KATEDRA FYZIKÁLNÍ CHEMIE
UNIVERZITY PALACKÉHO V OLOMOUCI

INSTITUTE OF MOLECULAR AND TRANSLATIONAL MEDICINE

7th Advanced *in silico* Drug Design

KFC/ADD

Drug design intro

Karel Berka

UP Olomouc, 29.1.-1.2. 2023

INSTITUTE OF PHYSICS
National academy of Sciences of Ukraine

ÚOCHB AV ČR
IOCB PRAGUE

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

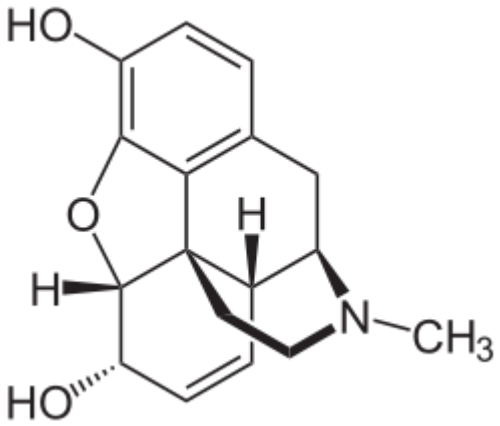
Outline

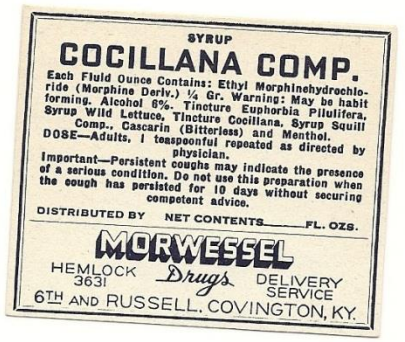
- Sources of drugs
  - Recently approved drugs – what are they
- Drug design problem
  - Money is not the only problem
- Drug targets
- Differences between drug design strategies for
  - Small molecules
  - Biologicals

SOURCES OF DRUGS

History of Drug Design

1806



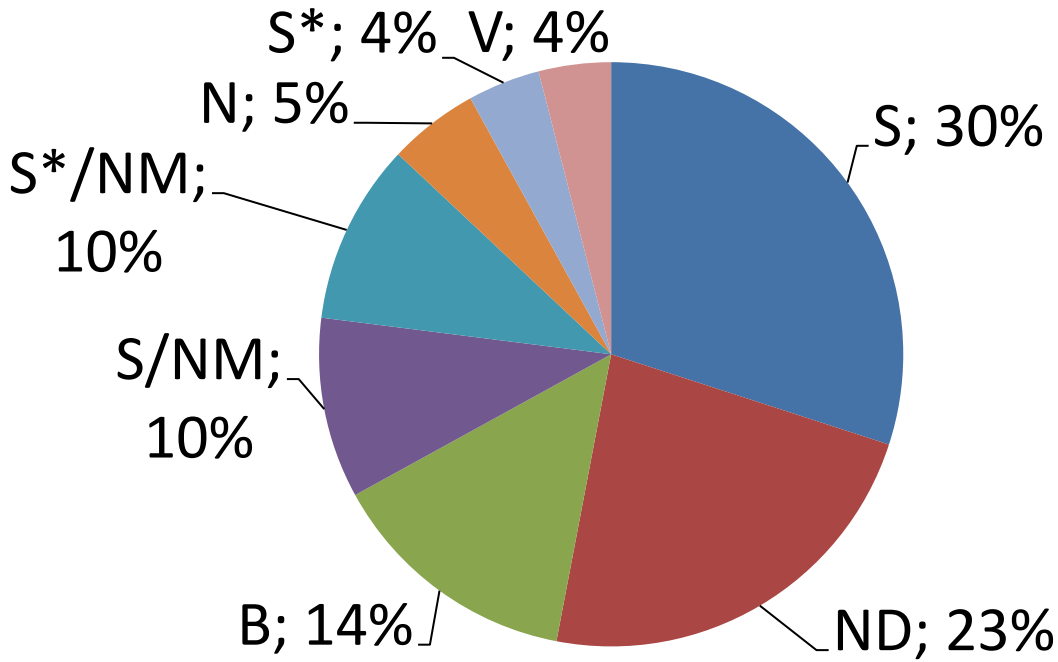


History of Drug Design Testing

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

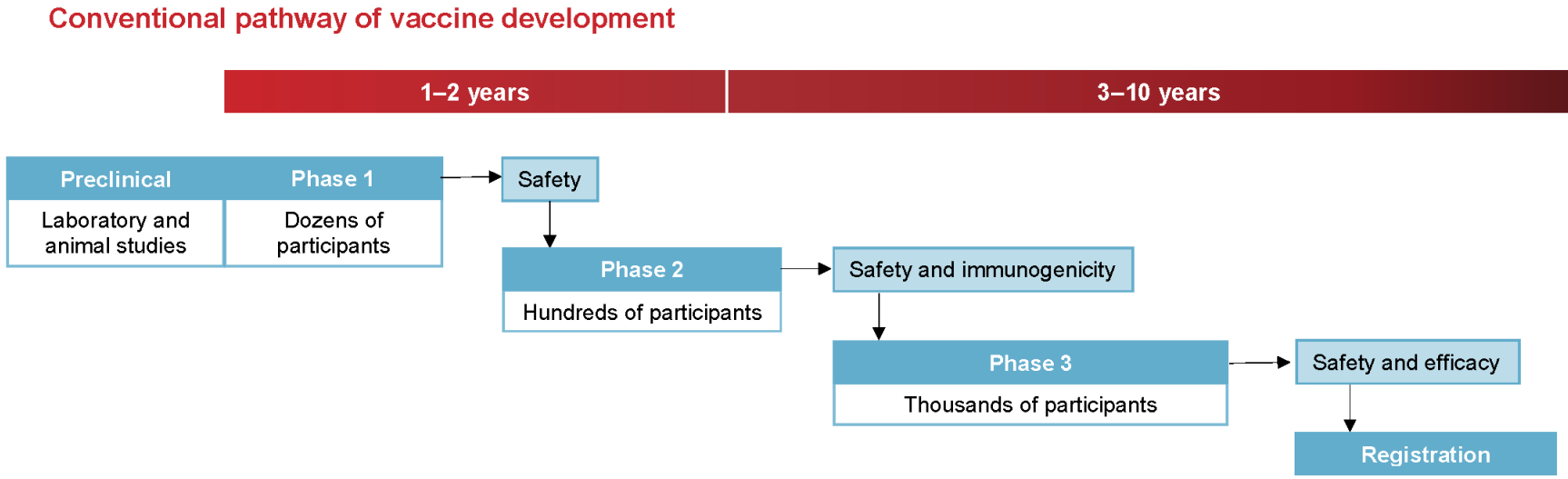
D. J. Newman and G. M. Cragg,
J. Nat. Prod. 70, 461-477 (2007)

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

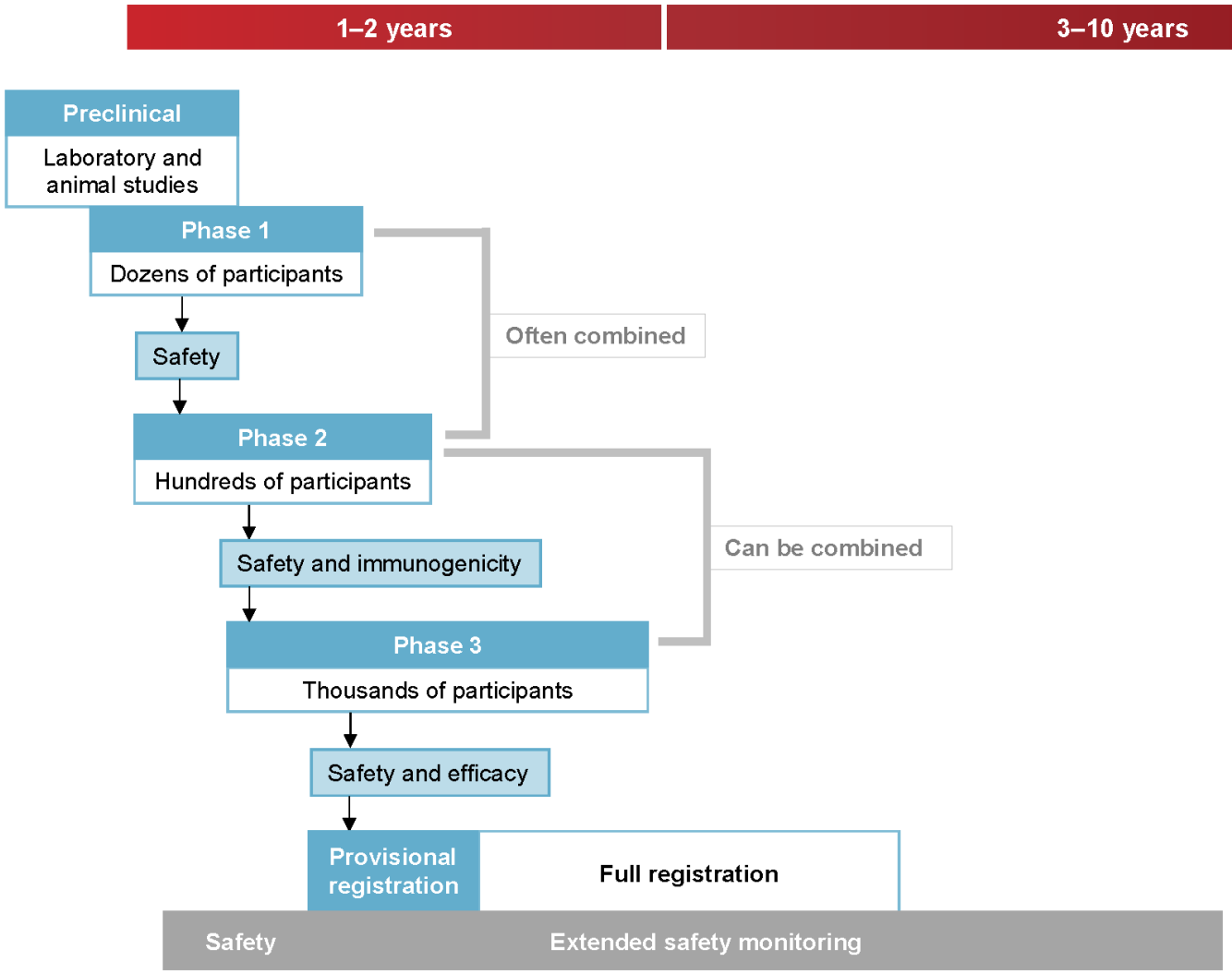
Drug Approval Timeline

- 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

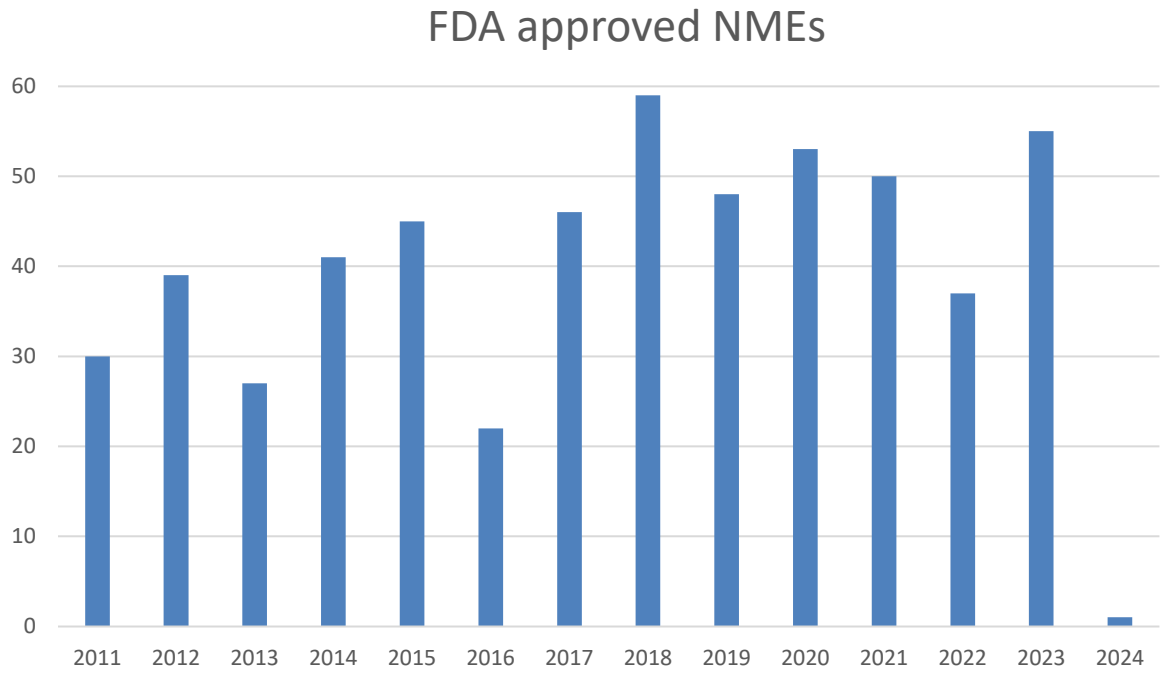
New Molecular Entities (NMEs)

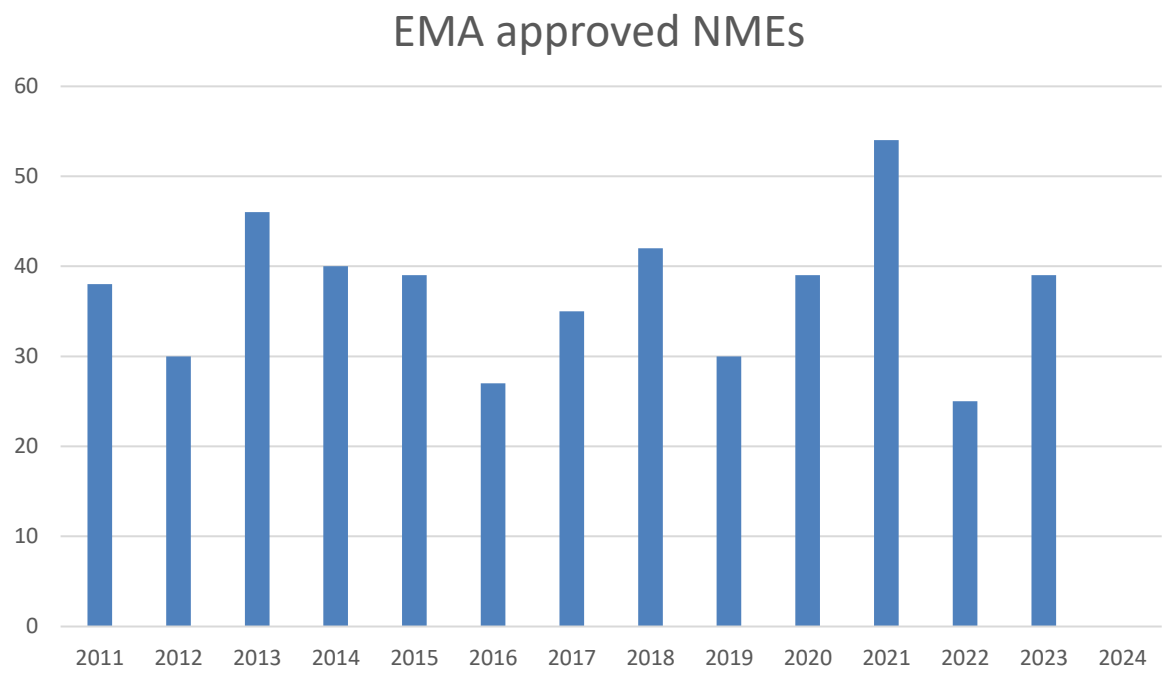
FDA's Center for Drug Evaluation and Research (CDER):

- First in class – average 40%
- Orphan diseases – around 50%
- Expedited – lower at 45% (used to be >70%)

EMA:

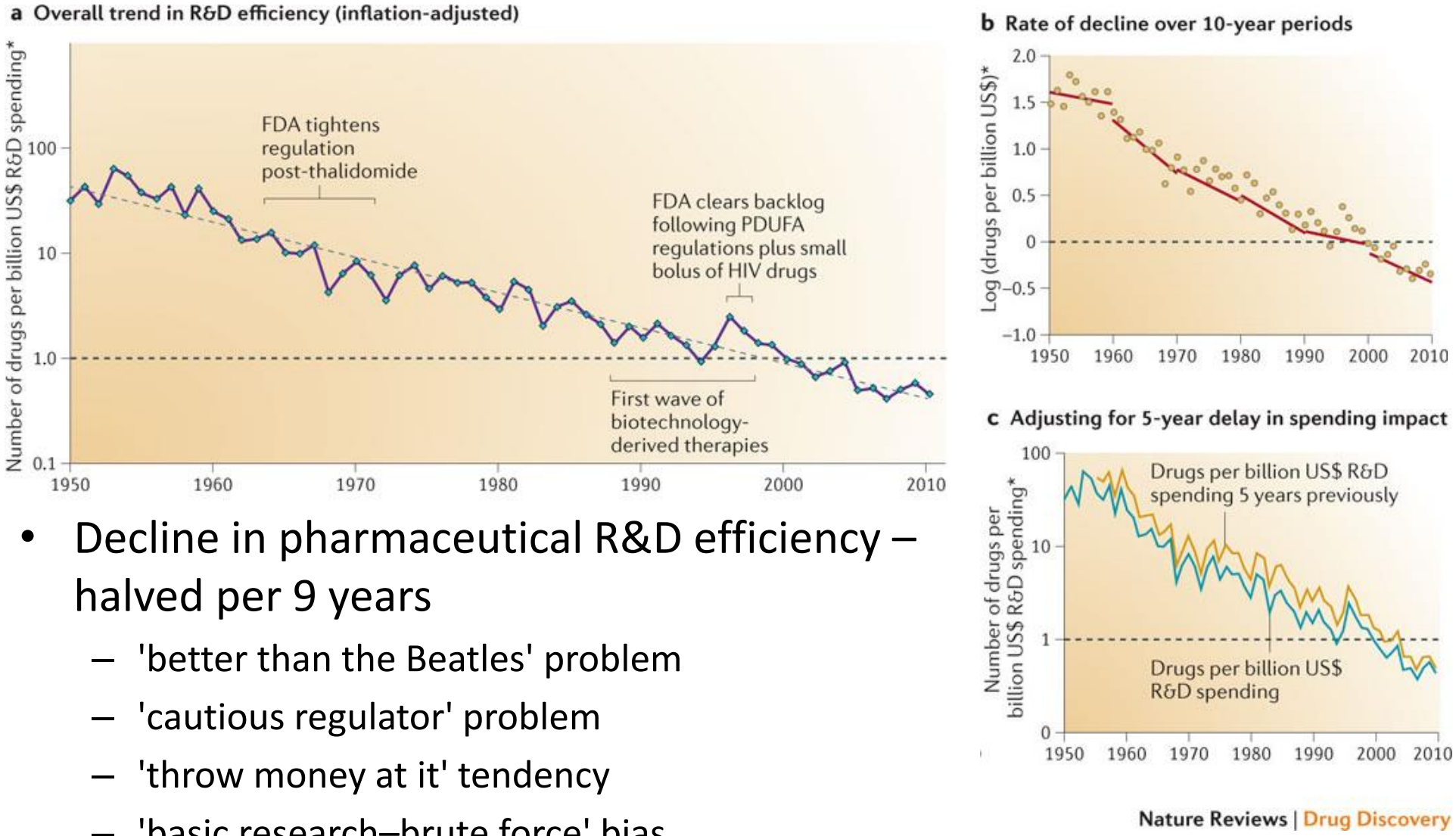
- Orphan diseases – 30% to 50% per year
- Expedited (accelerated and conditional market authorization) – fluctuates around 30%





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

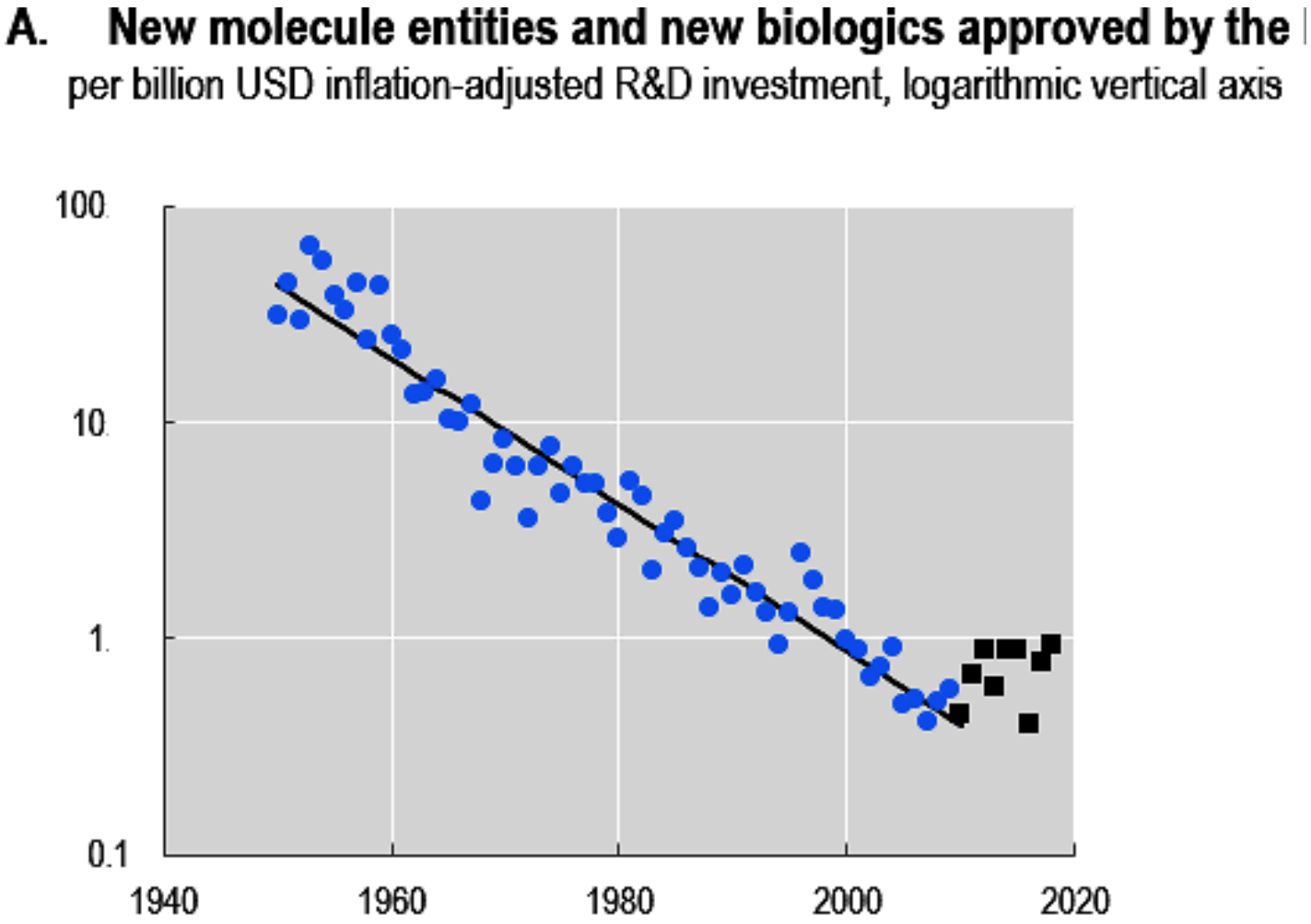
Eroom's Law



- Decline in pharmaceutical R&D efficiency – halved per 9 years
  - 'better than the Beatles' problem
  - '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?

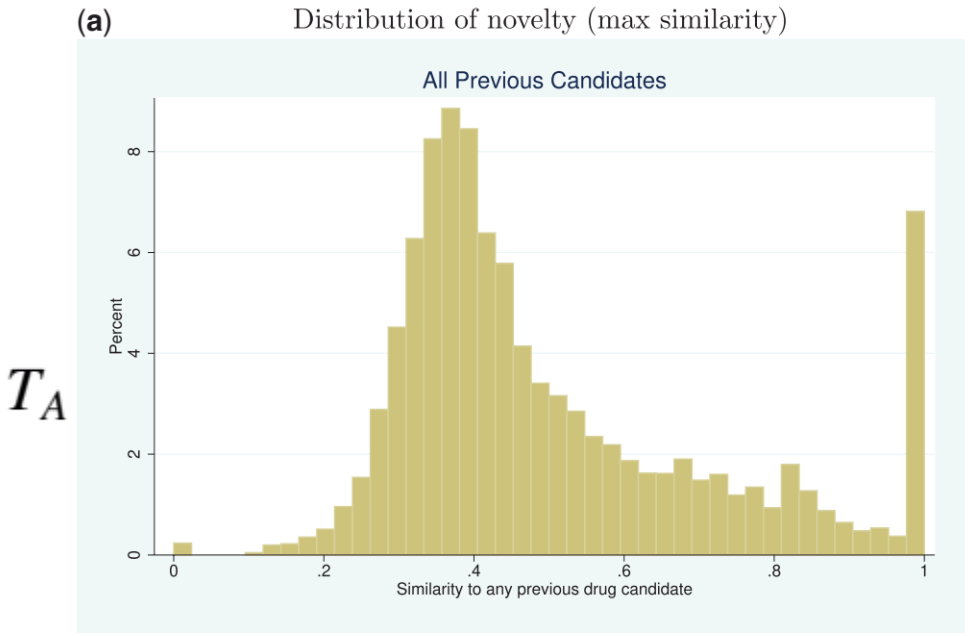


- Innovative efficiency lowered during times
- But Errom's law seems to stop recently
- Production of new chemical is easier
- Production of new valid screening models is harder

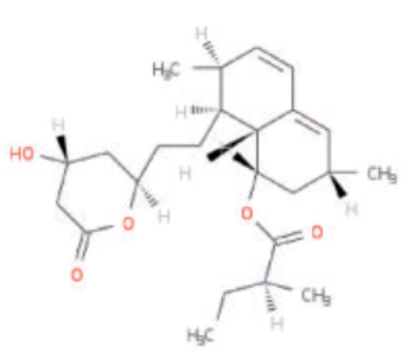
OECD (2023), *Artificial Intelligence in Science: Challenges, Opportunities and the Future of Research*, OECD Publishing, Paris, https://doi.org/10.1787/a8d820bd-en.

Missing Novelty in Drug Development

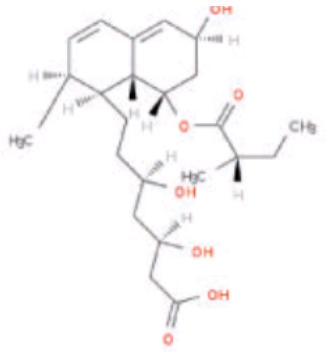
- Evidence that risk aversion leads to underinvest in innovation
- Chemical similarity -> novel drug candidates are less likely to obtain FDA approval (but more valuable if approved)



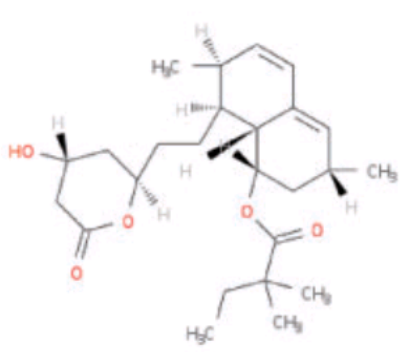
T_A



Mevacor
(Similarity Score=0.25)
Lovostatin Sep 1987



Pravachol
(Similarity Score =0.61)
Pravastatin Oct 1991

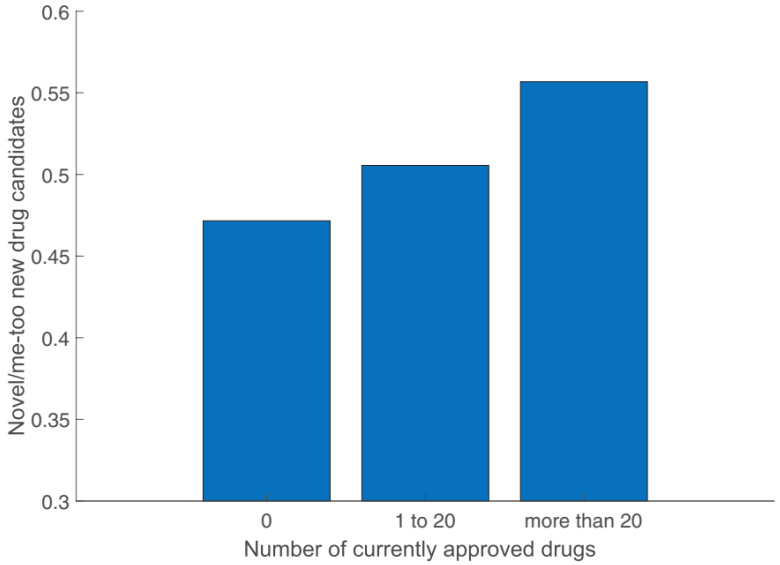


Zocor
(Similarity Score =0.82)
Simvastatin Dec 1991

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

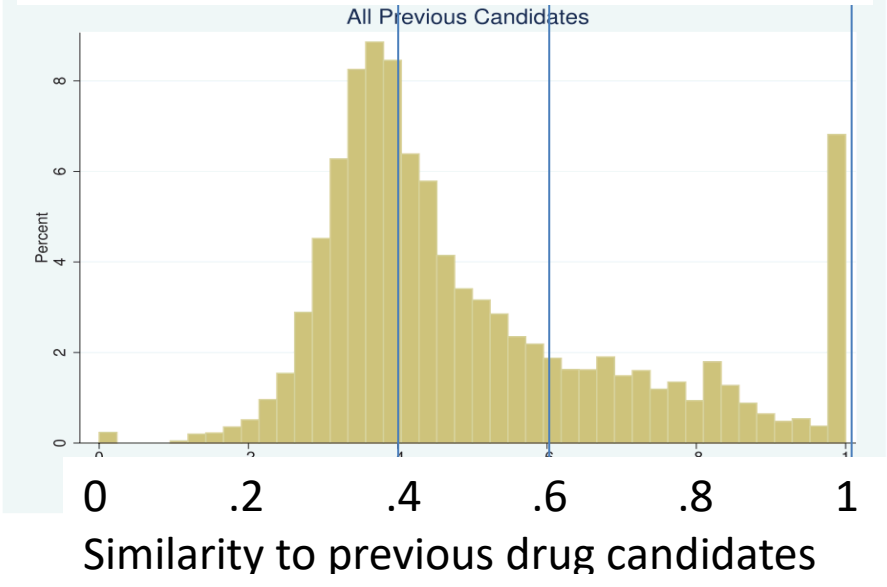
Missing novelty II

- 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

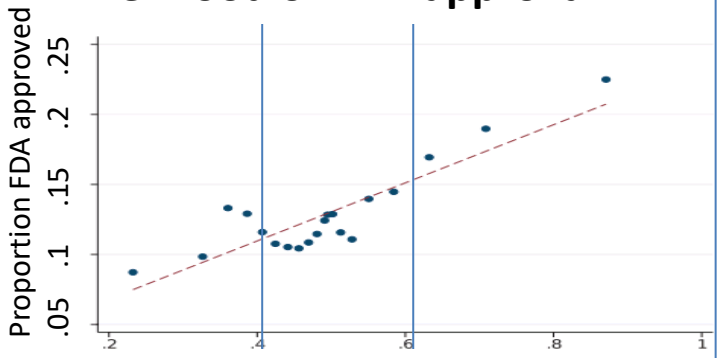


Krieger J, Li D, Papanikolaou – Missing Novelty in Drug Development. ***The Review of Financial Studies*** 35 (2022) 636-679

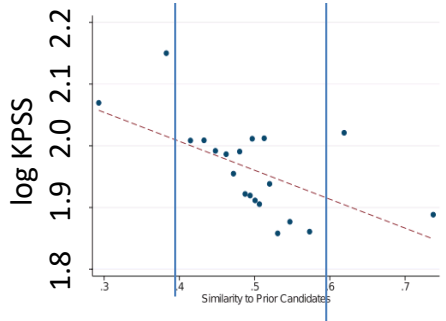
Distribution of novelty by max similarity



Likelihood of FDA approval



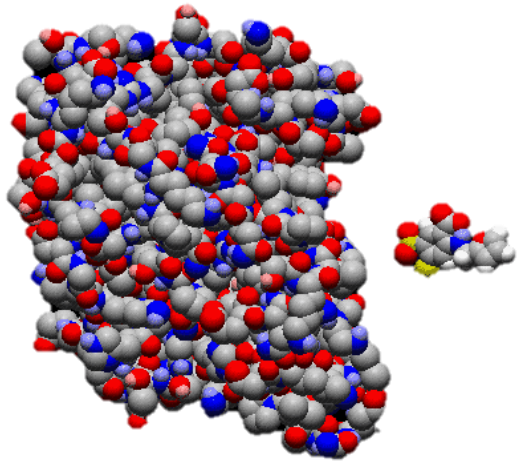
Patent value (log KPSS)



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*

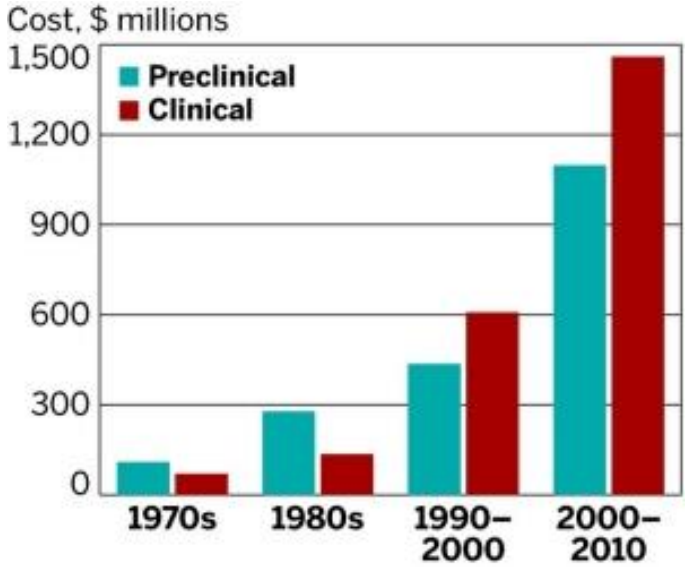
Drug Design

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*

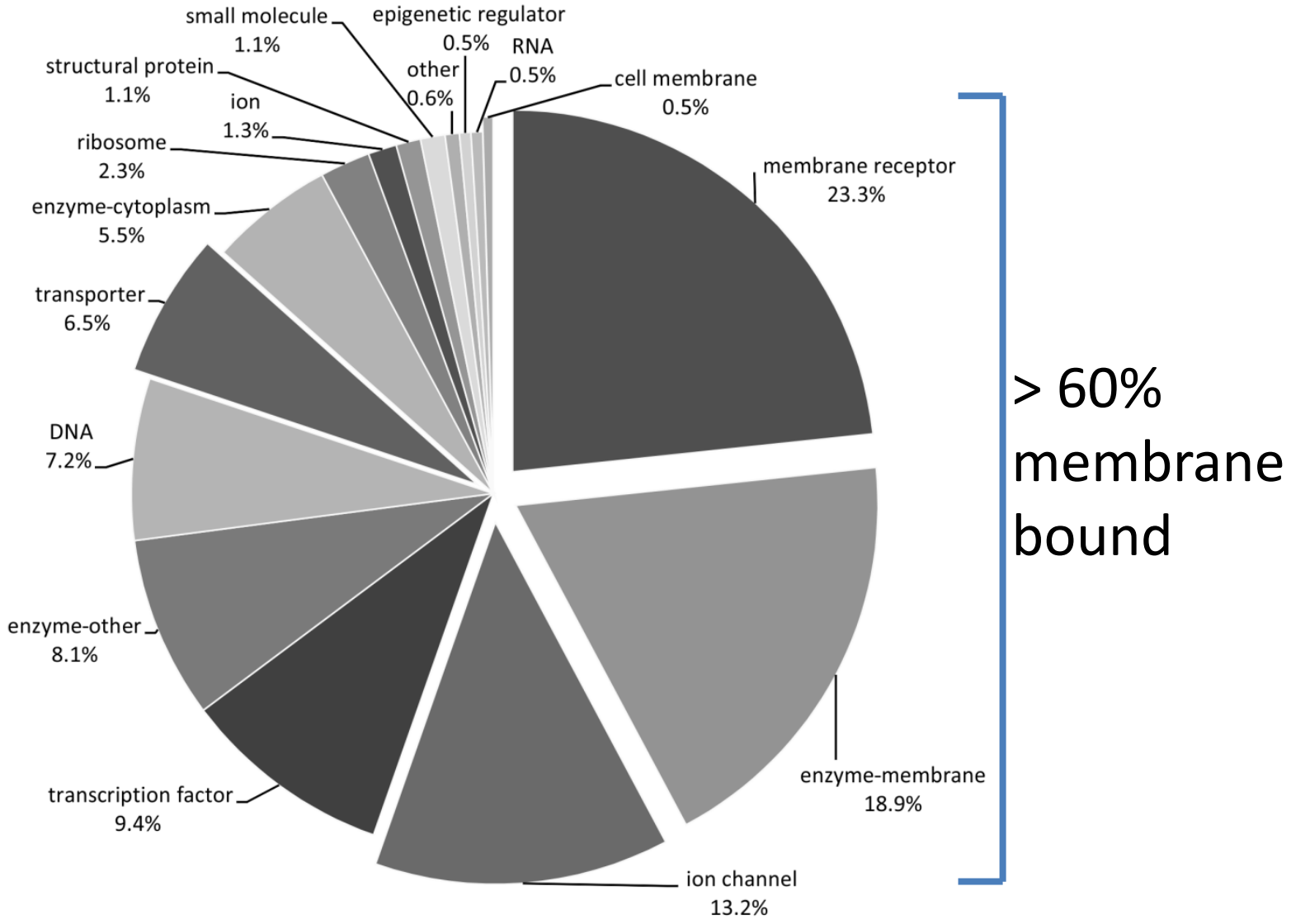
Illness Type

- 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

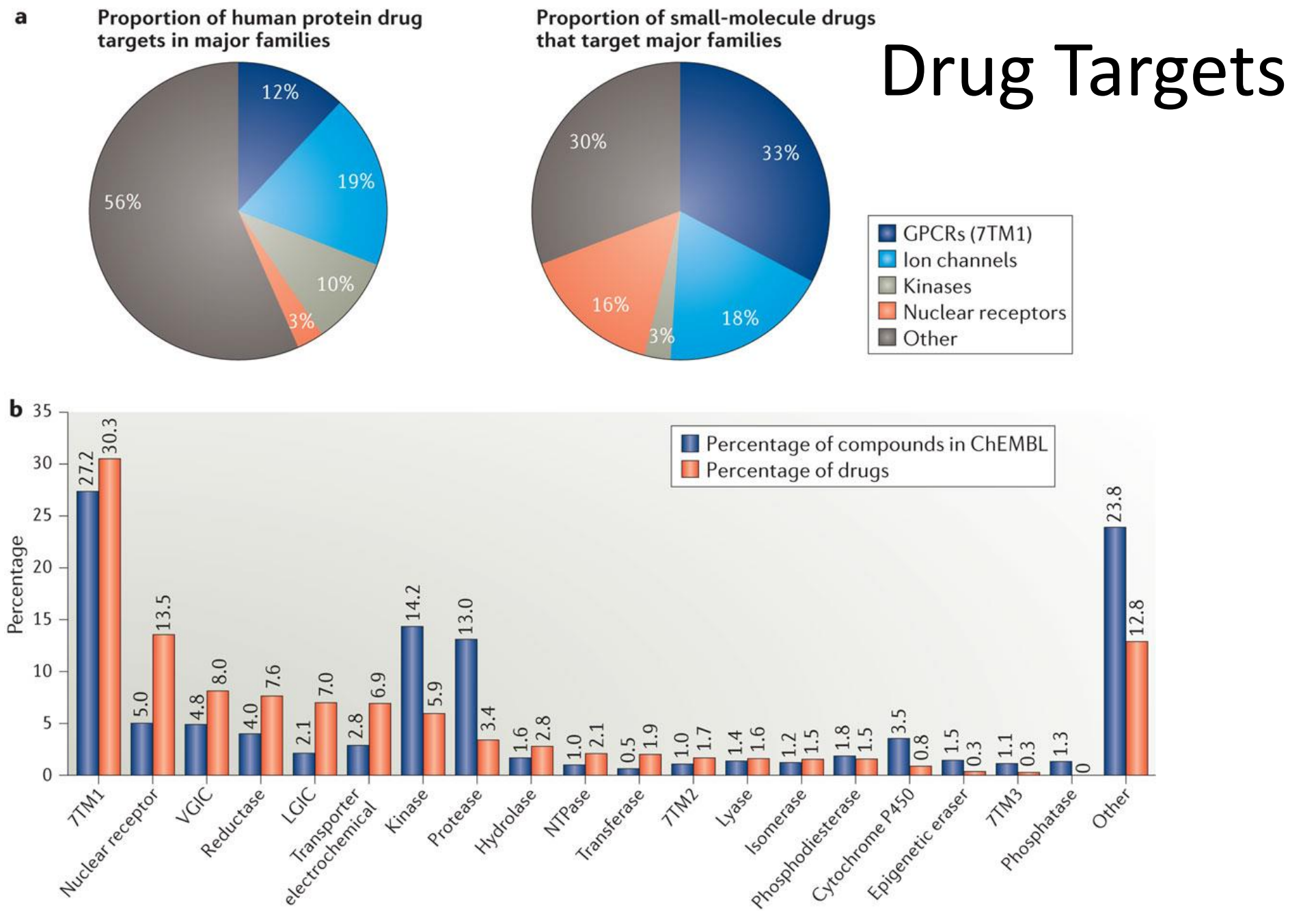
DRUG TARGETS

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*.

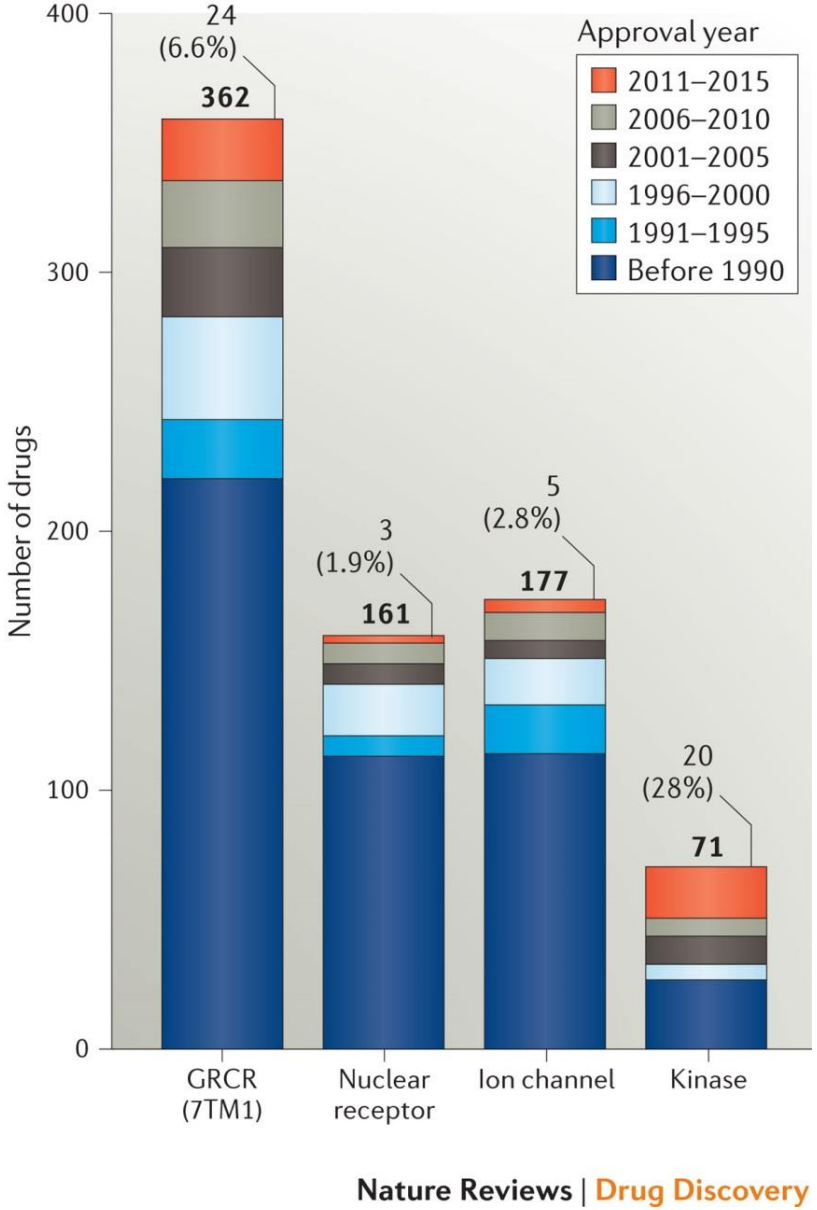
Drug Targets



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

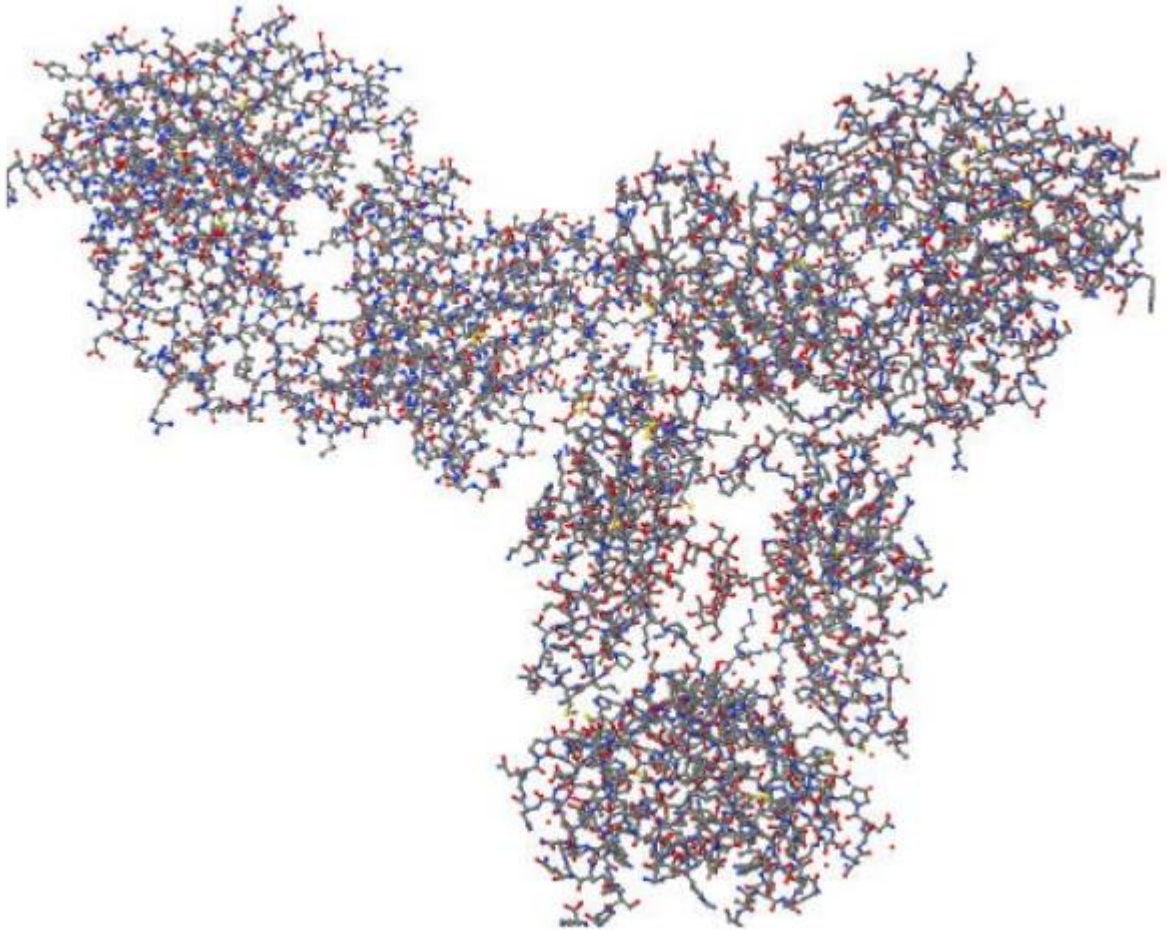
WHO INN Drug lists: http://www.who.int/medicines/publications/druginformation/innlists/en

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

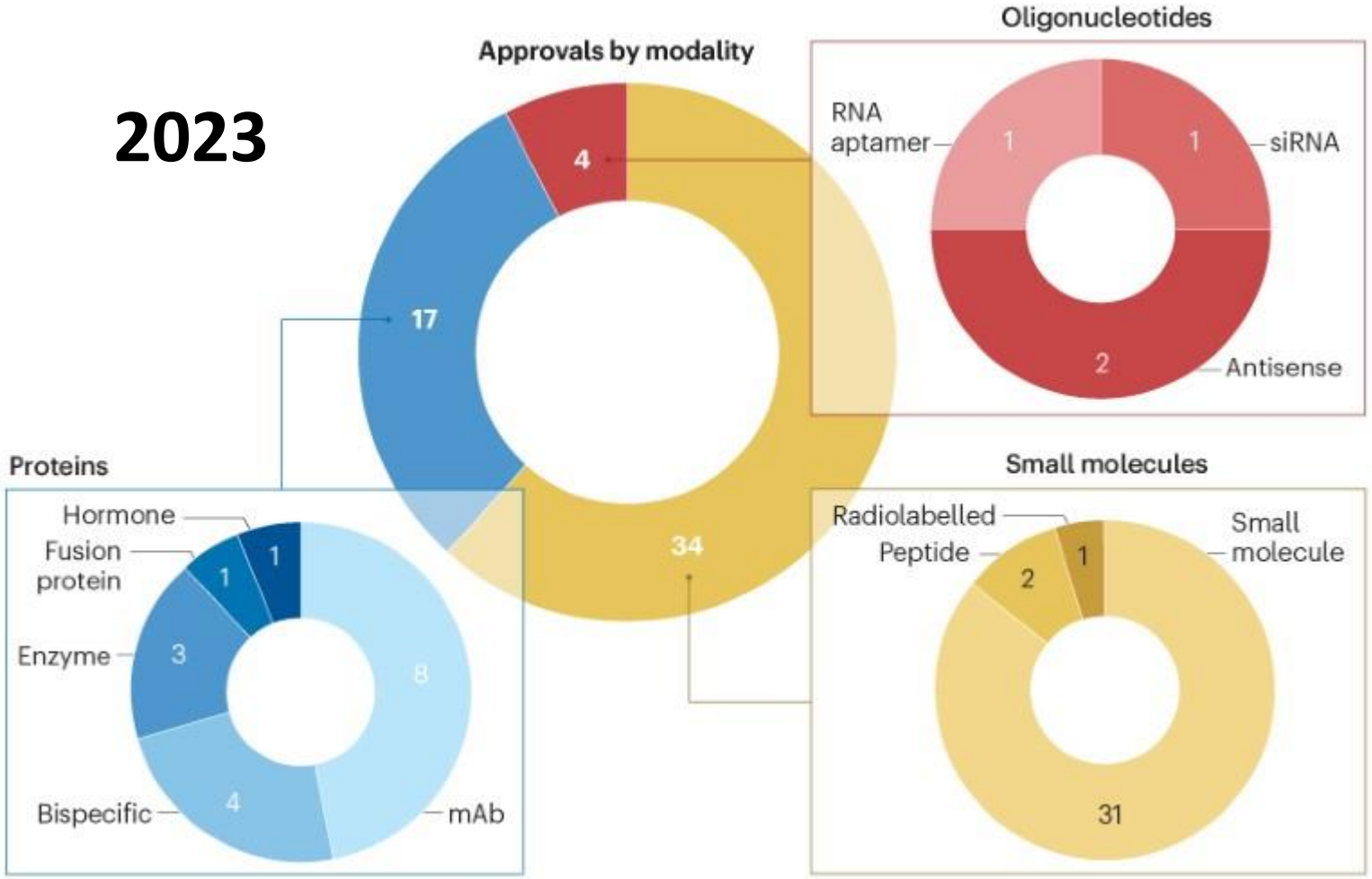
Aspirin 180 Da



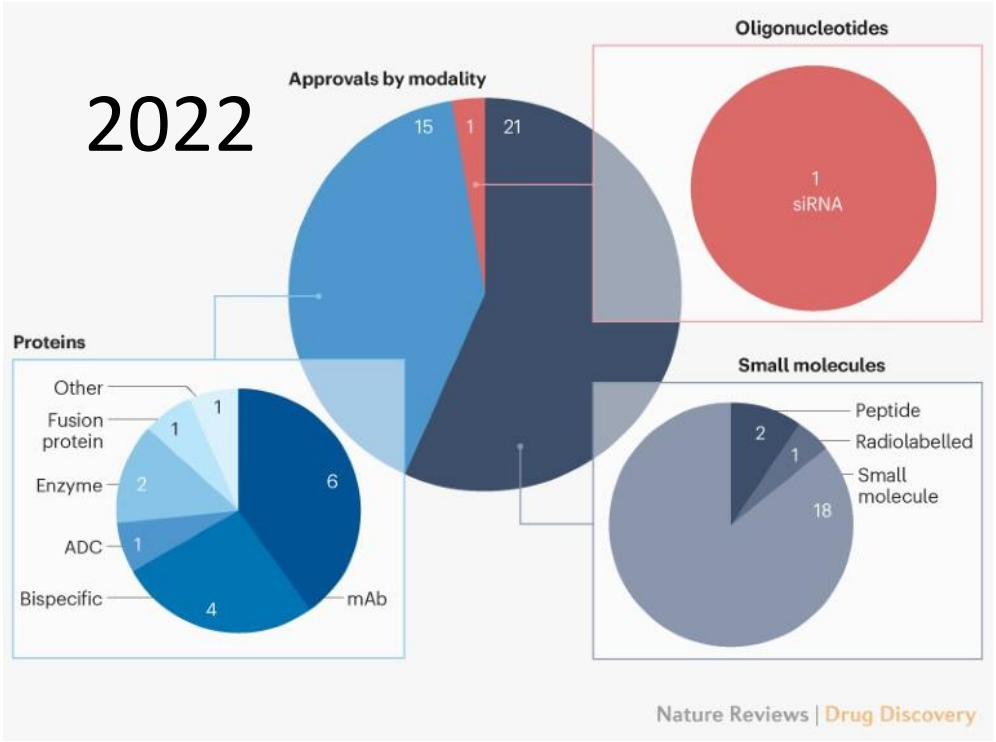
Monoclonal Antibody ~150,000 Da

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