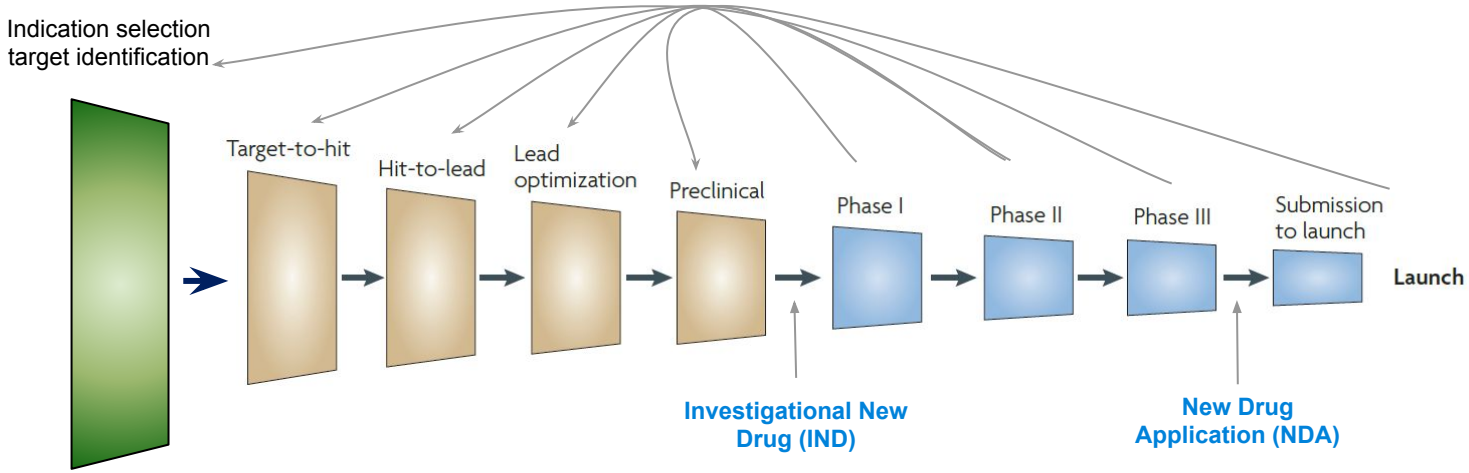
# AMIDD 2024 Lecture 2:
# Mathematics and informatics are essential for drug discovery

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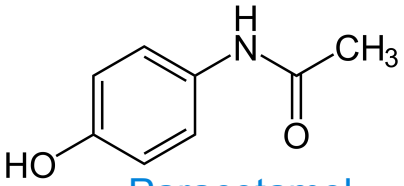
*[2] Department of Mathematics and Computer Sciences, University of Basel*

# Outline

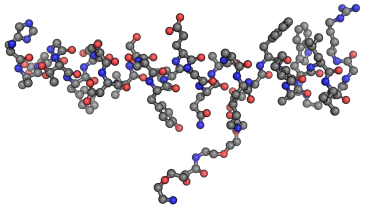
1. Drug modalities
2. Economy and productivity of drug discovery
3. Why mathematics and informatics are essential

# A zoo of modalities



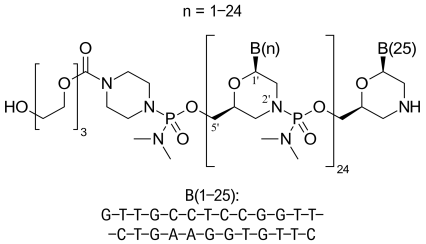

Paracetamol
Molecular weight (MW): 151 Da

Small molecule



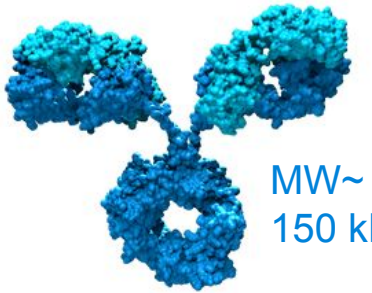
Semaglutide
MW~4 kDa

Peptide



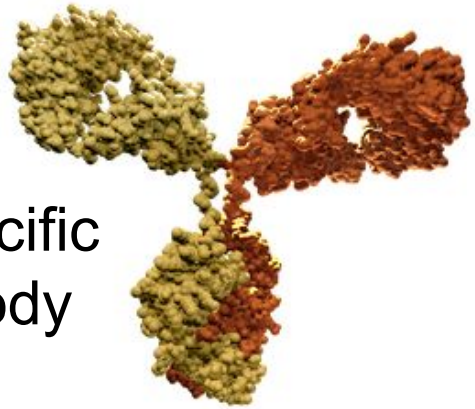

Golodirsen,
MW~5-30 kDa

Oligonucleotides

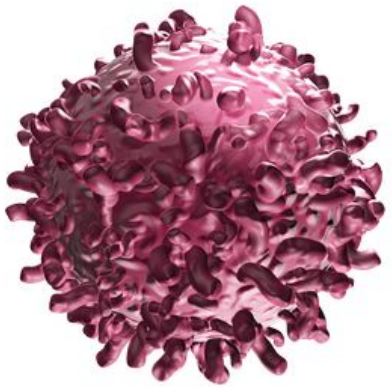


MW~
150 kDa

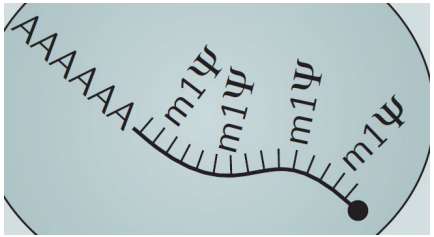
Monoclonal antibody



Bispecific antibody



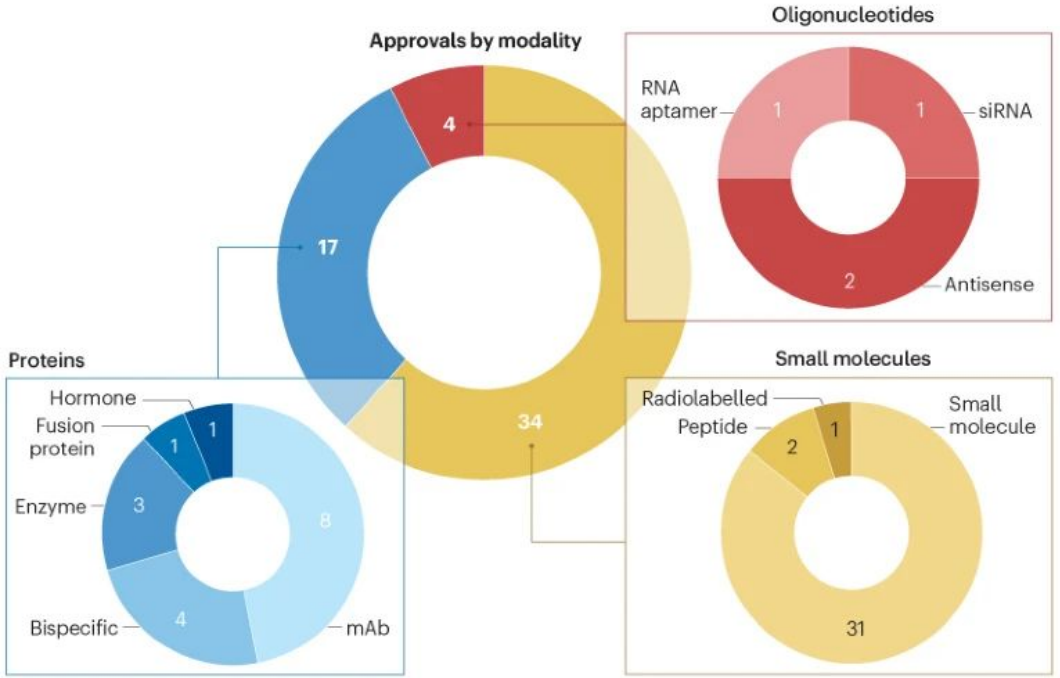
Chimeric Antigen Receptor (CAR) T-cells




mRNA vaccines

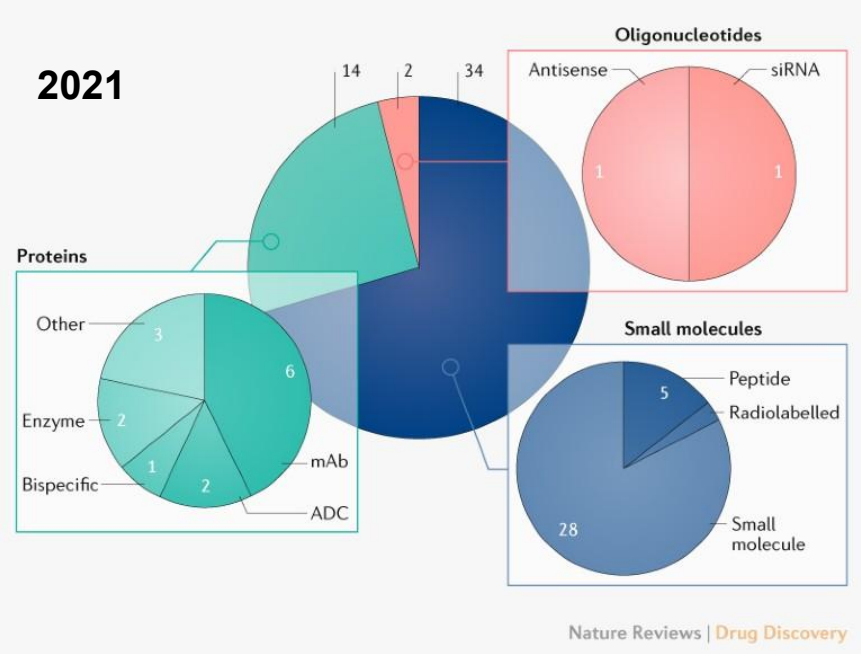
# Novel drugs approved by the FDA's Center for Drug Evaluation and Research (CDER) in 2023

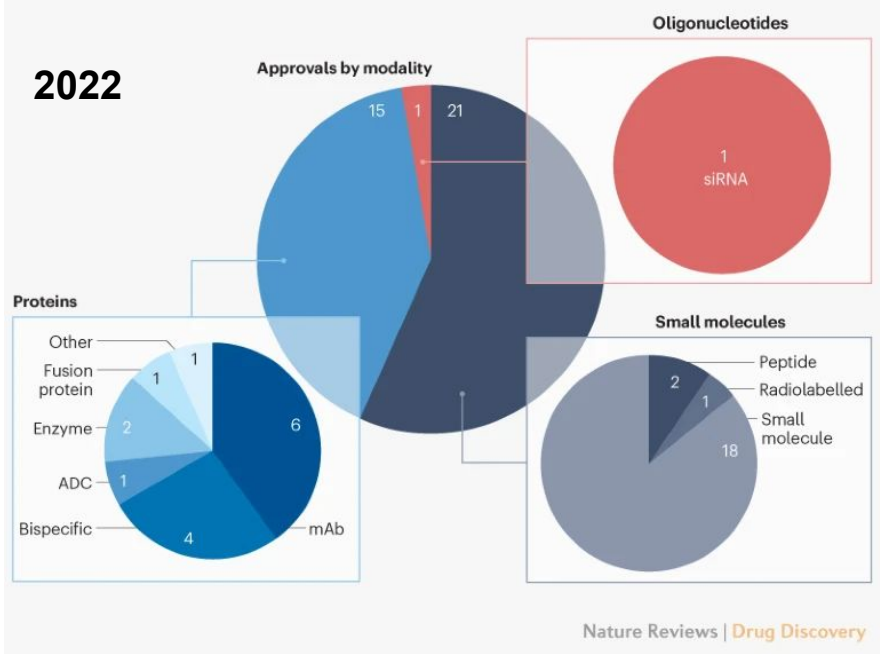
- Small molecules: molecular weight (MW) less than 1000 Daltons.
- Oligonucleotides: MW between 5 and 30 kDa (5000-30000 Da), negatively changed
  - siRNA: small interfering RNA
- Proteins: MW ~150 kDa
  - mAb: monoclonal antibody
  - Bispecific: antibodies that bind simultaneously to two antigens or two epitopes of the same antigen.



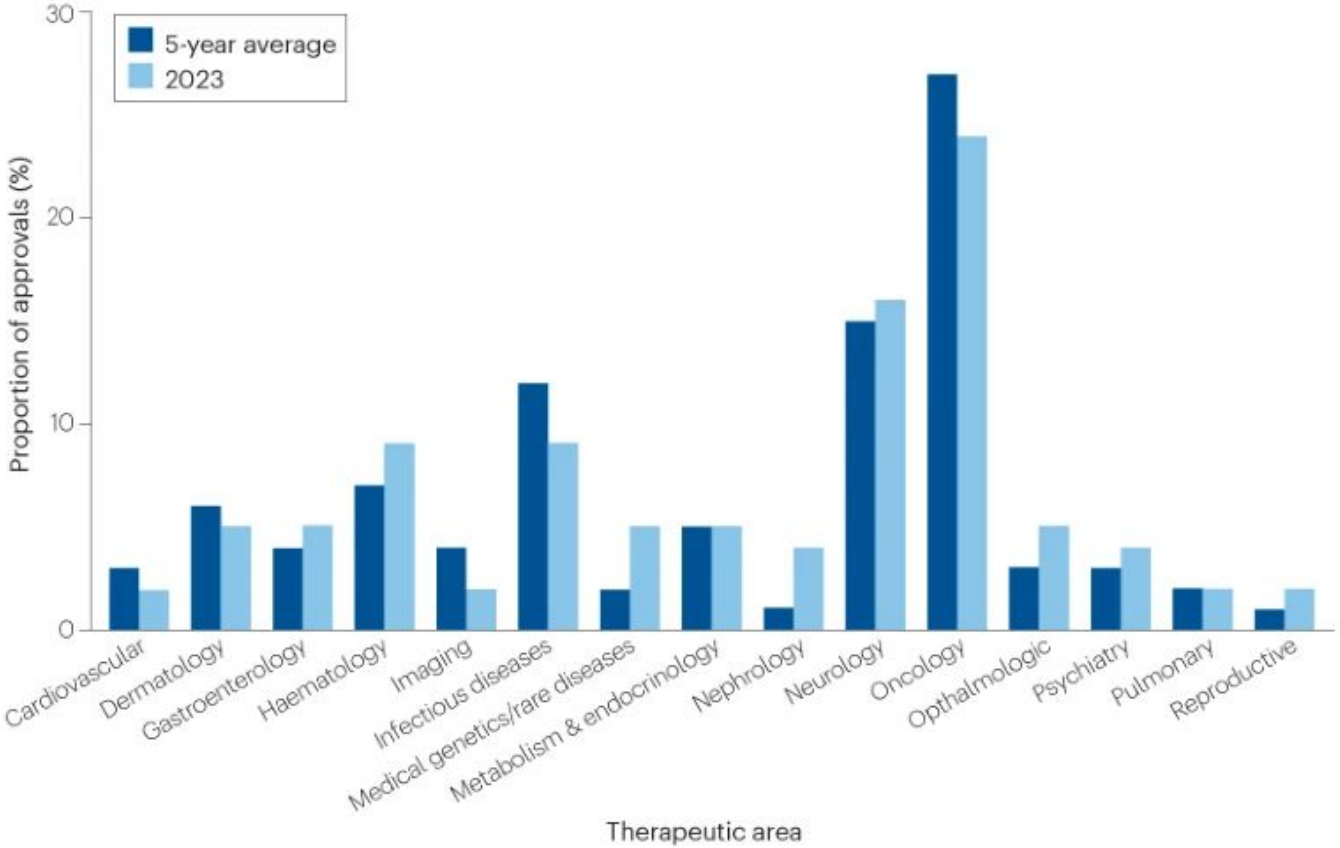

Source: Asher Mullard, Nature Reviews Drug Discovery, 2024. The list can be found on FDA's website

# Relative contributions of modalities remain constant in the past three years

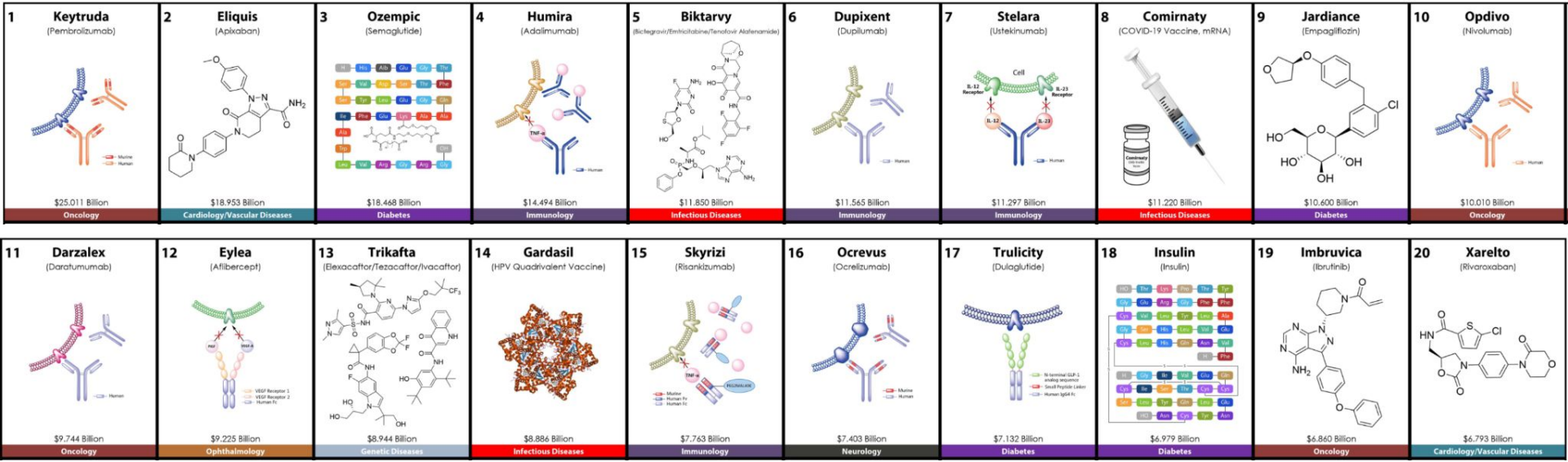


# New drug approvals vary between disease areas



# Offline activity for lecture 2




## Top 20 pharmaceuticals by sales in 2023

Poster compiled by the Jon Njardarson group at University of Arizona (https://njardarson.lab.arizona.edu). Citation: J. Chem. Ed. 2010, 87, 1348.

**Questions:** (1) How many are small molecules, proteins, and oligonucleotides each? (2) Are there other modalities? (3) What patterns do you observe? (4) Do you have explanations for these patterns?

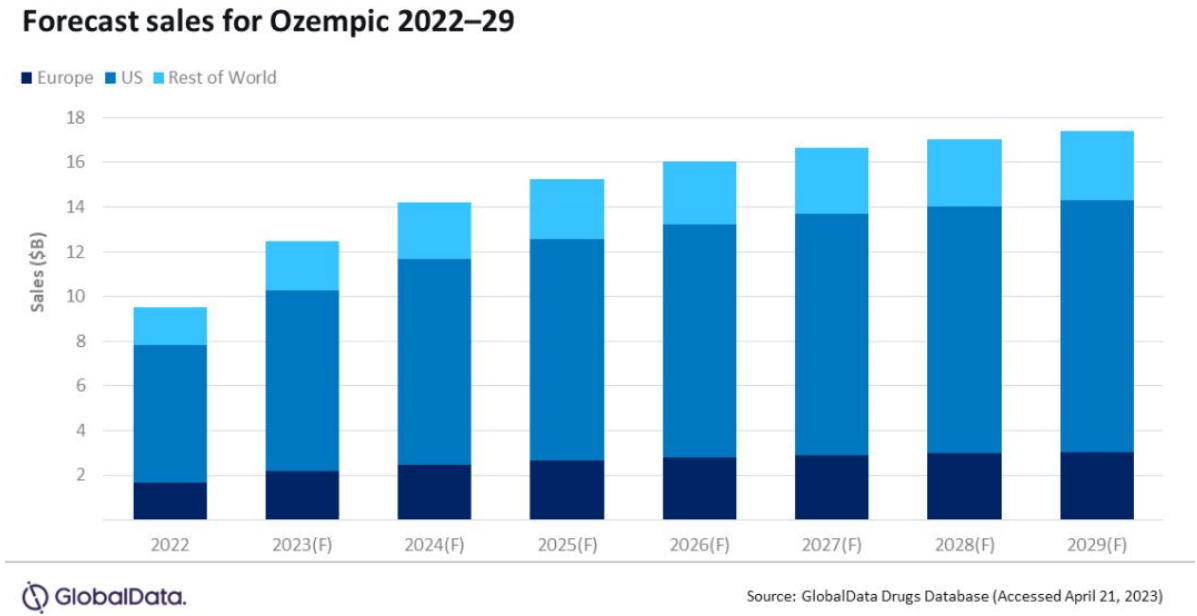
# Forms and market size of Semaglutide

*Ozempic*, as well as Wegovy and Rybelsus, are **brand names** of semaglutide.

*Ozempic* was approved by the FDA for type 2 diabetes.

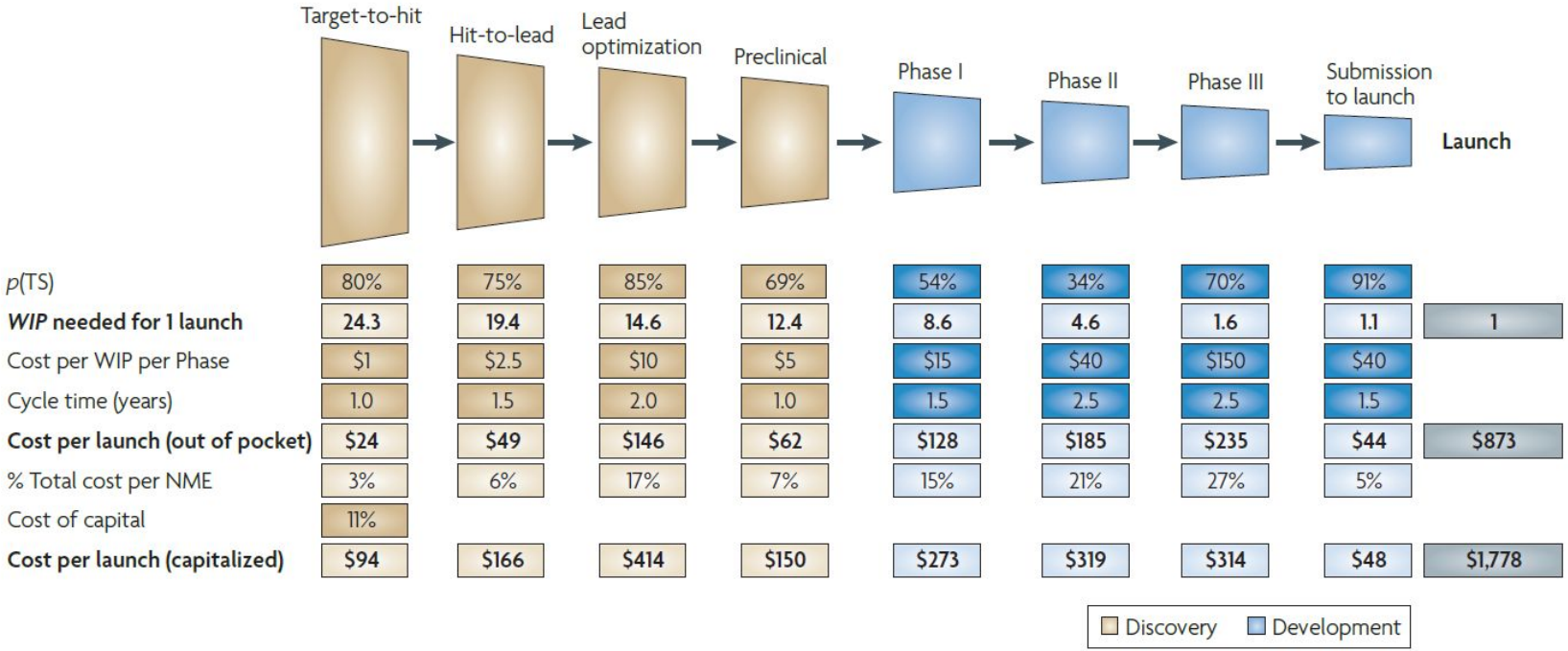
*Wegovy* was approved by the FDA for weight management at once-weekly 2.4 mg injectable doses in 2022.

Rybelsus tablets are approved by the FDA used for adults with type 2 diabetes to control blood sugar levels.



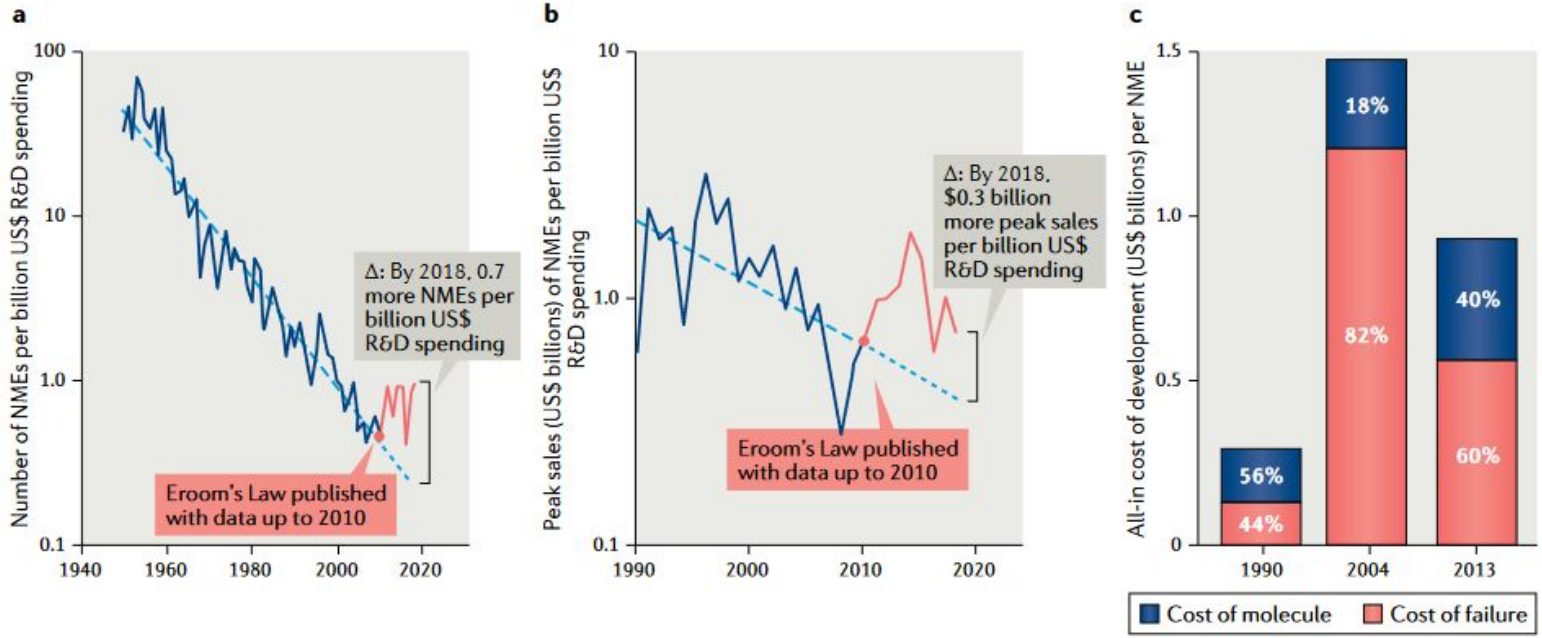

Data source: GlobalData

# Risks and costs associated with each stage of the linear view of drug discovery



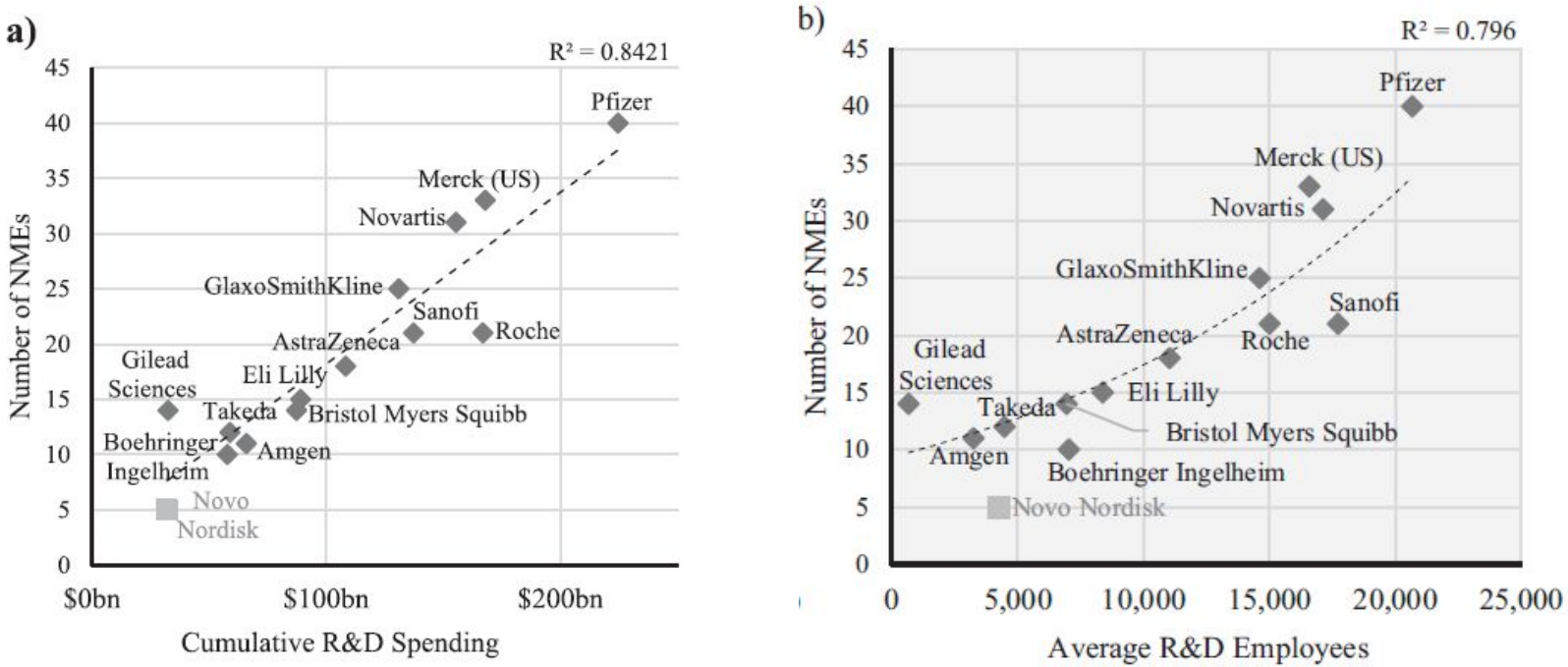

**pTS**: probability of technical success. **WIP**: work in progress; **Capitalized cost**: Out-of-pocket cost corrected for cost of capital, standard for long-term investments; **Out-of-pocket cost**: total cost required to expect one drug launch, taking into account attrition, but not the cost of capital; **Cost of capital**: annual rate of return expected by investors based on the level of risk of the investment. Paul *et al.*, Nature Reviews Drug Discovery, 2010.

# (Breaking?) The Eroom's Law



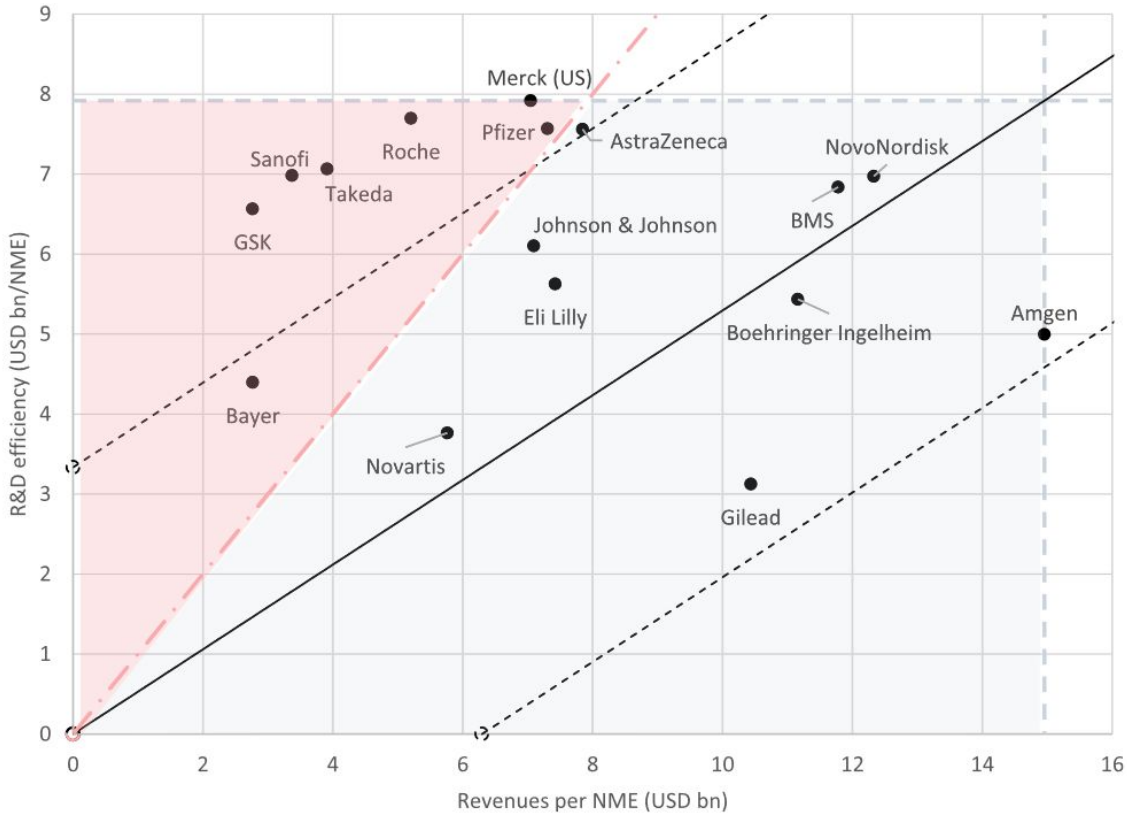

Ringel, Michael S., Jack W. Scannell, Mathias Baedeker, and Ulrik Schulze. "Breaking Eroom's Law." Nature Reviews Drug Discovery 19, no. 12 (April 16, 2020): 833–34.

# Drug discovery and development require huge investment and large interdisciplinary teams




Schuhmacher, Alexander, Lucas Wilisch, Michael Kuss, Andreas Kandelbauer, Markus Hinder, and Oliver Gassmann. "R&D Efficiency of Leading Pharmaceutical Companies – A 20-Year Analysis." *Drug Discovery Today* 26, no. 8 (August 1, 2021): 1784–89. https://doi.org/10.1016/j.drudis.2021.05.005.

# Profits generated by new molecule entities (NMEs) cannot cover the cost in some companies in the last 20 years



# 危机

~~*n.* crisis~~

Danger + Opportunity

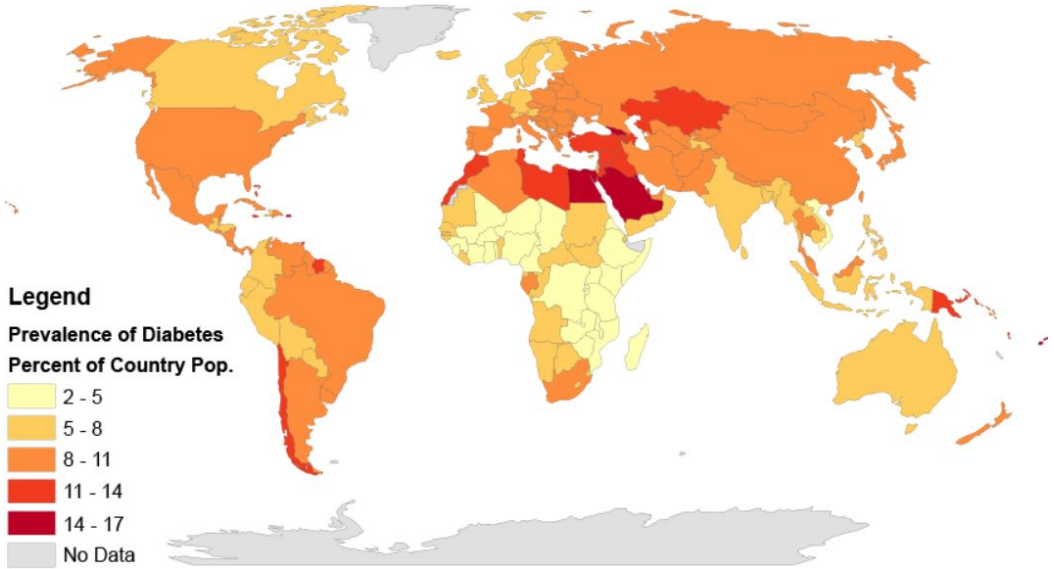
# The social context of drug discovery: a role-playing game

We consider a case study of developing new drugs to treat complications caused by type II diabetes, which affects on average 9.2% of the world population.

We divide the classroom into four personas.

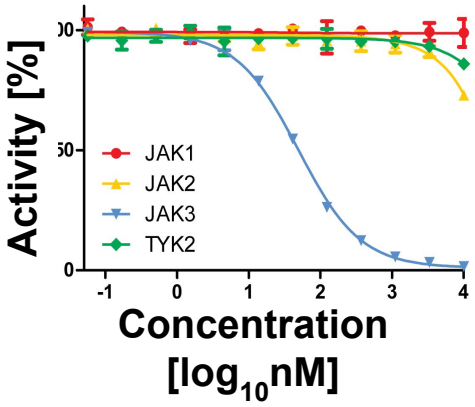
1. Patients
2. Medical doctors
3. Drug discovery company
4. Insurance company
5. The regulatory agency

**Questions for each group**: (1) What are your main interests and concerns? (2) With which other group do you have to work together and why? And what are your priorities? Rank the partners. (4) What are the ideal and worse scenarios for you?

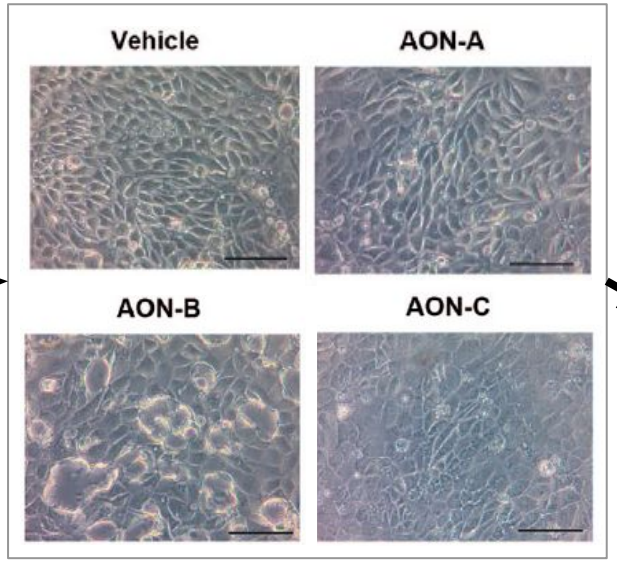



Global prevalence of diabetes from 2014, using data from 195 countries. Source: Wikimedia. Author: Walter Scott Wilkens. Reused with CC-AS 4.0 license.

# Classical workflow of efficacy and toxicity assessment

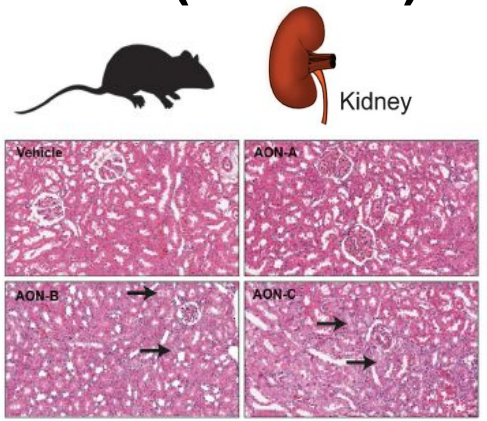



**Biochemical & biophysical assays**



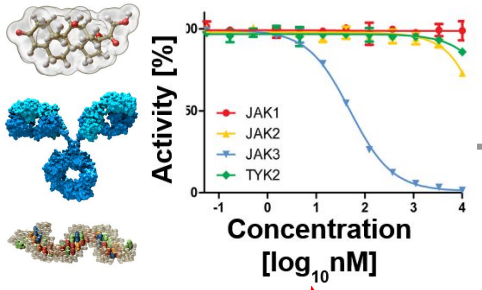

**Cellular assays (*in vitro*)**

## Animal experiments (*in vivo*)

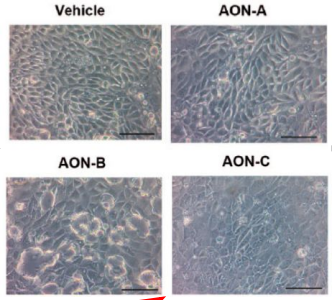


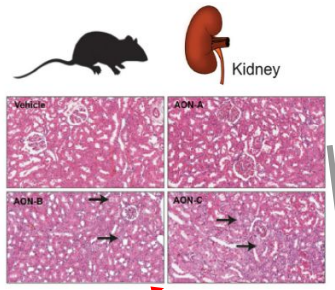

**Clinical trials**

# Computational methods empower efficacy and toxicity assessment



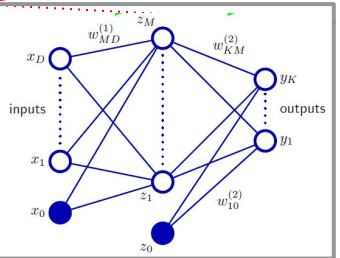


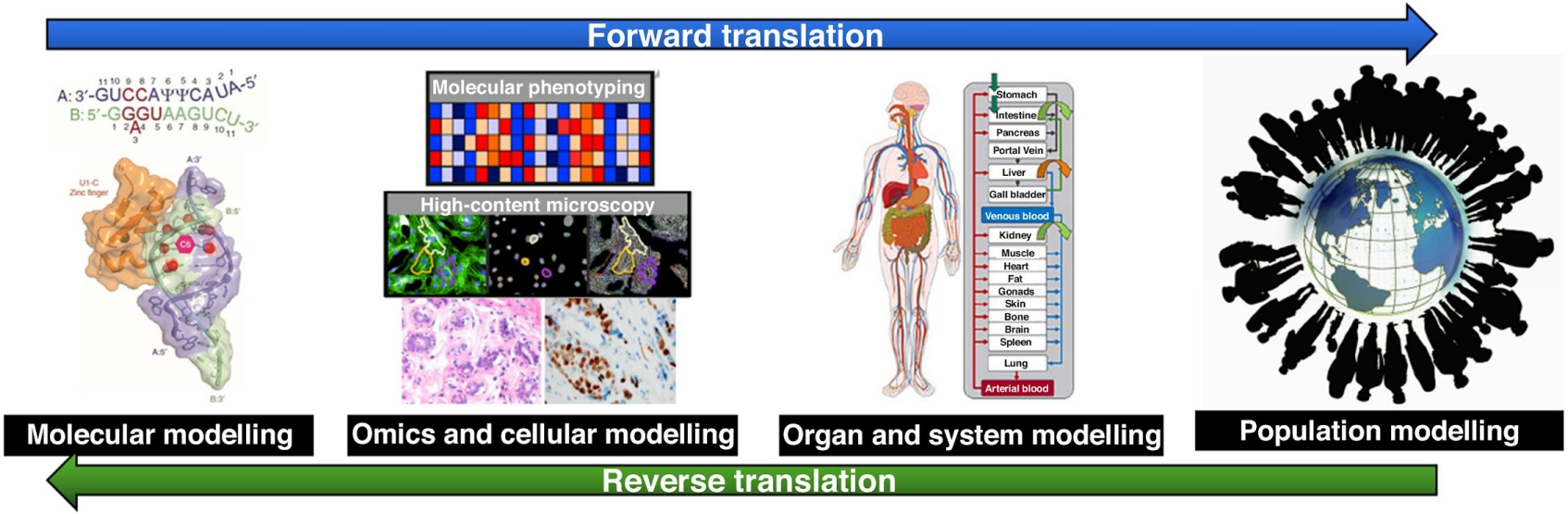

High-throughput technologies (omics, microscopy, etc.)

$$\frac{\partial u}{\partial t} = \underbrace{D\frac{\partial^2 u}{\partial x^2}}_{\text{Diffusion}} + \underbrace{ku}_{\text{Binding}}$$



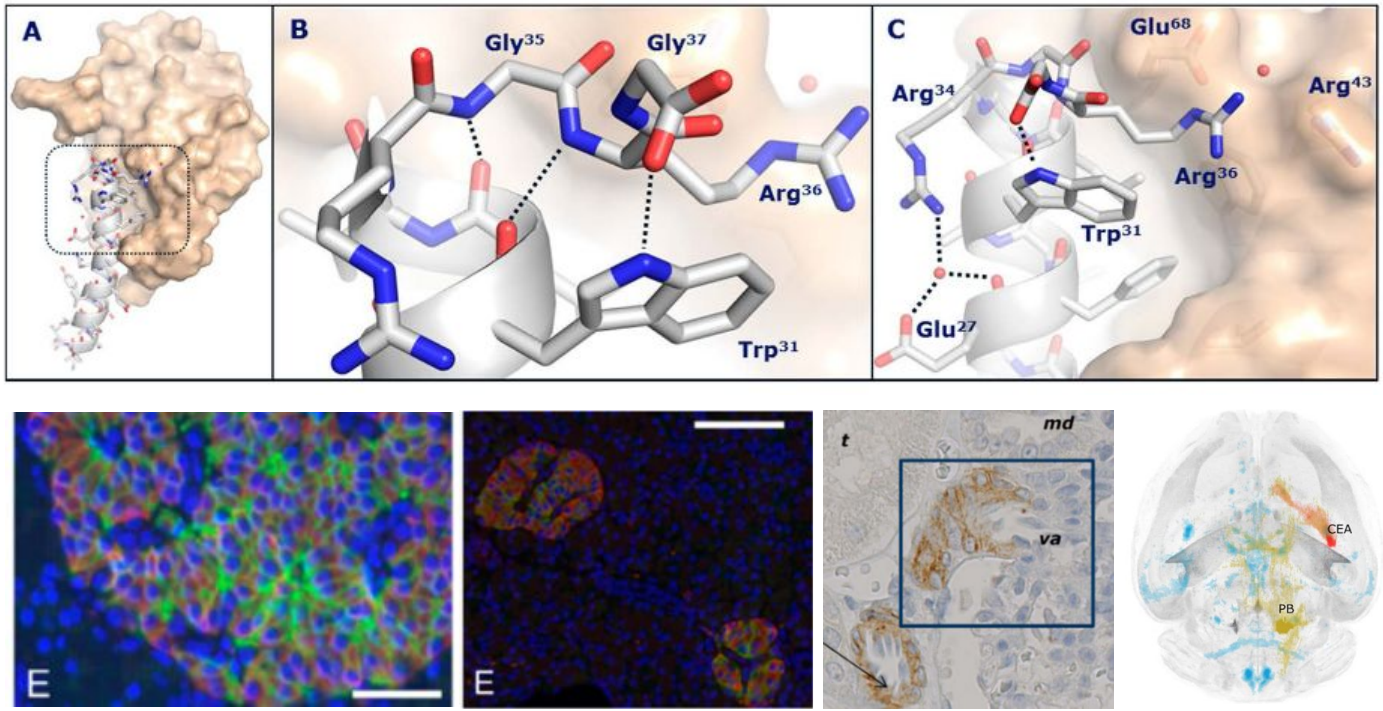

**Mechanistic, causal, and statistical models**

# The multiscale modelling view of drug discovery




Zhang, Jitao David, Lisa Sach-Peltason, Christian Kramer, Ken Wang, and Martin Ebeling. 2020. “Multiscale Modelling of Drug Mechanism and Safety.” Drug Discovery Today 25 (3): 519–34. https://doi.org/10.1016/j.drudis.2019.12.009.

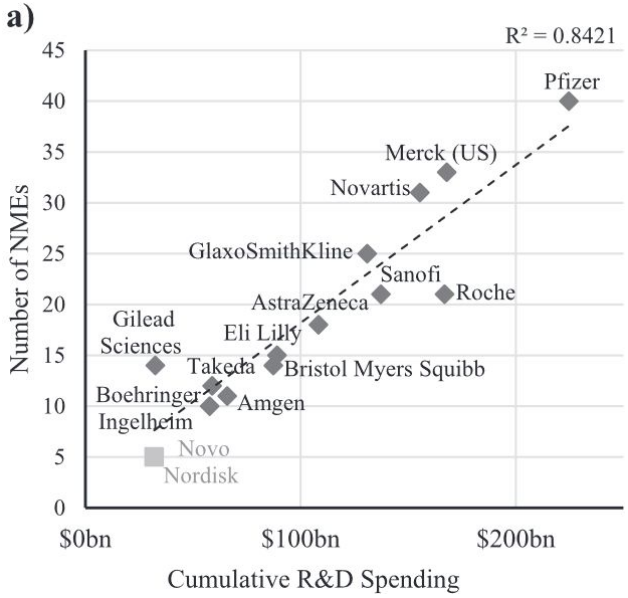
# An example of multiscale understanding with semaglutide



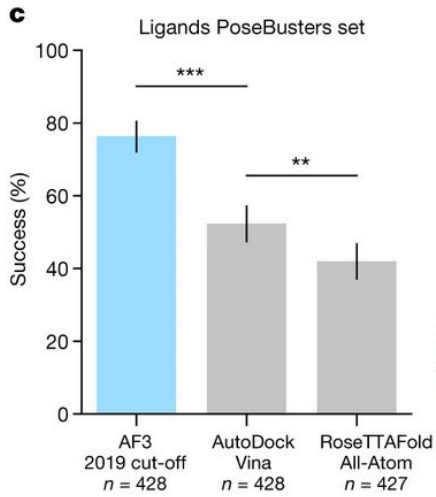

Top panels: crystal structure of the semaglutide peptide backbone (gray) in complex with its target, GLP-1 receptor (golden surfaces).

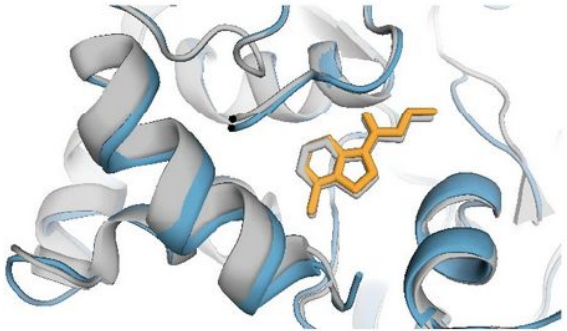
Bottom panels (from left to right): immunostaining of monkey pancreas, human pancreas, monkey muscle, and connectivity map of mice brain.

# Quest of the course: to make drug discovery efficient and sustainable with mathematics and informatics




R&D efficiency of leading pharma companies, 1999-2018 (Schumacher *et al.*, 2021)



Accurate structure prediction of biomolecular interactions with *AlphaFold3* (Abramson *et al.*, 2024). The *PoseBuster* set: 428 protein-ligand released to PDB after 2021. Success: pocket-aligned ligand Root Mean Square Deviation (RMSD) of atomic positions <= 2Å. Right: AF3 prediction for which docking tools *Vina* and *Gold* were less accurate (Human Notum bound to inhibitor ARUK3004556)

## Conclusions

1. Small molecules, proteins, and oligonucleotides are common modalities of drugs.
2. Major players in the game of drug discovery have distinct interests and concerns. They interact and give feedback to each other to identify new drugs.
3. Mathematical models and informatics tools integrate information and data across scales to inform drug discovery.

# The path of the course