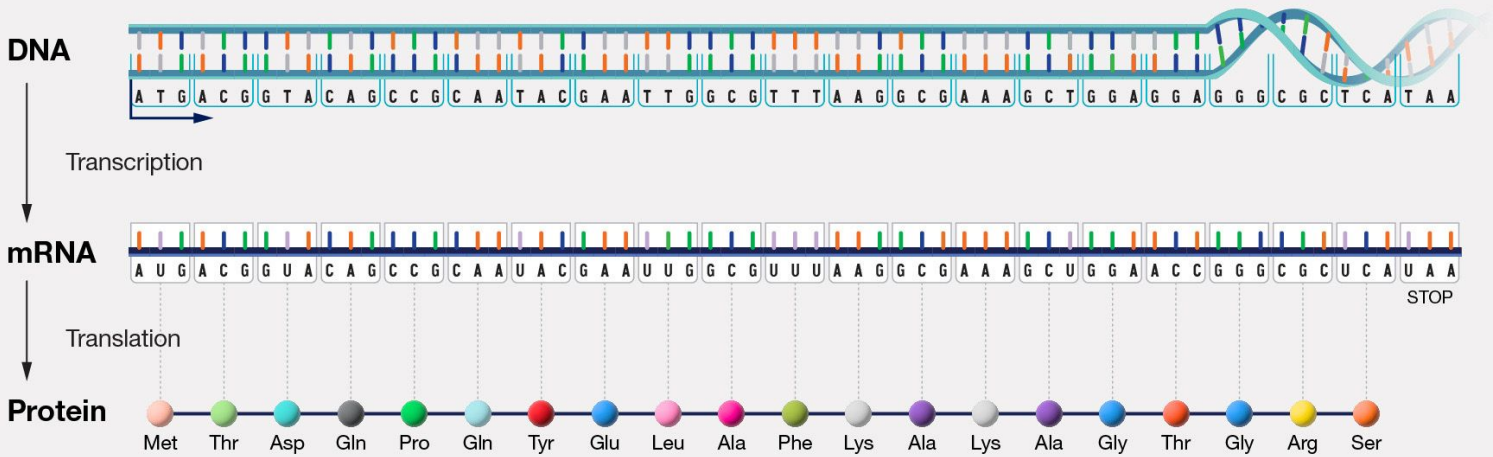
Follow up of questions on the video on Herceptin by Susan Desmond-Hellmann

Link to the video

Questions for the video

1. What is the **indication** of *Herceptin*? (Her2 positive breast cancer) What is its generic (USAN, or United States Adopted Name) name? (Trastuzumab)
2. What is the **gene target** of Herceptin? (Her2, ERBB2)
3. In which year was the **target** of Herceptin described? When was Herceptin **approved**? (1987; 1998 in metastatic cancer and 2005 in the adjuvant setting)
4. What was the **improvement** of Herceptin compared with earlier antibodies? (humanized)
5. Why does a **biomarker** matter besides developing drugs? (diagnostic, higher chance of success due to patient stratification)
6. In the clinical trial of *Herceptin* for **metastatic breast cancer**, how much improvement in the **median survival** did Herceptin achieve? And how much improvement is in the **adjuvant setting** (Herceptin applied directly after operation)? (5.1 months improvement in median survival for metastatic breast cancer. Time to remission doubled in the adjuvant setting)

AMIDD Lecture 2: The Central Dogma and Drug Discovery



Source: https://www.genome.gov/genetics-glossary/Central-Dogma

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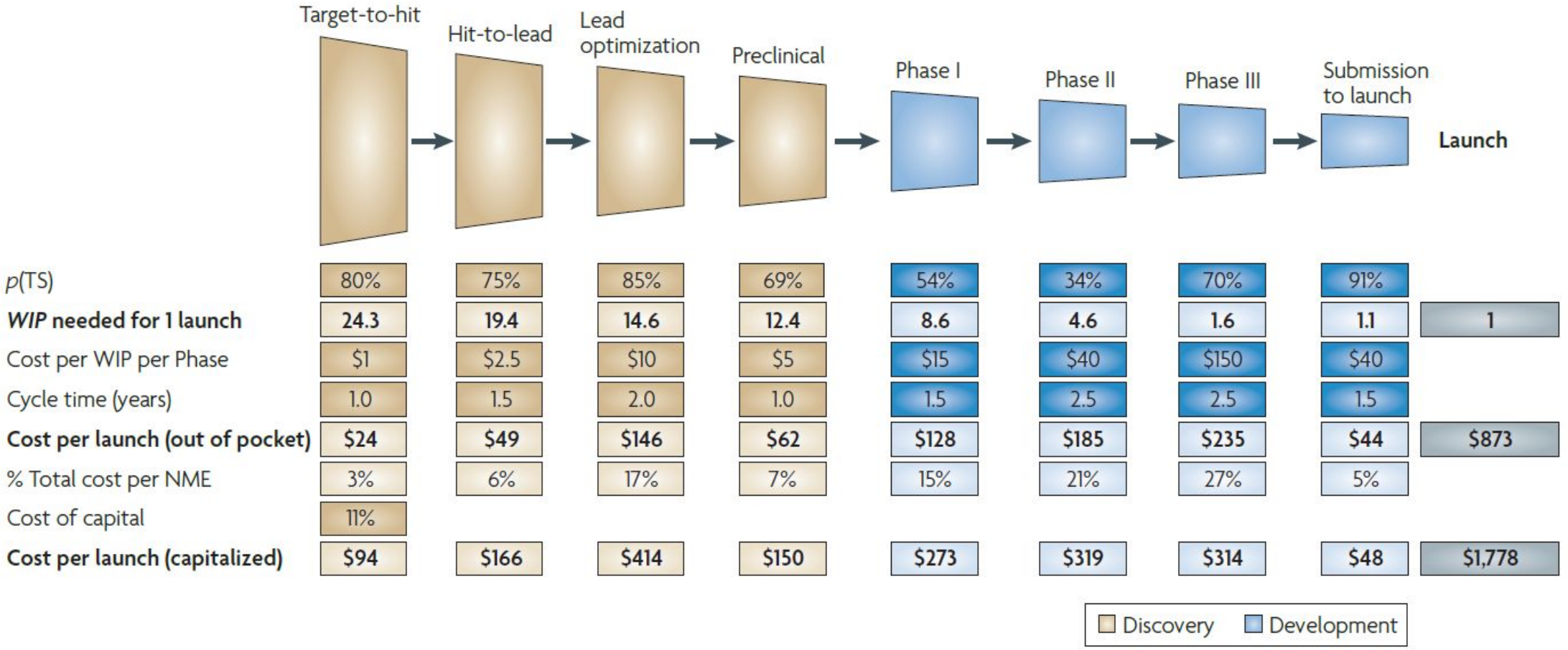
Today's goals

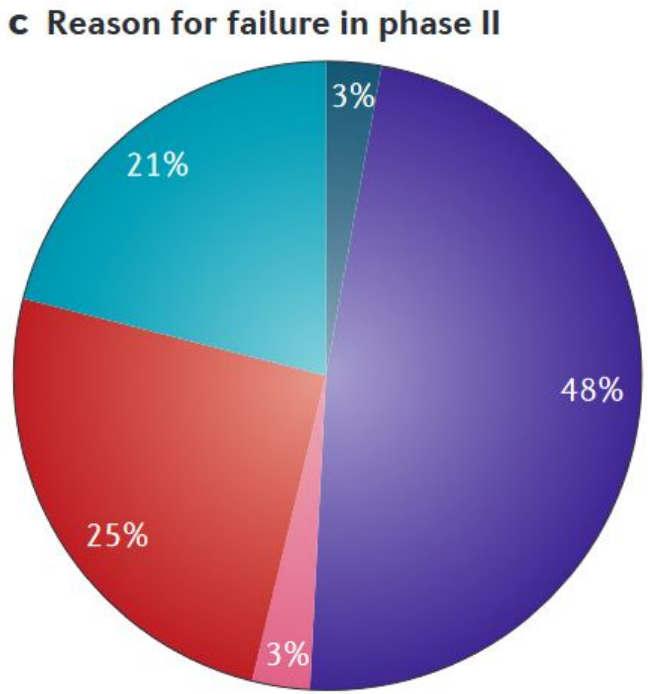
- Linear and multiscale view of drug discovery and development
- The central dogma of molecular biology in context of drug discovery
- Case study: discovery of *Vemurafenib*

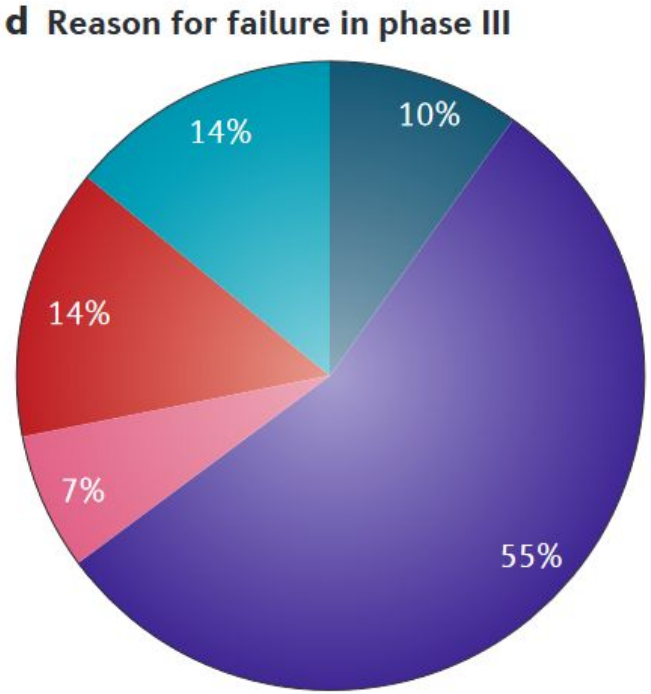
Risks and costs associated with each stage of the linear view of drug discovery



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.

Factors causing failures in Phase II and Phase III clinical trials, 2013-2015

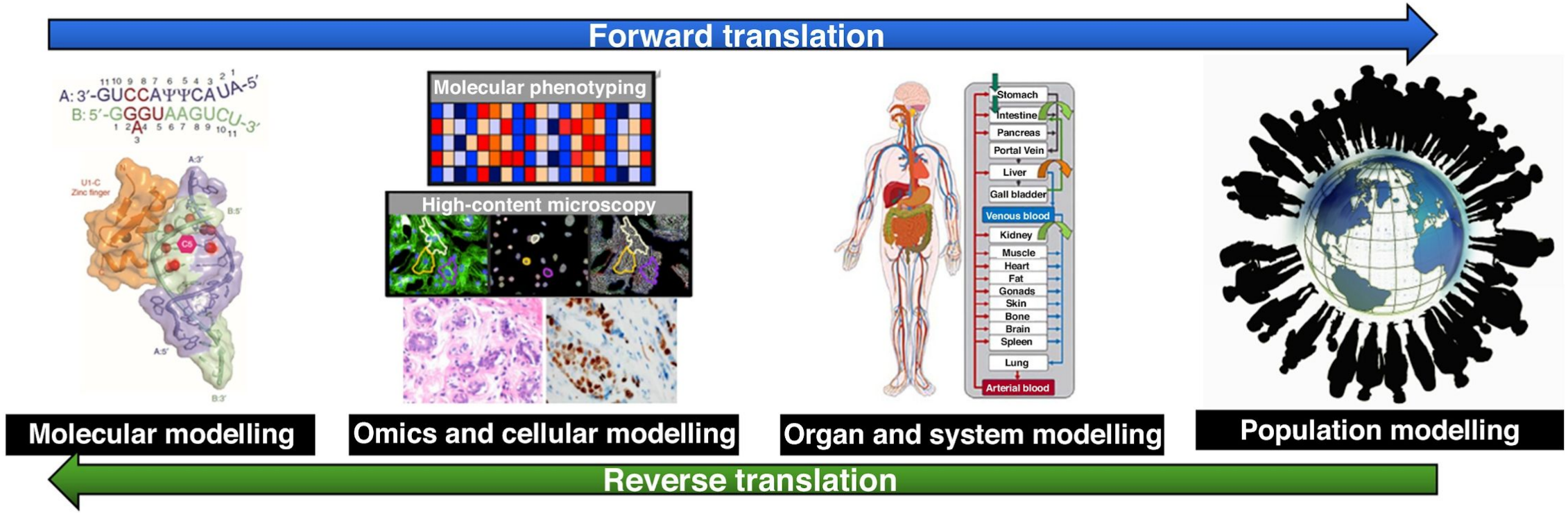




- Commercial
- Operational
- Efficacy
- Safety
- Strategy

Harrison, Richard K. "Phase II and Phase III Failures: 2013–2015." *Nature Reviews Drug Discovery* 15 (November 4, 2016): 817–18. https://doi.org/10.1038/nrd.2016.184.

The alternative, multiscale-modelling view of drug discovery

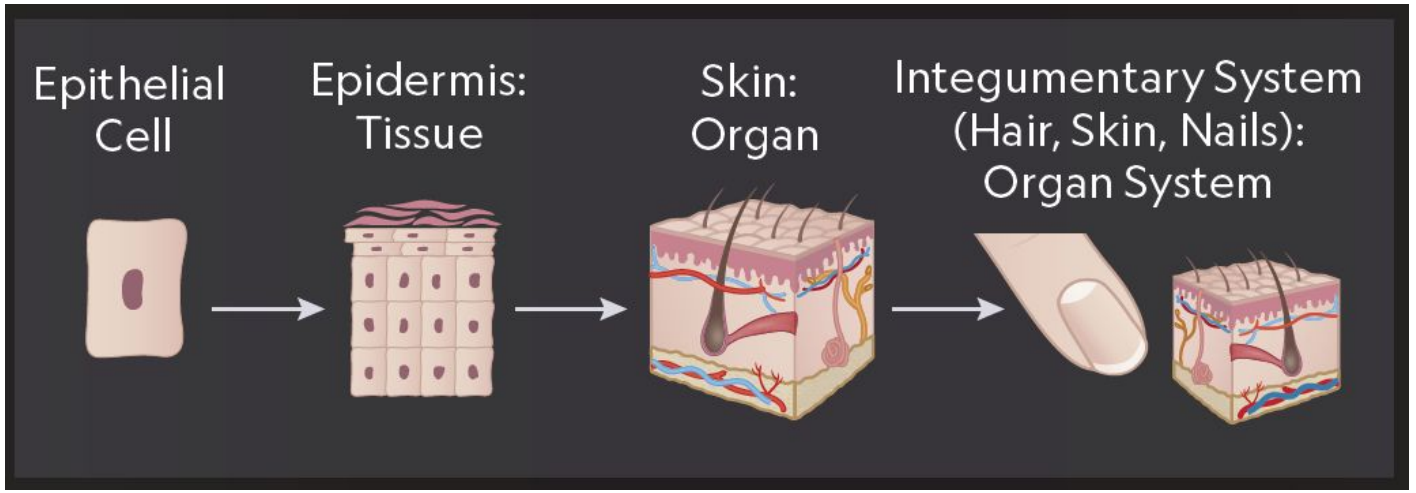


Zhang, Jitao David, Lisa Sach-Peltason, Christian Kramer, Ken Wang, and Martin Ebeling. 2020. “Multiscale Modelling of Drug Mechanism and Safety.” Drug Discovery Today 25 (3): 519–34. https://doi.org/10.1016/j.drudis.2019.12.009.

Five fundamental views of cells

- Material
- Producer and consumer of energy
- Vehicle of Information
- Product of evolution
- Computation unit

The human biological system is hierarchical

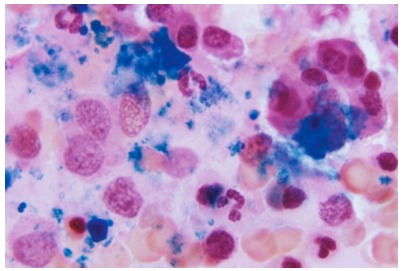


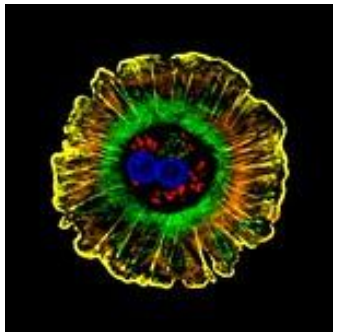
Cells: basic building blocks, variable morphologies and functions

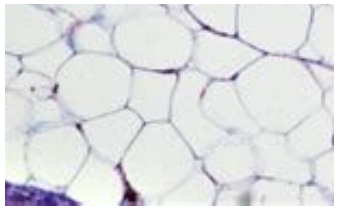
Tissues: groups of specialized cells that communicate and collaborate

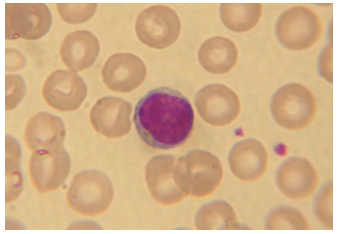
Organ: group of tissues to perform specific functions

Organ systems: group of organs and tissues







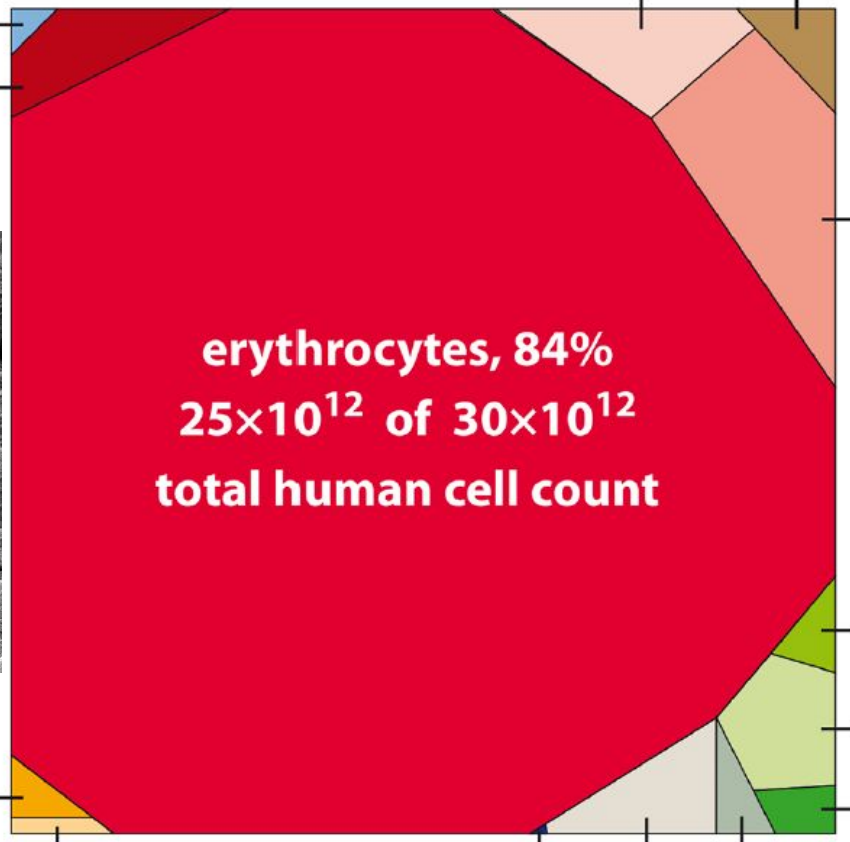


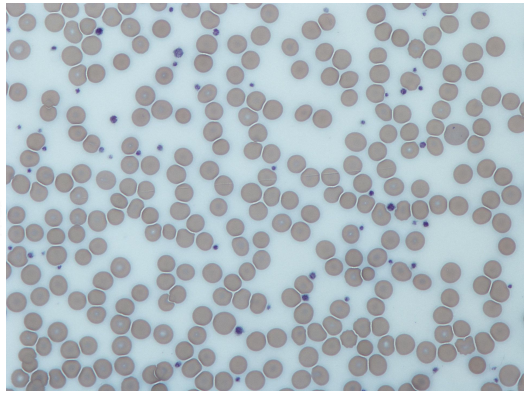
bone marrow cells 2.5%

hepatocytes 0.8%

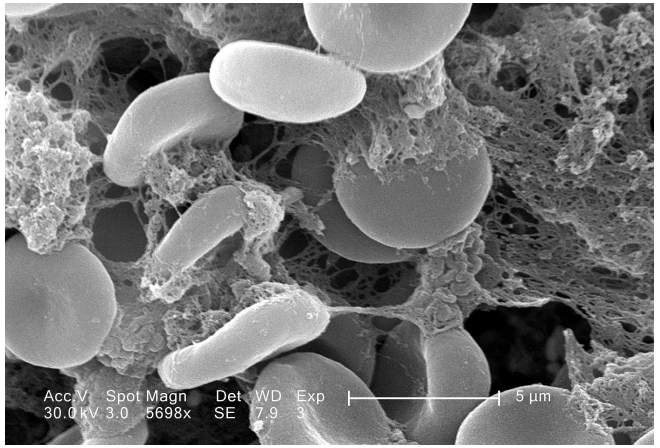
adipocytes 0.2%

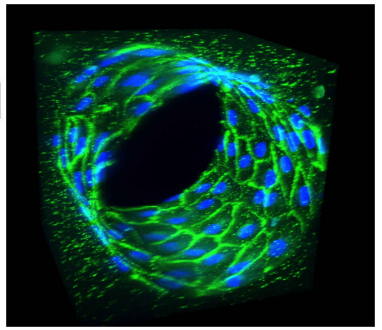
lymphocytes 1.5%





platelets 4.9%

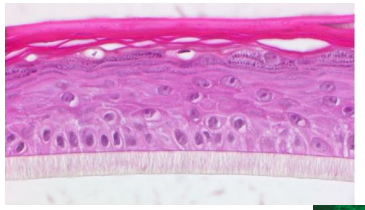




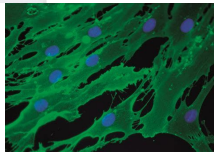
bronchial endothelial cells 0.5%

vascular endothelial cells 2.1%

respiratory interstitial cells 0.5%



epidermal cells 0.5%

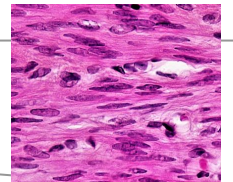


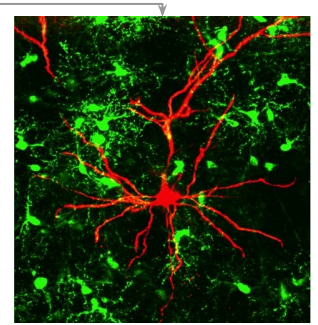
dermal fibroblasts 0.1%

muscle cells 0.001%

other 2.0%

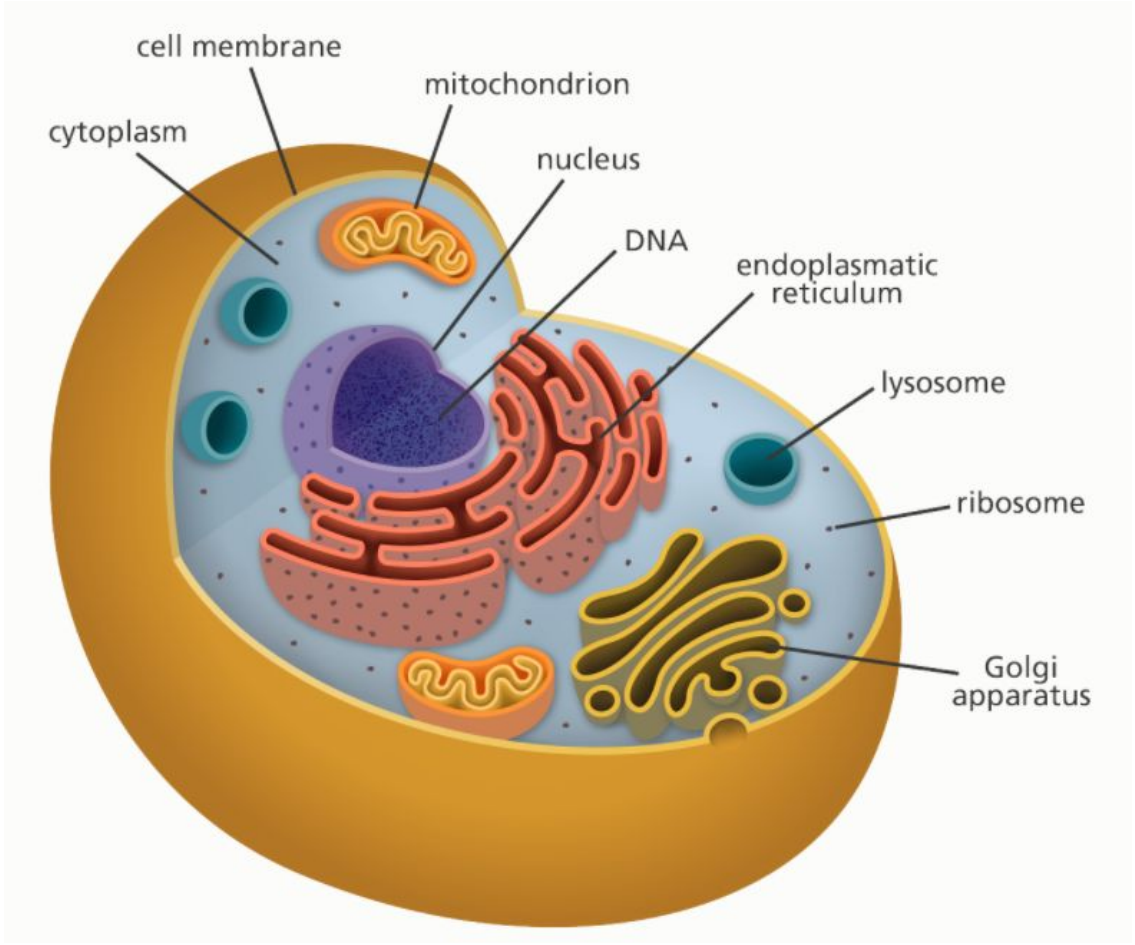
neurons and glia 0.6%

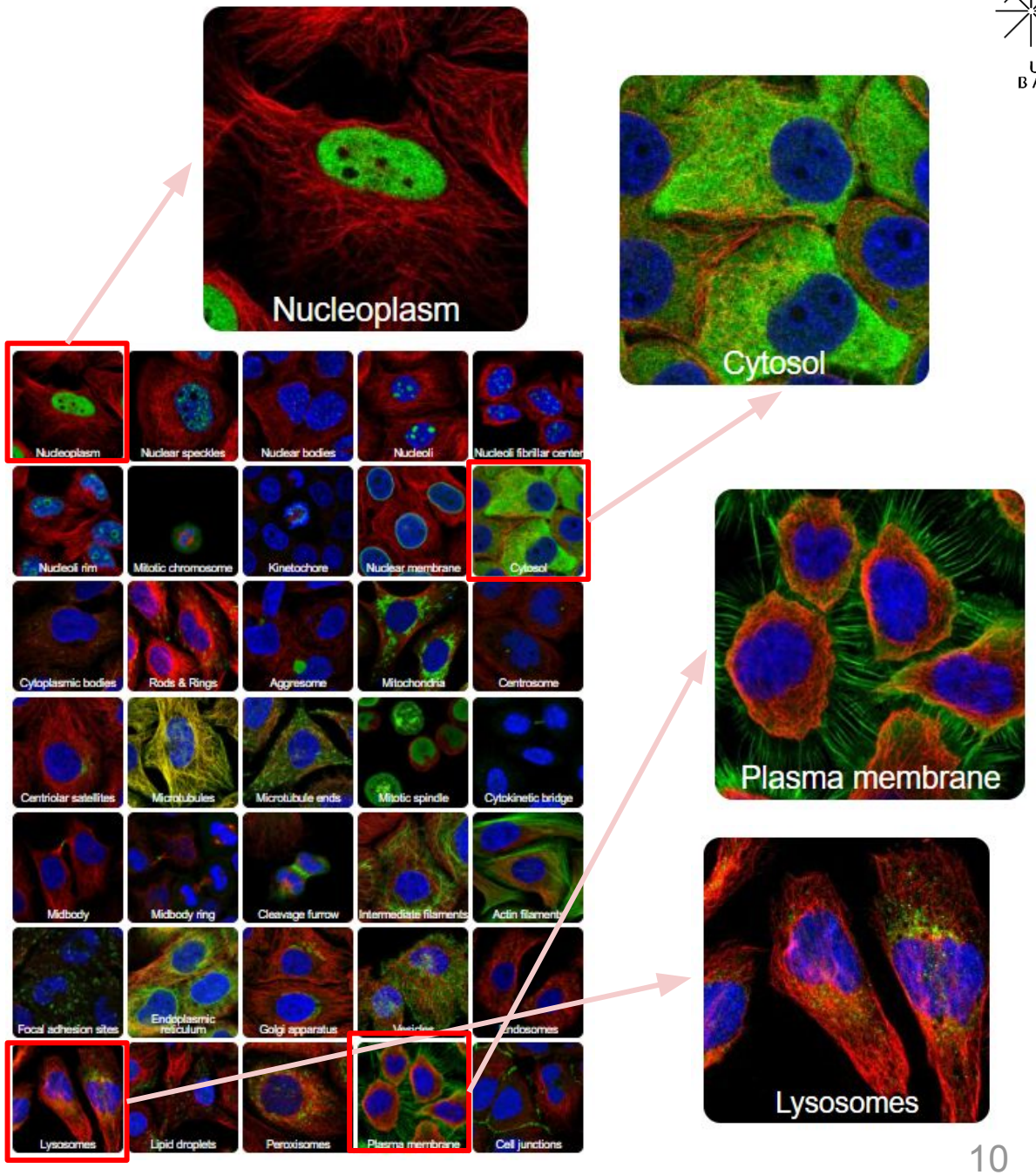




The human cell as a material entity

The Physics

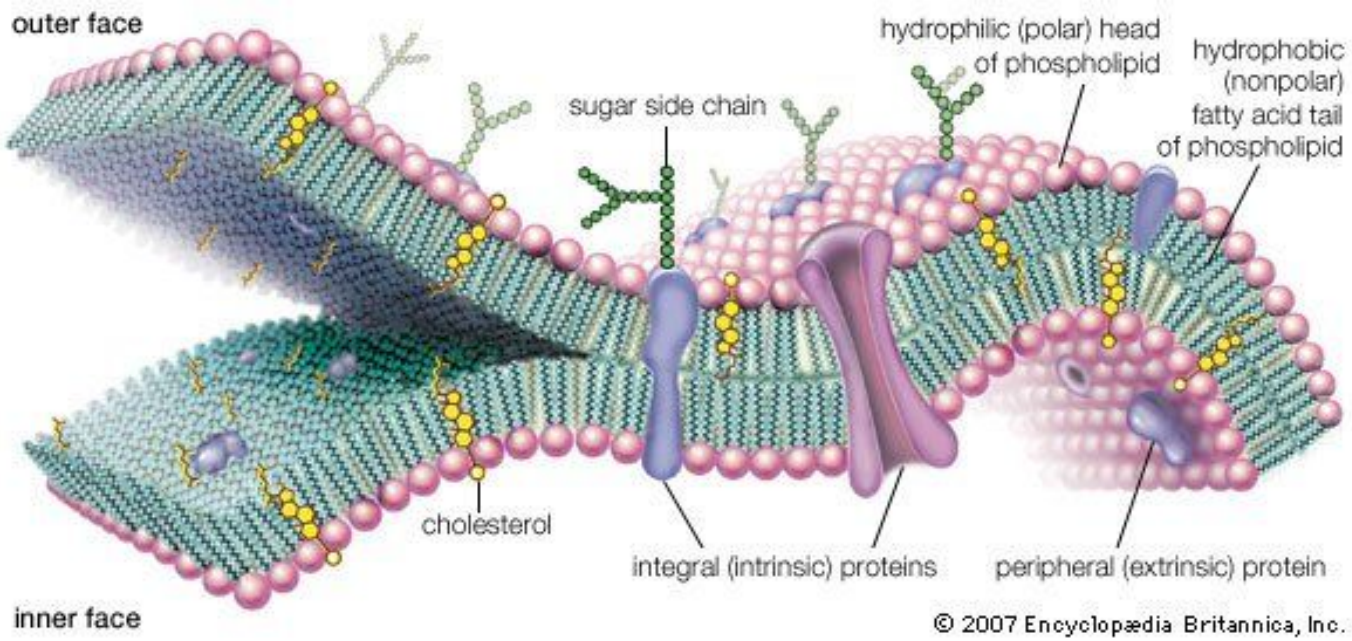


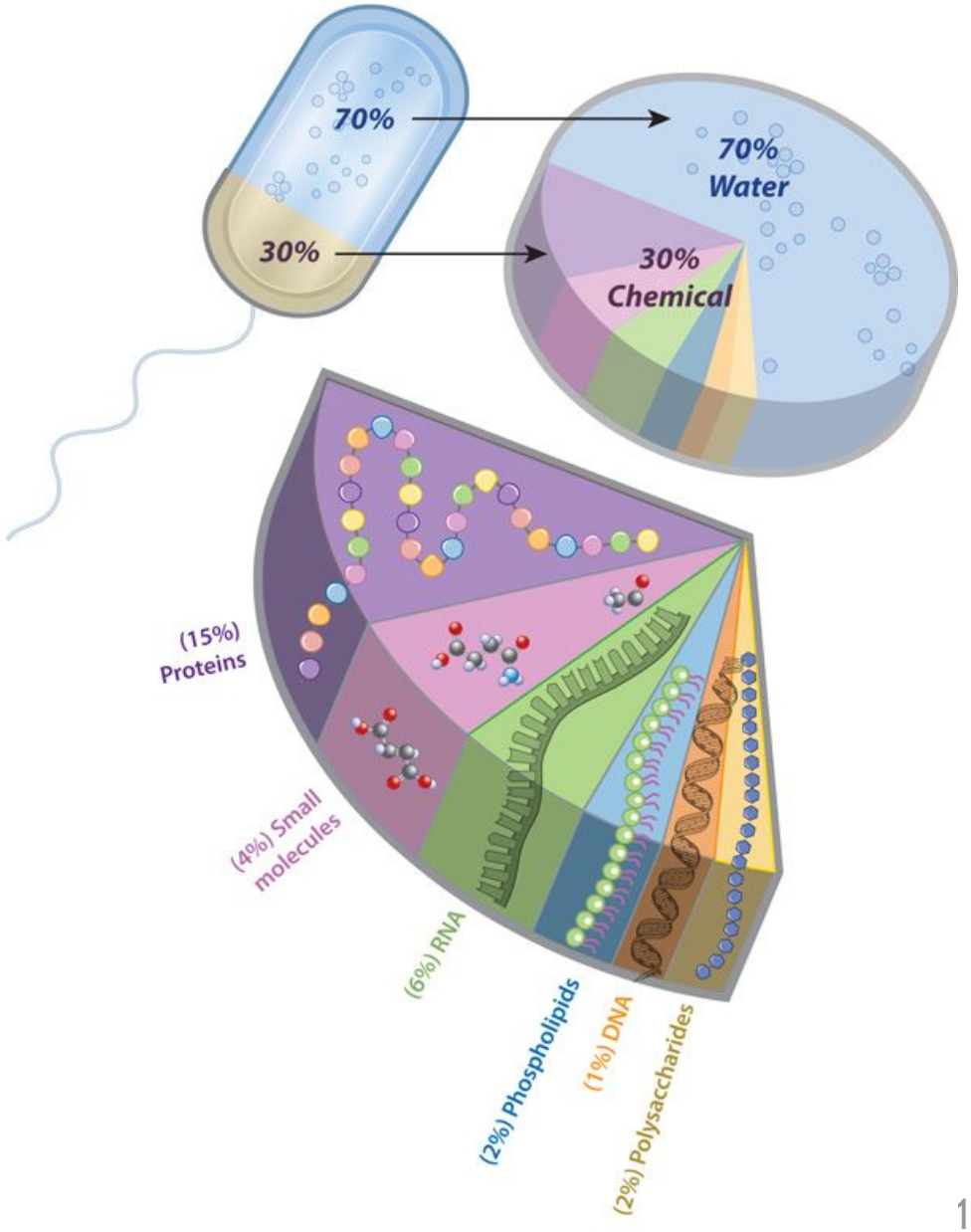


Left: Illustration showing the structures of an animal cell. Image credit: Genome Research Limited. Right: [Figure from The Human Protein Atlas]

The human cell as a material entity

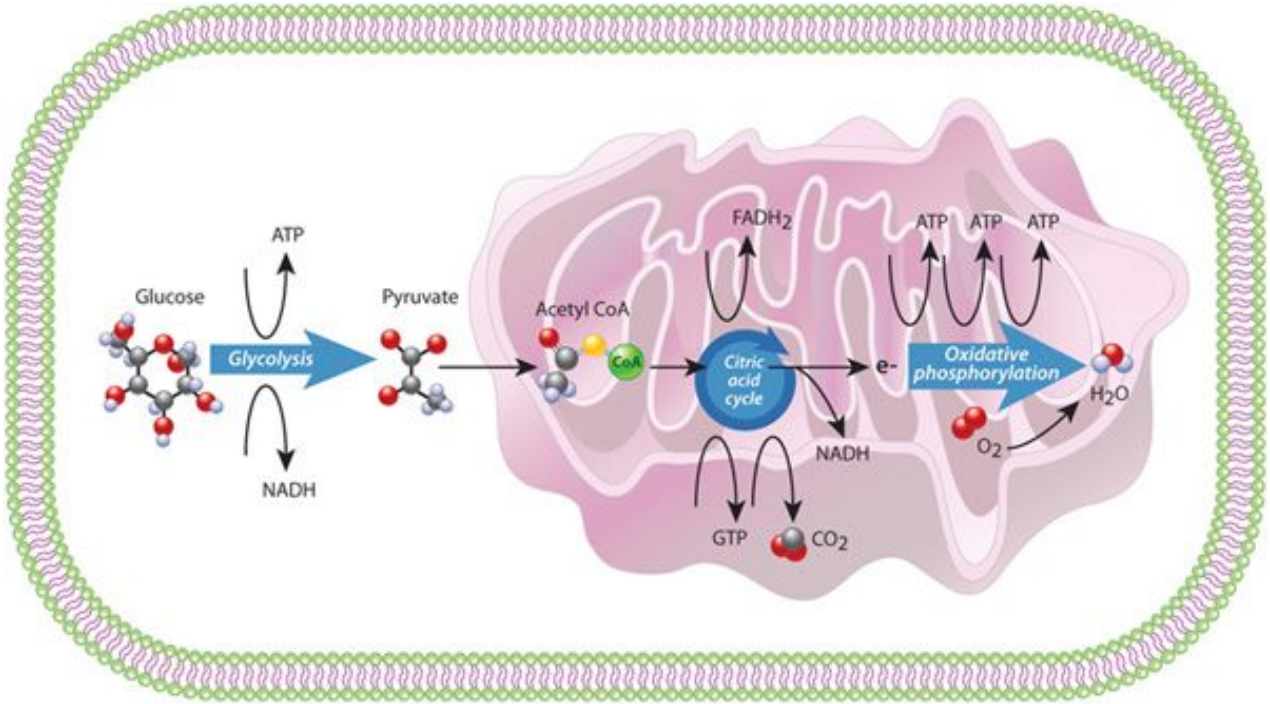
The Chemistry





Left: Cell membrane, copyright of Encylopedia Britannica, Inc.
Right: Chemical composition of a human cell, by Scitable Nature Education.

The human cell as an energy producer and consumer



Energy metabolism: glycolysis takes place in the cytoplasm. Within the mitochondrion, the citric acid cycle occurs in the mitochondrial matrix, and oxidative metabolism occurs at the internal folded mitochondrial membranes (cristae). Source: Nature Education.

tissue	protein synthesis	Na^+/K^+ ATPase	Ca^{+2} ATPase	other
liver	20%	5-10%	5%	gluconeogenesis (15-40%), substrate recycling (20%), proton leak (20%), urea synthesis (12%)
kidney	6%	40-70%	-	gluconeogenesis (5%)
heart	3%	1-5%	15-30%	actinomyosin ATPase (40-50%), proton leak (15% max)
brain	5%	50-60%	significant	a single cortical action potential was estimated to require 10^8-10^9 ATP, BNID 111183)
skeletal muscle	17%	5-10%	5%	proton leak (50%), nonmitochondrial (14%)

Distribution of major oxygen-consuming processes to total oxygen consumption rate of rate tissues in standard state, from Cell Biology By The Numbers. The total energy production rate is about 100W (or ~1W/kg) at rest.

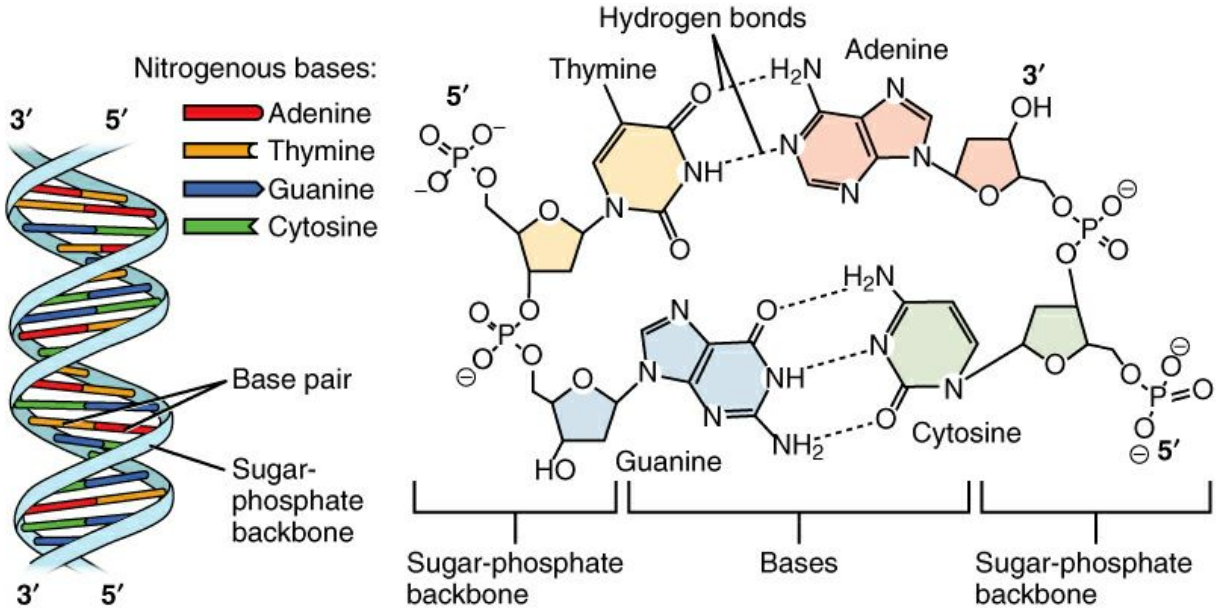
The central dogma of molecular biology: the human cell as an information vehicle

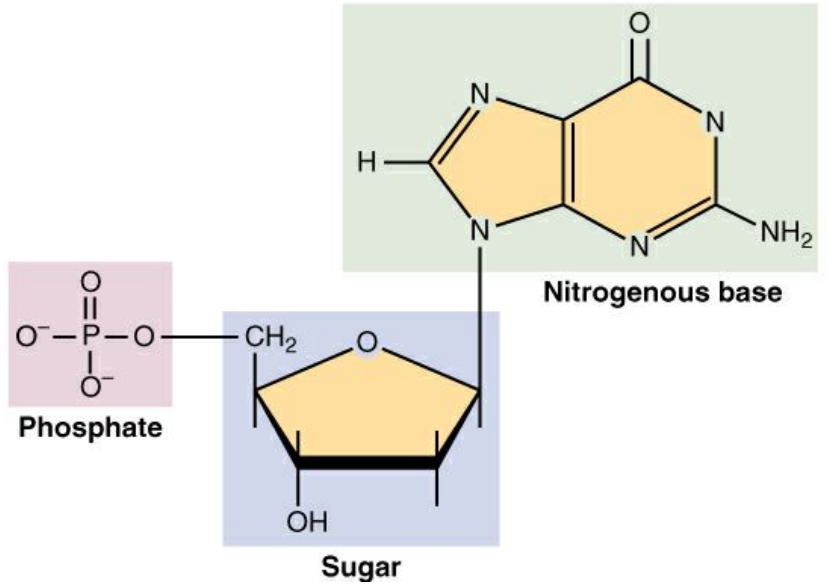
The Central Dogma can be represented by a graph of chemical information vehicles (nodes) and biological information flows (edges)

DNA: sequences and structure

Photo 51, X-ray diffraction image of DNA

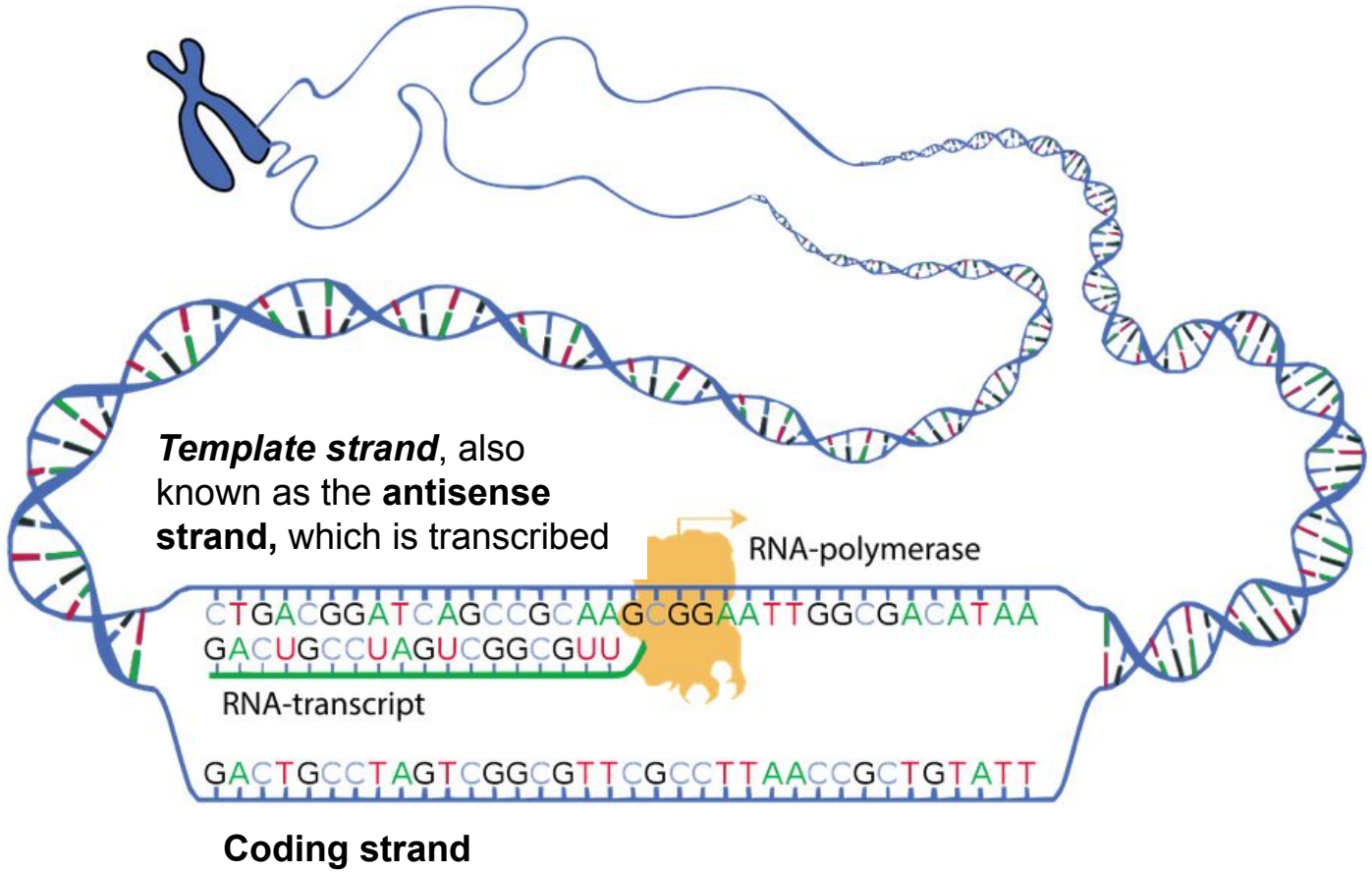
Franklin R, Gosling RG (1953) "Molecular Configuration in Sodium Thymonucleate". ***Nature*** 171**: 740–741.**

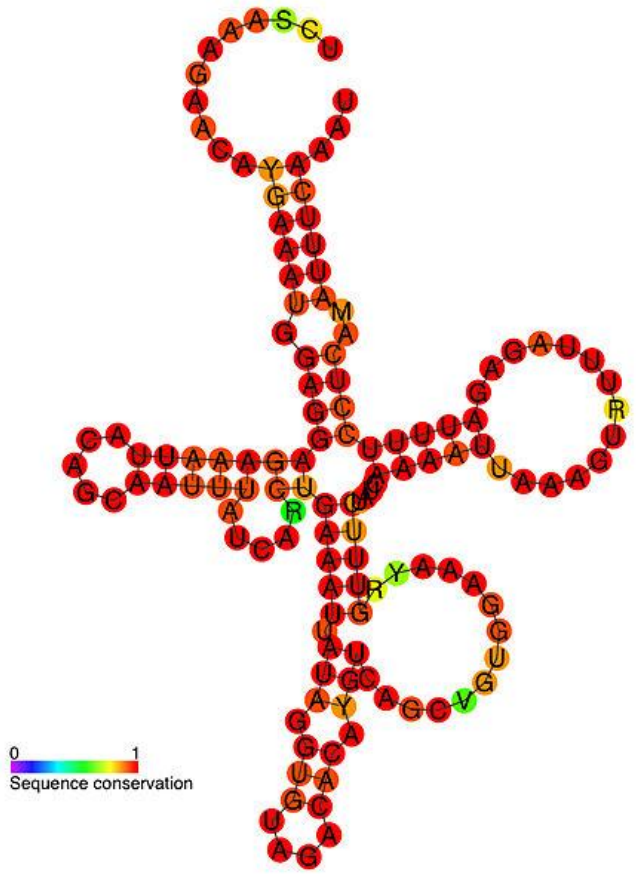




From the textbook OpenStax Anatomy and Physiology, discovered through Wikimedia, reused under the CC license.

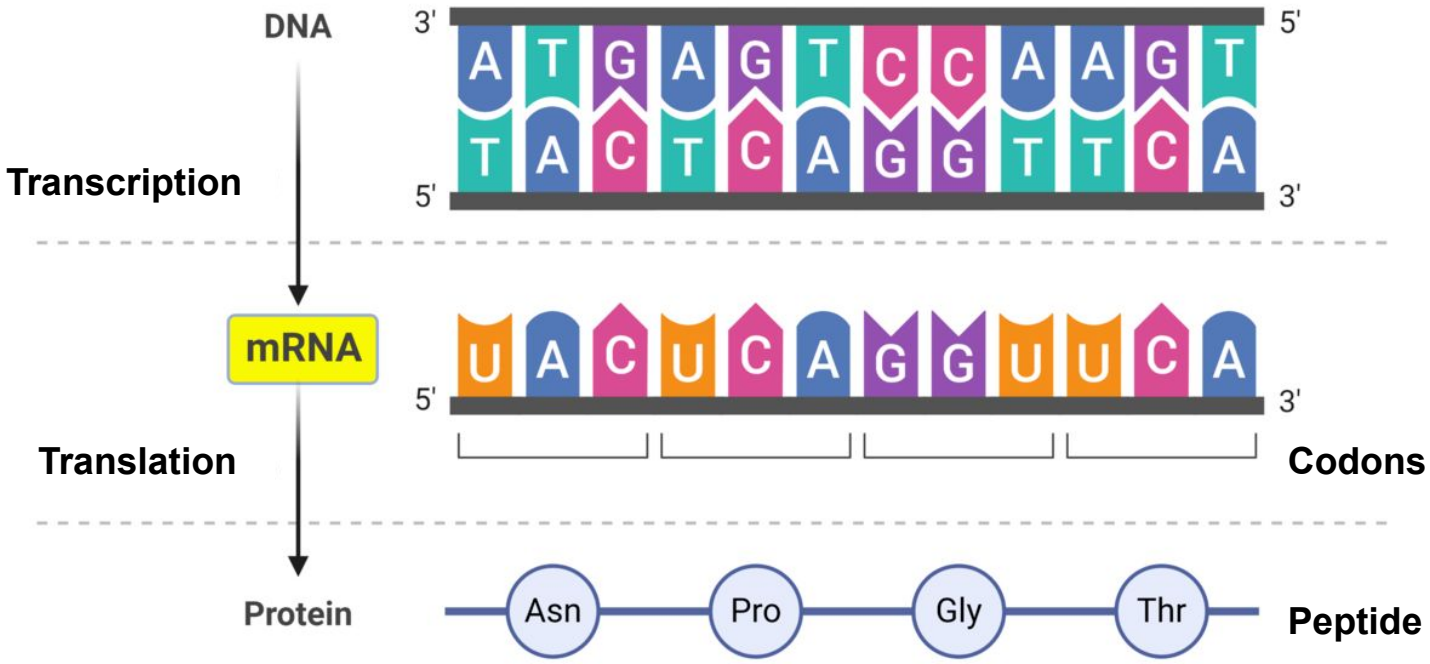
RNA: transcription and the secondary structure



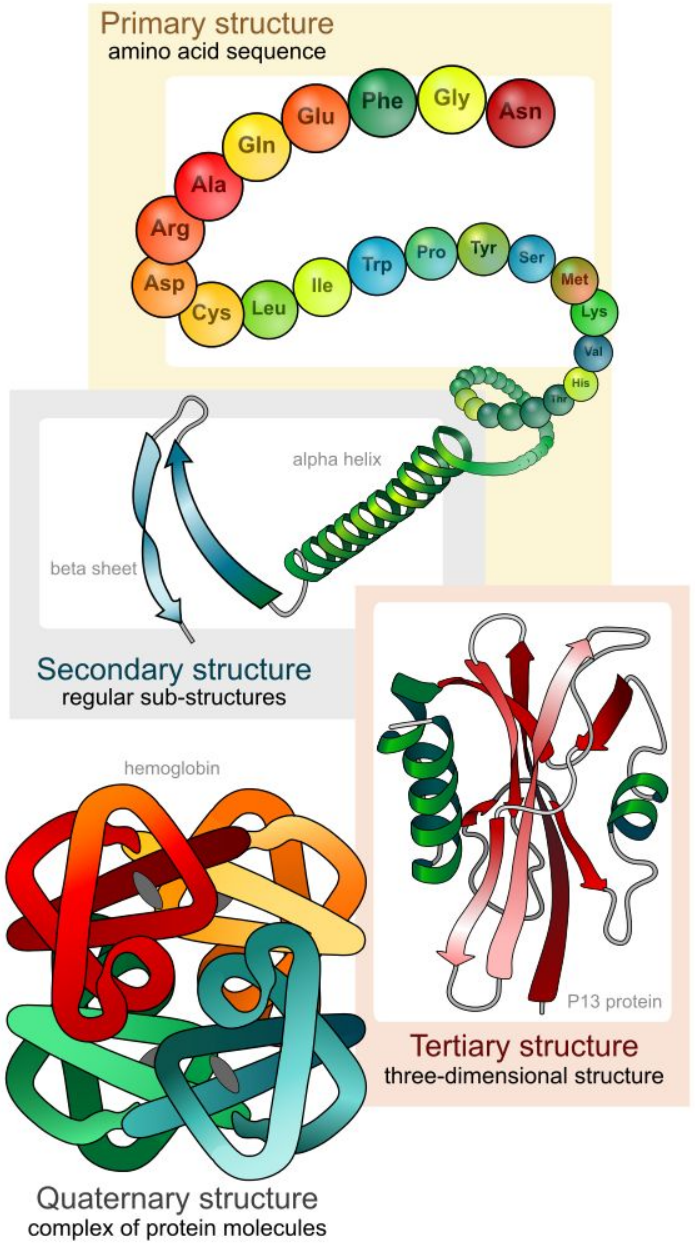


Downloaded and adapted from https://commons.wikimedia.org/wiki/File:DNA_transcriptie.svg and https://en.m.wikipedia.org/wiki/File%3AHAR1F_RF00635_rna_secondary_structure.jpg. Original work by wikipedia user: OrgreBot and user:Ppgardne. Used under CC-SA 3.0 license.

Translation of RNA into proteins

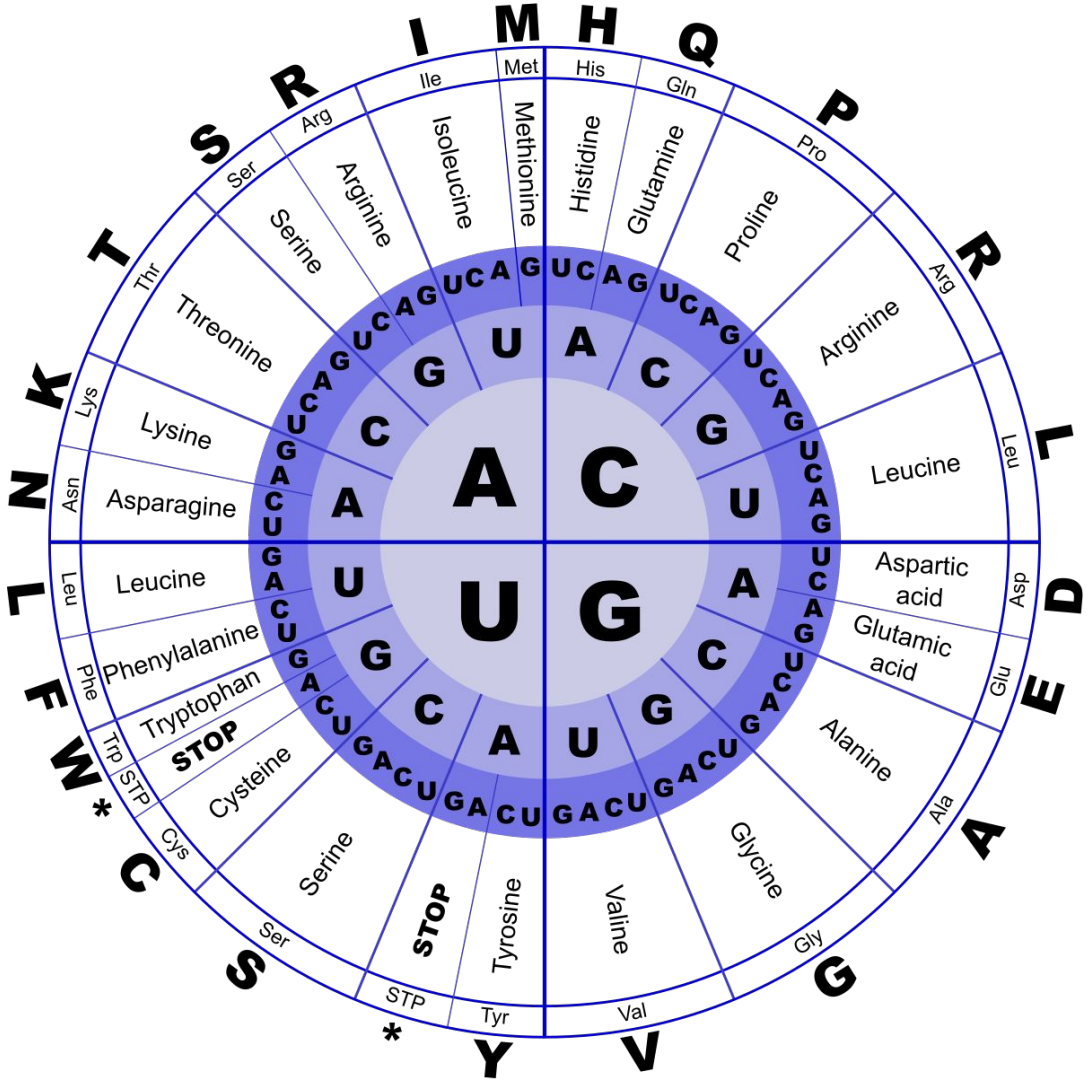


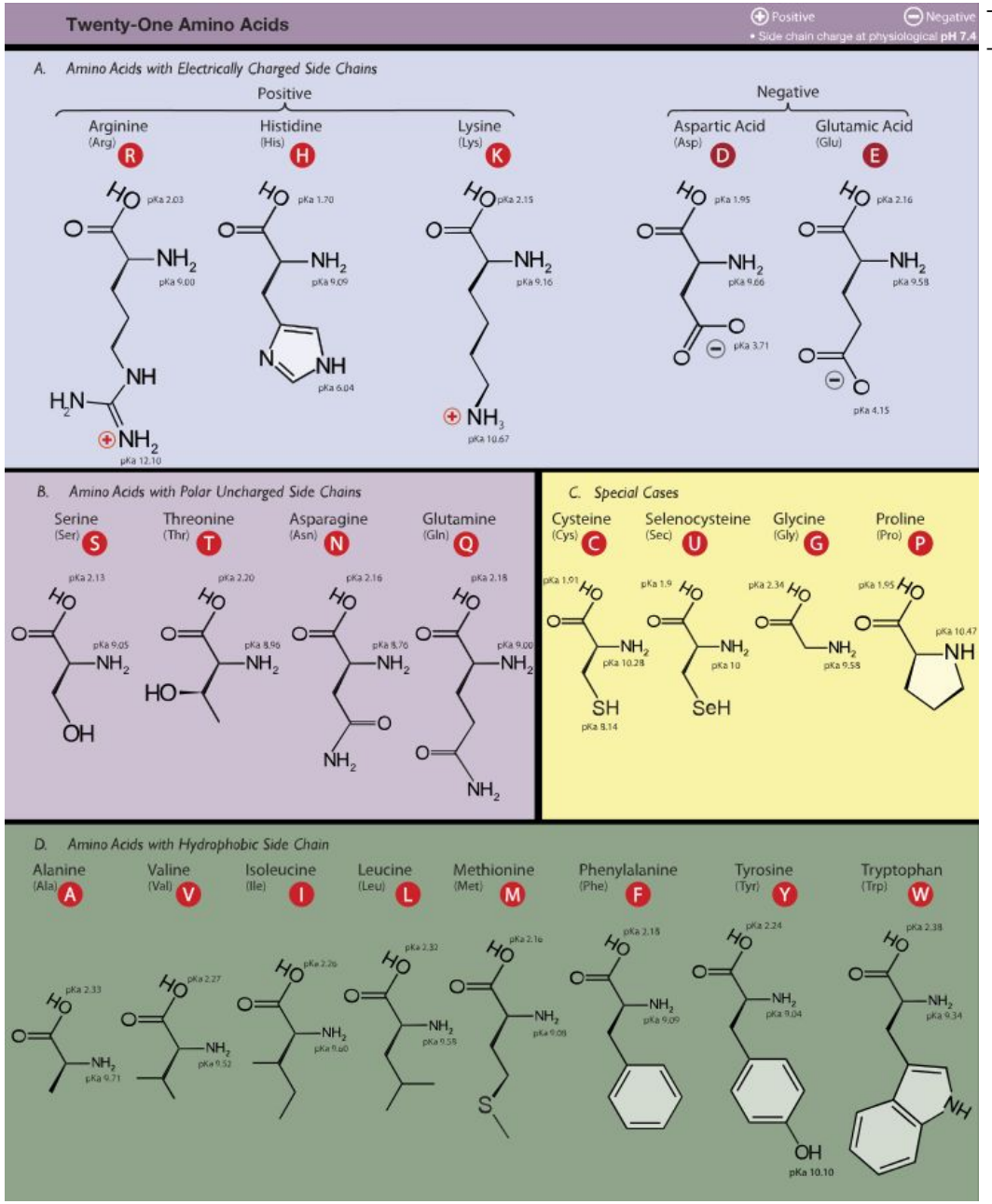
By Lene Martinsen/BioRender. License: CC BY NC SA 3.0



https://de.wikipedia.org/wiki/Datei:Main_protein_structure_levels_en.svg

Codes of the central dogma





Left: Genetic codes (OpenChart, public domain); Right:Dancojocari, CC BY-SA 3.0, via Wikimedia Commons

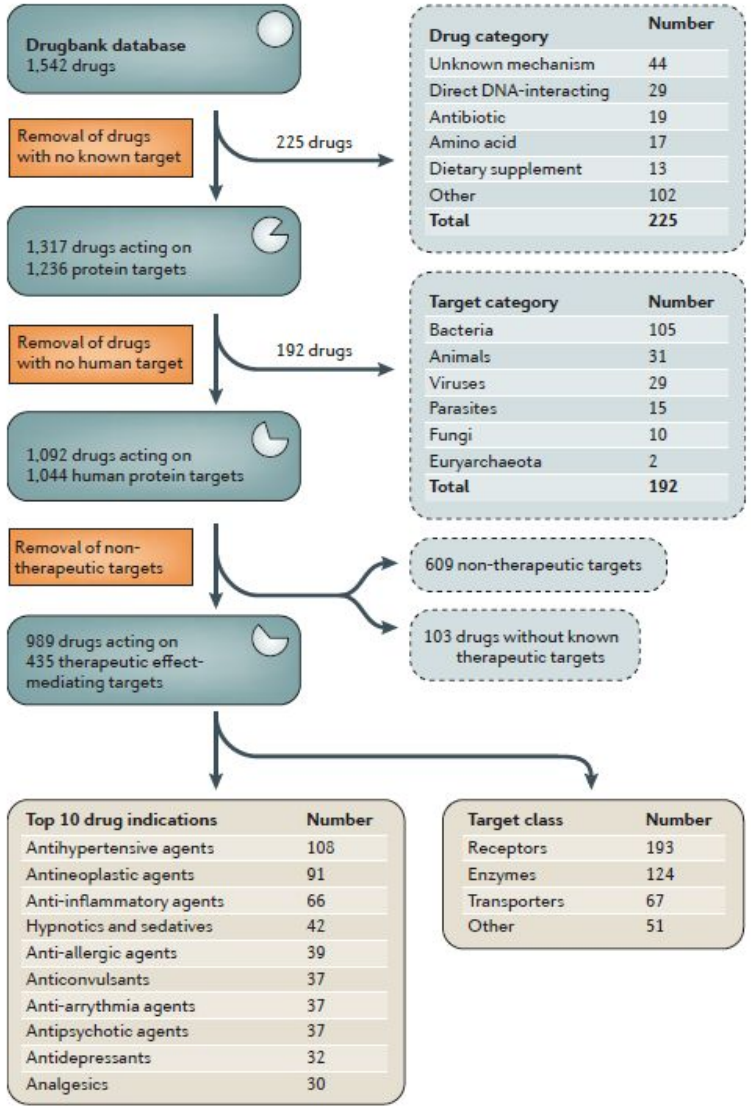
Break-out

1. Think of **three** drugs that you have used and/or used.
2. Look for their **chemical structures**, and identify whether they belong to small molecule, antibodies, oligonucleotides, or others.
3. Try to look after **their pharmacological targets**, and tell which part of the central dogma do they target?
4. (Optional) Try to learn their mechanism-of-action or mode-of-action (MoA), *i.e.* how do they work, and their indications, *i.e.* the diseases they try to cure.

Drugs work by targeting nodes or edges of the central dogma

Target	Example drugs or therapeutic candidates
Protein	• Most small-molecules, for instance GPCR modulators, kinase inhibitors, ion channel inhibitors • Most large-molecules (antibodies)
Translation	• Antimicrobial protein synthesis inhibitors • mTOR-pathway modulating drugs such as rapamycin
RNA	• Anti-sense oligonucleotides (ASO), for instance siRNA (silencing RNA) or locked nucleotide acids (LNA)
Transcription	• Antimicrobials such as actinomycin D and α-Amanitin • Evrysdi (Risdiplam, SMN2 splicing modulator)
Reverse transcription	• Reverse transcriptase inhibitors such as AZT (Zidovudine)
DNA	• Genome-editing therapies such as chimeric activated receptors in T-cells (CAR-T) or CRISPR-CAS9
DNA replication	• Topoisomerase inhibitors such quinolones • Chemotherapies

Most drugs so far target proteins



Drug category	Number
Unknown mechanism	44
Direct DNA-interacting	29
Antibiotic	19
Amino acid	17
Dietary supplement	13
Other	102
Total	**225**

Target category	Number
Bacteria	105
Animals	31
Viruses	29
Parasites	15
Fungi	10
Euryarchaeota	2
Total	**192**

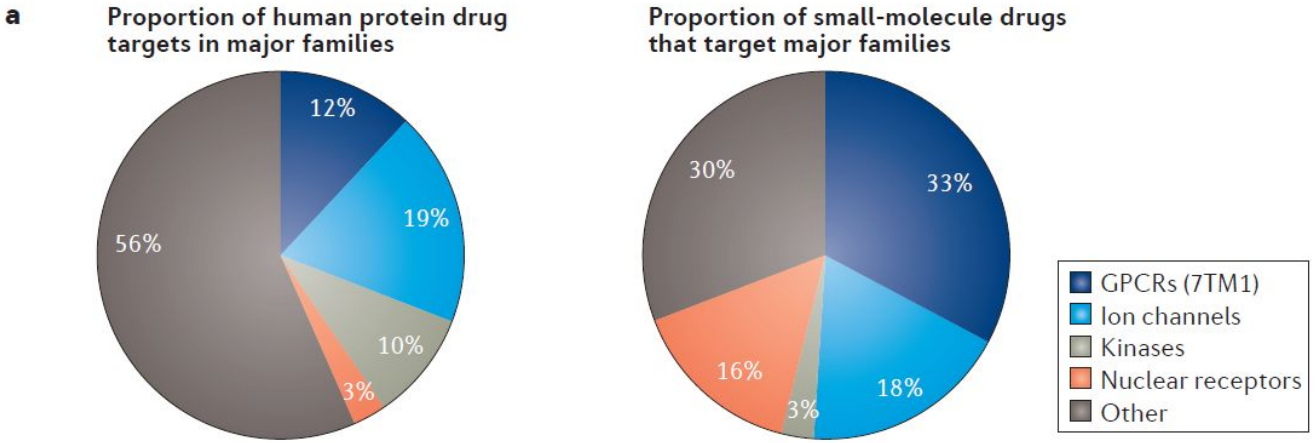
Top 10 drug indications	Number
Antihypertensive agents	108
Antineoplastic agents	91
Anti-inflammatory agents	66
Hypnotics and sedatives	42
Anti-allergic agents	39
Anticonvulsants	37
Anti-arrythmia agents	37
Antipsychotic agents	37
Antidepressants	32
Analgesics	30

Target class	Number
Receptors	193
Enzymes	124
Transporters	67
Other	51

Table 1 | **Molecular targets of FDA-approved drugs**

Drug target class	Targets			Drugs		
	Total targets	Small-molecule drug targets	Biologic drug targets	Total drugs	Small molecules	Biologics
Human protein	667	549	146	1,194	999	195
Pathogen protein	189	184	7	220	215	5
Other human biomolecules	28	9	22	98	63	35
Other pathogen biomolecules	9	7	4	79	71	8

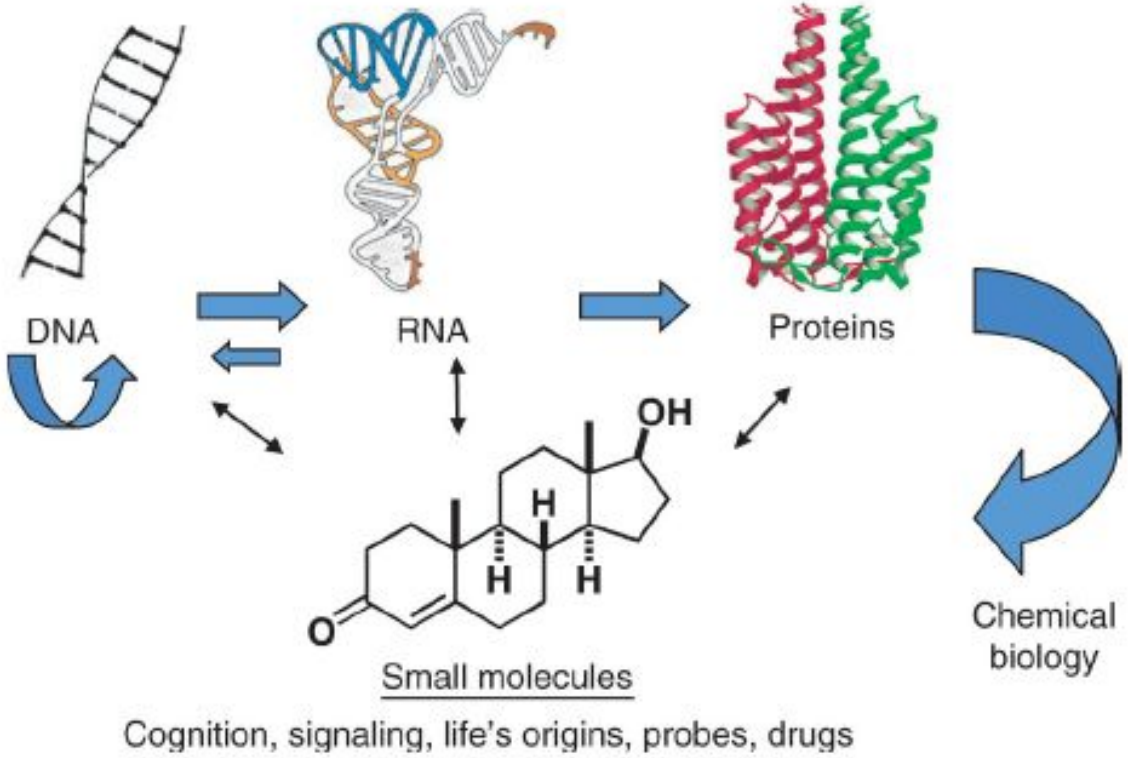
The list also includes antimalarial drugs approved elsewhere in the world.



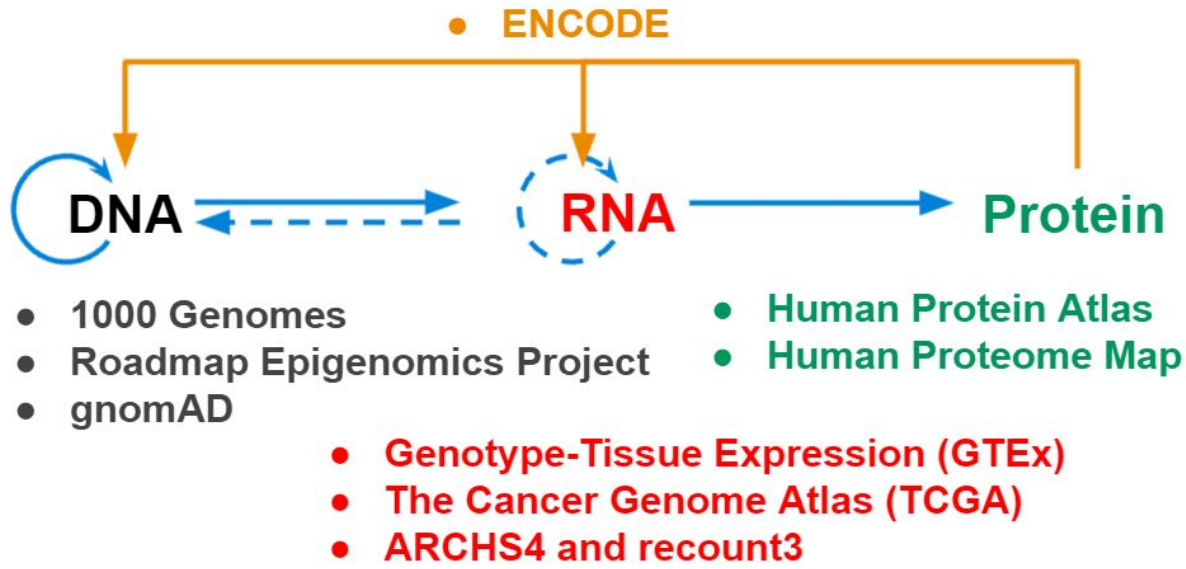
Left: Rask-Andersen, Mathias, Markus Sällman Almén, and Helgi B. Schiöth. 2011. "Trends in the Exploitation of Novel Drug Targets." Nature Reviews Drug Discovery 10 (8): 579–90. https://doi.org/10.1038/nrd3478.

Right: Santos, Rita, Oleg Ursu, Anna Gaulton, A. Patrícia Bento, Ramesh S. Donadi, Cristian G. Bologa, Anneli Karlsson, et al. 2017. "A Comprehensive Map of Molecular Drug Targets." *Nature Reviews Drug Discovery* 16 (1): 19–34. https://doi.org/10.1038/nrd.2016.230.

Extending the Central Dogma with small molecules, feedback regulations, and Big Data



Schreiber, Stuart L. "Small Molecules: The Missing Link in the Central Dogma." Nature Chemical Biology 1, no. 2 (July 2005): 64–66. https://doi.org/10.1038/nchembio0705-64.



Many references. Two for ENCODE are selected here: Moore, Jill E., Michael J. Purcaro, Henry E. Pratt, Charles B. Epstein, Noam Shoresh, Jessika Adrian, Trupti Kawli, et al. "Expanded Encyclopaedias of DNA Elements in the Human and Mouse Genomes." Nature 583, no. 7818 (July 2020): 699–710. https://doi.org/10.1038/s41586-020-2493-4; Van Nostrand, Eric L., Peter Freese, Gabriel A. Pratt, Xiaofeng Wang, Xintao Wei, Rui Xiao, Steven M. Blue, et al. "A Large-Scale Binding and Functional Map of Human RNA-Binding Proteins." Nature 583, no. 7818 (July 2020): 711–19. https://doi.org/10.1038/s41586-020-2077-3.

Questions about Bollag *et al.*, Nature 2010

1. What is the **indication** of *PLX4032*?
2. What is the **gene target** of *PLX4032*?
3. The malignancy depends on which biological **pathway***?*
4. What is the **Mechanism of Action** of *PLX4032?*
5. What went wrong in the first **Phase I clinical trial**? And how was it solved?
6. What was the **dosing regimen** in the final Phase I clinical trial, and what is the **response rate**?

Questions for further thinking

- In the video that you watched offline, Susan Desmond-Hellmann summarizes great drug development in four key concepts: (1) Having a deep understanding of the basic science and the characteristics of the drug. (2) Target the right patients. (3) Set a high bar in the clinic. (4) Work effectively with key regulatory decision makers. What parts of this abstract reflect these points?
- Susan Desmond-Hellmann emphasized the importance of collaboration. Is that true when you consider this abstract?
- How do you like the abstract? Anything that you can learn from it about writing?

Offline activities

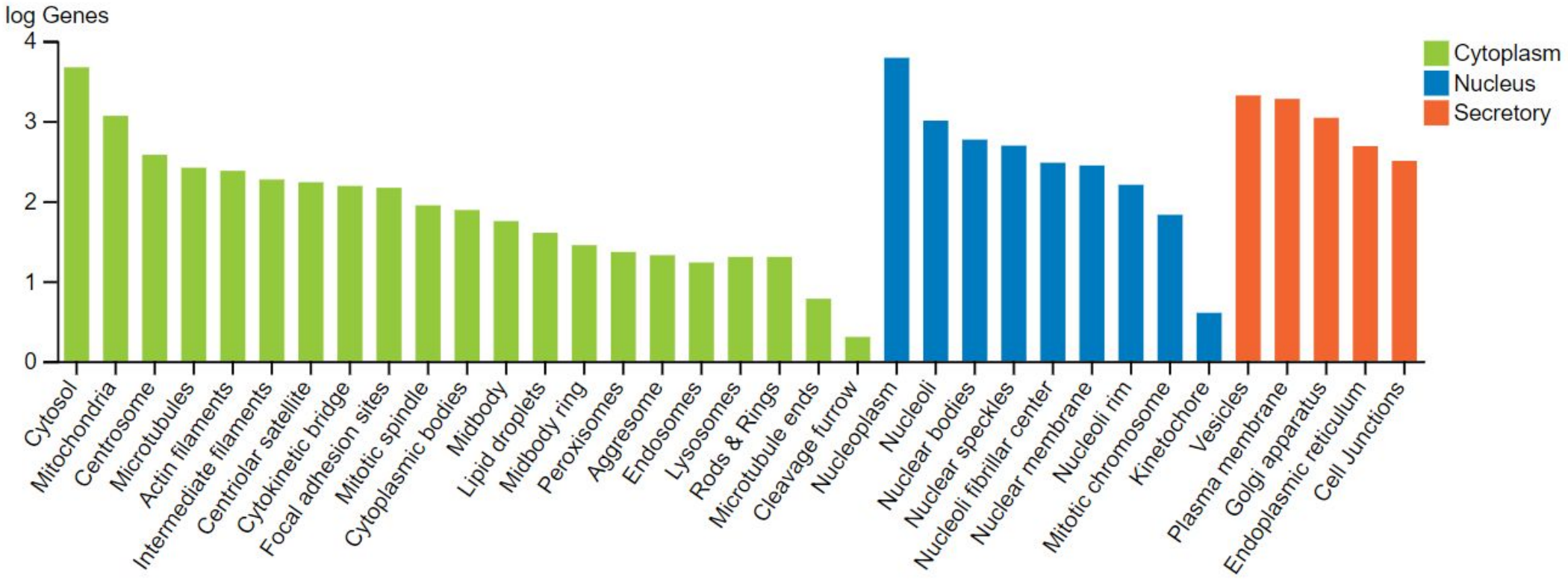
- Read the paper Bollag *et al.*, 2010, and answer questions here in Offline Activities.
- Optional read: Santos, Rita, Oleg Ursu, Anna Gaulton, A. Patrícia Bento, Ramesh S. Donadi, Cristian G. Bologa, Anneli Karlsson, et al. “A Comprehensive Map of Molecular Drug Targets.” Nature Reviews Drug Discovery 16, no. 1 (January 2017): 19–34. https://doi.org/10.1038/nrd.2016.230.

Questions for Bollag et al., 2010

1. We learned that many drugs target one of the four protein types: GPCRs, ion channels, kinases, and nuclear receptors. Which type does the target of PLX4032 belong to?
2. How was the efficacy of PLX4032 tested?
3. Why was PLX4032 chosen for further development, but not PLX4720?
4. How was the exposure of PLX4032 in the blood quantified? Which mathematical operation was used?
5. How was the final dosing regimen (960-mg BID) determined?
6. How did patients with the V600K mutation in BRAF respond?
7. What measures were taken to demonstrate the effect of BRAF inhibition in patient biopsies?
8. What side effects of PLX4032 were reported?
9. What measures were taken against side effects and safety concerns of PLX4032?
10. Where do you think mathematics and informatics is used in the discovery and development of PLX4032?

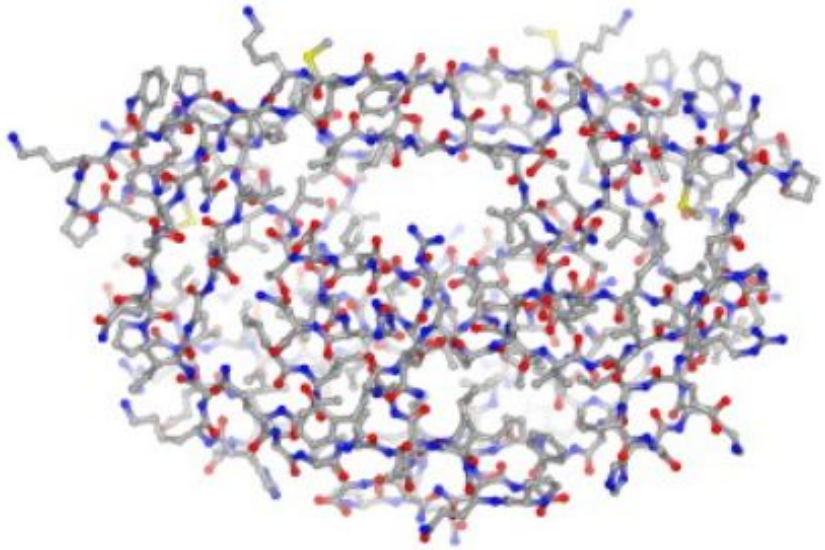
Backup slides

Protein distribution in the human cell

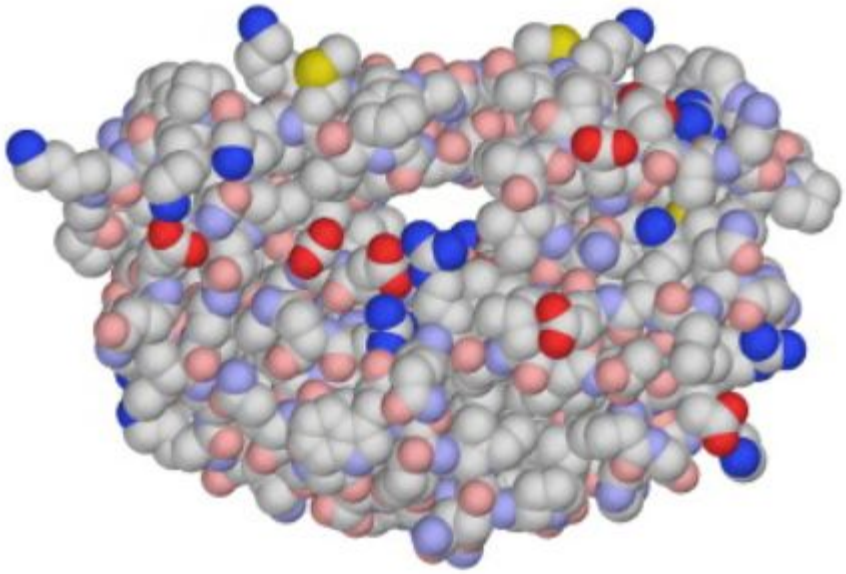


Source: The Human Protein Atlas. Among N=12813 cells, 55% (n=7106) of the proteins were detected in more than one location (*multilocalizing* proteins), and 25% (n=3141) displayed single-cell variation in expression level or spatial distribution.

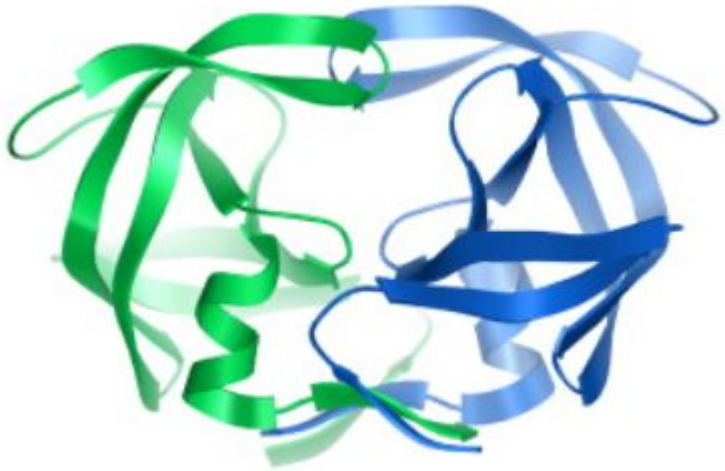
Three basic visual metaphors to display proteins



The bond diagram (balls-and-sticks)



The space-filling diagram



The ribbon diagram

Color codes: **Charged Nitrogen**, **Charged Oxygen**, **Uncharged Nitrogen**, **Unchard Oxygen**, **Carbon** (gray/white), **Sulfur**

Goodsell, David S. “Visual Methods from Atoms to Cells.” Structure 13, no. 3 (March 1, 2005): 347–54. https://doi.org/10.1016/j.str.2005.01.012.