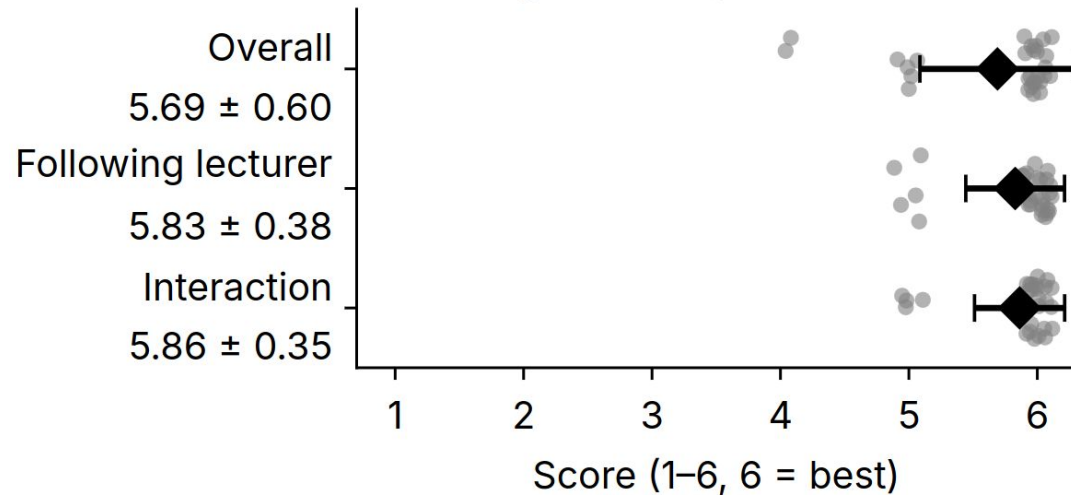
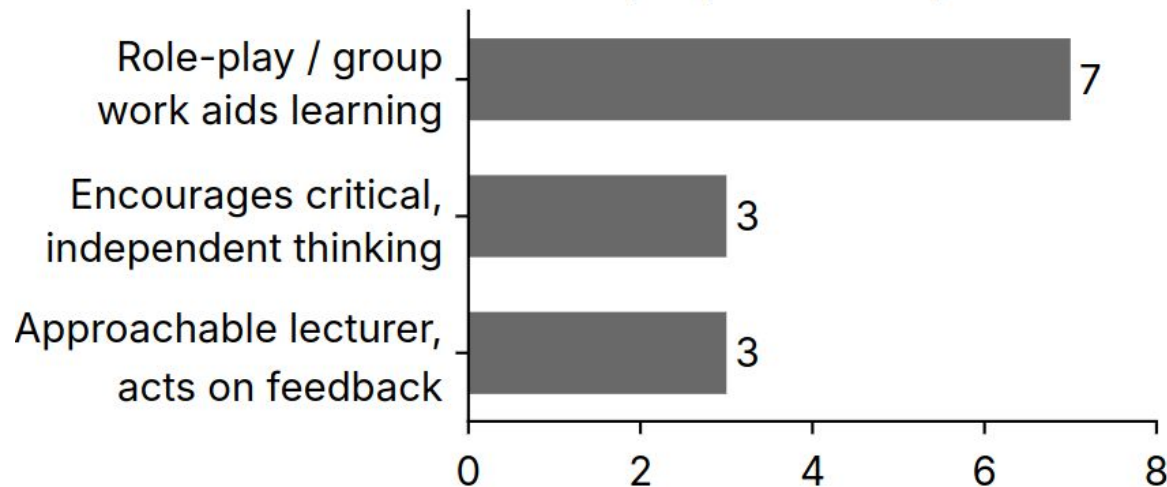


Feedback and questions about lecture 4

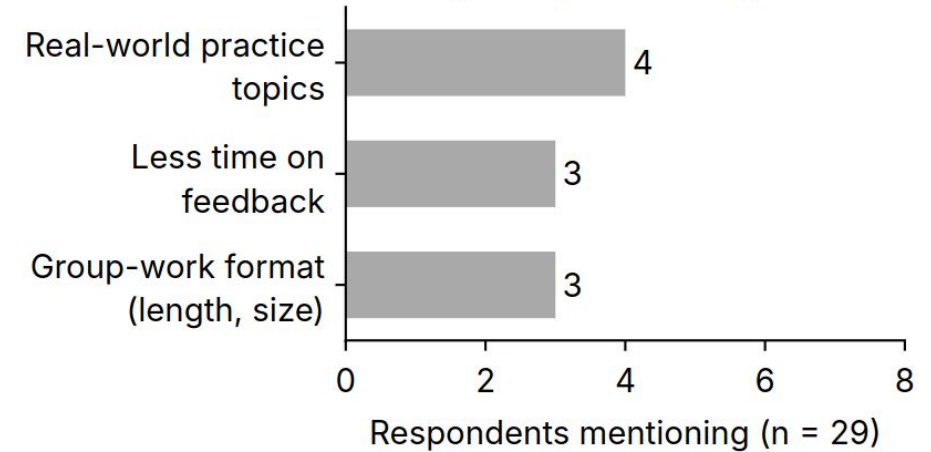
Ratings (n = 29, ♦ mean ± SD)



Top 3 positive aspects



Top 3 aspects to improve

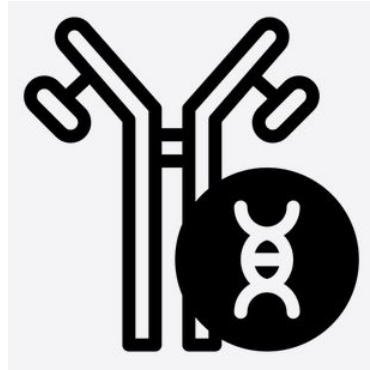


1. “What is the risk that highly promising research is stalled or lost because a researcher was denied funding?”
2. Academia vs. industry: “Do large pharmaceutical companies actively look for early-stage research in under-funded labs, and if so, how do they find it?” “If a major pharma company encountered a promising substance with adverse side effects, as mRNA initially had, would they invest decades of research into solving it?”
3. “What are the biggest obstacles today to using mRNA in other therapies?”

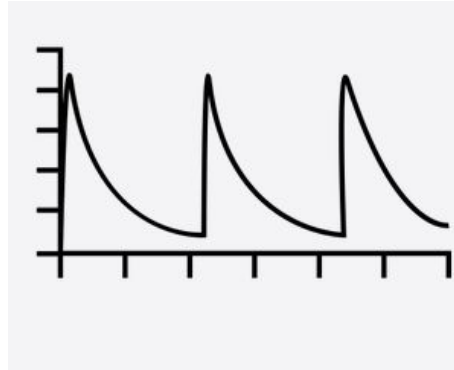
AMIDD 2026 Lecture 5: Biological foundations of key questions in drug discovery



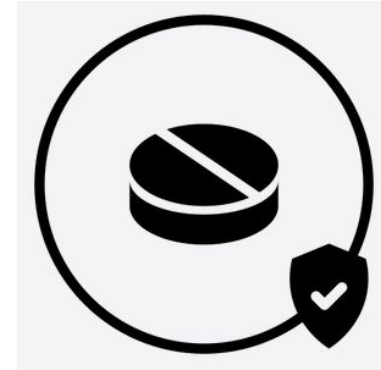
Medical Need



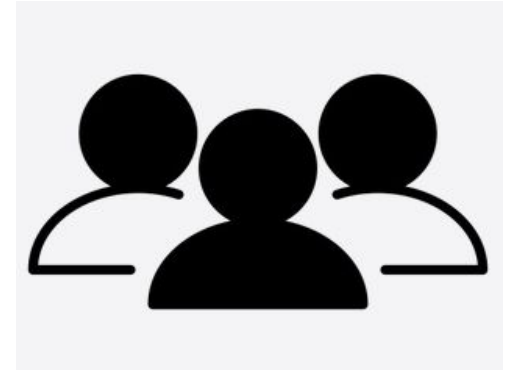
**Target &
modality**



PK/PD



Benefit/risk



**Patient
stratification**

Dr. Jitao David Zhang

¹ Computational Sciences Center of Excellence (CS CoE), Roche Innovation Center Basel, F. Hoffmann-La Roche;

² Department of Mathematics and Computer Sciences, University of Basel

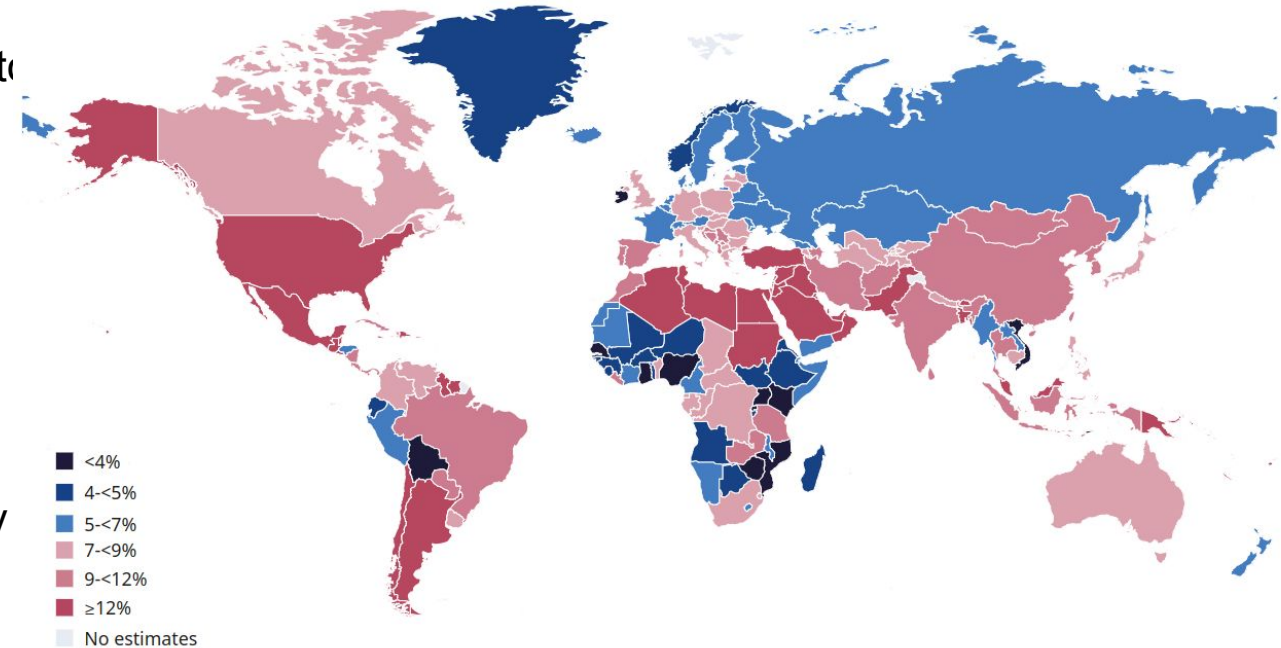
The social context of drug discovery: a role-playing game

We consider a case study of developing new drugs to treat complications caused by type 2 diabetes, affecting ~10% of adults (20–79 y) worldwide (Switzerland: 4-6%, of whom ~28% are not diagnosed), with the possibility to expand it to the obesity and other indications. We divide the classroom into the following personas:

1. Basic researchers (biology, medicine, AI, etc.): doing whatever research you want to do and getting funded
2. Research funding agency: giving fundings to any research problem, T2D is only one of them.
3. Patients: suffering, unfortunately, from T2D and its complications
4. Medical doctors: T2D experts who see patients regularly
5. Drug discovery company: determined to enter the T2D market
6. Insurance company: payer, negotiating the price
7. The regulatory agency: drug approval

Questions: (1) What are your main interests and concerns? (2) With which groups do you wish to collaborate and why? Rank the partners by priority. (3) What are the best-case and worst-case scenarios for you?

Map 3.2 Estimated age-standardised country prevalence of diabetes in adults (20–79 years), 2024.



[IDF Diabetes Atlas 2025](https://diabetesatlas.org/data-by-location/country/switzerland/) (11th version), The International Diabetes Federation (IDF). Swiss data is acquired from <https://diabetesatlas.org/data-by-location/country/switzerland/>

Main interests and concerns

	Interests	Concerns
Basic researcher	Etiology, Novelty, Publication	Funding, Meaningful, Competition
Funding agency	Wellbeing of as many people as possible, Funding research with broad applications,	Reduced total funding, wasted funding.
Patients	Health, Little side effects, insurance coverage	Lack of efficacy, adverse effects, expensive
Medical doctors	Cure, a working health system, work-life balance	Adverse effects, accessibility, long-term unpredictable effects
Pharma company	Working safe drug, IP, high revenue	Scooped, IP infringement, research not translated into drug
Insurance company	Low price, scrutiny over prescription, active market access including generic versions	Over-prescription, high price, people developing chronic disease
Regulatory Agency	Avoid scandals (including corruption), minimizing risk, guideline flexibility	Fake results, protests for drugs not approved, international collaboration

Partners by priority (inputs by the groups)

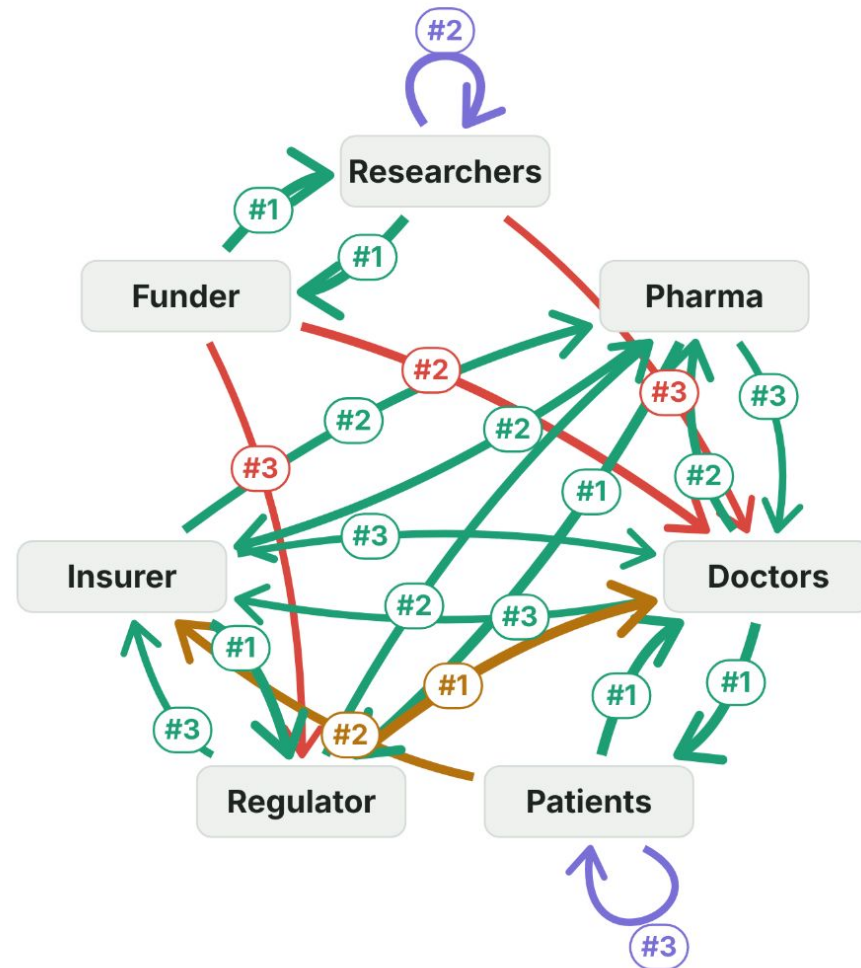


	Priority #1	#2	#3	#4	#5	#6	#7
Basic researcher (A)	F	C	M	P			
Funding agency (F)	C	I	R	A			
Patients (P)	M	I	P	A	R	C	F
Medical doctors (M)	P	C	R	I	F	A	
Pharma company (C)	A	R	M	F	P	I	
Insurance company (I)	R	C	M	P	F	A	
Regulatory Agency (R)	M	P	C	F	A	I	

Partners by priority (inputs by the groups and David)



	Priority #1	#2	#3	#4	#5	#6	#7
Basic researcher (A)	F	A	M	C	P		
Funding agency (F)	A	M	R	I	C		
Patients (P)	M	I	P	C	R	A	
Medical doctors (M)	P	C	I	R	M	F	A
Pharma company (C)	R	I	M	P	C	A	F
Insurance company (I)	R	C	M	P	I		
Regulatory Agency (R)	M	C	I	P	A	R	



- Returned (#1–3)
- Lukewarm (#4–5)
- Unrequited (#6+ or unranked)
- Own peers

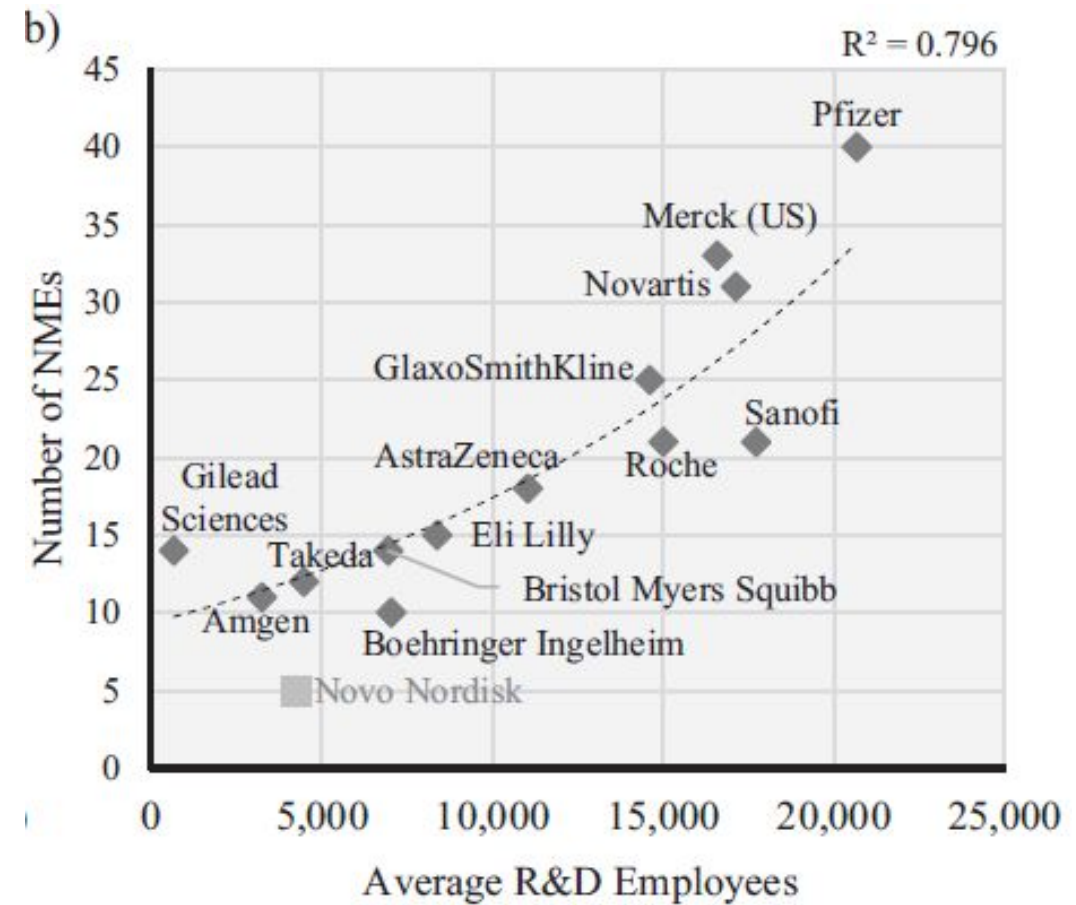
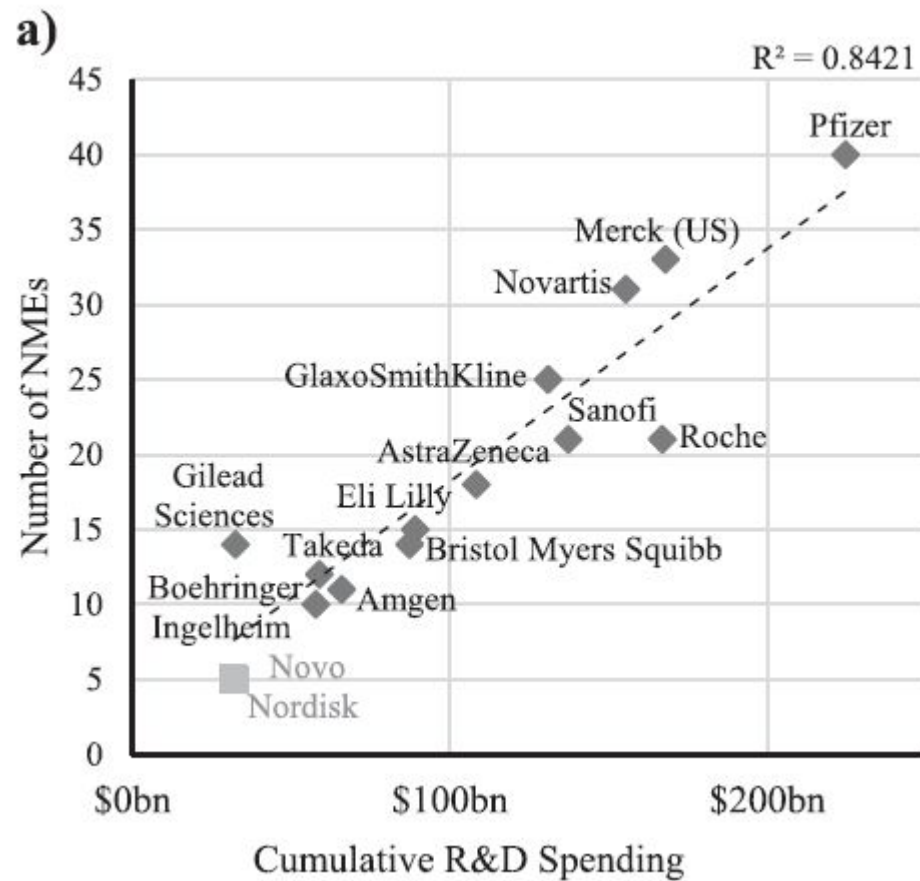
Groups and David: 14 of 19 top-3 picks are returned within the partner's top 3.

Interactive version: <https://claude.ai/artifact/XWrt2TtKb5X412yeJJWnaY>

Best and the worst scenarios

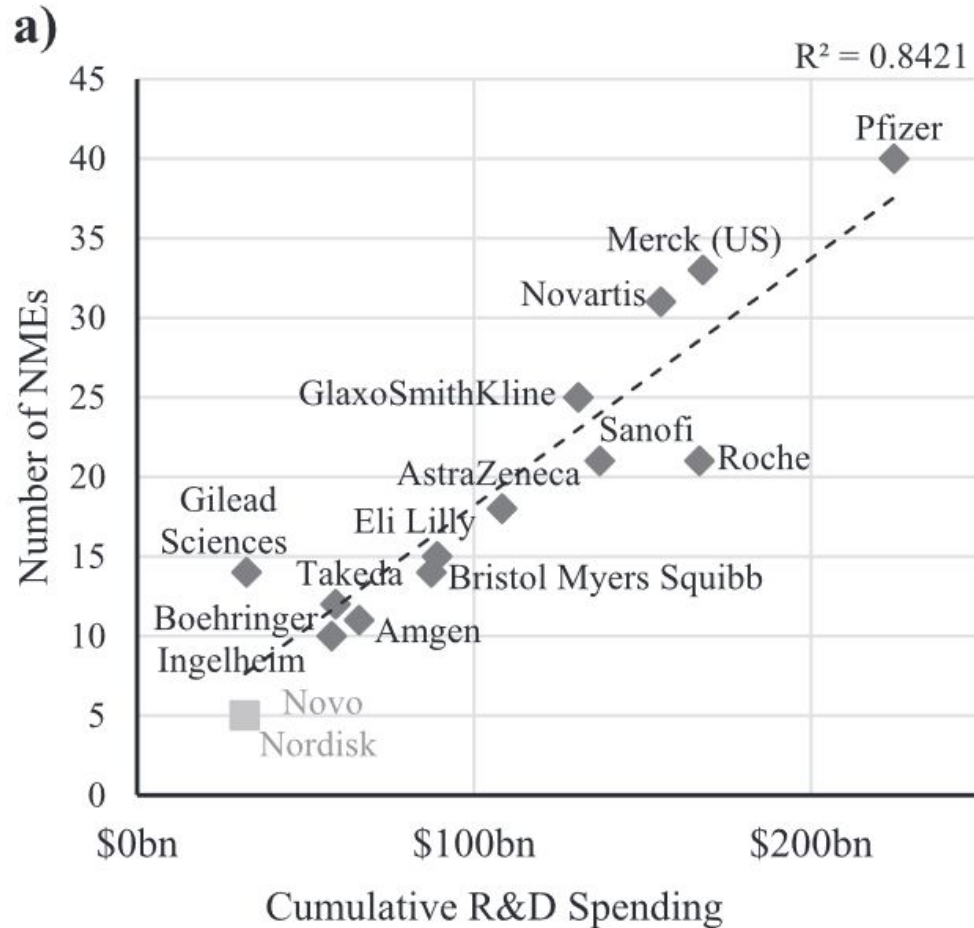
	Ideal scenario	Worst scenario
Basic researchers	Generate impact, get funded, recognition	Little impact, not funded, lack of recognition
Funding agency	Impactful research funded, return of investment, more funding	Funded research has little impact, lack of ROI, less funding
Patients	Improved health and life condition, minimized risks, affordable costs	Worsened health and life condition, high risks, high costs
Medical doctors	Improving patients' conditions, access to medicines, building up expertise	Failure to improve patients' conditions, no access to drugs, atrophy of expertise
Pharma company	Profits, manageable risks, investment in newer and better drugs	Financial and image loss, severe risks, failure to collaborate with other partners
Insurance company	Profits, ensure access to drugs, sustained access to healthcare and medicines	Financial and image loss, no access to healthcare and medicines, too high costs
Regulatory Agency	Approving drugs with benefits dominating over risks, encouraging discovery of new medicines, ensuring patients rights	Fail to improve helpful drugs, approval of drugs causing severe adverse effects, lack of drugs leading to degenerate healthcare

Drug discovery and development require huge investment and large interdisciplinary teams

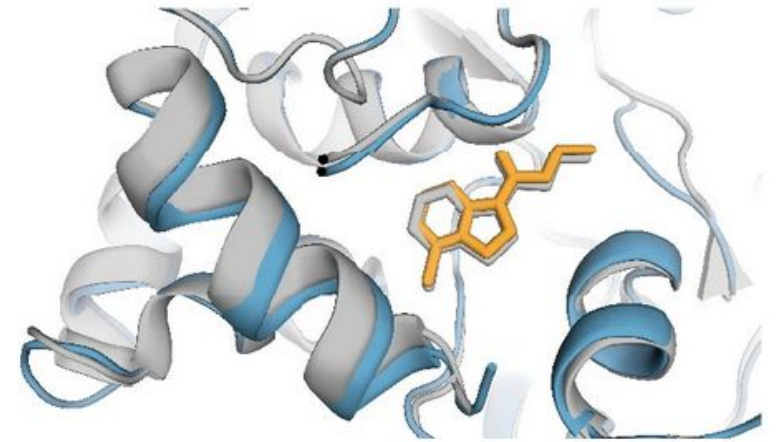
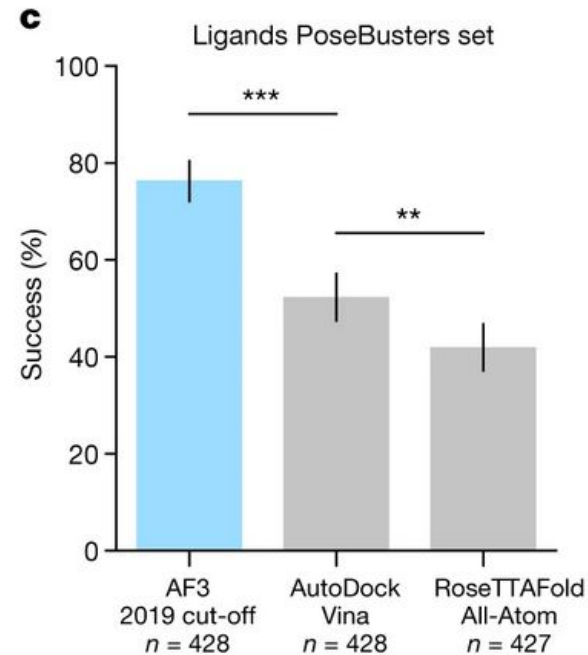


Schuhmacher, Alexander, Lucas Wilisch, Michael Kuss, Andreas Kandelbauer, Markus Hinder, and Oliver Gassmann. "R&D Efficiency of Leading Pharmaceutical Companies – A 20-Year Analysis." *Drug Discovery Today* 26, no. 8 (August 1, 2021): 1784–89. <https://doi.org/10.1016/j.drudis.2021.05.005>.

One quest: to make drug discovery efficient and sustainable with mathematics and informatics



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



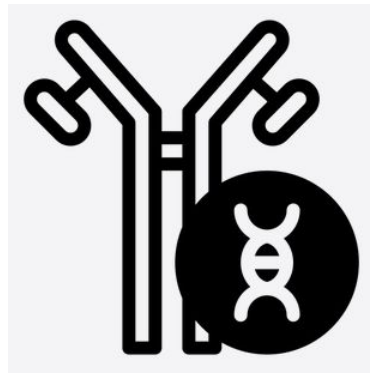
Accurate structure prediction of biomolecular interactions with *AlphaFold3* (Abramson *et al.*, 2024). The *PoseBuster* set: 428 protein-ligand released to PDB after 2021. Success: pocket-aligned ligand Root Mean Square Deviation (RMSD) of atomic positions $\leq 2\text{\AA}$. Right: AF3 prediction for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

Five key questions in drug discovery



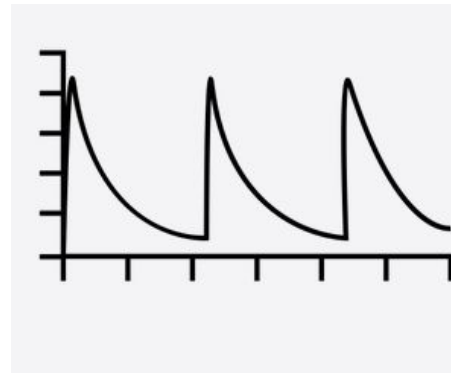
Medical Need

What is the unmet medical need to be addressed?



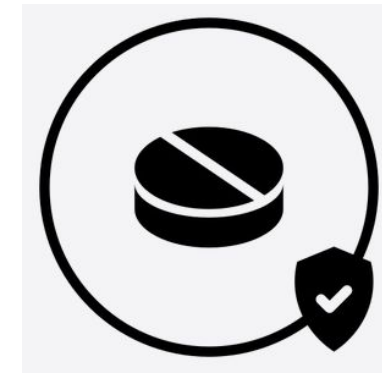
Target & modality

What is the target?
What is the modality?



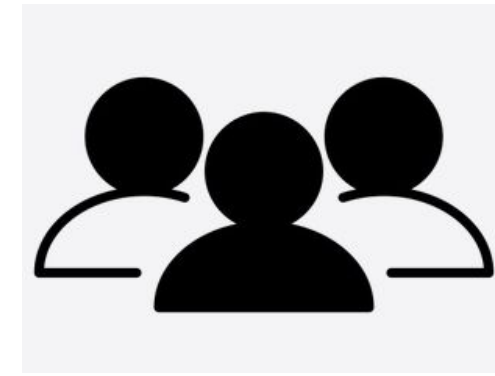
PK/PD

How much drug reach which body part? What does body do to the drug (PK)? What does the drug do to the body (PD)?



Benefit/risk

What is the toxicity of the drug? Is it justifiable given the benefits?

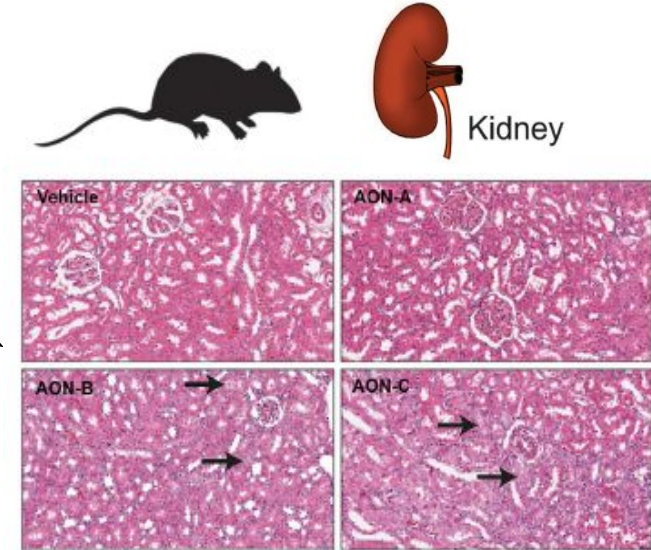
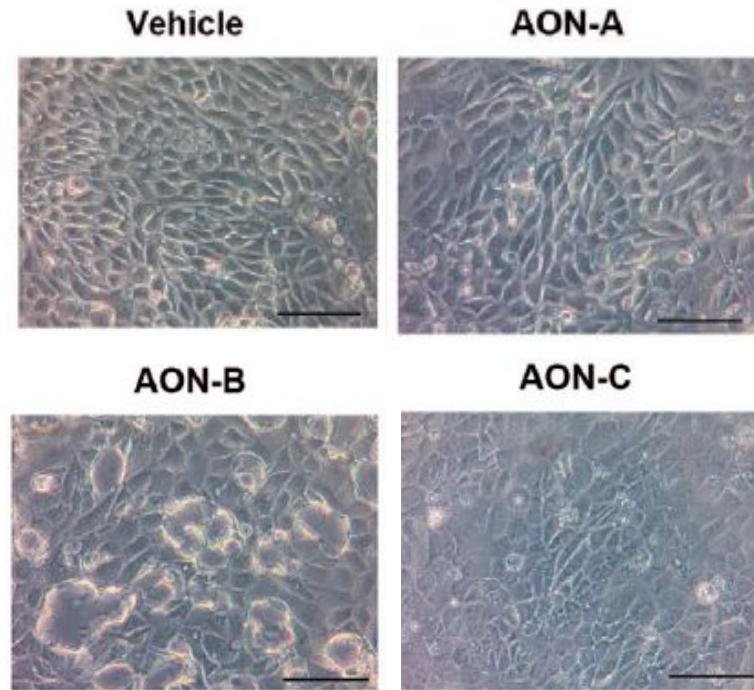
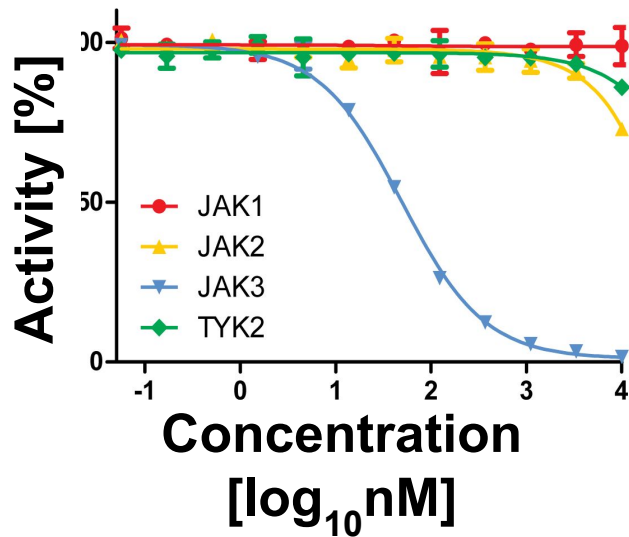


Patient stratification

Who are responsive to the drug? Who are susceptible to adverse events?

Classical workflow of drug discovery from models' perspective

Animal experiments (*in vivo*)



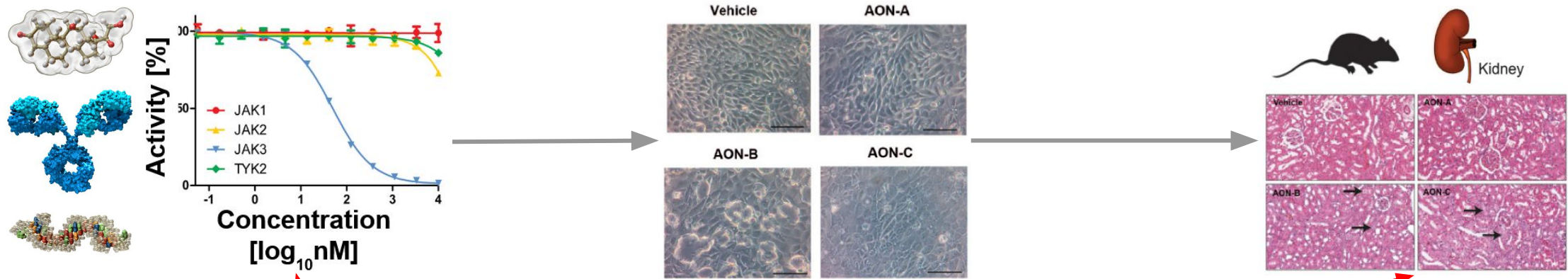
**Biochemical or
biophysical
assays**

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

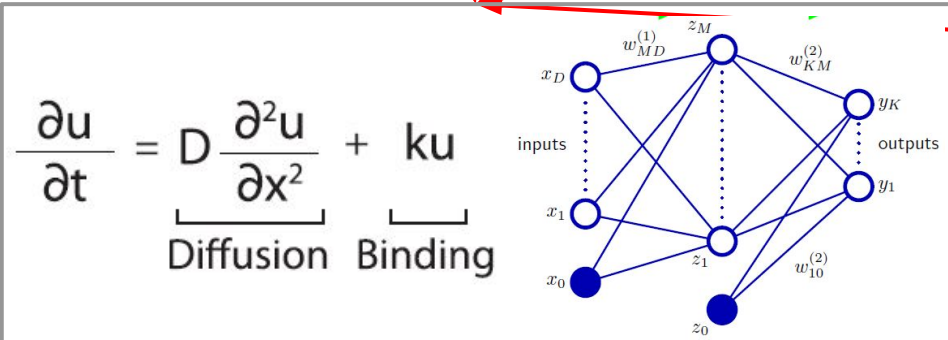


**Clinical
trials**

Mathematical and computational models integrate data across scales



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



Mechanistic, causal, and statistical models

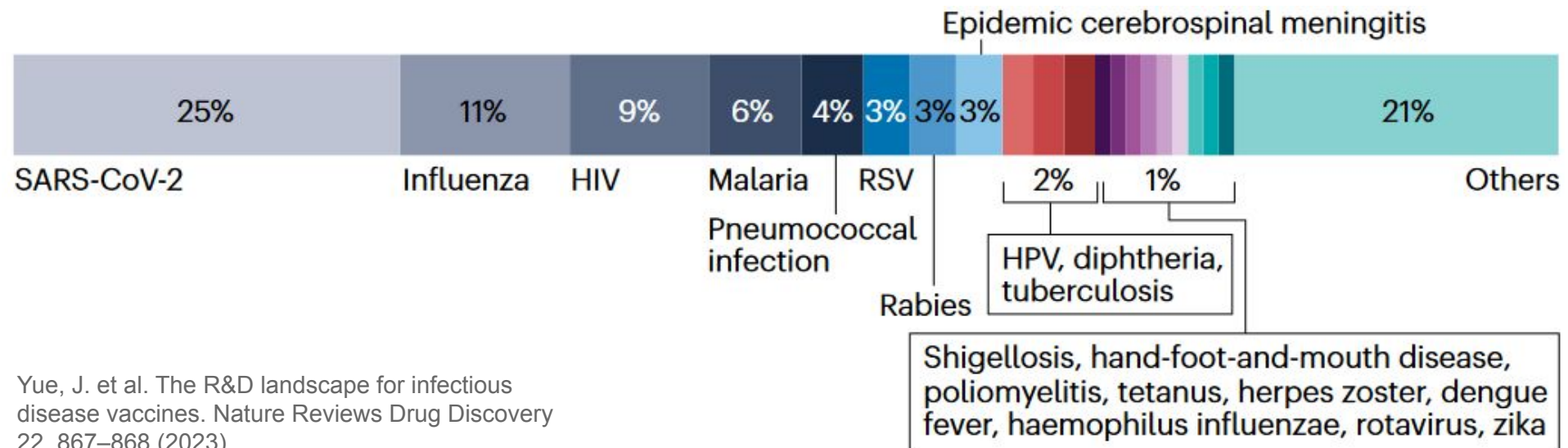
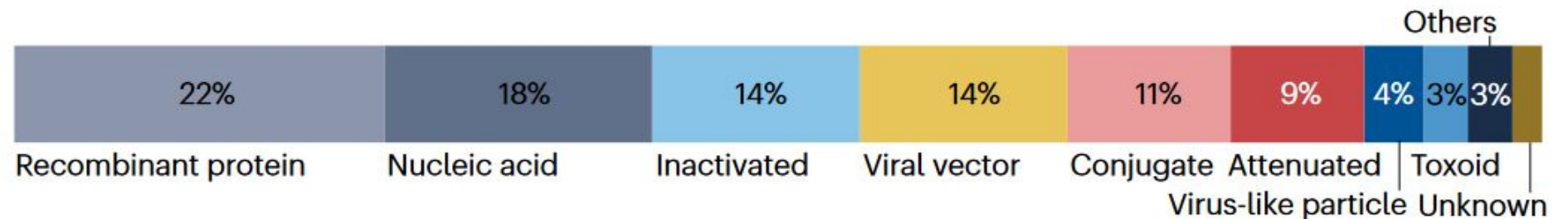


Nobel Prize in Physiology or Medicine 2023 was awarded to Katalin Karikó and Drew Weissman for “their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19”



Main methods for vaccine production before the COVID-19 pandemic:

- **Recombinant protein** (e.g. HBV)
- **Inactivated viruses** (e.g. Influenza and Polio)
- **viral vectors** (e.g. HIV).



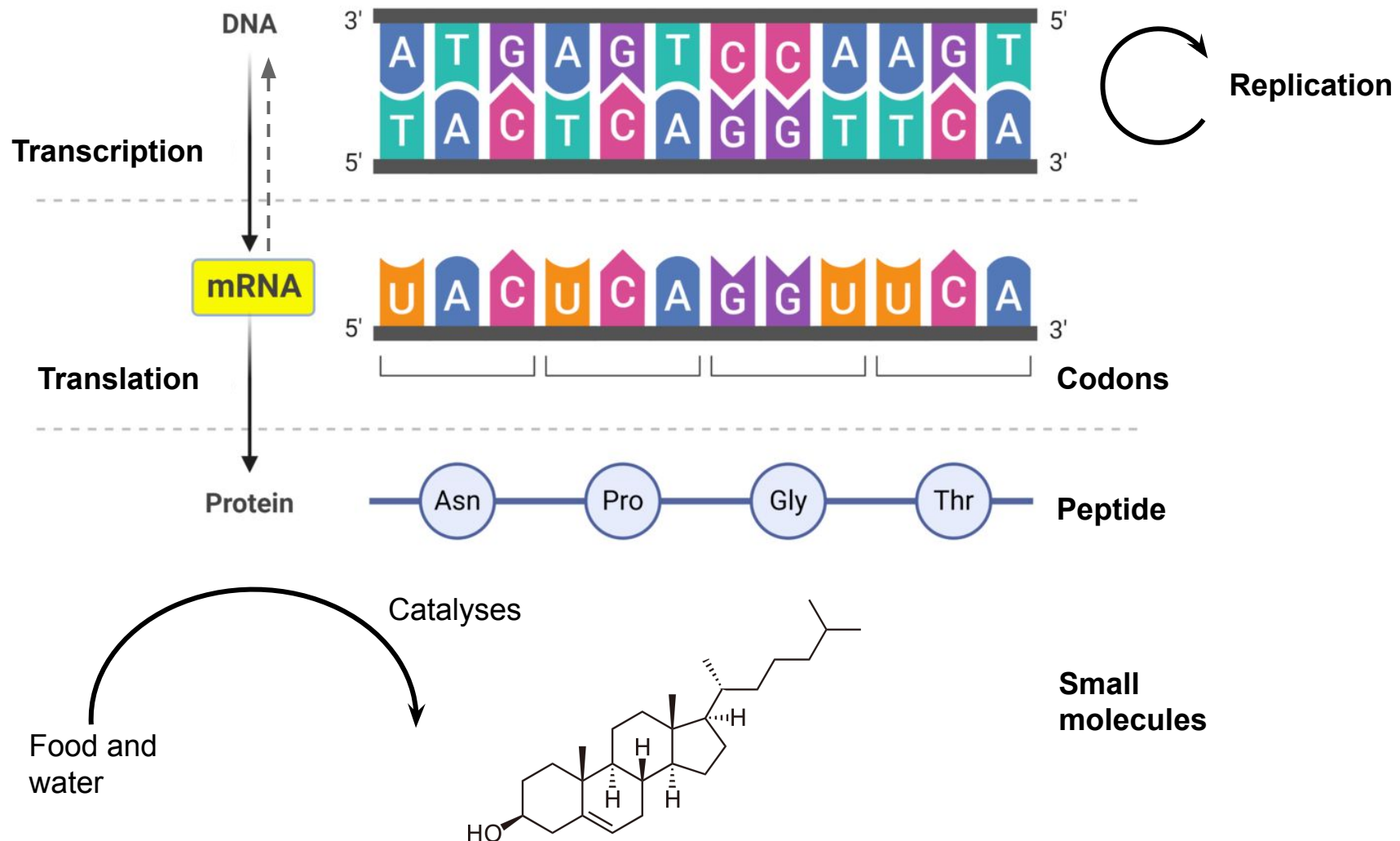
Issues: large-scale cell culture is required, which limits the possibilities for rapid production in response to pandemics.

Yue, J. et al. The R&D landscape for infectious disease vaccines. Nature Reviews Drug Discovery 22, 867–868 (2023).

Offline activities

1. Choose one of the following tasks, and share what you learned the most, both about the topic and about how to communicate science
 - a. Read the *Popular Information* of Nobel Prize in Physics 2024, <https://www.nobelprize.org/prizes/physics/2024/popular-information/>, on artificial neuron networks. If you are an expert, you can choose to read the *Advanced Information* in addition, <https://www.nobelprize.org/prizes/physics/2024/advanced-information/>, and compare the two versions.
 - b. Read the *Population Information* of Nobel Prize in Chemistry 2024, <https://www.nobelprize.org/prizes/chemistry/2024/popular-information/>, on protein structure prediction and protein design. If you are an expert, you can choose to read the *Advanced Information* in addition, <https://www.nobelprize.org/prizes/chemistry/2024/advanced-information/>, and compare the two versions
2. In the *Population Information* of Nobel Prize in Chemistry 2026 that we read last week, <https://www.nobelprize.org/prizes/chemistry/2026/popular-information/>, which drug(s) were mentioned? Why chirality matters in that case? Can you find 1-2 drugs of which chiral forms have similar effects? And 1-2 drugs of which chiral forms have distinct effects?

The central dogma applies to human and viruses including SARS-CoV-2



RNA is transcribed from DNA

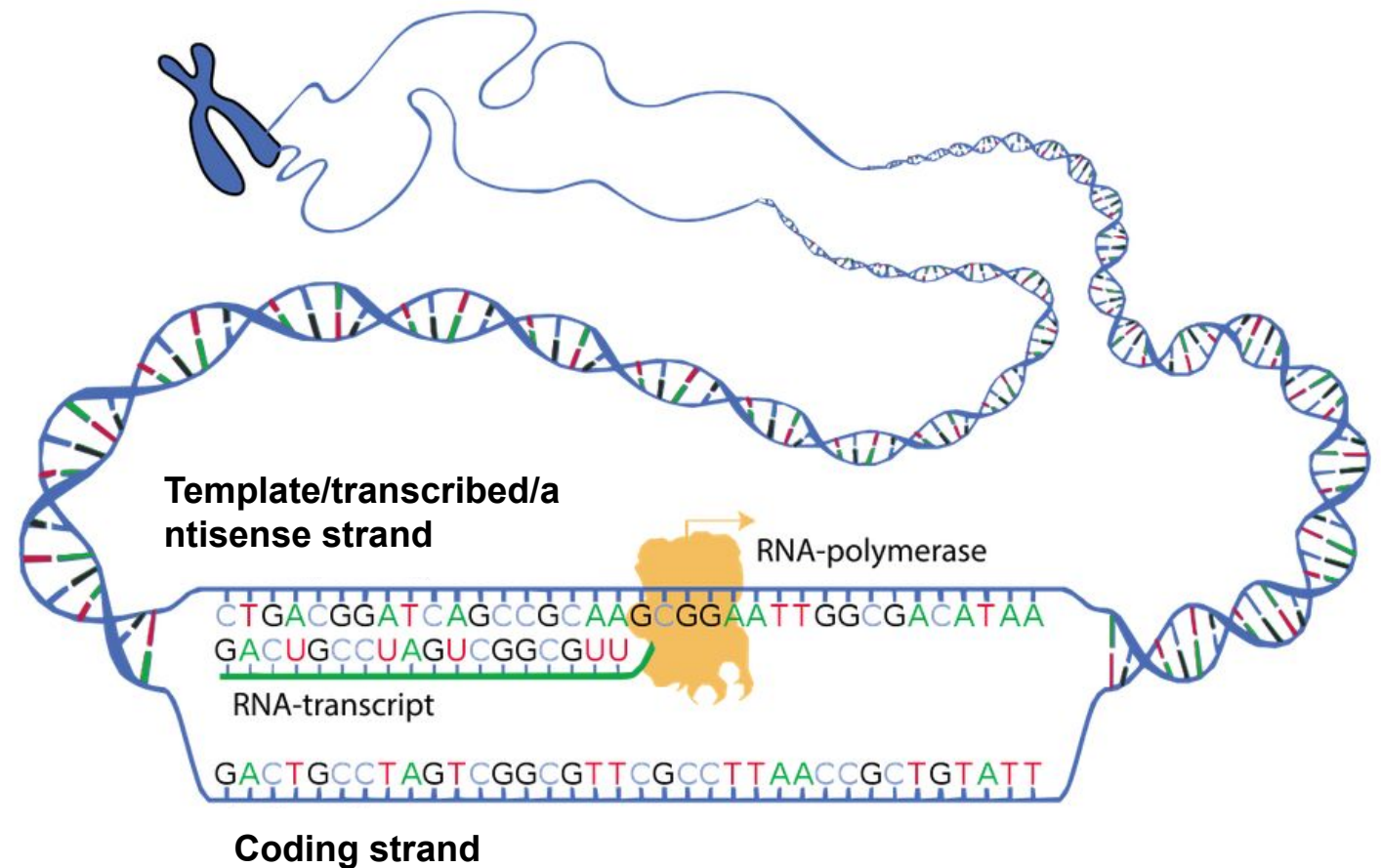
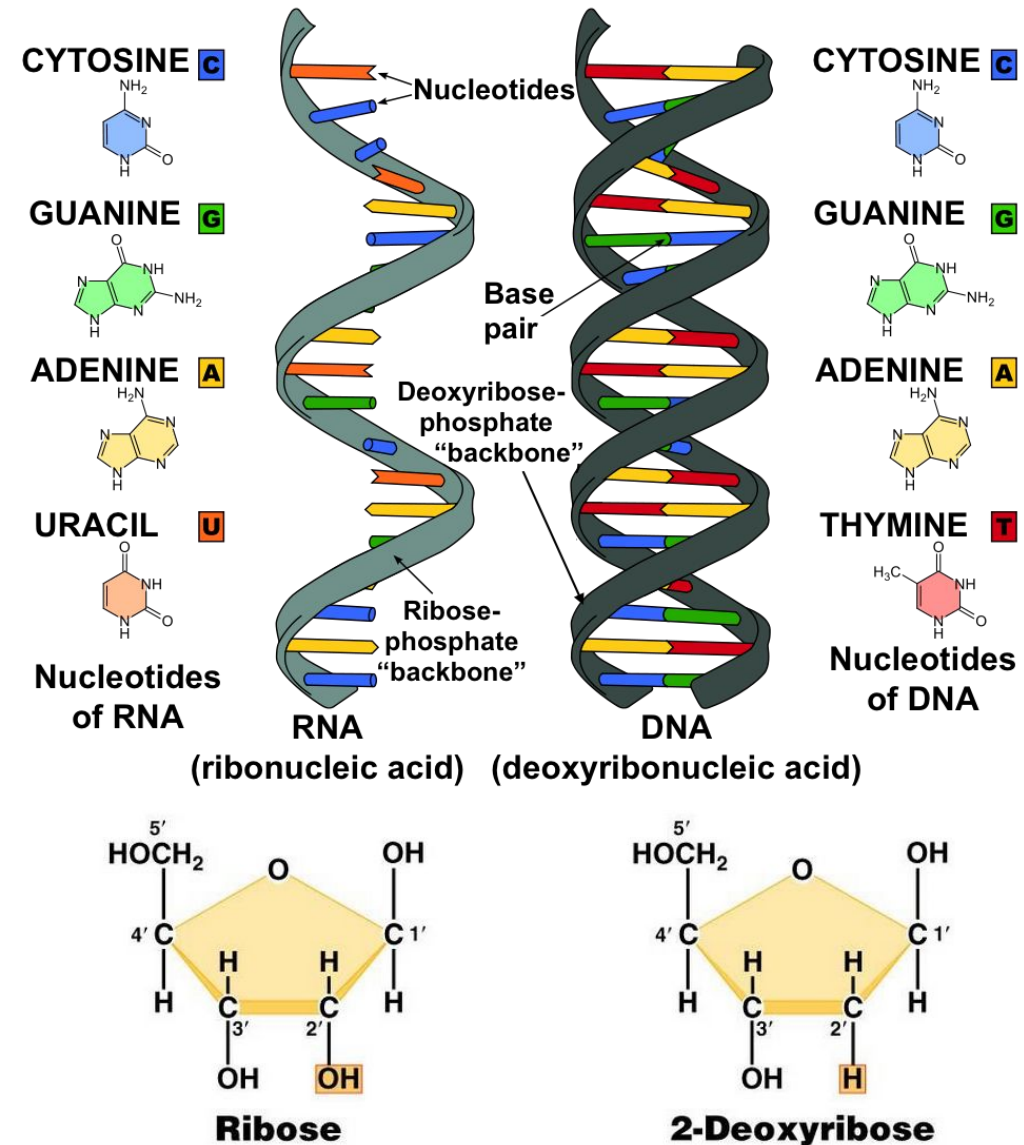


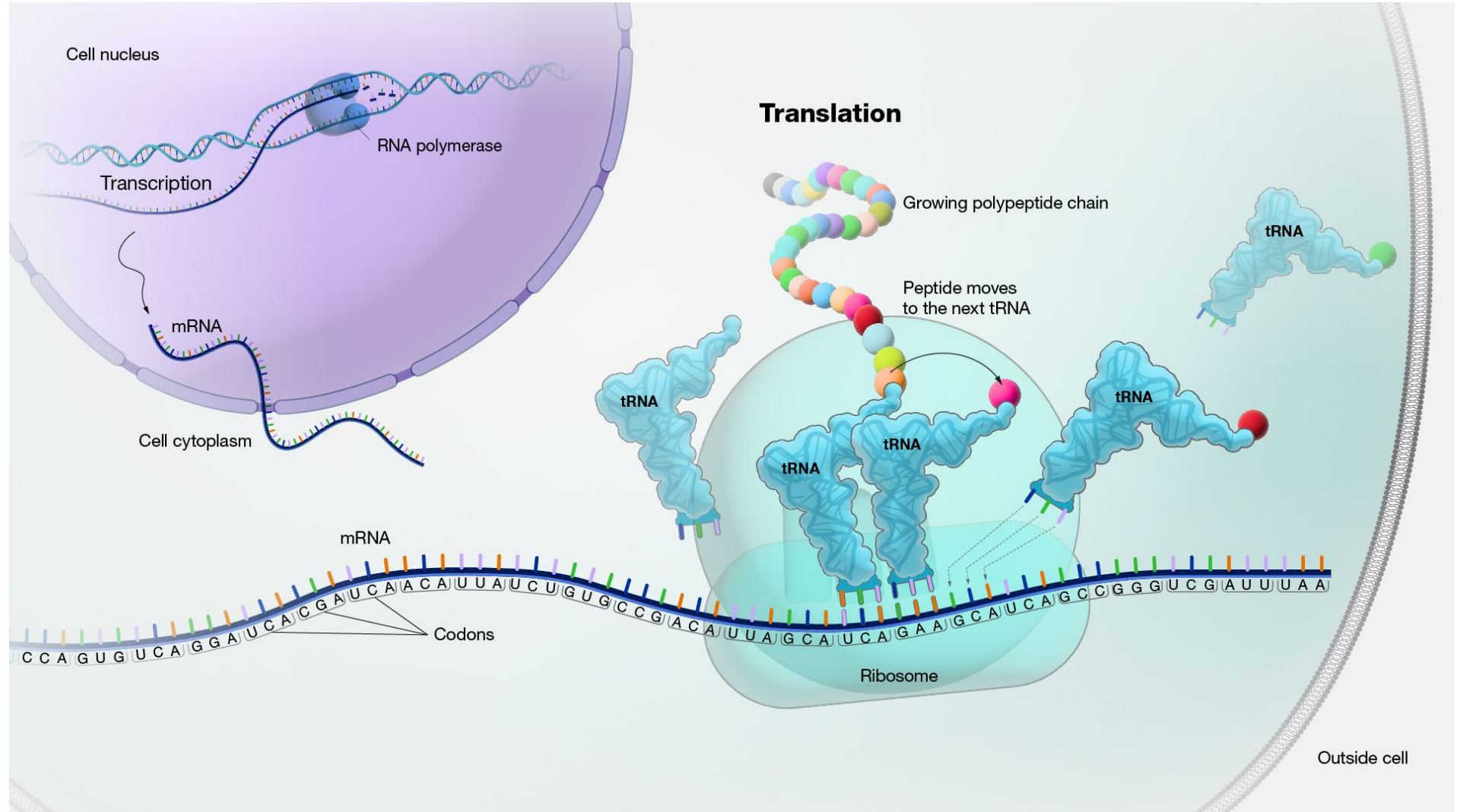
Figure: https://commons.wikimedia.org/wiki/File:DNA_transcriptie.svg and https://en.m.wikipedia.org/wiki/File%3AHAR1F_RF00635_rna_secondary_structure.jpg. Original work by wikipedia user: OrgreBot and user:Ppgardne. Used under CC-SA 3.0 license.

mRNA is translated into proteins

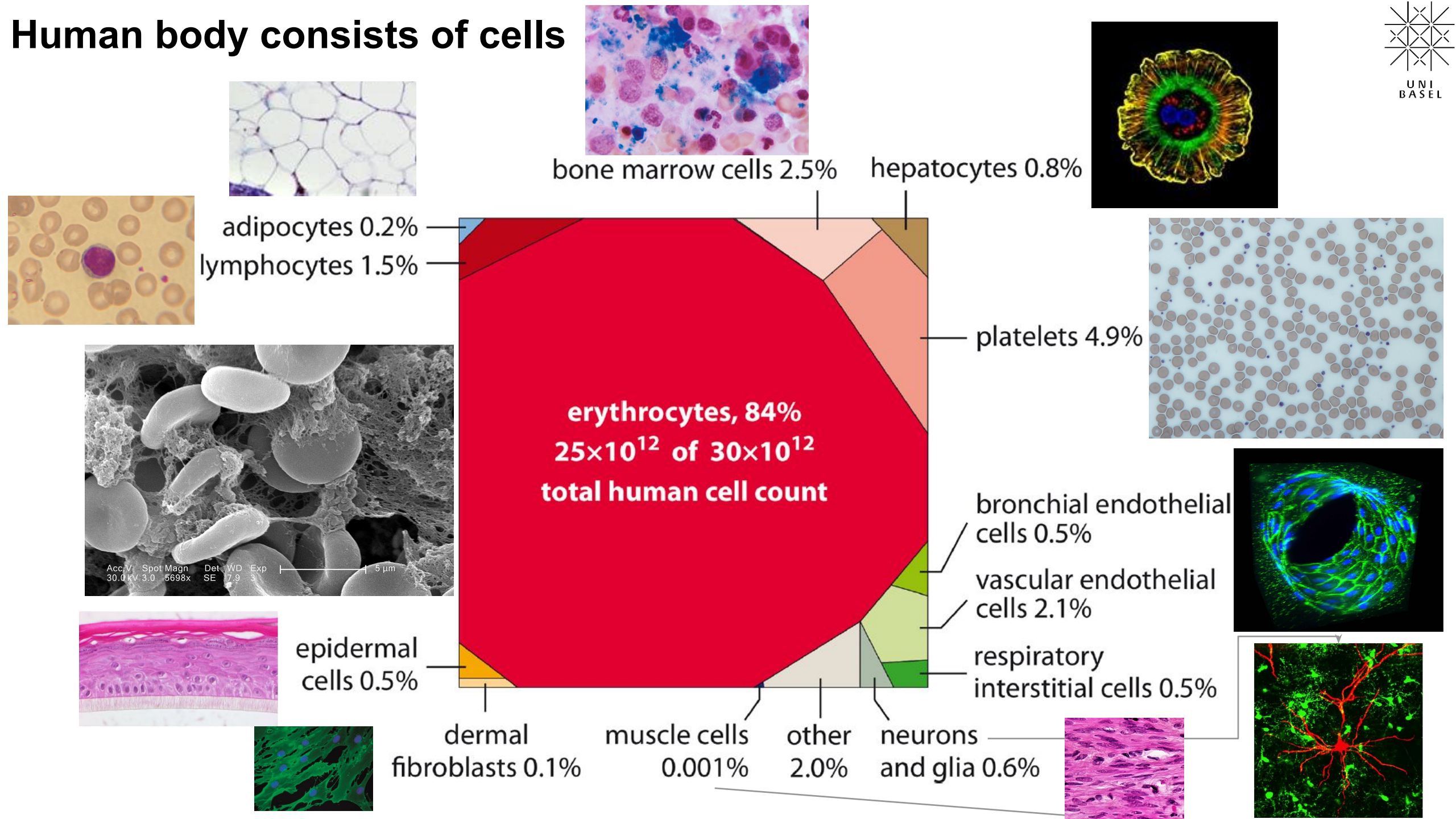
Information encoded in messenger RNA directs the addition of amino acids during protein synthesis.

The process, known as *translation*, takes place on ribosomes in the cell cytoplasm.

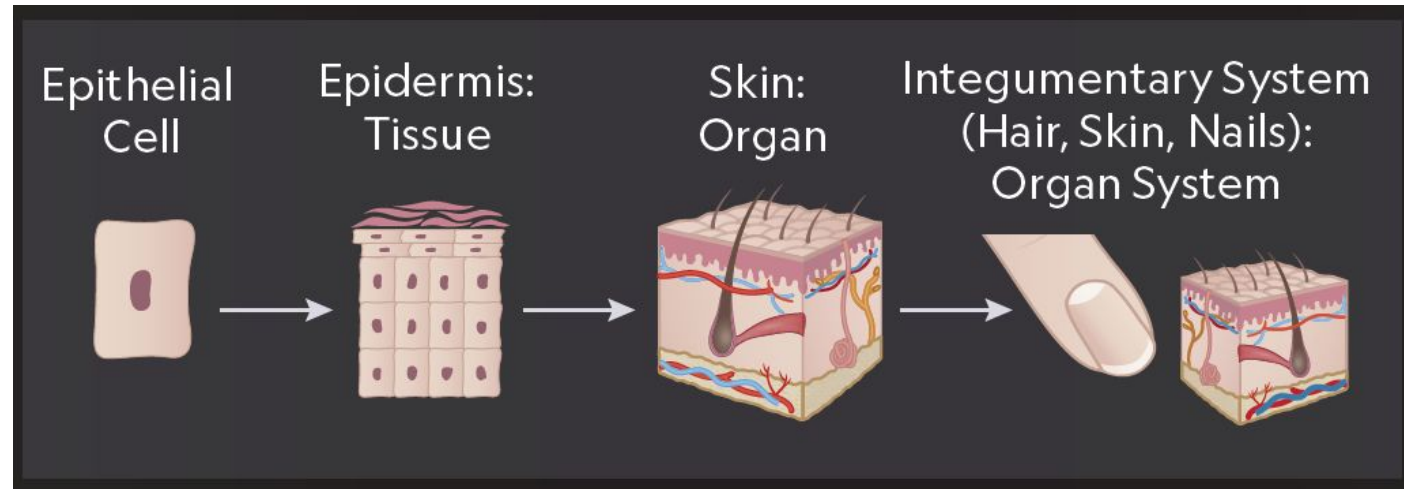
Different cells have different DNA segments 'active' and different RNAs/proteins expressed.



Human body consists of cells



A hierarchical system of cells, tissue, organ, organ system and human body



Cells: basic building blocks, variable morphologies and functions

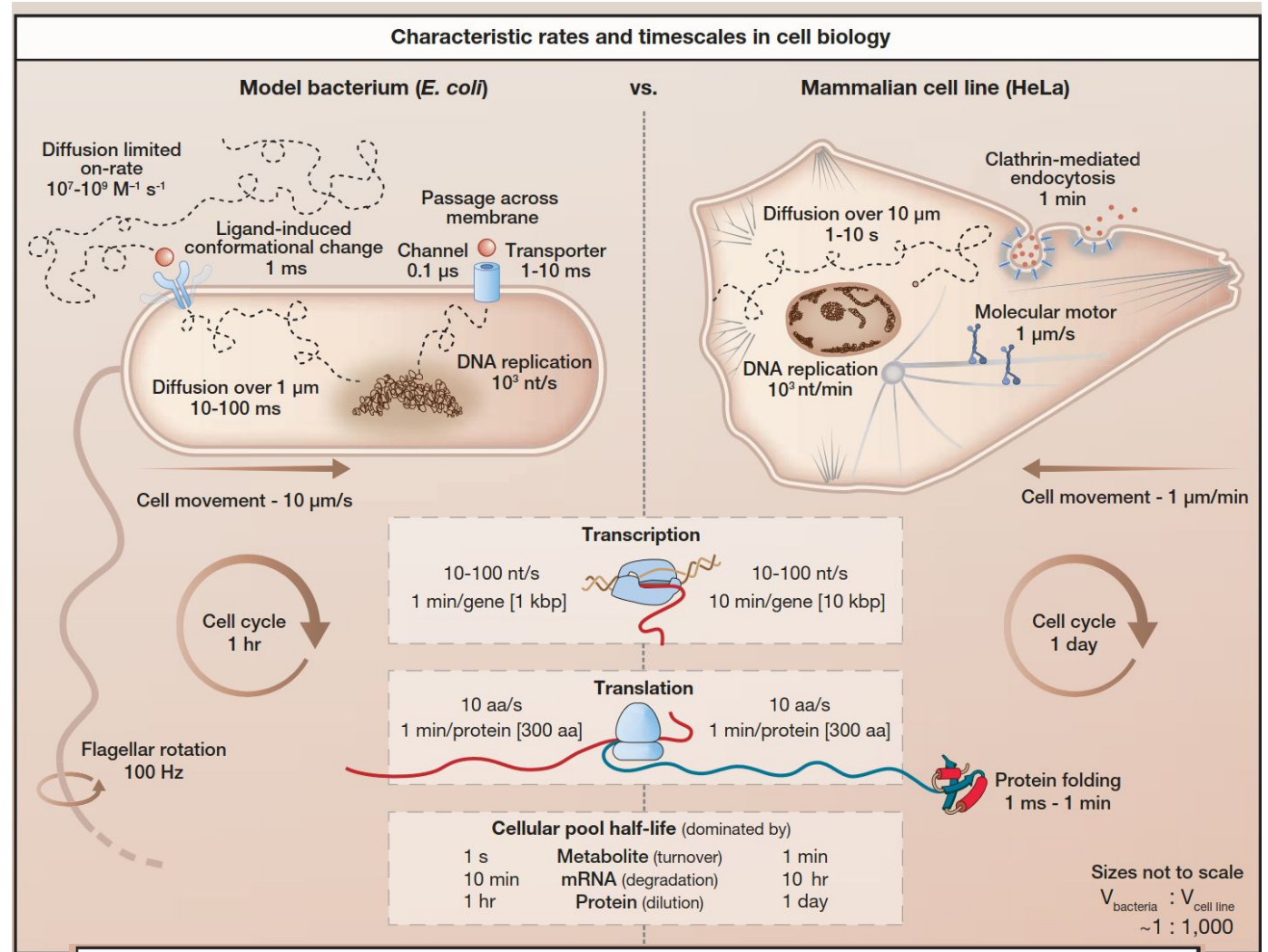
Tissues: groups of specialized cells that communicate and collaborate

Organ: group of tissues to perform specific functions

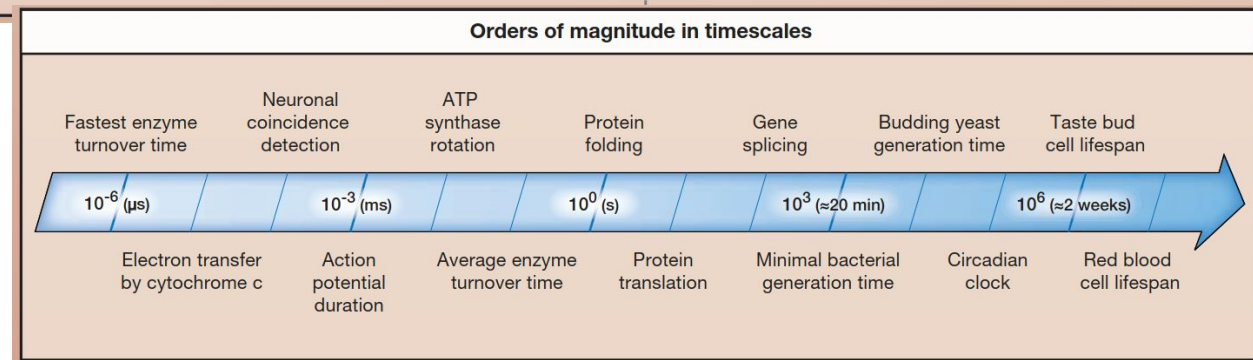
Organ systems: group of organs and tissues

Timescales in biology

Question: what is the relevant timescale of drugs? Why?



Shamir, Maya, Yinon Bar-On, Rob Phillips, and Ron Milo. "SnapShot: Timescales in Cell Biology." *Cell* 164, no. 6 (2016): 1302-1302.e1.
<https://doi.org/10.1016/j.cell.2016.02.058>.



Reductionist *versus* holistic approach



A Sunday Afternoon on the Island of La Grande Jatte, George Seurat
 Example inspired by Derek Lowe, author of *In the Pipeline*