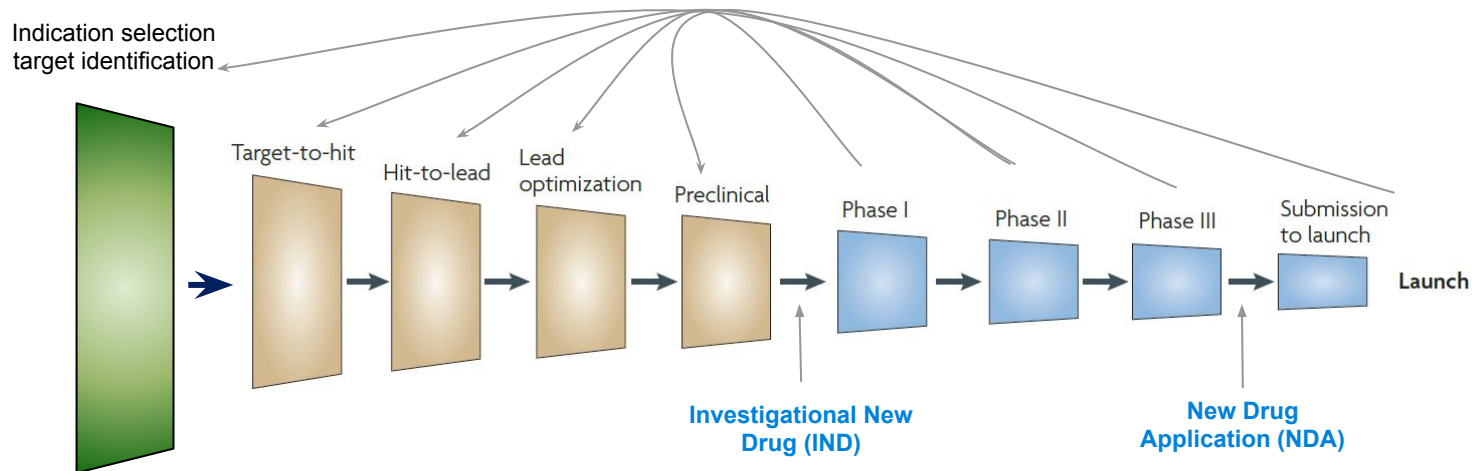


# AMIDD 2024 Lecture 2:

## Mathematics and informatics are essential for drug discovery



*Dr. Jitao David Zhang, Computational Biologist*

<sup>1</sup> *Pharmaceutical Sciences, Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche;*

<sup>2</sup> *Department of Mathematics and Computer Sciences, University of Basel*

# Outline

1. Major players in drug discovery with a role-play game
2. Economy and productivity of drug discovery
3. Mathematics and informatics are essential for drug discovery

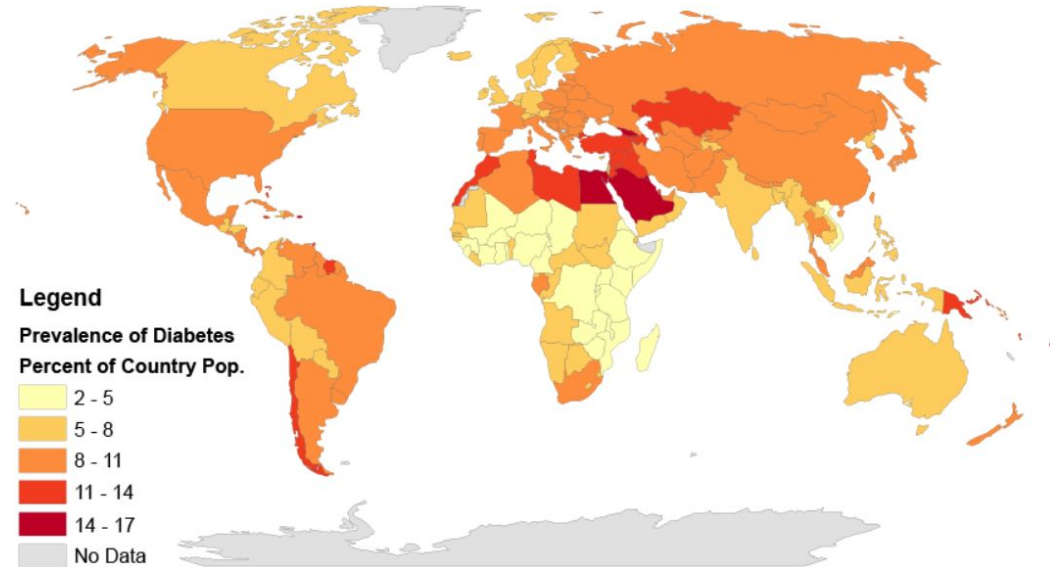
# The social context of drug discovery: a role-playing game

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.

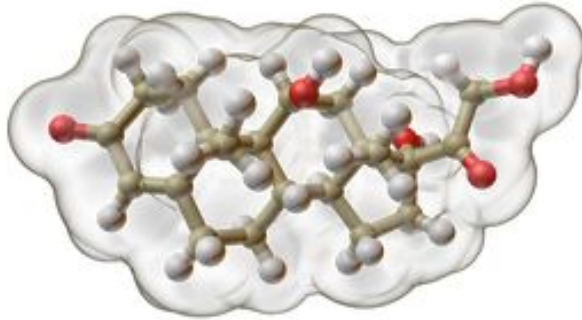
1. Patients
2. Medical doctors
3. Drug discovery company
4. The regulatory agency

**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?

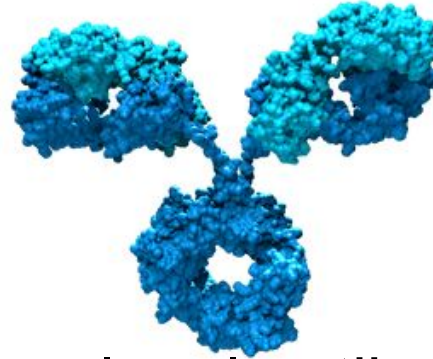


[Global prevalence of diabetes from 2014](#), using data from 195 countries.  
 Source: Wikimedia. Author: Walter Scott Wilkens. Reused with CC-AS 4.0 license.

# A zoo of modalities



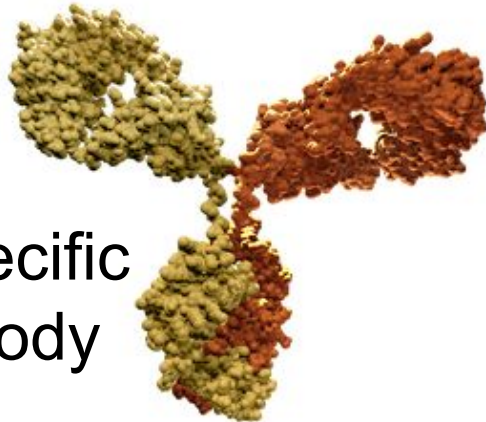
Small molecule



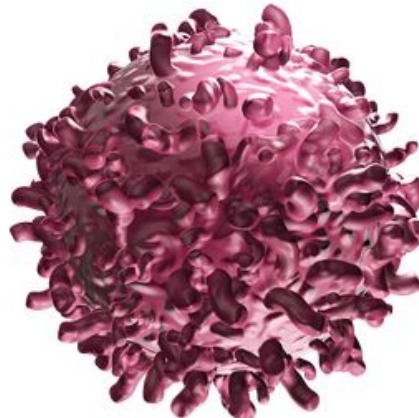
Monoclonal antibody



Oligonucleotides



Bispecific antibody



Chimeric  
Antigen  
Receptor  
(CAR)  
T-cells

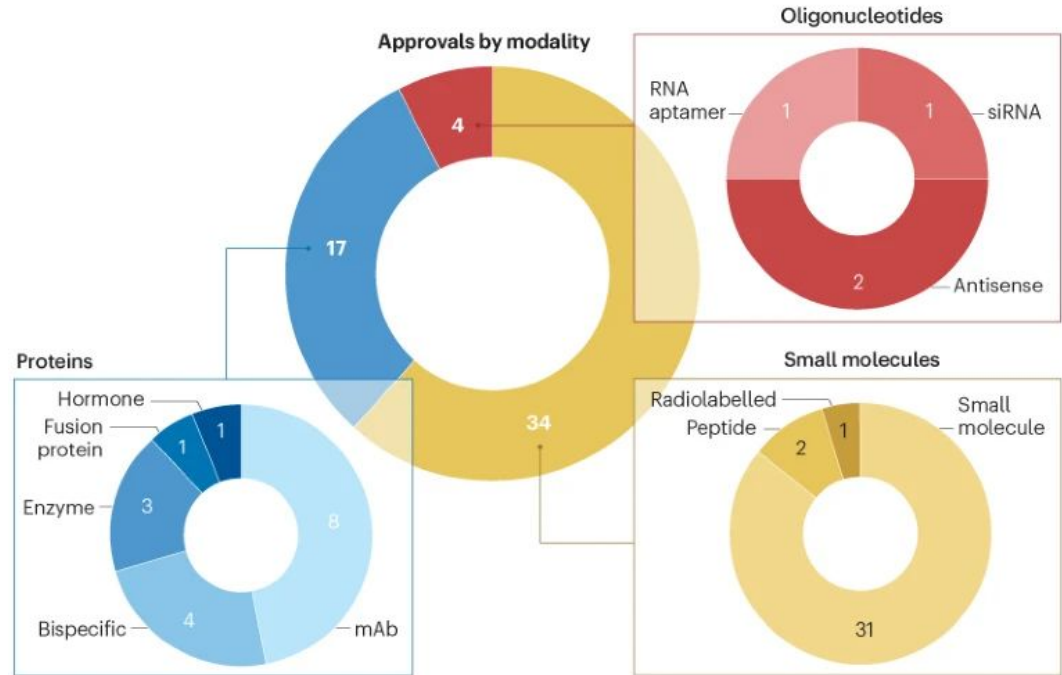


mRNA vaccines

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

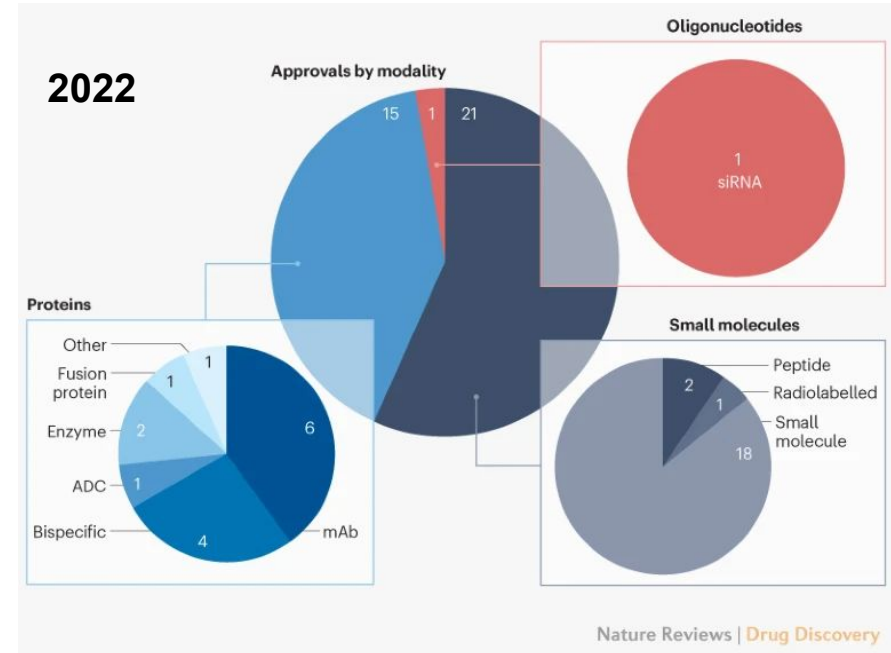
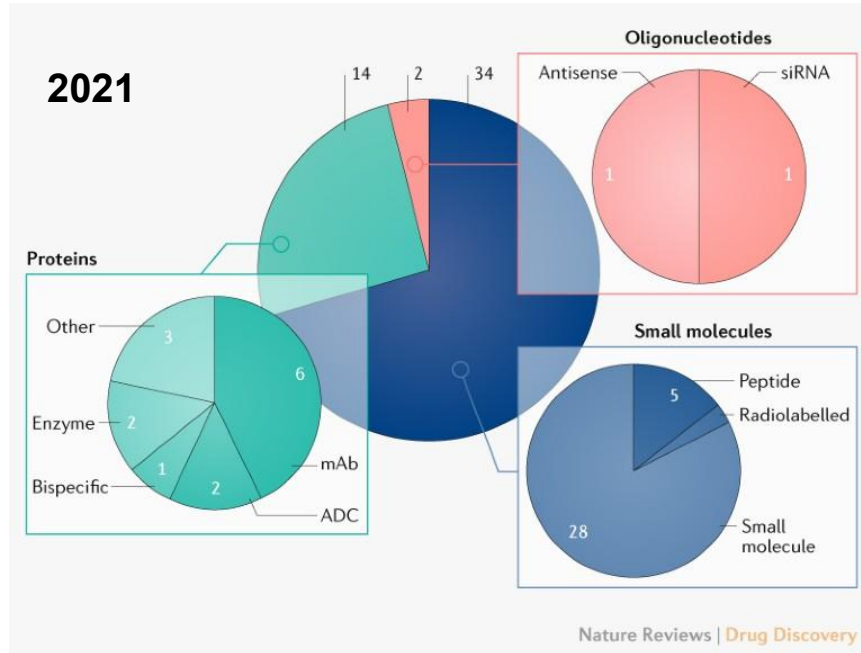
## Three modalities

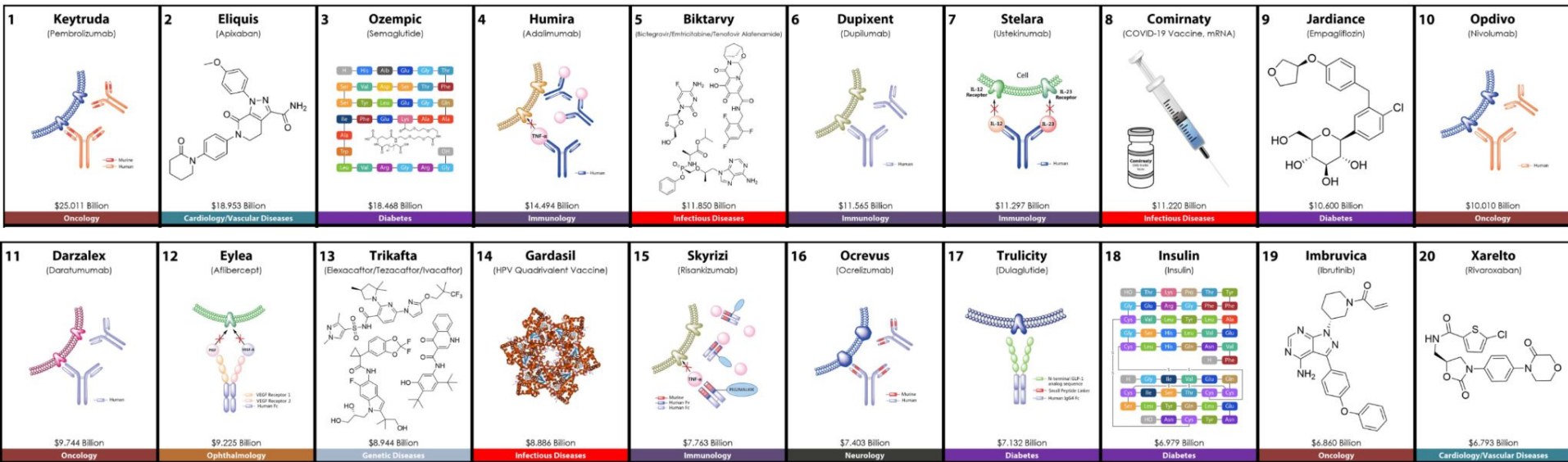
- Small molecules (molecular weight under 900 daltons)
  - mAb: monoclonal antibody
  - Bispecific: bispecific antibodies
- Proteins
  - siRNA: small interfering RNA
- Oligonucleotides



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





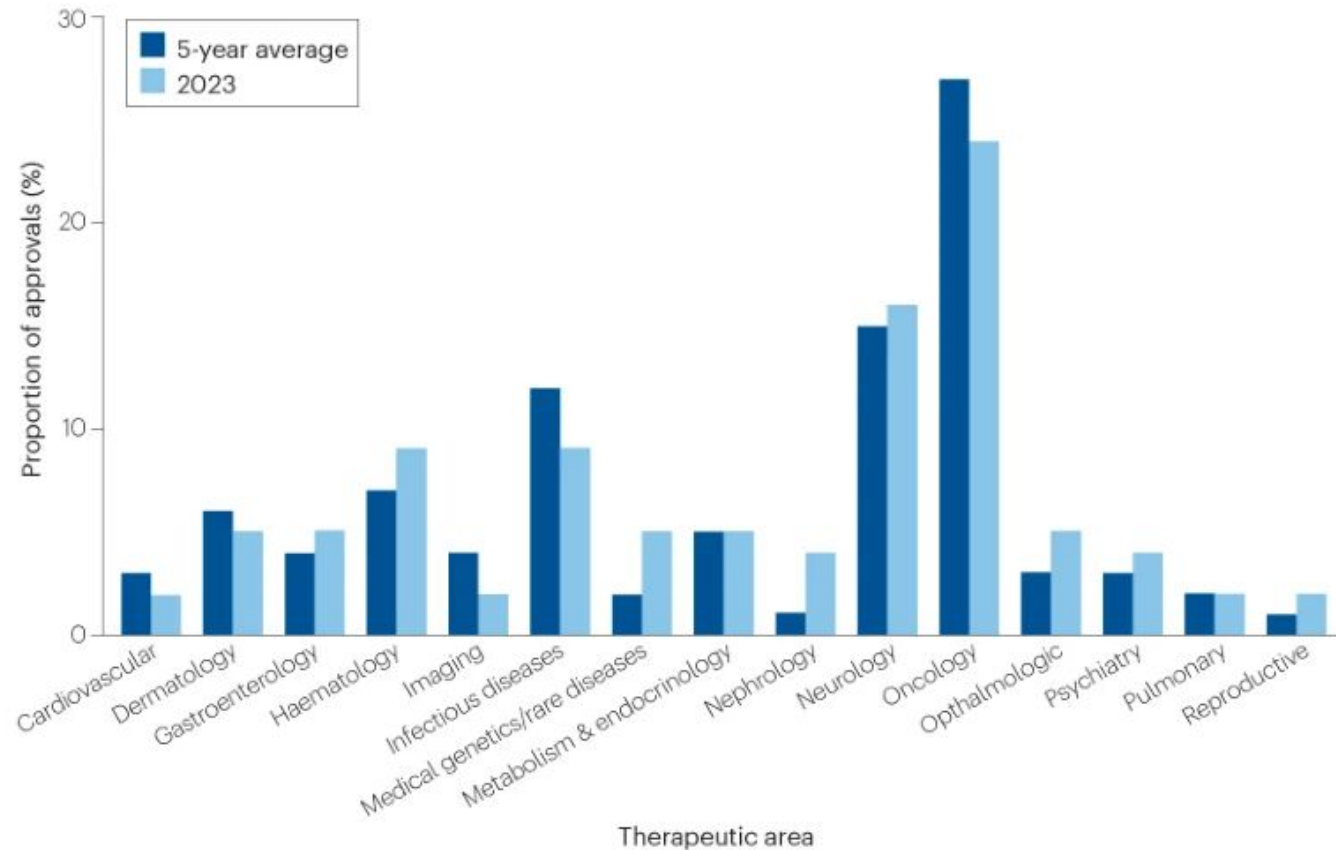
## Top 20 pharmaceuticals by sales in 2023

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?



# New drug approvals vary between disease areas





# Forms and market size of Semaglutide

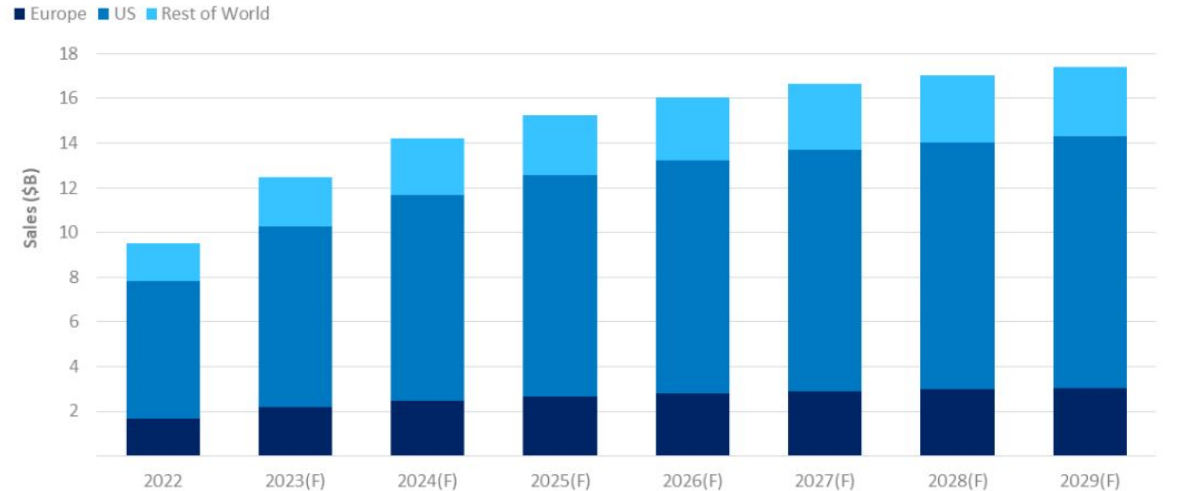
*Ozempic*, as well as *Wegovy* and *Rybelsus*, are **brand names** of semaglutide.

*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.

Forecast sales for Ozempic 2022–29

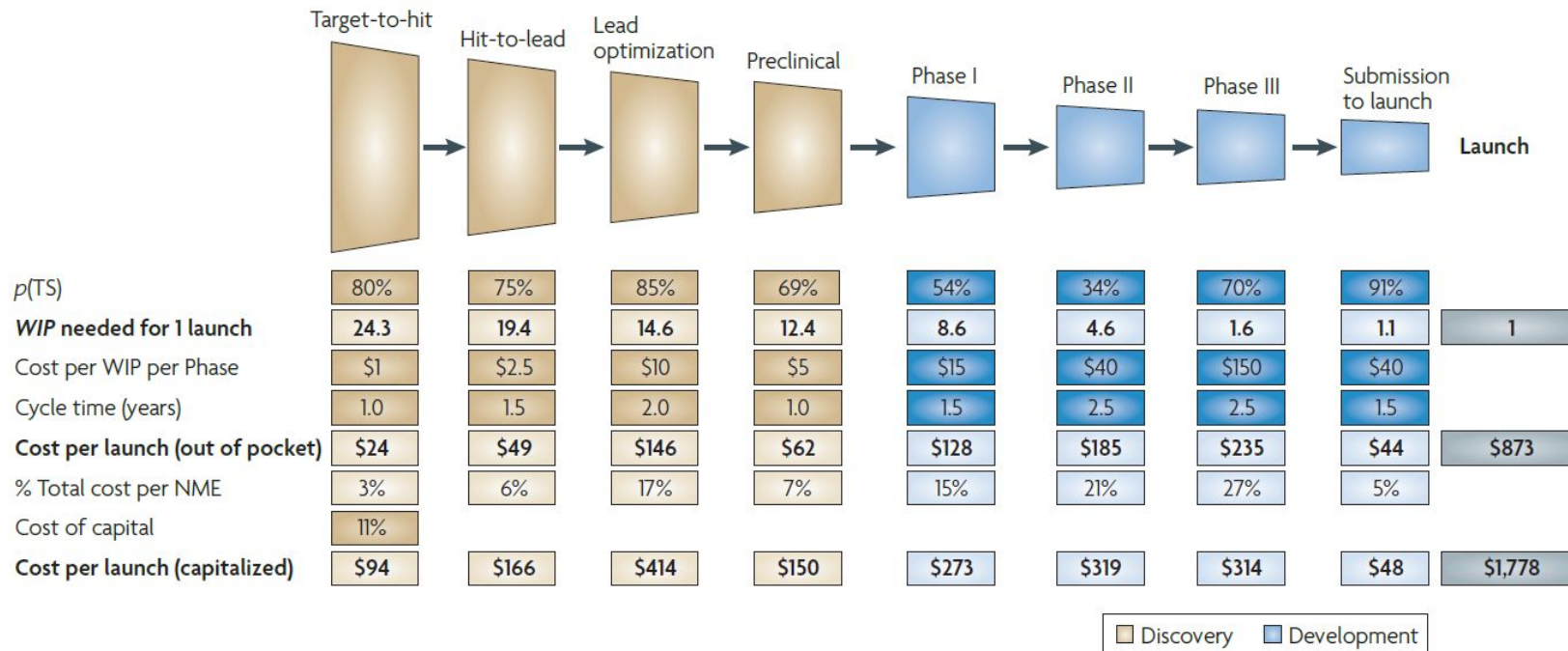


GlobalData.

Source: GlobalData Drugs Database (Accessed April 21, 2023)

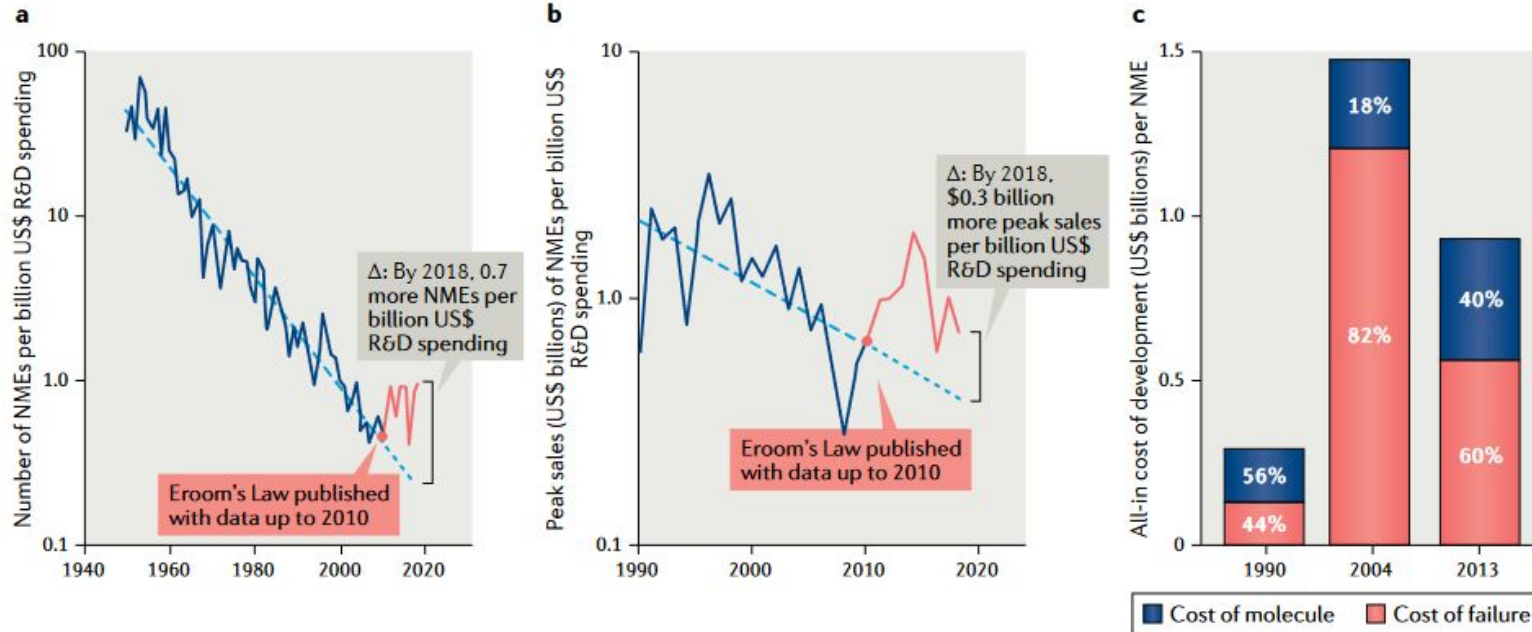
Data source: [GlobalData](https://www.globaldata.com)

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



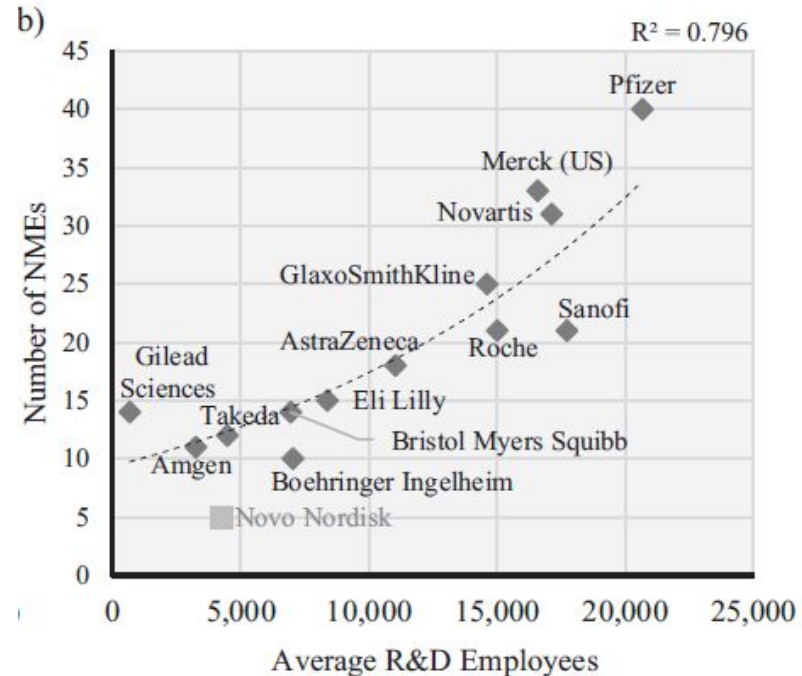
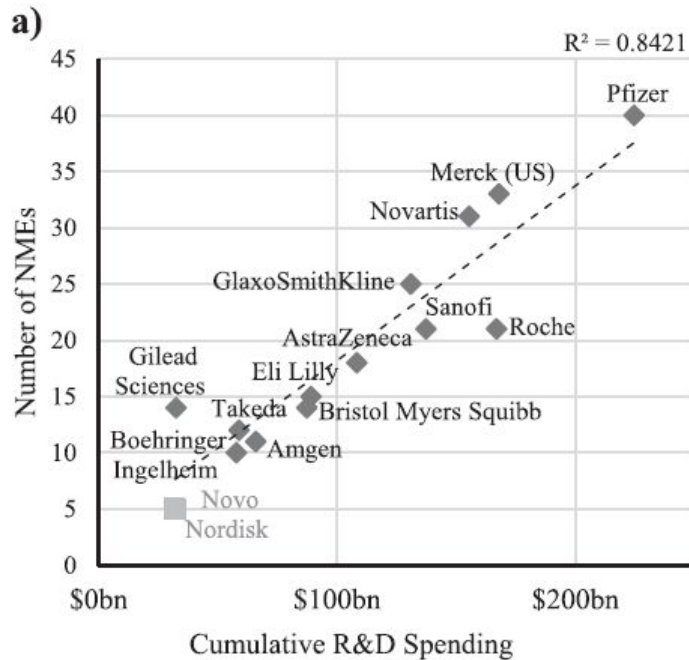
$p(TS)$ : probability of technical success. **WIP**: work in progress; **Capitalized cost**: Out-of-pocket cost corrected for cost of capital, standard for long-term investments; **Out-of-pocket cost**: total cost required to expect one drug launch, taking into account attrition, but not the cost of 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



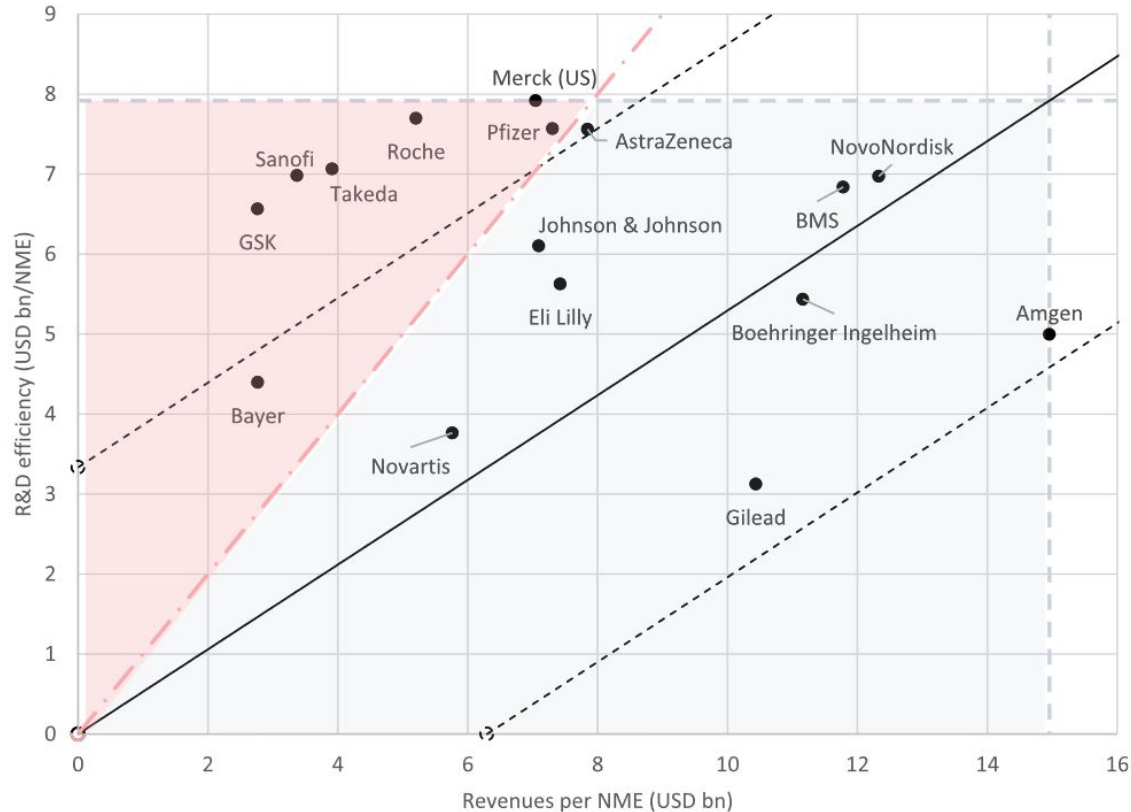
Ringel, Michael S., Jack W. Scannell, Mathias Baedeker, and Ulrik Schulze. "Breaking Eroom's Law." *Nature Reviews Drug Discovery* 19, no. 12 (April 16, 2020): 833–34.

# 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

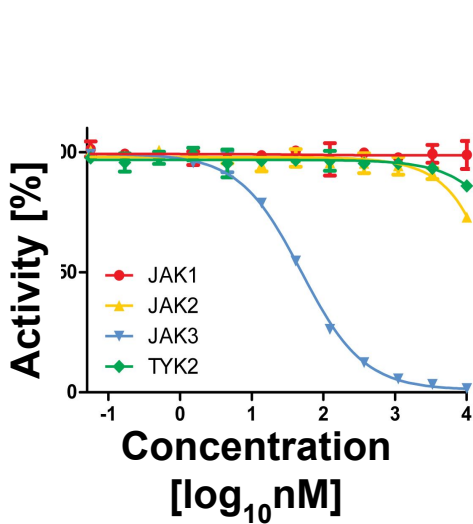


# 危机

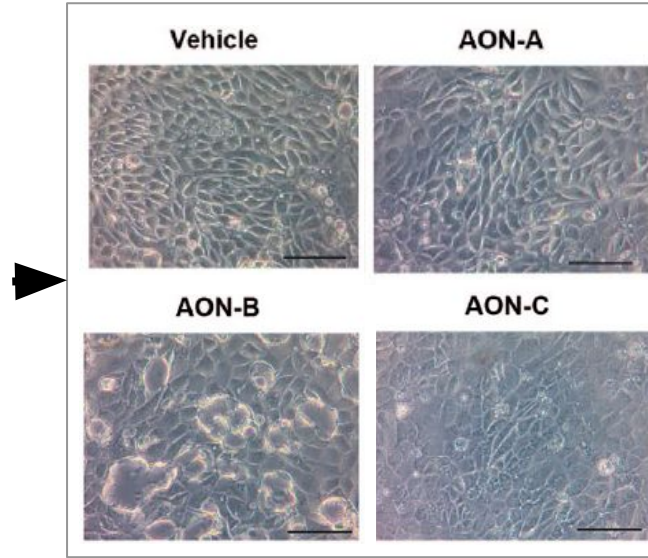
— *n. crisis* —

Danger + Opportunity

# Classical workflow of efficacy and toxicity assessment

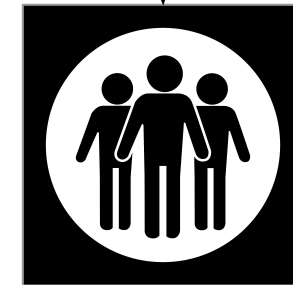
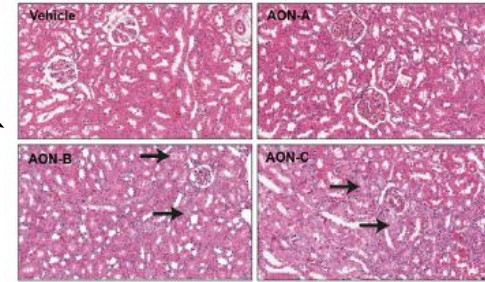


**Biochemical & biophysical assays**



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

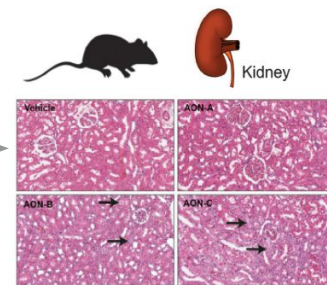
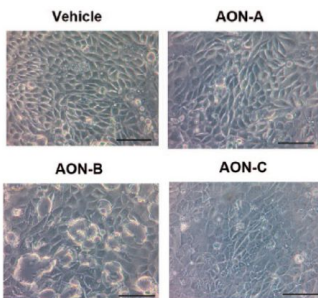
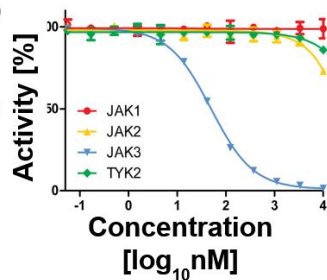
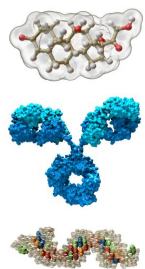
**Animal experiments  
(*in vivo*)**



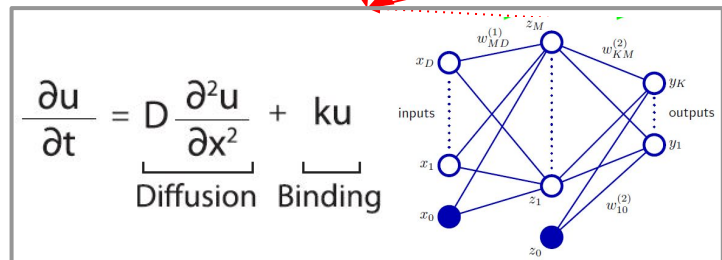
**Clinical trials**



# Computational methods empower efficacy and toxicity assessment



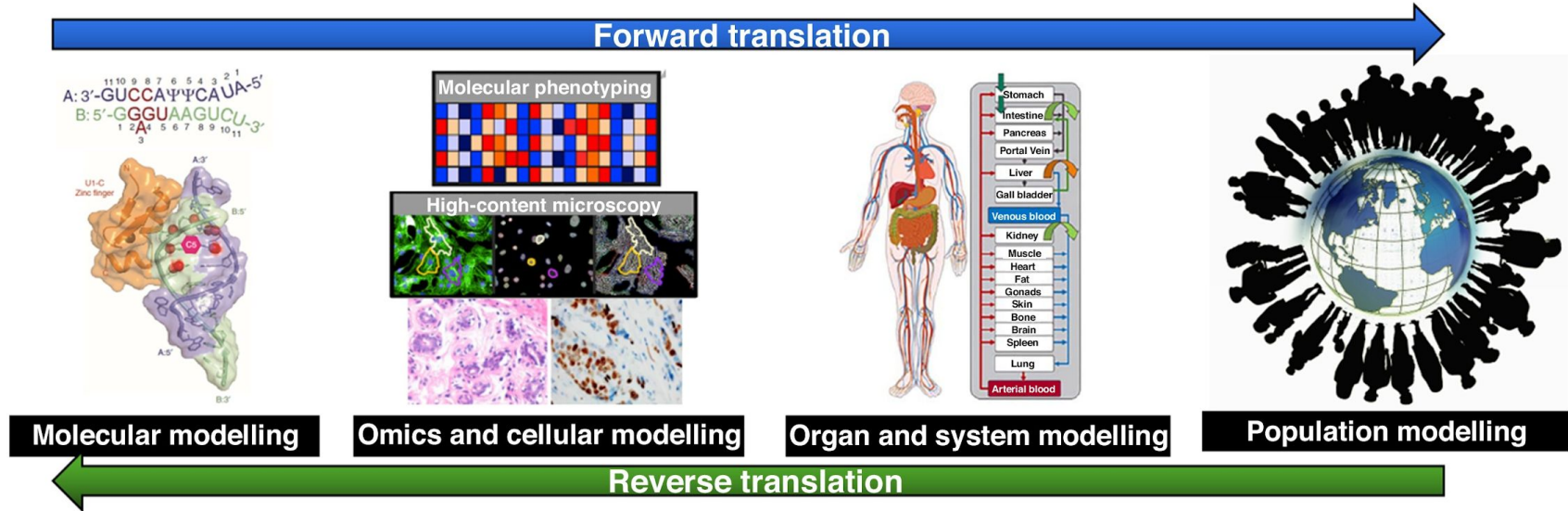
High-throughput technologies (omics, microscopy, etc.)



**Mechanistic, causal, and statistical models**



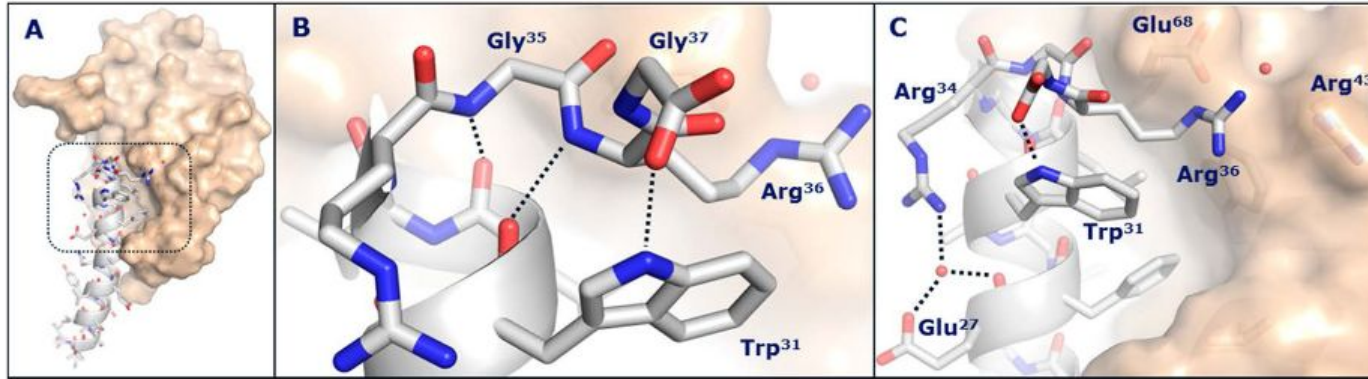
# The multiscale modelling view of drug discovery



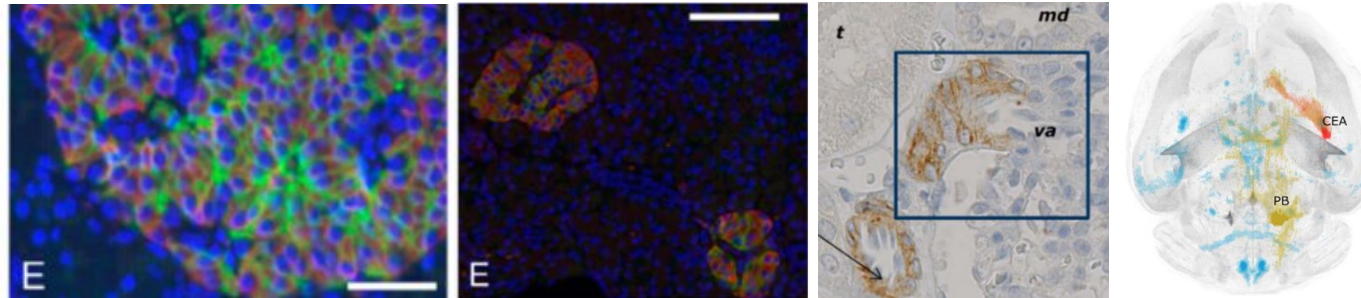
*Drug Discovery Today*

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

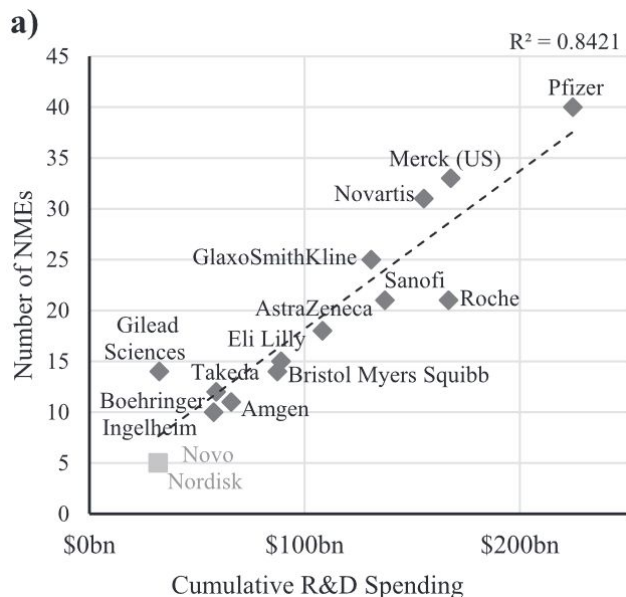


Top panels: crystal structure of the semaglutide peptide backbone (gray) in complex with its target, GLP-1 receptor (golden surfaces).

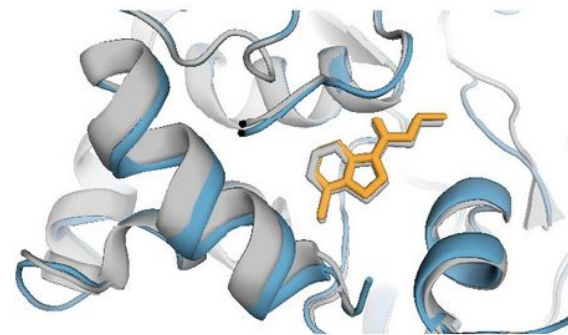
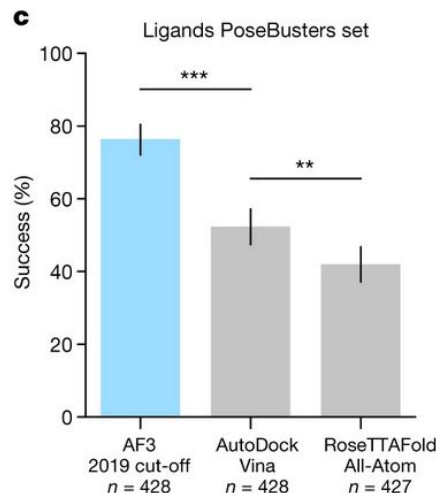


Bottom panels (from left to right): immunostaining of monkey pancreas, human pancreas, monkey muscle, and connectivity map of mice brain.

# 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  $\leq 2\text{\AA}$ . Right: AF3 prediction for which docking tools *Vina* and *Gold* were less accurate (Human Notum bound to inhibitor ARUK3004556)

# Backup slides

## Q1: What are the interests and concerns?

**Patients:** Interests: Time, Cost, Safety. Concerns: safety, convenience, cost. Addition: benefit/risk analysis; Trust. Efficacy compared to current standard of care.

**Medical doctors:** career, benefits of patients; concerns: does not work, responsible for it; conflict of interest (conferences, compensations), work with all other groups. Addition: overhead associated with the money, benefits (legal and illegal), who takes responsibility?

**Pharma:** money, good reputation (fast, working, low cost, low prize); concerns: failure, not approved by the agency, do harm (reputation). Intellectual Property. Cost effectiveness. Competitor. Research & Development staff/ideas. Patients/Doctors. Legal. Lack of reproducibility. How to diagnose? Technology debts. Length of life cycle. Agencies.

**Regulatory agency:** approving drugs that are safe and efficacious; concern: research integrity, fairness and evidence, cannot oversee everything, mistakes can do big harm. Understaffed. Legal. Patients pressure. Insider information. Corruption.

## Q2:

### Regulatory agencies

1. Patients
2. Company
3. Medical researcher (safety): integrity, security, transparency
4. Medical experts (efficacy, choice of prescribers)

Comments: company & medical experts, patient plays an ever more important role.

### Company

1. Patients
2. Agency
3. Medical doctors

Comments: agency, regulated interactions with medical experts, patient plays an ever more important role

### Medical doctors

1. Patients
2. Company
3. Agency (?) advice

Comments: patients, agency to give advice, regulated interactions with companies

### Patients

1. Medical doctors
2. Company<sup>22</sup>
3. Agencies

Comments: patients communicate a lot with other patients



## Patients

- Best outcome: it works, cured forever
- Worst scenario: worse or death, works for you but not approved, ignored diseases

## Medical doctors

- Patients are cured, positive results, impressive career
- Worsened condition, mistakes and liability

## Drug discovery company

- Fast development, little safety issue, high efficacy; Intellectual property; High sales
- Failure to find drugs; not approved; undetected harms/side effects; competitors; unengaged patients.  
Losing money

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## The regulatory agency

- Best: perfect working, company fully reliable and trusted
- Worse: large harm, held liability due to mistake and/or corruption, lost of trust