Any comments, suggestions, criticisms that you may have for David and/or for the course?

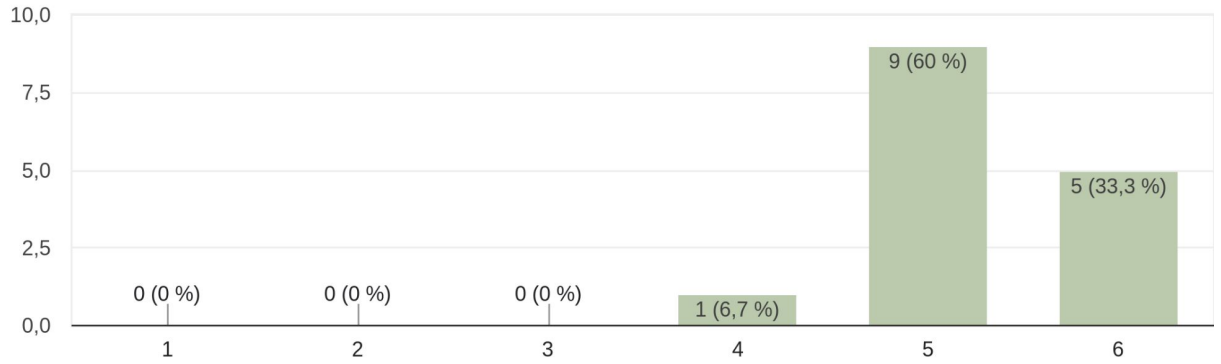
Make a 3x7m sign that says “SIT AT THE FRONT” …

Image: ChatGPT 5

Feedback and questions (Lecture 1)

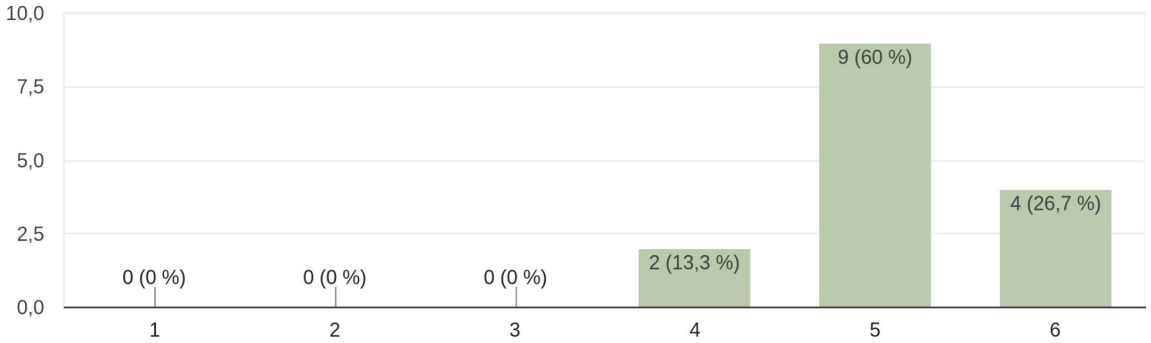
How was your overall impression of today's lecture?

15 Antworten



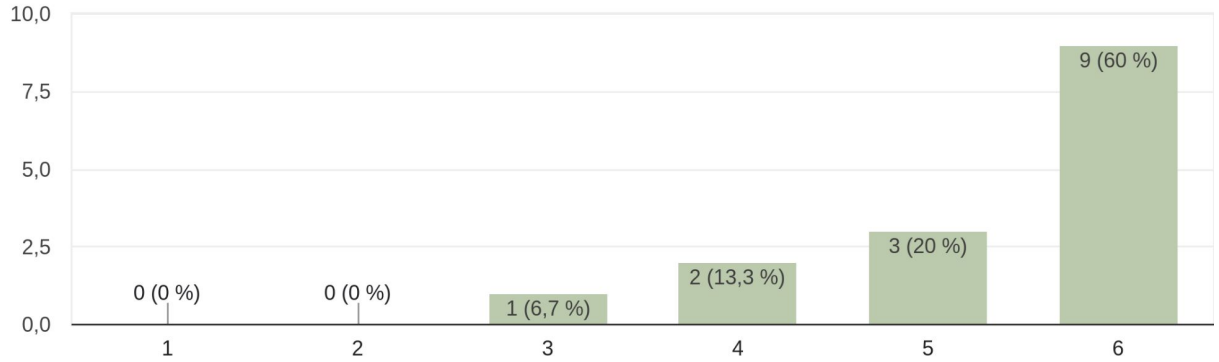
How did you experience the interactions between your peers and David, and among the peers?

15 Antworten



How well could you understand and follow David (the lecturer)?

15 Antworten

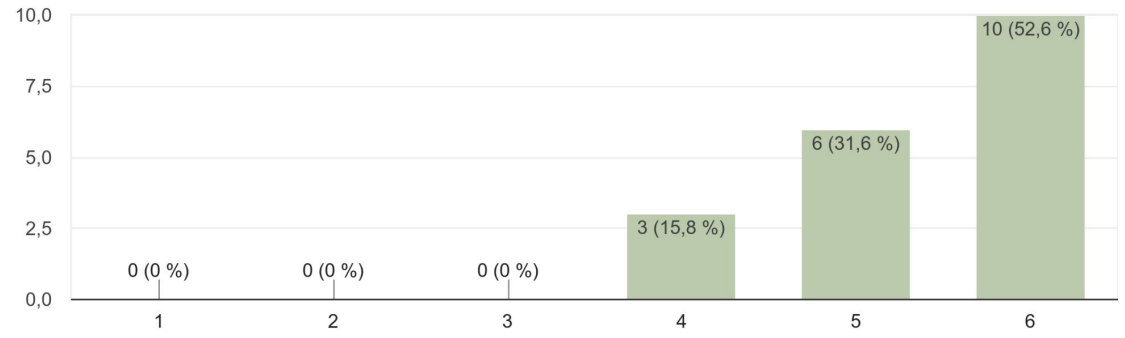


+ Introduction rough, but clear afterwards.
+ Enthusiastic and engaging style.
+ Collaboration encouraged, topic made interesting.
+ Pair discussions worked better than whole row.
- Room setup limited larger group discussions.
- Semester topic overview desired
- Accessible, interdisciplinary background wished
- On-the-spot questions are tough for some

Feedback and questions (Lecture 2)

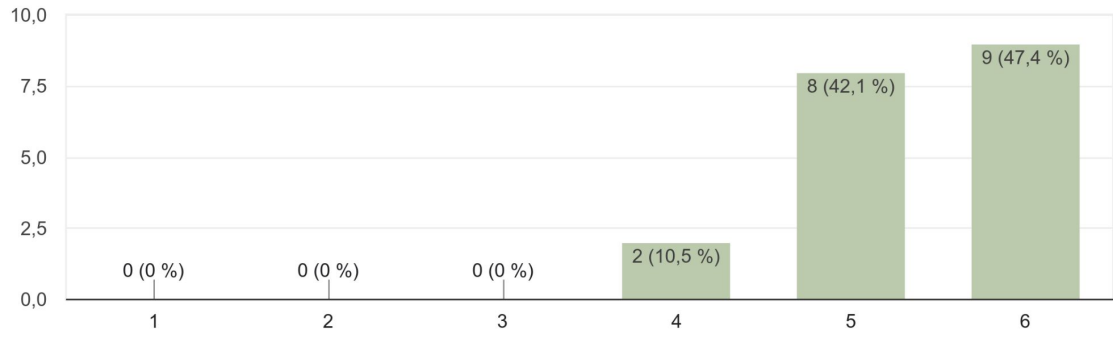
How was your overall impression of the second lecture?

19 Antworten



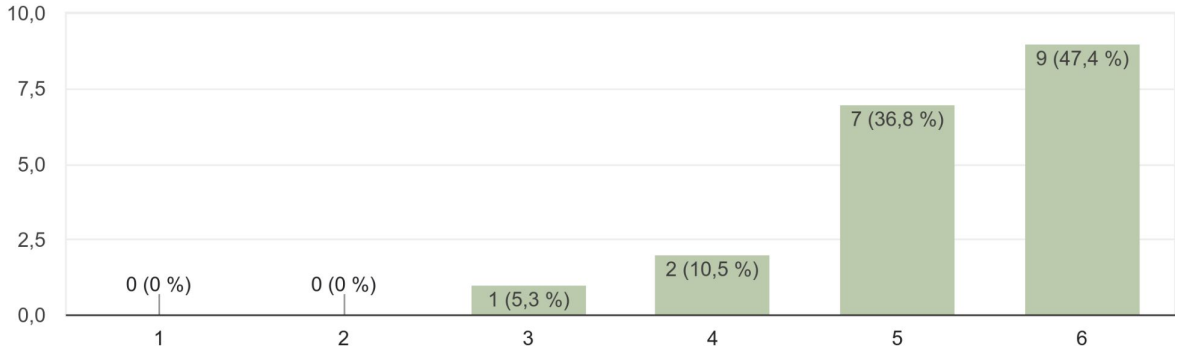
How did you experience the interactions between your peers and David, and among the peers?

19 Antworten



How well could you understand and follow David (the lecturer)?

19 Antworten



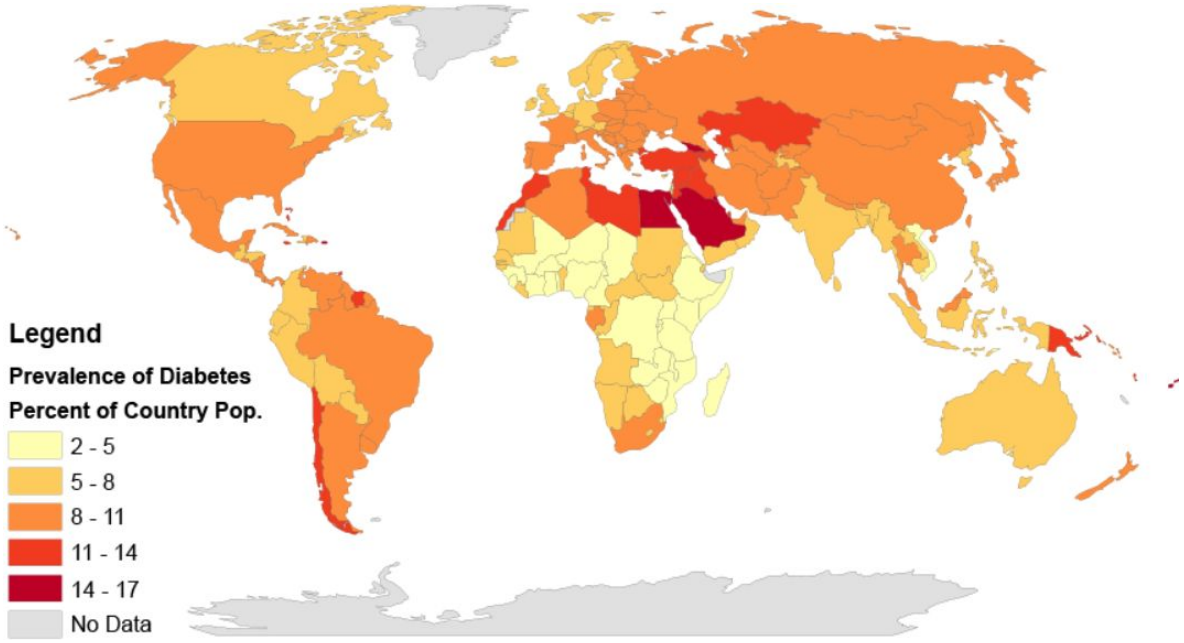
+ Group work fostered collaboration
+ Lecture more engaging, interactive
+ Relaxed pace, easier follow
+ Most engaging course so far
+ Grateful — best lecture yet
+ **Sitting front improved understanding**
- Interest groups felt chaotic
- Sometimes hard to transcribe
- Board and slides unclear sometimes
- Prefer pauses for reflection

AMIDD 2025 Lecture 3: Key questions in drug discovery

We divided the classroom into five personas:

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

Questions: (1) What are your main interests and concerns? (2) With which groups do you wish to collaborate? Why? Rank the partners by the priority. (3) What are the ideal and worse scenarios for you?



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

Main interests and concerns

	Interests	Concerns
Patients	• Safe, effective, and affordable medications • No or preventable side effects • Convenience • Agencies are honest about the risk	The opposites
Medical doctors	• Administrative burden • Side effects (safety profile) • Repayment • Easily accessible	The opposites
Pharma company	• Scientific advances • Effective drug targets • Ensuring safety and efficacy during clinical trials • Reg. Ag. Compliance • Country-specific rules • RWD (real-world evidence) and pharmacovigilance • Financial success of the drugs, and effectiveness	• Economic (R&D cost, time cycle) • Revenue loss • Fails to get approval (especially at late stages) • Regulatory specifies across countries • Ethical concerns • Profits & Access
Insurance company	• Keep the healthcare cost manageable • Planning and predicting risks • Ensure the patients stay healthy	• High price • Effectiveness • Side effects and legal liabilities
Regulatory Agency	• Approving new, efficient, safe drugs • Recognizing and disapproving non-safe drugs • Keep the patients and population's interest, Gov't	• Approving unsafe drug: legal/reputation liability • Pressure from gov., patients, meds, pharma • Funding

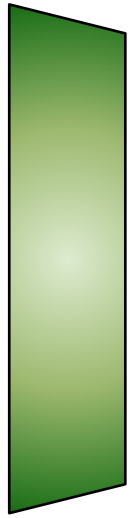
Partners by priority

	Priority #1	#2	#3	#4	#5
Patients	Med. Doc.	Insurance	Reg. Agency	Other patients	Pharma
Medical doctors	Patients	Other docs.	Insurance	Pharma	Reg. Agency
Pharma company	Reg. Agency	Med. Doc.	Patients	Insurance	Compet.
Insurance company (as payer)	Patients	Med. Doc.	Pharma	Reg. Agency	Other insurance
Regulatory Agency	Pharma	Med. Doc.	Patients	Insurance	Other agencies

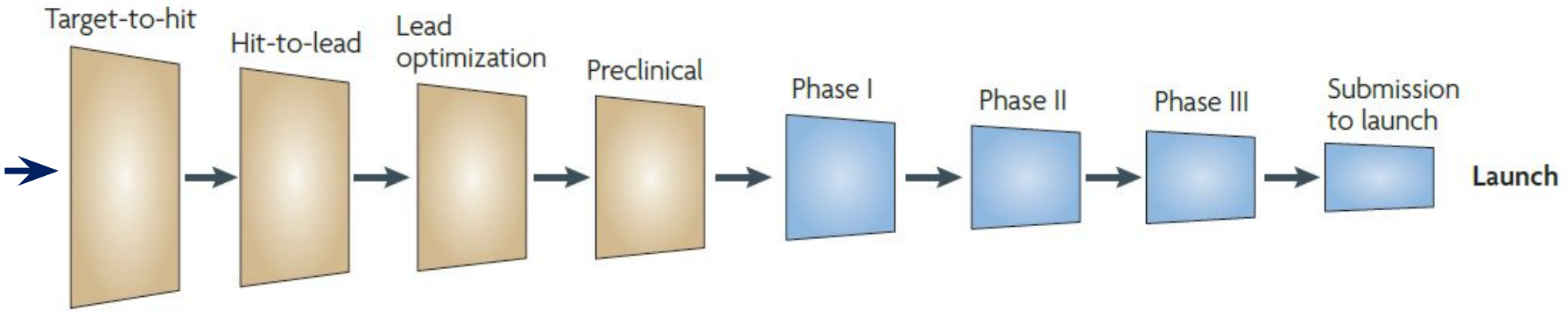
The ideal and the worse scenario

	Ideal scenario	Worst scenario
Patients	Safe and effective drug that improves QoL with minimal side effects and fair access	Unsafe, overpriced, health at risk
Medical doctors	Well known, accessible, easily administerable drug with manageable side effects	New, difficult to access, complicated to administer, and many side effects
Pharma company	Blockbuster (>=1B yearly sale), reputation, beat the competitors	Financial failures, revoke of the drugs, reputation lost
Insurance company (as payer)	Drugs are effective and safe, reasonably priced, prevention, good reputation	Expensive, not effective enough, side effects, reputation suffered
Regulatory Agency	Approving many new and innovative drugs that are safe, well and fast	Letting through a unsafe drug

The linear model of drug discovery



Target identification, validation & assessment

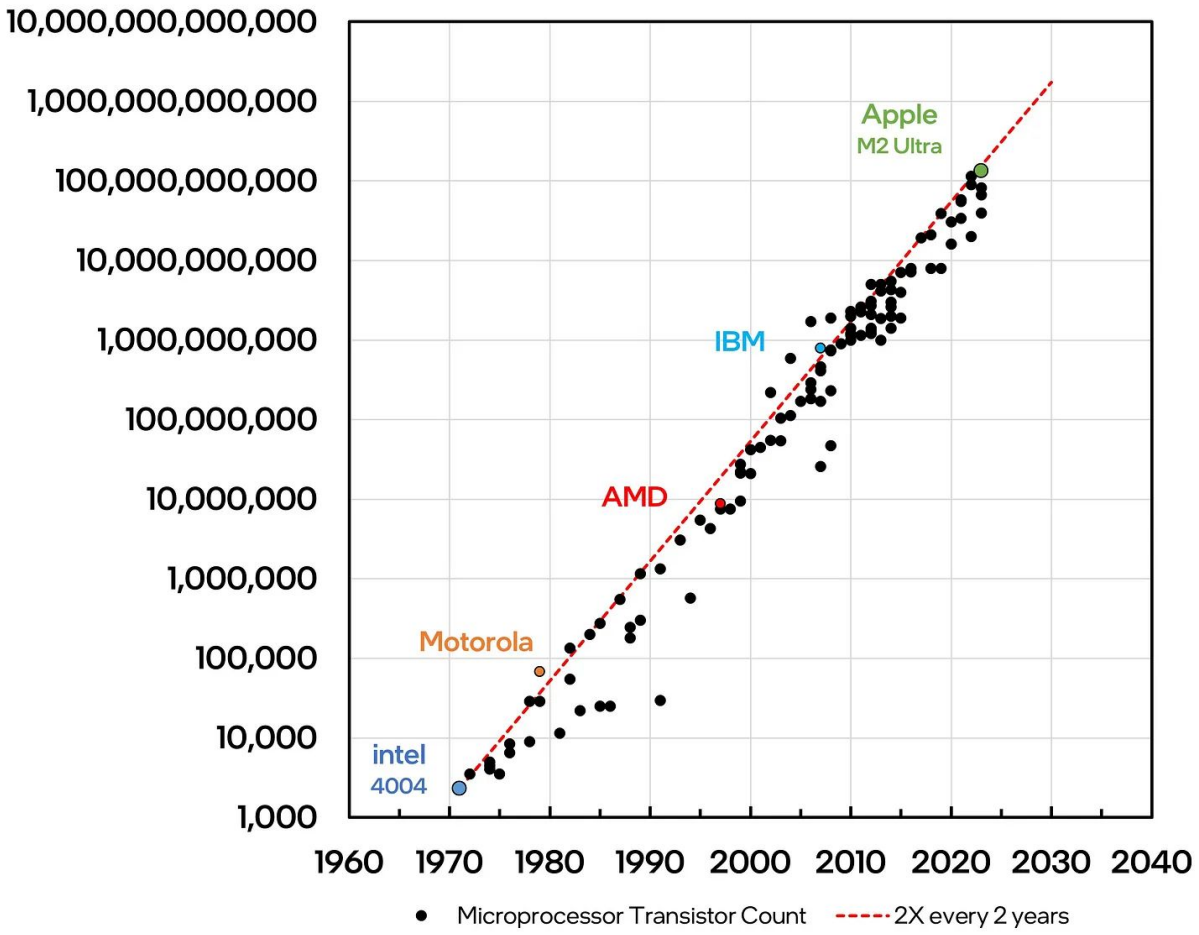


	Target-to-hit	Hit-to-lead	Lead optimization	Preclinical	Phase I	Phase II	Phase III	Submission to launch	
p(TS)	80%	75%	85%	69%	54%	34%	70%	91%	Total≅5%
***WIP* needed for 1 launch**	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1	1
Cost per WIP per Phase	$1	$2.5	$10	$5	$15	$40	$150	$40	
Cycle time (years)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5	Total≅12.5y
Cost per launch (out of pocket)	$24	$49	$146	$62	$128	$185	$235	$44	$873
% Total cost per NME	3%	6%	17%	7%	15%	21%	27%	5%	
Cost of capital	11%								
Cost per launch (capitalized)	$94	$166	$414	$150	$273	$319	$314	$48	$1,778

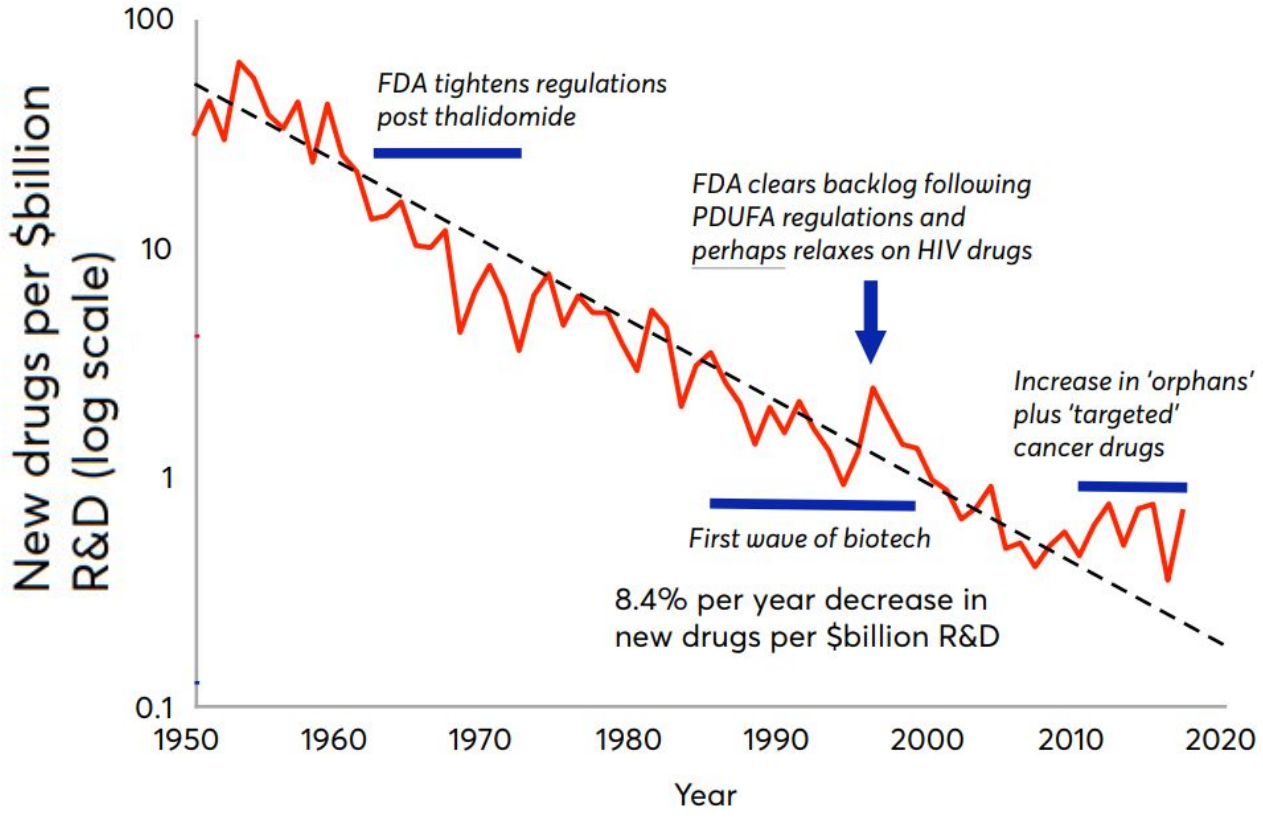
Discovery Development

Adapted from Paul, Steven M. *et al.* "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." Nature Reviews Drug Discovery, 2010. Cost ($) is in the unit of *1 Million* Dollar

Moore's *versus* Eroom's Law

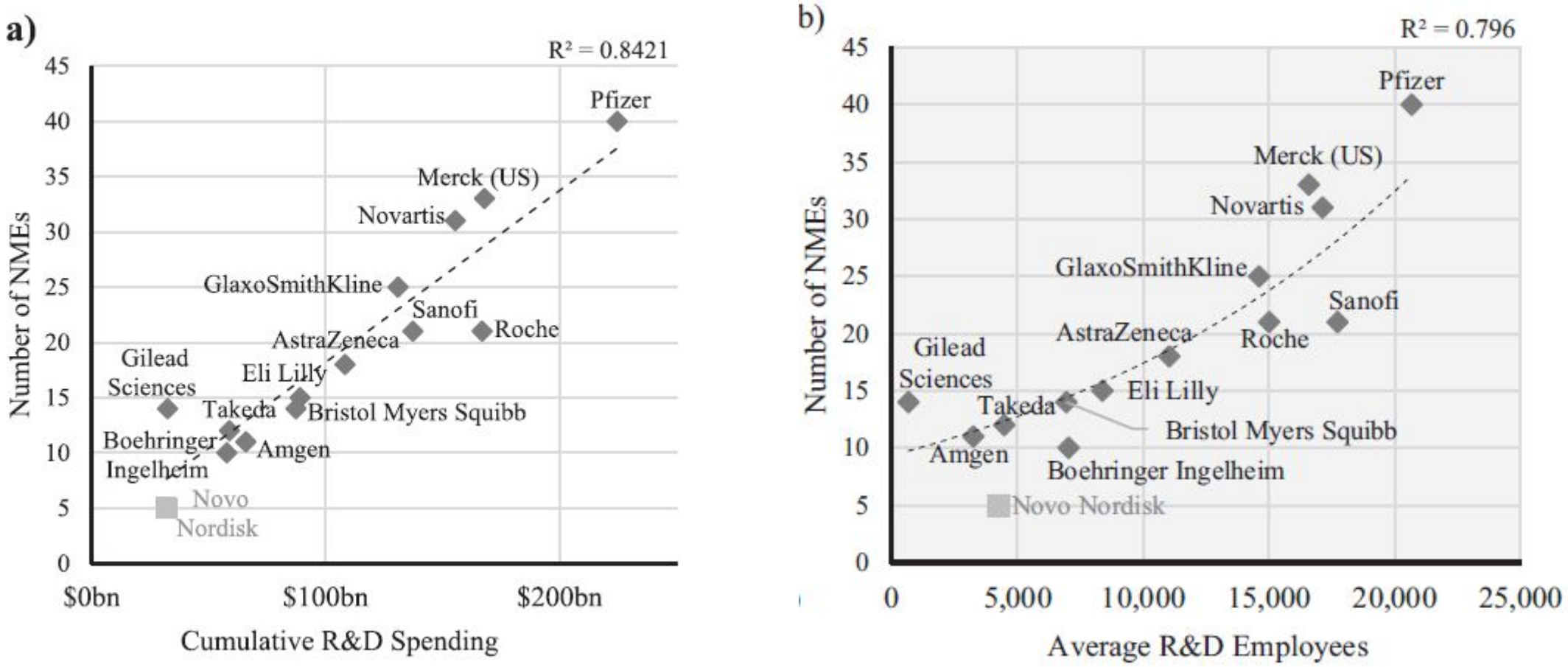


Adapted from graphs by Hannah Ritchie and Max Roser and by Jim Keller



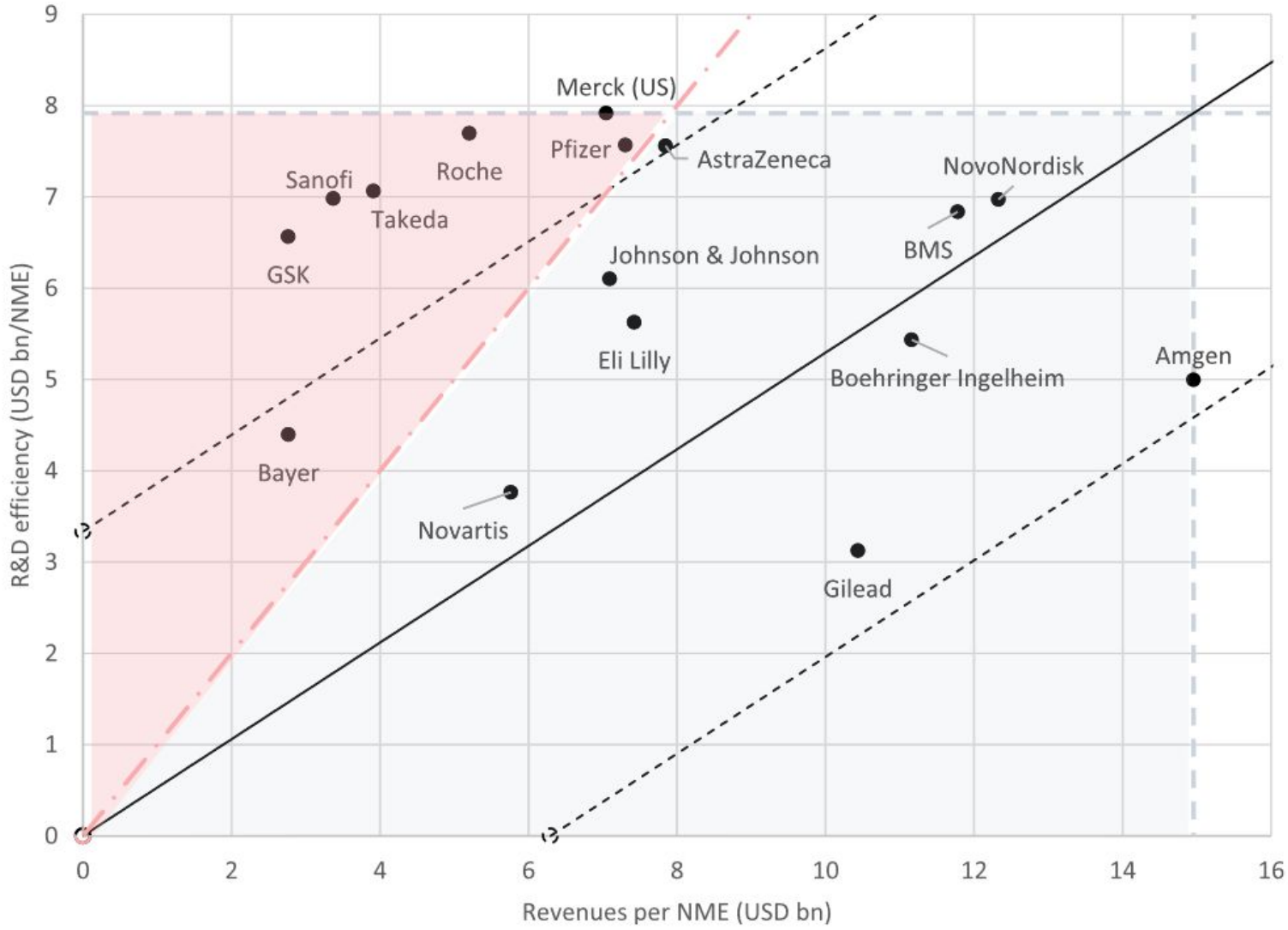
Data come from Scannell, etl al. (2012) Diagnosing the decline in pharmaceutical R&D efficiency. Nature Reviews Drug Discovery, and personal communication. Figure by Richard Jones and James Wilsdon

Drug discovery and development require huge investment and large interdisciplinary teams

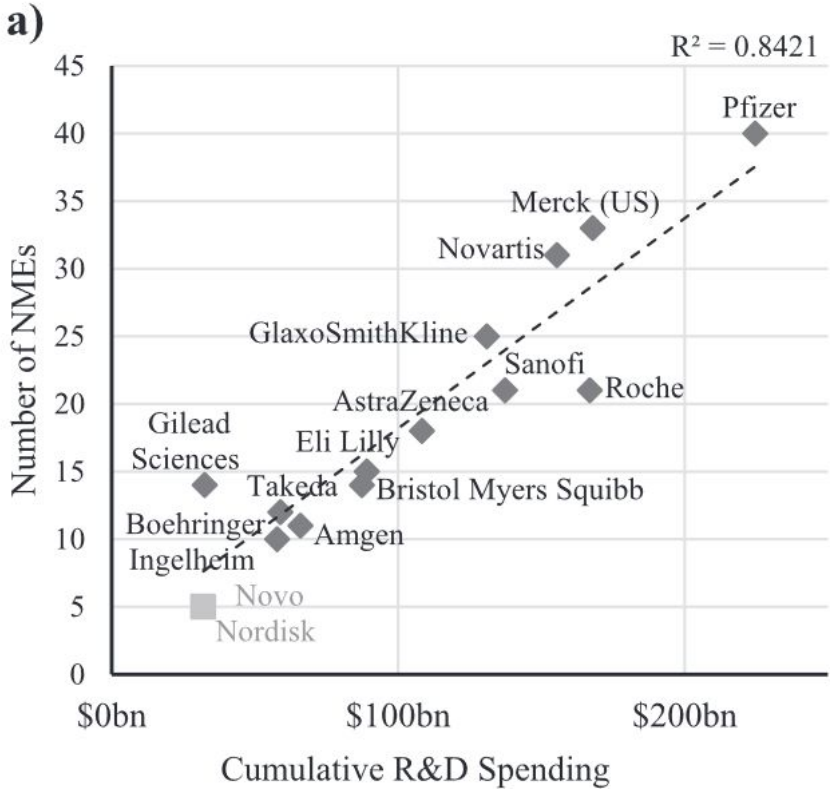


Schuhmacher, Alexander, Lucas Wilisch, Michael Kuss, Andreas Kandelbauer, Markus Hinder, and Oliver Gassmann. "R&D Efficiency of Leading Pharmaceutical Companies – A 20-Year Analysis." *Drug Discovery Today* 26, no. 8 (August 1, 2021): 1784–89. https://doi.org/10.1016/j.drudis.2021.05.005.

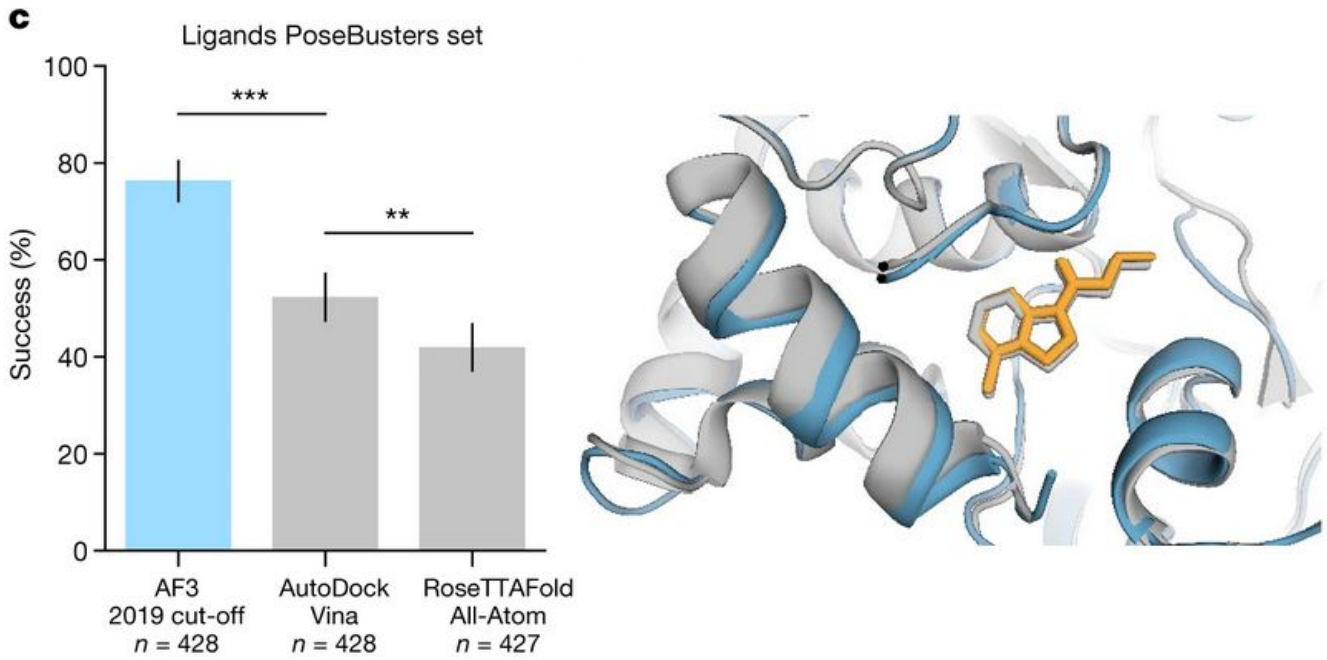
Profits generated by new molecule entities (NMEs) cannot cover the cost in some companies in the last 20 years



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)

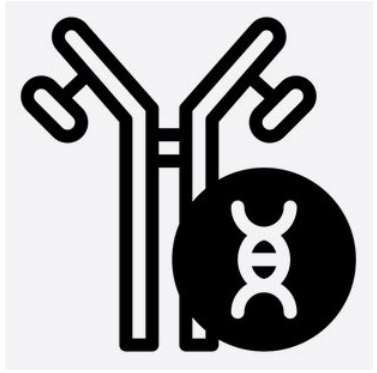


Accurate structure prediction of biomolecular interactions with *AlphaFold3* (Abramson *et al.*, 2024). The *PoseBuster* set: 428 protein-ligand released to PDB after 2021. Success: pocket-aligned ligand Root Mean Square Deviation (RMSD) of atomic positions <= 2Å. Right: AF3 prediction for which docking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

Five key questions in drug discovery

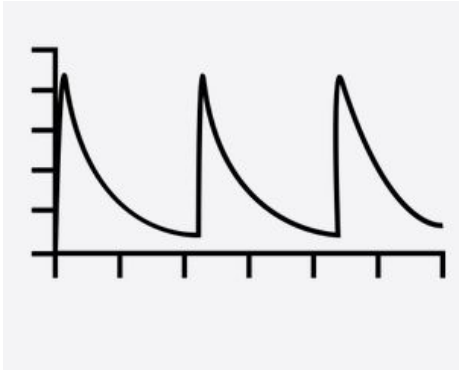
Medical Need

What is the unmet medical need to be addressed?



Target & modality

What is the target? What is the modality?

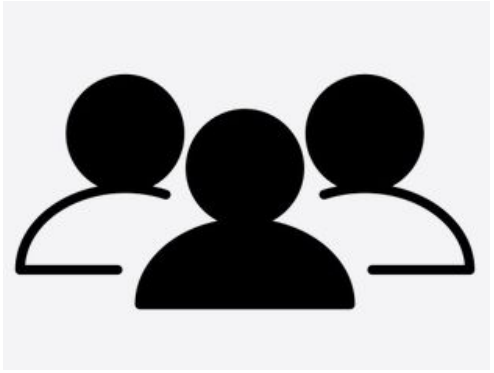


PK/PD

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

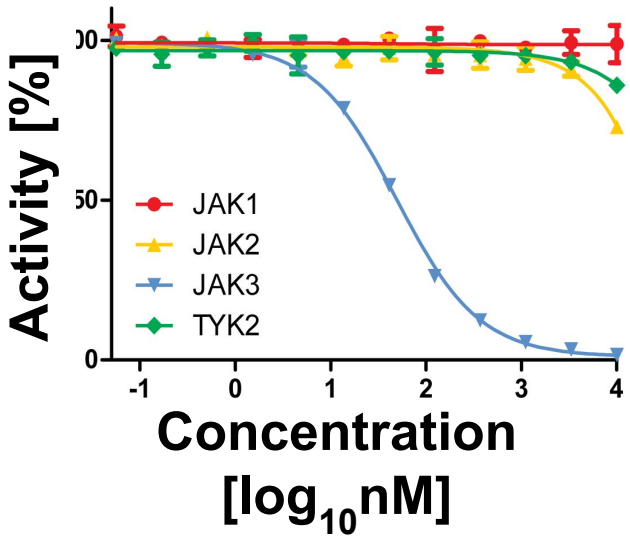
What is the toxicity of the drug? Is it justifiable given the benefits?



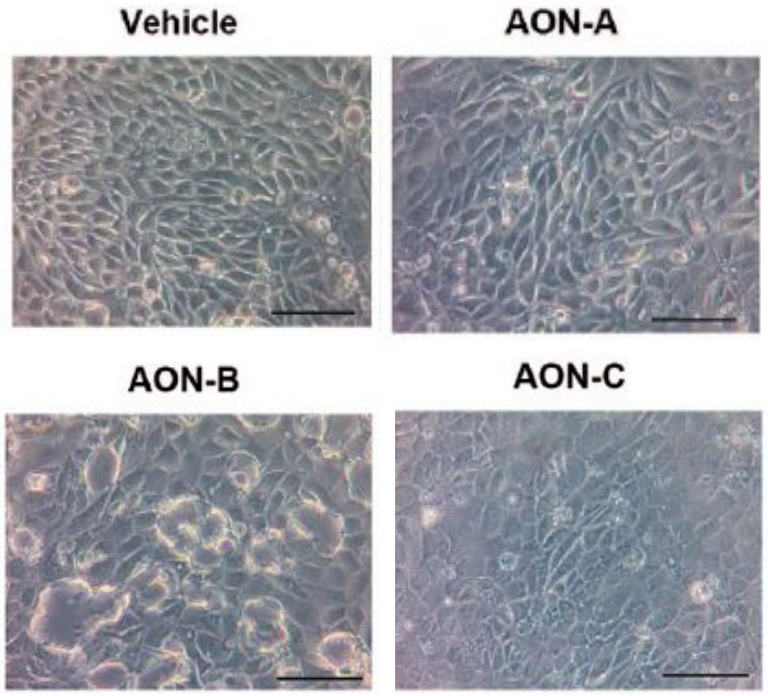
Patient stratification

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

Classical workflow of drug discovery from models' perspective

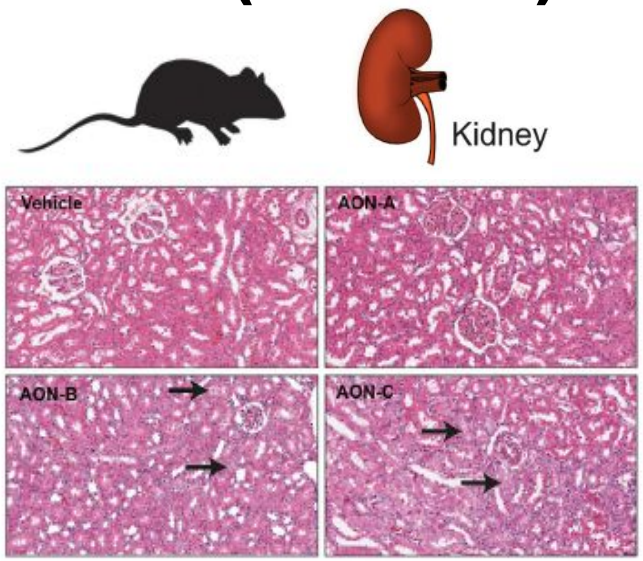


Biochemical or biophysical assays



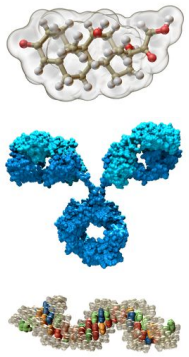
Cellular assays (*in vitro*)

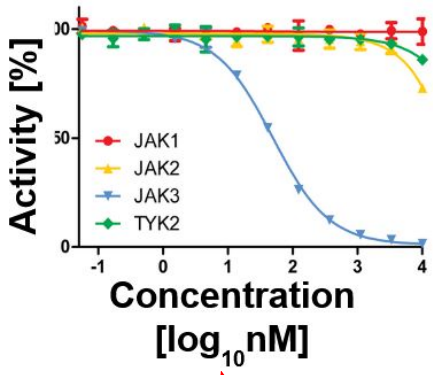
Animal experiments (*in vivo*)

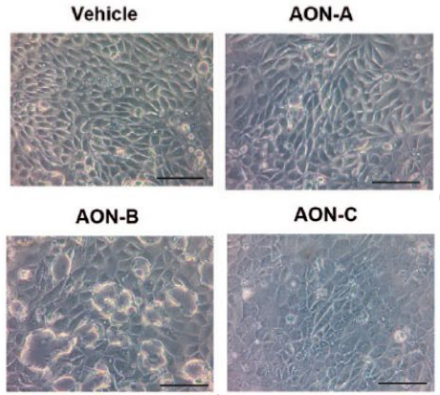


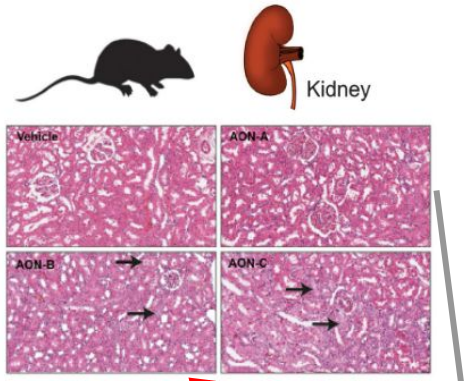
Clinical trials

Mathematical and computational models integrate data across scales



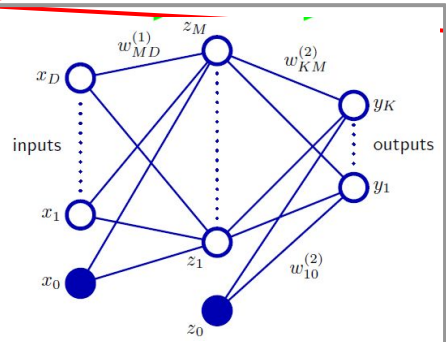






High-throughput technologies (omics, microscopy, etc.)

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



Mechanistic, causal, and statistical models

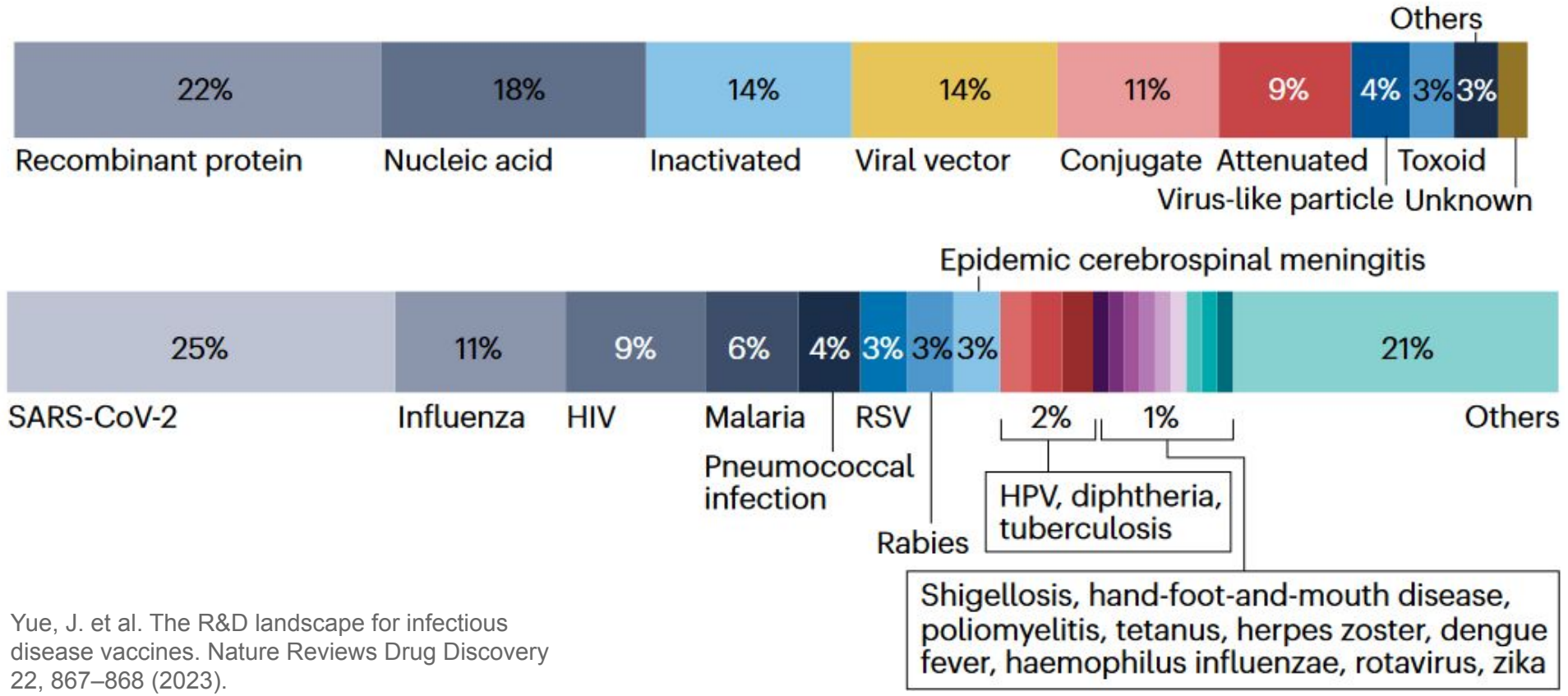
Backup slides

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) are.

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



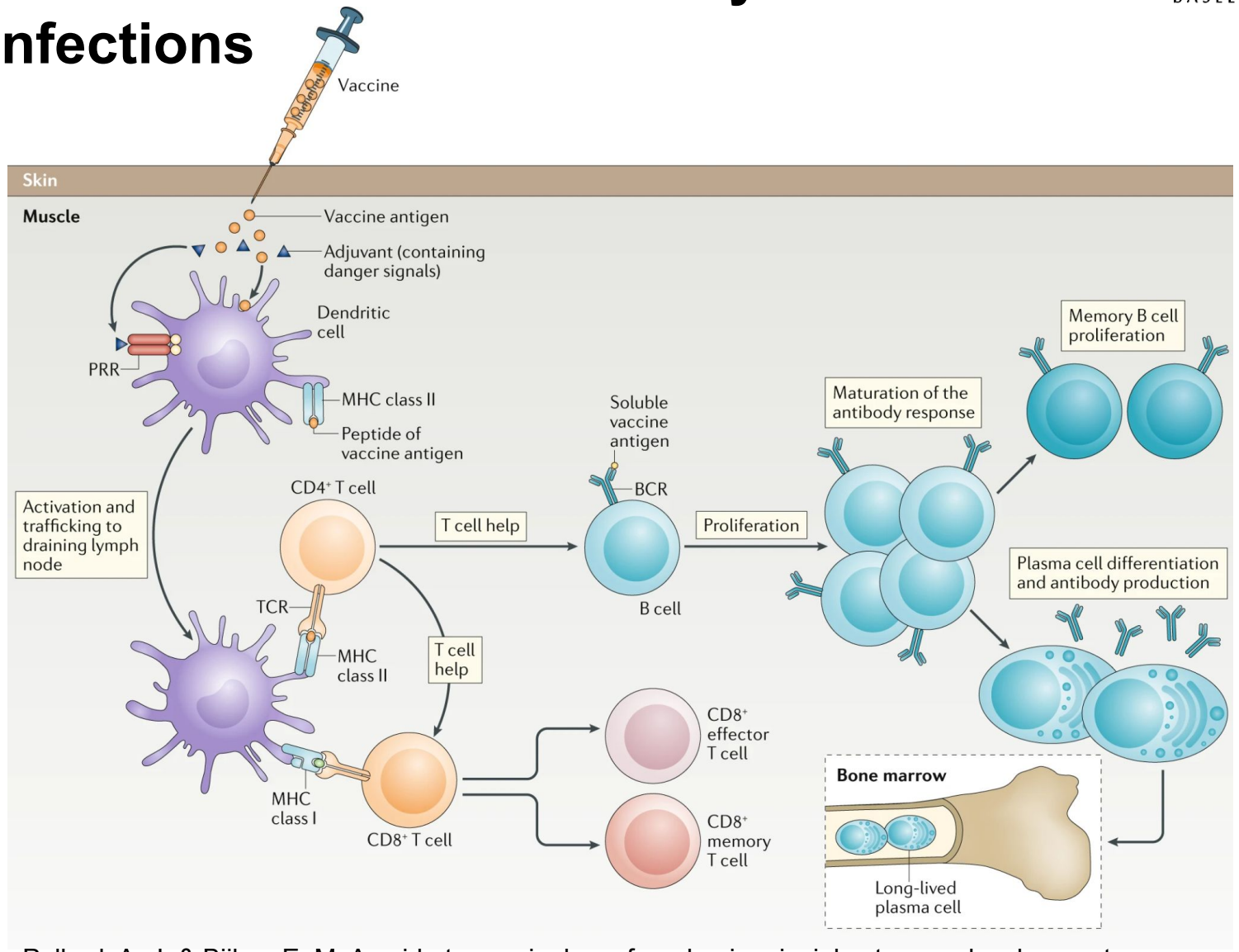
Yue, J. et al. The R&D landscape for infectious disease vaccines. Nature Reviews Drug Discovery 22, 867–868 (2023).

Vaccine mimics viral infection to activate the immune system to protect body from future infections

Vaccine mimics a viral infection to activate innate and adaptive immune system, while minimizing the pathogenic effects.

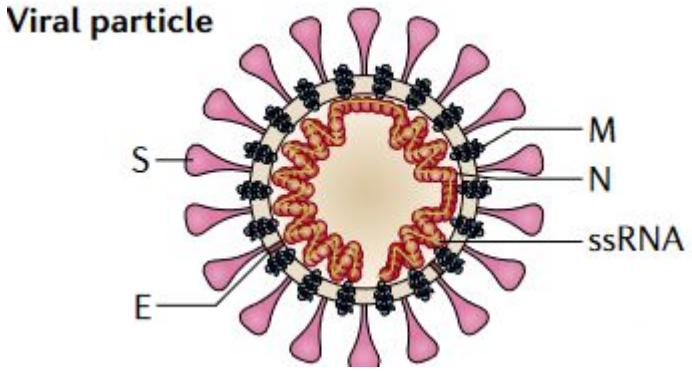
Key players in the game:

1. Viral proteins as *antigens*
2. Antigen-presenting cells (e.g. dendritic cells)
3. T cells (T comes from Thymus, because they mature there)
4. B cells (B comes from bone marrow).

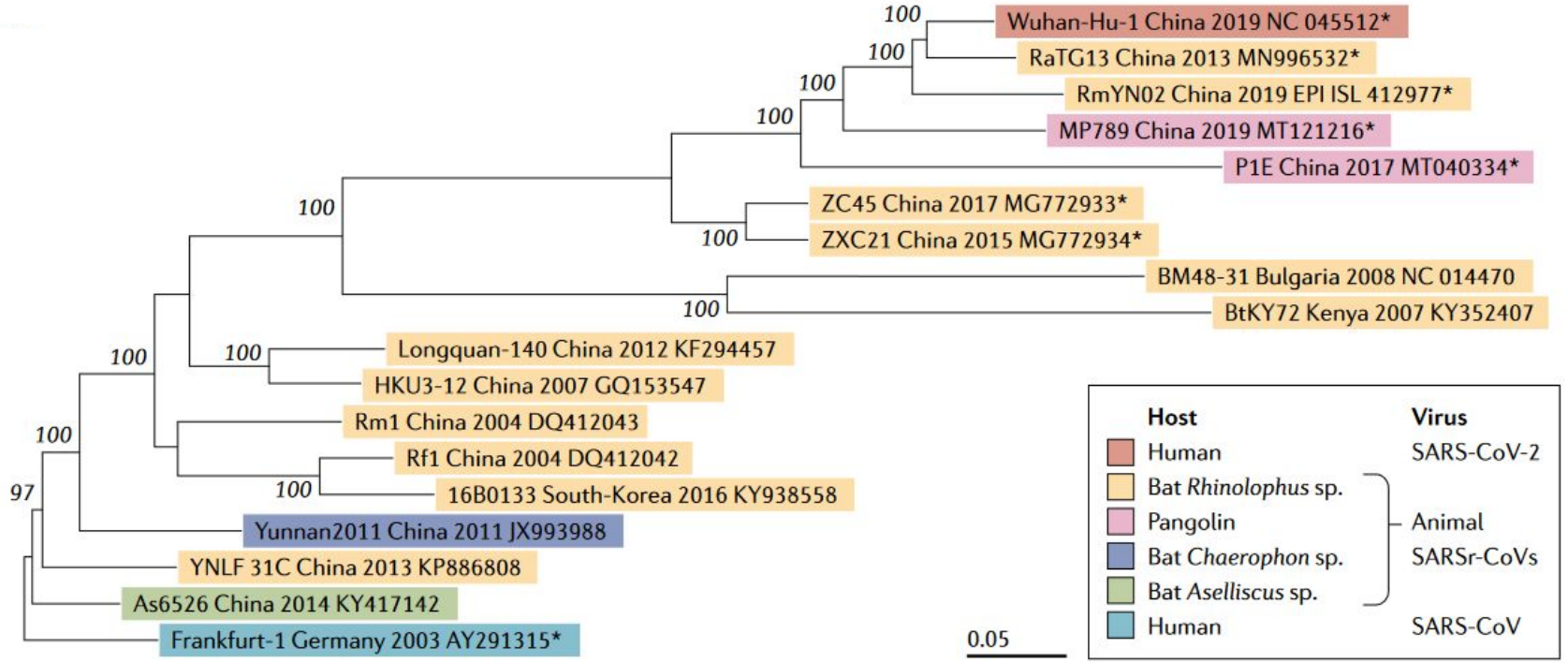


Pollard, A. J. & Bijker, E. M. A guide to vaccinology: from basic principles to new developments. Nature Reviews Immunology 21, 83–100 (2021).

Coronavirus is a RNA virus infecting human and other species



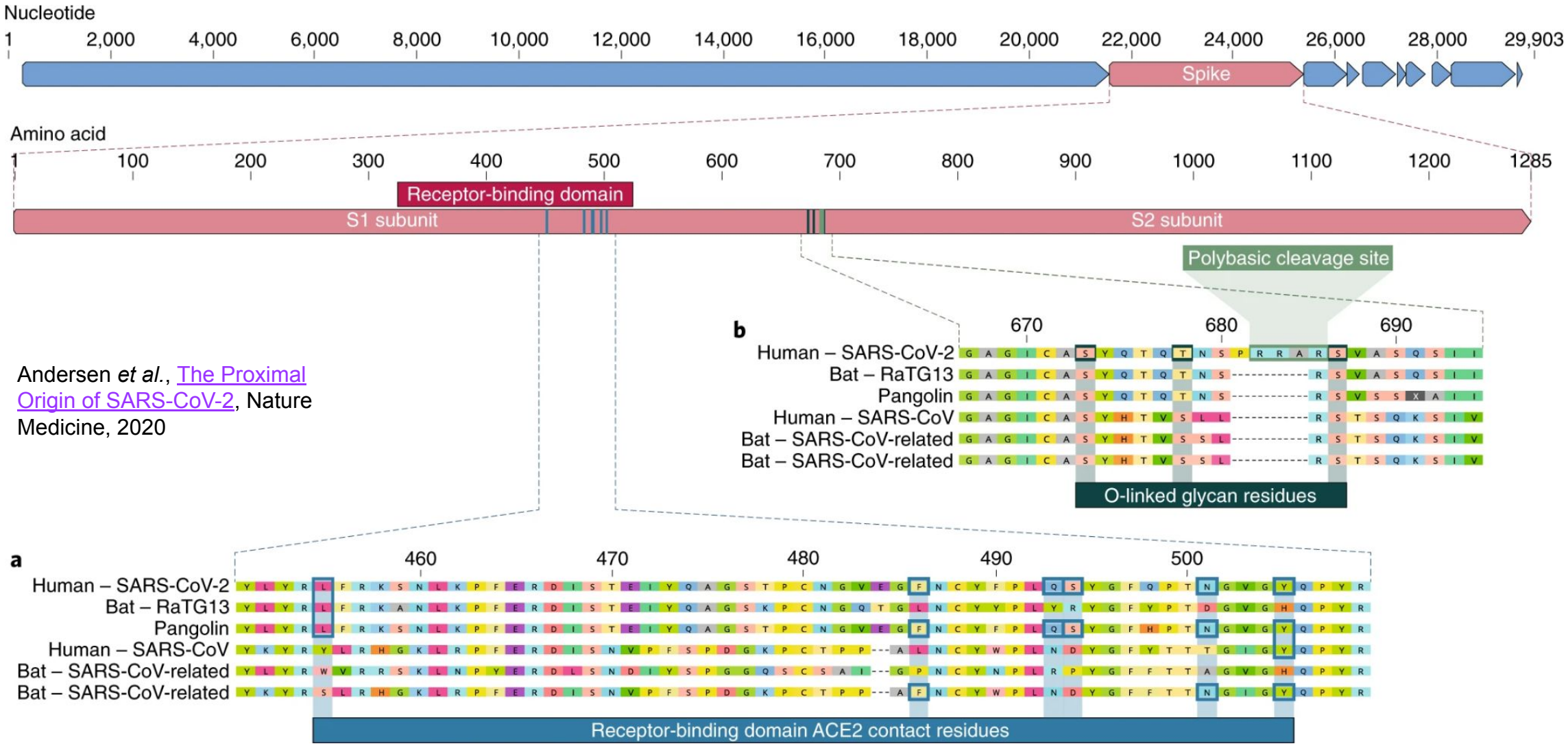
The coronavirus virion consists of structural proteins, namely spike (S), envelope (E), membrane (M), nucleocapsid (N)



Phylogenetic relationships of representative members of the species Severe Acute Respiratory Syndrome (SARS)-related coronavirus

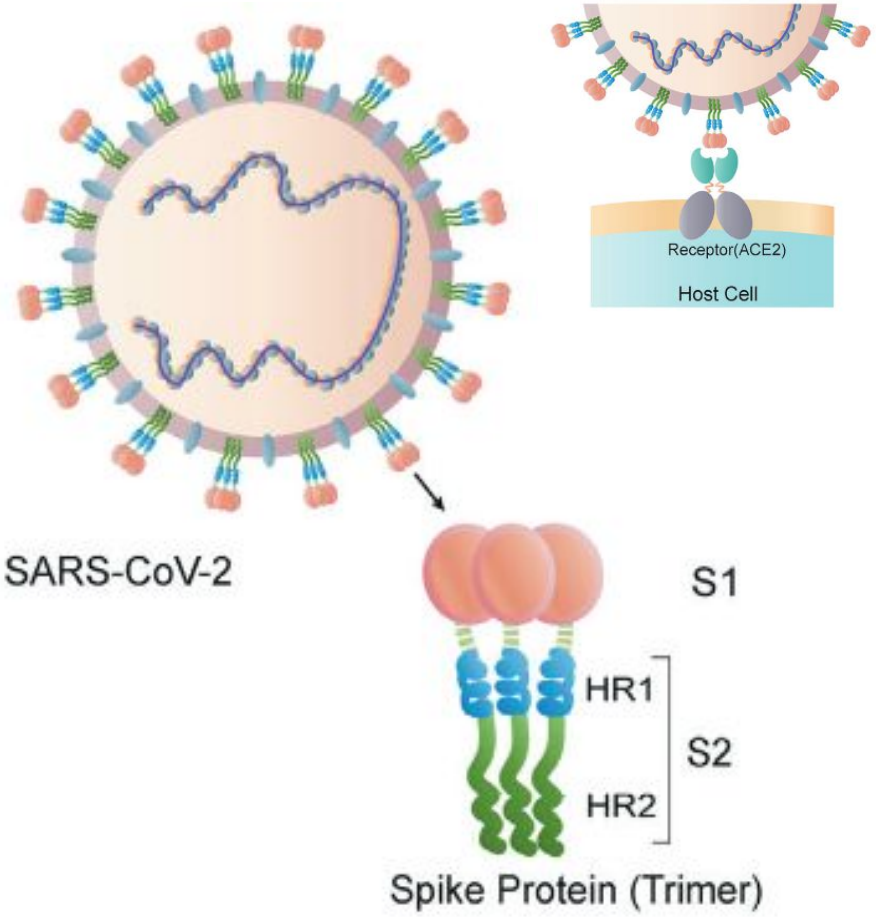
V'kovski, P., Kratzel, A., Steiner, S., Stalder, H. & Thiel, V. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol 19, 155–170 (2021).

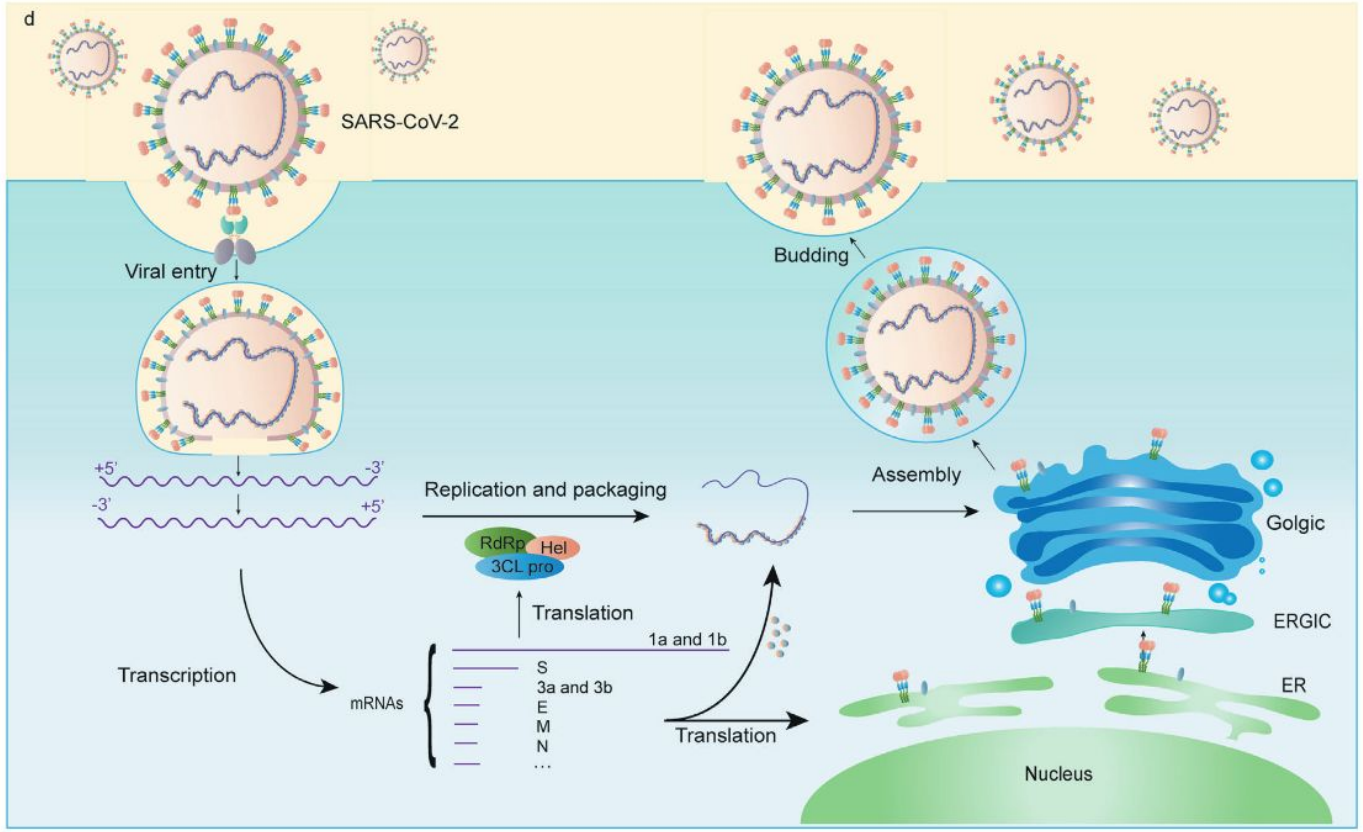
Sequence of the spike protein is largely conserved between corona and related viruses



Andersen *et al.*, The Proximal Origin of SARS-CoV-2, Nature Medicine, 2020

Spike protein of coronavirus is responsible for viral entry into human cells



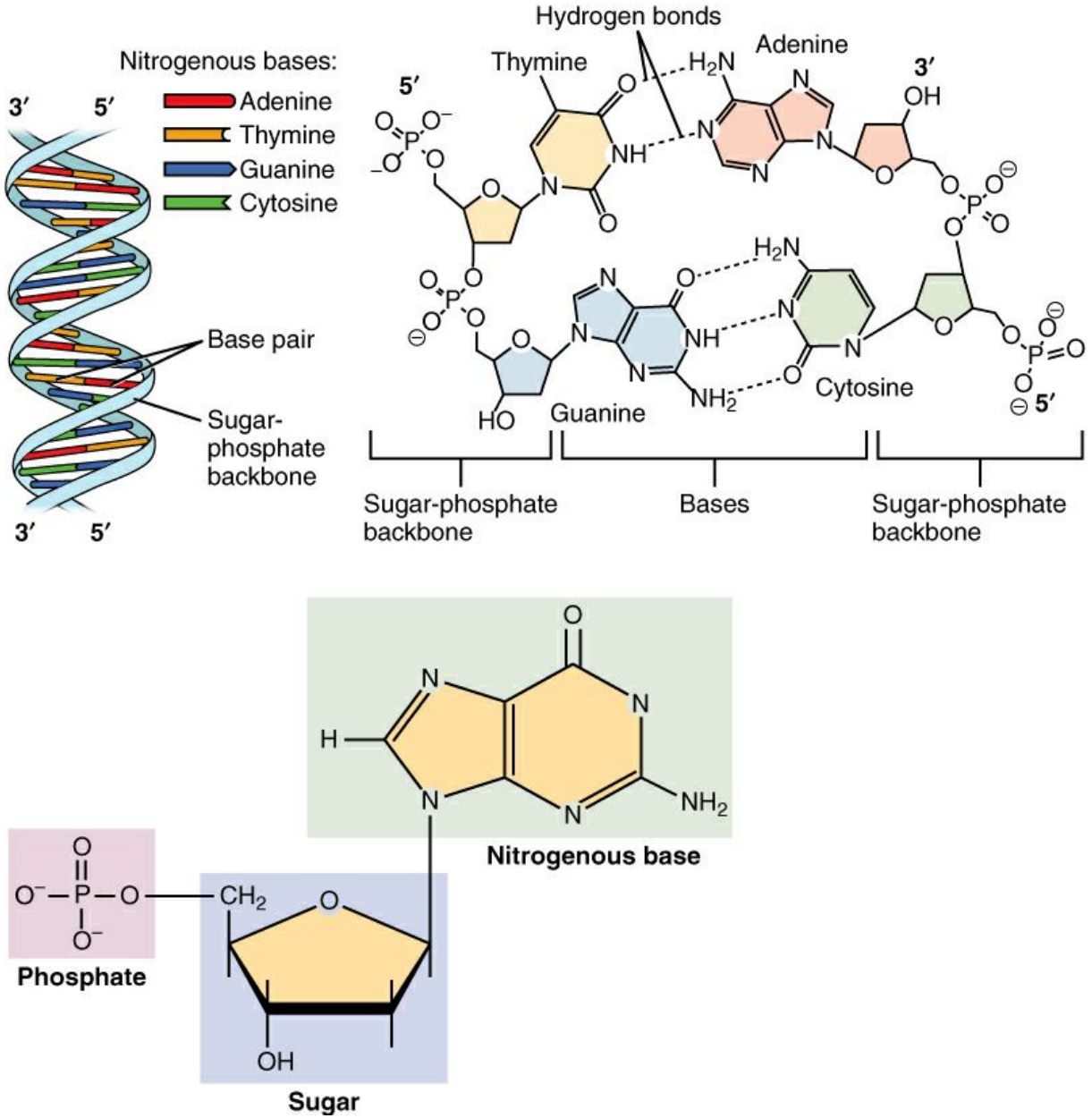


Huang, Y., Yang, C., Xu, X., Xu, W. & Liu, S. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin 41, 1141–1149 (2020).

DNA or RNA encodes genetic information of all life forms that we know, including viruses

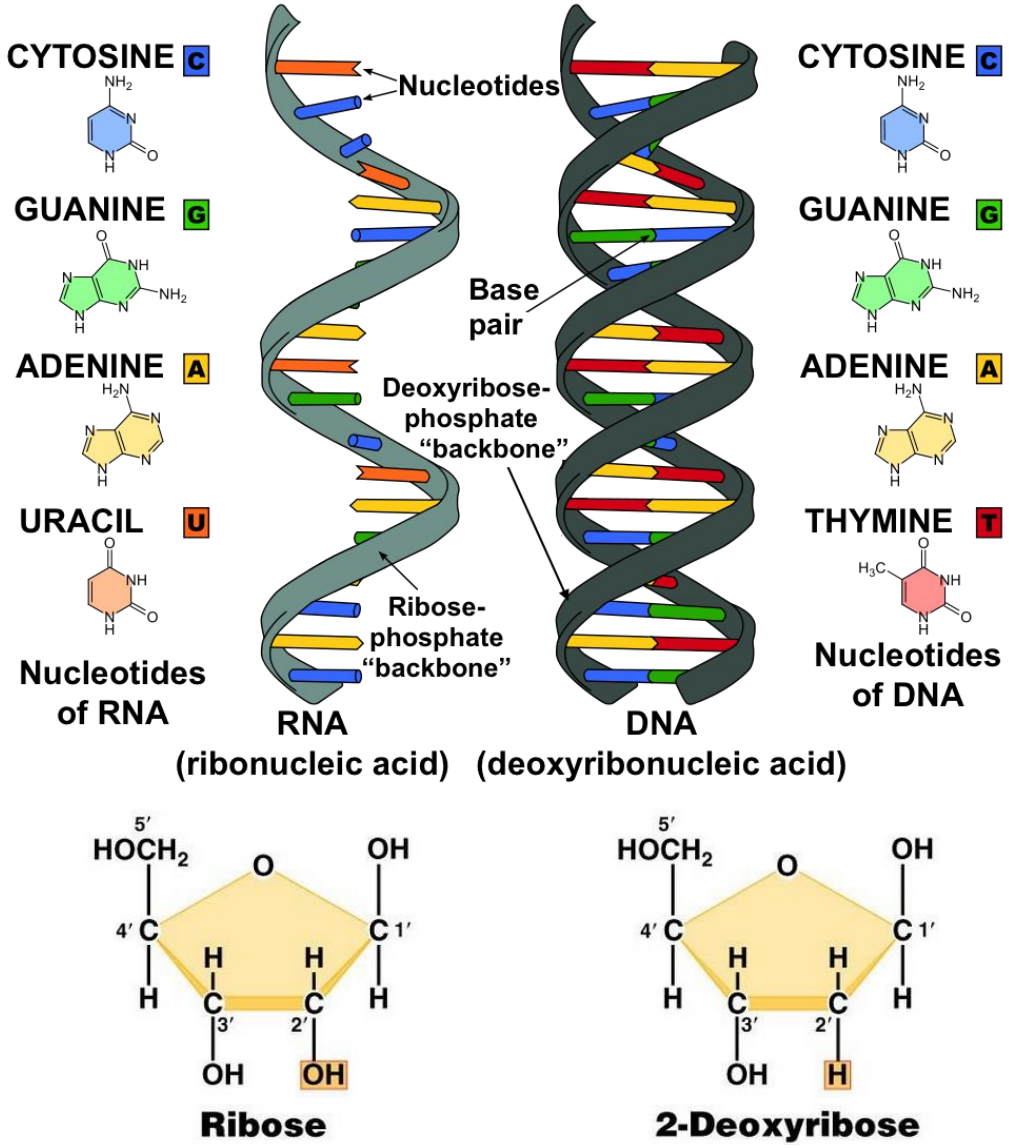
Photo 51, X-ray diffraction image of DNA

Franklin R, Gosling RG (1953) "Molecular Configuration in Sodium Thymonucleate". ***Nature*** 171**: 740–741.**



From the textbook OpenStax Anatomy and Physiology, discovered through Wikimedia, reused under the CC license.

RNA is transcribed from DNA and translated into protein



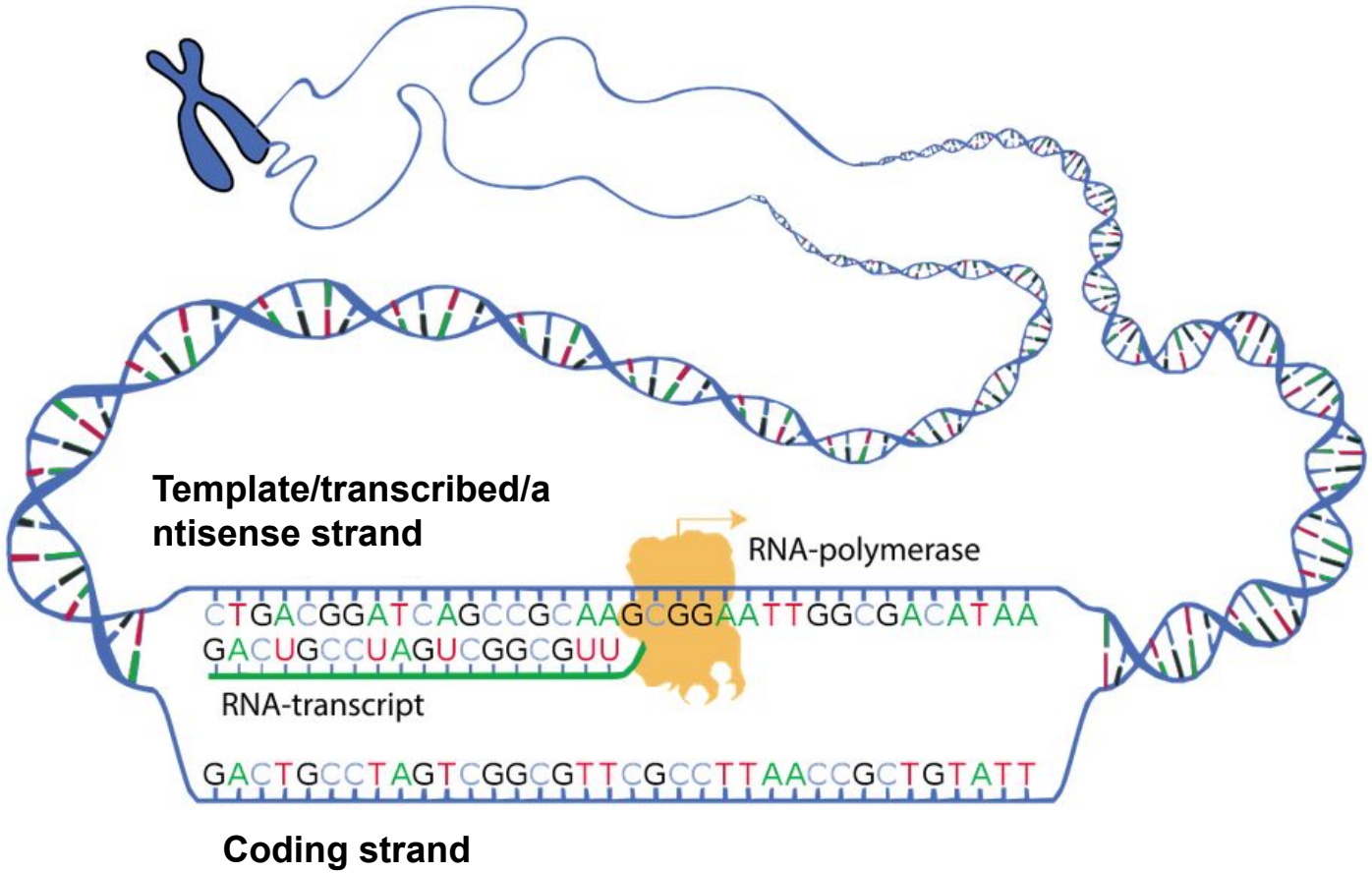
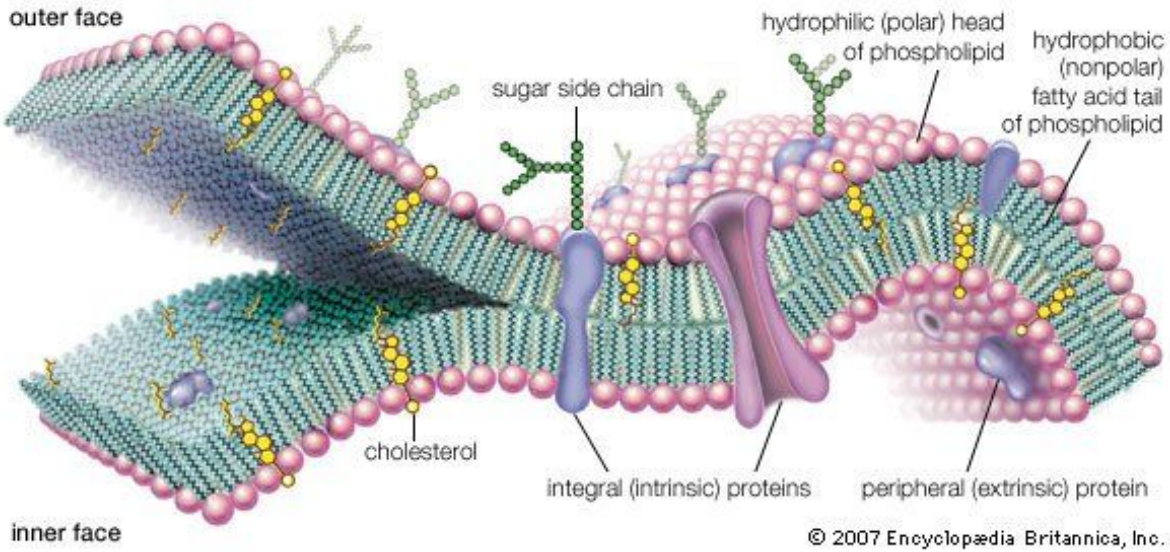


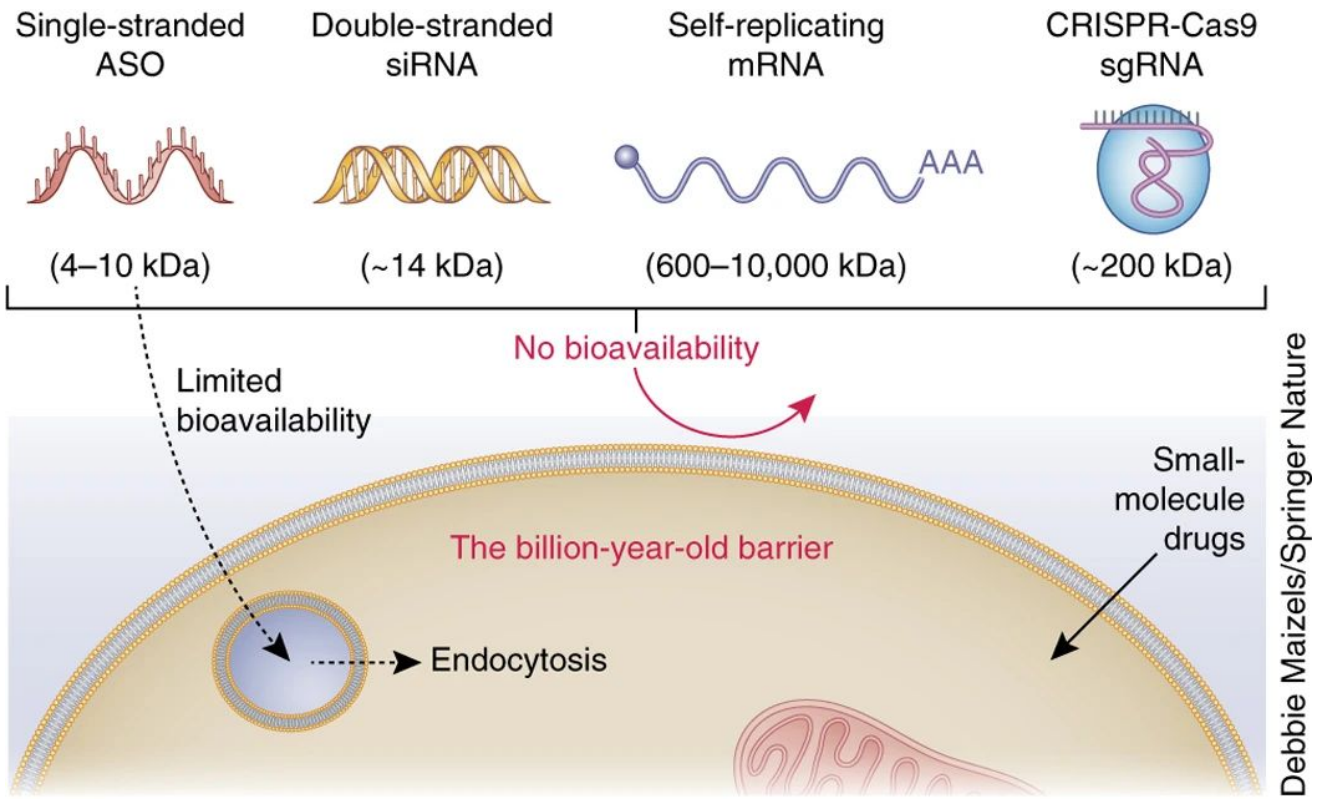
Figure: https://commons.wikimedia.org/wiki/File:DNA_transcriptie.svg and https://en.m.wikipedia.org/wiki/File%3AHAR1F_RF00635_rna_secondary_structure.jpg. Original work by wikipedia user: OrgreBot and user:Ppgardne. Used under CC-SA 3.0 license.

A summary of what we have learned so far in the context of coronavirus

1. What is the unmet medical need to be addressed? We need a vaccine to prevent a large population of individuals from being infected by coronavirus, which have severe consequences.
2. What are the target(s) of our drug? Spike protein is conserved: immune reaction is desired.
3. Where should the drug go in patient's body, what does body do to the drug, and what does the drug do to the body? Due to time constraints, classical vaccine may not meet the need. How about mRNA vaccines?
4. What is the safety profile of the drug in light of its benefits? To be investigated.
5. Who are responsive to the drug, or susceptible to adverse events? To be investigated.

Three essential challenges for mRNA-based therapies: delivery, stability, and *unwanted* immune responses





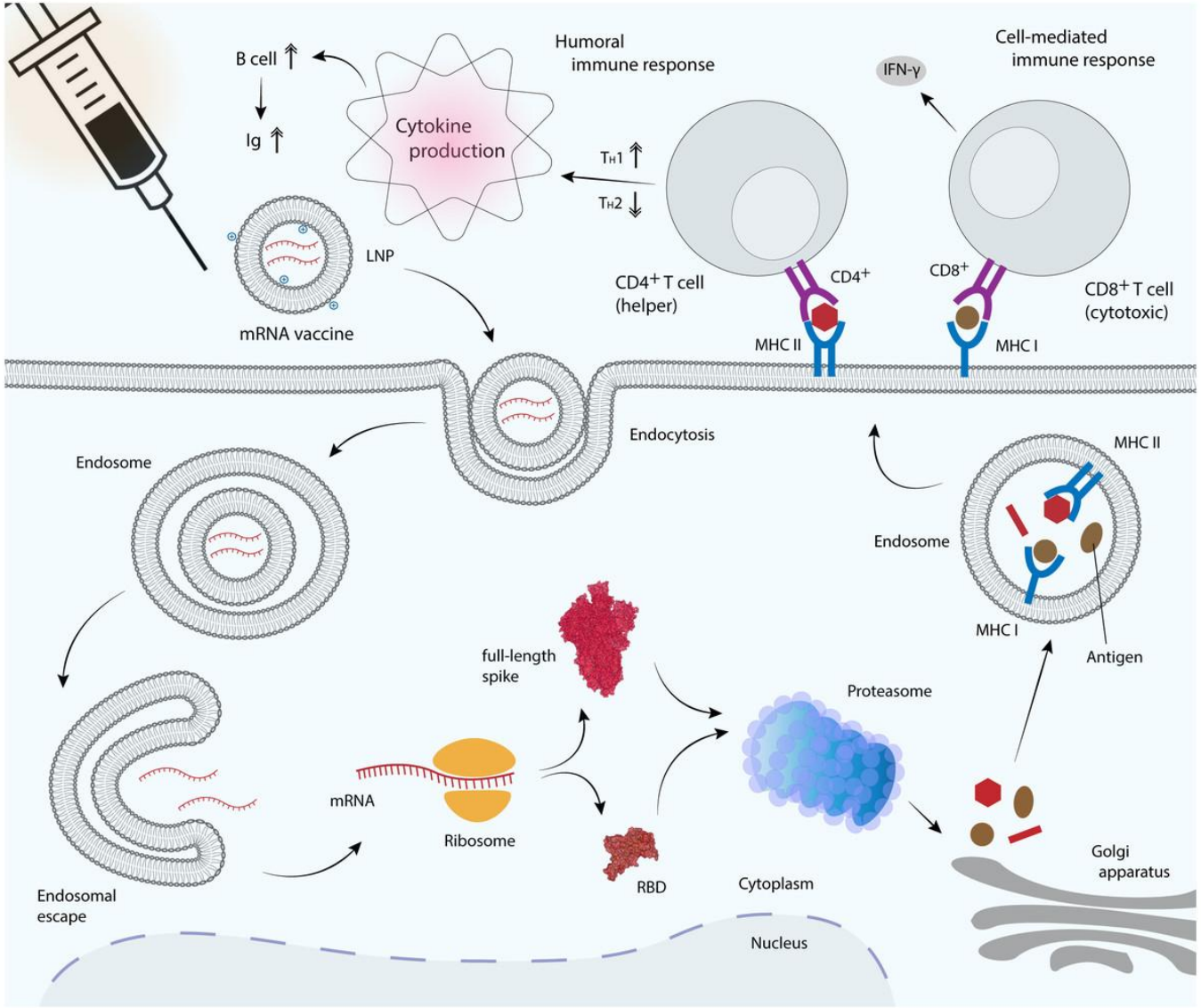
Key challenges:

- mRNAs are too large and charged to pass lipid bilayers.
- mRNAs are degraded, e.g. by ribonucleases.
- *Exogenous* mRNAs cause *immunogenicity*.

Left: Cell membrane, copyright of Encylopedia Britannica, Inc. Right: The four-billion-year-old barrier to RNA therapeutic

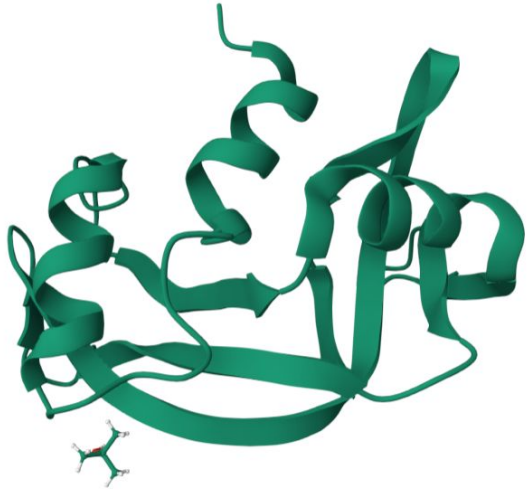
Lipid NanoParticles (LNP) helps delivering RNAs into cells

- Lipid nanoparticles can take mRNA vaccines as largos, and deliver them into human cells.
- In the cell, mRNA encoding the part of the spike protein sequence is translated into proteins with the human protein translation mechanism.
- Synthesized proteins will be degraded and exposed on cell surface, which will be recognized by antigen presenting cells.

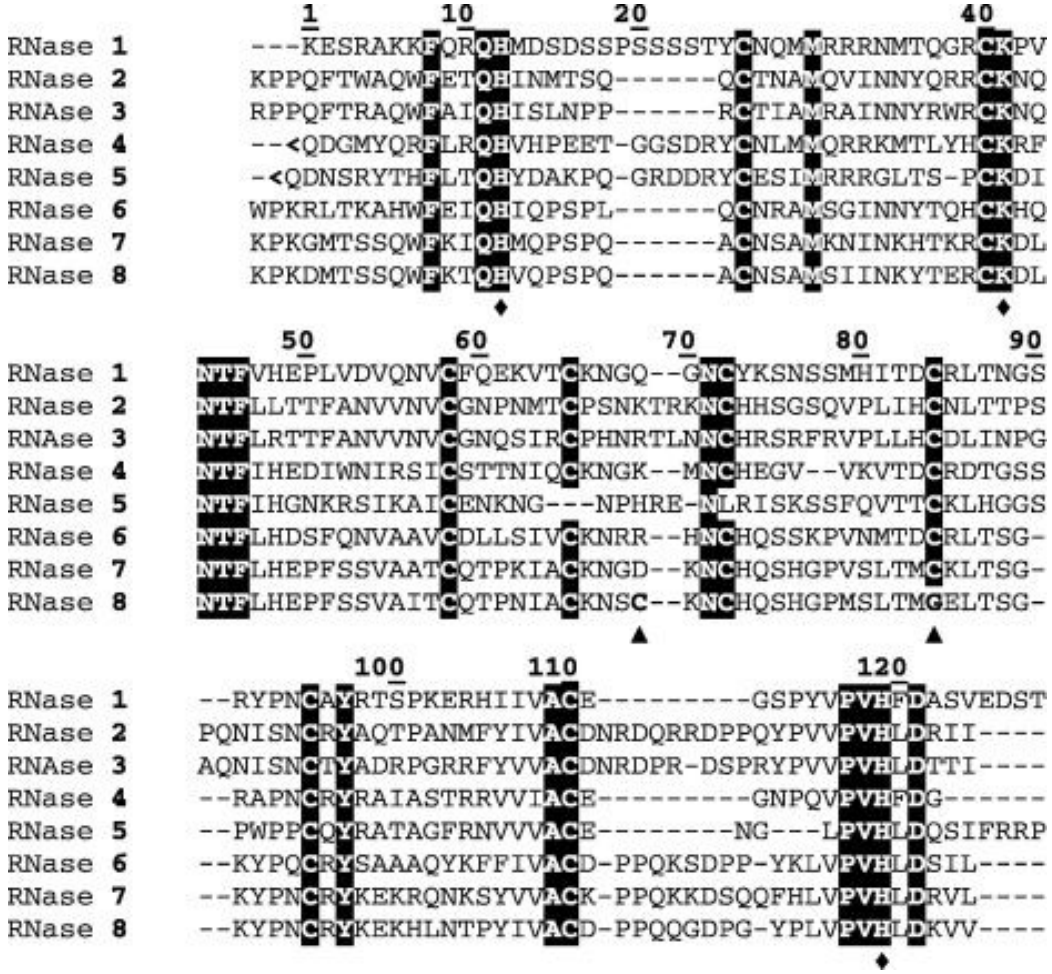


Salleh, Mohd Zulkifli *et al.* "Immunogenicity Mechanism of mRNA Vaccines and Their Limitations in Promoting Adaptive Protection against SARS-CoV-2." PeerJ 10 (March 9, 2022)

RNAs are degraded by proteins known as ribonucleases (RNAases)



- mRNAs are too large and charged to pass lipid bilayers.
- **mRNAs are degradable by ribonucleases (RNases).** RNases belong to *enzymes*, a class of proteins that catalyse chemical reactions.
- Exogenous mRNAs induce immunogenicity.



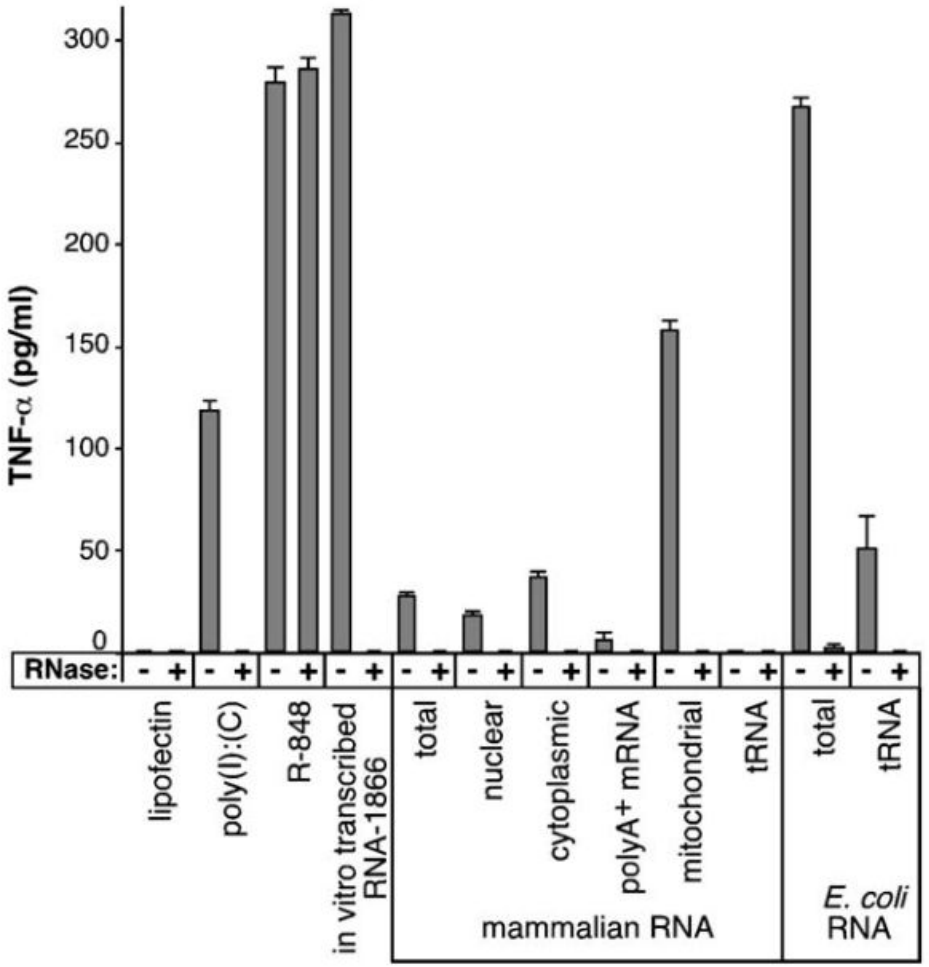
Left: Structure of PDB 7RSA. Right: alignment of protein sequences of 8 canonical human RNases (ribonuclease A family). Sorrentino FEBS Letters, 2010.

Unmodified RNA induces unwanted immune reactions: modifying RNA can reduce or remove them

***Exogenous* RNAs induce immunogenicity.** RNAs are synthesized from four ribonucleotides: ATP (adenosine triphosphate), CTP (cytidine triphosphate), UTP (uridine triphosphate), and GTP (guanosine triphosphate).

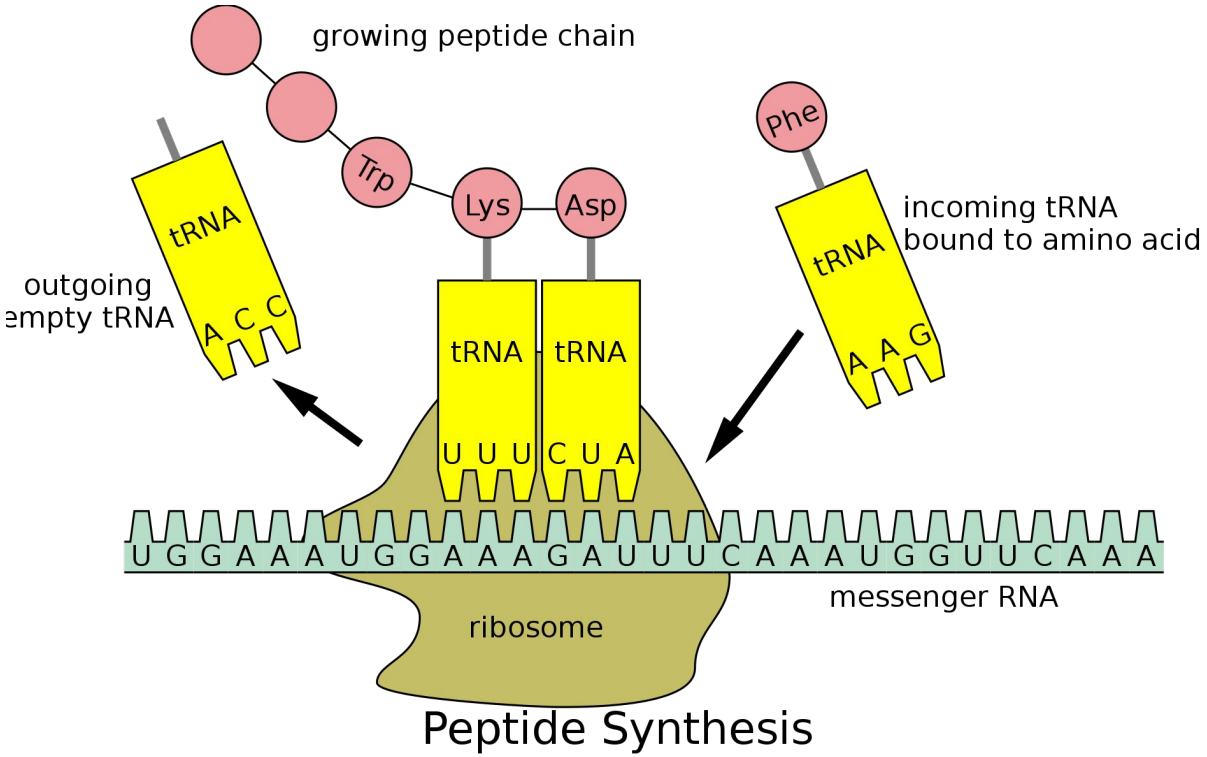
When unmodified RNAs are delivered into cells, they induce unwanted immune reaction. They activate the surface proteins known as Toll-like receptors (TLRs), which leads to the release of cytokines including the tumor necrosis factor alpha (TNF-alpha). TLRs and TNF-alpha are also activated by bacterial and viral infections and mediate their killing.

Some type of RNA, however, does not induce immunogenicity, for instance human *tRNA*. This finding by Karikó and Drewman made major contributions to the successful development of SARS-CoV-2 mRNA vaccines.



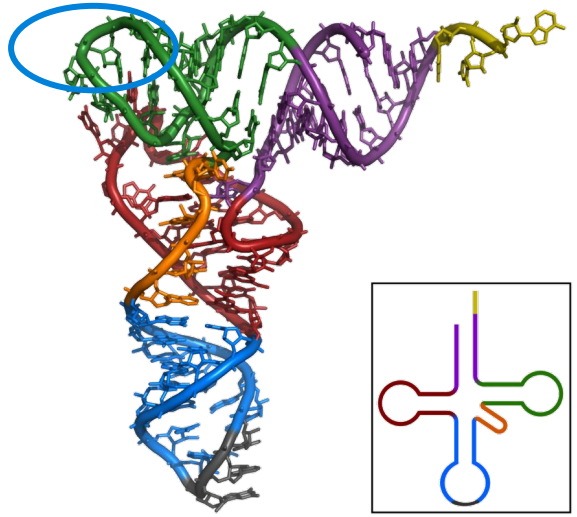
Karikó, K., Buckstein, M., Ni, H. & Weissman, D. Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA. Immunity 23, 165–175 (2005).

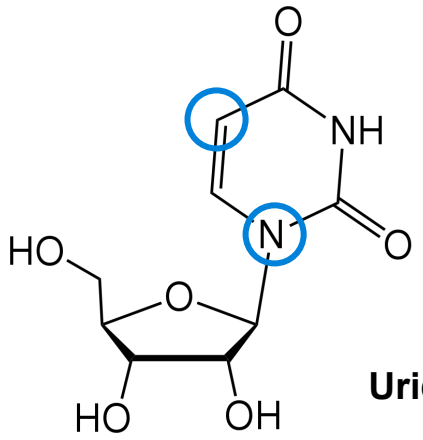
Human tRNA contains *pseudouridine*, a modified uridine, which does not induce immunogenicity



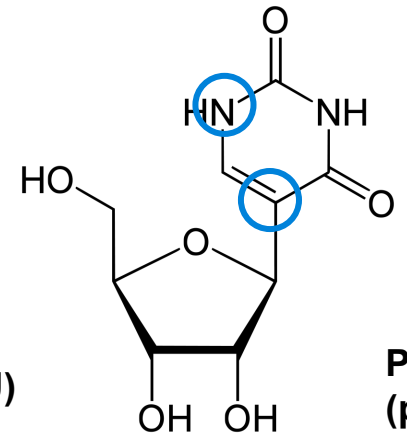
By Boumphreyfr vector conversion by Glrx - File:Peptide syn.png, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=101457889. By Yikrazuul, CC BY-SA 3.0, via Wikimedia Commons.

Left: tRNAs transfer amino acids to ribosome for protein translation. Top right: tRNA structure, with the TΨC loop highlighted in the blue ellipse. Below: structures of uridine and pseudouridine.



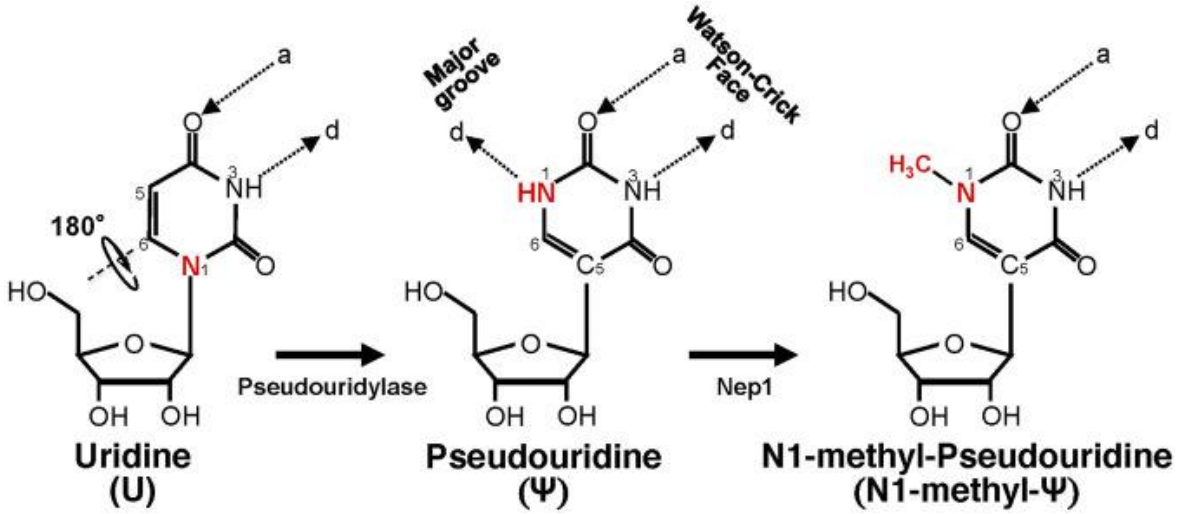


Uridine (U)

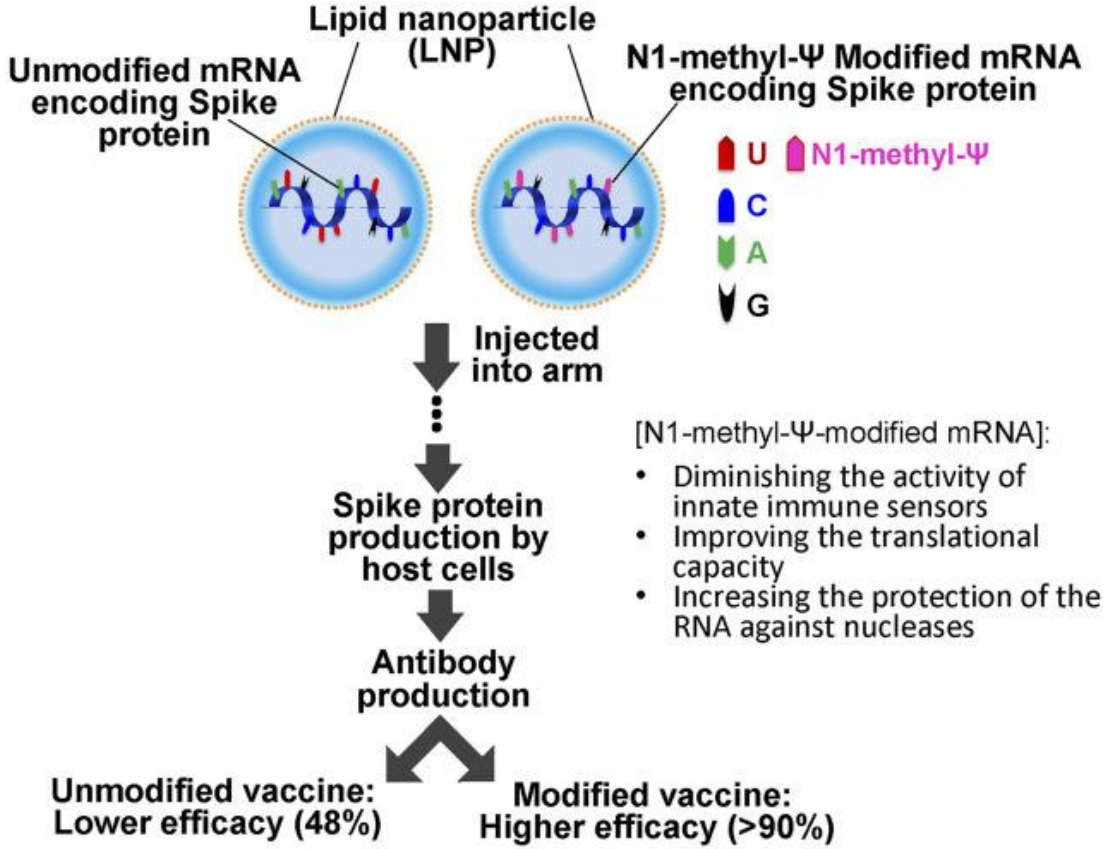


Pseudouridine (psi, Ψ)

Further modification (N1-methyl-Ψ) and LNP delivery are critical for the success of mRNA vaccines



mRNA vaccines against human SARS-Cov-2 viruses, developed in 2020 by Pfizer-BioNTech and Moderna Therapeutics (comirnaty® and spikevax®, respectively), reached clinical efficacies higher than 90%. Both benefited from modified RNA and LNP. Curevac mRNA vaccine (CVnCoV), which used LNP but not modified RNA, reached an efficacy of 48%.

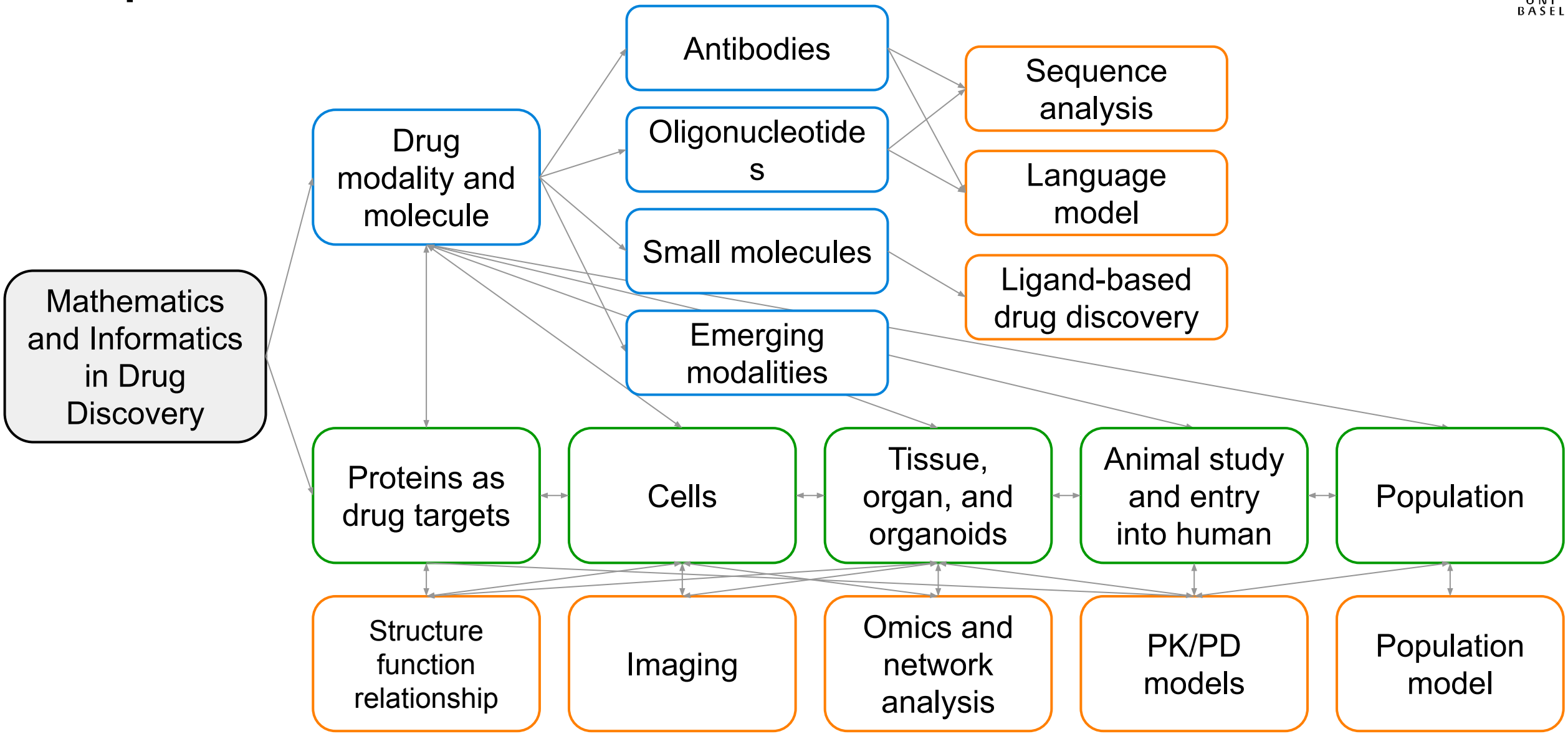


Morais, P., Adachi, H. & Yu, Y.-T. The Critical Contribution of Pseudouridine to mRNA COVID-19 Vaccines. Front Cell Dev Biol 9, 789427 (2021).

Conclusions

1. Drug discovery is an interdisciplinary effort to solve medical and technical challenges.
2. Biological understanding, including sequence analysis, is key for indication and target selection.
3. Modern drug discovery needs to address five key questions:
    a. **Unmet medical need**
    b. **Target(s) and modalities**
    c. **Pharmacokinetics** (what body does to the drug) **and pharmacodynamics** (what the drug does to the body)
    d. **Safety** (benefit/risk assessment)
    e. **Patient enrichment/stratification**

The path of the course



Interests and concerns of companies working on drug discovery: summary of our previous discussions

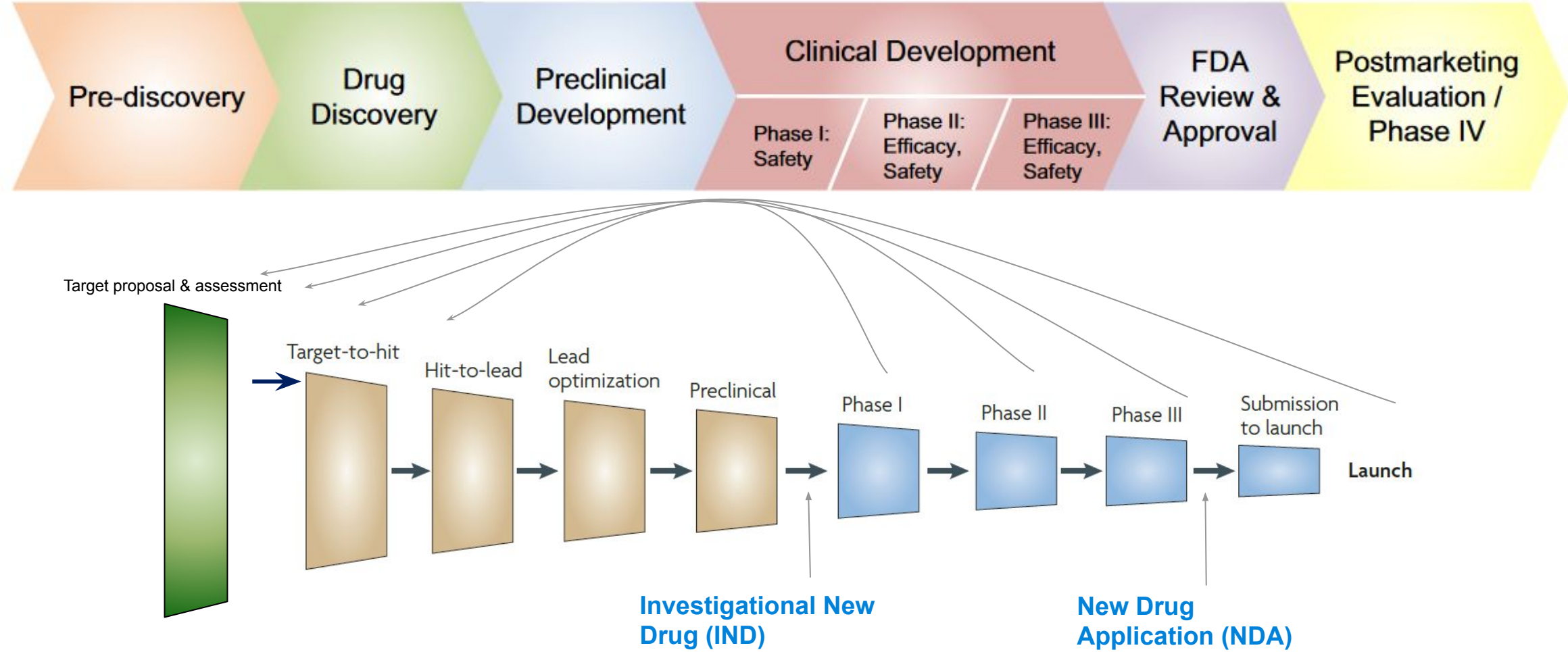
Interests

- Return of Investment
  - Commercial potential
  - Cycle time
- Good reputation
  - Efficacy of the drug
  - Safety of the drug
  - Market access
- Environmental, social, and governance (e.g. fighting internal corruption, diversity of board members).

Concerns

- Low or no return of investment
  - Lack of efficacy of drugs
  - Unfavorable benefit/risk profiles of the drug
  - No approval from agency
  - Cost, time, effectiveness of R&D
  - Competitor
  - Poor targets or disease models due to lack of reproducibility of published data
  - Companion diagnostic
- Intellectual property
- Idea and knowledge management
- Acceptance by doctors and patients
- Legal concerns

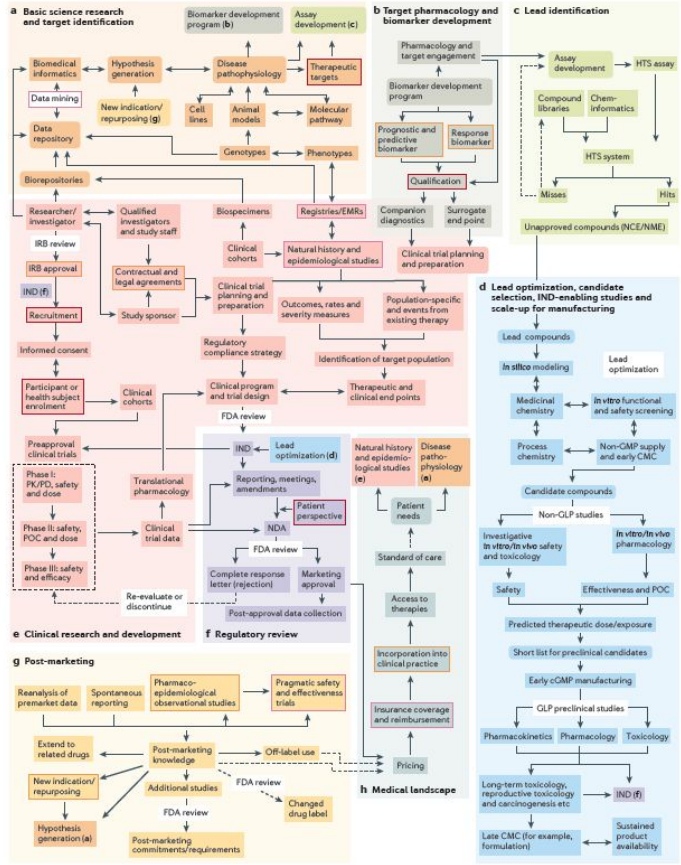
Chevron diagrams as a pipeline view of drug discovery and development



FDA: US Food and Drug Administration. Top: Wagner, J. A. et al. Application of a Dynamic Map for Learning, Communicating, Navigating, and Improving Therapeutic Development. Clinical and Translational Science 11, 166–174 (2018). Bottom: Adapted from Paul et al. How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge. Nature Reviews Drug Discovery, 2010.

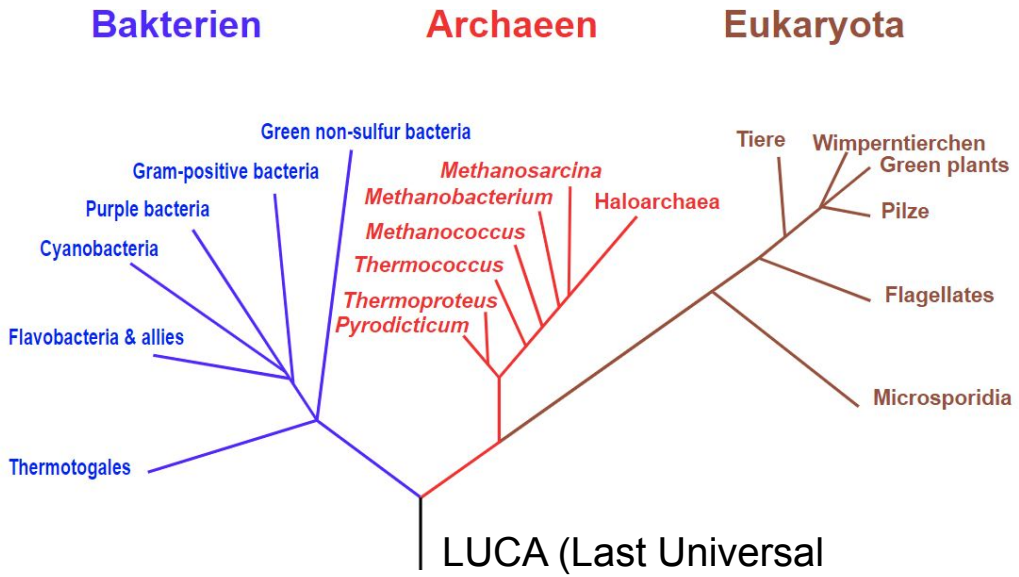
A dynamic map for drug discovery, development, and deployment

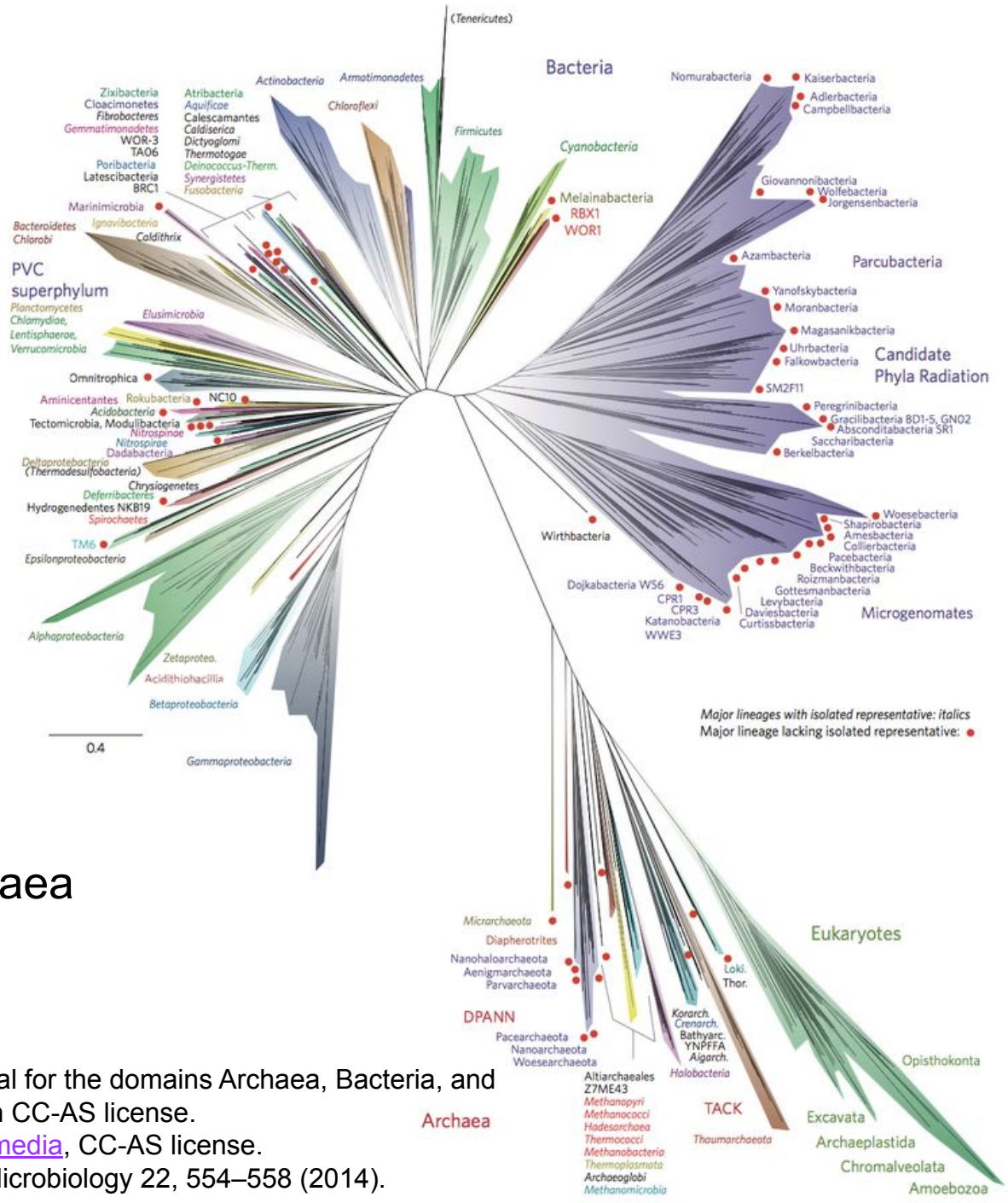
1. **Basic science research and target identification.** *What causes the disease? What do we want to achieve? Which protein can I target with which modality?*
2. **Target pharmacology and biomarker development.** *What is the effect of targeting the protein? What we can measure to confirm that the protein is properly targeted?*
3. **Lead identification.** *How can we find a starting point of a new drug?*
4. **Lead optimization and clinical candidate selection**. *What are criteria to define a good drug? How can I improve the starting material?*
5. **Clinical research and development**. *Does it work in human? How about efficacy and safety profiles?*
6. **Regulatory review**. *Should we approve the drug?*
7. **Post marketing**. *How does the drug work in real world?*



Wagner, J. et al. A dynamic map for learning, communicating, navigating and improving therapeutic development. Nat Rev Drug Discov 17, 150–150 (2018).

Virus is evolutionarily special

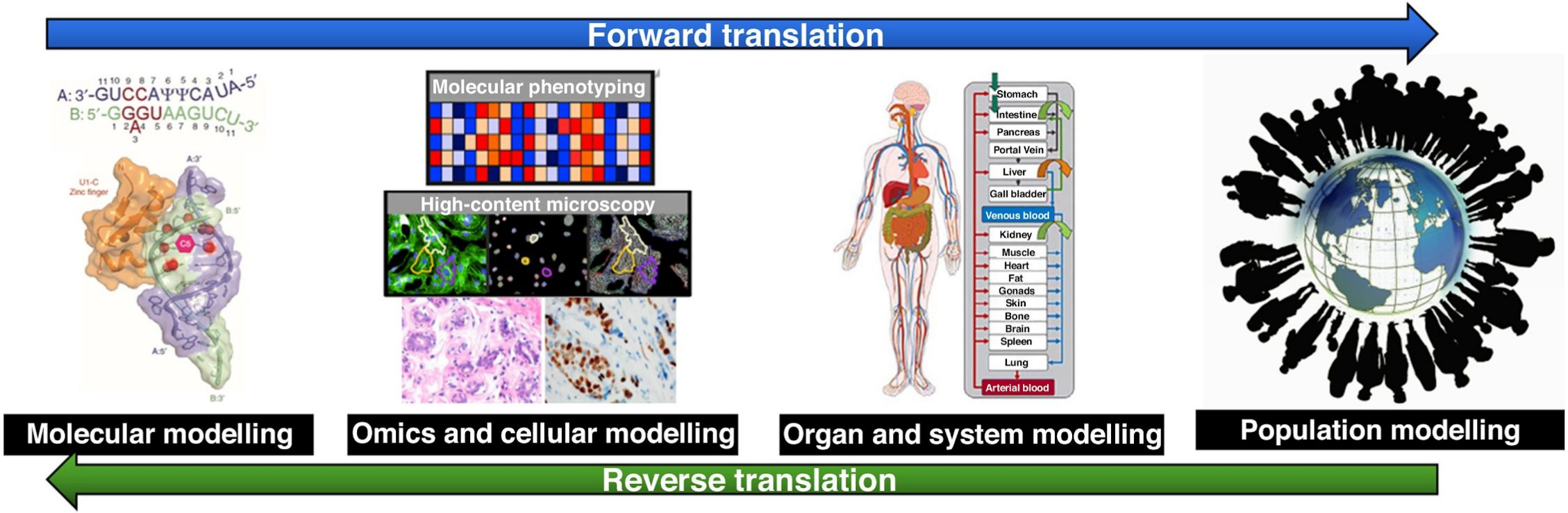




- The three-domain model of *cellular* life: (eu-)bacteria, archaebacteria, and eukaryotes.
- The two-domain model: bacteria as one branch, archaea and eukaryotes as the other.
- Virus fits in no domain of neither models.

1. Woese, C. R., Kandler, O. & Wheelis, M. L. Towards a natural system of organisms: proposal for the domains Archaea, Bacteria, and Eucarya. Proc Natl Acad Sci U S A 87, 4576–4579 (1990). Figure from Wikimedia, reused with CC-AS license.
1. Hug, L. A. et al. A new view of the tree of life. Nat Microbiol 1, 1–6 (2016). Figure from Wikimedia, CC-AS license.
1. Forterre, P., Krupovic, M. & Prangishvili, D. Cellular domains and viral lineages. Trends in Microbiology 22, 554–558 (2014).

The multiscale modelling view of drug discovery

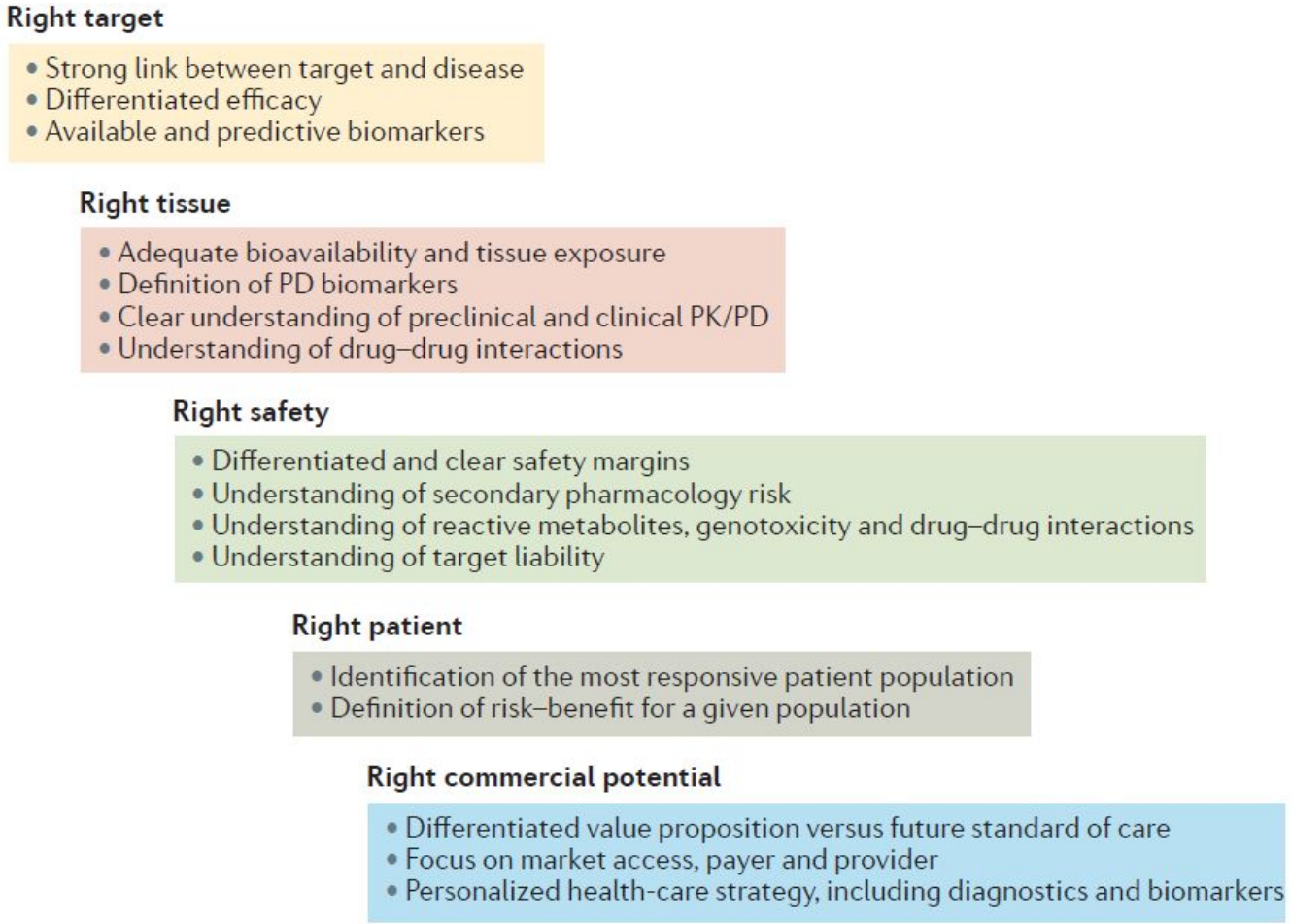


Zhang, Jitao David, Lisa Sach-Peltason, Christian Kramer, Ken Wang, and Martin Ebeling. 2020. “Multiscale Modelling of Drug Mechanism and Safety.” Drug Discovery Today 25 (3): 519–34. https://doi.org/10.1016/j.drudis.2019.12.009.

Five key questions in drug discovery

1. What is the unmet medical need to be addressed?
2. What are the target(s) and what is the modality of our drug?
3. Where should the drug go in patient's body, what does body do to the drug, and what does the drug do to the body?
4. What is the safety profile of the drug in light of its benefits?
5. Who are responsive to the drug, or susceptible to adverse events?

The *meta*-question: What knowledge, data, and tools do we have to address these questions?



Morgan, P. et al. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. Nature Reviews Drug Discovery 17, 167–181 (2018).