

Unit 1: Cell Biology

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Cellular and Molecular Pharmacology, subject code MPL104T, is a core Semester 1 subject of M.Pharm Pharmacology. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject takes pharmacology down to the level at which drugs actually act: the cell, its genome and its signaling machinery. Unit 1 covers cell biology: the organelles, genome organization, gene expression and its regulation (including siRNA and microRNA), the cell cycle and its checkpoints, and the three routes of cell death, apoptosis, necrosis and autophagy. Unit 2 covers cell signaling: the modes of intercellular signaling, the molecular structure of the four receptor families, the second messengers, and three pathways in detail, the cyclic AMP pathway, the MAP kinase cascade and the JAK/STAT pathway. Unit 3 covers the working tools of molecular pharmacology: DNA electrophoresis, PCR in its reverse transcription and real time forms, gene sequencing, microarrays, SDS-PAGE, ELISA and western blotting, then recombinant DNA technology and gene therapy. Unit 4 covers pharmacogenomics: mapping and cloning disease genes, the polymorphisms that change drug metabolism, transport and GPCR response, the omics family, and immunotherapeutics with the humanisation of antibodies. Unit 5 is the laboratory craft: cell culture techniques from media to cryopreservation, the viability, glucose uptake and calcium influx assays, flow cytometry, and a closing section on biosimilars.

1.1 Structure and functions of the cell and its organelles

The **cell** is the smallest unit at which pharmacology happens: every receptor, enzyme, transporter and gene in these notes sits inside one. The plasma membrane, a phospholipid bilayer studded with receptors, channels, transporters and pumps, separates the cytosol from the extracellular fluid and is the first barrier every drug crosses. Inside, each organelle carries work that maps directly onto a drug target or a drug fate.

Organelle	Main functions	Pharmacological relevance
Nucleus	Stores DNA as chromatin, site of transcription and ribosome assembly (nucleolus)	Target of anticancer drugs that damage DNA or block replication
Mitochondria	ATP production by oxidative phosphorylation, calcium buffering, heat production	Release cytochrome c to start intrinsic apoptosis; injured by some drug toxicities
Rough endoplasmic reticulum	Synthesis of membrane and secreted proteins (studded with ribosomes)	Antibody and protein drug production happens on this pathway in producer cells
Smooth endoplasmic reticulum	Lipid and steroid synthesis, detoxification	In hepatocytes it carries the cytochrome P450 enzymes of drug metabolism
Golgi apparatus	Modifies, sorts and packages proteins, adds carbohydrate chains (glycosylation)	Glycosylation pattern decides the quality of therapeutic proteins and biosimilars
Lysosomes	Acid digestion by hydrolytic enzymes, waste and organelle disposal	End point of autophagy; lysosomotropic drugs such as chloroquine accumulate here
Peroxisomes	Breakdown of very long chain fatty acids, detoxification of hydrogen peroxide	Their proliferation is switched on by fibrate drugs acting at PPAR alpha
Ribosomes	Protein synthesis (translation) on mRNA templates	The target of macrolide, aminoglycoside, tetracycline and oxazolidinone antibiotics in bacteria

Organelle	Main functions	Pharmacological relevance
Cytoskeleton	Shape, transport tracks, cell division spindle (microtubules), contraction (actin)	Microtubules are blocked by vinca alkaloids and stabilised by taxanes in cancer therapy

Two themes run through the whole subject. First, compartmentation: a drug that cannot reach the right compartment cannot act. Second, turnover: every protein in the table is continuously made and destroyed, so blocking synthesis or accelerating destruction are both workable drug strategies.

1.2 Genome organization

The human **genome** holds about 3 billion base pairs of DNA and roughly 20,000 protein coding genes, yet only a small fraction of the DNA codes for protein; the rest is regulatory sequence, introns, repetitive elements and structural DNA. The DNA of one cell, stretched out, would run to about two metres, and it fits into a nucleus a few micrometres wide because it is packaged in stages: DNA wraps around an octamer of histone proteins to form the **nucleosome**, nucleosomes coil into fibres, and the fibres loop and fold into chromosomes. Loosely packed **euchromatin** is accessible and transcriptionally active; densely packed **heterochromatin** is silent. Packaging is therefore the first layer of gene control: a gene wound into heterochromatin cannot be read, whatever signals arrive. Each gene itself is organised as a promoter where transcription machinery assembles, exons that survive into the mature messenger RNA, introns that are spliced out, and untranslated regions at both ends that tune how the message is used.

1.3 Gene expression: from DNA to protein

Gene expression is the flow of information from gene to functional product, summarised as DNA to RNA to protein. In **transcription**, RNA polymerase II (for protein coding genes) binds the promoter with the help of general transcription factors, unwinds the DNA and builds a messenger RNA copy of the coding strand. The primary transcript is processed before export: a 5 prime cap is added, introns are removed by **splicing** (which can join exons in alternative combinations, so one gene makes several proteins), and a poly A tail is added at the 3 prime end. In **translation**, the mature mRNA is read at the ribosome in three base codons; transfer RNAs deliver amino acids in the order the codons specify, and the growing chain folds into a protein.

GENE EXPRESSION: DNA TO PROTEIN

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DNA (gene)
|
| transcription (nucleus, RNA polymerase II)
v
primary transcript -- cap, splicing, poly A tail
|
|
v
mature mRNA -- exported to the cytosol
|
| translation (ribosome, codons read by tRNA)
v
polypeptide -- folding, modification, targeting
|
|
v
functional protein (enzyme, receptor, channel, hormone)

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Pharmacology intervenes at nearly every arrow: cytotoxic drugs damage the DNA template, antibiotics block bacterial ribosomes, antisense and siRNA drugs (Unit 1.5) destroy the message, and most conventional drugs act on the protein at the end of the line.

1.4 Regulation of gene expression

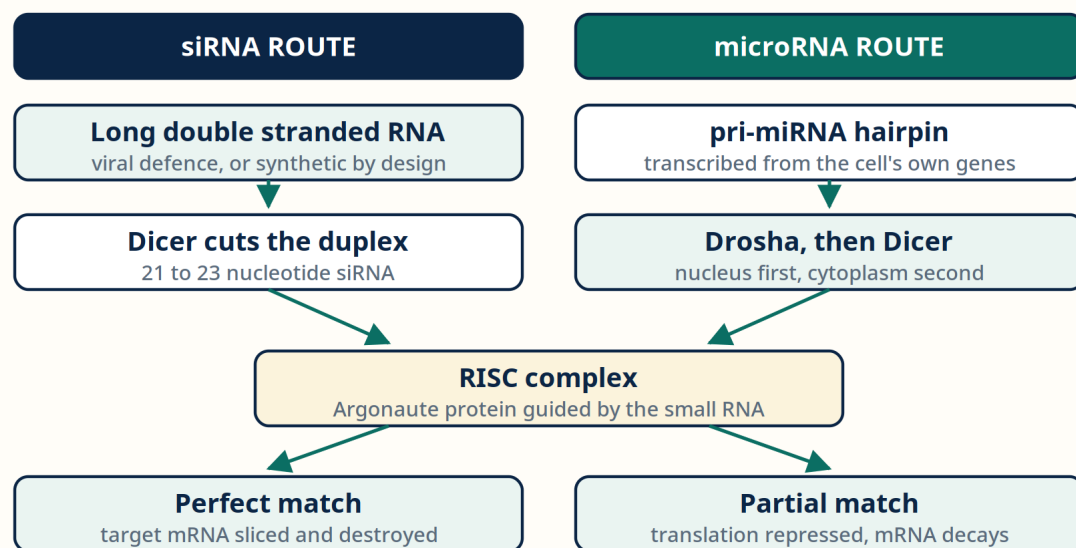
A liver cell and a neuron carry the same genome; they differ because different genes are switched on. Regulation works at several levels. **Transcriptional control** is the master level: specific **transcription factors** bind enhancer and silencer sequences and recruit or block the transcription machinery, and most hormone and drug signals that change cell behaviour end by changing which transcription factors are active. **Epigenetic control** changes expression without changing the DNA sequence: methylation of cytosine in CpG islands near a promoter usually silences the gene, while acetylation of histones by histone acetyltransferases loosens chromatin and favours expression, and deacetylation by histone deacetylases compacts it again. Both marks are drugged in practice: the hypomethylating agents azacitidine and decitabine are used in myelodysplastic syndromes, and the histone deacetylase inhibitor vorinostat is used in cutaneous T cell lymphoma. **Post transcriptional control** includes alternative splicing, regulation of mRNA stability and the small RNA silencing of the next section. **Translational and post translational control** tune how much protein each message yields and how the protein is modified, for example by phosphorylation, after it is made. The point for pharmacology is that the durable drug responses, tolerance, enzyme induction and most hormone actions, are written at the level of gene expression.

1.5 Small regulatory RNAs: siRNA and microRNA

Cells run a silencing system built on short RNA molecules about 21 to 23 nucleotides long, loaded into the **RNA induced silencing complex (RISC)**, whose Argonaute protein uses the short RNA as a guide to find matching messenger RNAs. The two classes differ in origin and in how completely they match their target.

Feature	siRNA (small interfering RNA)	microRNA (miRNA)
Origin	Long double stranded RNA, natural (viral defence) or synthetic by design	Endogenous genes, transcribed as hairpin precursors (pri miRNA, then pre miRNA)
Processing	Cut by the enzyme Dicer into short duplexes	Drosha in the nucleus, then Dicer in the cytoplasm
Match to target	Perfect complementarity to one target mRNA	Partial complementarity, mainly to the 3 prime untranslated region, so one miRNA tunes many mRNAs
Main outcome	Argonaute 2 slices and destroys the target mRNA	Translational repression plus deadenylation and decay of the target

Small RNA Silencing: siRNA and microRNA



One guide RNA, one outcome each: destruction for siRNA, fine tuning for microRNA.

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Figure: Two small RNAs, one silencing machine. siRNA arrives as a perfect match and orders destruction; microRNA is home made, matches loosely, and tunes many messages at once.

The **importance** the syllabus asks for is threefold. In research, synthetic siRNA is the standard tool for knocking down one gene at a time to learn its function and validate drug targets. In physiology, microRNAs fine tune whole programmes of expression, and their disturbance contributes to cancer and cardiovascular disease, making them candidate biomarkers. In therapy, siRNA has become a drug class: **patisiran**, a lipid nanoparticle siRNA, silences transthyretin production in hereditary transthyretin amyloidosis, and **inclisiran** silences PCSK9 in the liver to lower LDL cholesterol with twice yearly dosing. The delivery problem, getting a fragile charged RNA into the right cells, is the limiting step, and the liver targeting of the approved drugs shows where the technology works best today.

1.6 Gene mapping and gene sequencing

Gene mapping means fixing the position of a gene on a chromosome. Classical mapping uses **linkage**: genes close together are inherited together more often than chance predicts, so tracking how a disease travels through families alongside known DNA markers (microsatellites, now single nucleotide polymorphisms) narrows the disease gene to a chromosomal neighbourhood, measured in centimorgans of recombination frequency. Physical mapping then orders the actual DNA, assembling overlapping cloned fragments across the region into a map in base pairs. **Gene sequencing** reads the base order itself; the principle is introduced here and the laboratory methods are treated in Unit 3.4. Mapping and sequencing together converted genetics into a practical science: once a disease gene is mapped, it can be cloned (Unit 4.1), its protein identified, and the protein becomes a candidate drug target or the basis of a diagnostic test. The Human Genome Project, completed in 2003, delivered the reference sequence against which all mapping is now done.

1.7 The cell cycle and its phases

The **cell cycle** is the ordered sequence by which a cell duplicates its contents and divides. It runs in four phases: **G1** (growth and preparation, the cell decides whether conditions favour division), **S** (synthesis, the DNA is replicated), **G2** (a second gap, the cell checks the replication and prepares the division machinery)

and **M** (mitosis, chromosomes are separated and the cell divides into two). Cells that leave the cycle enter the resting state **G0**, where most adult cells sit; some, like neurons, stay there permanently, while others, like liver cells, can re-enter on demand. The engine of the cycle is a family of protein kinases, the **cyclin dependent kinases (CDKs)**, which are inactive alone and switched on by partner proteins, the **cyclins**, whose levels rise and fall in a fixed order: cyclin D with CDK4 and CDK6 drives early G1, cyclin E with CDK2 completes the G1 to S transition, cyclin A with CDK2 works through S phase, and cyclin B with CDK1 drives mitosis. Each cyclin is destroyed once its job is done, which makes the cycle unidirectional.

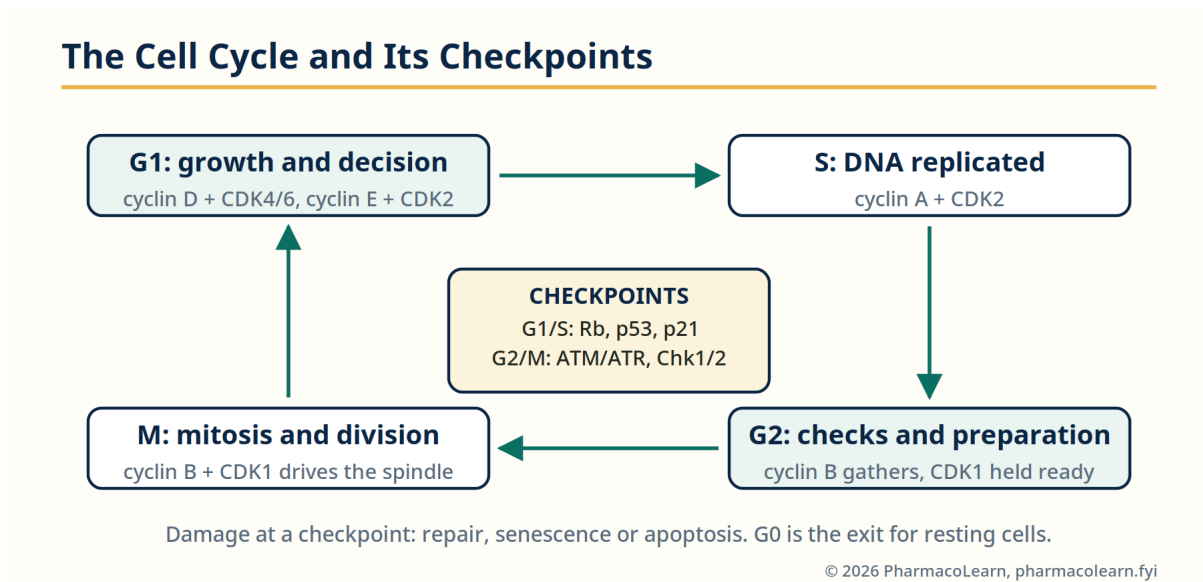


Figure: The cell cycle as a wheel of cyclin and CDK pairs, guarded by three checkpoints. Damage detected at a checkpoint halts the wheel for repair or diverts the cell to apoptosis.

1.8 Regulation of the cell cycle: checkpoints

A cycle that copies three billion base pairs cannot be allowed to run unchecked, so the cell stations **checkpoints** that halt progress when something is wrong. At the **G1/S checkpoint**, the retinoblastoma protein **Rb** is the gatekeeper: unphosphorylated Rb holds the E2F transcription factors silent, and cyclin D and E kinases phosphorylate Rb to release E2F and start S phase. DNA damage activates the protein **p53**, the guardian of the genome, which switches on the CDK inhibitor p21, freezing the cycle for repair; if the damage is beyond repair, p53 pushes the cell into apoptosis or permanent senescence instead. At the **G2/M checkpoint**, the ATM and ATR kinases sense unreplicated or damaged DNA and, through Chk1 and Chk2, block the cyclin B and CDK1 complex until replication is complete. The **spindle assembly checkpoint** in mitosis holds the separation of sister chromatids until every chromosome is correctly attached to the spindle. The pharmacology is direct. p53 is mutated in more than half of human cancers, and Rb pathway failure releases cells from G1 control, which is precisely why **CDK4/6 inhibitors** (palbociclib, ribociclib, abemaciclib) work in hormone receptor positive breast cancer: they restore the G1 brake that the tumour still depends on losing. Most cytotoxic chemotherapy also exploits the cycle, killing cells preferentially in S phase (antimetabolites) or M phase (vinca alkaloids, taxanes).

1.9 Cell death: the events and regulators of apoptosis

Cells die by controlled demolition or by catastrophe, and the difference decides whether the surrounding tissue is inflamed. **Apoptosis**, programmed cell death, is an active, energy requiring process with a recognisable sequence of **events**: the cell shrinks and detaches, the membrane throws out blebs, chromatin condenses against the nuclear envelope, the DNA is cut into regular fragments, and the cell breaks into membrane bound **apoptotic bodies** that phagocytes engulf at once, so no contents spill and

there is no inflammation. Apoptosis sculpts the embryo (separating the fingers), deletes self reactive immune cells, removes cells whose DNA is damaged, and balances cell production in renewing tissues. The executioners are the **caspases**, cysteine proteases that cut after aspartate residues: initiator caspases (8, 9 and 10) start the cascade and executioner caspases (3, 6 and 7) dismantle the cell. The **regulators** sit above the caspases: the Bcl-2 family controls the mitochondrial gate (next section), inhibitor of apoptosis proteins restrain caspases directly, and p53 can order apoptosis from the nucleus when damage is unrepairable.

1.10 The intrinsic and extrinsic pathways of apoptosis

Two routes converge on the executioner caspases. The **intrinsic (mitochondrial) pathway** responds to internal trouble: DNA damage, growth factor withdrawal, oxidative and endoplasmic reticulum stress. These signals activate the BH3 only proteins of the Bcl-2 family (Bid, Bim, Puma, Noxa and others), which tip the balance against the anti apoptotic guardians Bcl-2, Bcl-xL and Mcl-1 and free the effectors **Bax and Bak** to punch pores in the mitochondrial outer membrane. **Cytochrome c** escapes to the cytosol, joins Apaf-1 and procaspase 9 to form the **apoptosome**, and caspase 9 switches on caspase 3. The **extrinsic (death receptor) pathway** responds to orders from outside: Fas ligand or TNF binds its death receptor (Fas, TNFR1) on the cell surface, the receptor recruits the adaptor FADD, and the resulting death inducing signaling complex activates caspase 8, which activates caspase 3 directly. The pathways talk to each other: caspase 8 also cuts Bid to its active form tBid, which engages the mitochondrial route and amplifies the signal.

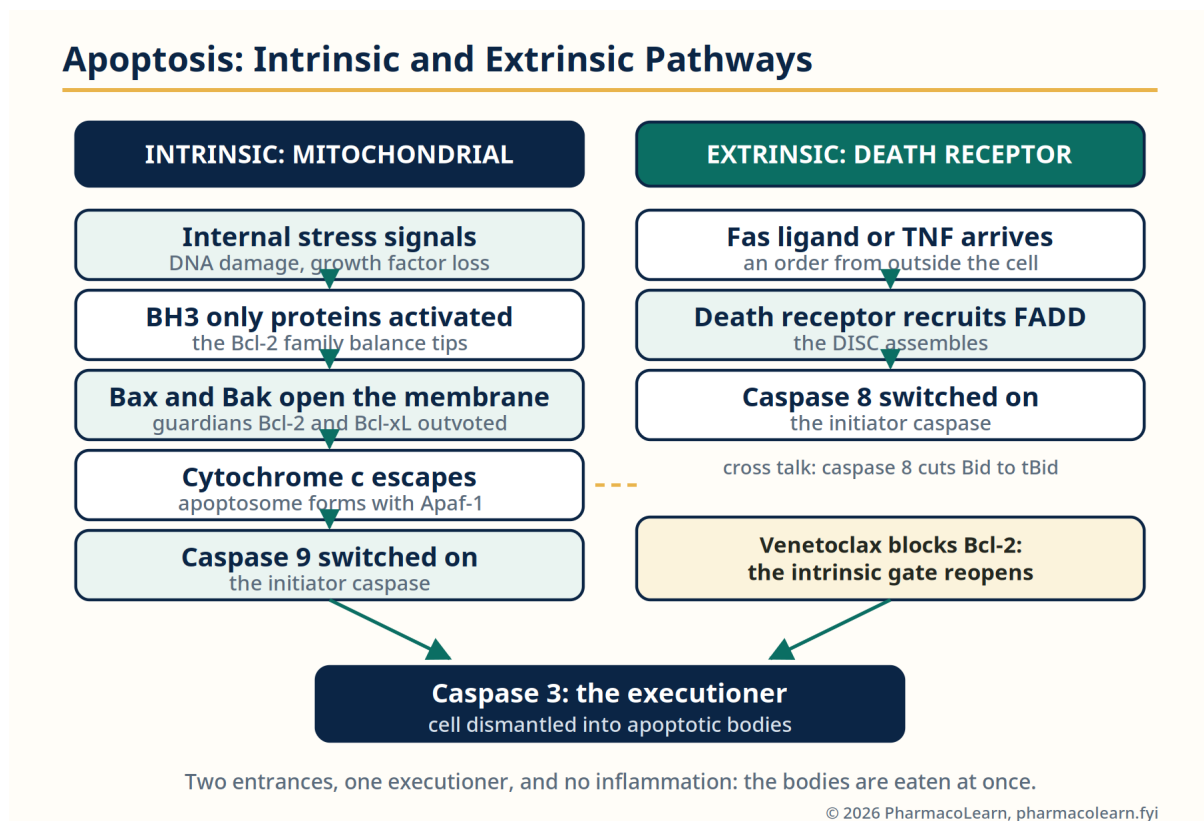


Figure: Two doors into the same execution chamber. The intrinsic pathway reads internal damage through the mitochondria; the extrinsic pathway reads external orders through death receptors; both end at caspase 3.

Cancer is in large part a failure of this machinery: tumours overexpress Bcl-2 or lose p53 and so refuse to die. The refusal can be drugged. **Venetoclax** is a BH3 mimetic that blocks Bcl-2 itself, freeing Bax and Bak in chronic lymphocytic leukaemia cells that depend on Bcl-2 for survival; it is the clearest example of an

apoptosis regulator becoming a medicine.

1.11 Necrosis and autophagy

Necrosis is the catastrophic route: overwhelming injury (ischaemia, toxins, trauma, infection) exhausts ATP, ion pumps fail, the cell and its organelles swell, the membrane ruptures and the contents spill into the tissue, provoking inflammation that damages neighbours. A regulated variant, **necroptosis**, runs through the kinases RIPK1 and RIPK3 and the pore forming protein MLKL, and can be triggered when apoptosis is blocked; it matters in inflammatory and ischaemic disease.

Feature	Apoptosis	Necrosis
Trigger	Programmed signals, damage sensed by the cell	Overwhelming external injury
Energy	Required (active process)	Fails as ATP is exhausted
Cell volume	Shrinks	Swells
Membrane	Intact, blebbing, bodies pinched off	Ruptures early
DNA	Cut into regular fragments	Random digestion
Inflammation	None, bodies are phagocytosed cleanly	Marked, contents spill

Autophagy, self eating, is the third route and is as much about survival as death. The cell wraps damaged organelles and protein aggregates in a double membrane **autophagosome**, marked by the protein LC3, and fuses it with a lysosome so the contents are digested and recycled. The nutrient sensor **mTOR** normally restrains autophagy; starvation or the drug **rapamycin** (sirolimus) releases the brake by inhibiting mTOR, and the energy sensor AMPK pushes the same direction. In cancer and infection the process cuts both ways: it keeps stressed cells alive (a resistance mechanism, which is why the lysosome blocking drugs chloroquine and hydroxychloroquine have been studied as chemotherapy partners) and it disposes of intracellular bacteria and damaged mitochondria. For the pharmacologist, Unit 1 ends with a complete set: the cell builds proteins under genomic control, divides under checkpoint control, and dies by three routes, every one of which is now a drug target.

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