KATEDRA FYZIKÁLNÍ CHEMIE
UNIVERZITY PALACKÉHO V OLOMOUCI

INSTITUTE OF MOLECULAR AND TRANSLATIONAL MEDICINE

elixir CZECH REPUBLIC

8th Advanced *in silico* Drug Design

KFC/ADD

Drug design intro

Karel Berka

UP Olomouc, 27.1.-31.1. 2025

ÚOCHB AV ČR IOCB PRAGUE

RECEPTOR.AI

Deep MedChem

Bar-Ilan University

Carnegie Mellon University

Motto

A pharmaceutical company utilizing computational drug design is like an organic chemist utilizing an NMR. It won't solve all of your problems, but you are much better off with it than without it.

DAVID C. YOUNG

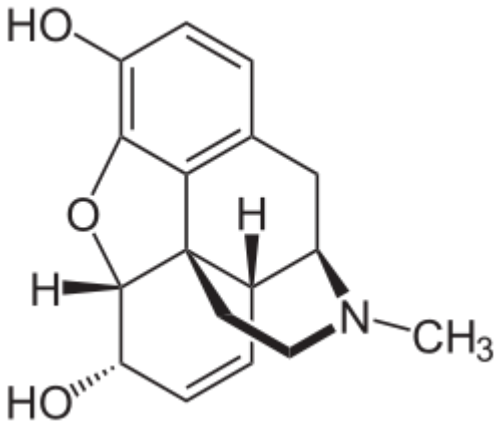
Outline

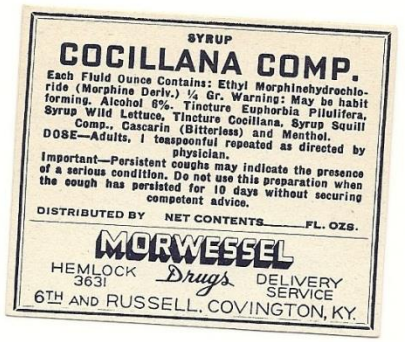
- Sources of drugs
  - Recently approved drugs – what are they
- Drug design problem
  - Money is not the only problem
- Drug targets
- Differences between drug design strategies for
  - Small molecules
  - Biologicals

SOURCES OF DRUGS

History of Drug Design

1806





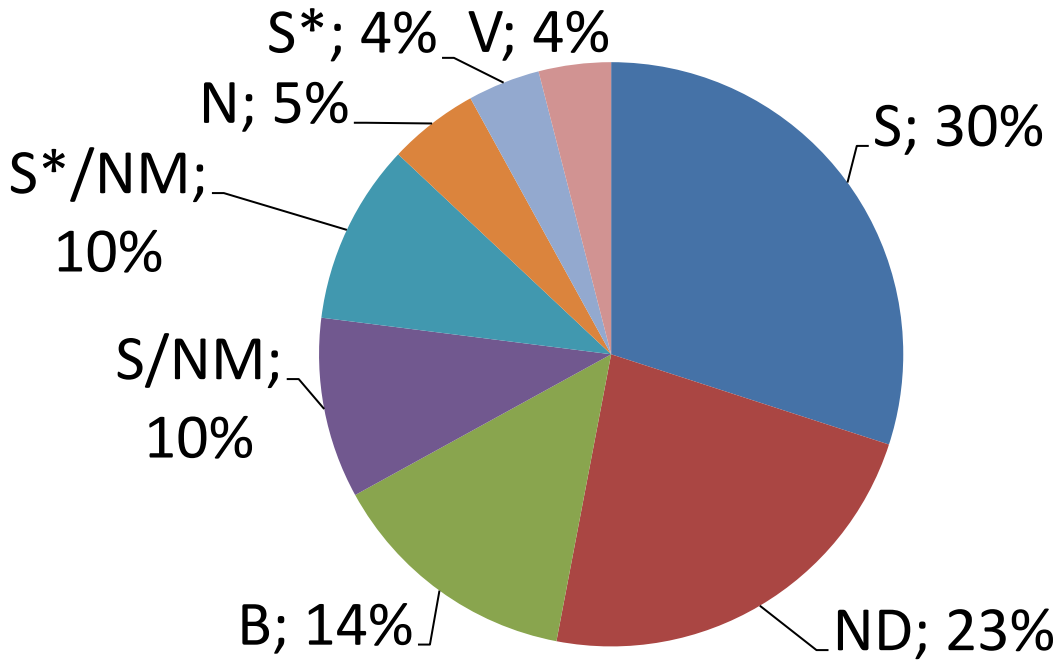
A. Cherkasov

History of Drug Design Testing

Time	*New Sources*	*Testing Subjects*
- ancient & middle ages	plants, poisons (Paracelsus) minerals ... natural sources	humans
- 1806	morphine (first extracted)	humans
- 1850	chemicals (chinin)	humans (prisoners)
- 1890	synthetics, pigments	animals
- 1920		animals, isolated organs
- 1970-1980		enzymes, cell lines (HeLa)
- 1990	High throughput libraries	recombinant proteins
- 2000	chemical libraries	chips, virtual screening, ADMET testing

Sources of Drugs

All drugs by source, registered 01/1981 - 06/2006, FDA, n = 1184



B – biologicals,
N – nature compounds,
ND – nature compounds derivatized,
S – synthetic compounds,

S/NM – synthetics mimicking natural compounds,
S* - synthetic, with pharmacophore from natural compounds
V - vaccines

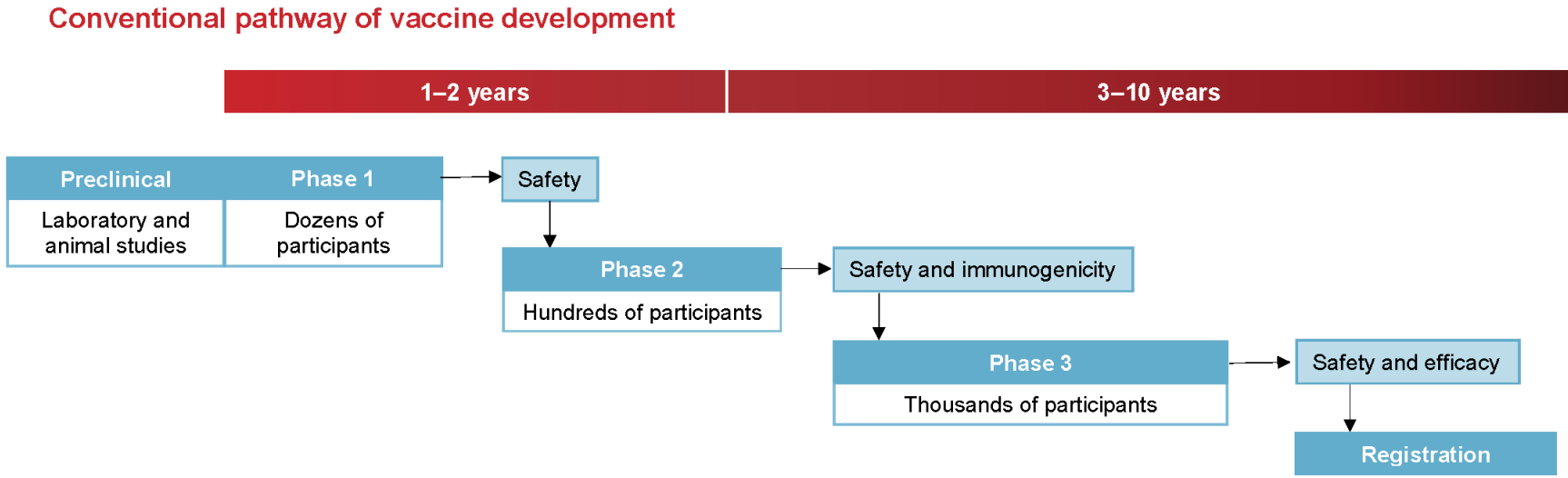
D. J. Newman and G. M. Cragg,
J. Nat. Prod. 70, 461-477 (2007)

Vocabulary

- Target
  - Biomolecule interacting with the drug
- Lead
  - Base molecular structural motif of developed drug
- Hit
  - Compound with positive hit in initial screening
- Candidate compounds
  - Selected compounds used for next testing
- Efficacy
  - Qualitative property – (drug heals or not)
- Activity
  - Quantitative property – dosage needed for effect to happen (pM – great, nM – excellent, μM – sufficient, mM – well…)
- Bioavailability
  - Availability of compound in site of target in necessary concentration

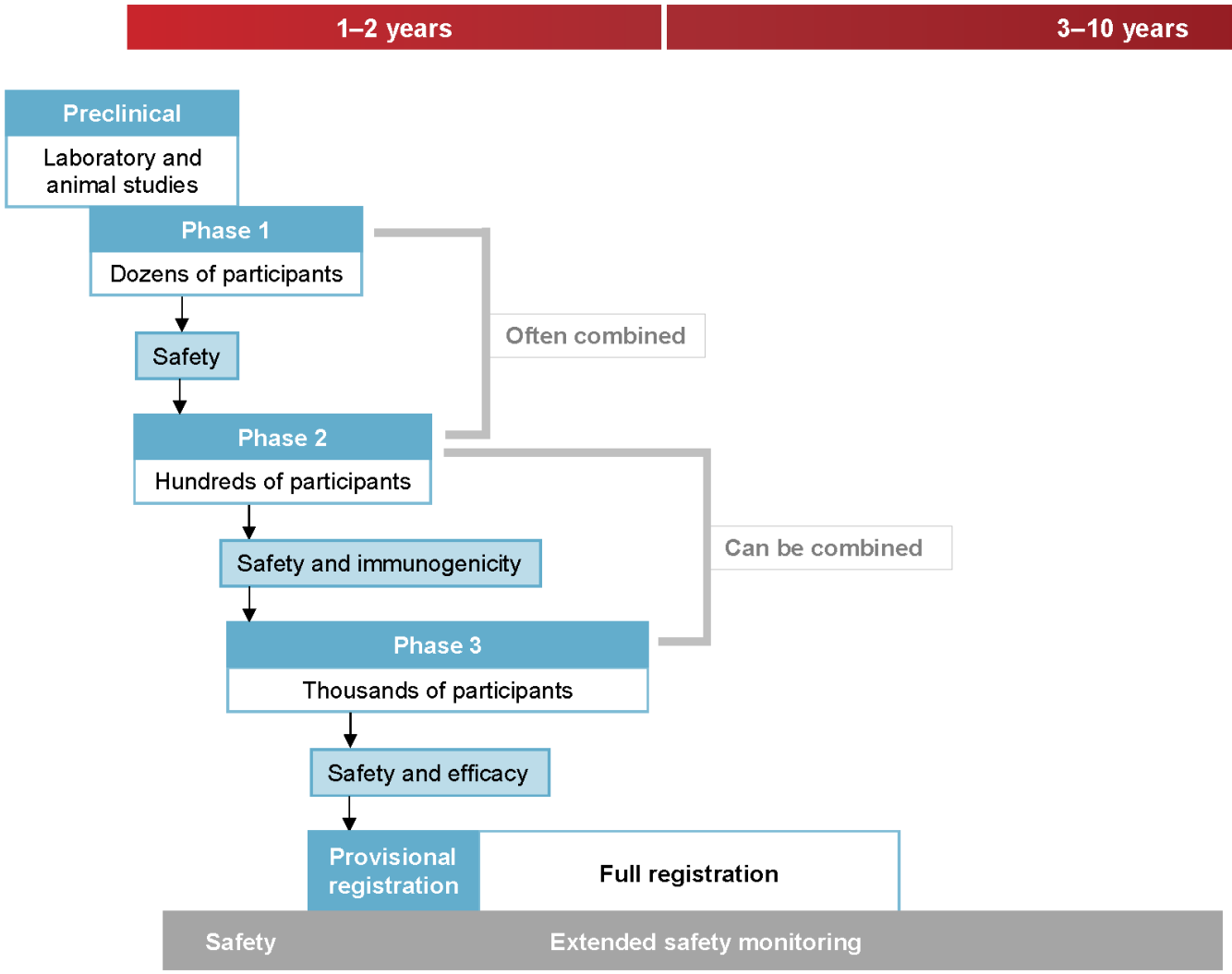
Drug Approval Timeline

- Target Identification
  - Biology (GWAS)
- Finding actives
  - (Q)SAR
  - Pharmacophore
  - De novo design
- MoA evaluation, optimization
  - Molecular docking
  - Molecular dynamics



Accelerated Drug Approval Timeline

COVID-19 vaccine development at pandemic speed



- First in class
  - New targets
- Orphan
  - Rare diseases
- Breakthrough
  - Serious or life-threatening diseases
- Accelerated
  - Better efficacy (no need to prolong testing)
- Conditional Market Approval

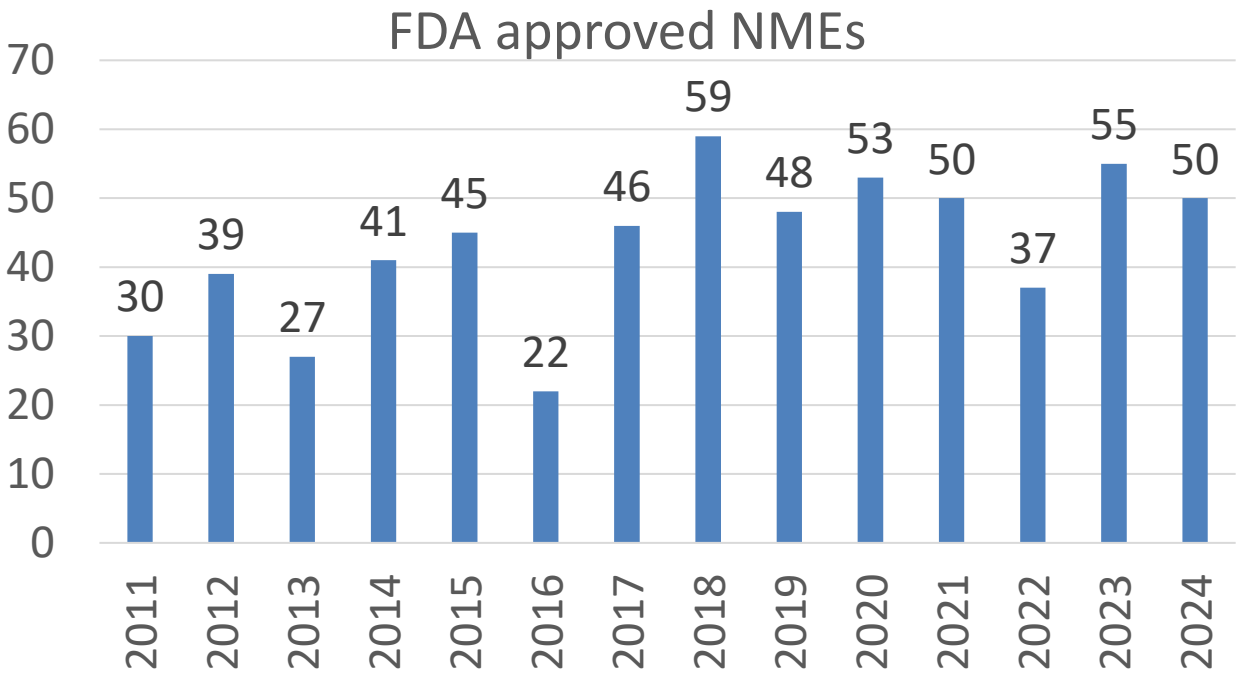
New Molecular Entities (NMEs)

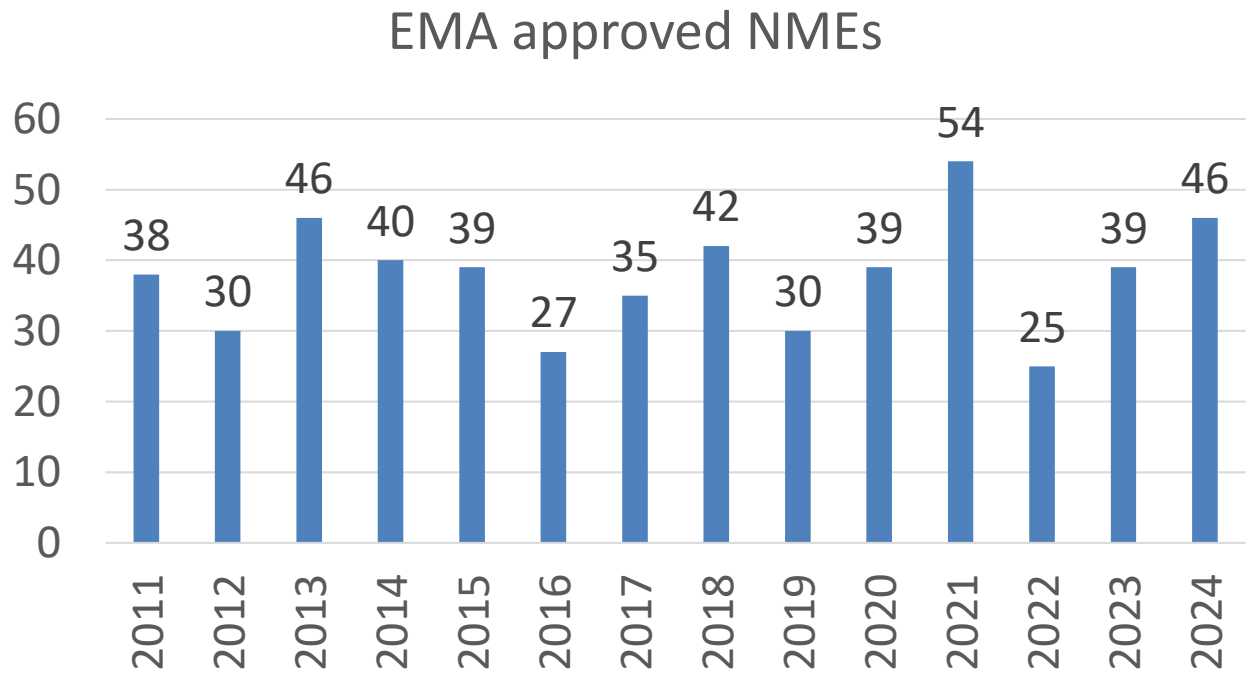
FDA's Center for Drug Evaluation and Research (CDER):

- First in class – average 40%
- Orphan diseases – around 50%
- Expedited – around 50% (used to be >70%)

EMA:

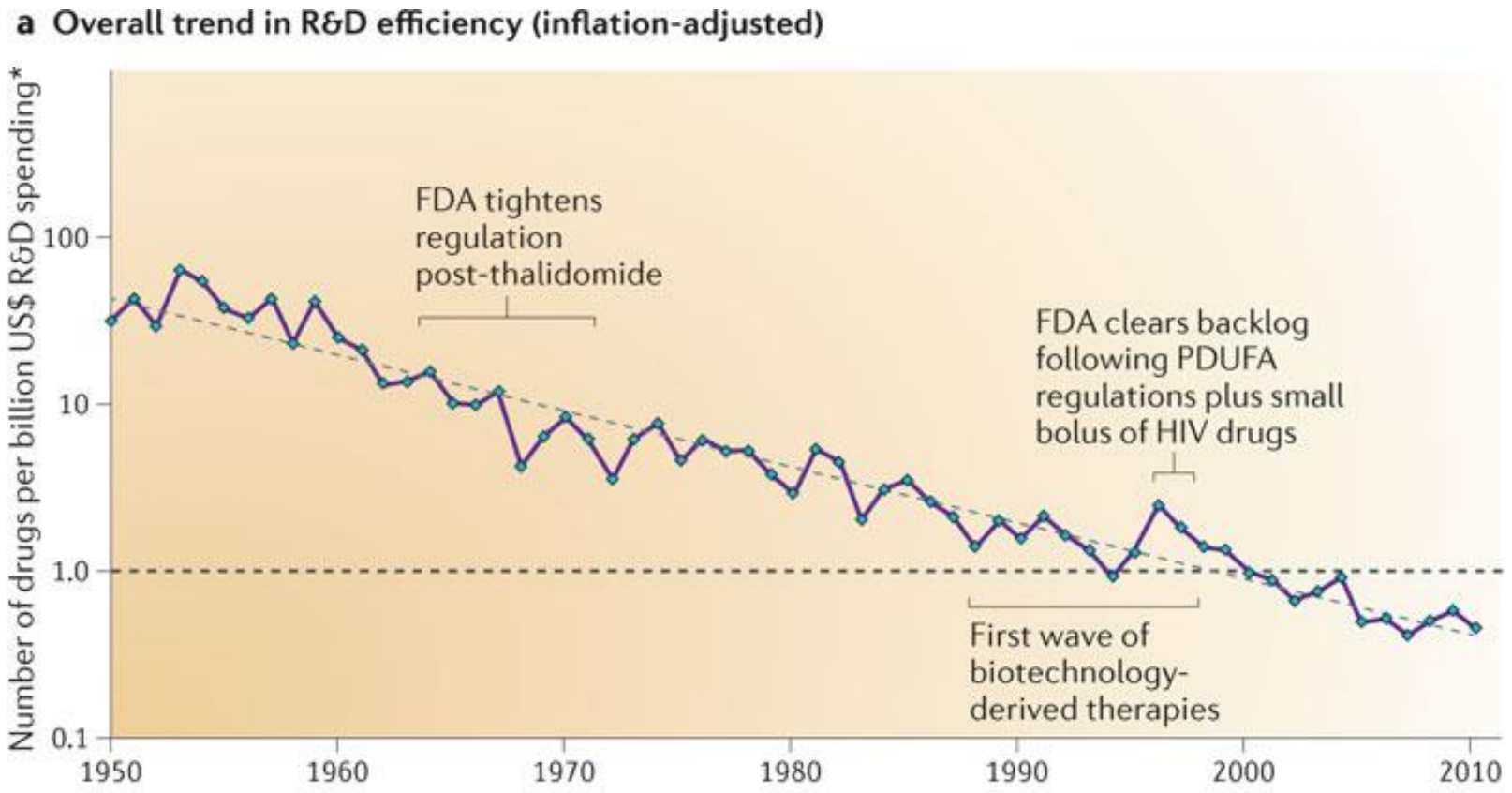
- Orphan diseases – 30% to 50% per year
- Expedited (accelerated and conditional market authorization) – fluctuates around 30%





- https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/
- https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/medicine-evaluation-figures

Eroom's Law

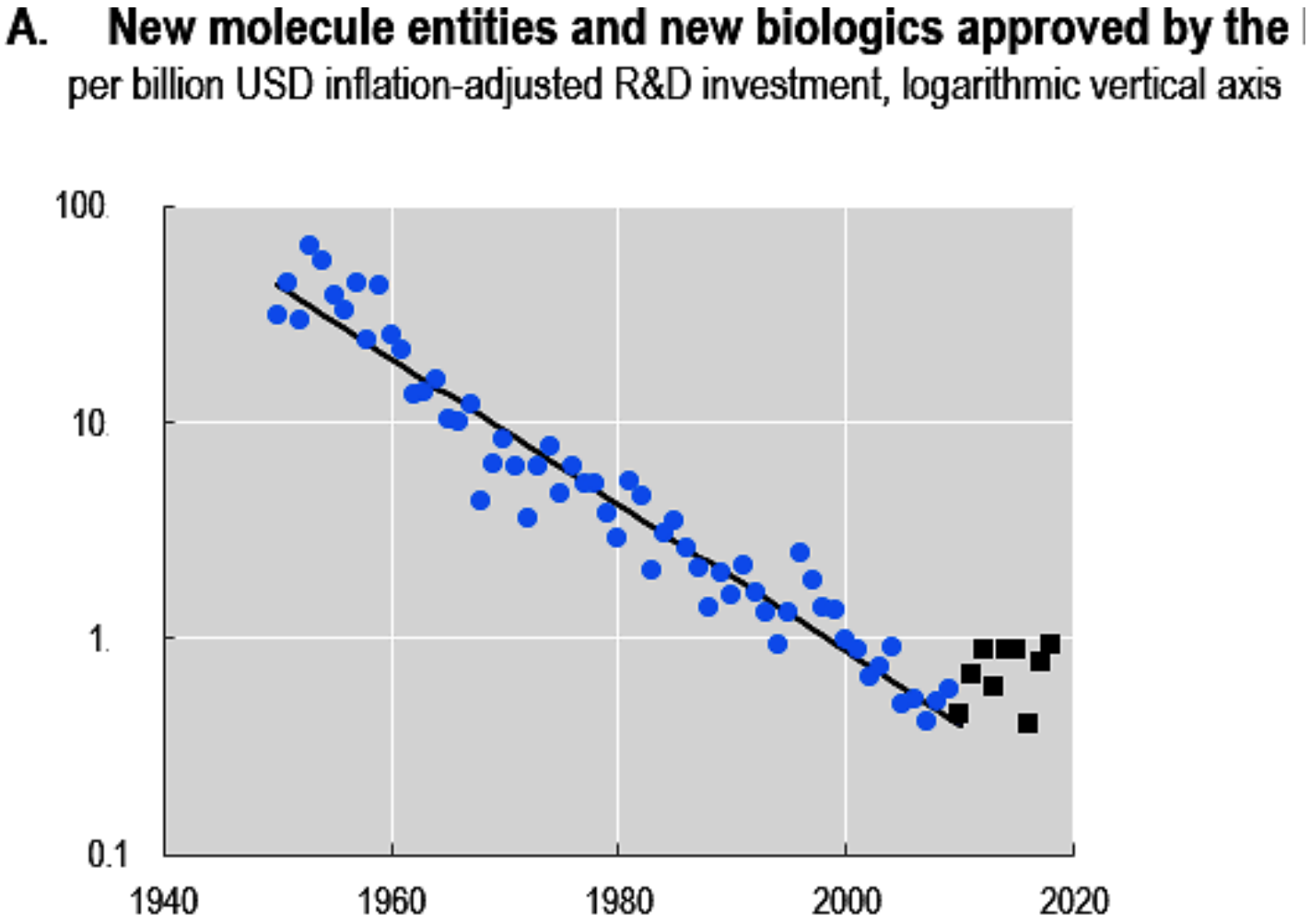


Decline in pharmaceutical R&D efficiency – halved per 9 years

- 'better than the Beatles' problém
- 'cautious regulator' problem
- 'throw money at it' tendency
- 'basic research–brute force' bias.

Scannell JW, Blanckley A, Boldon H, Warrington B: Nature Reviews Drug Discovery 11, 191-200 (2012) doi:10.1038/nrd3681

End of Eroom's law?

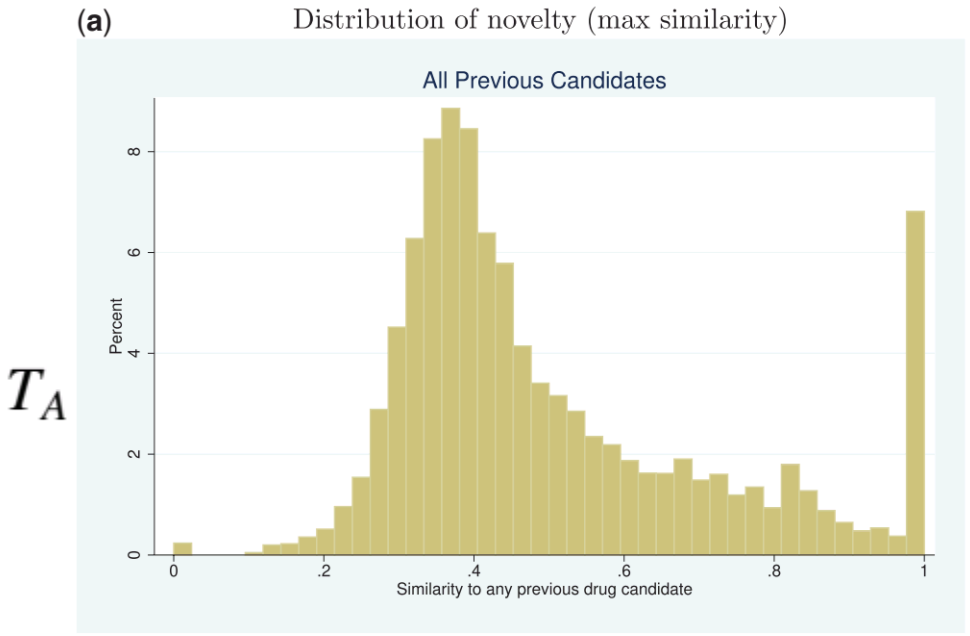


- Innovative efficiency lowered during times
- But Errom's law seems to stop recently
- Production of new chemical is easier
- Production of new valid screening models is harder

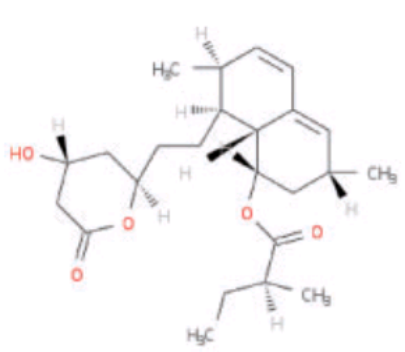
OECD (2023), *Artificial Intelligence in Science: Challenges, Opportunities and the Future of Research*, OECD Publishing, Paris, https://doi.org/10.1787/a8d820bd-en.

Missing Novelty in Drug Development

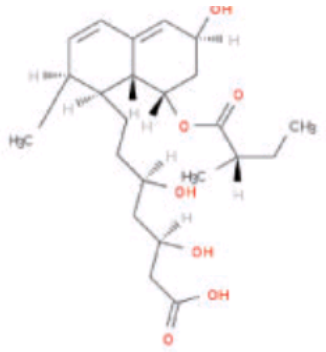
- Evidence that risk aversion leads to underinvest in innovation
- Chemical similarity -> novel drug candidates are less likely to obtain FDA approval (but more valuable if approved)



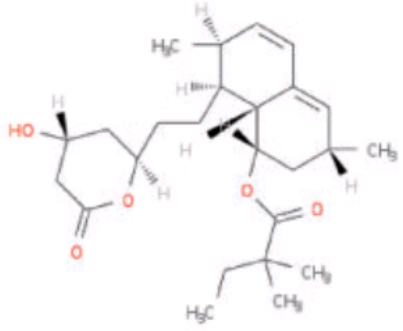
T_A



Mevacor
(Similarity Score=0.25)
Lovostatin Sep 1987



Pravachol
(Similarity Score =0.61)
Pravastatin Oct 1991

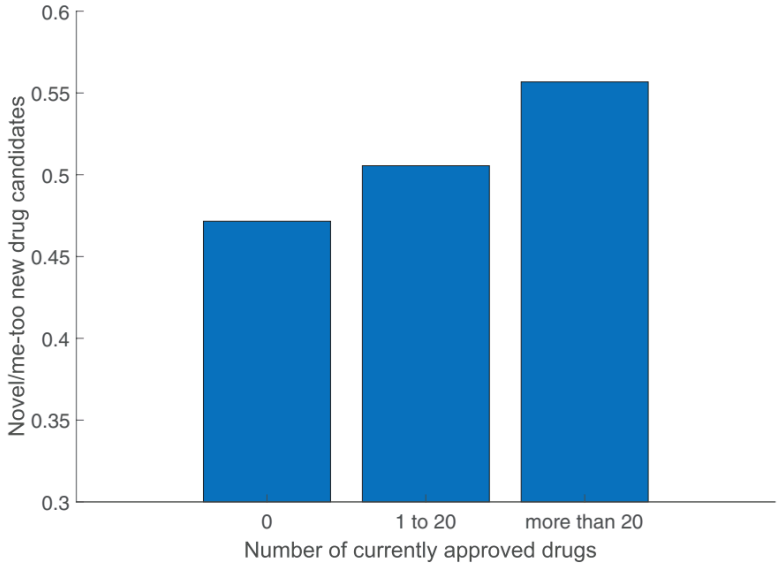


Zocor
(Similarity Score =0.82)
Simvastatin Dec 1991

Krieger J, Li D, Papanikolaou – Missing Novelty in Drug Development. ***The Review of Financial Studies*** 35 (2022) 636-679

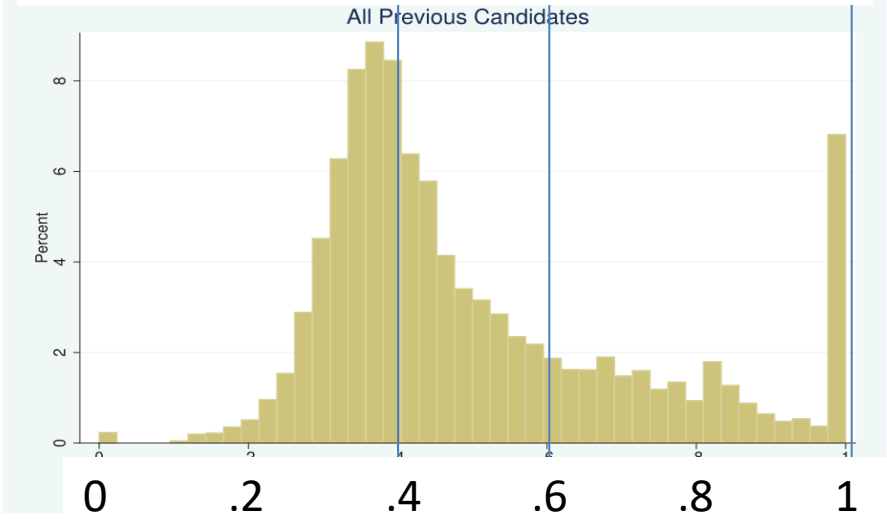
Missing novelty II

- Larger firms (>20 drugs) are more likely to engage in novel drug development
- Highly uncertain investment + small companies problem with raising capital -> but it pays of

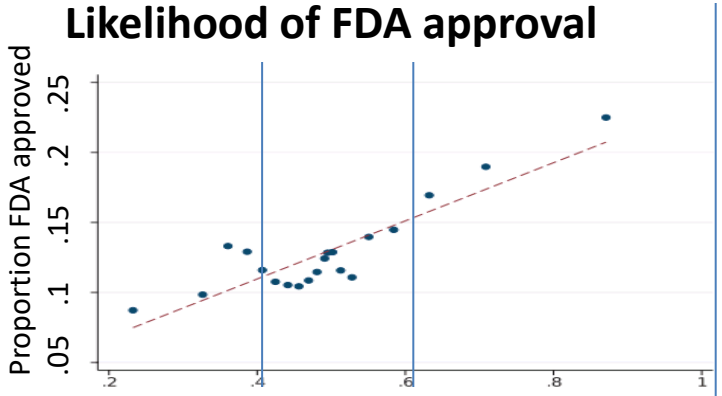


Krieger J, Li D, Papanikolaou – Missing Novelty in Drug Development. ***The Review of Financial Studies*** 35 (2022) 636-679

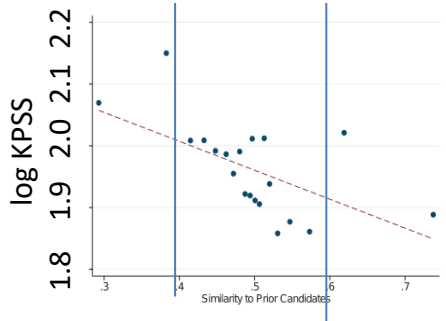
Distribution of novelty by max similarity



Likelihood of FDA approval



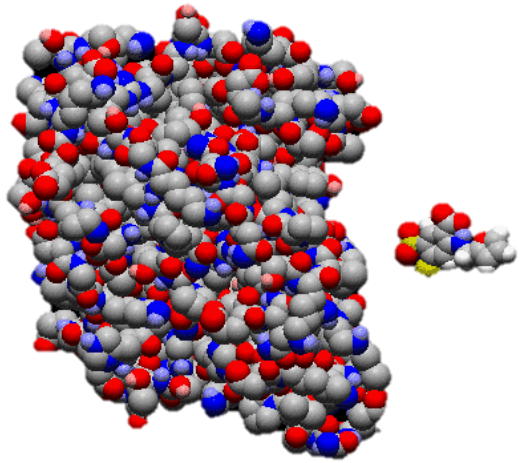
Patent value (log KPSS)



DRUG DESIGN PROBLEM

Most Typical Mechanism of Drug Action

- Lock and Key Analogon, 1894



"Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glykosid zueinander passen müssen, wie Schloss und Schlüssel, um eine chemische Wirkung aufeinander ausüben zu können."

Emil Fischer, *Nobel Laureate 1902*

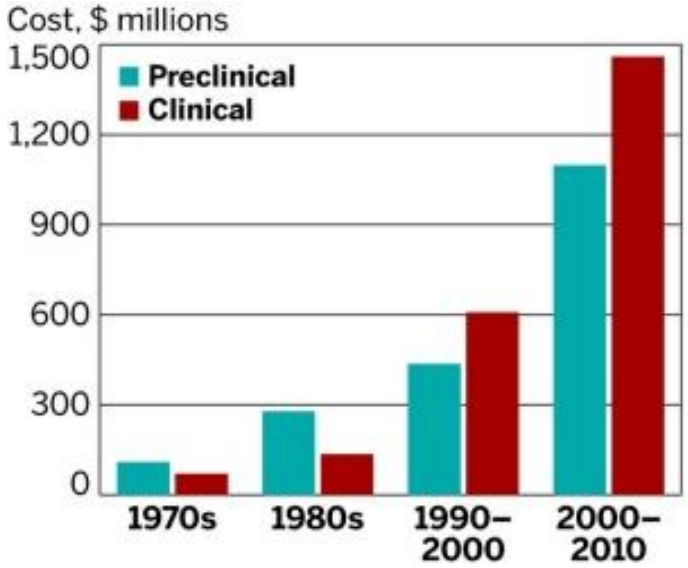
Drug Design

Identification of new drug:

- Expensive problem
  - Expenditures per 1 drug development - 2 600 000 000 USD[1]

  + expenses for production, patents, distribution…

  ⇒ New drugs are expensive >1 000 USD/dose of drug[2]
- Hard problem
  - Identification of target-drug pair is not simple
  - ADMET
  - Side-effects



1 - Tufts Center for the Study of Drug Development, 2014

2 – SÚKL, 3Q 2011, average price tag for most expensive drug category in CZ (over 10kCZK)

Possible Obstacles

- Nonexistent testing model
  - Example: HIV is human disease!
  - Ethically not possible to test directly on people (cf. OS)
- Rare disease – orphan disease
  - Future sales would not pay for regular development
  - **Orphan drug** have lower requirements for registration and individual incentives
- Too low activity of found drug
  - Too toxic, bad bioavailability
- Active compounds are already patented
  - Me2drugs
  - *Product has to be just as good as the one from competition and patentable under our name*

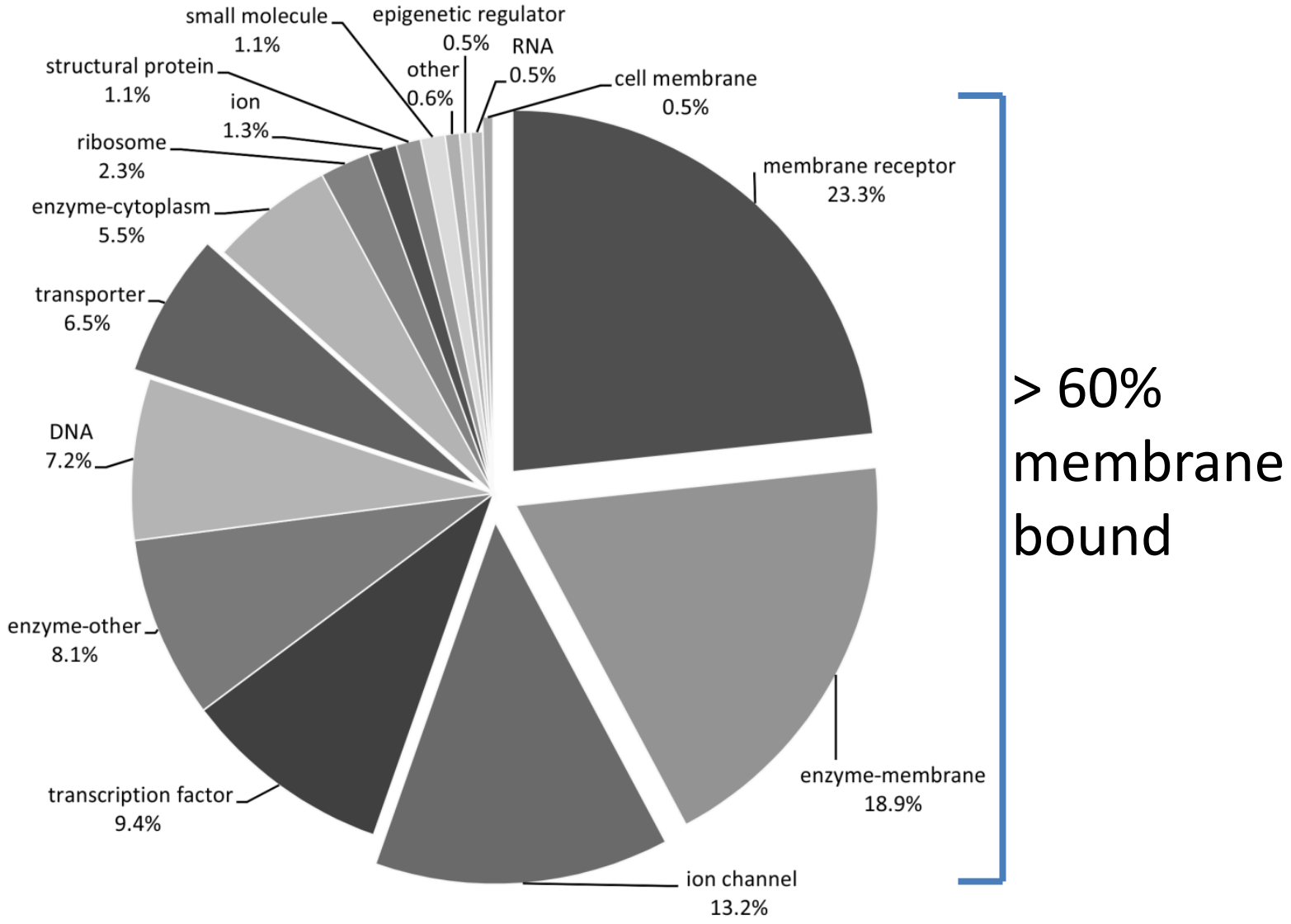
Illness Type

- Enzyme overproduction - some cancer types
  - **Inhibition** (e.g. kinase inhibitors)
- High response of receptor – COX in pain
  - **Antagonists** (e.g. pain relievers)
- Low response of receptor – neurological GPCRs
  - **Agonists** (e.g. serotonin receptor agonists)
- Regulation peptide – CGRP peptide in migraine
  - Antibodies (e.g. **biologicals**)
- RNA – RNAi, RNA aptamers…
  - Emerging field

Small ligand with protein

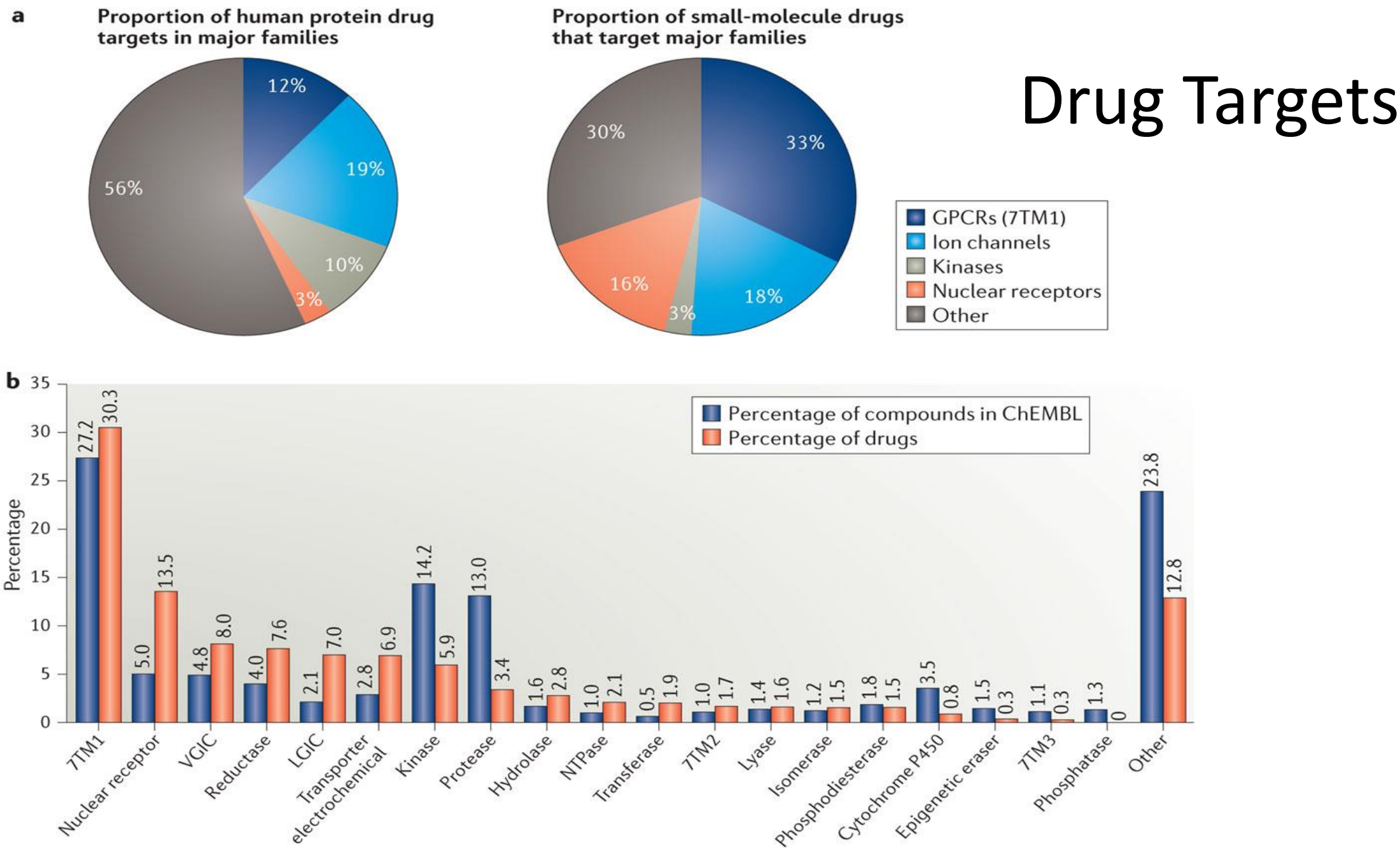
DRUG TARGETS

Drug Target by target biomolecule



Di Meo F, Fabre G, Berka K, Ossman T, Chantemargue B, Paloncýová M, Marquet P, Otyepka M, Trouillas P: In Silico Pharmacology: Drug Membrane Partitioning and Crossing. *Pharmacol. Res., 111, 471–486, 2016*.

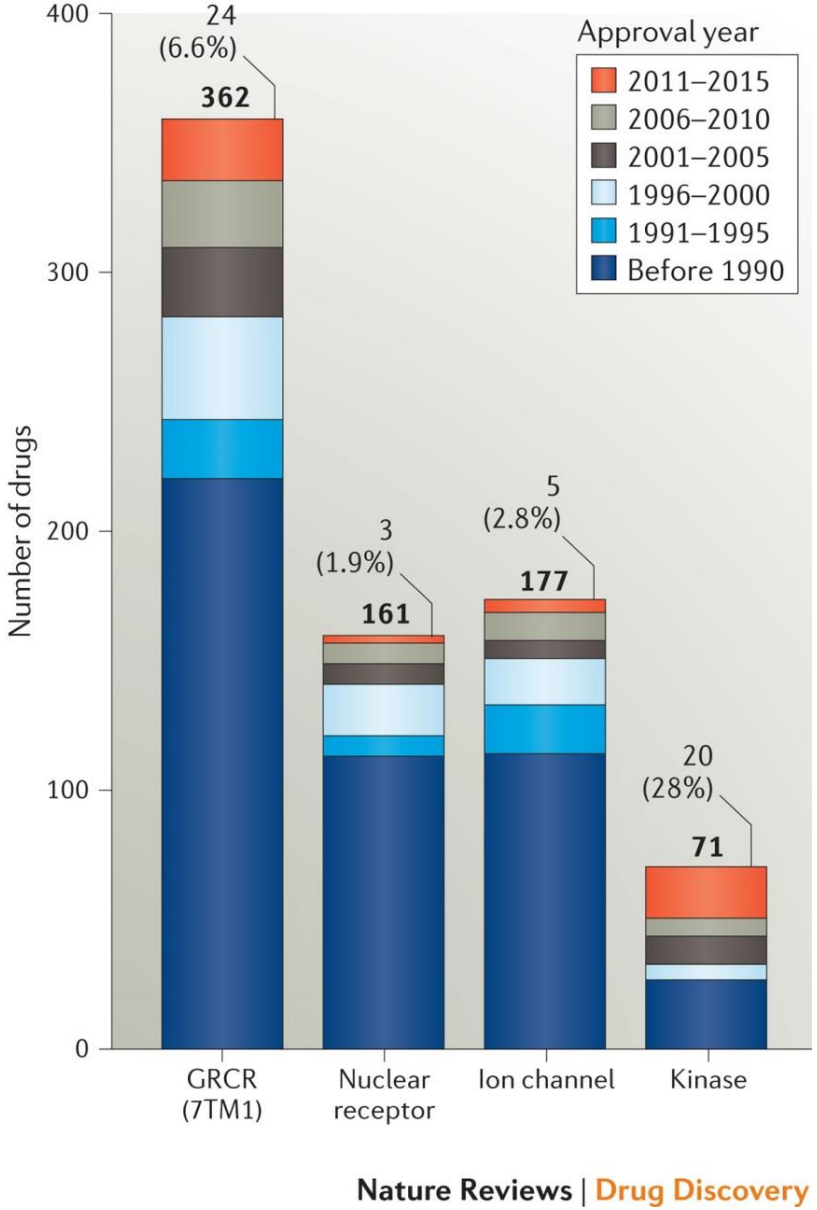
Drug Targets



R. Santos, …, JP Overington: A comprehensive map of molecular drug targets. Nature Rev. Drug Discovery, 16, 19-34, 2017. doi: 10.1038/nrd.2016.230

Nature Reviews | Drug Discovery

Innovation Patterns in Privileged Classes



FURTHER INFORMATION

canSAR: https://cansar.icr.ac.uk

ChEMBL: https://www.ebi.ac.uk/chembl

Companion diagnostic test: http://www.fda.gov/companiondiagnostics

Dronedarone prescribing information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022425s021lbl.pdf

DrugCentral: http://drugcentral.org

Illuminating the Druggable Genome: https://pharos.nih.gov/idg/index

IUPHAR/BPS Guide to Pharmacology: http://www.guidetopharmacology.org/GRAC

NCATS Pharmaceutical Collection: https://tripod.nih.gov/npc/

ATC/DDD Index: http://www.whocc.no/atc_ddd_index

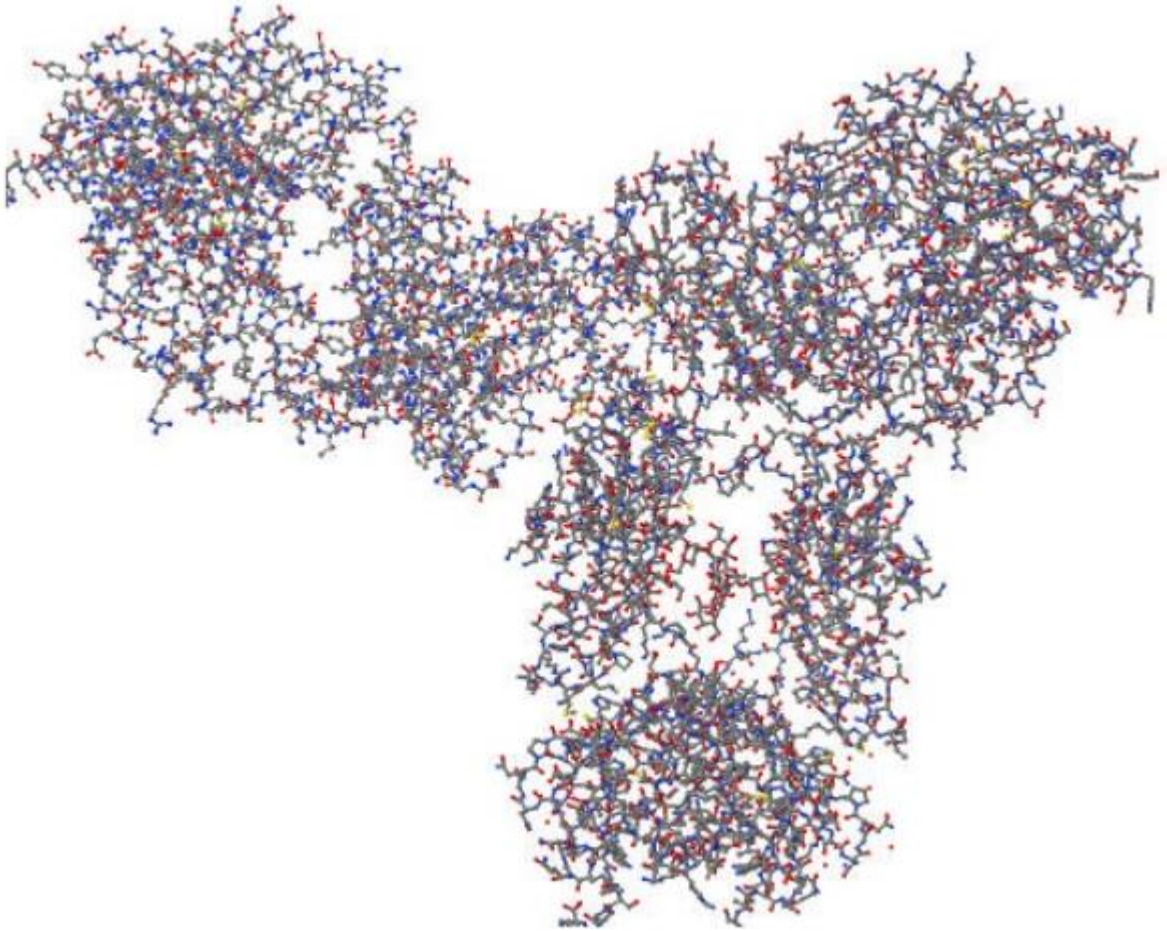
WHO INN Drug lists: http://www.who.int/medicines/publications/druginformation/innlists/en

R. Santos, …, JP Overington: A comprehensive map of molecular drug targets. Nature Rev. Drug Discovery, 16, 19-34, 2017. doi: 10.1038/nrd.2016.230

SMALL MOLECULES VZ BIOLOGICALS

Size and Complexity of Biologicals in Comparison with Small Molecules

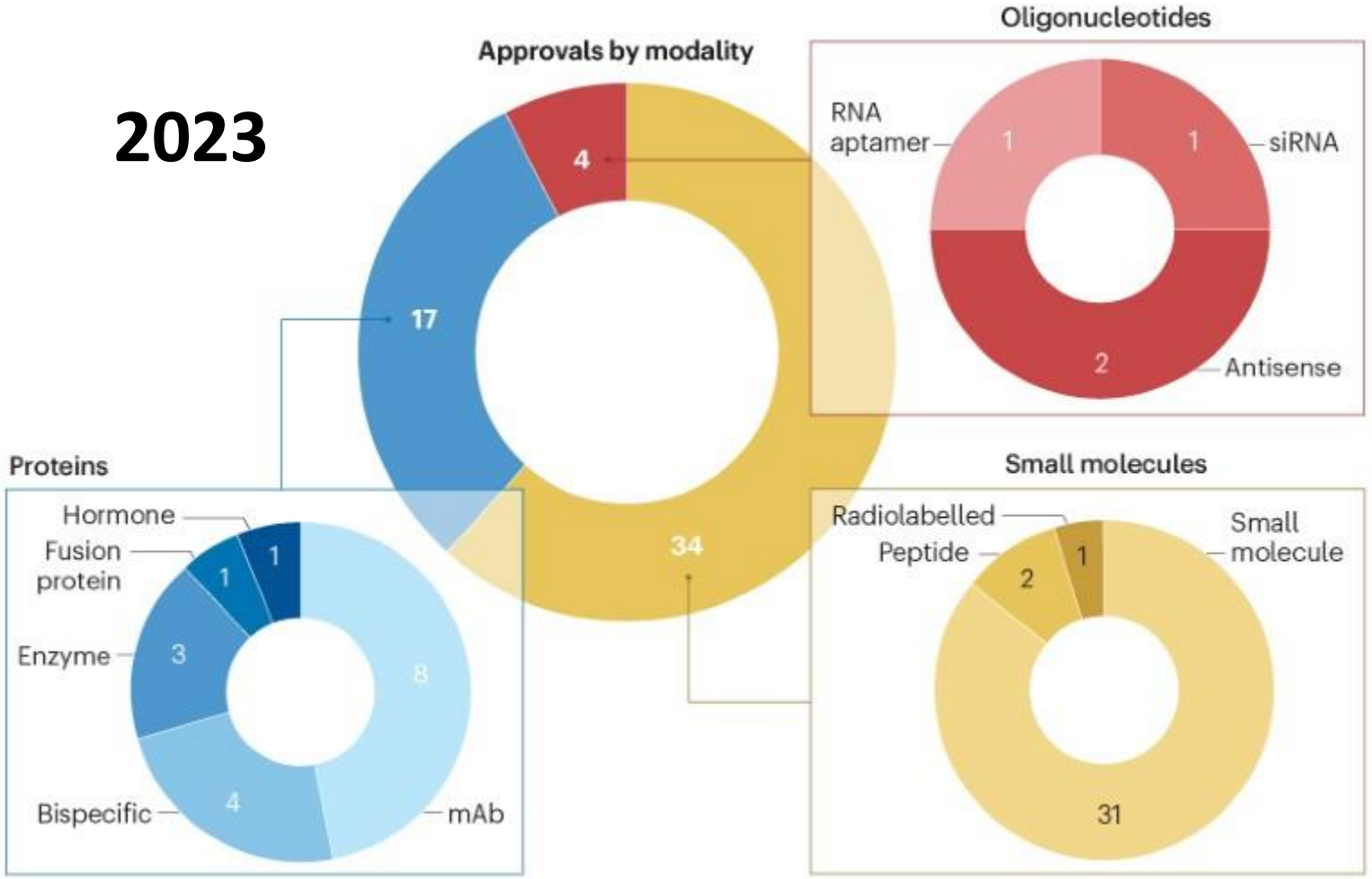
Aspirin 180 Da



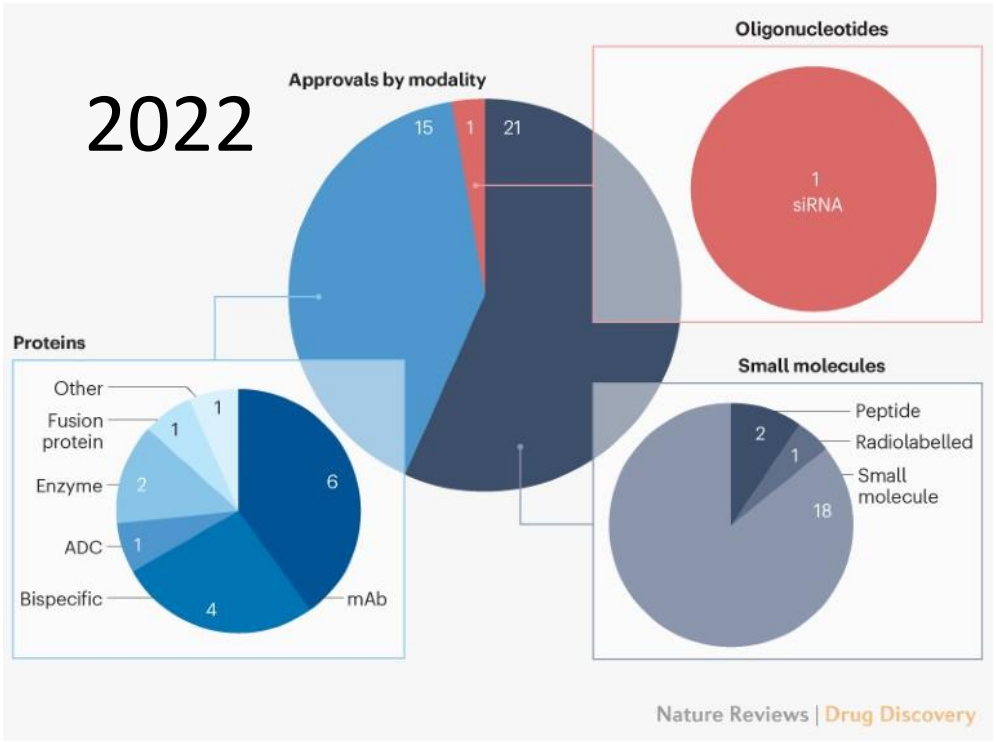
Monoclonal Antibody ~150,000 Da

FDA CDER approvals by modality

2023



2022



Source: *Nature Reviews Drug Discovery*, https://www.nature.com/articles/d41573-024-00001-x

TAKE HOME MESSAGE

Take Home Message

- Drugs comes from various sources
- Drug design is hard and expensive problem
  - Mainly due to the biology and clinical trials costs!
- Most typical drug targets are:
  - GPCRs, ion channels, nuclear receptors, kinases
  - But - long tail of other drug targets – **Orphans**!
- Biologicals are more complex to produce than small molecules
- There is **no gold path** for drug design – the methods have to be tied up to the current project

UNUSED SLIDES

What are Biologicals?

Definition of Biological Product

- US:
  - The term “**biological product**” or biologics means a "any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man“
- EU:
  - 'biological medicinal products' as "a protein or nucleic acid–based pharmaceutical substance used for therapeutic or *in vivo* diagnostic purposes, which is produced by means other than direct extraction from a native (nonengineered) biological source"

Ronald A Rader **(Re)defining biopharmaceutical** *Nature Biotechnology* **26**, 743 - 751 (2008) doi:10.1038/nbt0708-743

34

WHERE TO FIND THEM
CHEMICAL DATABASES PRIMER

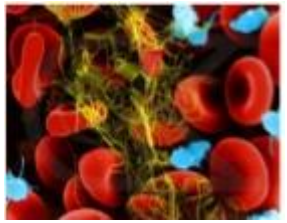
Drug design related databases

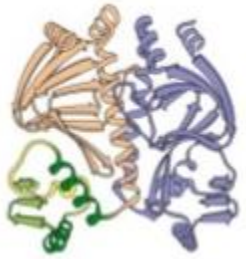
- drugbank.ca – comprehensive drug&target info
- ebi.ac.uk/chembl - bioactive molecules
- pubchem.ncbi.nlm.nih.gov – free chemical info
- zinc.docking.org – com.available compounds for VS
- ebi.ac.uk/pdbe or www.rcsb.org – macromolecular structures

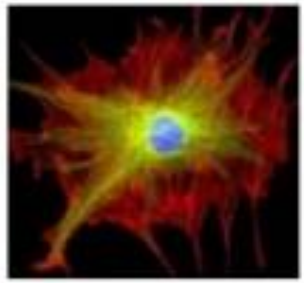
BIOLOGICALS

Types of Biological Products

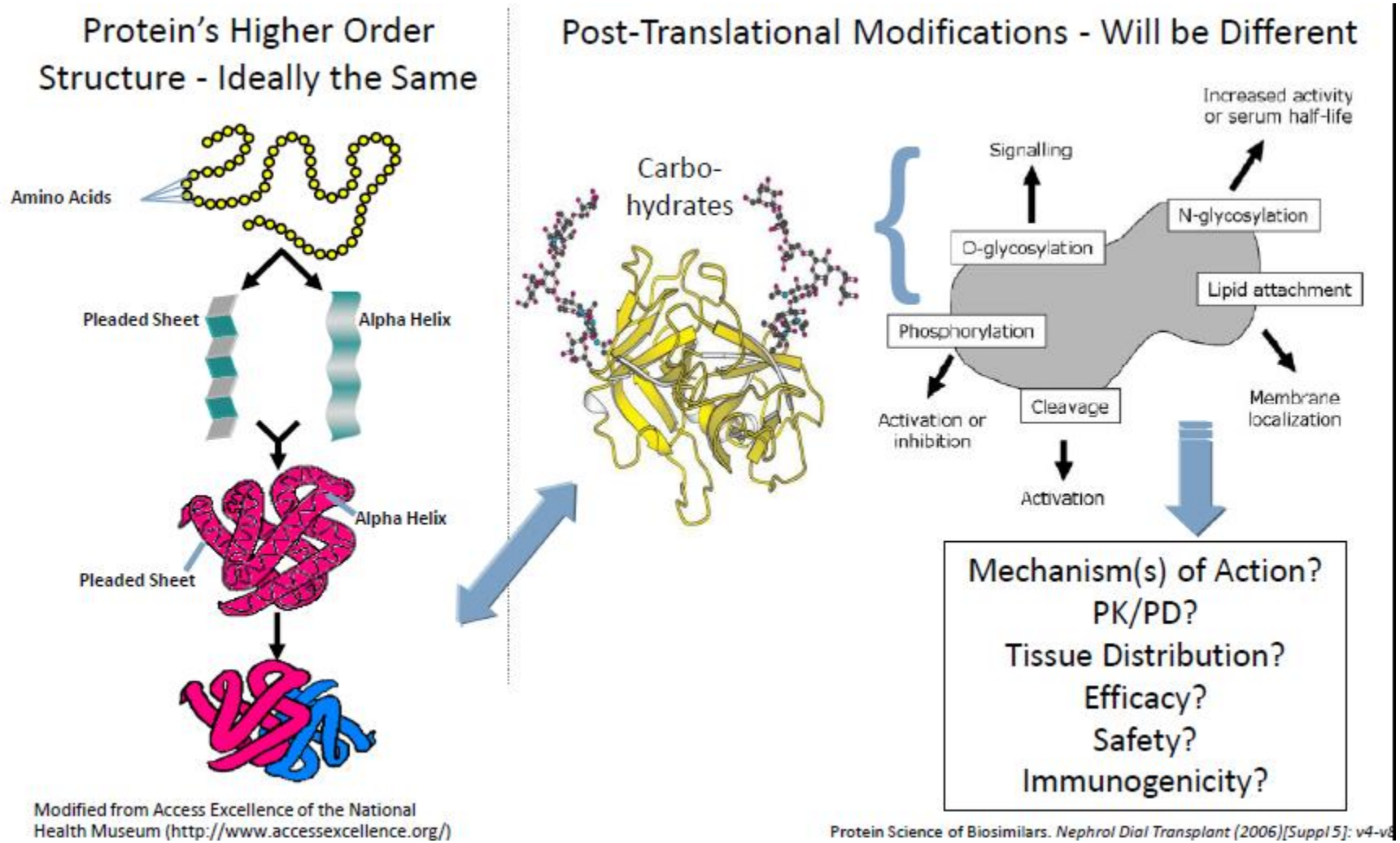
- Blood Derivatives
- Whole Blood
- Blood Components
- Proteins
- Human Tissues
- Xenotransplantation Products
- Cellular & Gene Therapies
- Vaccines
- Allergenic Extracts







Protein Function Depend on Final Configuration



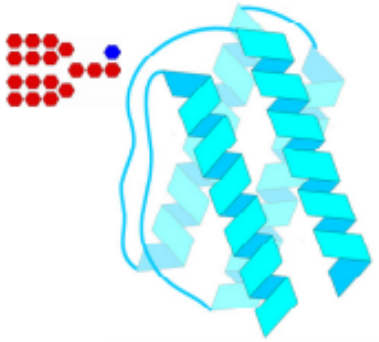
Current Opinion in Drug Discovery & Development 2005 **8**(5):590-600

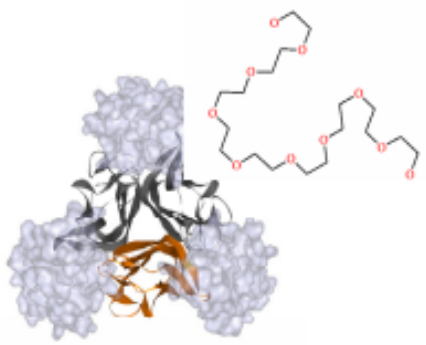
Rational Protein Drug Design

Figure 1. Transforming proteins into drugs with improved physical properties and biological activities.

Protein engineering toolbox

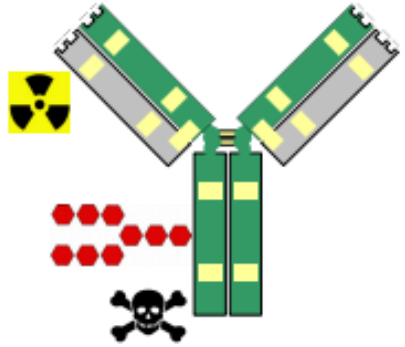
- Introduction of glycosylation sites
- Domain fusions to modulate pharmacokinetics
- Substitution of exposed non-polar amino acids
- Removal of agretopes to reduce immunogenicity
- Complete chemical synthesis





- Introduction of unpaired cysteines for pegylation
- Removal of deamidation-prone asparagines
- Alteration of protease-sensitive sites
- Removal of cysteines to reduce aggregation
- Amino acid substitutions for potency and selectivity

- Construction of chimeras or humanization to, eg, improve safety and half-life
- Radioactive antibodies to increase toxicity
- Removal of glycosylation sites for expression
- Introduction of unnatural amino acids
- Defucosylation to improve tumor cell killing
- Toxin conjugates for tumor toxicity



Desired drug properties

- Increased protein thermal stability, longer shelf-life
- Improved solubility and formulation
- Faster or slower onset of action
- Elimination of degradation products
- Reduced immunogenicity
- Improved potency
- Enhanced tumor cell-killing by antibodies
- Improved half-life in serum
- Increased bioavailability
- Improved expression levels
- New expression hosts
- Introduction of novel functions
- New receptor selectivity
- Generation of intellectual property, freedom-to-operate

Current Opinion in Drug Discovery & Development 2005 8(5):590-600

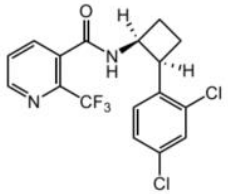
SMALL MOLECULES DRUG DESIGN STRATEGIES

Possibilities of *in silico* Drug Design

	Known ligand	Unknown ligand
Known target structure	**Structure-based drug design (SBDD)** Docking	***De novo* design**
Unknown target structure	**Ligand-based drug design (LBDD)** *1 or more ligands* • Similarity search *Several ligands* • Pharmacophore *Large number of ligands (20+)* • Quantitative Structure-Activity Relationships (QSAR)	**CADD not possible** some experimental data needed ADMET filtering

Recent Approved Agrichemicals

37 **Cyclobutrifluram (Tymirium™)**

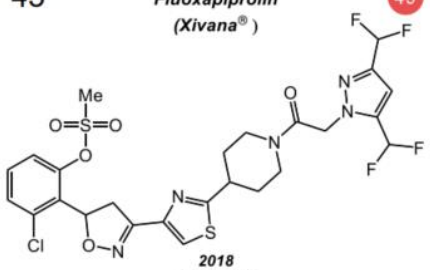


2020 Approved

syngenta

Nematicide

45 **Fluoxapiprolin (Xivana®)** 49

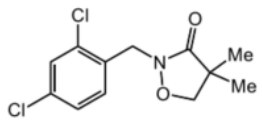


2018 Launched

Bayer CropScience

Fungicide

47 **Bixlozone** 13

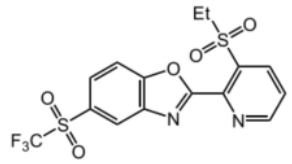


2018 Approved

FMC

Herbicide

55 **Oxazosulfyl (Alles™)**

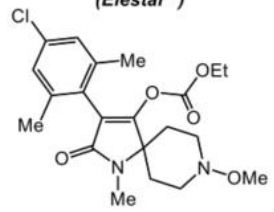


2017 Launched

SUMITOMO CHEMICAL Co, Ltd.

Insecticide

60 **Spiropidion (Elestal®)** 23

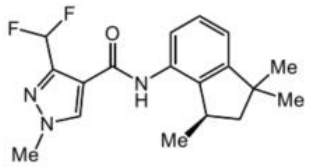


2017 Launched

syngenta

Insecticide

62 **Inpyrfluxam (Indiflin™)** 7

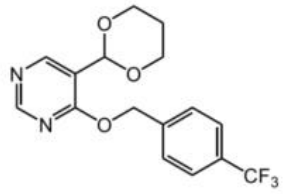


2017 Launched

SUMITOMO CHEMICAL Co, Ltd.

Fungicide

64 **Benzpyrimoxan (Orchestra™)** U

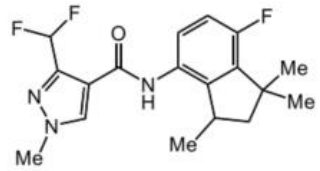


2018 Approved

NIHON NOHYAKU CO., LTD.

Insecticide

66 **Fluindapyr** 7

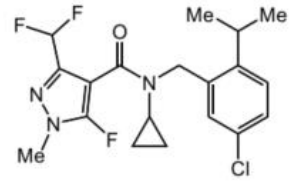


2017 Approved

ISAGRO FMC

Fungicide

67 **Isoflucypram (Vimoy Iblon™)** 7



2017 Approved

Bayer CropScience

Fungicide

2022: 0 Approved,
14 in Development
2021: 0 A, 18 in D
2020: 1 A, 8 in D
2019: 0 A, 1 in D,
2018: 3 A, 6 in D
2017: 5 A, 11 in D

Version 2.0. Updated: December 2022.
Corresponding Author: Tejas.Shah@corteva.com T_K_Shah

Expensive Problem

Experiment	Estimated cost per 1 compound
Virtual screening	3 EUR
Biochemical analysis	300 EUR
Cell culture testing	3 000 EUR
Acute toxicity on mice	10 000 EUR
Protein structure evaluation	100 000 EUR
Efficiency testing on animals	200 000 EUR
Chronic toxicity on rats	500 000 EUR
Clinical testing on volunteers	400 000 000 EUR

Lower price tag allow testing of more drug candidates

David C. Young - Computational Drug Design: A guide for computational and medicinal chemists. Wiley-Blackwell, New York, 2009, ISBN 978-0470126851

Hard Problem

- Human genom ~27 321 ORF (AlphaFoldDB)

- Alternative splicing => ~500 000 proteins

~ 60 944 experimental structures - human in PDB (12 100 unique)

- RNA role

- protein-protein interactions role

- 2 – 10 years from lead molecule identification to clinical testing (patents last 20 years)
- 1 successful out of 10 drug development projects

www.rcsb.org - 30.1.2023

ATC code

- The Anatomical Therapeutic Chemical Classification System code (ATC code) is attributed to a drug by the WHO Collaborating Centre (WHOCC) for Drug Statistics Methodology.
  - Level 1 – organ - (G): genito urinary system and sex hormones
  - Level 2 – pharmacological action - (G04): urologicals
  - Level 3 – pharmacological subgroup (G04B): urologicals
  - Level4 – pharmacological subsubgroup (G04BE): in erectile dysfunction
  - Level 5 - specific drug or combination (G04BE03): sildenafil
- a drug can have multiple codes,
  - **aspirin** (B01AC06, A01AD05, N02BA01, N02BA51 and N02BA71)

Drugs by ATC code

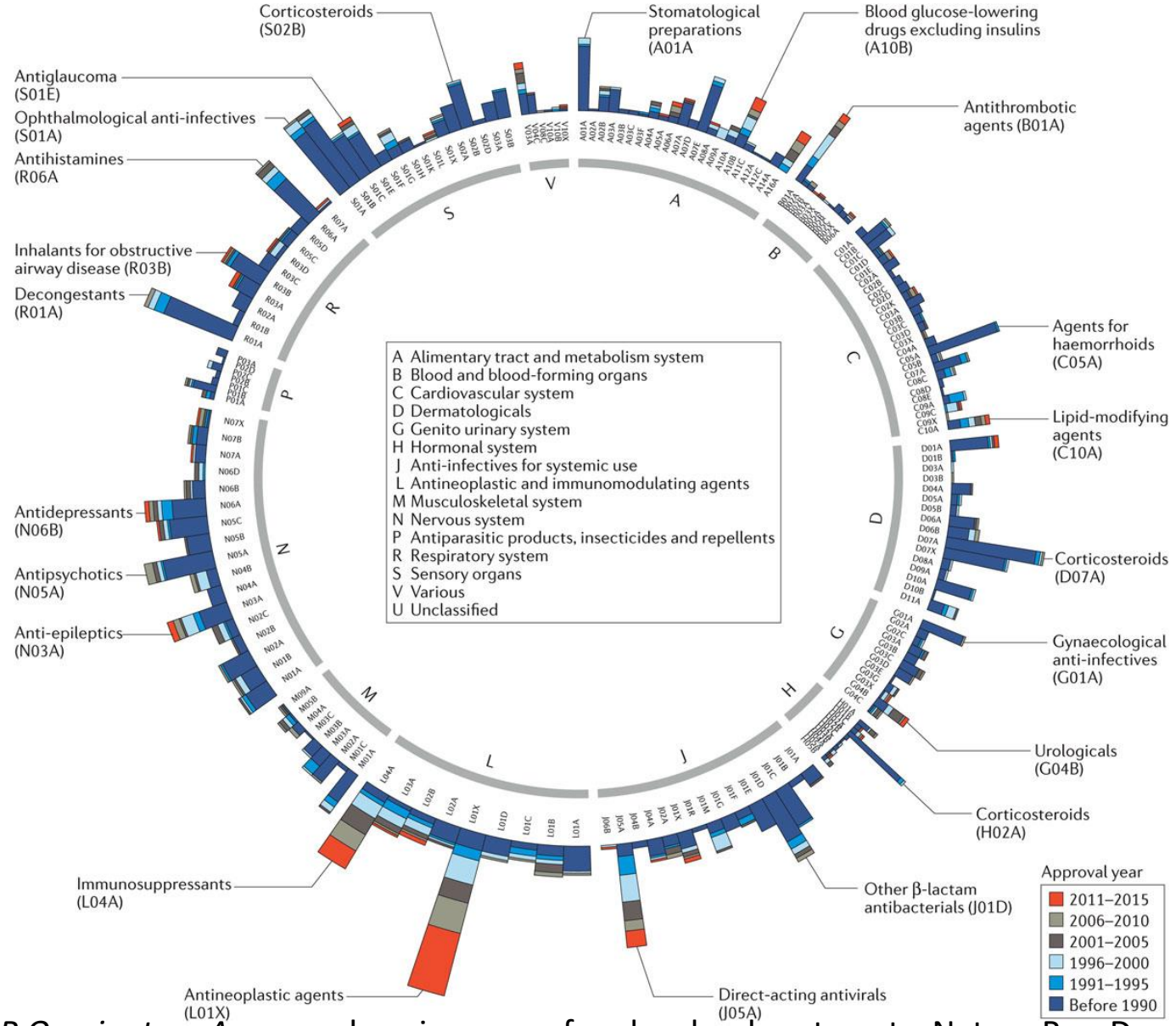
Table 2 | **Therapeutic areas of FDA-approved drugs**

ATC category	Therapeutic area	Number of small molecules	Number of biologics
A	Alimentary tract and metabolism system	158	32
B	Blood and blood-forming organs	33	28
C	Cardiovascular system	200	5
D	Dermatologicals	141	5
G	Genito urinary system	94	5
H	Hormonal system	44	31
J	Anti-infectives for systemic use	194	10
L	Antineoplastic and immunomodulating agents	142	67
M	Musculoskeletal system	62	6
N	Nervous system	239	1
P	Antiparasitic products, insecticides and repellents	38	1
R	Respiratory system	118	4
S	Sensory organs	143	11
V	Various	30	12
U	Unclassified	156	51

The list also includes antimalarial drugs approved elsewhere in the world. ATC, WHO Anatomical Therapeutic Chemical Classification System.

R. Santos, …, JP Overington: A comprehensive map of molecular drug targets. Nature Rev. Drug Discovery, 16, 19-34, 2017. doi: 10.1038/nrd.2016.230

Drug Targets by ATC

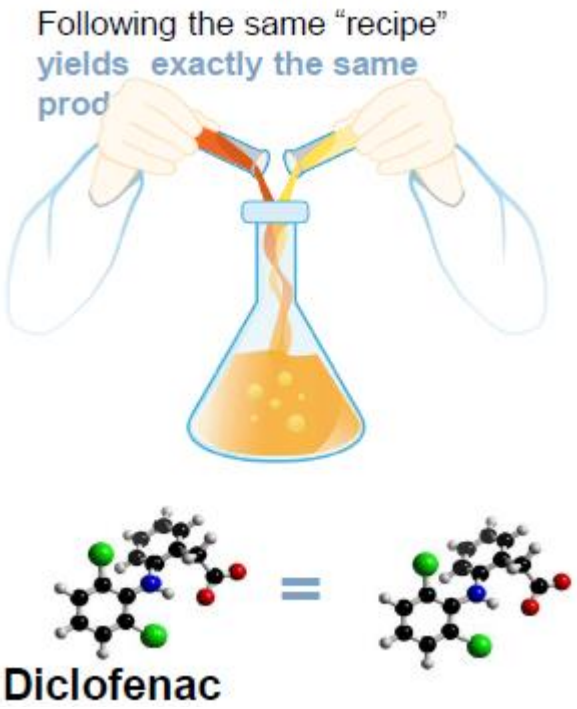


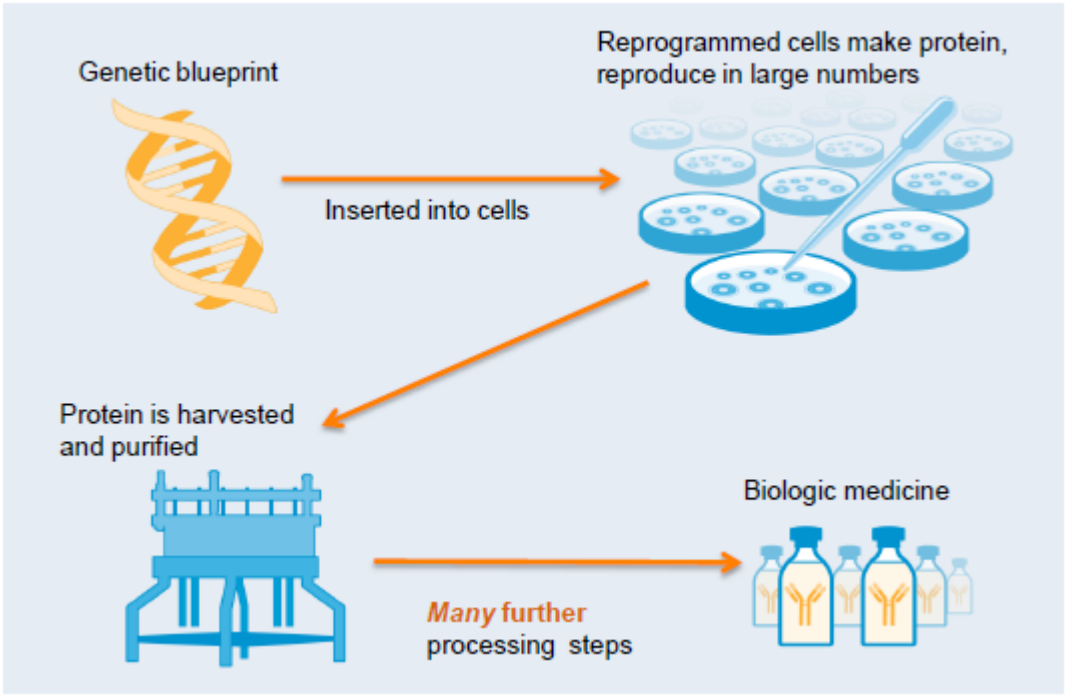
R. Santos, …, JP Overington: A comprehensive map of molecular drug targets. Nature Rev. Drug Discovery, 16, 19-34, 2017. doi: 10.1038/nrd.2016.230

Small Molecules vz Biologicals

Chemical medicines are chemicals made by chemists out of other chemicals

Biologics are *grown* from living things
Biologics are highly sensitive to manufacturing conditions





Current Opinion in Drug Discovery & Development 2005 8(5):590-600