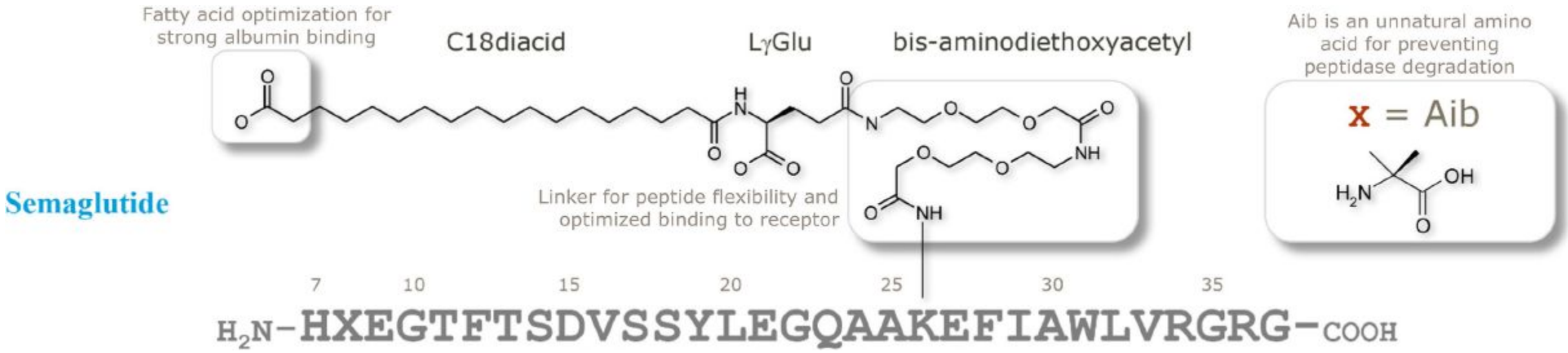
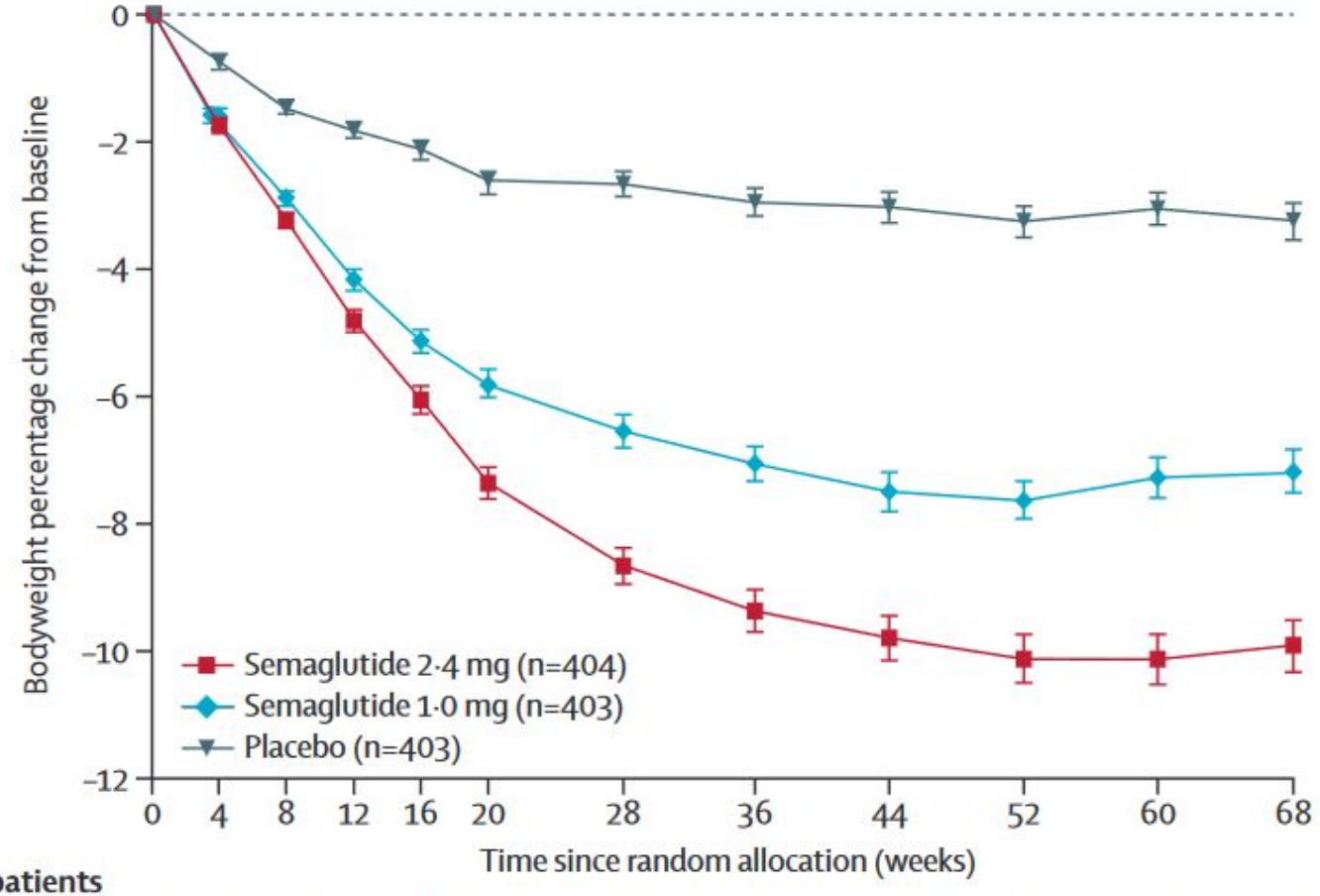
Applied Mathematics and Informatics In Drug Discovery (2023)



Dr. Jitao David Zhang, Computational Biologist

[1] Pharmaceutical Sciences, Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche;
[2] Department of Mathematics and Computer Sciences, University of Basel

STEP2: a clinical trial for Semaglutide 2.4mg once a week for overweight, obesity, and type-2 diabetes

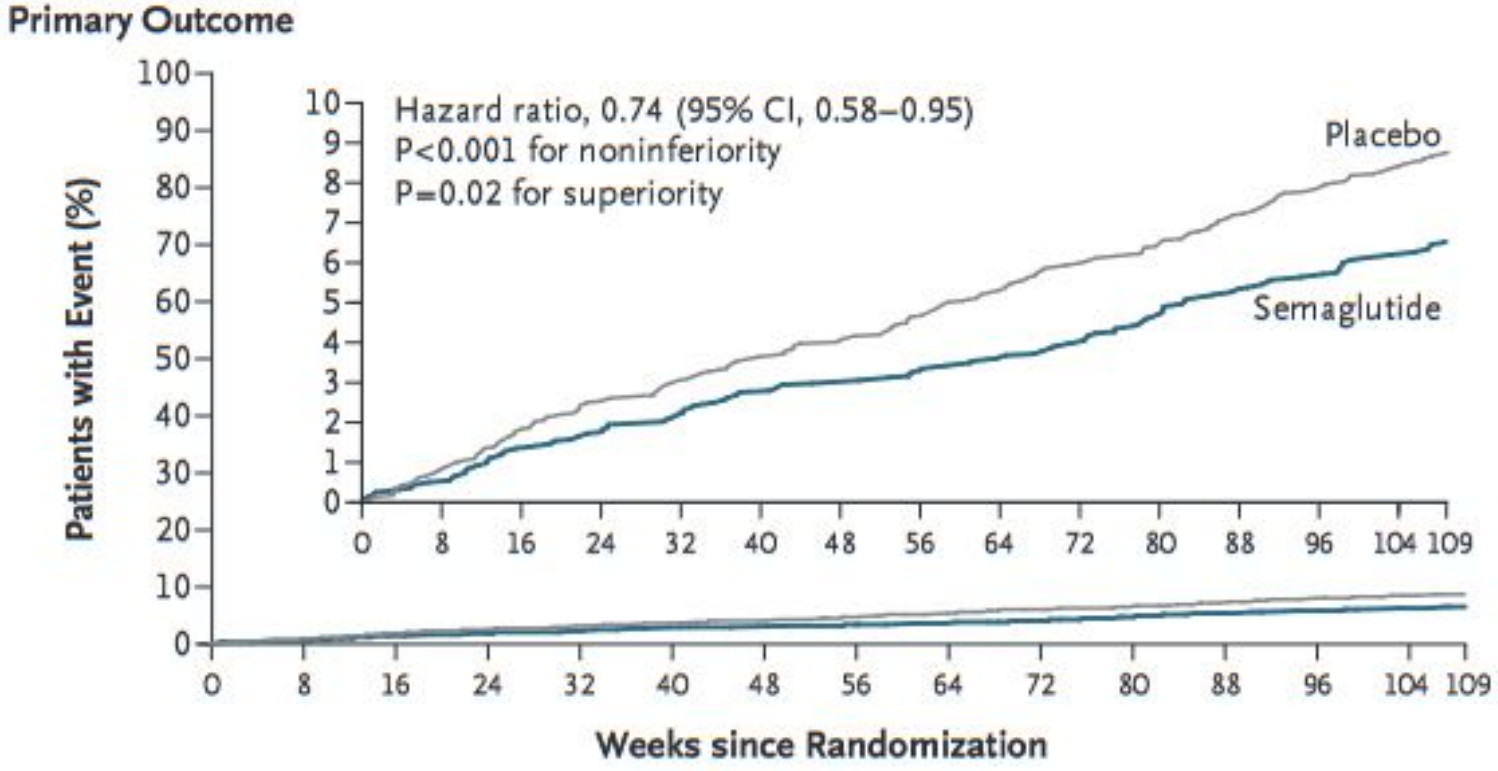


Number of patients

Semaglutide 2·4 mg	404	395	397	390	388	392	386	383	381	381	378	388
Semaglutide 1·0 mg	403	394	392	385	383	383	378	377	373	370	374	380
Placebo	403	398	394	389	387	383	381	377	371	367	366	376

Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial, Davies *et al.*, 2021

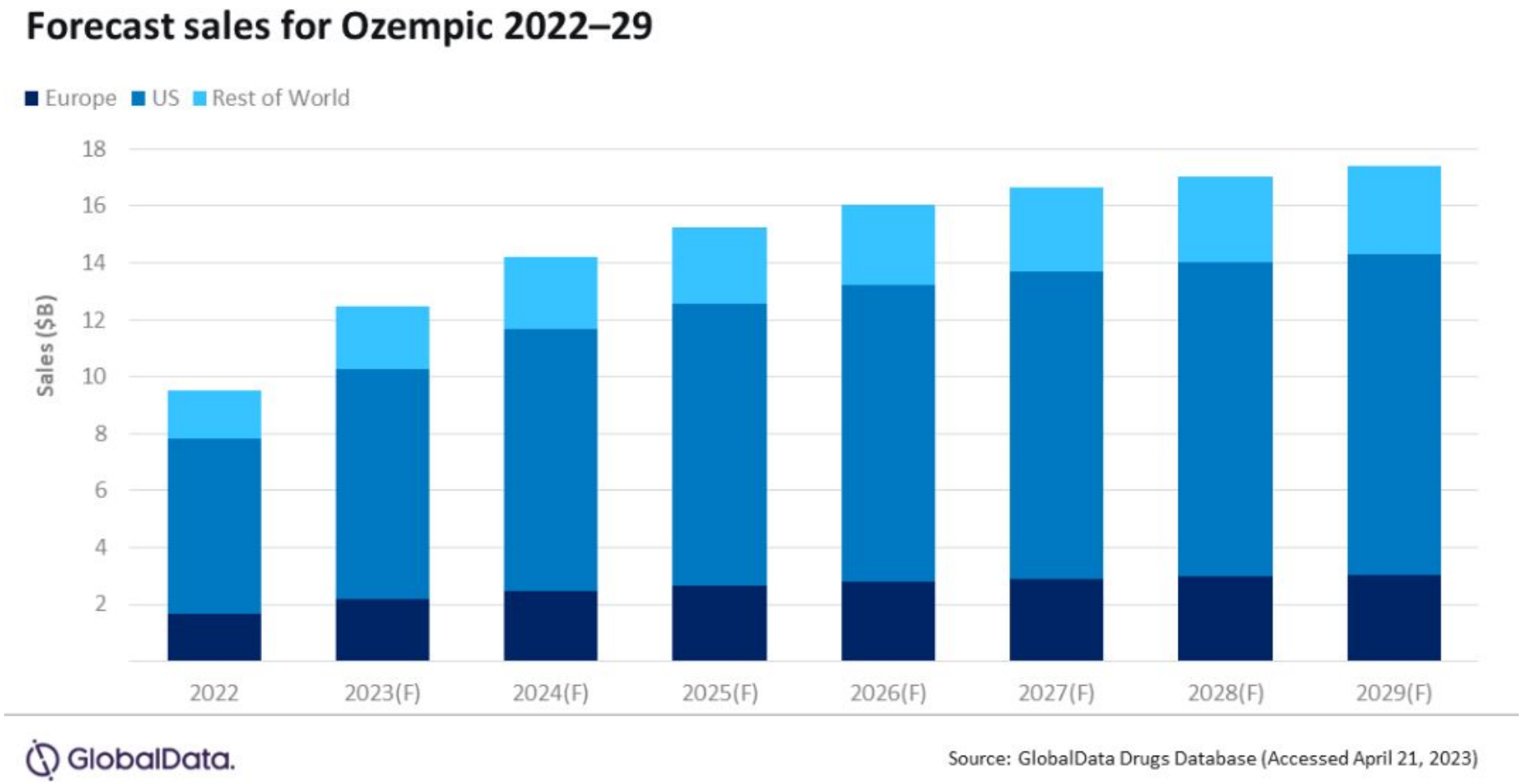
SUSTAIN-6: a non-inferiority clinical trial of semaglutide for cardiovascular safety in patients with type-2 diabetes



No. at Risk							
Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

[Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes](), Marso *et al.*, 2023

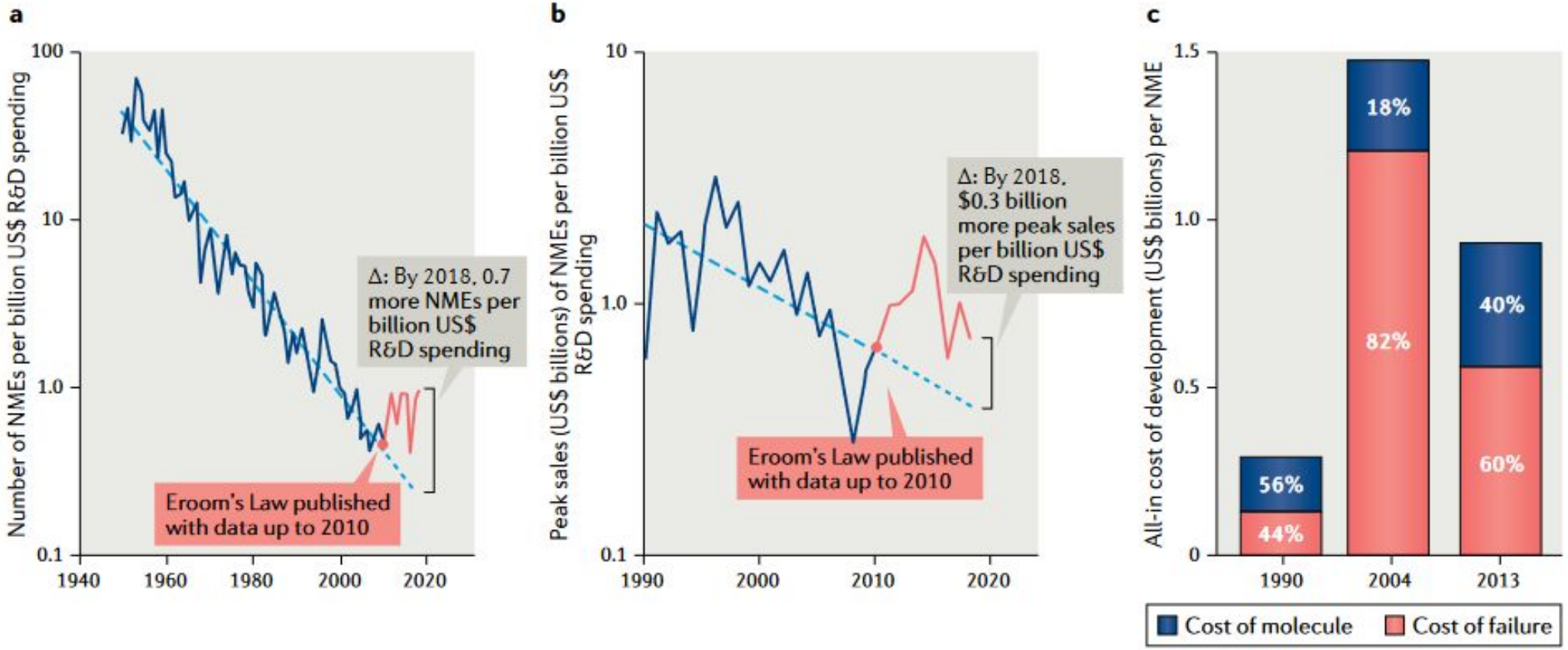
Market size and forecast for *Ozempic*



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

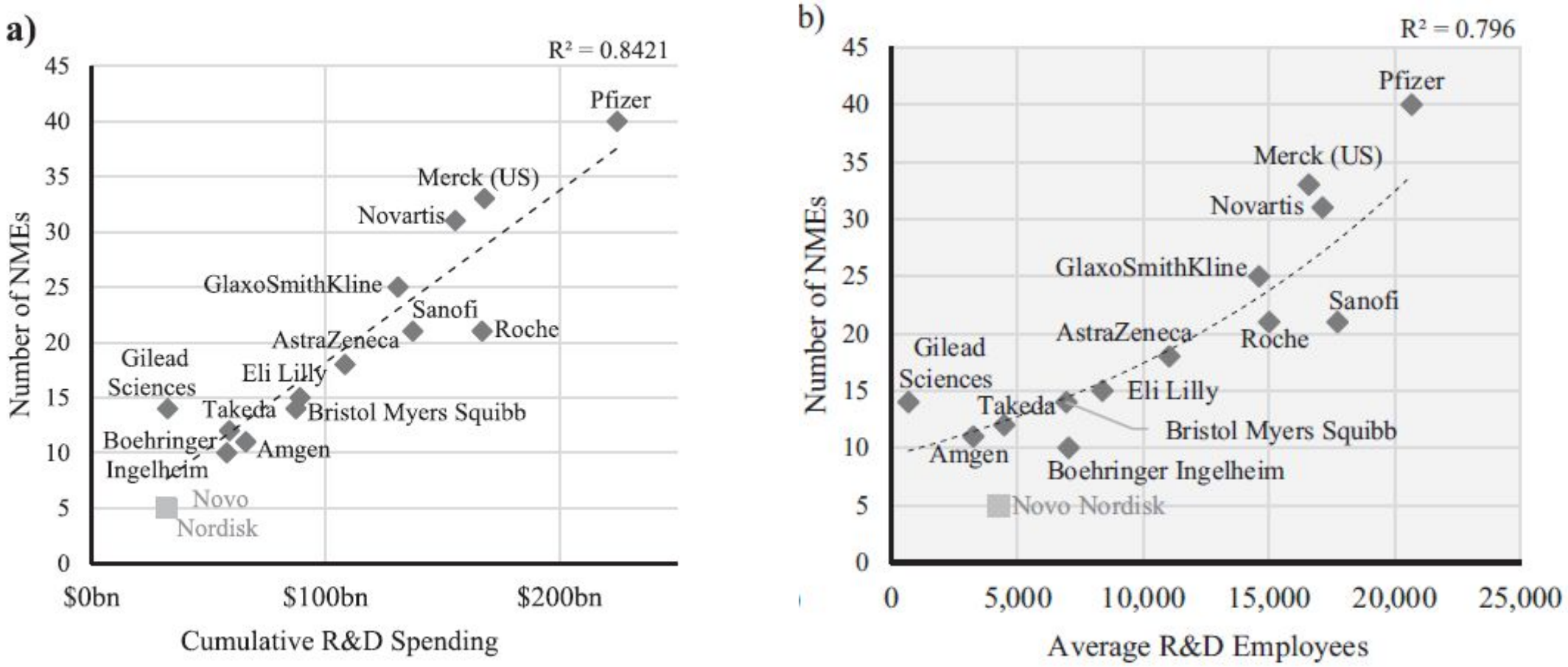
Data source: GlobalData

(Breaking?) The Eroom's Law



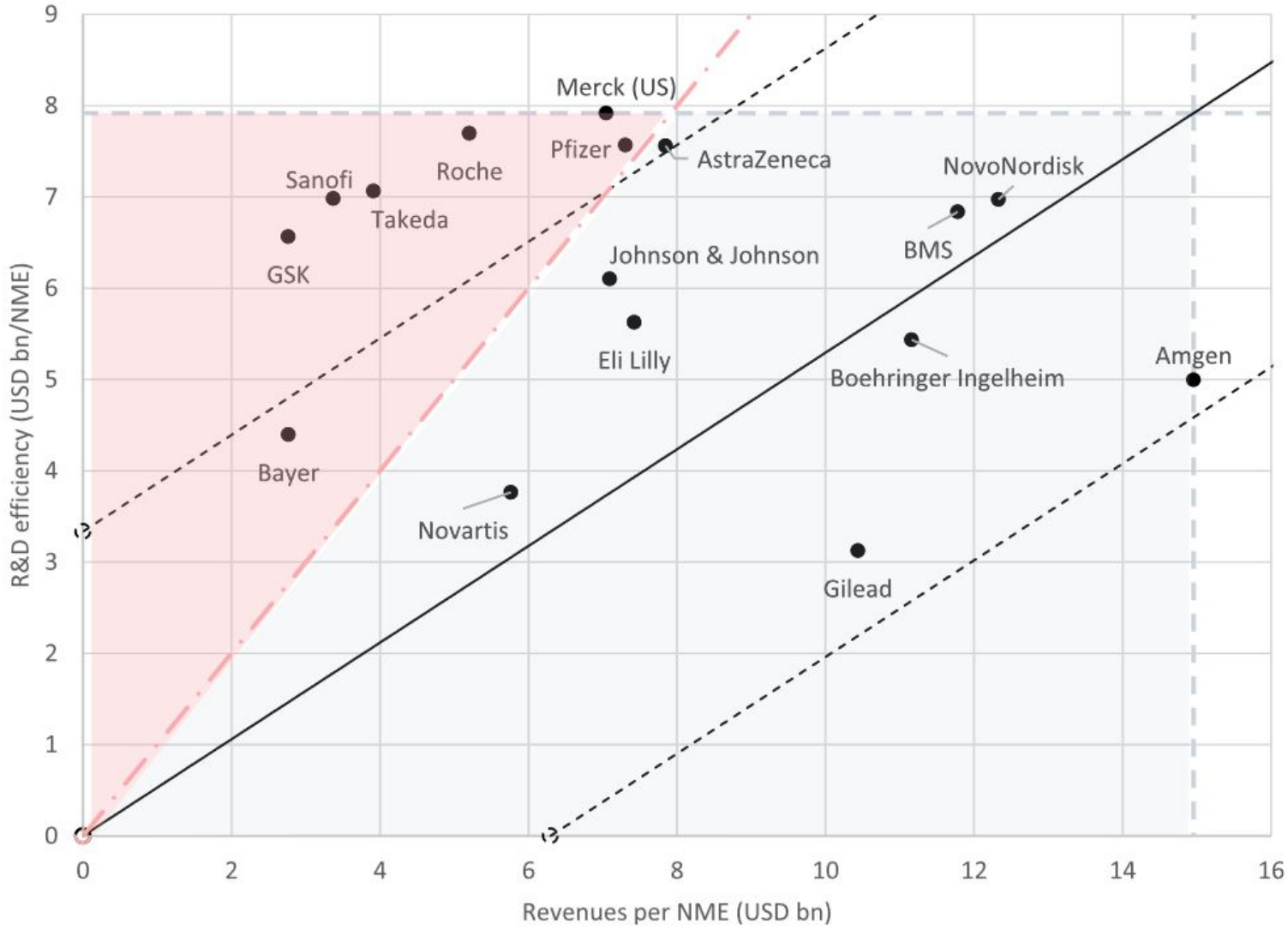
Ringel, Michael S., Jack W. Scannell, Mathias Baedeker, and Ulrik Schulze. "Breaking Eroom's Law." Nature Reviews Drug Discovery 19, no. 12 (April 16, 2020): 833–34.

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

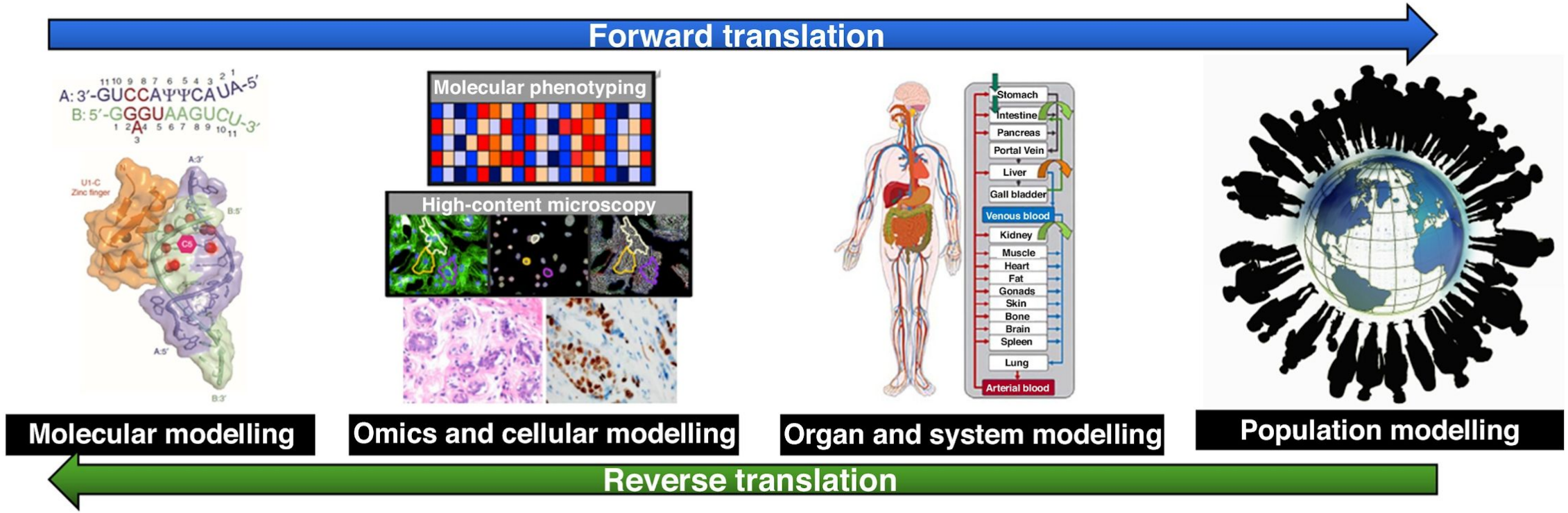


危机

~~*n.* crisis~~

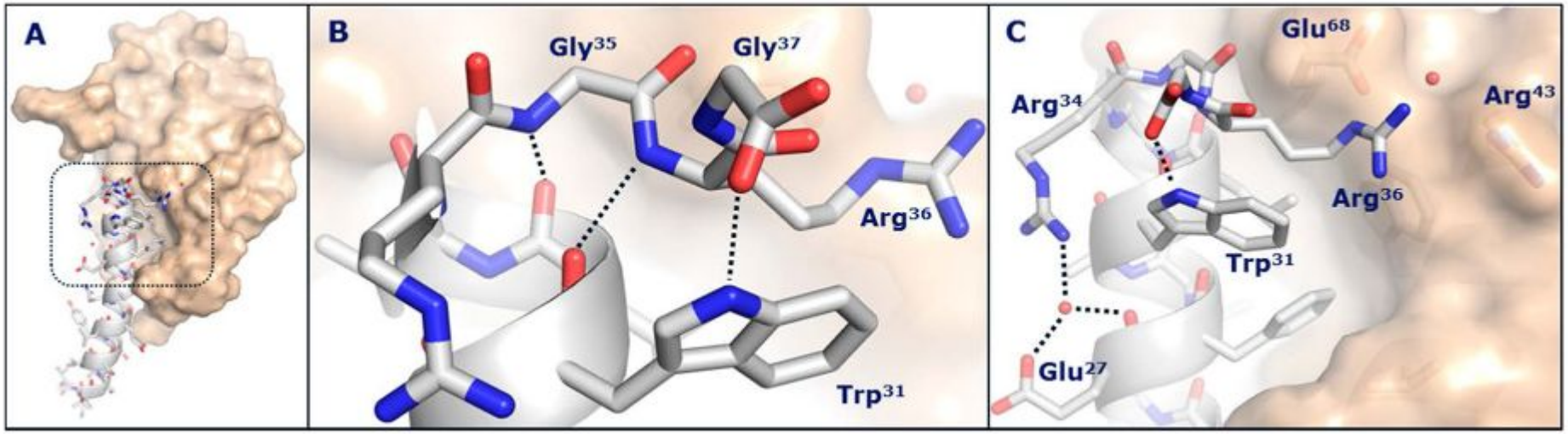
Danger + Opportunity

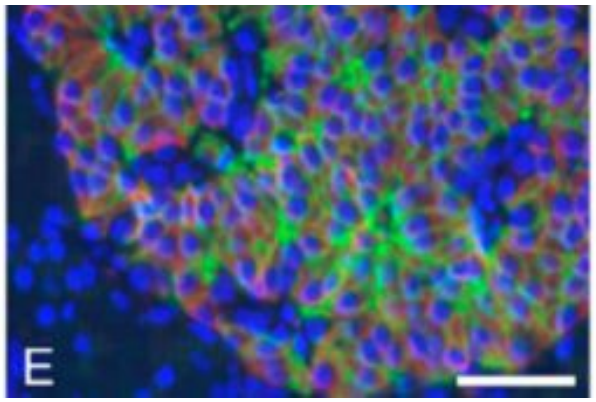
Biological and computational models are required at multiple levels to understand whether and how drugs work

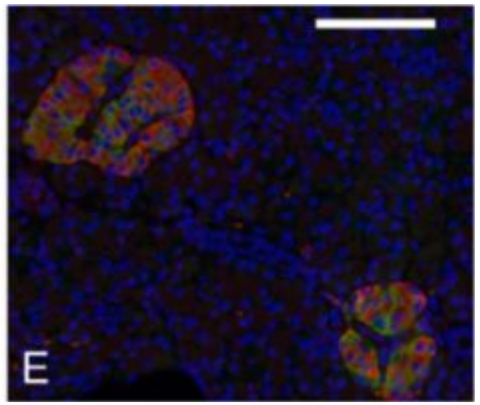


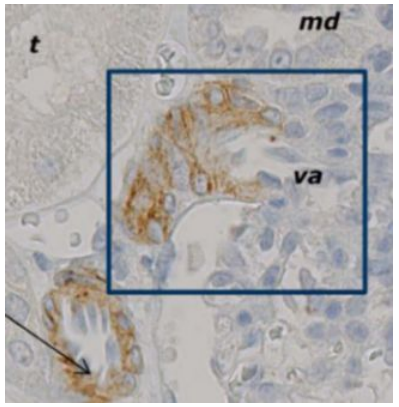
Zhang, Jitao David, Lisa Sach-Peltason, Christian Kramer, Ken Wang, and Martin Ebeling. 2020. “Multiscale Modelling of Drug Mechanism and Safety.” Drug Discovery Today 25 (3): 519–34. https://doi.org/10.1016/j.drudis.2019.12.009.

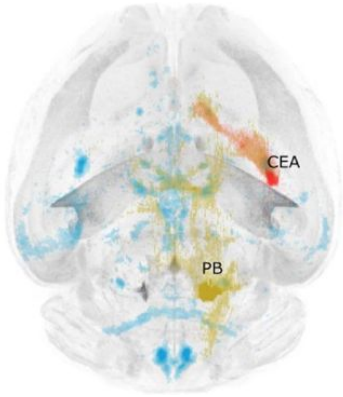
An example of multiscale understanding with semaglutide







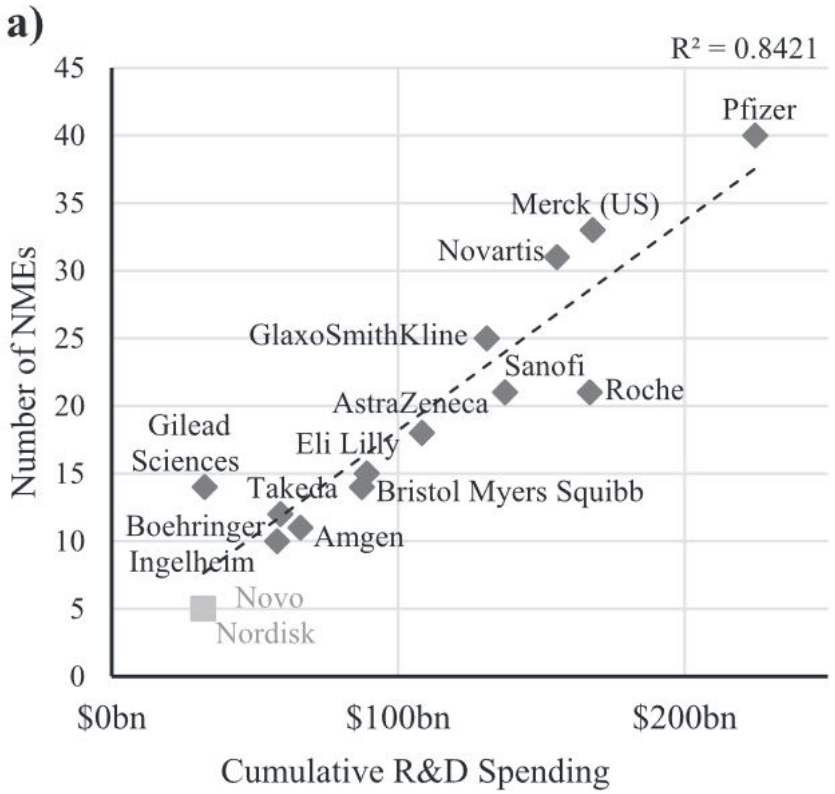




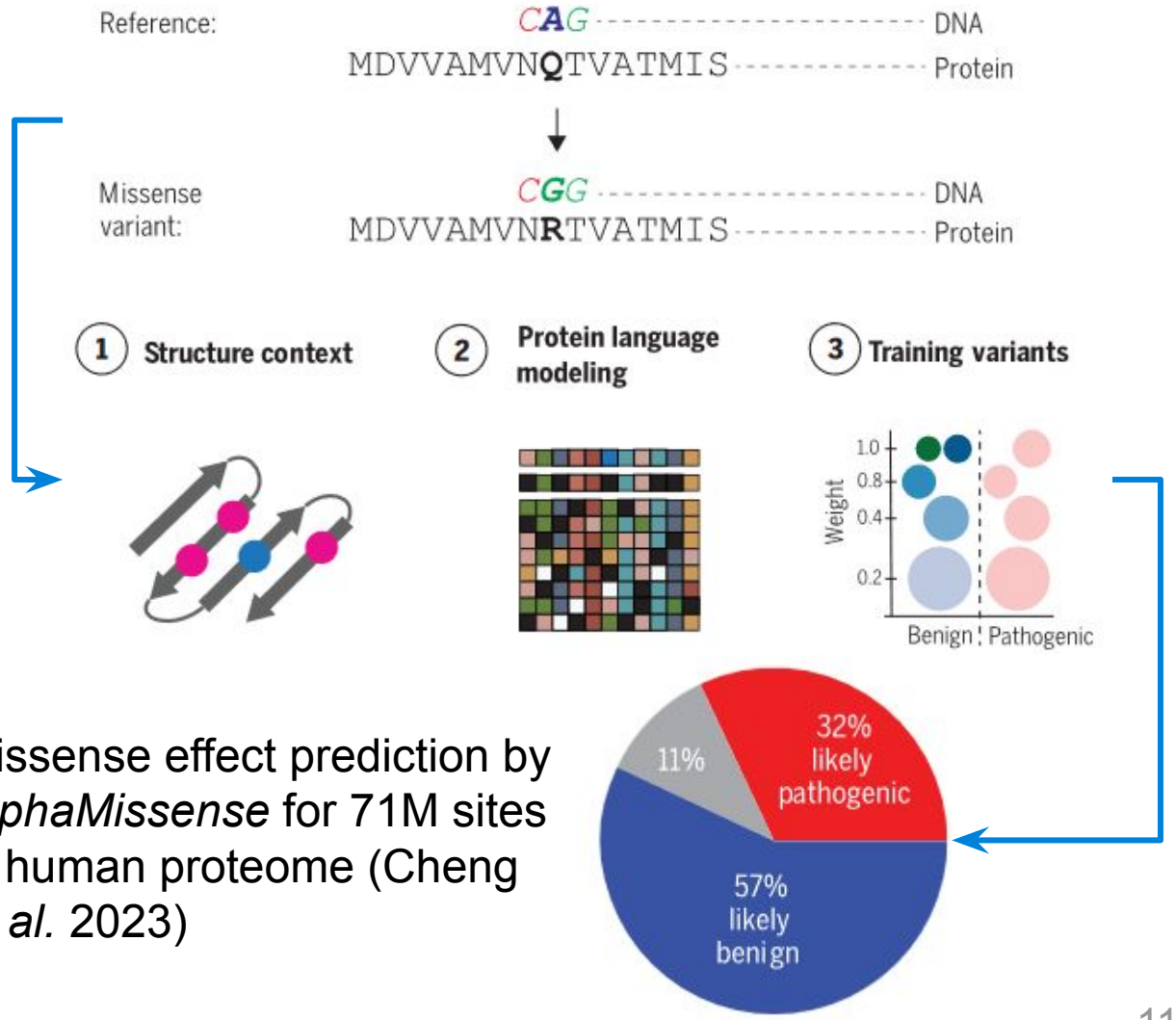
Top panels: crystal structure of the semaglutide peptide backbone (gray) in complex with its target, GLP-1 receptor (golden surfaces).

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



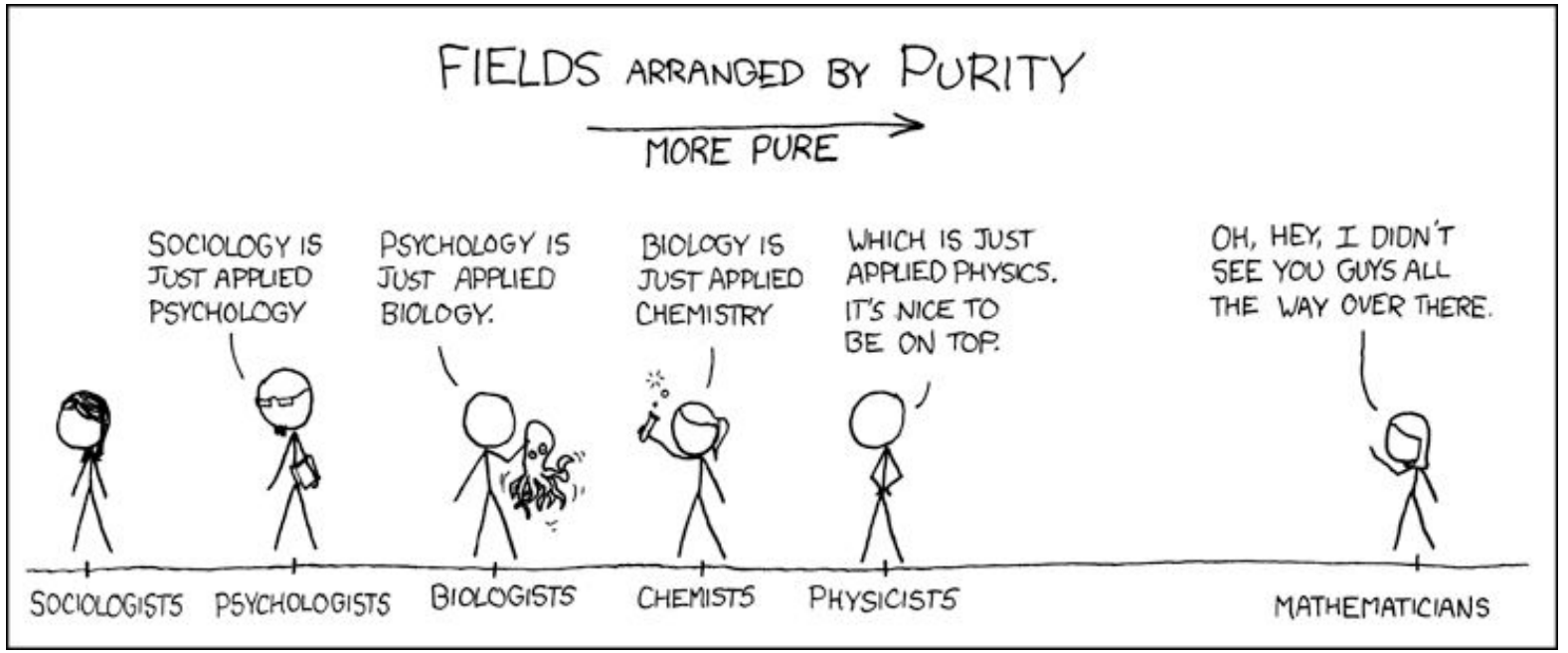
R&D efficiency of leading pharma companies, 1999-2018 (Schumacher *et al.*, 2021)



Missense effect prediction by *AlphaMissense* for 71M sites in human proteome (Cheng *et al.* 2023)

Purity

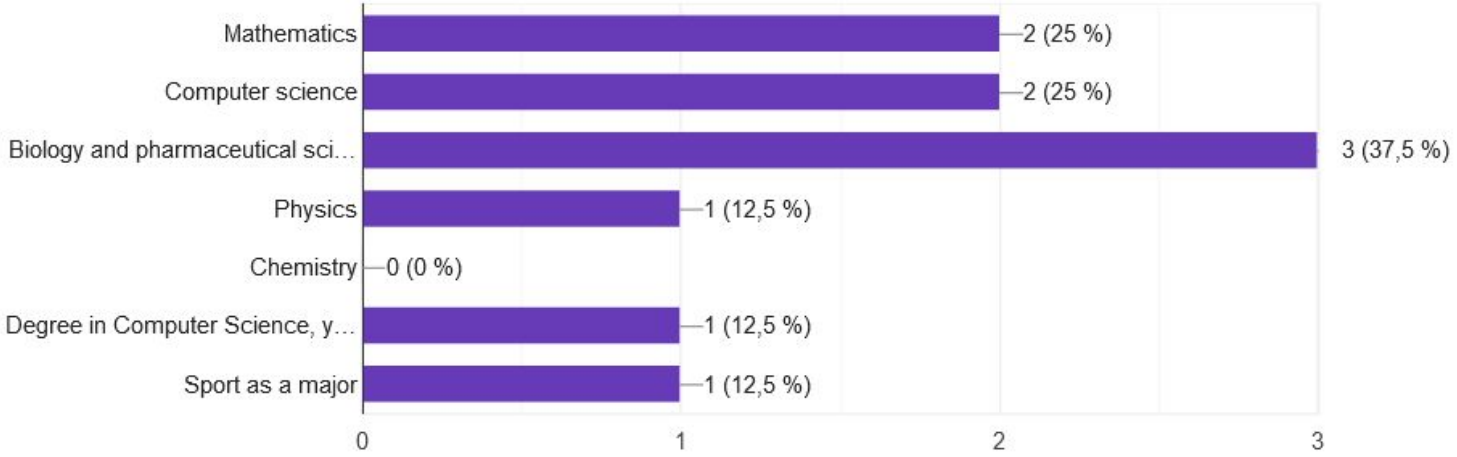
https://xkcd.com/435/



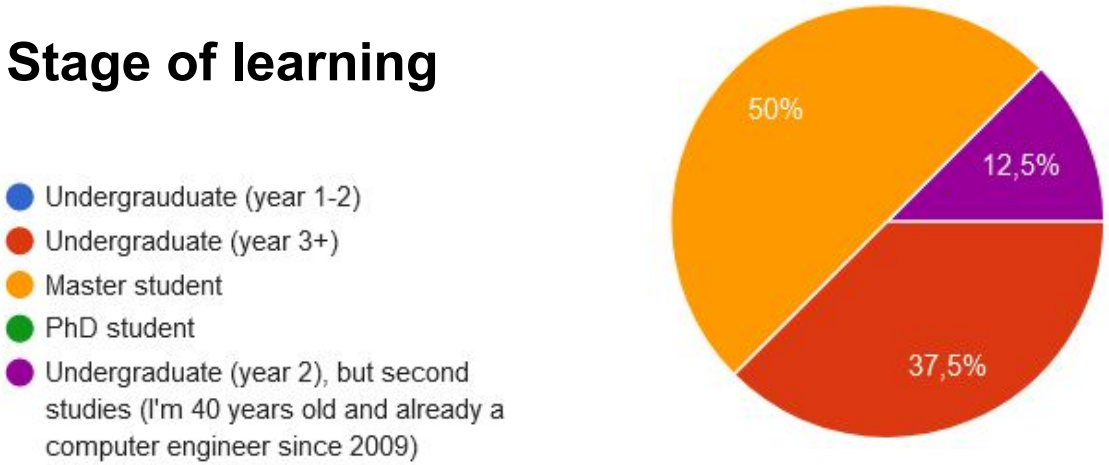
This course aims to bring people together and to promote interdisciplinary research

Our strength: we have a diverse classroom!

Background



Stage of learning



Selected Motivations

- Seems interesting
- Less “theoretical + abstract” mathematics for a change
- Combines my passion (math and physics) with the passion of my wife (pharmacy).
- Credit points in mathematics,a Applications of mathematics to the real world (not particularly biology)
- How the drug discovery is used in criminalistics
- I'm excited to see a direct application of math in a field that I only now a glance about.
- Have an overview and learn how Biology, Physics, Chemistry and Informatics are connected together in the field of drug discovery.

Course information for AMIDD 2023

- Lecturer: Jitao David Zhang (jitao-david.zhang@unibas.ch)
- Website: AMIDD.ch
- Thirteen lectures this semester
  - Introduction(1 session)
  - Mechanistic, statistical, and causal models (2 sessions)
  - Molecular level modelling (2 sessions)
  - Omics- & cellular models (2 sessions)
  - Organ- and system models (2 sessions)
  - Population modelling (2 sessions)
  - Invited guest speakers (1 session)
  - A collaboration challenge (1 session)

- Fridays 12:15-14:00
- Slides, exercises, pre-reading and post-reading articles are shared on the course's website http://www.amidd.ch. Unfortunately we do not provide recordings.
- The final note is given by participation including quizzes (30%), offline activities (40%), and a collaboration challenge in the final session (30%). The topic of collaboration challenge will be announced in the last session.
- **Questions**?

I am glad to share my experience in drug discovery, and to learn from you!

Disclaimer

Teaching is my personal engagement. My opinions and views do not necessarily reflect those by F. Hoffmann-La Roche, my employer.

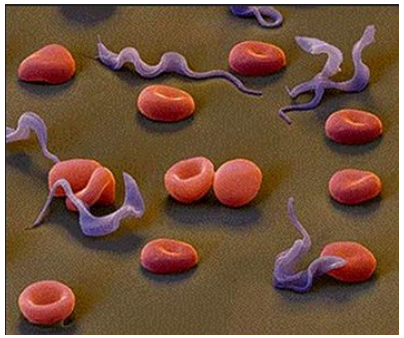
Please be aware of my biases and limitations.

- I am a computational biologist working in drug discovery, with limited understanding of mathematics, computer science, biology, and medicine.
- I see my task is to share with you the mathematical concepts and computational approaches used in drug discovery that I find beautiful and useful.
- I look forward to learning from you mathematics and other expertise that I did not know.

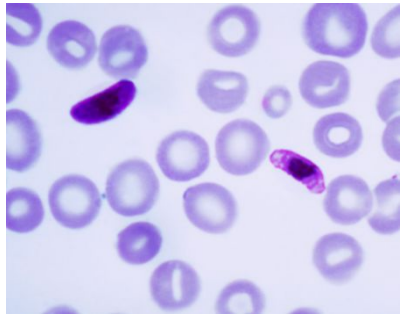
Why applied mathematics and informatics in drug discovery, why now?

- Now is the best time in human history to fight diseases
- Applied mathematics and informatics approaches are indispensable to modern drug discovery
- Applied mathematics and informatics will join interdisciplinary efforts to transform drug discovery in the coming decades

The history of *Homo sapiens* is a history of living with, understanding, and fighting diseases



Trypanosomes



Plasmodium

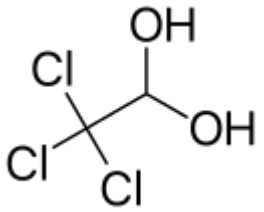
Tropical diseases

~500,000 years ago

A young patient of smallpox,
the first eradicated infectious disease

Hygiene, vaccination, and antibiotics

~250 years ago



Chloral hydrate,
the first synthesized drug

Pharmaceutical drugs

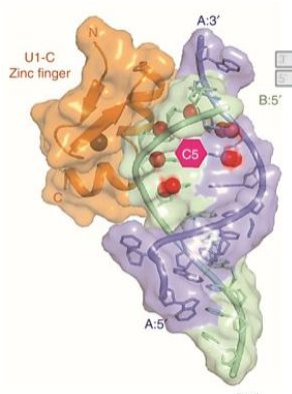
~150 years ago

Nobel prize laureates 2018,
immune checkpoints,
and drugs targeting the pathways

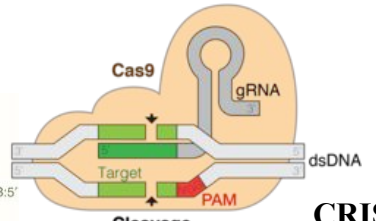
Personalized precise healthcare

~20 years ago

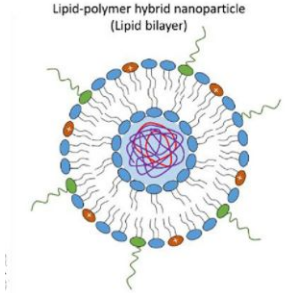
Now is the best time in human history to fight diseases



Risdiplam, a SMN2 splicing modifier



CRISPR-CAS9 gene editing system



mRNA delivery with nano lipid particles

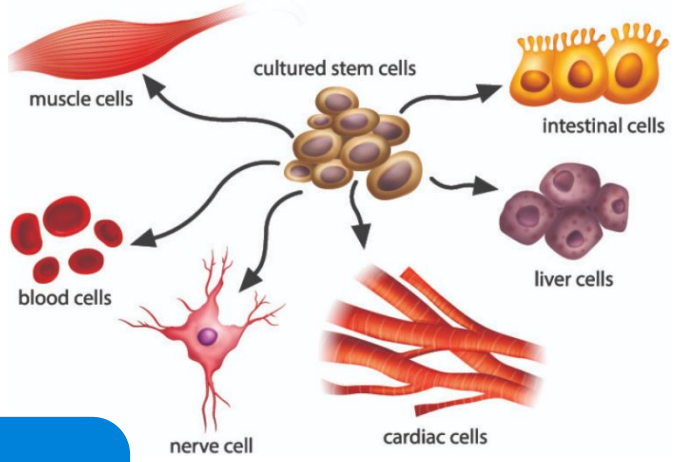
More biological, chemical, and medicinal knowledge

New disease-modelling systems

Digitalization of molecular mechanisms in living organisms

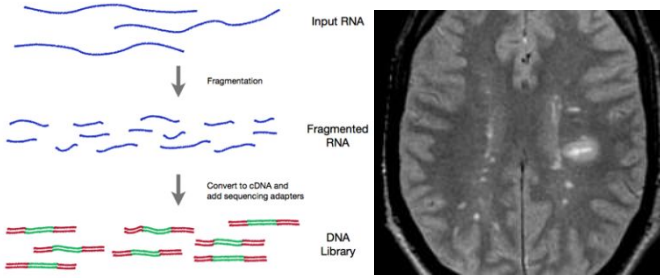
Better algorithms, models, and more computing resources

New therapeutic modalities



Stem cells

Comprehensive Sensing

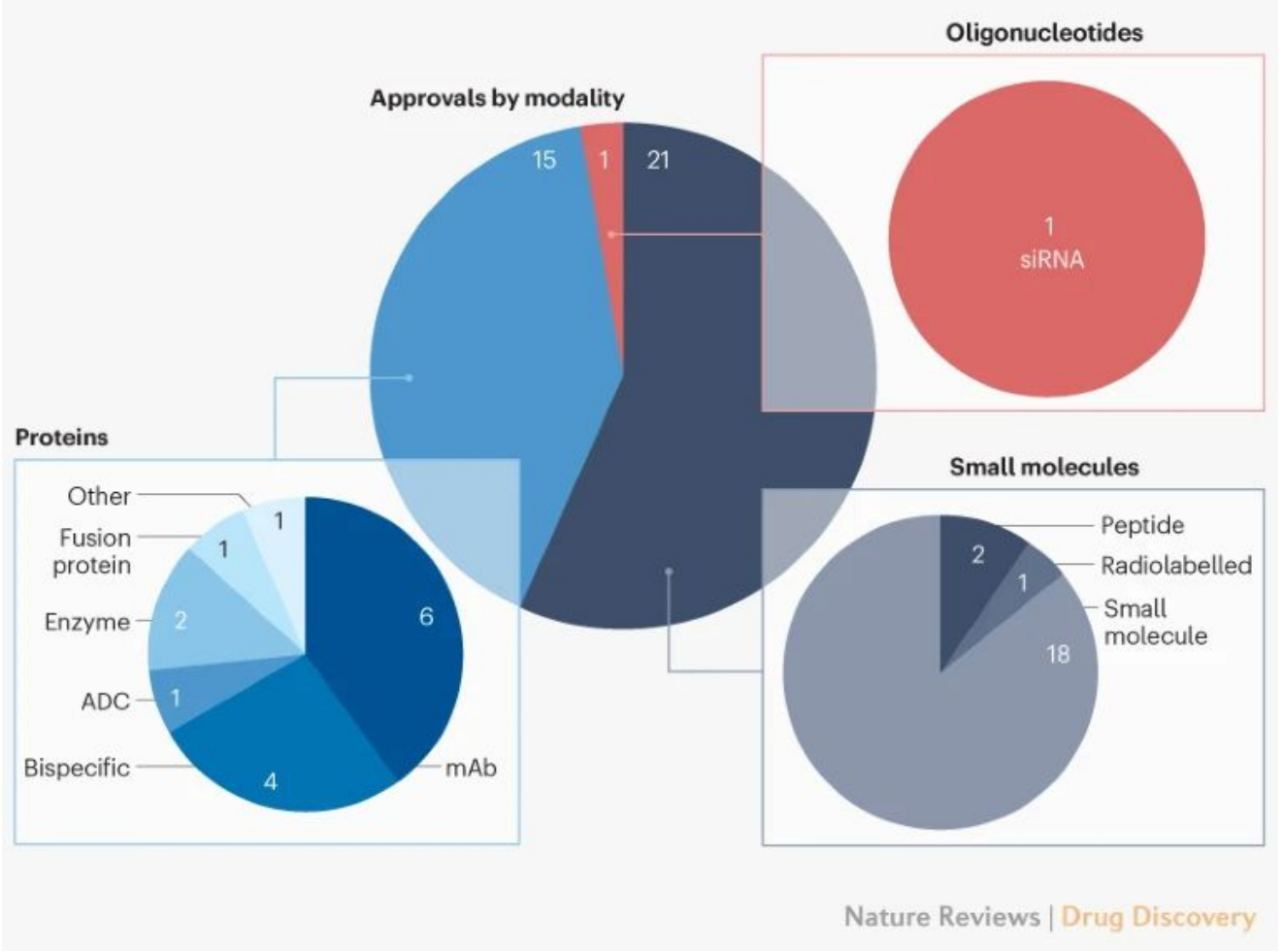


Single-cell biology, multi-modal omics profiling, and imaging

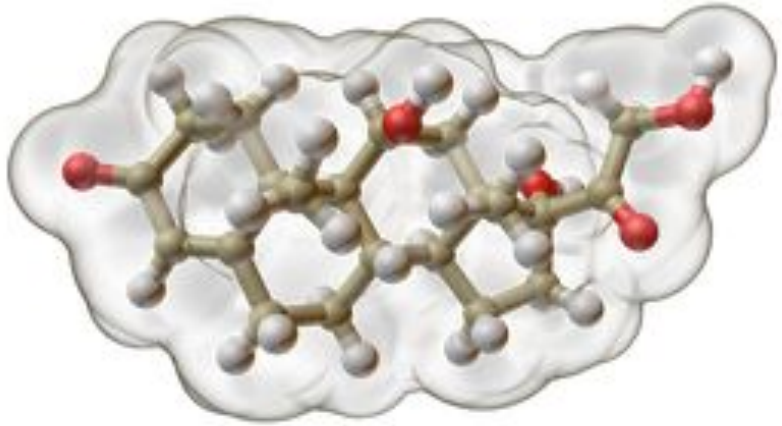
Novel drugs approved by the FDA's Center for Drug Evaluation and Research (CDER) in 2022

Three modalities

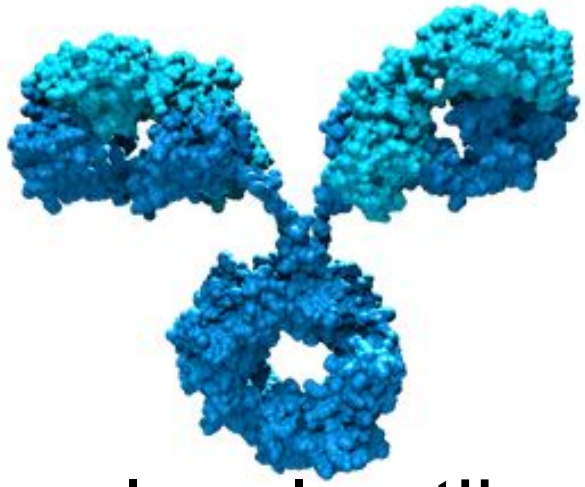
- Small molecules (molecular weight under 900 daltons)
- Proteins
  - mAb: monoclonal antibody
  - Bispecific: bispecific antibodies
  - ADC: antibody-drug conjugate
- Oligonucleotides



A zoo of modalities

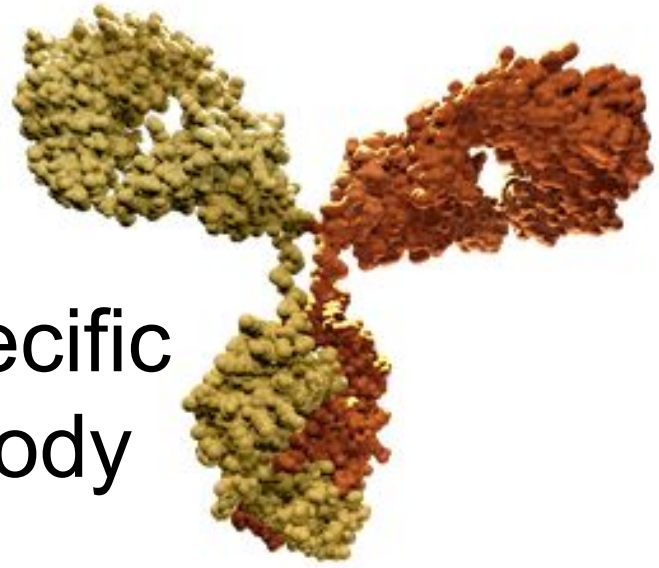


Small molecule

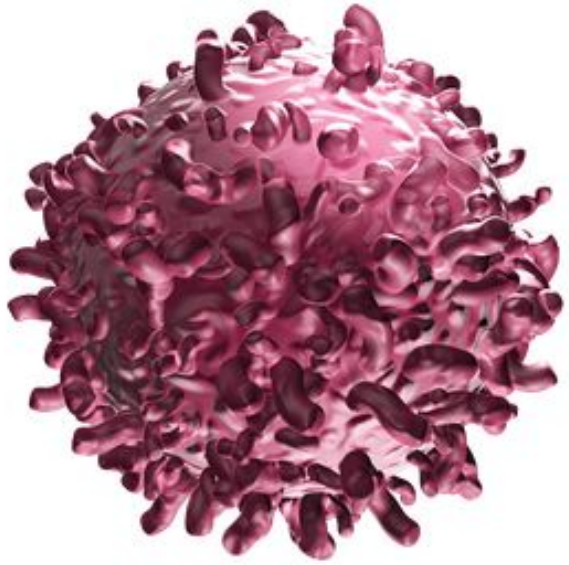


Monoclonal antibody

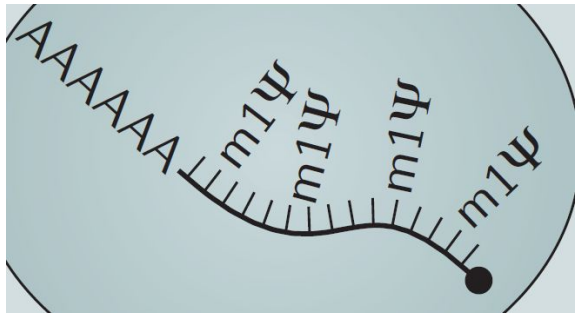
Oligonucleotides



Bispecific antibody

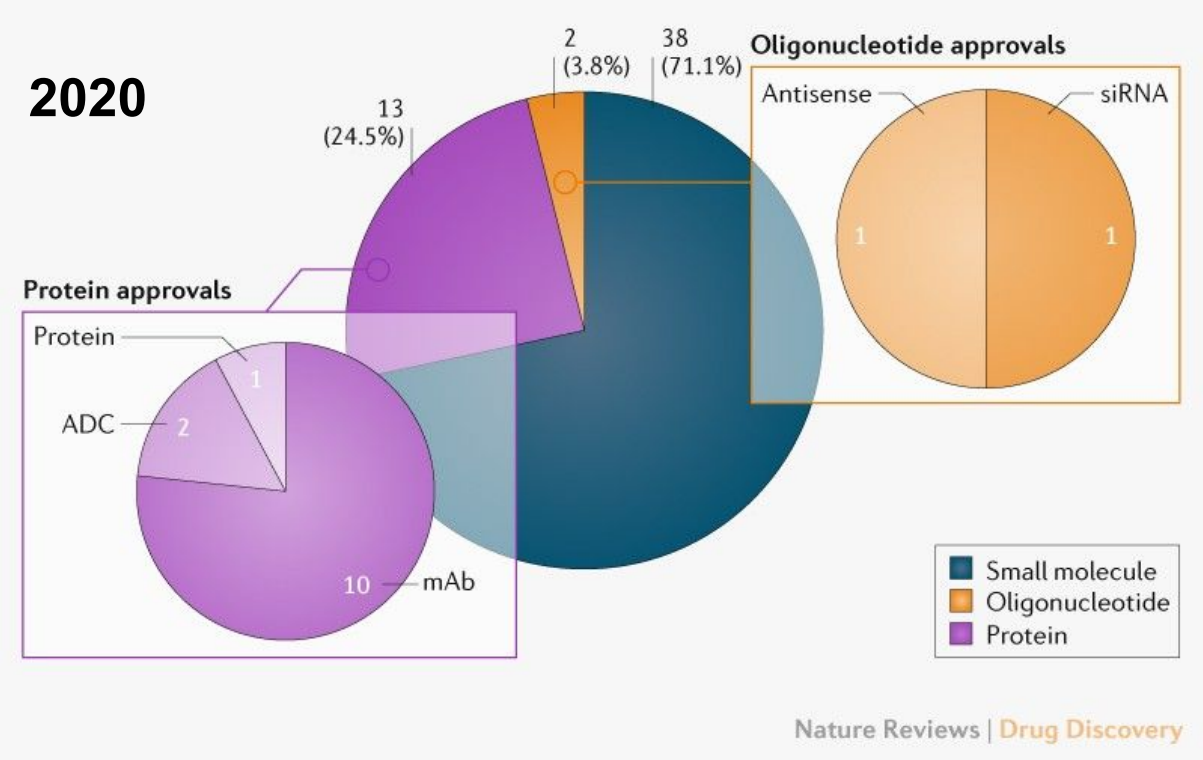


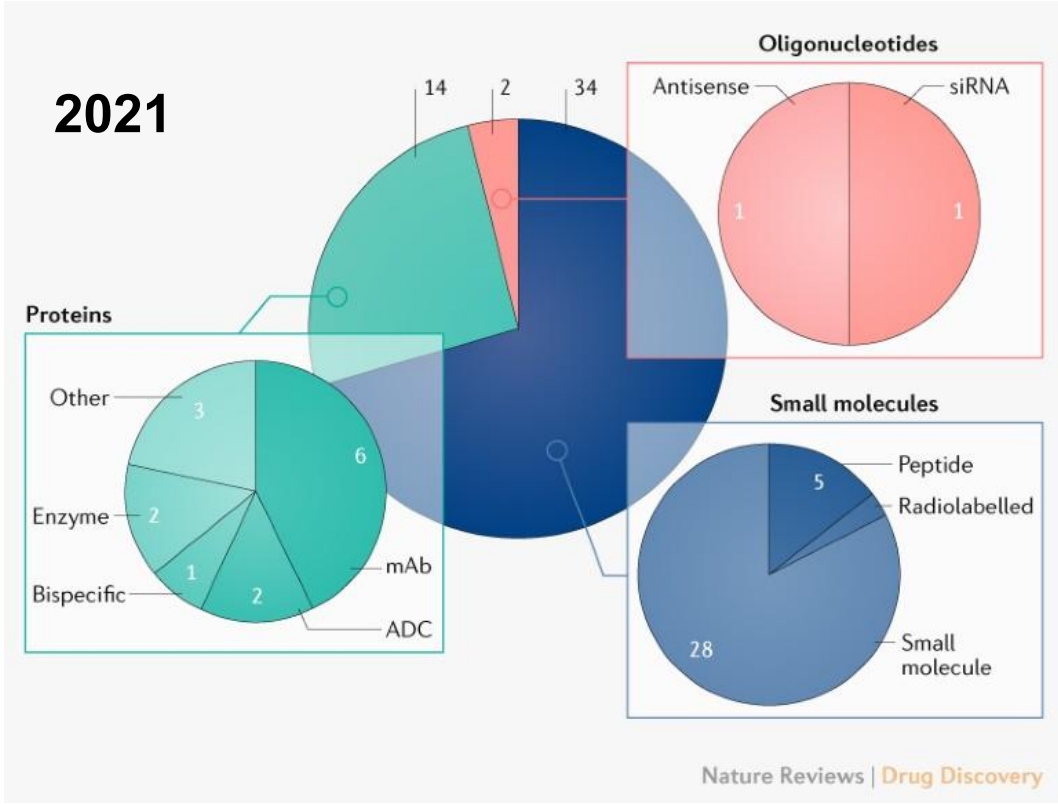
Chimeric Antigen Receptor (CAR) T-cells



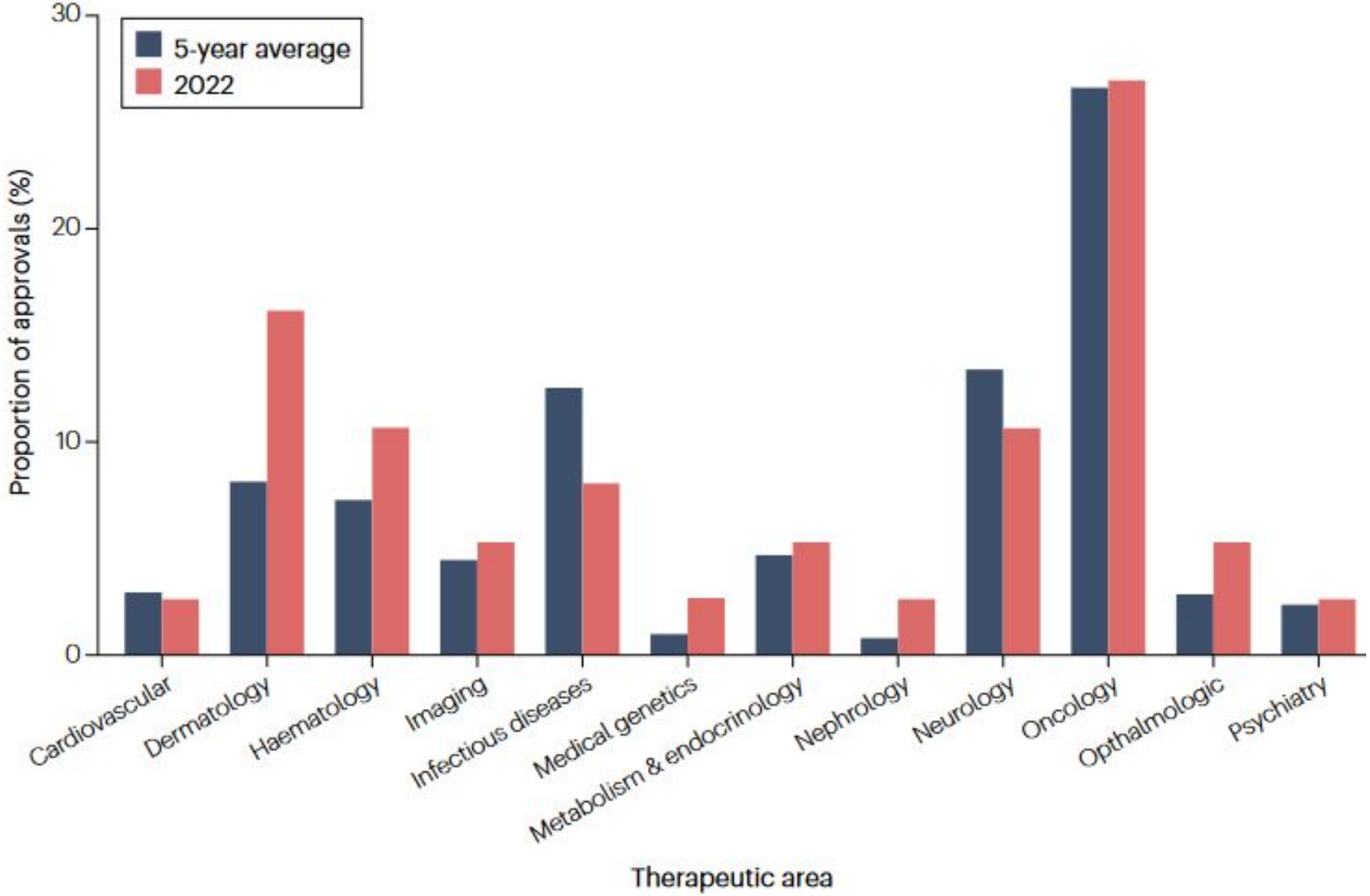
mRNA vaccines

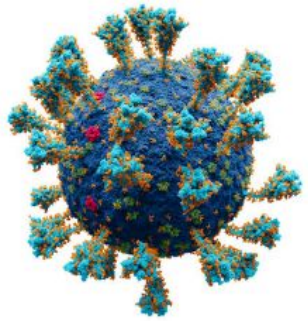
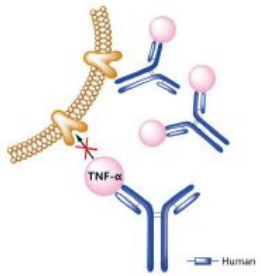
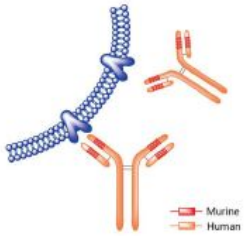
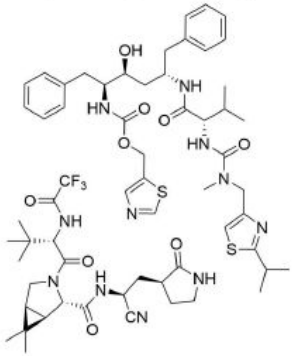
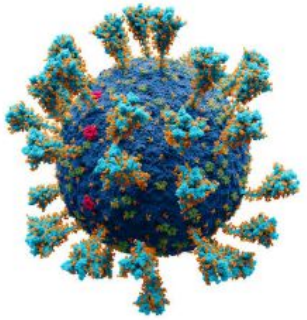
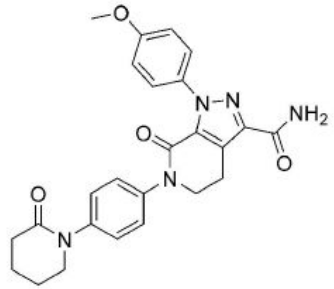
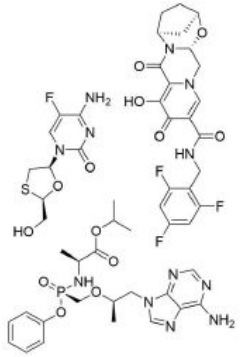
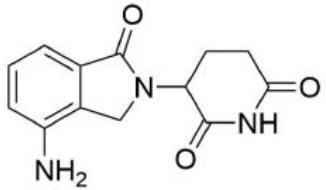
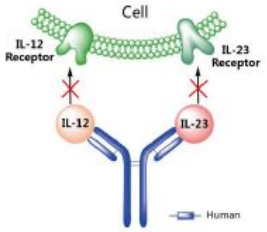
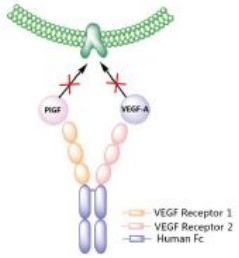
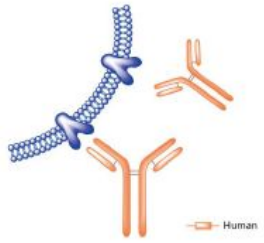
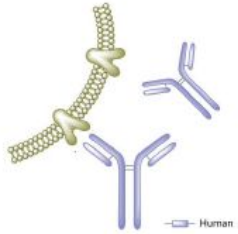
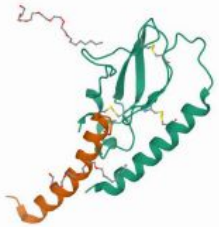
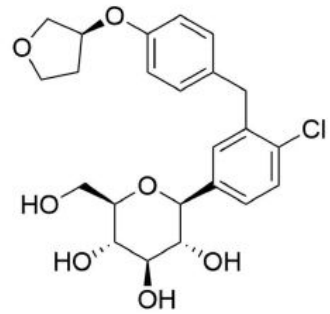
Relative contributions of modalities remain constant in the past three years





New drug approvals vary between disease areas



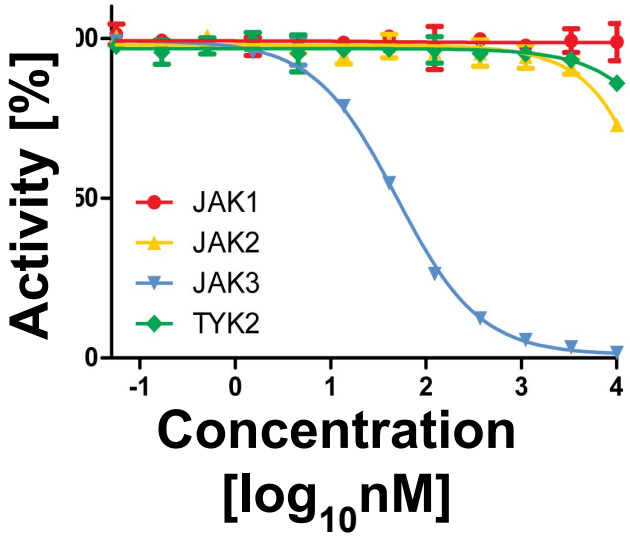
1 **Comirnaty** (COVID-19 Vaccine)  $37.806 Billion **Infectious Diseases**	2 **Humira** (Adalimumab)  $21.237 Billion **Immunology**	3 **Keytruda** (Pembrolizumab)  $20.937 Billion **Oncology**	4 **Paxlovid** (Ritonavir/Nirmatrelvir)  $18.933 Billion **Infectious Diseases**	5 **Spikevax** (CX-024414)  $18.435 Billion **Infectious Diseases**	6 **Eliquis** (Apixaban)  $11.789 Billion **Cardiology/Vascular Diseases**	7 **Biktarvy** (Bictegravir/Emtricitabine/Tenofovir Alafenamide)  $10.390 Billion **Infectious Diseases**
8 **Revlimid** (Lenalidomide)  $9.978 Billion **Oncology**	9 **Stelara** (Ustekinumab)  $9.723 Billion **Immunology**	10 **Eylea** (Aflibercept)  $9.639 Billion **Ophthalmology**	11 **Opdivo** (Nivolumab)  $9.299 Billion **Oncology**	12 **Dupixent** (Dupilumab)  $9.095 Billion **Immunology**	13 **Ozempic** (Semaglutide)  $8.713 Billion **Diabetes**	14 **Jardiance** (Empagliflozin)  $8.388 Billion **Diabetes**

Top 14 pharmaceuticals by sales in 2022

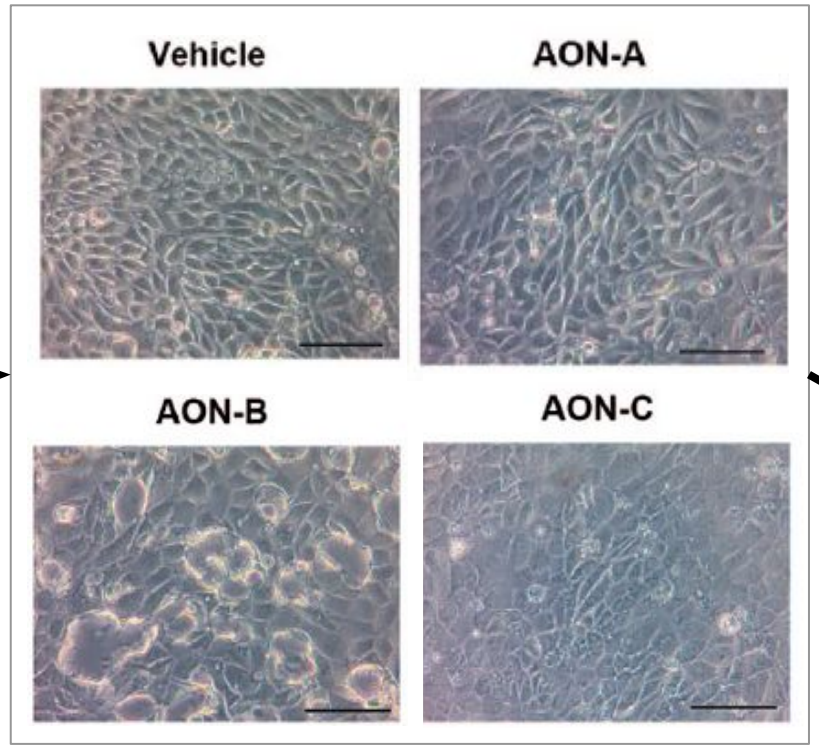
Poster compiled by the Jon Njardarson group at University of Arizona (https://njardarson.lab.arizona.edu). Citation: J. Chem. Ed. 2010, 87, 1348.

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?

Classical workflow of efficacy and toxicity assessment

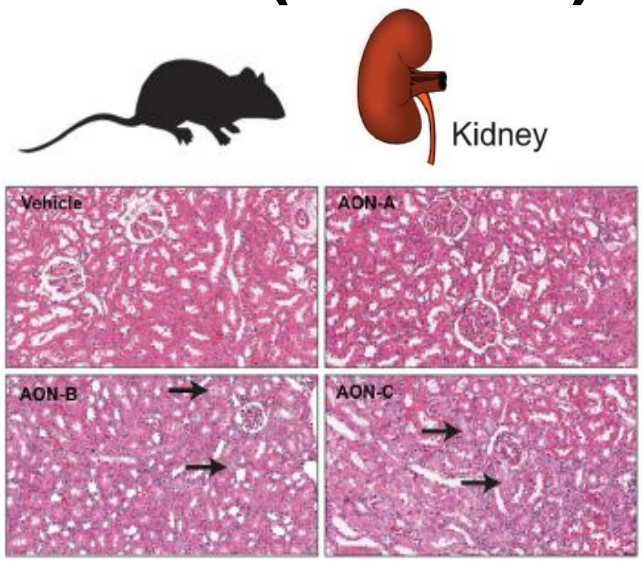


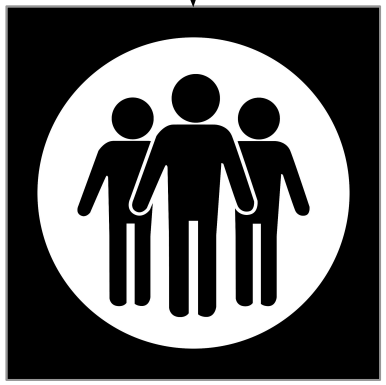
Biochemical & biophylical assays



Cellular assays (*in vitro*)

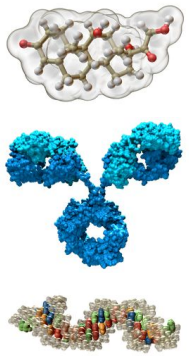
Animal experiments (*in vivo*)

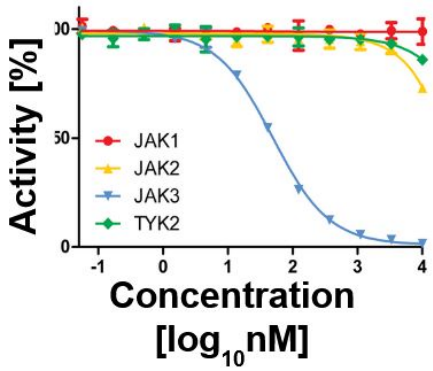


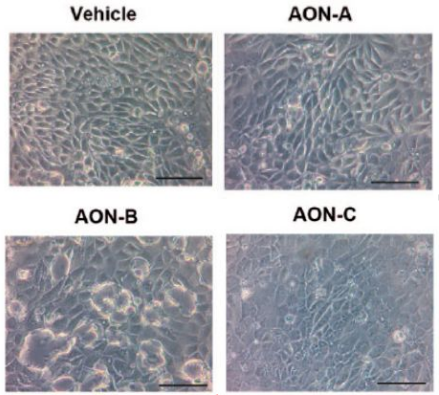


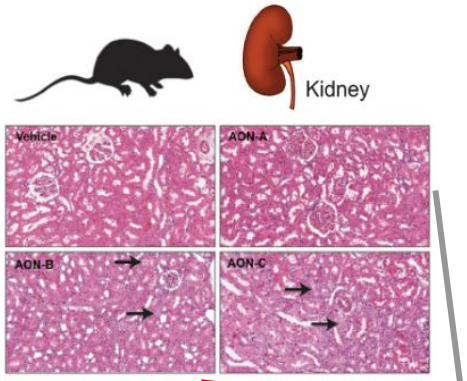
Clinical trials

Computational methods empower efficacy and toxicity assessment



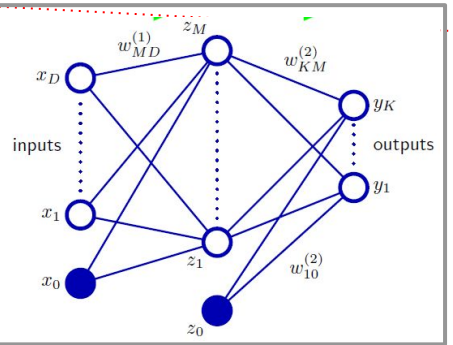






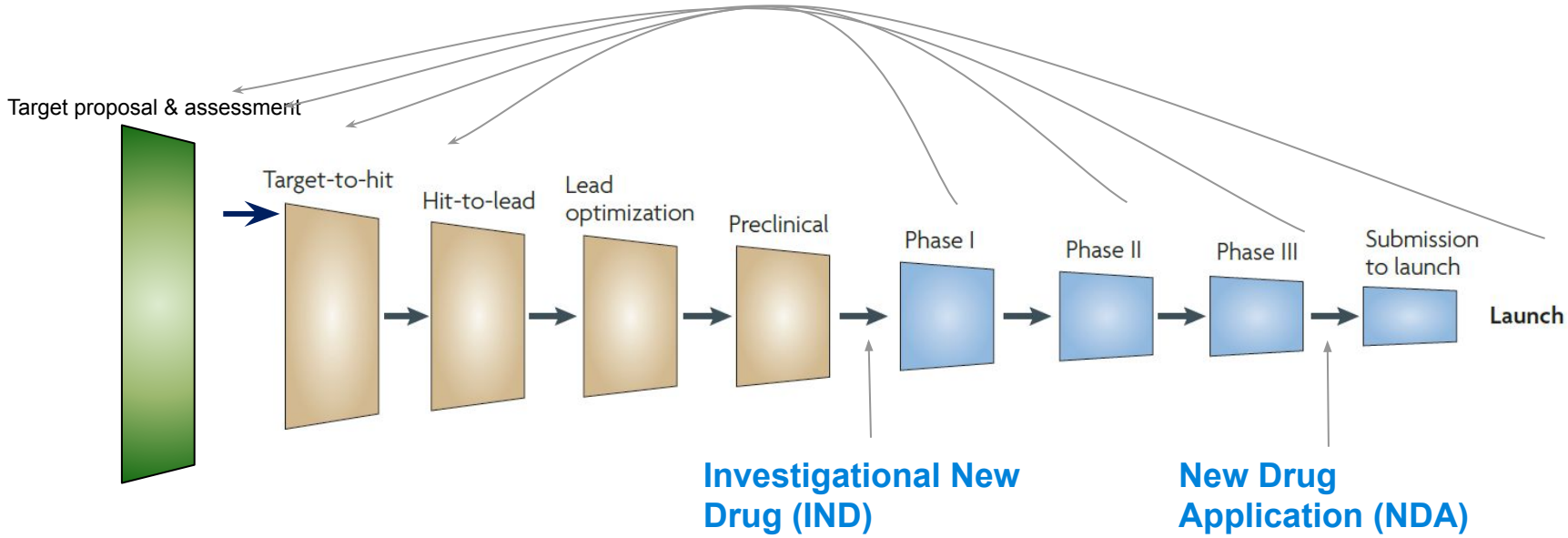
High-throughput technologies (omics, microscopy, etc.)

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



Mechanistic, causal, and statistical models

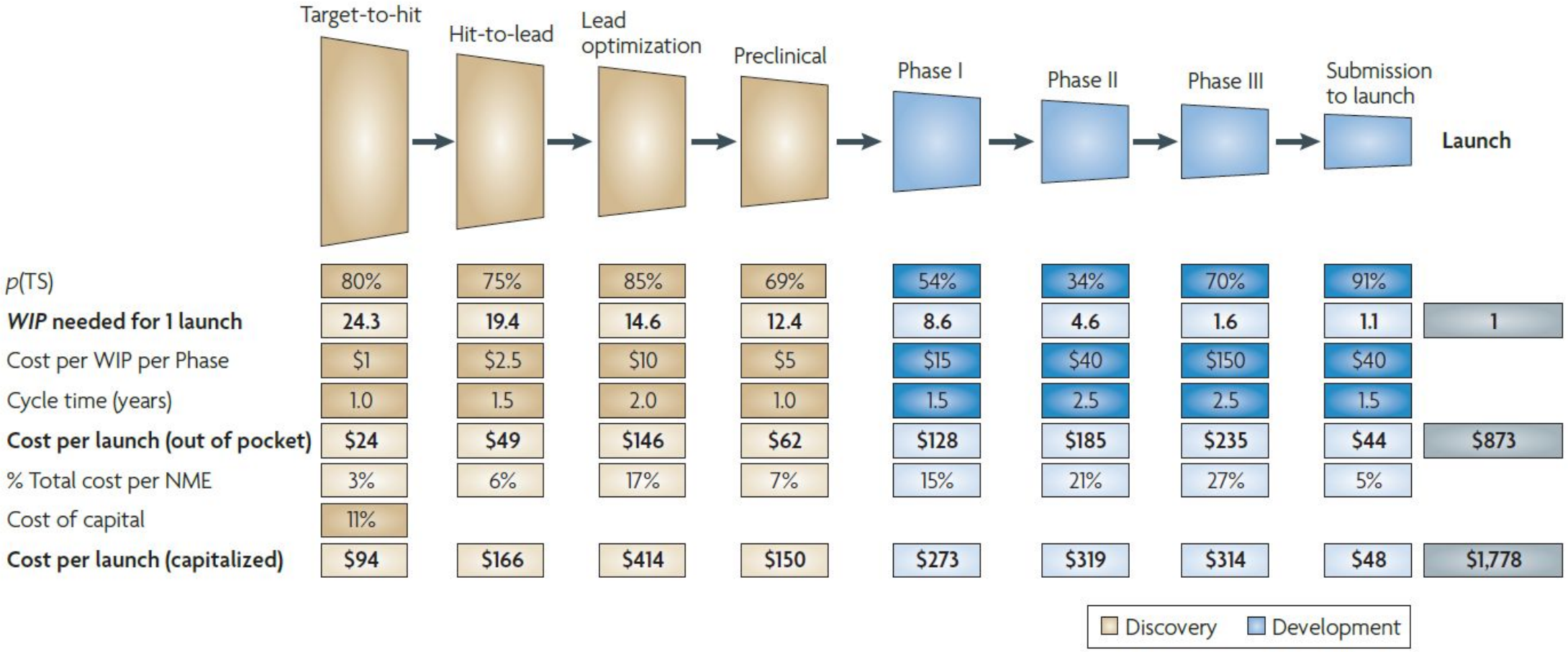
The linear view of drug discovery



Acronym	TI/TA/TV	Screening	LI	LO
Description	Target identification/ target assessment/ target validation		Lead identification	Lead optimization

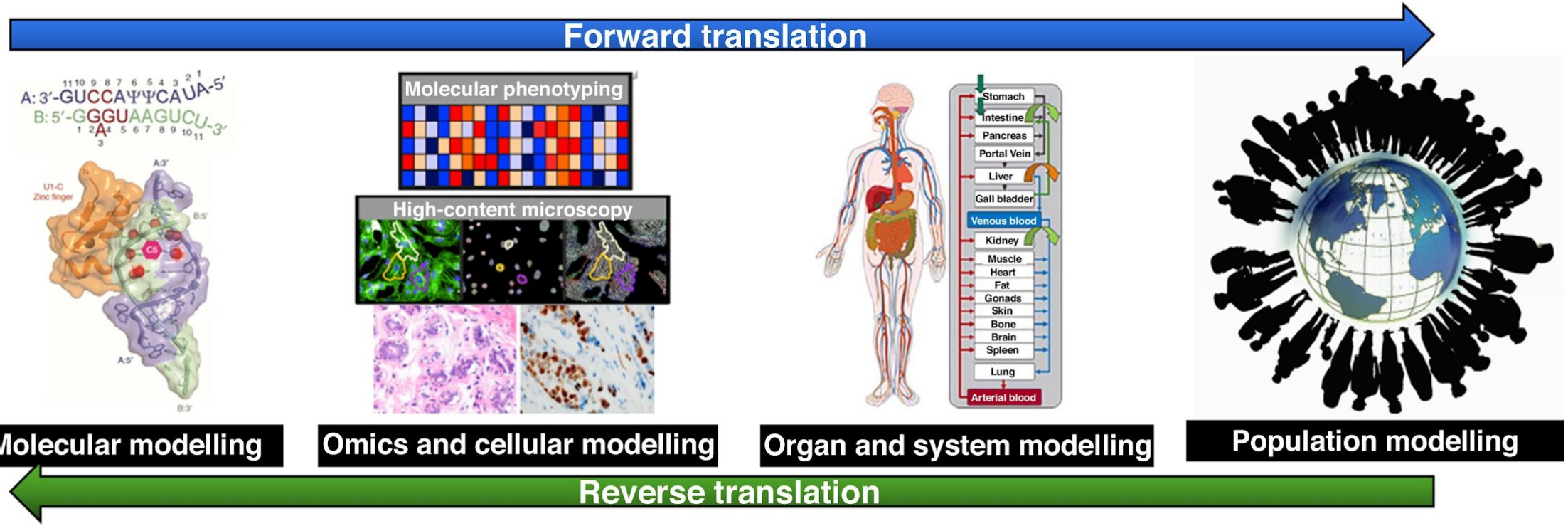
Adapted from Paul *et al.* "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." Nature Reviews Drug Discovery, 2010

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.

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.

Introduction to Applied Mathematics and Informatics in Drug Discovery (*AMIDD*)

A course series at DMI, University of Basel

- **Introduction to drug discovery**
- **Three types of models: mechanistic, statistical, and causal models**
- **Molecular modelling**
  - Biological sequence analysis
  - Protein sequence and structure
  - Molecular modelling and dynamics
- **Omics and cellular modelling**
  - From drug-target interactions to networks
  - Gene expression profiling
  - Cell-based phenotypic drug discovery
- **Mathematical modelling**
  - Principles and applications of modelling in pharmacology
  - Pharmacokinetics (PK) and pharmacodynamics (PD) modelling
  - Clinical pharmacology and pharmacometrics
- **Population modelling**
  - Non-linear mixed-effect models (NLMEs)
  - Essentials of clinical trials
- **Guest lectures**
- **Your presentations**

It is hoped that AMIDD builds a bridge between students and quantitative aspects of drug discovery

Conclusions and perspectives

- Drug discovery and development are expensive and involve many people.
- While successful drugs generate high profits, success rates remain low.
- It is now probably the best time in human history to join the fight against diseases.
- We learned about modalities and the drug discovery and development process.
- In the AMIDD course, we will learn some basic concepts and tools we use to model interactions between biological systems and drugs at multiple levels.

Contact the author