

Unit 3: Chemotherapy of Protozoa, Helminths and Cancer; Immunopharmacology

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3.1 Antiprotozoal drugs I: the antimalarials

Malaria teaches chemotherapy against a parasite with a staged life cycle, because each stage has its own drugs. Sporozoites from the mosquito infect liver cells (the silent exoerythrocytic stage); merozoites then cycle through red cells, causing the fever; in *Plasmodium vivax* and *P. ovale* some liver forms sleep as **hypnozoites** and relapse months later; gametocytes return to the mosquito. **Chloroquine** concentrates in the parasite's food vacuole and blocks detoxification of haem into haemozoin, so free haem poisons the parasite; resistance, spread from two foci to most of the world through the PfCRT efflux transporter, ended its reign against *P. falciparum*. The **artemisinins** (artesunate, artemether) carry an endoperoxide bridge that iron from haem splits into carbon radicals, damaging parasite proteins wholesale; they clear parasites faster than any other class and anchor **artemisinin based combination therapy** (such as artemether lumefantrine), the partner drug guarding against the artemisinin resistance now creeping through Kelch13 mutants in Southeast Asia. Intravenous artesunate is the treatment of severe malaria and has saved more lives than any recent antimalarial decision. **Quinine** remains a reserve parenteral agent, with cinchonism and hypoglycaemia as its costs. **Primaquine** alone kills hypnozoites (the radical cure of vivax and ovale) and gametocytes, but it oxidatively stresses red cells and can haemolyse patients with **glucose 6 phosphate dehydrogenase deficiency**, which must be considered before use. **Antifolate combinations** (sulfadoxine pyrimethamine) block the parasite's folate pathway at two sequential steps; mefloquine, atovaquone proguanil and doxycycline fill prophylaxis and treatment niches. Every one of these assignments follows the life cycle stage, which is the only way the list makes sense.

3.2 Antiprotozoal drugs II: amoebiasis, leishmaniasis and the rest

Metronidazole is the tissue amoebicide of amoebic dysentery and liver abscess: anaerobic and microaerophilic organisms reduce its nitro group to cytotoxic radicals that shred DNA, a trick that also makes it the workhorse against anaerobic bacteria and *Giardia*. Because it is absorbed before reaching the colonic lumen, it must be followed by a **luminal amoebicide** (diloxanide furoate or paromomycin) to clear cysts. Visceral leishmaniasis (kala azar) is treated in India chiefly with **liposomal amphotericin B**, the polyene of Unit 2 redirected against the leishmania amastigote's membrane sterols; the older pentavalent antimonials are neurotoxic and cardiotoxic and largely abandoned here, and **miltefosine**, an oral membrane lipid drug, is teratogenic and losing ground to resistance. African trypanosomiasis uses suramin and melarsoprol (an arsenical whose own encephalopathy is feared), Chagas disease benznidazole and nifurtimox, toxoplasmosis in the immunocompromised pyrimethamine with sulfadiazine, and pneumocystis pneumonia, a fungus by taxonomy but treated here by tradition, co trimoxazole. The pattern is less tidy than the antibacterial field because each parasite is its own pharmacology problem.

3.3 Drugs for helminthiasis

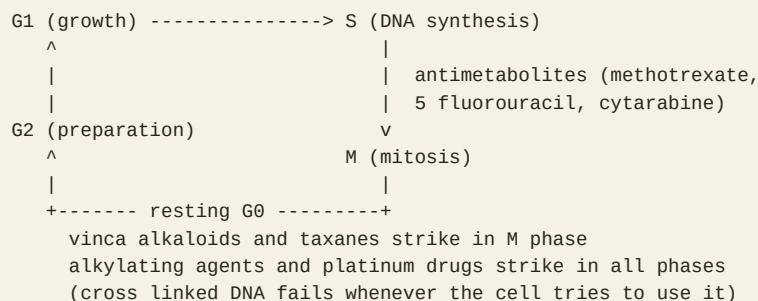
Worms are multicellular animals, and the drugs exploit their neuromuscular and energy machinery, paralysing or starving the worm so the gut expels it. The **benzimidazoles** (**albendazole**, **mebendazole**) bind worm beta tubulin far more avidly than the mammalian form, stopping microtubule assembly and glucose uptake; albendazole, with its active metabolite reaching tissues, is the broad agent for roundworm,

hookworm, whipworm, threadworm and the tissue diseases hydatid cyst and neurocysticercosis, where killing cysts in the brain demands corticosteroid cover against the inflammatory fallout. **Praziquantel** raises calcium permeability of the fluke and schistosome tegument, causing spastic paralysis and surface damage that exposes the worm to immunity; it is the drug of schistosomiasis and tapeworm infections and is remarkably safe. **Ivermectin** opens glutamate gated chloride channels found only in invertebrates, paralysing nematodes and ectoparasites; it transformed onchocerciasis (river blindness) control and treats strongyloidiasis and scabies. **Diethylcarbamazine** immobilises microfilariae of filariasis and alters their surface so the host destroys them, and **pyrantel pamoate** depolarises worm muscle as a nicotinic agonist; niclosamide, a luminal tapeworm agent, uncouples worm oxidative phosphorylation. Local reactions after worm killing (the Mazzotti reaction of onchocerciasis) are immunopathology, not drug toxicity, an important bedside distinction.

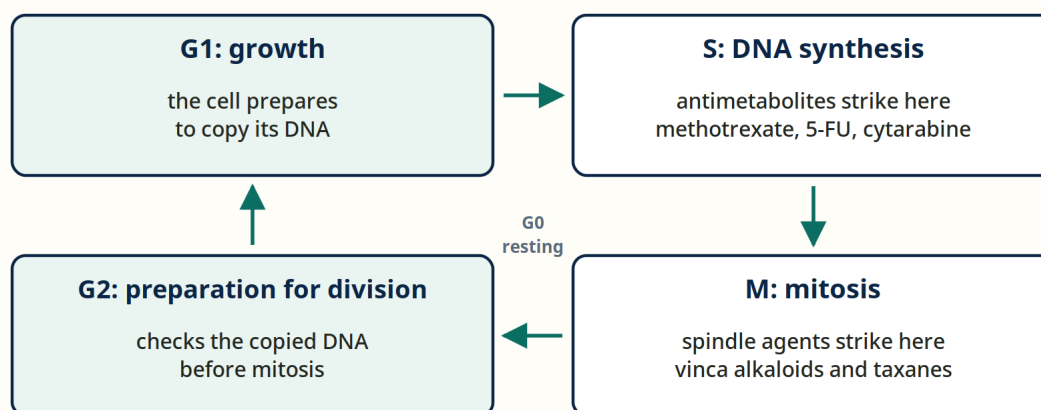
3.4 Chemotherapy of cancer: principles and the cell cycle

Cancer chemotherapy began with nitrogen mustards and remains governed by three ideas. First, **log kill**: a given treatment kills a constant fraction, not a constant number, of tumour cells, so repeated cycles are needed to drive a burden of billions of cells toward zero, and small tumours respond better than large ones. Second, most cytotoxic drugs damage DNA or the machinery of division, so they hurt cells in proportion to how fast they divide; the same logic explains the toxicity pattern, since marrow, gut lining, hair follicles and gonads are the body's own fast dividing tissues (myelosuppression, mucositis, alopecia and infertility are the expected class prices). Third, tumours are genetically unstable populations that evolve resistance (by drug efflux through P glycoprotein, target change, DNA repair and blocked apoptosis), so **combination regimens** of drugs with different mechanisms and non overlapping toxicities are used, exactly the arithmetic of TB therapy in Unit 2.

THE CELL CYCLE AND WHERE THE CYTOTOXIC DRUGS STRIKE



The Cell Cycle and Where Anticancer Drugs Strike



Alkylating agents and platinum drugs are cycle non specific: cross linked DNA fails in every phase.

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Figure: The cell cycle and the phase specificity of the cytotoxic classes. Phase specific drugs work best against tumours with a high growth fraction and in schedules that expose cells as they enter the sensitive phase.

3.5 The anticancer drug classes

Class and examples	Mechanism	Signature toxicities and notes
Alkylating agents: cyclophosphamide, chlorambucil, busulfan	Covalent cross links in DNA; cycle non specific	Cyclophosphamide's metabolite acrolein causes haemorrhagic cystitis, prevented by mesna and hydration
Platinum compounds: cisplatin, carboplatin, oxaliplatin	Intrastrand DNA cross links	Cisplatin: severe emesis, nephrotoxicity, ototoxicity; oxaliplatin: cold triggered neuropathy
Antimetabolites: methotrexate, 5 fluorouracil, cytarabine, mercaptopurine	Fraudulent substrates starving DNA synthesis; S phase specific	Methotrexate is rescued by folinic acid (leucovorin); 5 fluorouracil toxicity explodes in DPD enzyme deficiency
Antitumour antibiotics: doxorubicin, bleomycin, dactinomycin	Intercalation, topoisomerase II trapping, free radical strand breaks	Doxorubicin: cumulative, dose related cardiomyopathy; bleomycin: pulmonary fibrosis, and skin toxicity because skin lacks its inactivating enzyme
Microtubule agents: vincristine, paclitaxel	Vinca alkaloids prevent spindle assembly; taxanes freeze disassembly; both arrest mitosis	Vincristine: peripheral neuropathy, dangerous if given intrathecally; paclitaxel: neuropathy and hypersensitivity
Topoisomerase inhibitors: etoposide, irinotecan	Trap topoisomerase II or I cleavage complexes	Irinotecan: early and late diarrhoea, the late form from its active metabolite in the gut
Hormonal agents: tamoxifen, aromatase inhibitors, androgen deprivation	Block the growth signal of hormone dependent breast and prostate cancers	Tamoxifen is a selective oestrogen receptor modulator, antagonist in breast, agonist in uterus and bone
Targeted small molecules: imatinib and successors	Inhibit the driver kinase, here the BCR ABL fusion of chronic myeloid leukaemia	Imatinib converted CML into a chronic oral therapy; resistance by kinase mutation (T315I) drove later generations

Class and examples	Mechanism	Signature toxicities and notes
Monoclonal antibodies: trastuzumab, rituximab	Bind HER2 or CD20 and recruit immune killing as well as signal blockade	Trastuzumab cardiotoxicity, watched by echocardiography
Immune checkpoint inhibitors: pembrolizumab, nivolumab	Block PD-1 or PD-L1, releasing T cells from tumour induced braking	Immune related adverse events in any organ: colitis, pneumonitis, endocrinopathies

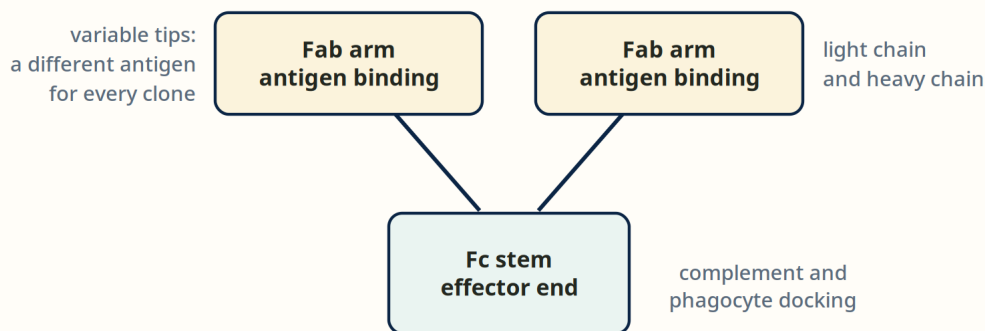
3.6 Immunopharmacology: the cells and mediators of inflammation and immune response

The immune system defends with an innate arm (immediate, pattern based) and an adaptive arm (slow, specific, with memory), and inflammation is the visible form of both at work in tissue. The **cellular players**: neutrophils that phagocytose and degranulate, macrophages that phagocytose, present antigen and secrete cytokines, mast cells and basophils carrying IgE and preformed histamine, eosinophils of allergy and helminth defence, and the lymphocytes, T cells (helper, cytotoxic and regulatory) commanding, B cells becoming antibody factories, and natural killer cells surveying for missing self.

The **biochemical mediators** are the pharmacology, since most are drug targets or drug mimics:

Mediator family	Source and signal	Pharmacological handles
Histamine	Mast cells and basophils; H1 and H2 receptors (Unit 5 of Semester 1)	Antihistamines, H2 blockers
Eicosanoids	Arachidonic acid through COX and lipoxygenase (Semester 1)	NSAIDs, corticosteroids upstream, montelukast
Cytokines: TNF alpha, interleukins 1, 6, 17, interferons	Macrophages and T cells; protein signals between immune cells	Monoclonal antibodies against TNF (infliximab, adalimumab), IL-6 receptor (tocilizumab), IL-17; JAK inhibitors inside the cell
Complement	Plasma cascade, C3a and C5a anaphylatoxins, membrane attack complex	Eculizumab blocks C5
Bradykinin and nitric oxide	Plasma kallikrein system; endothelium and macrophages	Icatibant; corticosteroids suppress iNOS induction
Platelet activating factor and chemokines	Membranes; many cell types; direct cell traffic	Fewer direct drugs, but they explain recruitment patterns

The Antibody (Immunoglobulin) Molecule



Five classes: IgG, IgM, IgA, IgE and IgD, divided by the heavy chain of the Fc stem.

Therapeutic monoclonals (trastuzumab, rituximab) are engineered IgG versions of this molecule.

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Figure: The antibody molecule. The variable tips bind antigen, the constant Fc stem decides what the immune system does next, and therapeutic monoclonal antibodies are engineered versions of this molecule.

3.7 Allergic and hypersensitivity reactions

The Gell and Coombs classification sorts immune injury into four mechanisms, and drug allergy distributes across all four:

Type	Mechanism	Time course	Drug examples
I, immediate	IgE on mast cells cross linked by antigen; histamine and leukotriene release	Minutes	Penicillin anaphylaxis, urticaria, angioedema
II, cytotoxic	IgG or IgM against cell surface antigens; complement and phagocyte destruction	Hours to days	Drug induced haemolytic anaemia (methyldopa, penicillin hapten type), immune thrombocytopenia (quinine, heparin HIT in its own category)
III, immune complex	Antigen antibody complexes deposit in vessels and tissues, complement inflammation	Days to weeks	Serum sickness (antitoxins, some monoclonals), drug induced vasculitis
IV, delayed	T cell mediated, no antibody; macrophages and cytotoxic T cells	48 to 72 hours and beyond	Contact dermatitis (topical agents), Stevens Johnson syndrome and toxic epidermal necrolysis (allopurinol, carbamazepine, lamotrigine), DRESS

Management repeats one rule: stop the drug, because no antidote outruns continued exposure; anaphylaxis is treated with intramuscular adrenaline first (antihistamines and steroids are supporting acts), and Stevens Johnson syndrome is a burns unit emergency. Cross reactivity questions (penicillin and cephalosporin, sulfonamide antibiotic and non antibiotic sulfonamides) are decided by side chain and structure, not by the word sulphur, a precision examiners test.

Hypersensitivity Reactions: The Gell and Coombs Types

Type	Mechanism	Onset	Drug example
Type I	IgE on mast cells	minutes	penicillin anaphylaxis
Type II	IgG or IgM vs cell surface	hours to days	drug haemolytic anaemia
Type III	immune complexes deposit	days to weeks	serum sickness
Type IV	T cell mediated	delayed, 48 h plus	Stevens Johnson syndrome

The mechanism decides the timing, and the timing is the first diagnostic clue.

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Figure: The four hypersensitivity types. The mechanism decides the timing, and the timing is the first diagnostic clue at the bedside.

3.8 Pharmacotherapy of asthma

Asthma is chronic airway inflammation with reversible bronchoconstriction and hyperresponsiveness; the mediators of section 3.6 (histamine, leukotrienes, eosinophilic cytokines) are its machinery, and treatment divides into **controllers** (daily anti inflammatory therapy) and **relievers** (as needed bronchodilators).

Inhaled corticosteroids (beclomethasone, budesonide, fluticasone) are the foundation: genomic suppression of airway inflammation, with local adverse effects (oral candidiasis, dysphonia) minimised by spacers and mouth rinsing, and systemic effects small at ordinary inhaled doses. **Long acting beta2 agonists** (salmeterol, formoterol) relax airway smooth muscle for twelve hours and are never used alone in asthma, only with an inhaled steroid, because bronchodilation without inflammation control masks deterioration; formoterol's fast onset lets a steroid formoterol inhaler serve as reliever too, the modern single inhaler strategy. **Short acting beta2 agonists** (salbutamol) remain the universal reliever, by inhaler or nebuliser. **Leukotriene receptor antagonists** (montelukast) suit allergic and aspirin sensitive asthma and exercise induced symptoms. **Theophylline**, a narrow index phosphodiesterase inhibitor and adenosine antagonist, survives as an add on where resources or responses dictate, with level monitoring. For severe allergic and eosinophilic asthma, biologics aim at single mediators: **omalizumab** (anti IgE), **mepolizumab** and **benralizumab** (anti IL-5 pathway), and **dupilumab** (anti IL-4 and IL-13 signalling). Acute severe asthma is oxygen, nebulised salbutamol with ipratropium, systemic corticosteroids and intravenous magnesium sulfate, in that order of urgency.

3.9 Pharmacotherapy of COPD

Chronic obstructive pulmonary disease is progressive, largely smoking driven airflow obstruction with less reversibility and a different inflammatory flavour (neutrophils and macrophages more than eosinophils), so the pharmacotherapy leans on bronchodilation. **Long acting muscarinic antagonists** (tiotropium) and **long acting beta2 agonists** are the maintenance core, singly or combined; **inhaled corticosteroids** are added only for patients with frequent exacerbations and higher blood eosinophils, because in COPD they raise pneumonia risk without the broad benefit seen in asthma. **Roflumilast**, an oral phosphodiesterase 4 inhibitor, helps the chronic bronchitis phenotype with exacerbations, at the cost of weight loss and GI effects. Smoking cessation, vaccination, pulmonary rehabilitation and long term oxygen in chronic

hypoxaemia change survival more than any inhaler. Exacerbations are treated with short acting bronchodilators, a short systemic steroid course, antibiotics when infection is likely, and controlled oxygen with ventilatory support when needed.

3.10 Immunosuppressants

Transplantation and autoimmune disease require deliberate weakening of immunity, and each class suppresses a different step of T cell activation. **Calcineurin inhibitors** (ciclosporin, tacrolimus) block the phosphatase calcineurin, so the transcription factor NFAT never switches on interleukin 2 production and T cell clonal expansion stalls at its start; both are nephrotoxic, level monitored, CYP3A4 substrates with dense interaction lists, tacrolimus being more potent and more diabetogenic. **Antiproliferatives**: azathioprine, a purine antimetabolite (its breakdown by TPMT decides toxicity, and allopurinol dangerously blocks one of its exits), and **mycophenolate**, which blocks the de novo purine synthesis lymphocytes depend on and is kinder to kidneys. **mTOR inhibitors** (sirolimus, everolimus) block the response to interleukin 2 downstream, trading nephrotoxicity for impaired wound healing and mouth ulcers.

Glucocorticoids (Unit 1) remain the broad background suppressant. The **biologics** aim precisely: basiliximab against the IL-2 receptor for induction, antithymocyte globulin to deplete T cells, rituximab against B cells, abatacept blocking costimulation, and the anti TNF agents of section 3.6 in autoimmune disease. The universal costs are infection (including reactivated TB and hepatitis B, screened for before starting) and a raised long term malignancy risk: immunosuppression is a subscription, not a cure.

3.11 Immunostimulants

The opposite prescription is rarer and more specific. **Levamisole**, an old anthelmintic, restores depressed T cell and phagocyte function and survives in some steroid dependent nephrotic syndrome and adjuvant settings. **BCG**, the live tuberculosis vaccine strain, instilled into the bladder provokes a local immune attack that remains standard therapy for superficial bladder cancer, immunotherapy's first success. The **interferons** defend against viruses and modulate immunity (interferon beta in multiple sclerosis). **Colony stimulating factors** (filgrastim, G-CSF; sargramostim, GM-CSF) rebuild the neutrophil count after chemotherapy, converting section 3.4's dose limiting toxicity into a manageable one. **Thymic peptides, inosine derivatives and microbial preparations** occupy weaker evidence ground, and **intravenous immunoglobulin**, though listed with stimulants in some texts, works mainly as replacement and as an immunomodulator in autoimmune cytopenias and Kawasaki disease. Recombinant interleukin 2 (aldesleukin) can cure a small fraction of metastatic melanoma and renal cancer at the price of capillary leak, the sharpest demonstration that stimulating immunity is not gentler than suppressing it.

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