CHEMOTHERAPY

ANTIVIRALS

Gamma Globulin	Initial attachment	Antibodies against viral proteins to 'neutralise' the binding of the virus to its host receptor
Zintevir	Initial attachment	Polyanionic compounds that discourage receptor binding of HIV gp120 to CD4.
AMD 3100	Initial attachment	Antagonist of CXCR4 chemokine coreceptor of HIV (need to be sure normal function of receptor isn't damaged; advantage is as well as antagonising, continuous binding leads to a downregulation of receptors)
TAK 779	Initial attachment	Antagonist of CCR5 chemokine coreceptor of HIV. As above.
Amantadine and rimantadine	Viral penetration	Influenza **A** (not B) M_2 channel responsible for acidification of endosome, required for viral fusion. Drugs block this channel. May have a role in viral release also.
Enfuvirtide	Viral penetration	HIV fusion process requires hairpin formation. Pre-hairpin complex is a high energy transient state, resolved by protein flipping. Drug binds to this complex and prevents hairpin formation
Interferon	Protein Translation	Activates RNAase as well as interfering with initiation and elongation factors. Expensive with side effects such as fever. Used successfully in Hep B
Acyclovir	Nucleic acid synthesis	Nucleoside analogue, activation and incorporation relies on viral enzymes so specific. **No 3' OH** so chain terminating (DNA polymerase)
Azidothymidine	Nucleic acid synthesis	Nucleoside analogue, activation relies on cellular kinases. Much higher affinity for reverse transcriptase; but lower specificity and sometimes used in cancer. Chain terminating (reverse transcriptase)
Tenofovir	Nucleic acid synthesis	Acyclic nucleoside phosphonate. No need for kinases. Advantage because thought that kinases may mutate to not recognise nucleoside analogues – therefore resistance.
Nevirapine	Nucleic acid synthesis	Non nucleoside reverse transcriptase inhibitor. Non competitive binding to hydrophobic pocket near catalytic active site = denatured. But HIV mutates – rapid drug resistance.
Zintevir		Inhibits integrase activity. Thus preventing proviral integration into host chromosome. This only occurs in isolated enzyme ?
Saquinavir ritonavir	Final processing	Polyprotein translation, e.g. HIV, requires virus specific protease to cleave. Drugs are protease inhibitors which prevent this cleavage and thus final viral processing.

ANTIBACTERIAL AGENTS

Cell membrane

Polymixins	Cytomplasmic membrane	Cyclic peptides with detergent properties disrupting membrane of preferentially **Gram –** organisms.
Nigercin	Cytoplasmic membrane	Ionophore antibiotic disrupting membrane function
Daptomycin	Cytoplasmic membrane	Lipopeptide disrupting membrane of preferentially **Gram +** organisms because unable to cross G- outer membrane.
Amphotericin B	**Fungal** cytoplasmic membrane	Binds preferentially to ERGOSTEROL facilitating pore formation. Affinity for mammalian membranes thus administered in liposomes.
Nyastatin	**Fungal** cytoplasmic membrane	*Pore formation* in fungal membrane.
Fluconazole	**Fungal** cytoplasmic membrane	Imidazole inhibiting an enzyme involved in ergosterol synthesis. Thus alters fluidity of membrane and thus interfering with membrane associated functions. NOTE contraindicated with amphotericin B because having antagonistic effects (amphotericin B requires ergosterol)

Cell Wall

Fosfomycin	Bacterial cell wall synthesis	Inhibits NAG rearrangement to NAMA
Cycloserine	Bacterial cell wall synthesis	Inhibits isomerisation of L-ala to D-ala and therefore correct peptide of NAMA
Bacitracin	Bacterial cell wall synthesis	Inhibits dephosphorylation of lipid membrane carrier (too large to cross G- outer membrane thus only **G+**)
Vancomycin	Bacterial cell wall synthesis	Inhibits transglycosylation by interfering with D-ala-D-ala by steric hindrance thus blocking cross linking. Also too large to cross G- outer membrane So **G+** action. It prevents release of the building block unit from the carrier.
Penicillin	Bacterial cell wall synthesis	B lactam (4 membered cyclic amide ring structure – acyl D-ala-D-ala analogue that irreversibly inactivates transpeptidation enzyme (PBP) upon cleavage. Then inactivates an inhibitor of autolytic enzymes of the cell wall inducing lysis) but sensitive to lactamases.
Methicillin	Bacterial cell wall synthesis	β-lactam – resistant to lactamase but large side group so cannot enter G- outer membrane. **G+** specific

Ampicillin	Bacterial cell wall synthesis	β-lactam – broad spectrum but reduced lactamase resistance.
Cephalosporins	Bacterial cell wall synthesis	β-lactam
Monobactams	Bacterial cell wall synthesis	MONOcyclic BACterial β-lacTAM
Carbapenems	Bacterial cell wall synthesis	Broad spectrum β-lactam
Clavulanic acid	Bacterial cell wall synthesis	Acetylates, thus inhibiting β-lactamases. Used in conjunction with amoxicillin as Augmentin

Protein synthesis

Mupirocin	Protein synthesis	Mimics iso-leucine thus competitively inhibiting iso-leucyl tRNA synthetase (interfering with formation of aminoacyl tRNA)
Tetracyclines	Protein synthesis	Bind to 30S subunit distorting codons interfering with codon recognition so preventing tRNA interaction. Selectively toxic to bacteria (30S)
Aminoglycosides – Gentamycin, Neomycin, Streptomycin	Protein synthesis	Bind to the 30S subunit inhibiting initiation and/or translocation. Highly **polar** so no GI absorption (used for G- enteric organisms) must be given im or iv. May have ototoxicity and nephrotoxicity. Require an oxygen dependent active transport uptake mechanism thus minimal action on anaerobic organisms. (Streptomycin is bactericidal – may distort codons resulting in anomalous protein formation that may be able to damage the cell)
Chloramphenicol	Protein synthesis	Binds to the 50S subunit and prevents the peptidyl transferase reaction. **Reversible** so must maintain concentration
Fusidic acid	Protein synthesis	Forms stable complex with ribosome, preventing further rounds of peptide transfer.
Macrolides – erythromycin clarithromycin	Protein synthesis	Bind to 50S subunit and interrupt completion of peptide possibly be inducing dissociation of peptidyl tRNA during elongation
Puromycin	Protein synthesis	Structural analogue of aminoacyl part of tRNA terminating chain elongation. NO specificity thus only experimental use.

THF Synthetic pathway

Sulphonamides – sulphamethoxazole	THF synthetic pathway	Are structural analogues of p aminobenzoic acid required for folic acid synthesis in bacteria. Act as alternative substrates for dihydropteroate synthetase
Diamino pyrimidines –	THF synthetic	Competitively inhibits DHFR – 80,000 x more active against bacterial isoforms

trimethoprim	pathway	
Co trimoxazole	THF synthetic pathway	Trimethoprim and sulphamethoxazole given in combination to inhibit both points of pathway simulataneously – acting synergistically.

Nucleic acid

Rifampicins	Nucleic acid	Inhibits DNA dependent RNA polymerase in prokaryotic cells. It can enter phagocytic cells and act on intracellular organisms
Quinolones	Nucleic acid	Binds and inactivates DNA gyrase, analogous to topoisomerase II thus responsible for unwinding to allow for transcription. Such inactivation can bring about strand breaks.

Antitubercular

Rifampicin	Anti-tubercular	Inhibits DNA dependent RNA polymerase in prokaryotic cells. It can enter phagocytic cells and act on intracellular organisms. One of the most active antitubercular agents known
Cycloserine	Anti-tubercular	Inhibits isomerisation of L-ala to D-ala and therefore correct peptide of NAMA (L-ala isomerase)
Pyrazinamide	Anti-tubercular	Inactive at neutral pH but tuberculostatic at acid pH. It is effective against the intracellular organisms in macrophages, since after phagocytosis, some are contained within a phagolysozome in which pH is low
Isoniazid	Anti-tubercular	Inactive prodrug, converted to isonicotinic acid. Interaction with molecules leads to inhibition of mycolic acid synthesis increasing porosity of cell membrane/wall. But also leads to production of damaging free radicals. M t sensitive because of low levels of protective systems. However up regulation of them leads to resistance.

ANTIPLASMODIAL

Sulphonamides – sulphadoxine	THF synthetic pathway	Are structural analogues of p aminobenzoic acid required for folic acid synthesis in bacteria. Act as alternative substrates for dihydropteroate synthetase
Diamino pyrimidines – pyrimethamine	THF synthetic pathway	Competitively inhibits DHFR – more active against plasmodial isoforms
Fansidar	THF synthetic pathway	Sulphadoxine and pyrimethamine combination. (c.f. co timoxazole)
Proguanyl	THF synthetic	Prodrug metabolised to cycloguanine also

	pathway	plasmodial isoforms of DHFR inhibitor.
Chloroquine	Haemoglobin digestion	Schizonticidal of all 4 species. No action on extraerythrocytic stages. Uncharged at neutral pH so cross membranes easily - act on intracellular organisms. Upon entry into a plasmodial acidic food vacuole, protonation occurs. Thus allowing drug concentration. Inhibits haem polymerase which polymerises toxic haem to non toxic haemozoin. Haem causes lysis and leakiness of membranes resulting in depleted source of nutrients – especially amino acids required for plasmodium viability (normally acquired from Hb digestion). Many strains are now resistant due to expression of human mdr transporter p-glycoprotein.
Mefloquine quinine	Haemoglobin digestion	Resistance has lead to their use. Schizonticidal of all 4 species. No action on extraerythrocytic stages. Mechanism associated with haem polymerase inhibition, but because concentration as with chloroquine does not occur, other mechanisms could be involved. Often combined with pyrimethanine
Artemesinin	Schizonticidal	Rapidly acting schizonticide, used in emergencies (suppository). Short half life. Derived from herb so low cost and plentiful supply. Interacts with the haem that is released during digestion catalysing the opening of peroxide bridges and generating free radicals which are damaging to the parasite. Often combined with mefloquine.

ANTICANCER AGENTS

Hormone Therapy

Prednisone (glucocorticoid)	Hormone therapy where hormones directly inhibit growth	Used because of its lymphocytolytic effect (by inducing proteins involved in apoptosis) against leukaemias. Normally in combination
Oestrogens	Hormone therapy where hormones directly inhibit growth	Used in postmenopausal women for breast cancer
Progestagens	Hormone therapy where hormones directly inhibit growth	Used against endometrial tumours

Oestrogens	Hormone therapy where hormones facilitate growth	Used to produce a negative feedback effect on GnRH and LH to inhibit testosterone release which promotes prostate growth
Leuprolide	Hormone therapy where hormones facilitate growth	LHRH **agonist** – slow dissociation so promotes receptor internalisation thus reducing testosterone
Flutamide	Hormone therapy where hormones facilitate growth	Androgen receptor antagonist used against prostate cancer
Tamoxifen	Hormone therapy where hormones facilitate growth	Oestrogen receptor antagonist – BUT conformational change induced preserves coactivator 1 binding site thus anti-osteoporotic effects.
Anastrozole	Hormone therapy where hormones facilitate growth	Aromatase inhibitor reduces plasma oestrogen levels, but although more potent does have osteoporotic effects.

Anitimetabolites

Methotrexate	Antimetabolite	Human isoforms specific DHFR inhibitor
Leucovorin	Antimetabolite	Salvages normal tissues from folate depletion because can be metabolised to THF derivatives
Flurouracil	Antimetabolite	Pyrimidine antagonist. Converted to fdUMP which interacts with thymidylate synthetase but cannot be converted to dTMP thus inhibits DNA (not RNA) synthesis
Mercaptopurine	Antimetabolite	Purine antagonist. Converted to 'fraudulent' nucleotide, as above, inhibiting DNA synthesis
Cytarabine (pyrimidine) Fludarabine (purine)	Antimetabolite	Sugar modified nucleoside analogues. Phosphorylated to become active metabolites (arabinoside triphosphates) and incorporated into DNA – chain terminating thus inhibiting DNA pol.

Topoisomerase inhibitors

Etoposide	Topoisomerase inhibitor	Inhibitor of Topo II (replication) Stabilises cleavable complex and inhibits the religation step.
Anthracyclines Dauno/Doxo – rubicin	Topoisomerase inhibitor	Inhibitor of Topo II (replication) Stabilises cleavable complex and inhibits the religation step.
Camptothecins	Topoisomerase inhibitor	Inhibitor of Topo I (transcription) Stabilises cleavable complex and inhibits the religation step.

Covalent Interaction with DNA

Cyclophosphamide	Covalent DNA interactions Note with all such molecules, these interactions are mutagenic and carcinogenic so increase chance of second tumour with long term use. E.g. alkylated G is read by as a T thus resulting in point mutations in nucleic acid derived from parental strand.	Nitrogen mustard (bifunctional alkylators). Prodrug, following hepatic oxidation P_{450}, (aldophosphamide) taken up by tumour cells and transformed by a non enzymatic path to the active cytotoxic mustard (phosphoramide mustard). (aldehyde dehydrogenase is involved with an enzymatic pathway that converts the compound into a non cytotoxic metabolite hence why liver is protected and no effect on GI tumours) Mechanism of action involves cyclisation of chloroethyl chain, yielding Cl^-. The reactive intermediate reacts with N7 of guanine in DNA covalently. Then the second chain repeats allowing intrastrand crosslinking. Such interactions impede DNA replication and transcription resulting in DNA damage such as strand breaks which results in triggering apoptosis.
Melphalan	Covalent DNA interactions	(phenyl alanine) Nitrogen mustard.
Mitomycin	Covalent DNA interactions	An **aziridine**. Functions as a bifunctional alkylating agent. Requires enzymatic bioreductive activation (favoured by hypoxic conditions) consequently containing moieties that are reactive with nucleophilic groups on DNA, alkylating (preferentially O6 of guanine) crosslinking the DNA. Such hypoxic conditions are found in tumours.
Carmustine	Covalent DNA interactions	Nitrosurea – alkylating agent binding preferentially to O6 position on guanine. Lipophilic enough to cross **BBB** and is one of the few compounds that can be used to target CNS tumours
Cisplatin	Covalent DNA interactions	Planar coordination complex involving a central platinum molecule and two chlorine atoms and 2 ammonia groups. Cis isomer active. Upon cell entry, Cl^- dissociates leaving reactive intermediate that can interact with DNA causing intrastrand crosslinking probably between N7 and O6 of adjacent guanines – causing local denaturation.

DNA Intercalator

Anthracyclines – Doxorubicin, Daunorubicin	DNA Intercalator	*Linear 3 aromatic ring structure* intercalates into DNA non specifically leading to local uncoiling of helix. Acts to stabilise the opoisomerase – DNA complex once DNA nicked, effectively inhibiting Topo II and thus DNA replication. BUT compounds have a hydroxyl-quinone moiety that when oxidised posseses an O_2^- moiety that can interact with Fe(III) to lead to OH· formation. This can lead to a lipid peroxidation chain propagated reaction. (this is not necessarily part of antitumour effect) This can occur in cardiac tissue and lead to cardiotoxicity (encapsulation within liposomes may reduce this effect)
Mitoxantrone	DNA Intercalator	Anthracycline *analogue* lacking quinine moiety and thus free radical generation. Thus avoiding cardiotoxicity.
Actinomycin D	DNA intercalator	Base specific intercalation. Requires two adjacent guanine moieties.

Antimitotic

Vinblastine Vincristine	Antimitotic agents	*Vinca alkaloids*. Bind to tubulin and inhibit polymerisation, which prevents spindle formation in mitosing cells and thus arrests in metaphase. (Also inhibit other cellular activities dependent on microtubules such as leucocyte phagocytosis + chemotaxis; and axonal transport.)
Taxol	Antimitotic agent	Derived from Yew bark and needles. Same mechanism as above

Antiemetic

Ondansetron	$5HT_3$ antagonist	Used as an anti emetic due to such effects from many of the agents above.

Herceptin	Growth factor targeting	Humanised MAb to EGF receptor. Used in combination with taxol for advanced breast cancer
Gleevec	Growth factor targeting	Prevents activation of selectively Abl PDGF receptor kinases. Used successfully in CML
Iressa	Growth factor targeting	Inhibits autophosphorylation of tyrosine kinase receptors, thus blocking downstream pathways.
Batimastat	Invasion +	Matrix metalloproteinase inhibitor to

Marimastat	metastasis	reduce degradation of ECM that allows for such invasion.
Endostatin	Angiogenesis	Direct inhibitor – targets endothelial cells, inhibiting proliferative response to the angiogenic factors
Iressa	Angiogenesis	Indirect inhibitor – target synthesis by tumour cells of angiogenic factors or *their receptors on the endothelial cell.*