UNIVERSIDADE DE SÃO PAULO
Instituto de Química de São Carlos - IQSC
Grupo de Química Medicinal & Biológica do IQSC/USP
NEQUIMED/IQSC/USP. Email: nequimed@usp.br

Disciplina SQM5811

A Química Medicinal e o Planejamento de Fármacos

Carlos Montanari
Carlos.Montanari@usp.br

Sigla: SQM5811 - 5

Medicinal Chemistry and Drug Design

Período: 19/08/2020 a 01/12/2020 (15 semanas)

Quarta-feira: 15:00 às 18:00

meet.google.com/kxv-ohem-wnj

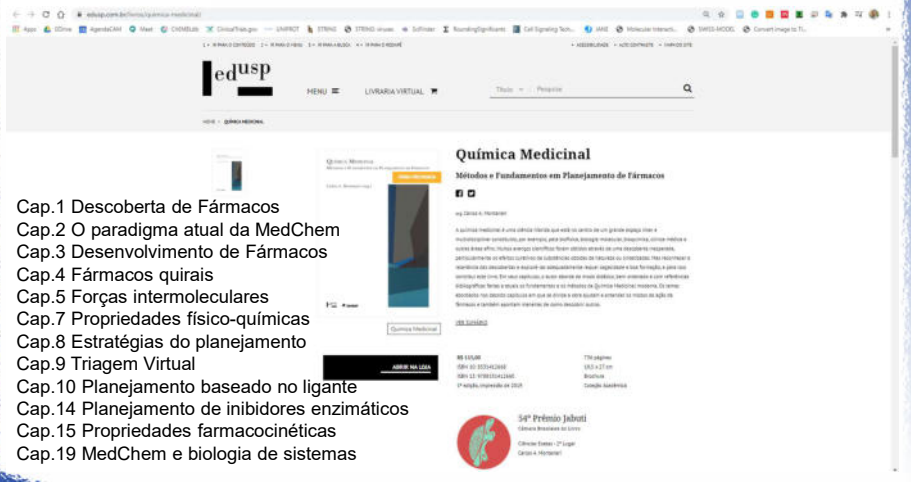
Método de Aula Durante a Pandemia COVID-19

a) Plataforma e/ou ferramentas de software a serem utilizadas
Google Meet (kxv-ohem-wnj)

b) Método
Videoaulas

c) Descrição geral das atividades
(i) Apresentação das videoaulas com conteúdo em powerpoint;
(ii) oferecimento de artigos científicos relacionados aos tópicos;
(iii) discussão sobre os tópicos abordados com base nos artigos;
(iv) aprendizado baseado em problemas via bancos de dados online;
(v) avaliação via apresentação de seminário dirigido (individual) e elaboração de um projeto virtual de planejamento molecular (em duplas, quádruplas e consensual).

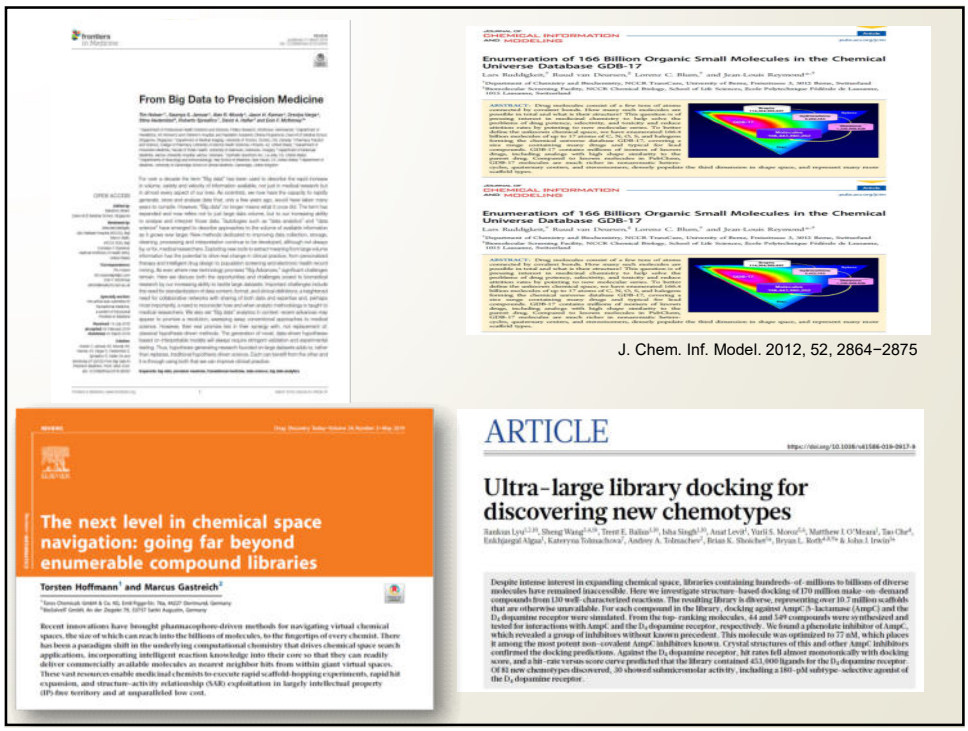
Referências



Cap.1 Descoberta de Fármacos
Cap.2 O paradigma atual da MedChem
Cap.3 Desenvolvimento de Fármacos
Cap.4 Fármacos quirais
Cap.5 Forças intermoleculares
Cap.7 Propriedades físico-químicas
Cap.8 Estratégias do planejamento
Cap.9 Triagem Virtual
Cap.10 Planejamento baseado no ligante
Cap.14 Planejamento de inibidores enzimáticos
Cap.15 Propriedades farmacocinéticas
Cap.19 MedChem e biologia de sistemas

NATURE REVIEWS | DRUG DISCOVERY
VOLUME 13 | AUGUST 2014 | 577

NATURE REVIEWS | DRUG DISCOVERY
VOLUME 10 | JULY 2011 | 507



J. Chem. Inf. Model. 2012, 52, 2864−2875

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JOURNAL OF NATURAL PRODUCTS

pubs.acs.org/jnp

Review

Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019

David J. Newman* and Gordon M. Cragg

Cite This: J. Nat. Prod. 2020, 83, 770−803

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ABSTRACT: This review is an updated and expanded version of the five prior reviews that were published in this journal in 1997, 2003, 2007, 2012, and 2016. For all approved therapeutic agents, the time frame has been extended to cover the almost 39 years from the first of January 1981 to the 30th of September 2019 for all diseases worldwide and from ~1946 (earliest so far identified) to the 30th of September 2019 for all approved antitumor drugs worldwide. As in earlier reviews, only the first approval of any drug is counted, irrespective of how many "biosimilars" or added approvals were subsequently identified. As in the 2012 and 2016 reviews, we have continued to utilize our secondary subdivision of a "natural product mimic", or "NM", to join the original primary divisions, and the designation "natural product botanical", or "NB", to cover those botanical "defined mixtures" now recognized as drug entities by the FDA (and similar organizations). From the data presented in this review, the utilization of natural products and/or synthetic variations using their novel structures, in order to discover and develop the final drug entity, is still alive and well. For example, in the area of cancer, over the time frame from 1946 to 1980, of the 75 small molecules, 40, or 53.3%, are N or ND. In the 1981 to date time frame the equivalent figures for the N* compounds of the 185 small molecules are 62, or 33.5%, though to these can be added the 58 S* and S*/NMs, bringing the figure to 64.9%. In other areas, the influence of natural product structures is quite marked with, as expected from prior information, the anti-infective area being dependent on natural products and their structures, though as can be seen in the review there are still disease areas (shown in Table 2) for which there are no drugs derived from natural products. Although combinatorial chemistry techniques have succeeded as methods of optimizing structures and have been used very successfully in the optimization of many recently approved agents, we are still able to identify only two de novo combinatorial compounds (one of which is a little speculative) approved as drugs in this 39-year time frame, though there is also one drug that was developed using the "fragment-binding methodology" and approved in 2012. We have also added a discussion of candidate drug entities currently in clinical trials as "warheads" and some very interesting preliminary reports on sources of novel antibiotics from Nature due to the absolute requirement for new agents to combat plasmid-borne resistance genes now in the general populace. We continue to draw the attention of readers to the recognition that a significant number of natural product drugs/leads are actually produced by microbes and/or microbial interactions with the "host from whence it was isolated"; thus we consider that this area of natural product research should be expanded significantly.

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Journal of Natural Products pubs.acs.org/jnp Review

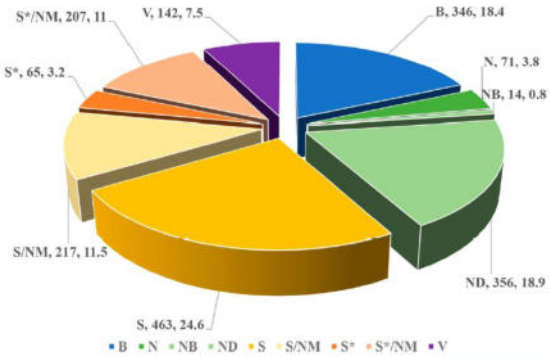

Figure 1. All new approved drugs 01JAN81 to 30SEP19; n = 1881.

Table 1. Codes Used in Analyses

code	brief definition/year
B	biological macromolecule, 1997
N	unaltered natural product, 1997
NB	botanical drug (defined mixture), 2012
ND	natural product derivative, 1997
S	synthetic drug, 1997
S*	synthetic drug (NP pharmacophore), 1997
V	vaccine, 2003
/NM	mimic of natural product, 2003

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Summary

1. Fundamentals of drug design & discovery
2. Molecular structure
3. Properties of chemical substances
4. Drug properties
5. The planned genesis of drugs
6. Molecular design strategies
7. Biochemical and biological targets
8. The pharmaceutical, pharmacodynamics and pharmacokinetic phases
9. Drug repurposing
10. Gene-disease-drug interrelationship

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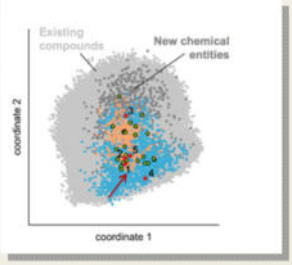
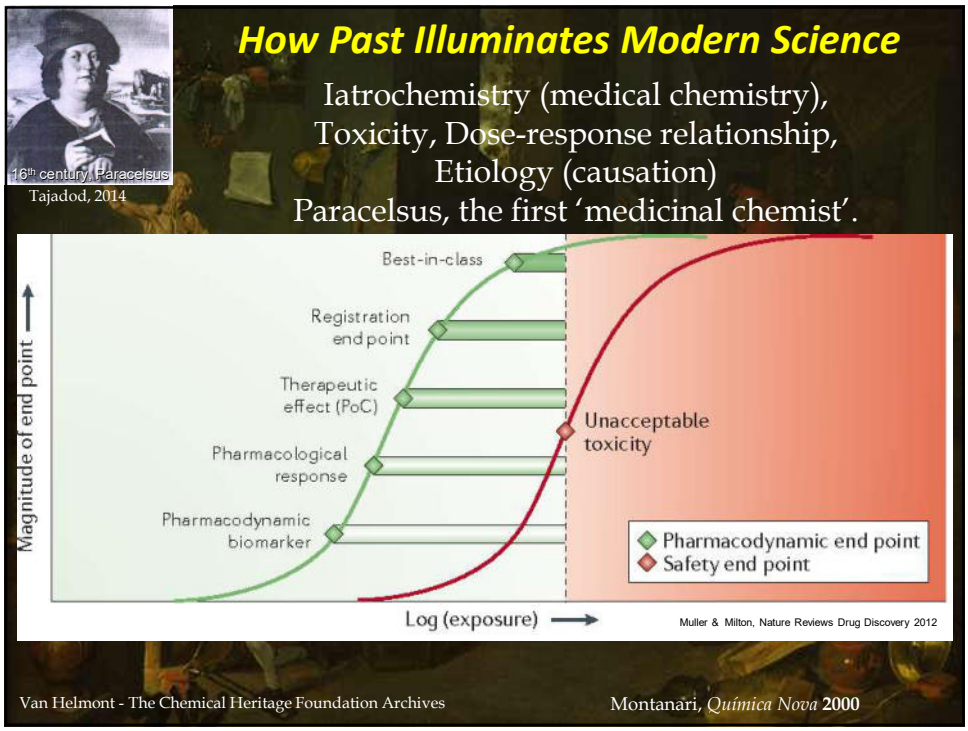
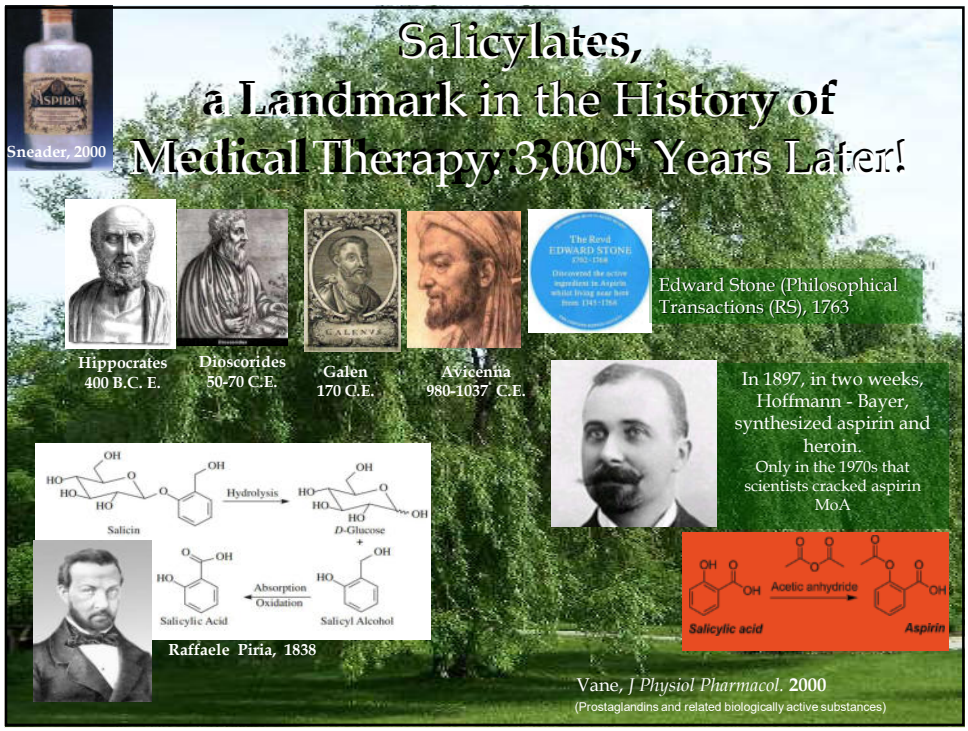
1. Fundamentals of drug design & discovery

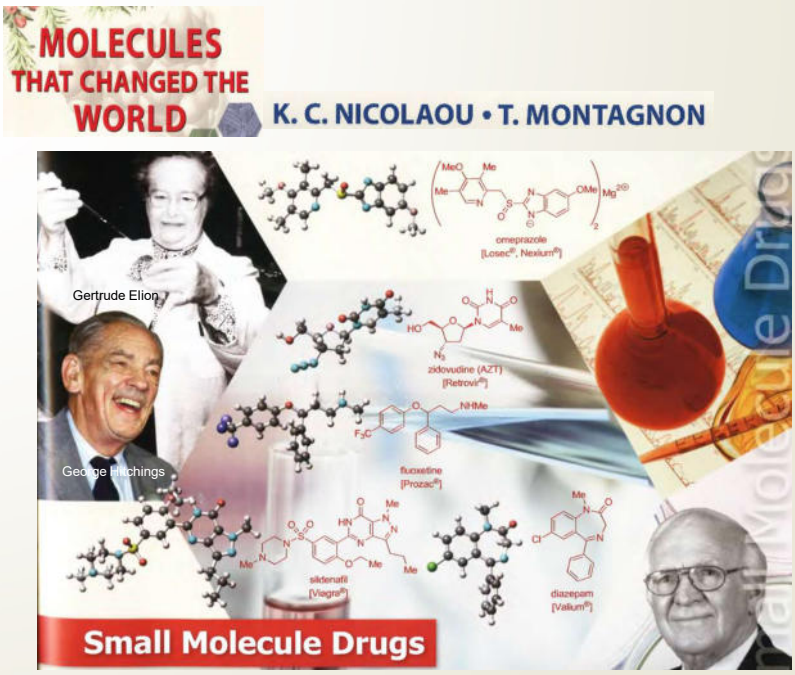
A Philosophical Provocation

Do not be afraid of the epistemological pluralism of chemistry




How Past Illuminates Modern Science
Iatrochemistry (medical chemistry),
Toxicity, Dose-response relationship,
Etiology (causation)
Paracelsus, the first 'medicinal chemist'.
16th century, Paracelsus
Tajadod, 2014
Best-in-class
Registration end point
Therapeutic effect (PoC)
Pharmacological response
Pharmacodynamic biomarker
Unacceptable toxicity
Magnitude of end point
Log (exposure)
Pharmacodynamic end point
Safety end point
Muller & Milton, Nature Reviews Drug Discovery 2012
Van Helmont - The Chemical Heritage Foundation Archives
Montanari, Química Nova 2000


Salicylates,
a Landmark in the History of
Medical Therapy: 3,000+ Years Later!
Sneader, 2000
Hippocrates
400 B.C. E.
Dioscorides
50-70 C.E.
Galen
170 C.E.
Avicenna
980-1037 C.E.
Edward Stone (Philosophical Transactions (RS), 1763
In 1897, in two weeks, Hoffmann - Bayer, synthesized aspirin and heroin.
Only in the 1970s that scientists cracked aspirin MoA
Salicin
Hydrolysis
D-Glucose
Salicylic Acid
Absorption
Oxidation
Salicyl Alcohol
Raffaele Piria, 1838
Acetic anhydride
Salicylic acid
Aspirin
Vane, J Physiol Pharmacol. 2000
(Prostaglandins and related biologically active substances)



Montanari e Bolzani, *Química Nova* **2001**

Sir James Black

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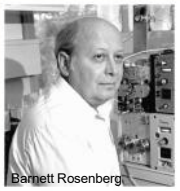
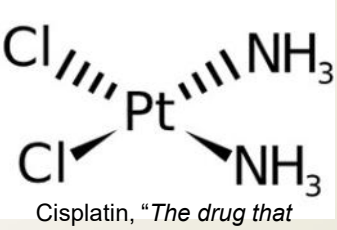
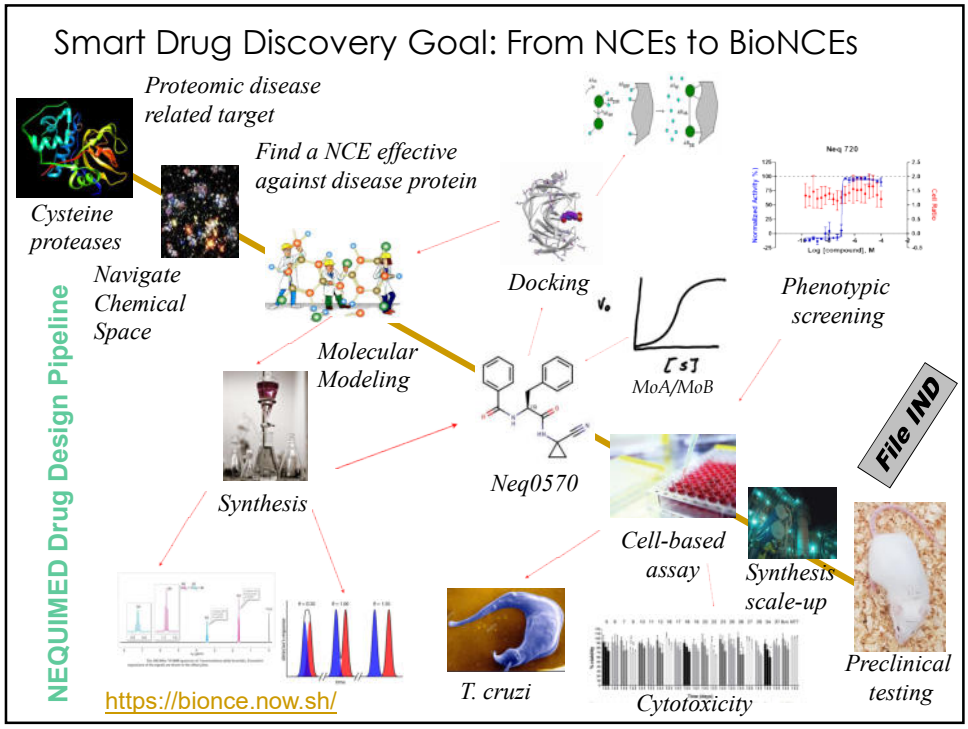


Barnett Rosenberg



Cisplatin, "*The drug that changed cancer treatment*"



M. Tute, ex-Pfizer, UK

Common Decisions that a Medicinal Chemist Faces During a Typical Drug Discovery Project

Tute & Montanari *et al. JCAMD* **1995** . Jenkins , Montanari *et al. J.Braz.Chem. Soc.* **1998**

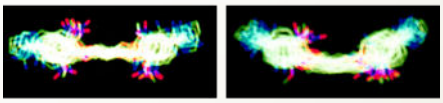
Lusher *et al., Drug Discov Today* **2014**

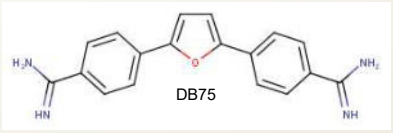
M. Tute, ex-Pfizer, UK

Common Decisions that a Medicinal Chemist Faces During a Typical Drug Discovery Project

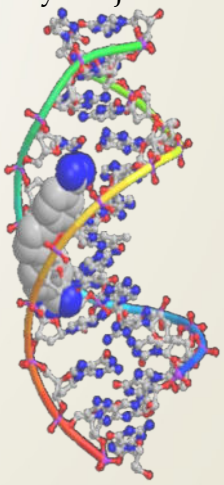
Extended conformation

Isohelical pharmacophoric **conformation**





DB289



GDL036 (NDB)

Tute & Montanari *et al. JCAMD* **1995** . Jenkins , Montanari *et al. J.Braz.Chem. Soc.* **1998**

Lusher *et al., Drug Discov Today* **2014**

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From idea to product

Illustration by David de la Iglesia (Senior Product Designer @jobandtalent)

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Entrepreneurship Can Be Learned

Mike Peña, Stanford University

...doing science for better health!

Entrepreneurship Can Be Learned...

1. a personal passion to solve a problem
2. a vision for what's innovative
the skills to build a product or service, and a business around it
3. the tenacity to constantly seek feedback, iterate and pivot
4. the ability to empathize with and inspire those around you.

Mike Peña, Stanford University

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But,

"The overall process from idea to product can therefore take from 9 to 16+ years to complete. Furthermore, historically only one in 20 compounds that start the development process ever become marketed drugs.

This is not an enterprise for people with a low tolerance for failure or for those who need immediate gratification."

LAMATTINA, J. L. Drug truths - Dispelling the Myths About Pharma R&D. New Jersey: Wiley, 2009. p. 24-25.

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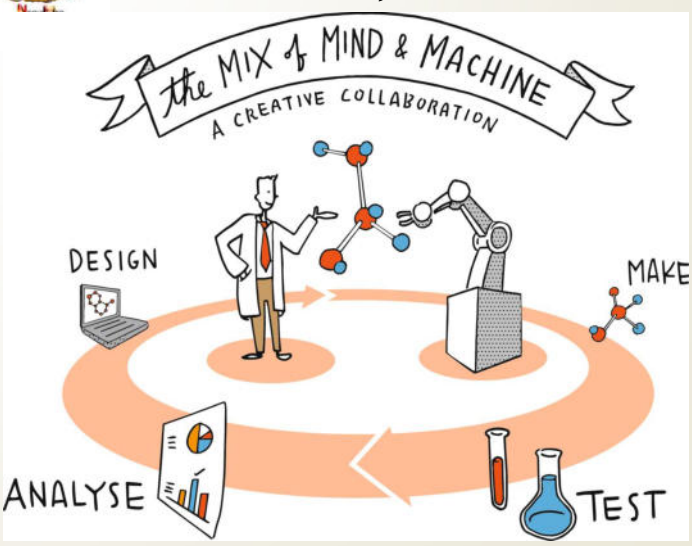
So, what?



Schneider et al. Nature Reviews Drug Discovery (2019)

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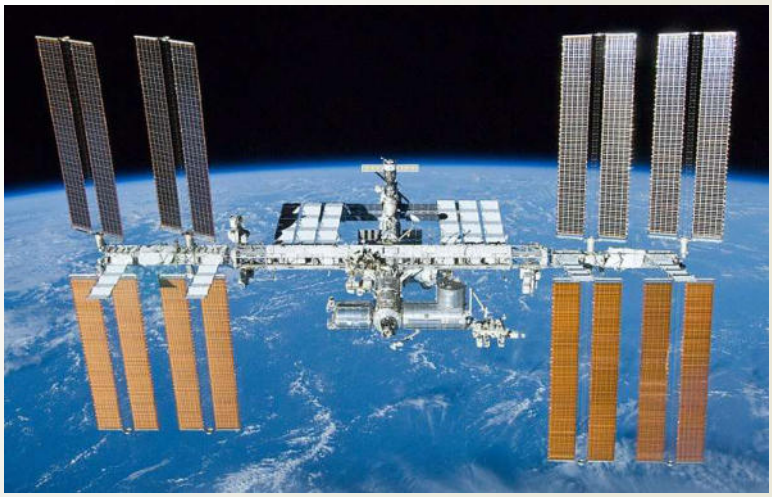
Deterministic Building of the International Space Station (ISS)



By NASA/Crew of STS-132 - http://spaceflight.nasa.gov/gallery/images/shuttle/sts-132/hires/s132e012208.jpg(http://spaceflight.nasa.gov/gallery/images/shuttle/sts-132/html/s132e012208.html), Public Domain, https://commons.wikimedia.org/w/index.php?curid=10561008

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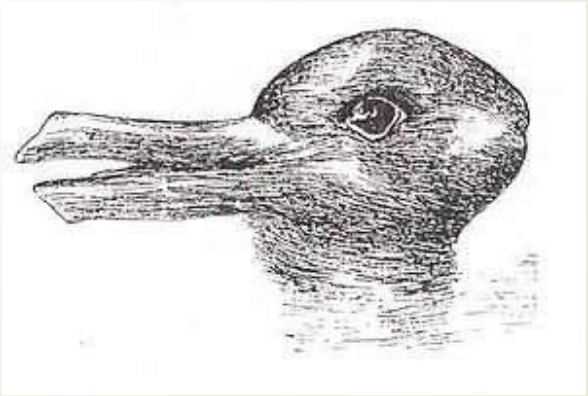
Probabilistic Process of Biol MedChem and the optical illusion of the duck-rabbit



Por Thomas Kuhn

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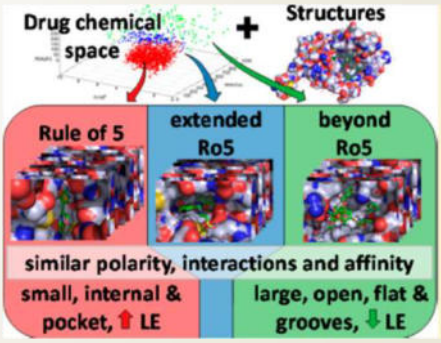
Combinatorial paradigm

The Chemical Universe at CAS: > 165.10^6



(Kihlberg et al. J. Med. Chem. 2016)

All living organisms: CHONPS 99%+

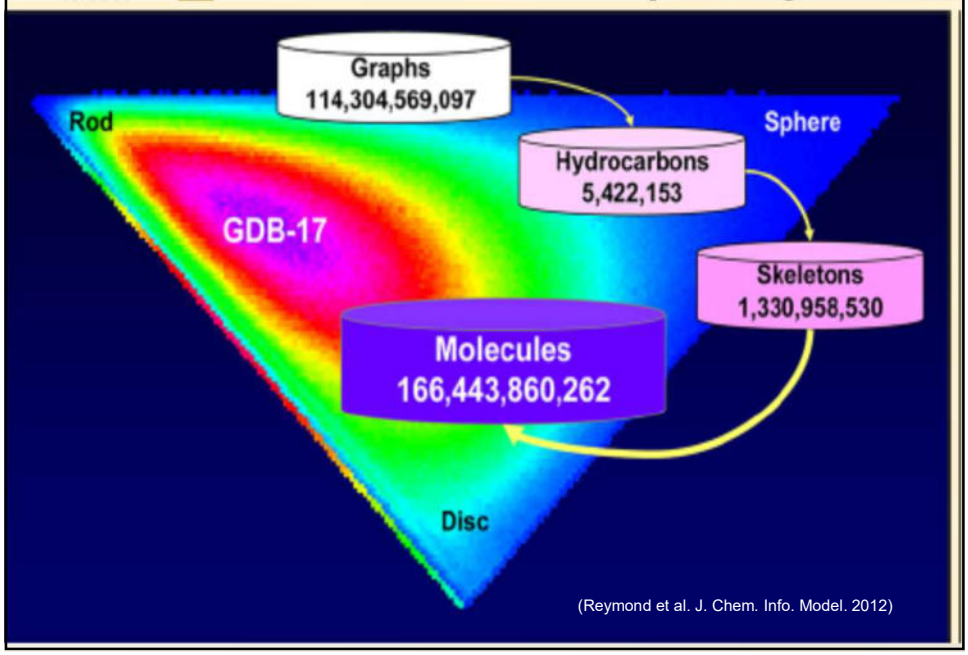
How many substances can be synthesized?

??? CHEMICAL SUBSTANCES

C. H. O. N. P. S and MM < ??? Da

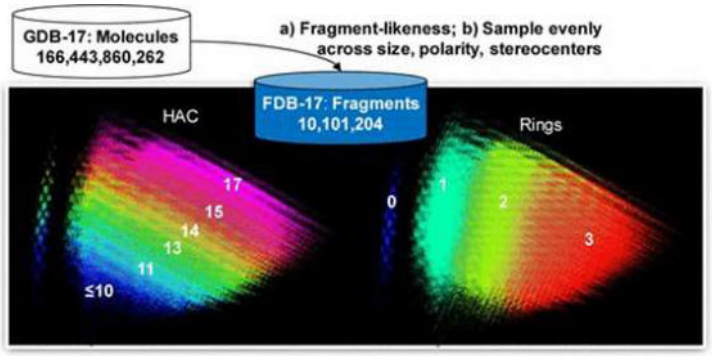
...doing

Combinatorial paradigm



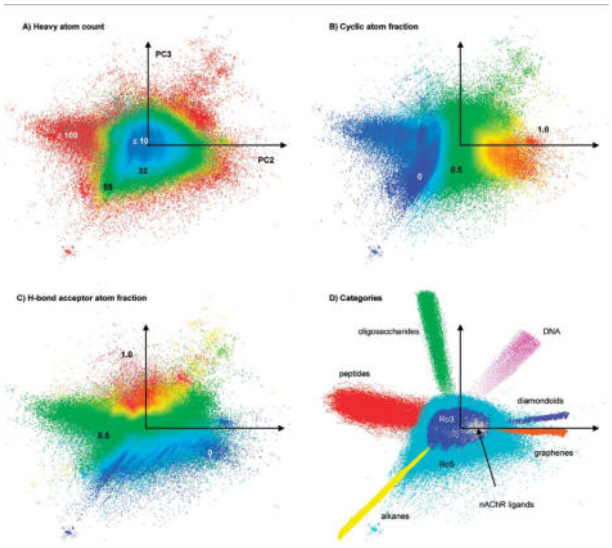
(Reymond et al. J. Chem. Info. Model. 2012)

Tamanho do Banco de Dados: Aberto a nossa imaginação

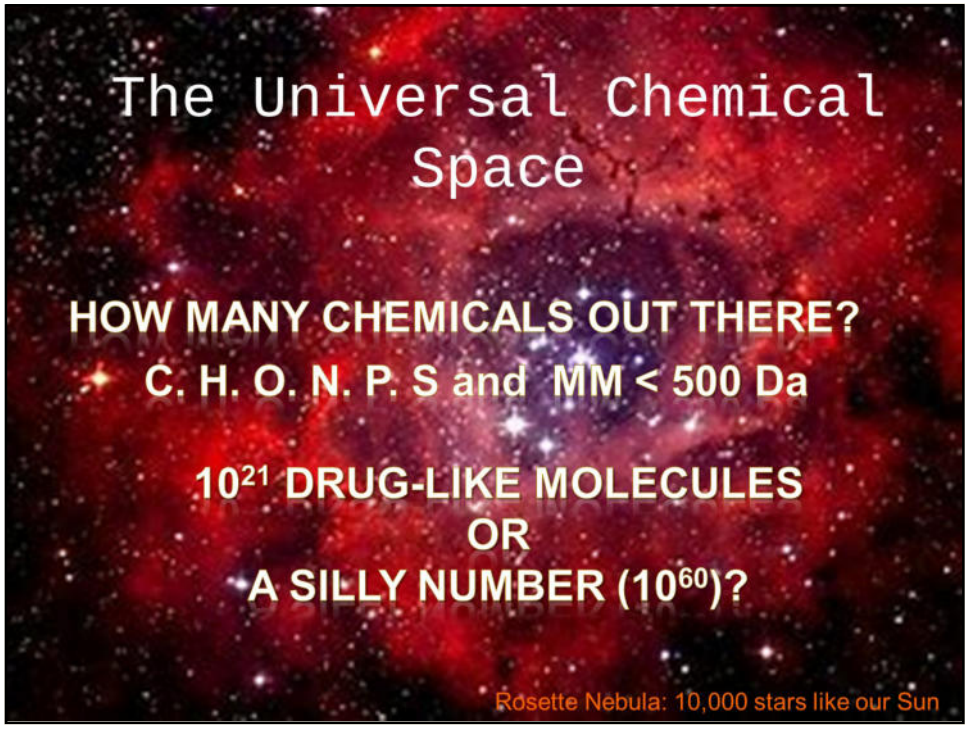


Reymond, *Acc. Chem. Res.* 2015

Classification



Reymond, *Acc. Chem. Res.* 2015



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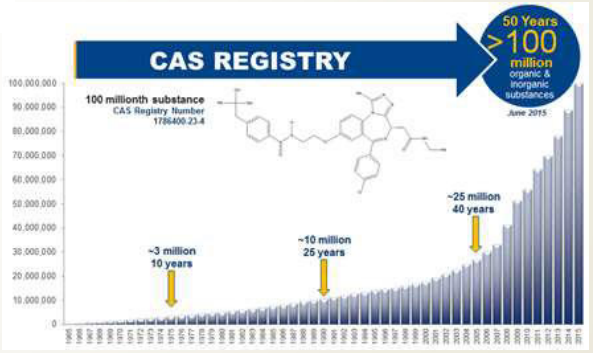
Data continue to grow…



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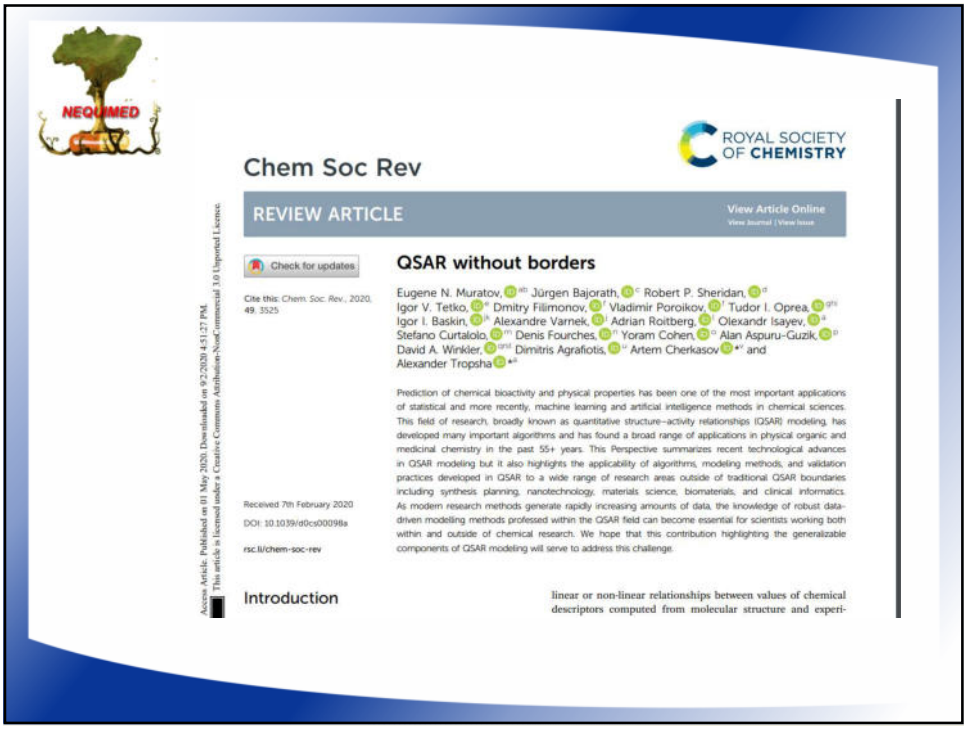
Our Imagination is now Open to the Medical Periodic Table

Barry & Sadler, *Chem. Commun.*, **2013**

White: known to be essential in man
Blue background: found in the structures of known drugs

NEQUIMED



Chem Soc Rev

ROYAL SOCIETY OF CHEMISTRY

REVIEW ARTICLE

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QSAR without borders

Eugene N. Muratov, Jürgen Bajorath, Robert P. Sheridan, Igor V. Tetko, Dmitry Filimonov, Vladimir Poroikov, Tudor I. Oprea, Igor I. Baskin, Alexandre Varnek, Adrian Roitberg, Olexandr Isayev, Stefano Curtalolo, Denis Fourches, Yoram Cohen, Alan Aspuru-Guzik, David A. Winkler, Dimitris Agrafiotis, Artem Cherkasov and Alexander Tropsha

Cite this: *Chem. Soc. Rev.*, 2020, **49**, 3525

Received 7th February 2020

DOI: 10.1039/d0cs00098a

rsc.li/chem-soc-rev

Prediction of chemical bioactivity and physical properties has been one of the most important applications of statistical and more recently, machine learning and artificial intelligence methods in chemical sciences. This field of research, broadly known as quantitative structure–activity relationships (QSAR) modeling, has developed many important algorithms and has found a broad range of applications in physical organic and medicinal chemistry in the past 55+ years. This Perspective summarizes recent technological advances in QSAR modeling but it also highlights the applicability of algorithms, modeling methods, and validation practices developed in QSAR to a wide range of research areas outside of traditional QSAR boundaries including synthesis planning, nanotechnology, materials science, biomaterials, and clinical informatics. As modern research methods generate rapidly increasing amounts of data, the knowledge of robust data-driven modelling methods professed within the QSAR field can become essential for scientists working both within and outside of chemical research. We hope that this contribution highlighting the generalizable components of QSAR modeling will serve to address this challenge.

Introduction

linear or non-linear relationships between values of chemical descriptors computed from molecular structure and experi-

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Drug design/discovery endeavor is...

to search the needle in a haystack!

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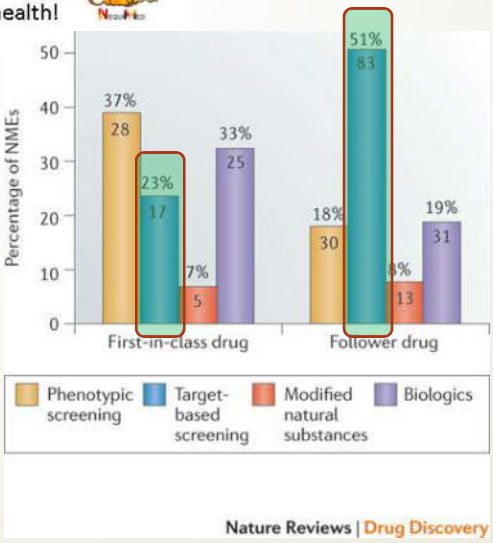
How to discover a new drug?



Sir James Black

'the most fruitful basis for the discovery of a new drug is to start with an old drug'

(Swinney & Anthony. NAT. REV. DRUG DISCOV. 2011)

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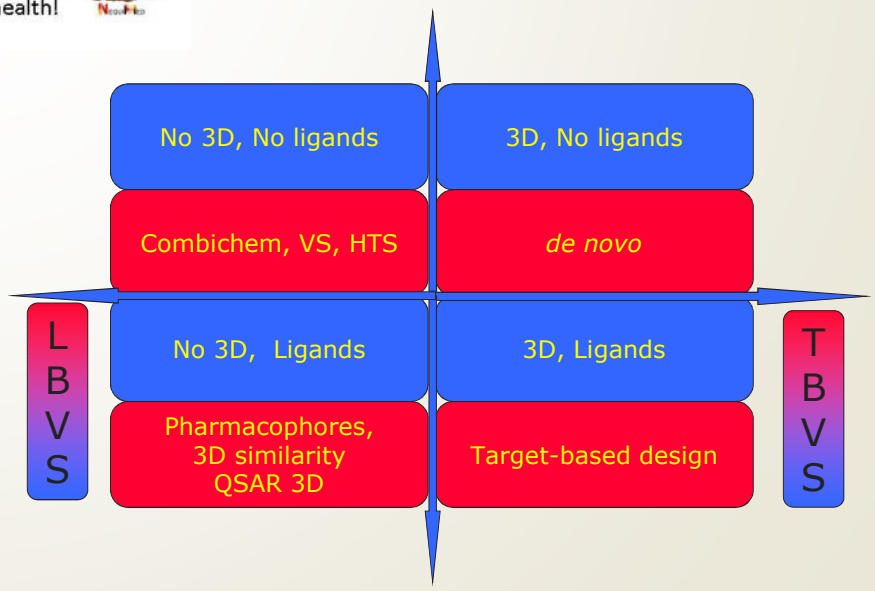
Drug design strategies



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Challenges of drug discovery: Finding a substance with multiple aggregated values

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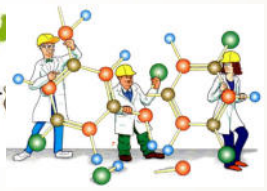
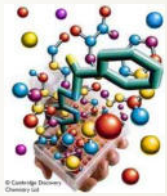
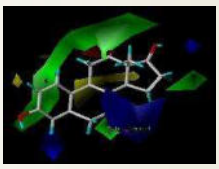


MM



SAR

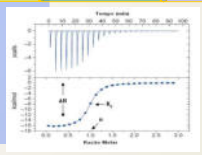


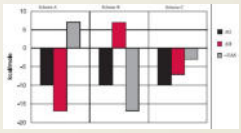
QSAR 2D and 3D

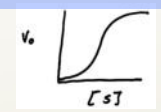
Synthesis

Target Validation | Ligands | Leads | Pre- and clinical phases | Drug approval | Drug

Calorimetry (MOA/TD signature)

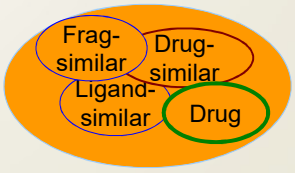






Enzyme kinectics (MOA)

TD (MoB)



Chem-Bio space

Optimized PD & PK

(**Montanari. *et al.*** *J. Med. Chem.* **2000**; **Montanari. et al.** Burger's MedChem **2010**. vol.7. 685)

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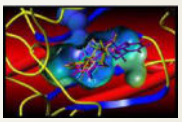
Integrating Technologies...

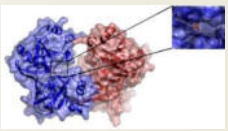
DB

Social molecules

Chemical space navigation

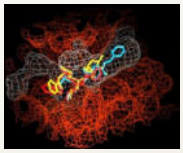


Virtual Screening

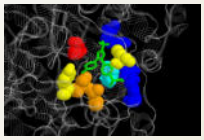


X ray (PDB)

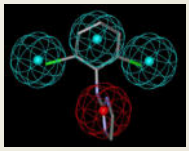
Cloning. Expression. Isolation. Purification



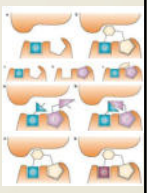
Docking



Receptor mapping



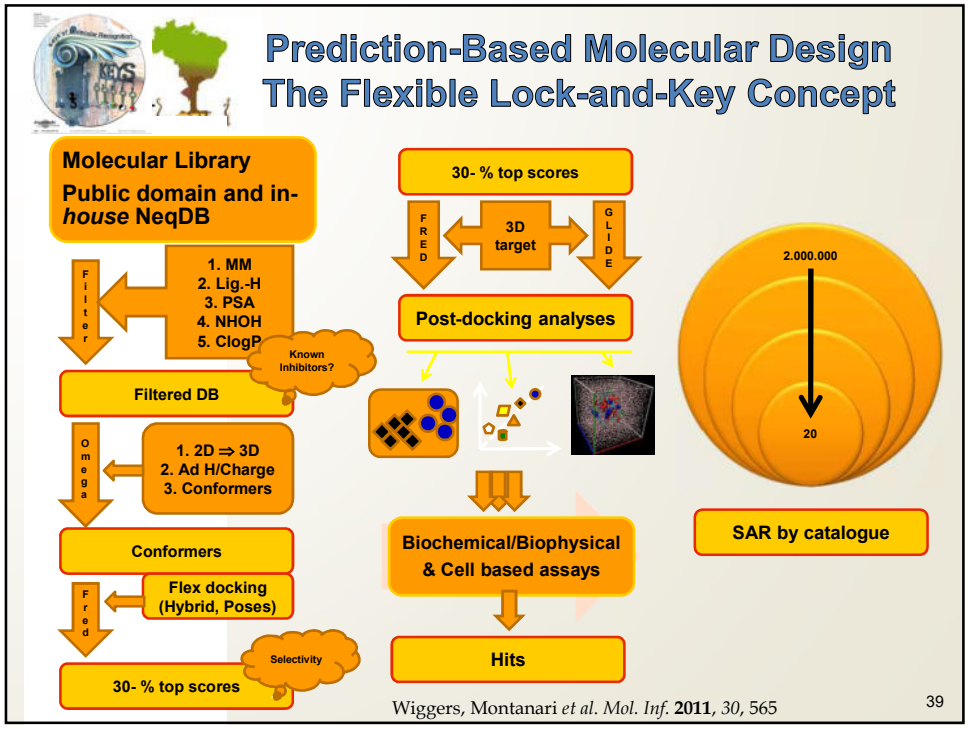
Pharmacophore hypothesis

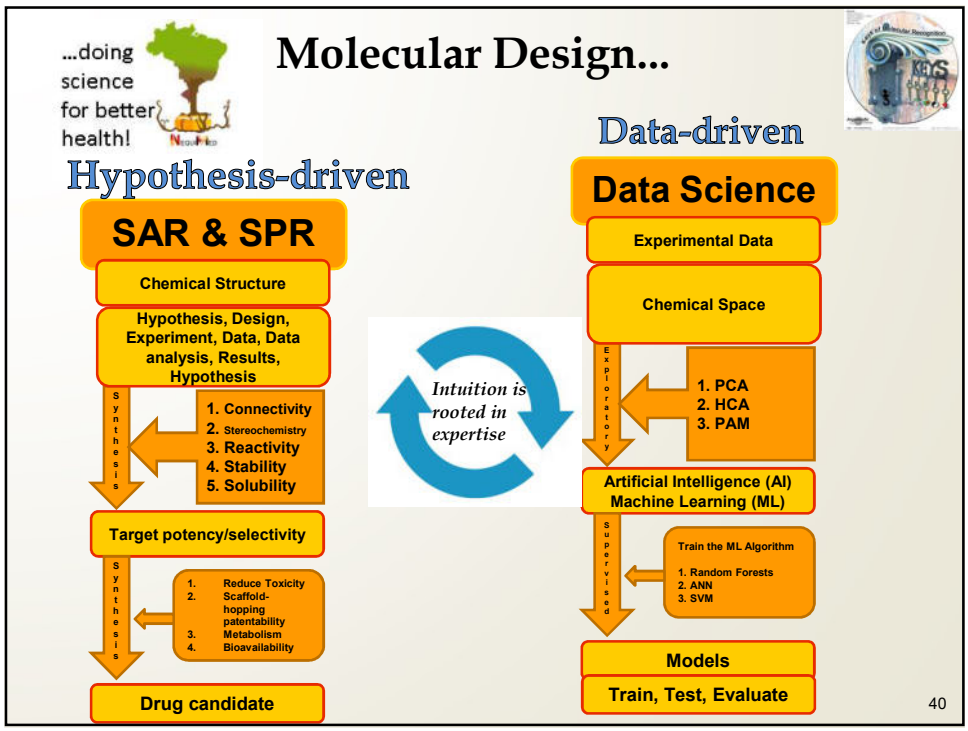


Ro3

(**Montanari** *et al. Eur. J. Med. Chem.* **2008**)

(Gaudio **e Montanari** *J. Comput.-Aided Mol. Des.* **2002**
Montanari *et al. Bioorg. Med. Chem.* **2008**)


Prediction-Based Molecular Design
The Flexible Lock-and-Key Concept
Molecular Library
Public domain and in-house NeqDB
Filter
1. MM
2. Lig.-H
3. PSA
4. NHOH
5. ClogP
Known Inhibitors?
Filtered DB
Omega
1. 2D ⇒ 3D
2. Ad H/Charge
3. Conformers
Conformers
Fred
Flex docking (Hybrid, Poses)
Selectivity
30- % top scores
30- % top scores
FRED
3D target
GLIDE
Post-docking analyses
Biochemical/Biophysical & Cell based assays
Hits
2.000.000
20
SAR by catalogue
Wiggers, Montanari et al. Mol. Inf. 2011, 30, 565
39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Molecular Design...
Hypothesis-driven
SAR & SPR
Chemical Structure
Hypothesis, Design, Experiment, Data, Data analysis, Results, Hypothesis
Synthesis
1. Connectivity
2. Stereochemistry
3. Reactivity
4. Stability
5. Solubility
Target potency/selectivity
Synthesis
1. Reduce Toxicity
2. Scaffold-hopping patentability
3. Metabolism
4. Bioavailability
Drug candidate
Intuition is rooted in expertise
Data-driven
Data Science
Experimental Data
Chemical Space
Exploratory
1. PCA
2. HCA
3. PAM
Artificial Intelligence (AI) Machine Learning (ML)
Supervised
Train the ML Algorithm
1. Random Forests
2. ANN
3. SVM
Models
Train, Test, Evaluate
40

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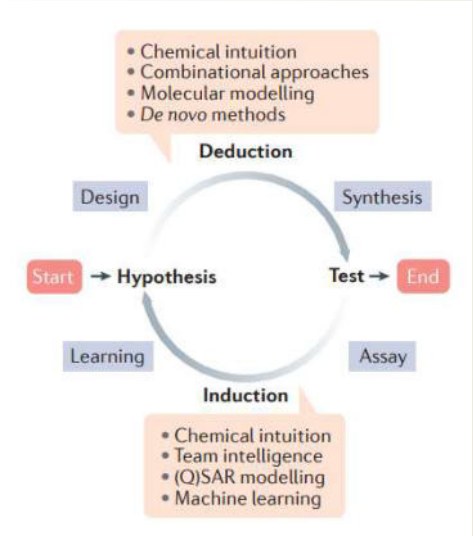
The Scientific Knowledge and Science4.0



Schneider, *Nature Rev. Drug Discov.* **2017**

41

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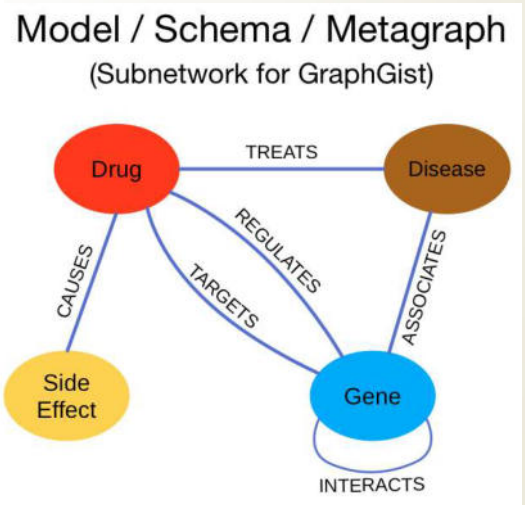
Drugs, genes, diseases



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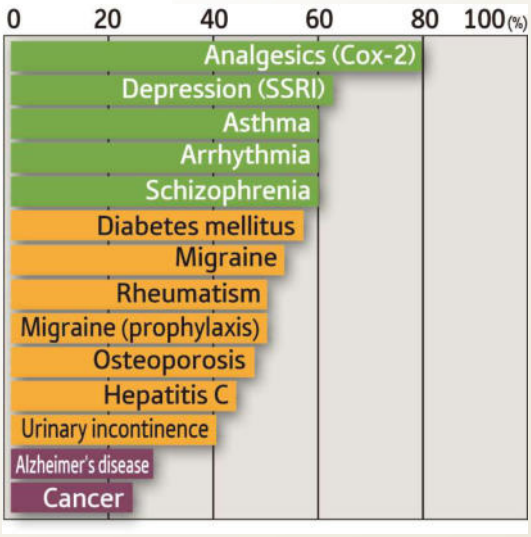
Drugs



https://medicalxpress.com/

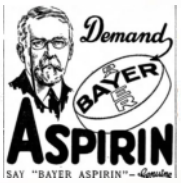
A little bit of history+

The most promiscuous drug in the history of the pharmaceutical industry?

Uses of Aspirin

- As analgesic (300 to 600 mg during 6 to 8 h) for headache, backache, pulled muscle, toothache, neuralgias.
- As antipyretic in fever of any origin in the same doses as for analglesia. However, *paracetamol and metamizole are safer*, and generally preferred.
- Acute rheumatic fever. *Aspirin is the first drug of choice. Other drugs substitute Aspirin only when it fails or in severe cases.* Antirheumatic doses are 75 to 100 mg/kg/24 h (resp. 4–6 g daily) in the first weeks.
- Rheumatoid arthritis. Aspirin a dose of 3 to 5 g/24 h *after meal* is effective in most cases. Since large doses of Aspirin are poorly tolerated for a long time, the new NSAIDs (diclofenac, ibuprofen, etc.) in depot form are preferred.

Waheed, Nonsteroidal anti inflammatory drugs (NSAIDS), 2014

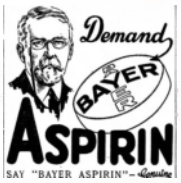


A little bit of history+

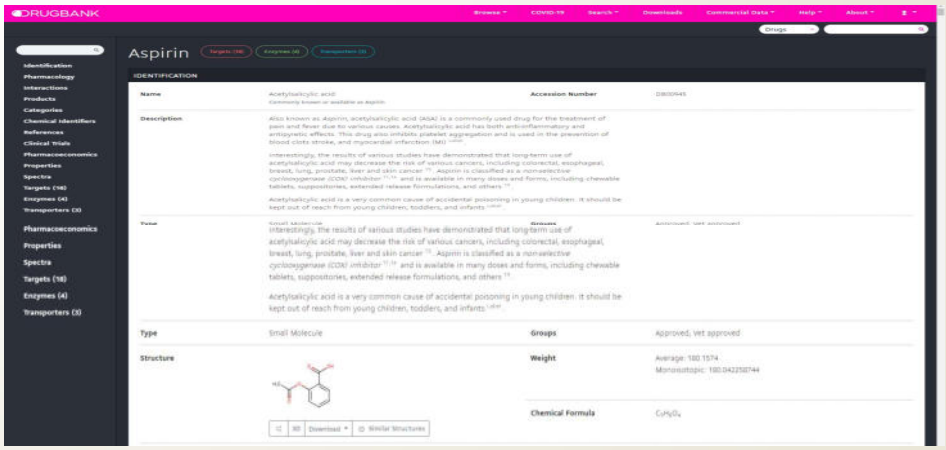
The most promiscuous drug in the history of the pharmaceutical industry?

https://vkool.com/uses-for-aspirin/

"Take two aspirins and stick your head in the sand."



A little bit of history+



https://www.drugbank.ca/drugs/DB00945

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End of the video lesson

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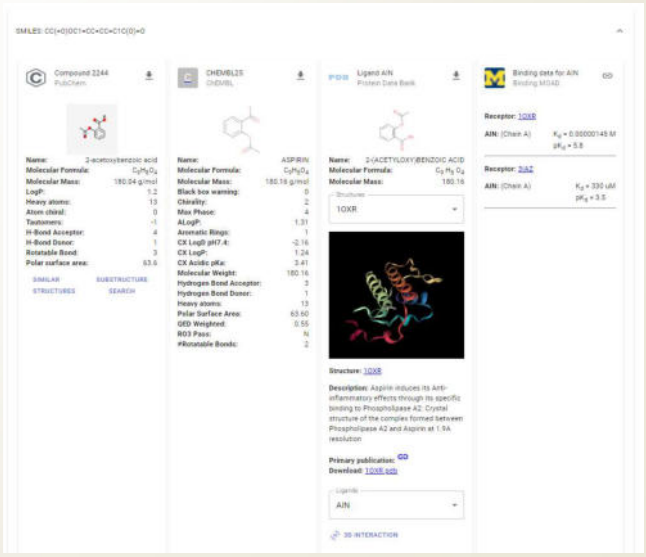
NEQUIMED/IQSC/USP/BioNCE at https://bionce.now.sh/



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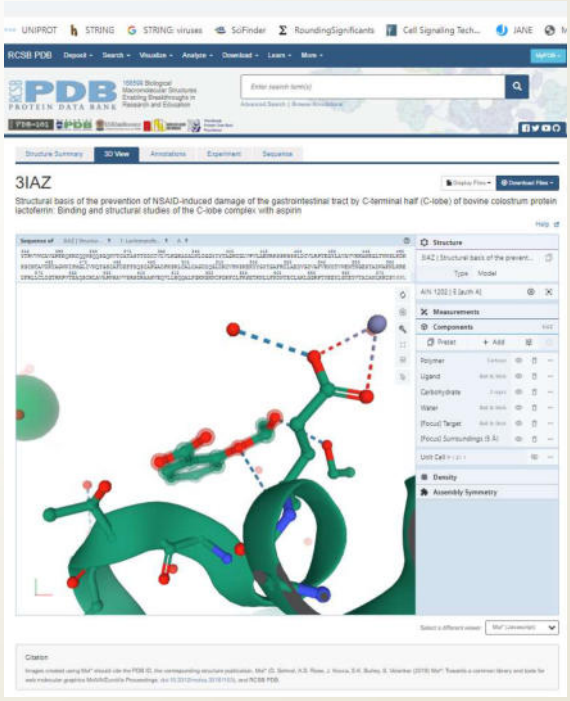

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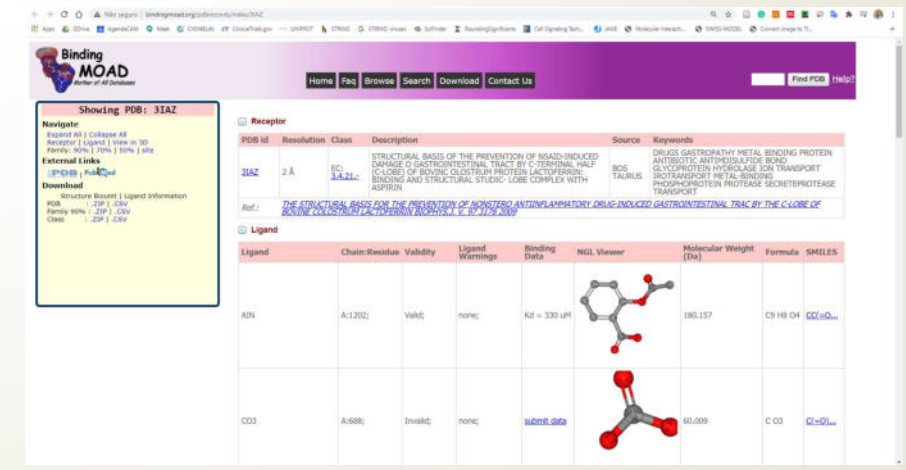

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Aspirin chemical reactivity

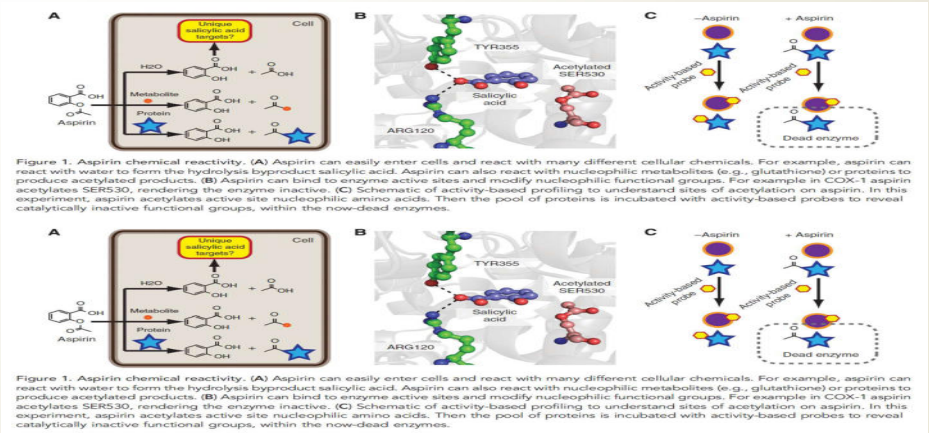

Figure 1. Aspirin chemical reactivity. (**A**) Aspirin can easily enter cells and react with many different cellular chemicals. For example, aspirin can react with water to form the hydrolysis byproduct salicylic acid. Aspirin can also react with nucleophilic metabolites (e.g., glutathione) or proteins to produce acetylated products. (**B**) Aspirin can bind to enzyme active sites and modify nucleophilic functional groups. For example in COX-1 aspirin acetylates SER530, rendering the enzyme inactive. (**C**) Schematic of activity-based profiling to understand sites of acetylation on aspirin. In this experiment, aspirin acetylates active site nucleophilic amino acids. Then the pool of proteins is incubated with activity-based probes to reveal catalytically inactive functional groups, within the now-dead enzymes.

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Bhat et al. British Journal of Cancer (2014) 111, 61–67 | doi: 10.1038/bjc.2014.271

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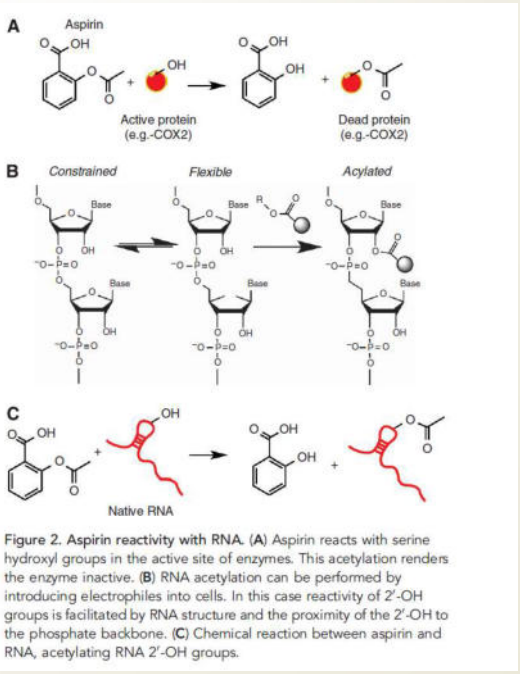

Figure 2. Aspirin reactivity with RNA. (**A**) Aspirin reacts with serine hydroxyl groups in the active site of enzymes. This acetylation renders the enzyme inactive. (**B**) RNA acetylation can be performed by introducing electrophiles into cells. In this case reactivity of 2′-OH groups is facilitated by RNA structure and the proximity of the 2′-OH to the phosphate backbone. (**C**) Chemical reaction between aspirin and RNA, acetylating RNA 2′-OH groups.

Bhat et al. British Journal of Cancer (2014) 111, 61–67 | doi: 10.1038/bjc.2014.271

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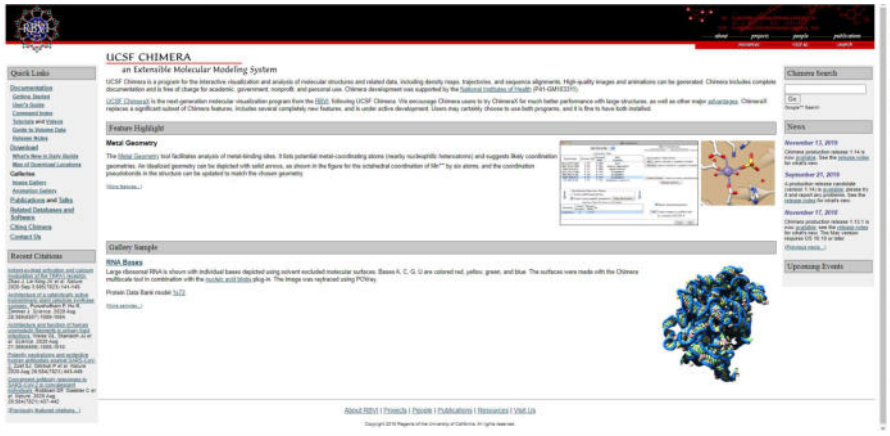

https://www.cgl.ucsf.edu/chimera/

UCSF Chimera - Getting Started: https://www.cgl.ucsf.edu/Outreach/Tutorials/GettingStarted.html

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Some important definitions

What is a ligand (binder)?

A ligand is a substance that forms a complex with a biomacromolecule to modulate a biological function.

What is a biochemical/biological target?

A target is anything within a living organism to which some other entity (like an endogenous ligand or a drug) is directed and/or binds, resulting in a change in its behavior or function. ...

Biological targets are most commonly proteins such as enzymes, ion channels, and receptors. (https://en.wikipedia.org/)

Cruzipain EC Tree
- 3 Hydrolases
  - 3.4 Acting on peptide bonds (peptidases)
    - 3.4.22 Cysteine endopeptidases
      - 3.4.22.51 cruzipain

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Targets in ChEMBL27

Number of Target Proteins **4,906**

Number of hydrolases **792**

Number of proteases **549**

~ 12,257 drug molecules (+ 2 mi assayed...)

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FDA targets

Table 1 | **Molecular targets of FDA-approved drugs**

Class of drug target	Species	Number of molecular targets
Targets of approved drugs	Pathogen and human	324
Human genome targets of approved drugs	Human	266
Targets of approved small-molecule drugs	Pathogen and human	248
Targets of approved small-molecule drugs	Human	207
Targets of approved oral small-molecule drugs	Pathogen and human	227
Targets of approved oral small-molecule drugs	Human	186
Targets of approved therapeutic antibodies	Human	15
Targets of approved biologicals	Pathogen and human	76

Overington *et al.* Nat. Rev. Drug Discov. 2006

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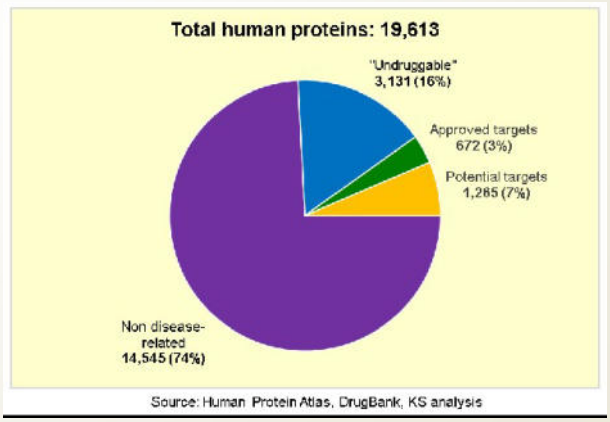
FDA targets



https://www.proteinatlas.org/

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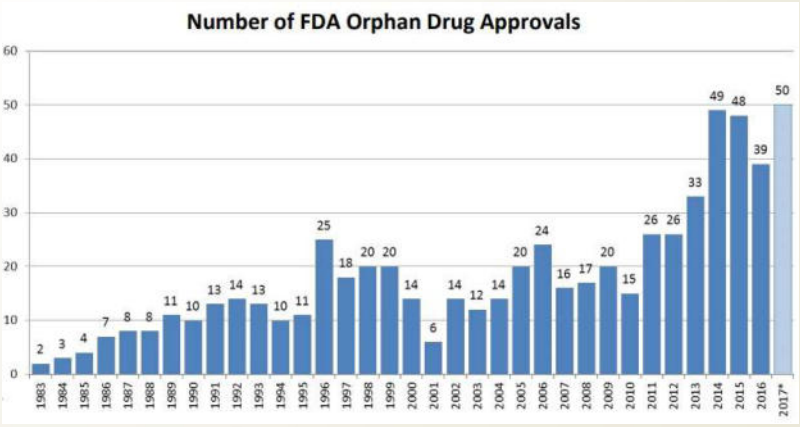
Drug Development for Very Rare Diseases



A rare disease is generally considered to be a disease that affects fewer than 200,000 people in the United States at any given time.

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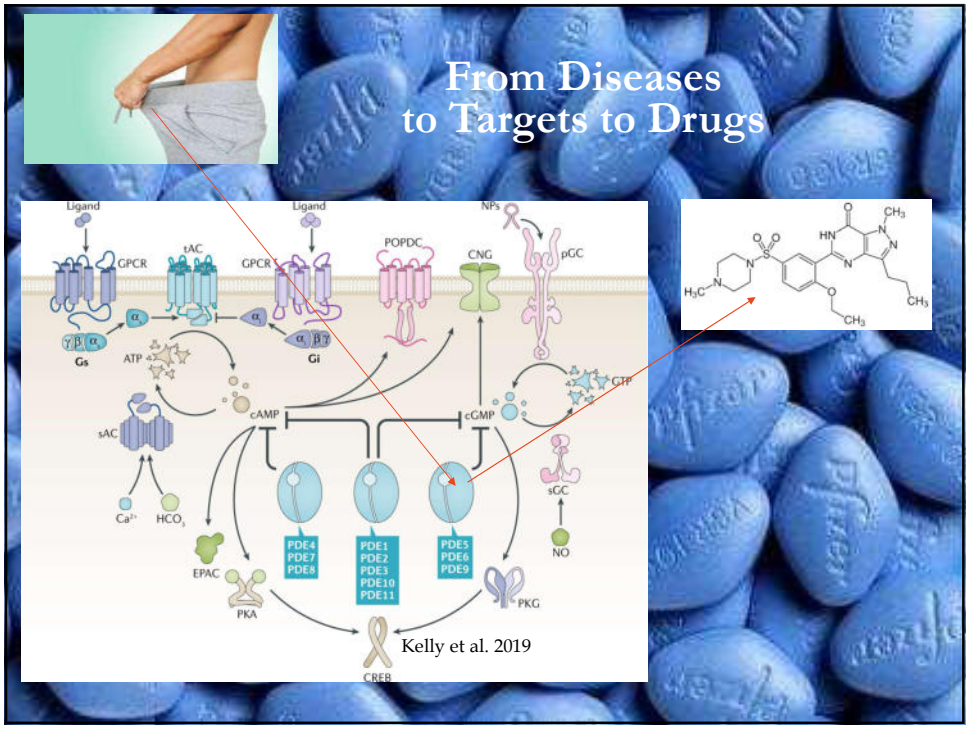
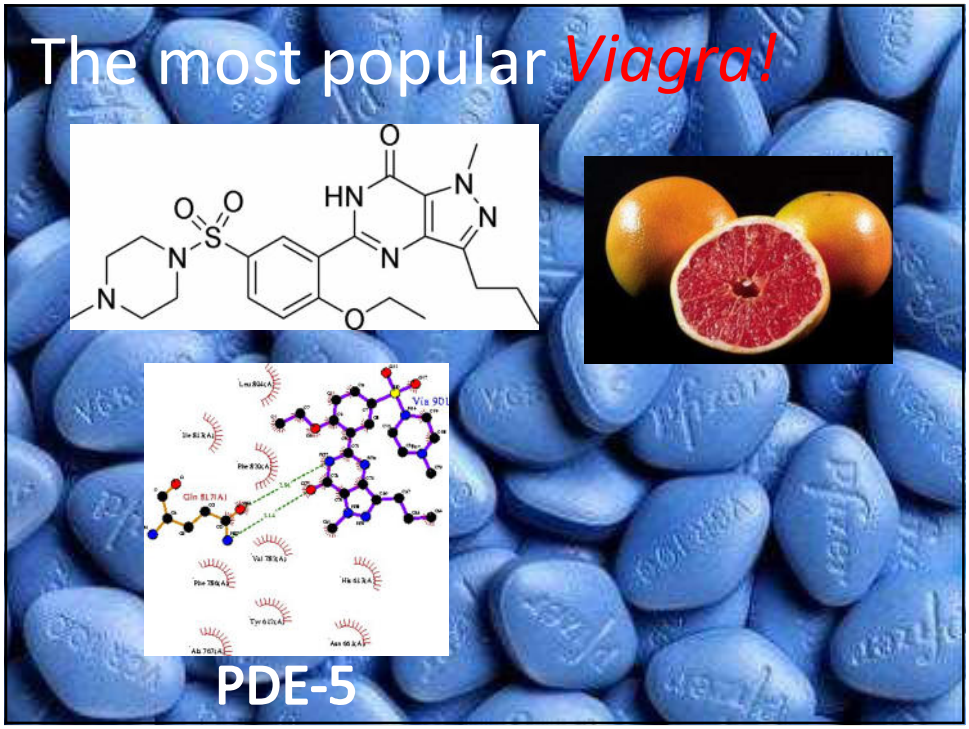
For instance, acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria

Acquired hemophilia A.
Acral lentiginous melanoma.
Acromegaly.
Acute intermittent porphyria.
Acute lymphoblastic leukemia.
Acute myeloid leukemia.
Acute promyelocytic leukemia.
Adenosine deaminase deficiency…

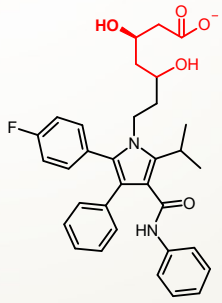
…between 5,000 and 8,000 depending on the source

Oprea et al. Nat. Rev. Drug Discov. 2020


From Diseases
to Targets to Drugs
Ligand
GPCR
tAC
Gs
ATP
cAMP
sAC
Ca2+
HCO3
EPAC
PKA
PDE4
PDE7
PDE8
PDE1
PDE2
PDE3
PDE10
PDE11
PDE5
PDE6
PDE9
cGMP
GTP
sGC
NO
PKG
CREB
Gi
POPDC
CNG
NPs
pGC
Kelly et al. 2019

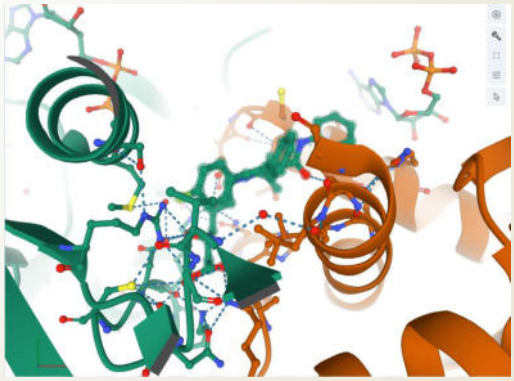

The most popular Viagra!
PDE-5

The billionaire drug!

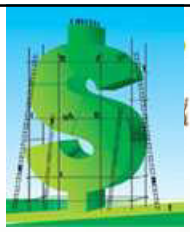


Atorvastatina, IC_{50} = 8 nM

Tipo 2



Lipitor: each C atom = US$ 142 mi!

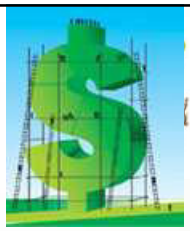


BLOCKBUSTER DRUGS

Best selling pharmaceuticals of U.S. Market [edit]

The top 5 best selling pharmaceuticals 2015-2019. Sales in billion USD.[1]

Rank	Drug	Main indication	Trade name	2015	2016	2017	2018	2019
1	adalimumab	rheumatoid arthritis	Humira	10.1	13.5	16.3	18.4	21.4
2	apixaban	anticoagulant	Eliquis	1.6	3.0	4.6	7.1	9.9
3	etanercept	rheumatoid arthritis	Enbrel	7.2	7.6	7.9	8.0	8.1
4	ustekinumab	psoriasis	Stelara	2.0	2.6	3.7	5.0	6.6
5	pembrolizumab	oncology	Keytruda	0.4	0.7	2.2	4.3	6.5



BLOCKBUSTER DRUGS

Best selling pharmaceuticals of 2017/18 [edit]

The top 16 best selling pharmaceuticals of 2017/18.[2]

Rank	Drug	Main indication	Trade name	2018 sales (million USD)	2017 sales (million USD)
1	adalimumab	rheumatoid arthritis	Humira	19 936	18427
3	apixaban	anticoagulant	Eliquis	9872	7395
4	lenalidomide	multiple myeloma	Revlimid	9685	8187
5	nivolumab	oncology	Opdivo	7570	5763
6	pembrolizumab	oncology	Keytruda	7171	3809
7	etanercept	rheumatoid arthritis	Enbrel	7126	7885
8	trastuzumab	breast cancer	Herceptin	6981	7013
9	bevacizumab	colon cancer	Avastin	6847	6686
10	rituximab	non-Hodgkin's lymphoma	Rituxan, MabThera	6750	7298

Best selling pharmaceuticals of 2017/18 [edit]

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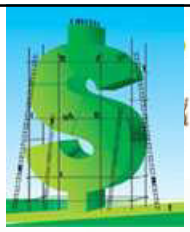
9	bevacizumab	colon cancer	Avastin	6847	6686
10	rituximab	non-Hodgkin's lymphoma	Rituxan, MabThera	6750	7298

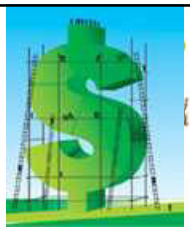


BLOCKBUSTER DRUGS

Largest selling pharmaceutical products of 2015 [edit]

Drugs with sales above $5 billion in 2015 included:[3]

Rank	Drug	Trade name	Type	Main indications	Company	Sales (USD millions/year)	Δ vs 2014
1	Adalimumab	Humira	Biologic	Rheumatoid arthritis	AbbVie Inc.	14,012	1,469
12	Rosuvastatin	Crestor	Small molecule	Cardiovascular diseases	AstraZeneca	5,017	(495)



BLOCKBUSTER DRUGS

Best selling pharmaceuticals of 2013 [edit]

For the fourth quarter of 2013, the largest selling drugs were:[4]

Rank	Brand Name(s)	Generic Name	Sales Q1 2014 Sales ($000)	Change from Q4 2013	Company(ies)	Disease/Medical Use	First Approval Date	Patent Expiration Date[5][6]
1	Abilify	Aripiprazole	1,602,329	2.23%	Generic	Psychosis; depression	Nov-2002	2014-Oct
2	Humira	Adalimumab	1,561,861	3.86%	AbbVie	Crohn's disease; Rheumatoid arthritis	Dec-2002	2016-Dec
3	Nexium	Esomeprazole	1,536,435	0.74%	Generic	Gastrointestinal disorders	Mar-2000	2014-May

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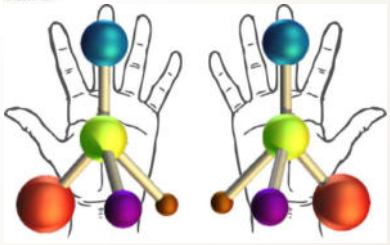
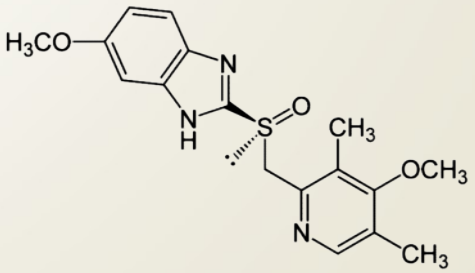


Esomeprazol: Chiral switch.



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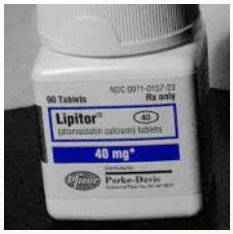
What about the famous "old"?

Worldwide drug market accounted for just over 50% (skincare, haircare, others ~ 45%)



Pfizer's cholesterol-lowering drug Lipitor amounted to **1.9 billion U.S.** dollars in **2019**

USA market 2019: US$ 521 million

The American College of Cardiology and American Heart Association, states that

"Aspirin should be used infrequently in the routine primary prevention of atherosclerotic cardiovascular diseases due to lack of evidence"

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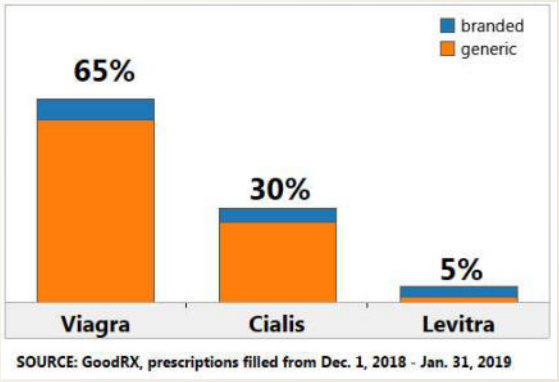
What about the famous "old"?

Worldwide drug market accounted for just over 50% (skincare, haircare, others ~ 45%)

Pfizer lost exclusive rights to the drug in December 2017

USD 1.65 billion in 2016 and is expected to reach a valuation of USD **2.95 billion by 2023**



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World Health Organization Model List of Essential Medicines

21st List 2019

2. MEDICINES FOR PAIN AND PALLIATIVE CARE

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)	
acetylsalicylic acid	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg.
ibuprofen [a]	**Oral liquid:** 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol*	**Oral liquid:** 120 mg/5 mL; 125 mg/5 mL. **Suppository:** 100 mg. **Tablet:** 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

12.6 Lipid-lowering agents	
□ simvastatin*	**Tablet:** 5 mg; 10 mg; 20 mg; 40 mg. * For use in high-risk patients.

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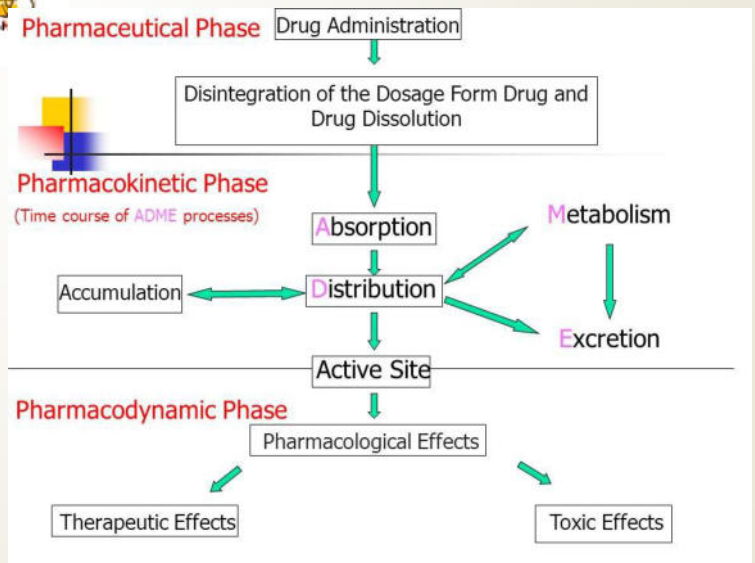
Properties of bioactive compounds

From dose to effect!



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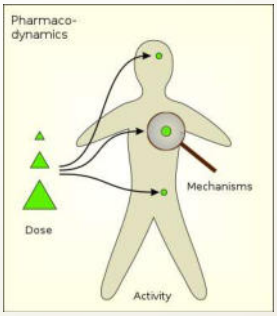
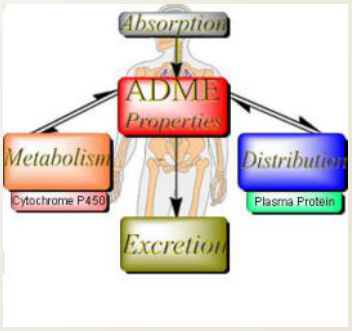
Properties of bioactive compounds

Pharmacodynamic phase: what does the drug do in the body?



Pharmacokinetic phase: what does the body do with the drug?



https://en.wikipedia.org/wiki/Pharmacodynamics

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Properties of bioactive compounds

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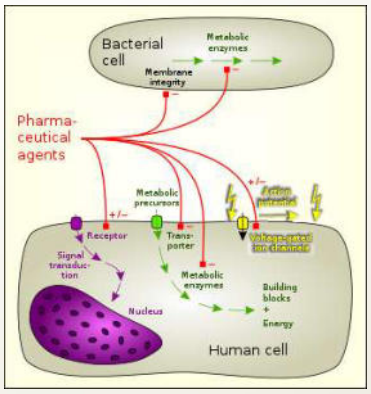

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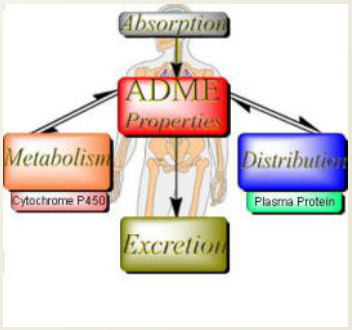

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Portinari

MUITO OBRIGADO

CARLOS.MONTANARI@USP.BR