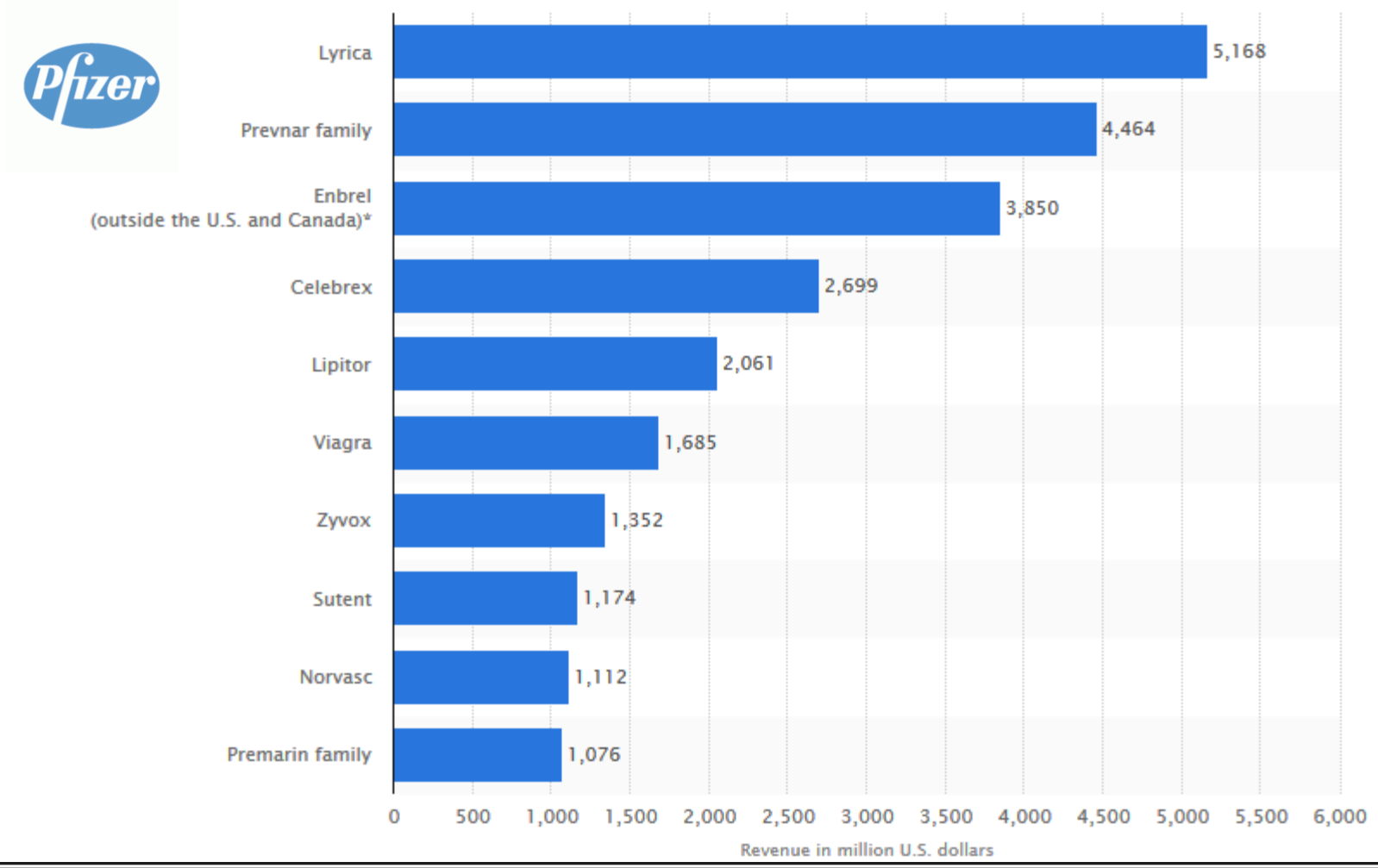


A *blockbuster* is:

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

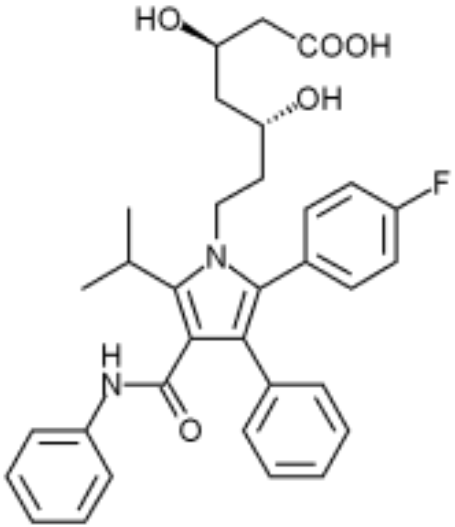
Pfizer's top 10 products based on revenue in 2014 (in million U.S. dollars)



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

Company:
Pfizer

US sales in 2011:
$9.6 billion



What does it do:
Lipitor (*atorvastatin*) lowers LDLs or "bad cholesterol", reducing the risk of heart attack and stroke. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in the liver that plays a role in producing cholesterol.

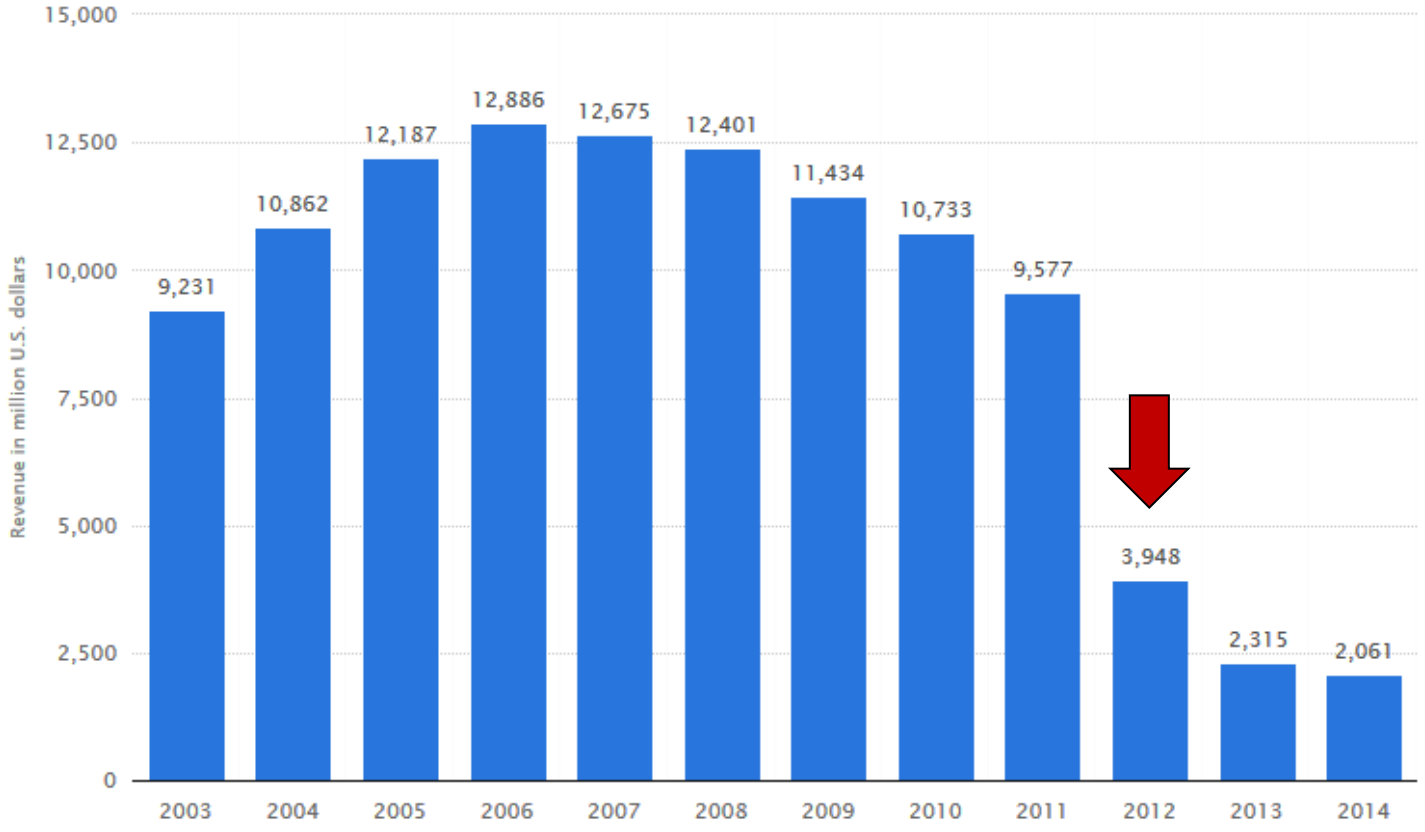
Important dates:
Approved December, 1996. US patent expired November, 2011.

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

Important dates:

Approved December, 1996.

US patent expired November, 2011.



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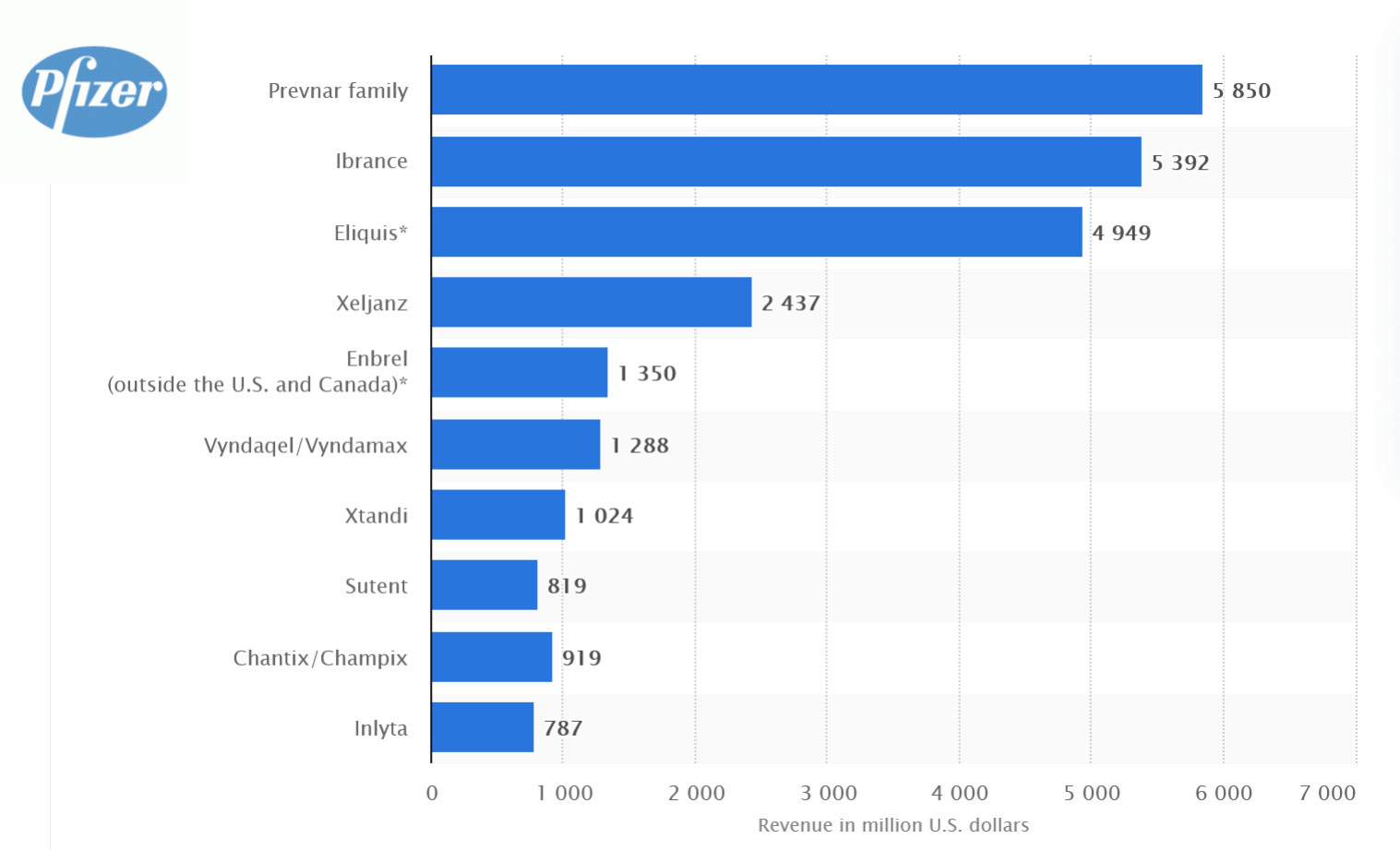
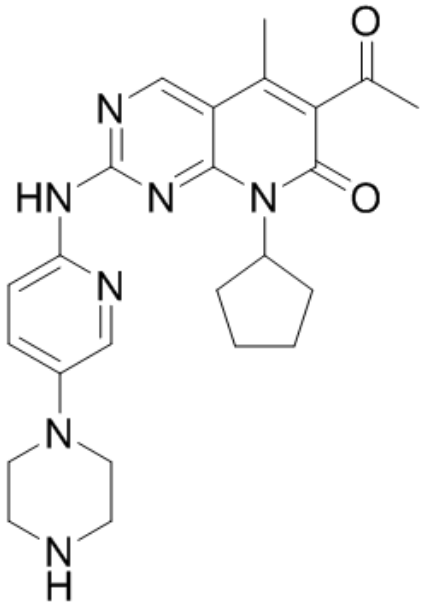


https://www.statista.com/statistics/253788/pfizers-top-products-based-on-revenues/

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

Company:
Pfizer

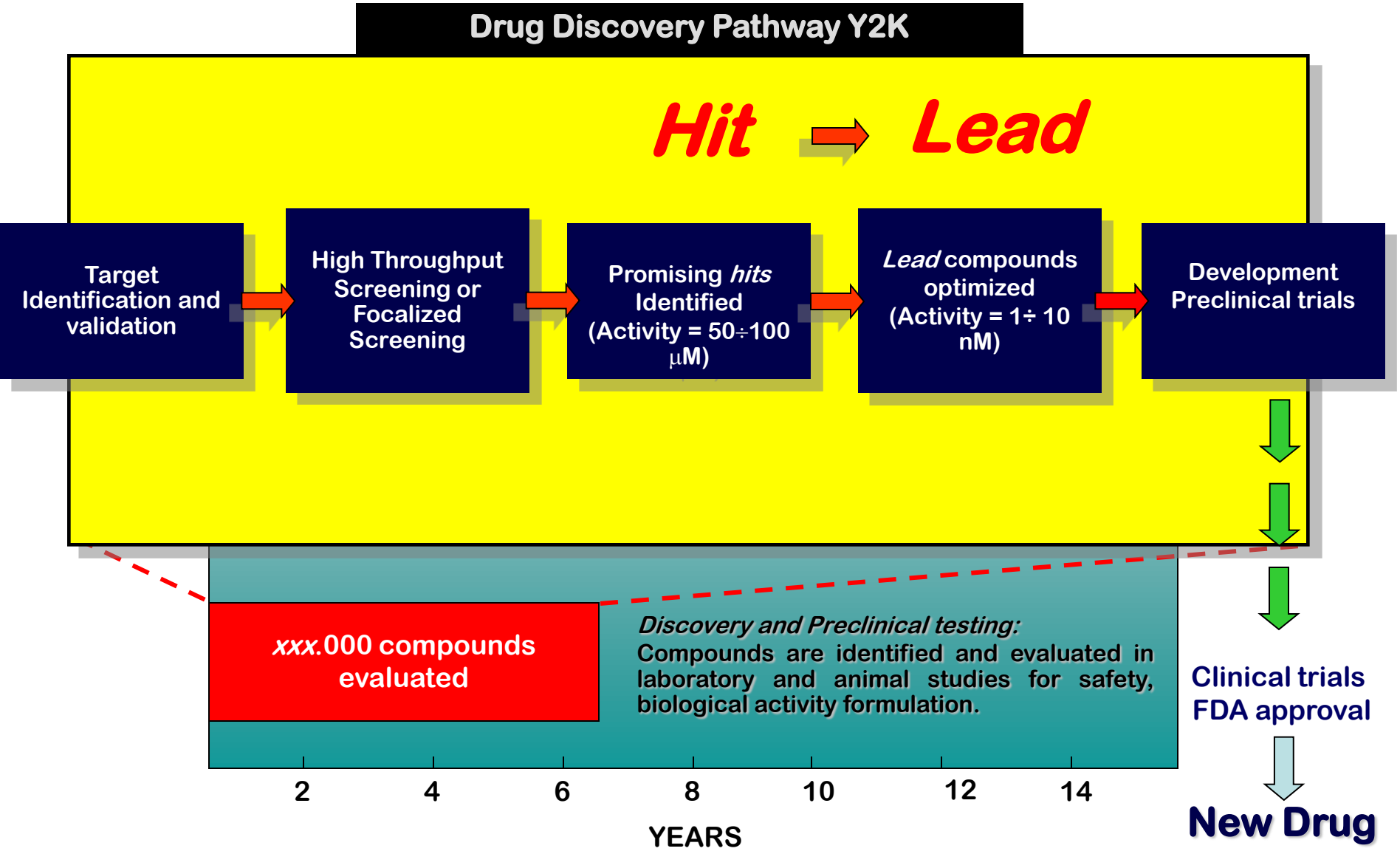
US sales in 2020:
$5.4 billion



What does it do:
Palbociclib, (Ibrance) is a medication for the treatment of HR-positive and HER2-negative breast cancer. It is a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6. Palbociclib was the first CDK4/6 inhibitor to be approved as a cancer therapy.

Important dates:
Approved February, 2015. US patent expired January, 2023.

The “right” road to drug discovery?

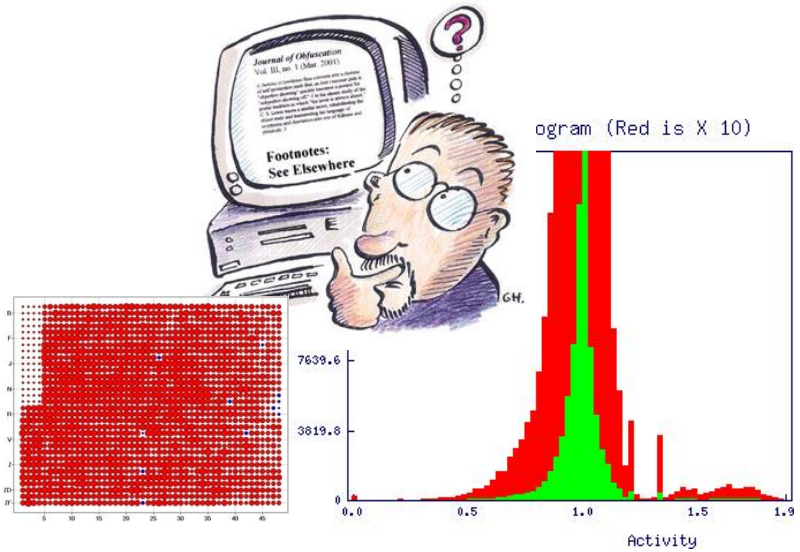


Hit to lead …

- **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.

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

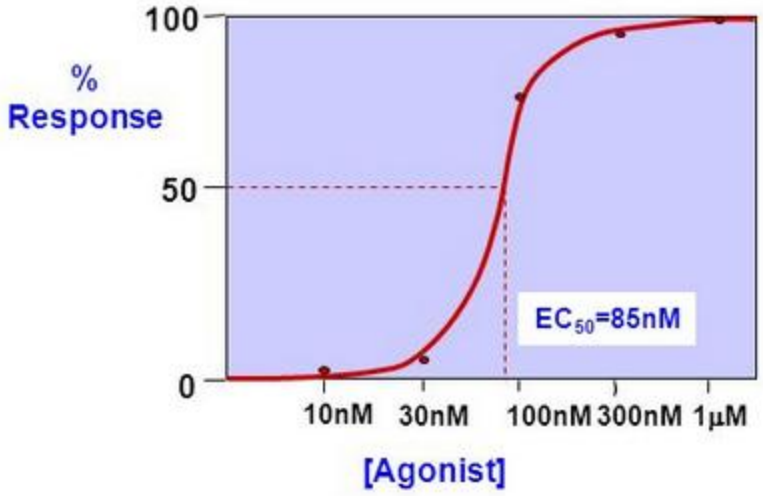


- >1,000,000 — *Initial HTS campaign*
- 1,000,000 — *Quality control*
- 1,000 — *Primary hit selection*
- 100 — *Hit validation*

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

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

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

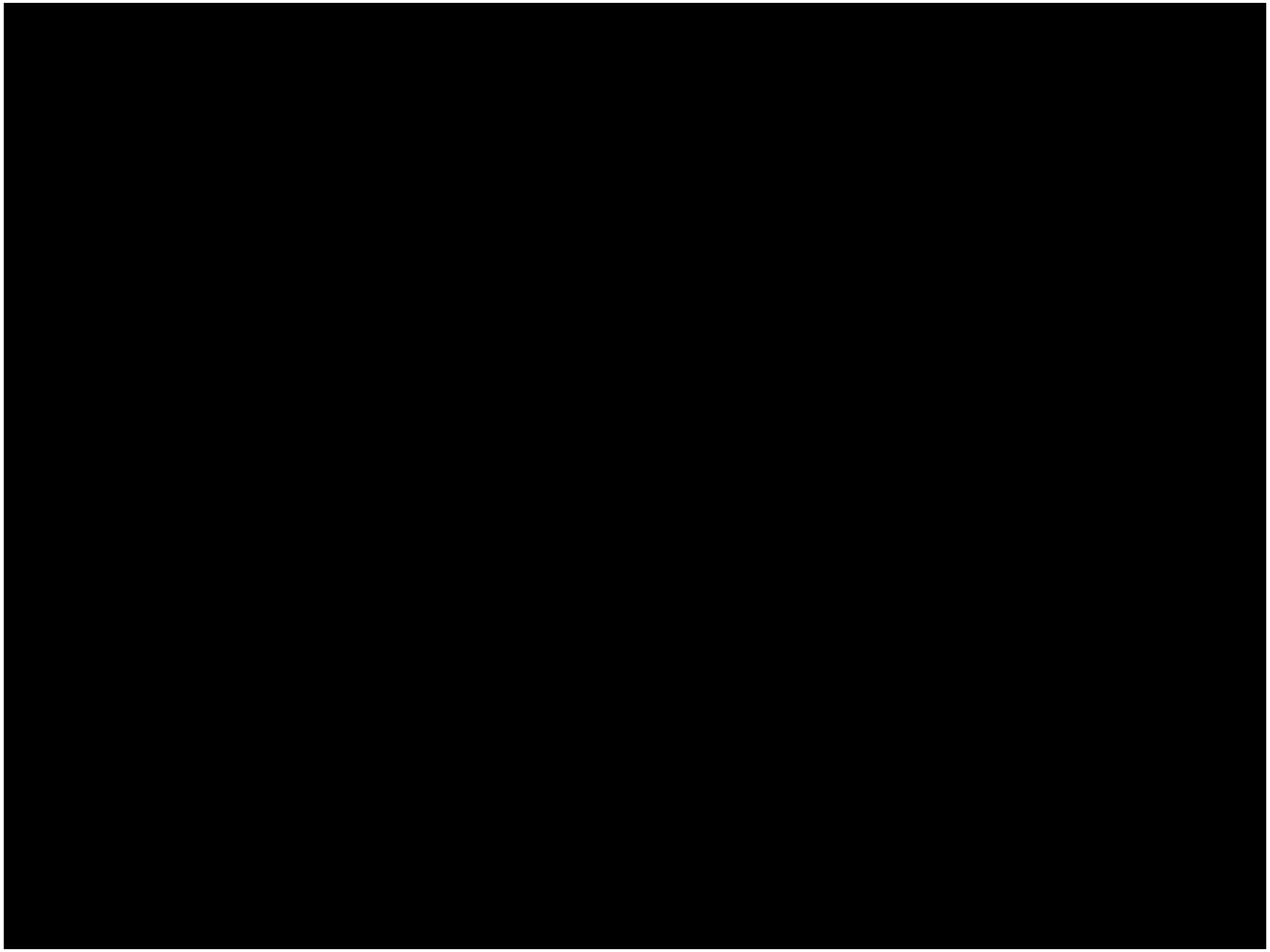
IC_{50} 1μM = pIC_{50} 6.0
IC_{50} 1nM = pIC_{50} 9.0

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)

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 !!!

Hit to lead …

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

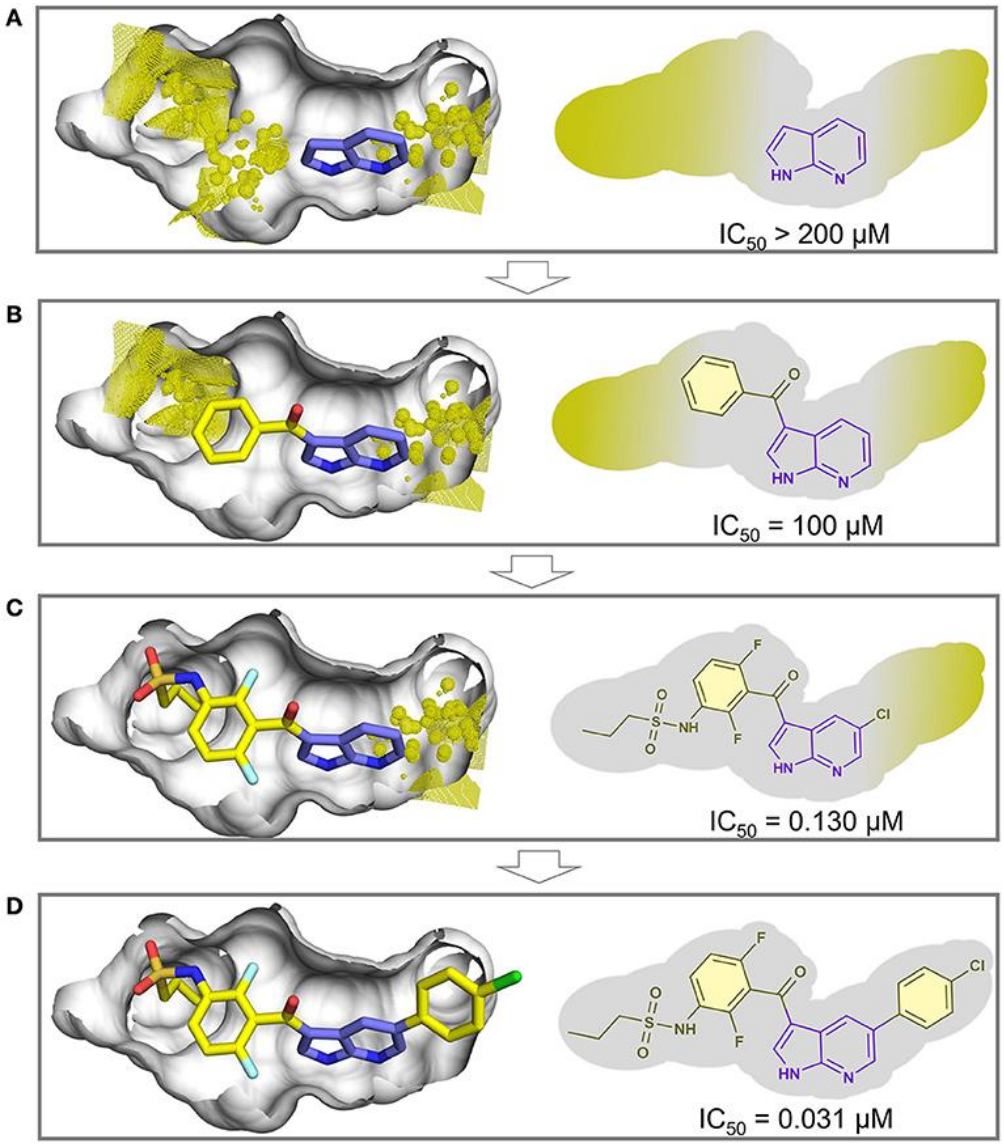
I don't have to add anything !!!

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
Animal efficacy trial	200.000
Rat 2-year chronic oral toxicity	550.000
Human clinical trial	3.500.000

Hit2Lead

Hit2Lead… a pragmatic view:



PM = 118.14; logP = 1.56

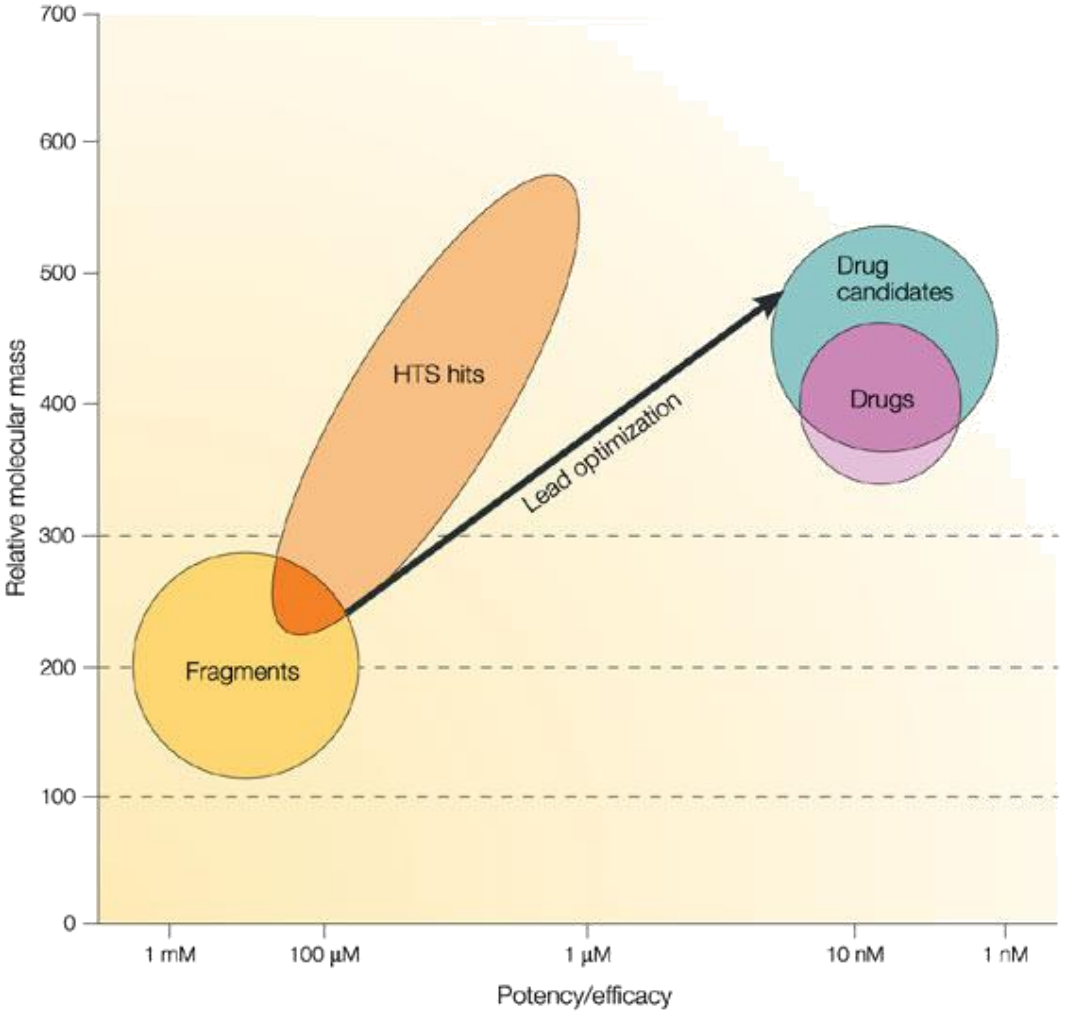
PM = 222.25; logP = 2.79

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

Remember this graph…



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

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