Cell and Molecular Biology for Medicine

Curated preclinical study track (not a medical degree, no licensure claim). Original explanations and practice only, following the reviewed course handout.

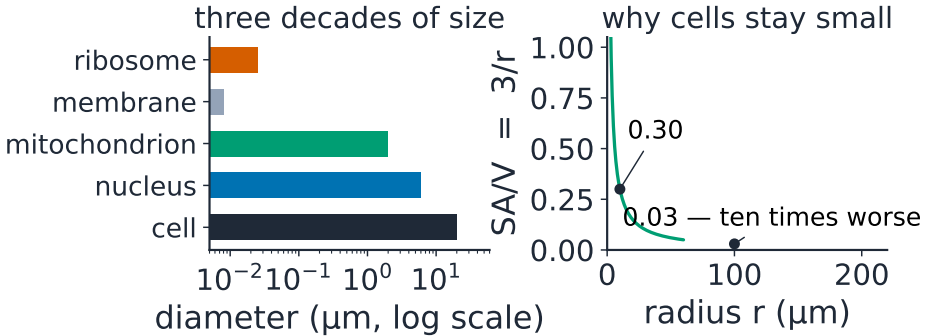
The preclinical foundation

- Cells and membranes first, then the information line (replication, expression, regulation), then decisions (signalling, cycle and death).
- Every number is recomputed - a Nernst potential, a compaction ratio, a mutation probability.

Organelles: a factory of compartments

1. **Ladder Ribosome** 25 nm, membrane 8 nm, **mitochondrion** 2 µm, **nucleus** 6 µm, cell 20 µm - three decades; a ribosome is to a cell as a cell is to a 1.6 cm marble.
2. **Ratio** A 20 µm cell has SA/V $= 0.3$; a 200 µm oocyte 0.03 - ten times worse, which is why big cells are rare and membrane-folded.
3. **Packing** 2.2 m of DNA (6.4×10^9 bp $\times$ 0.34 nm) packs into a 6 µm nucleus: a linear factor of about 10^5.

Three decades of size

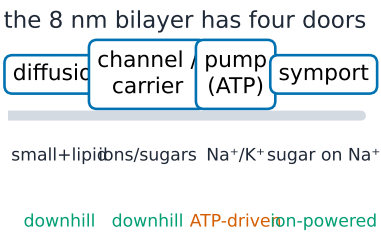


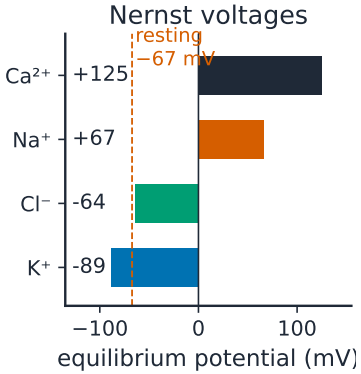
From 25 nm **ribosome** to 20 µm cell - and $SA/V = 3/r$ halves with every doubling of radius.

Membranes: four doors and a voltage

1. **Voltages** K^+ -89 mV, Cl^- -64 mV, Na^+ $+67$ mV, Ca^{2+} $+125$ mV - the **resting potential** sits about 20 mV above E_K because P_K dominates.
2. **Emergency** Extracellular K^+ doubles $5 \rightarrow 10$ mM: E_K shifts $+18.5$ mV $= 61.5 \cdot \log10(2)$ - the hyperkalaemia mechanism is one logarithm.
3. **Pump** 3 Na^+ out, 2 K^+ in, 1 ATP: the pump holds the gradients the leak channels spend; Vm rests just above E_K.

The four doors



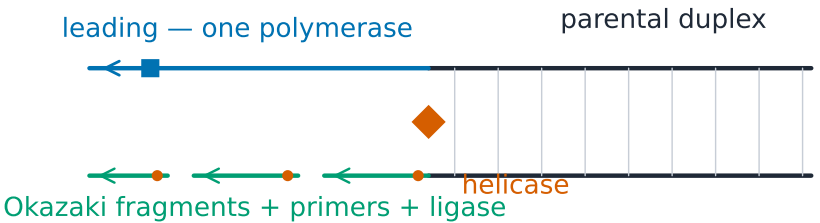


Four doors cross the 8 nm bilayer; the Nernst bars show why K^+ sets the resting voltage.

Replication: copy 6.4 billion letters

1. **Budget** 6.4×10^{9} bp $\times$ $10^{-9} \approx 6$ mutations survive per division - the number oncology and genetics both lean on.
2. **Timing** One fork pair at 50 bp/s would need 2 years; 30 000 origins give ~35 min of pure synthesis inside an 8 h S phase.
3. **Repair** Each repair pathway owns one lesion class: UV dimers to excision repair, mismatches to MMR - absence names a syndrome.

The fork



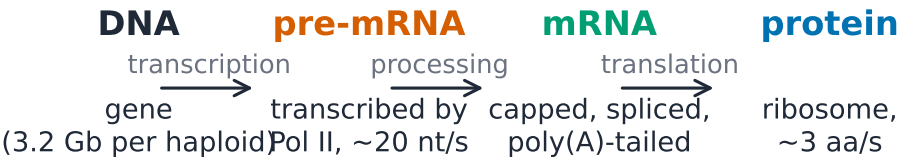
rule: polymerases make 5′→3′,
so the fork needs a lagging strand

Antiparallel templates plus a $5'\to3'$ enzyme force a leading and a **lagging strand**.

Expression: recipe to machine

1. **Timing** Preproinsulin (110 aa): $110/3 \approx 37$ s to translate, its 0.5 kb mRNA ~25 s to transcribe - one molecule $\approx$ one minute.
2. **Splice** A new splice site inside a β-globin intron: part of the intron kept, frame shifted, premature stop - thalassaemia with no amino-acid change.
3. **Code** Two bases give $16 < 20$ amino acids - too few; three give 64 with spare for degeneracy.

Central dogma with processing



splicing: one gene → several proteins (alternative exons)

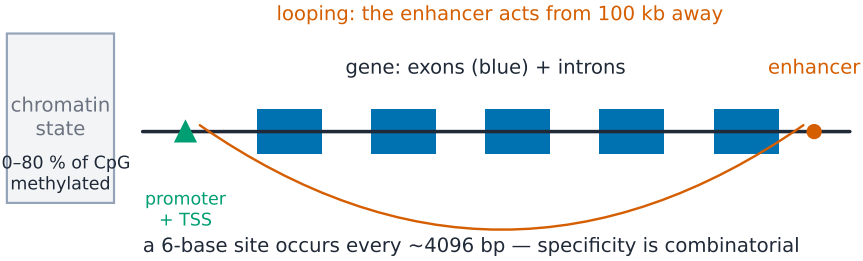
the code: $4^3 = 64$ codons = 61 sense + 3 stop, for 20 amino acids

Transcription, processing, **translation** - three stages, three chances for regulation, 64 codons for 20 amino acids.

Regulation: the gene is a switch

1. **Enhancer** Lactase persistence: one base 14 kb upstream strengthens an **enhancer**, LCT stays on into adulthood - a zero-protein-change continental trait.
2. **Epigenetic** Fictional twins, identical genotypes, different severity: promoter **methylation** silences one copy - access, not letters.
3. **Packing** 2.2 m of DNA wraps ~200 bp nucleosomes into a ~30 nm fibre - compaction near 10^4-fold.

Regulatory regions

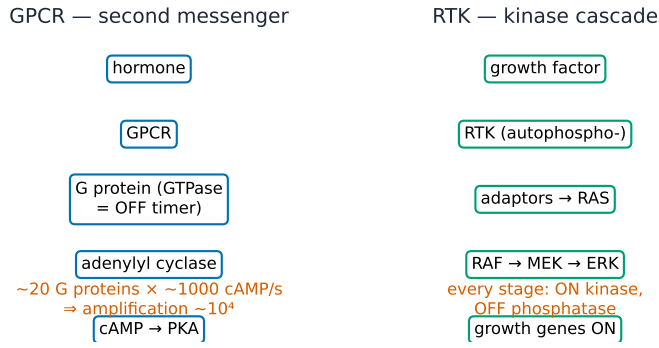


Enhancer, promoter, **transcription** start, exons - with the **chromatin** gate in front and looping from 100 kb away.

Signalling: amplify and reset

1. **Ledger** Resting cAMP $\approx$ 12 000 molecules per hepatocyte; ten cyclases at 1000/s replace the pool in a second - OFF matters as much as ON.
2. **Switch** cAMP switches 10 nM $\rightarrow$ 1 µM (a hundredfold) in seconds - a maximal hormone pulse.
3. **Welded** Cholera toxin disables the Gαs GTPase: cyclase runs constitutively, Cl^- and water pour out - the OFF enzyme IS the story.

Two cascades



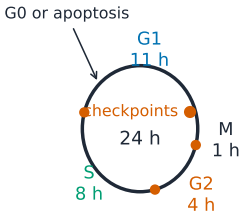
GPCR-cAMP and RTK-RAS side by side: $\sim 10^4$ amplification, every stage resettable.

Cycle and cancer: three gates

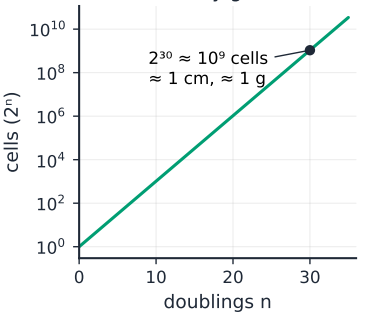
1. **Guardian** p53 pauses the cycle after damage for repair or commits to **apoptosis** - the gate cancer must pass.
2. **Drivers** ~6 mutations per division, mostly passengers; 4–7 drivers plus immortality (telomerase) and apoptosis escape make a cancer.
3. **Two-hit** Fictional Li–Fraumeni pedigree: inherit one bad p53 allele, lose the second somatically - tumour suppressors need two hits.

The cycle and the exponential

one cycle, three gates



a tumour is thirty generations old



Three checkpoints around a 24 h cycle - and thirty doublings from one cell to a visible tumour.

Check yourself

- K^+ (140 in / 5 out): E_K = ? (-89 mV.)
- Fidelity ladder: $10^{-5} \rightarrow ? \rightarrow 10^{-9}$ (**proofreading** then **mismatch repair**, each $\times 100$.)
- Codons: $4^3 = 64 =$? sense + 3 stop (61.)
- Visible tumour $\approx$ how many doublings? ($2^{30} \approx 10^9$ cells $\approx$ 1 cm.)