Pharmacology of Chemotherapy

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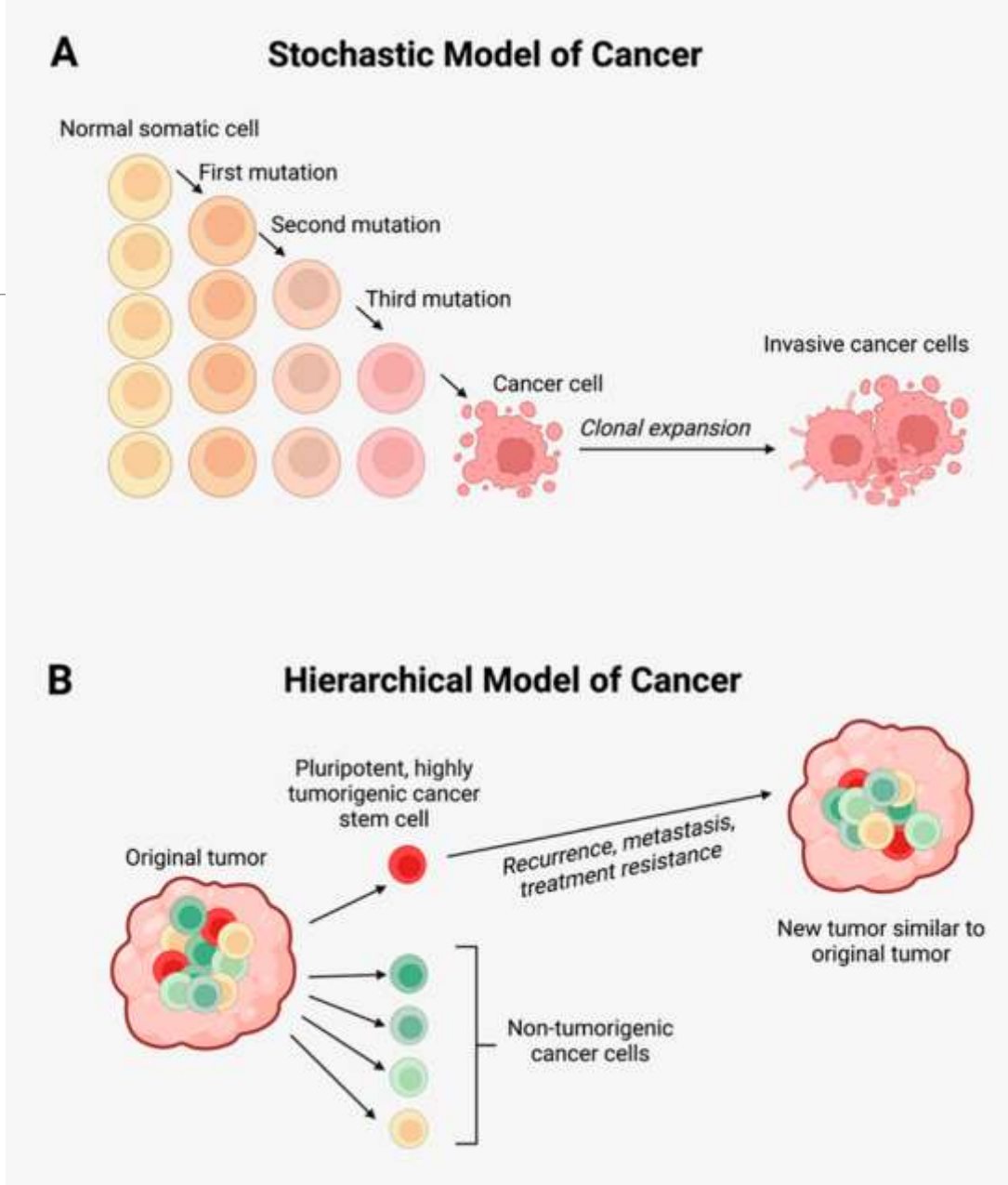
Learning objectives

1. Explain the role of chemotherapy in the treatment of cancer
2. Explain the importance of DNA as a target for cancer chemotherapy
3. Describe the mechanism of action and basis for selective toxicity of various cytotoxic drugs
   - Alkylating agents
   - Antimetabolites
   - Topoisomerase inhibitors
   - Tubulin inhibitors
   - Antitumour antibiotics
4. Explain the limitations associated with cytotoxic drug therapy

What is cancer?

- A group of diseases that arise from heritable changes in the genetic material of somatic cells
- Characterised by uncontrolled growth with local tissue invasion and/or systemic metastases



Approaches to cancer treatment

- Surgery
- Radiotherapy

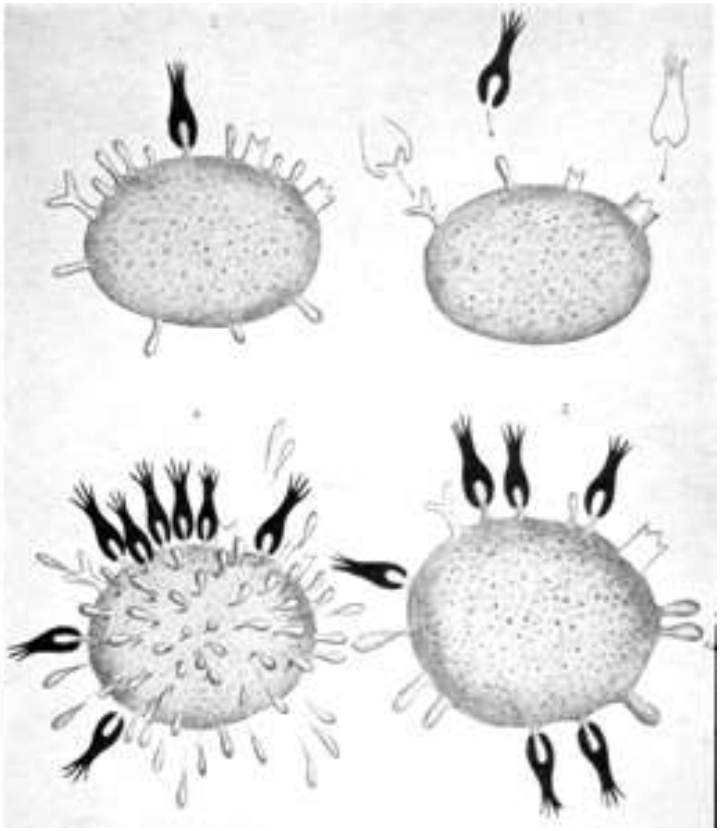
} Local disease

- Chemotherapy
- Hormone therapy
- Targeted therapy
- Immunotherapy

} Systemic disease

Cancer Chemotherapy

- The use of drugs to achieve the selective killing of cancer cells



Clinical Applications of Chemotherapy

- Primary systemic treatment
  - For advanced or disseminated disease
- Neoadjuvant treatment
  - Prior to surgery to achieve debulking of locally advanced tumours
- Adjuvant treatment
  - Following surgery / radiotherapy to reduce risk of disease recurrence
- Combined with radiotherapy
  - To achieve radio-sensitisation
- Regional therapy
  - To achieve higher local concentrations of drug in a specific region

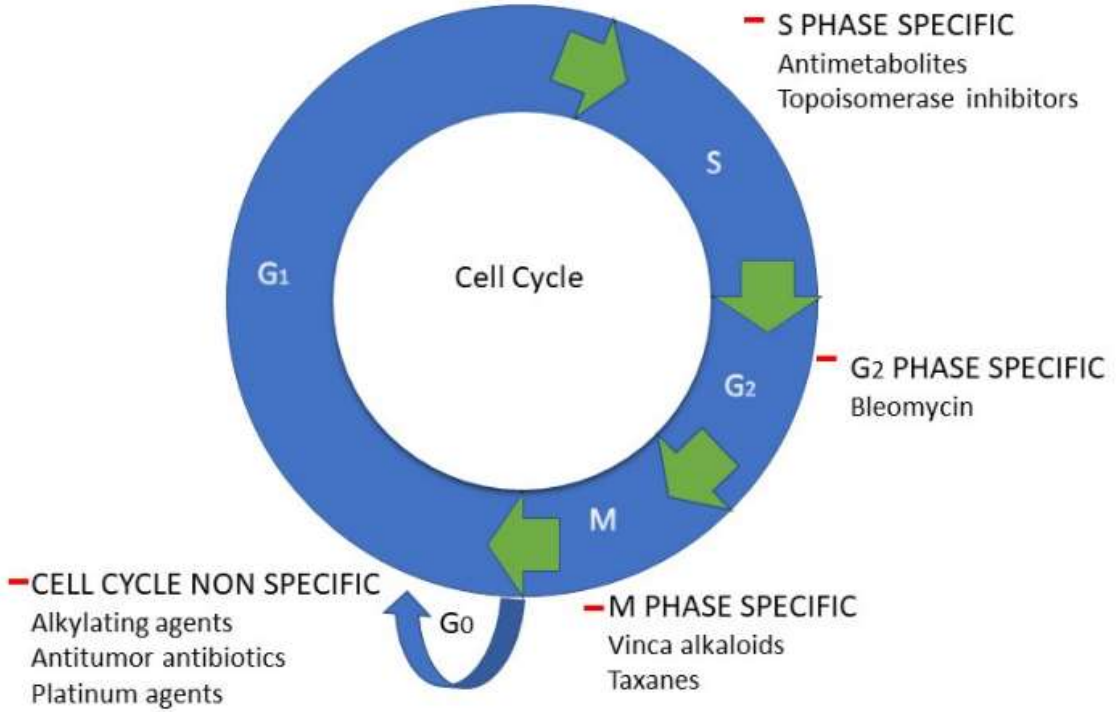
Goals of Chemotherapy

- Cure the cancer (curative intent)
  - Aiming to destroy the cancer completely so it doesn't come back
- Control cancer growth
  - Slow down growth or shrink the tumour
- To ease symptoms (palliative intent)
  - To improve comfort and quality of life

Cytotoxic Drug Therapy

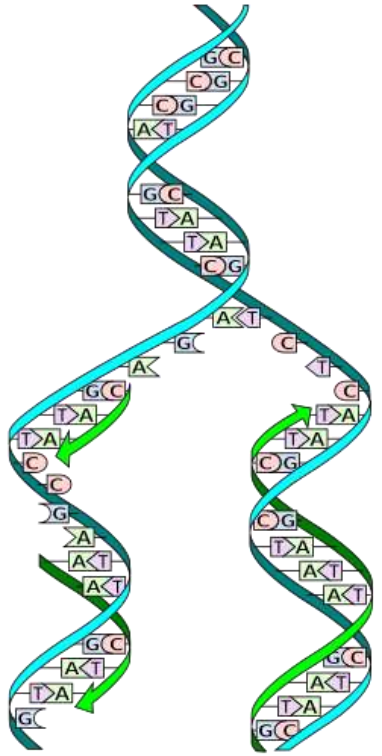
- Most conventional chemotherapy drugs do not kill cells directly, but interrupt processes involved in cell division, and therefore inhibit cell proliferation

- Drugs may be toxic to tumour cells, as well as normal/healthy cells and are therefore described as cytotoxic drugs



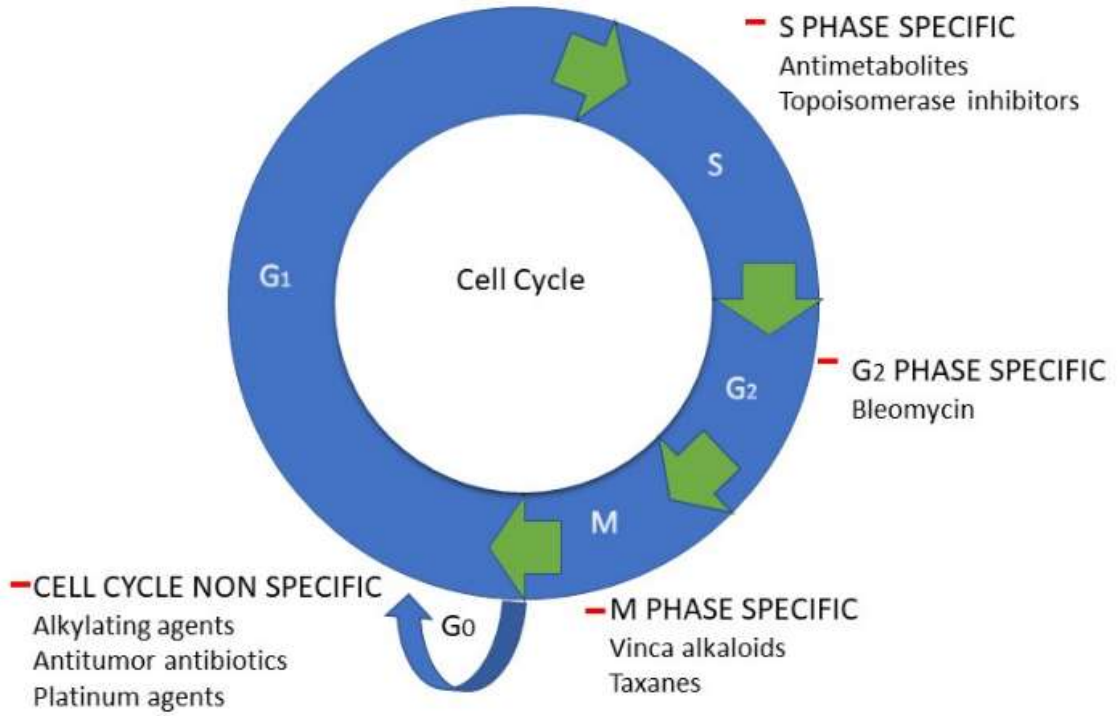
DNA as Target for Cytotoxic Drug Therapy

- Most cytotoxic drugs achieve their cell killing effects by acting directly or indirectly to induce damage to DNA
- High doses of cytotoxic drugs may cause sufficient damage to induce cell lysis
- Lower doses may induce apoptosis in response to DNA damage



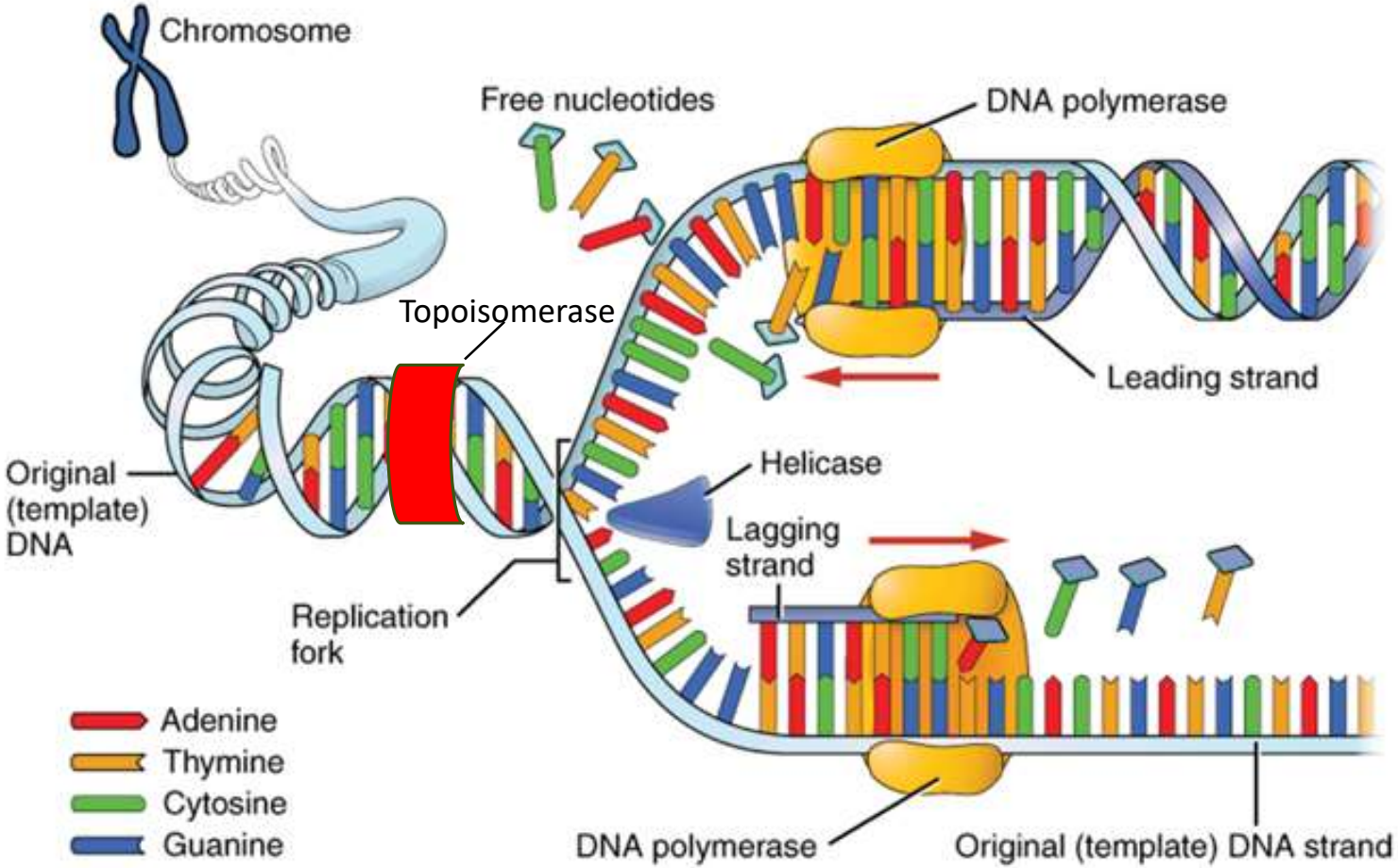
Cell Replication Cycle

- Interphase
  - G1 phase
    - Growth
  - S phase
    - DNA synthesis
  - G2 phase
    - Growth and preparation
- M phase
  - Mitosis and cell division



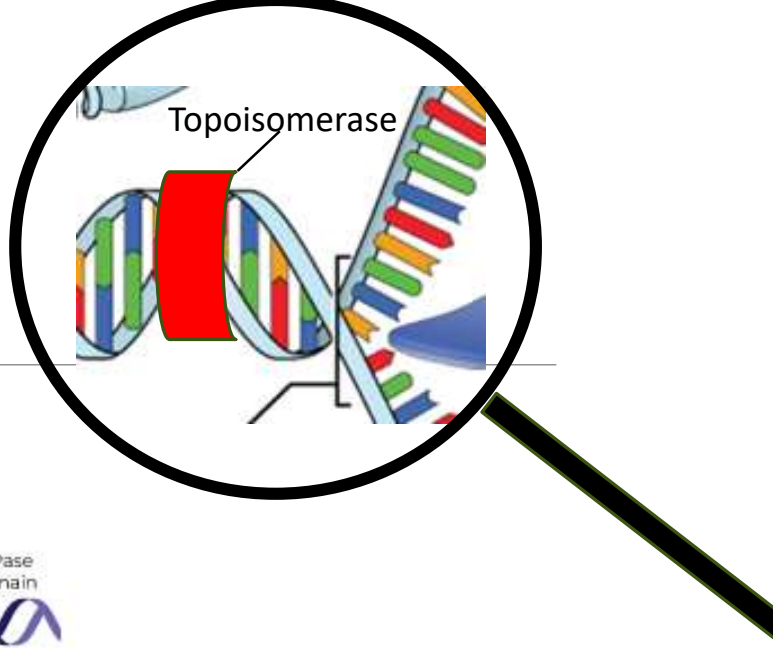
S Phase

- DNA Replication

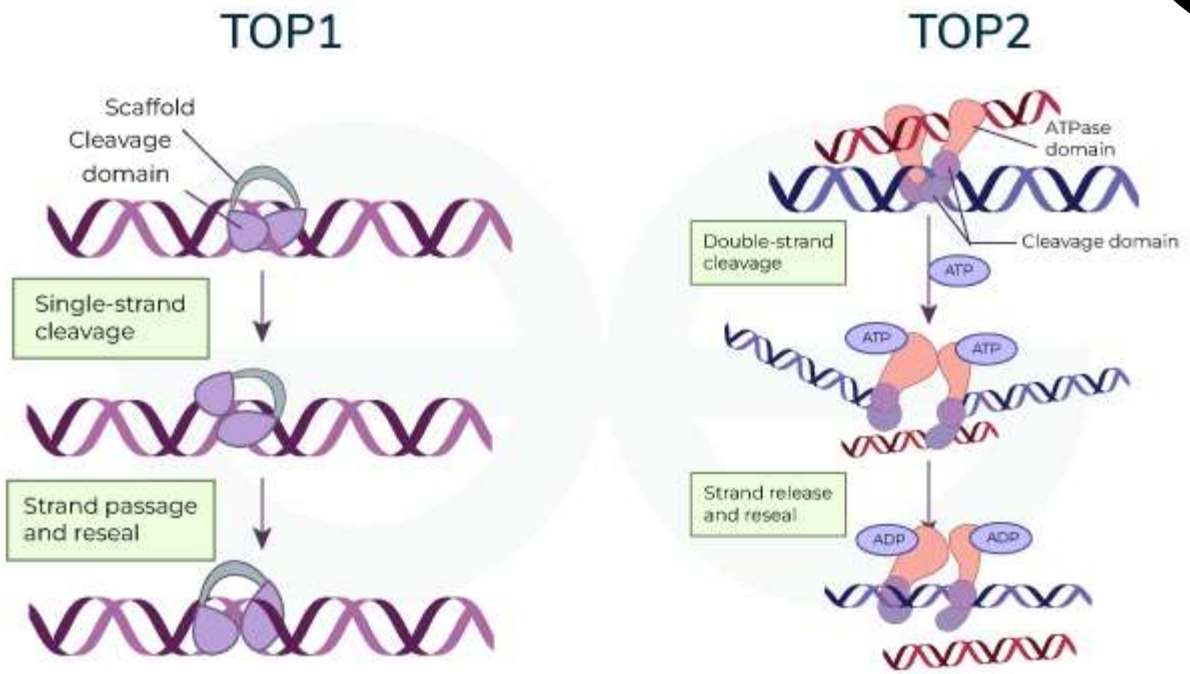


S Phase

- Topoisomerase



Topoisomerase I
- Cleaves ONE strand of DNA

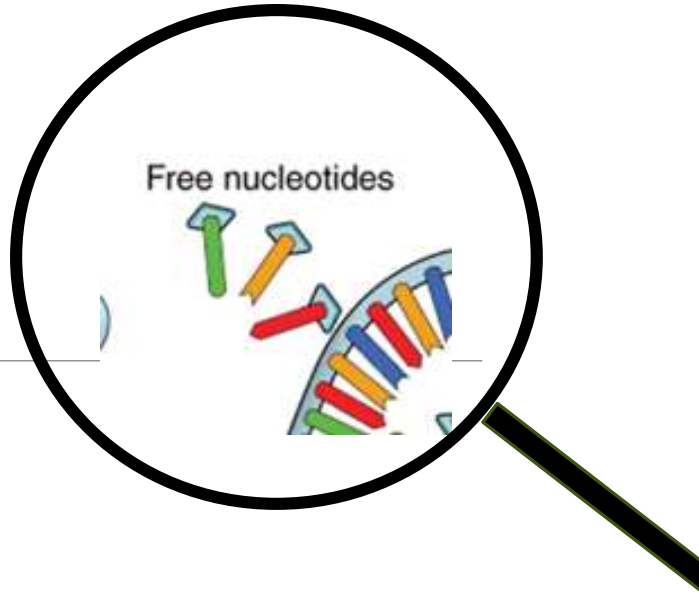


Topoisomerase II
- Cleaves TWO strands of DNA

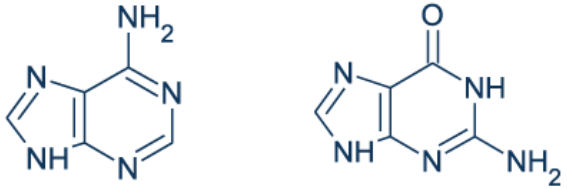
Cut the DNA backbone → allows DNA to unwind → DNA backbone is resealed

S Phase

- Nucleotide synthesis



Purines

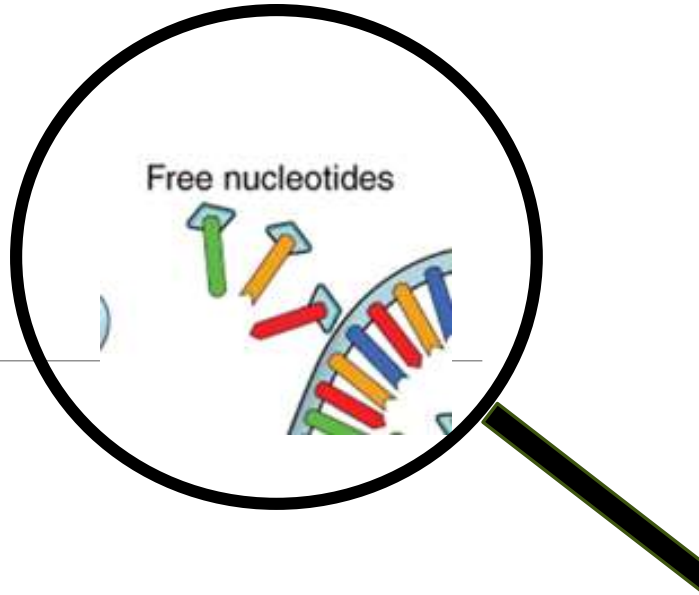


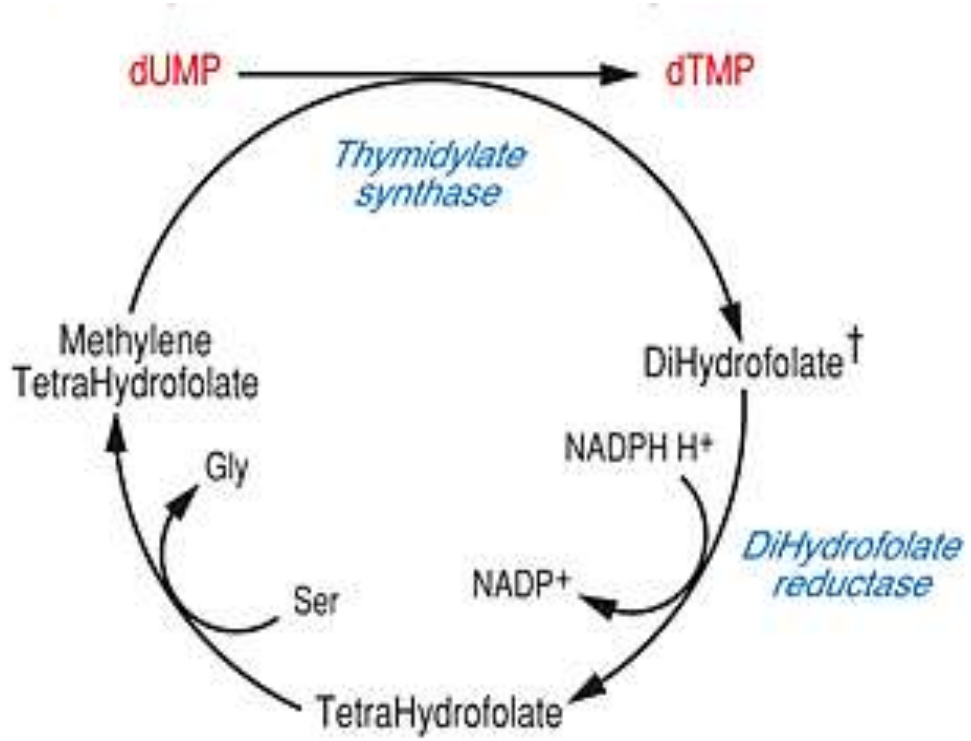
Pyrimidines

- Building blocks of DNA/RNA
- Hydrogen bonds form between complimentary base pairs
- Stabilises the double helix structure of DNA

S Phase

- Thymine synthesis

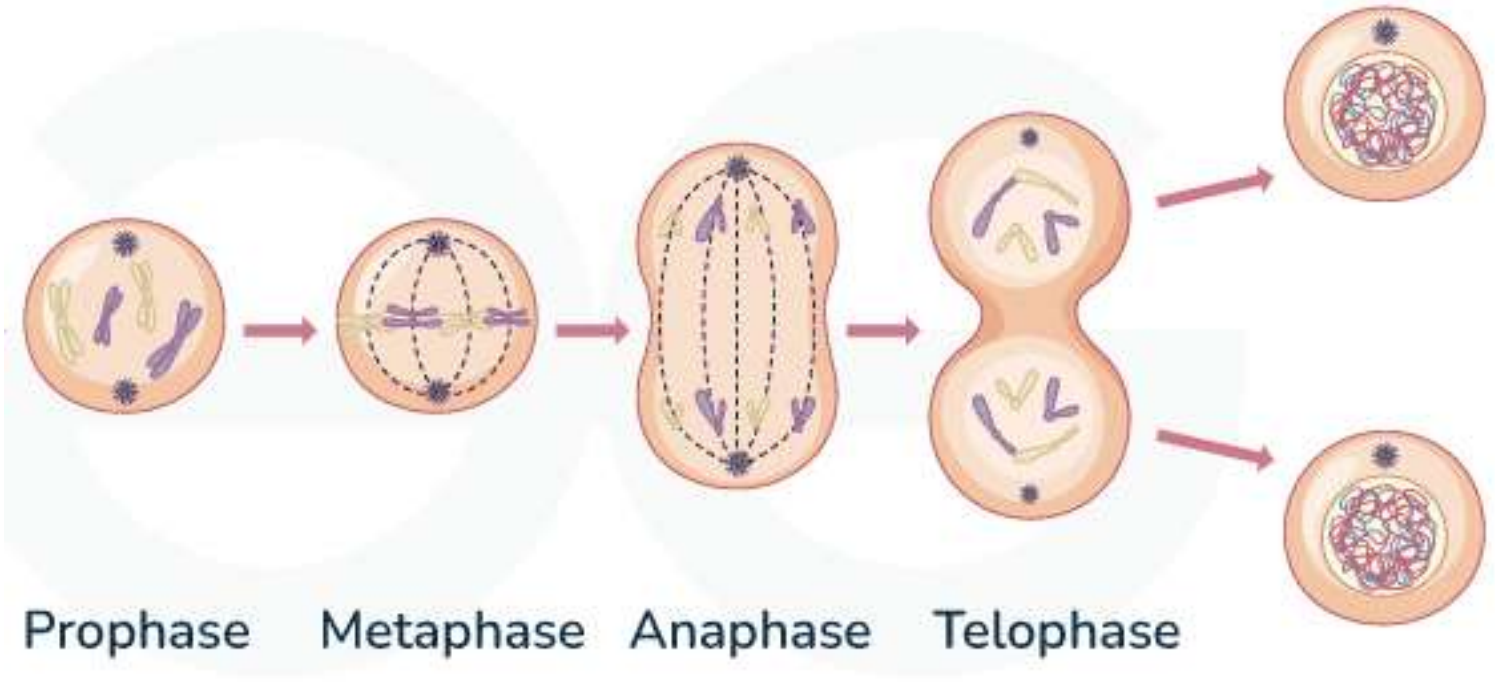




- dTMP (deoxythymidine monophosphate)
  - = thymine nucleotide (thymine attached to a sugar and phosphate group)
  - Building block of DNA
- Two important enzymes involved in the formation of dTMP
  - Thymidylate synthase
  - Dihydrofolate reductase

M Phase

- Cell Division



Classes of Cytotoxic Drugs

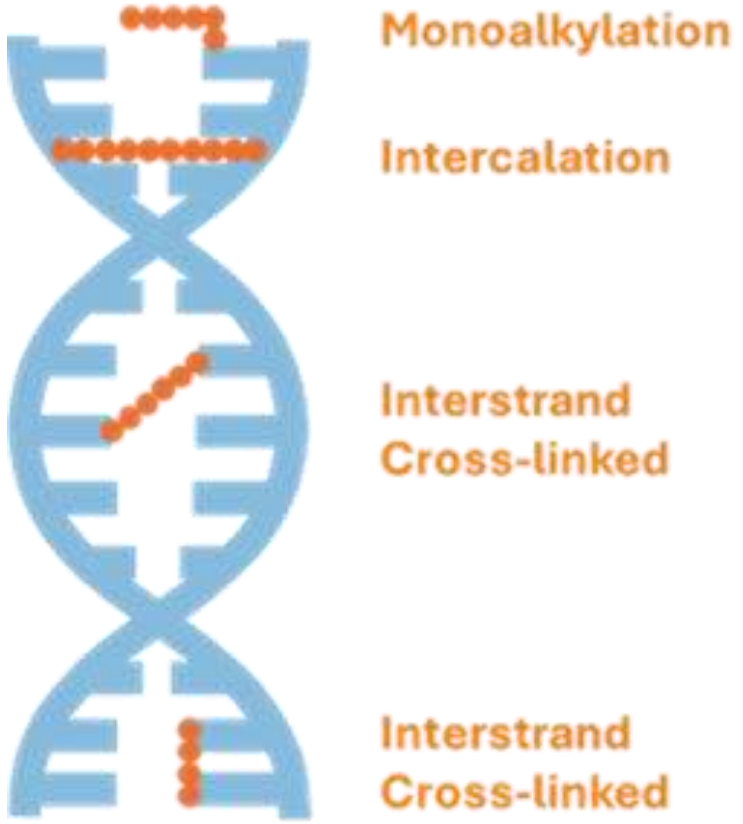
- Cell cycle non-specific agents
  - Alkylating agents incl. platinum compounds
- Cell cycle specific agents
  - Antimetabolites
  - Topoisomerase inhibitors
  - Tubulin inhibitors
- Other

Alkylating Agents

- Form covalent bonds by addition of alkyl groups (-CH_3, -C_2H_5) to nucleophilic groups on proteins and nucleic acids.

- Monofunctional drugs produce monoadducts → mutations and single-strand DNA breaks (SSBs).

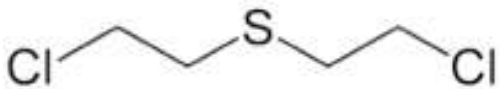
- Bifunctional drugs produce interstrand DNA cross-links preventing DNA strand separation → double-strand DNA breaks (DSBs).



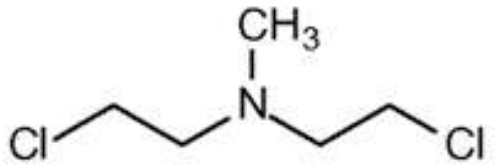
Alkylating agents

-Nitrogen mustards

- Mustard gas = chemical warfare used during WWI
  - Soldiers exposed developed severe leukopenia
  - This led to clinical trials in lymphoma patients



Mustard gas



Nitrogen mustard

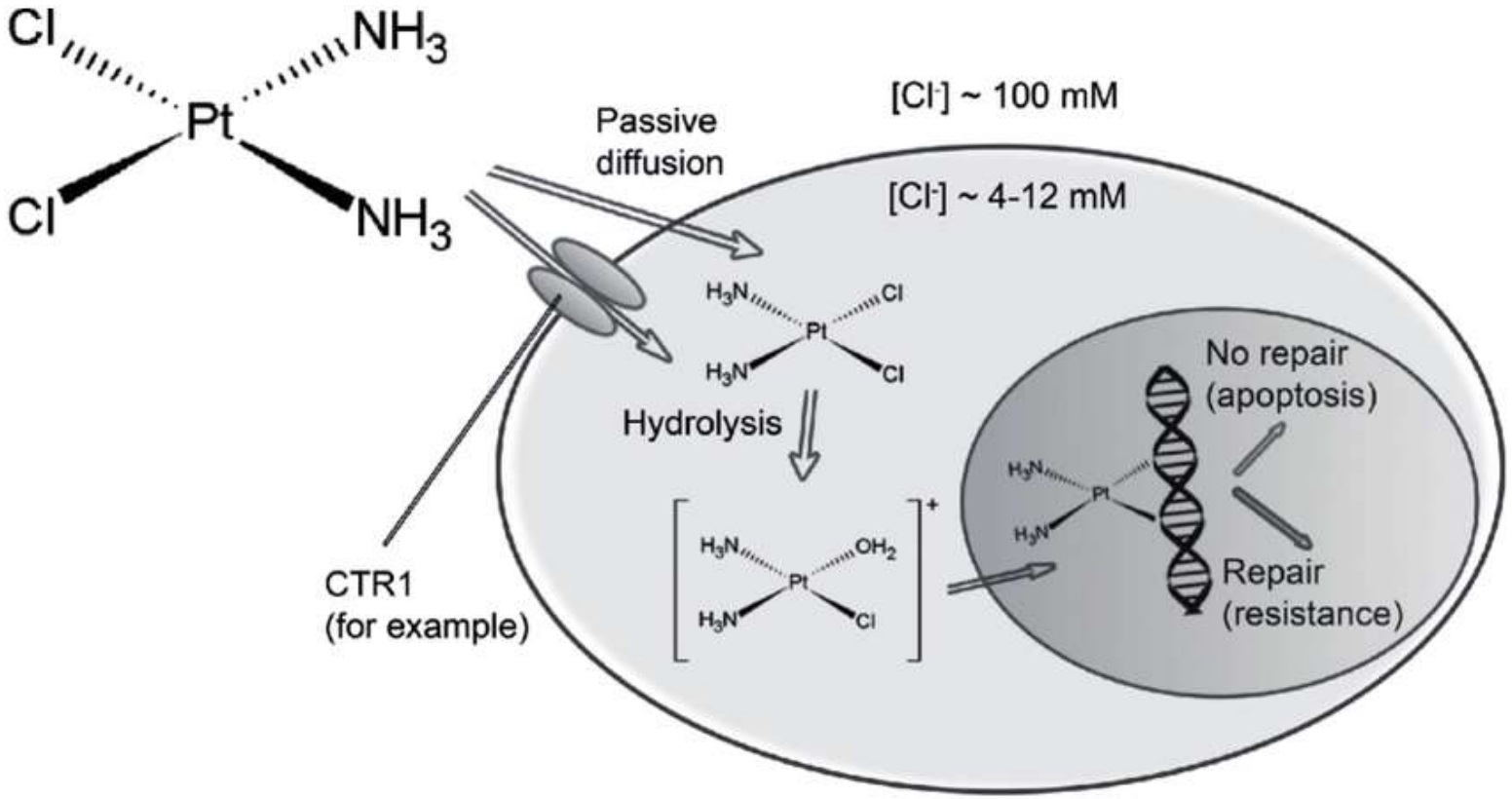
Alkylating agents

-Different chemical classes

- Nitrogen Mustards
  - Cyclophosphamide, ifosfamide, chlorambucil, melphalan, bendamustine
- Ethylene imines
  - Thiotepa
- Alkyl sulfonates
  - Busulphan
- Nitrosoureas
  - Carmustine (BCNU), lomustine (CCNU)
- Triazenes
  - Mitomycin C, dacarbazine (DTIC), temozolomide

Alkylating agents

-Platinum compounds



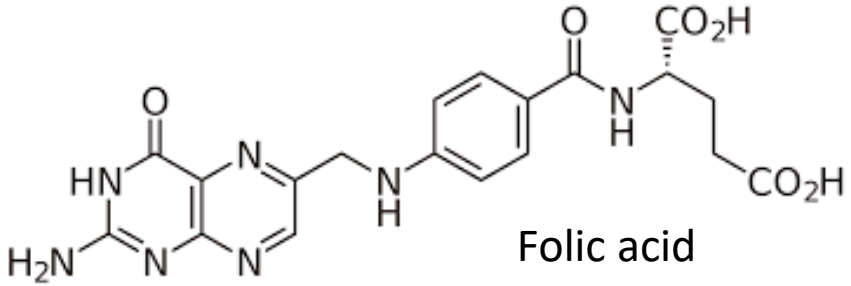
- Displacement of chloride ions by water molecules produces an alkylating agent

Antimetabolites

- Antimetabolites exert their effects by:
  - Interfering with the synthesis of DNA and RNA by substituting erroneous metabolites or structural analogues during this process
  - Inhibiting specific enzymes needed for the synthesis of essential compounds

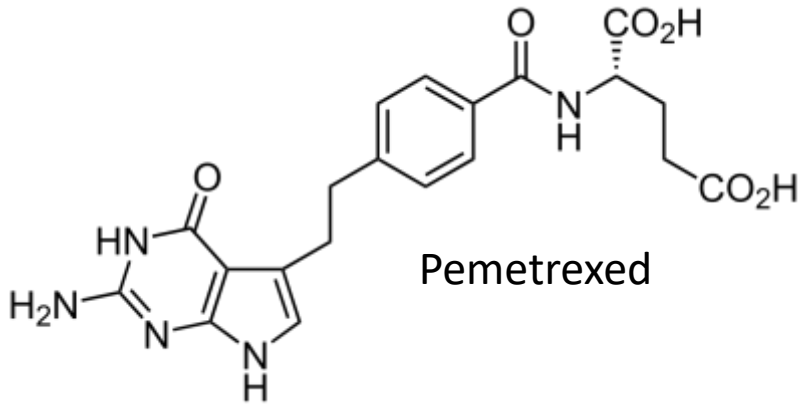
Antimetabolites

- Folic acid antagonists

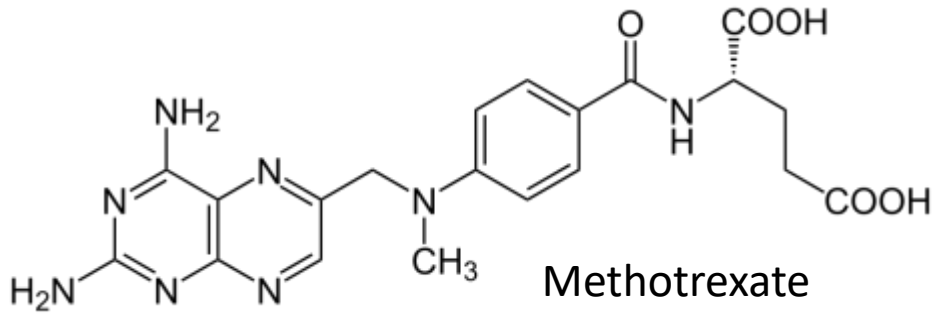


Folic acid

- Analogues of folic acid
- Inhibit DHFR (dihydrofolate reductase)
  - Converts DHF → THF
  - Essential for de novo synthesis of purine nucleotides and thymine
- Inhibit TS (thymidylate synthase)
  - Enzyme responsible for thymine synthesis
- Inhibition of DNA / RNA synthesis → cell death
- S phase specific



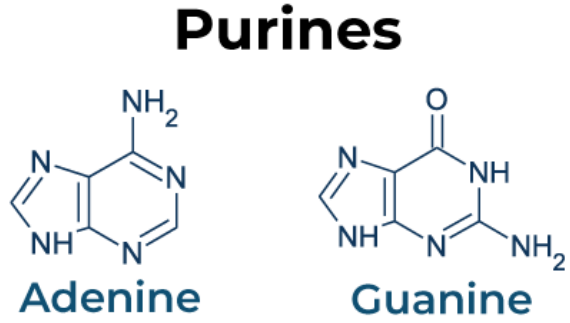
Pemetrexed

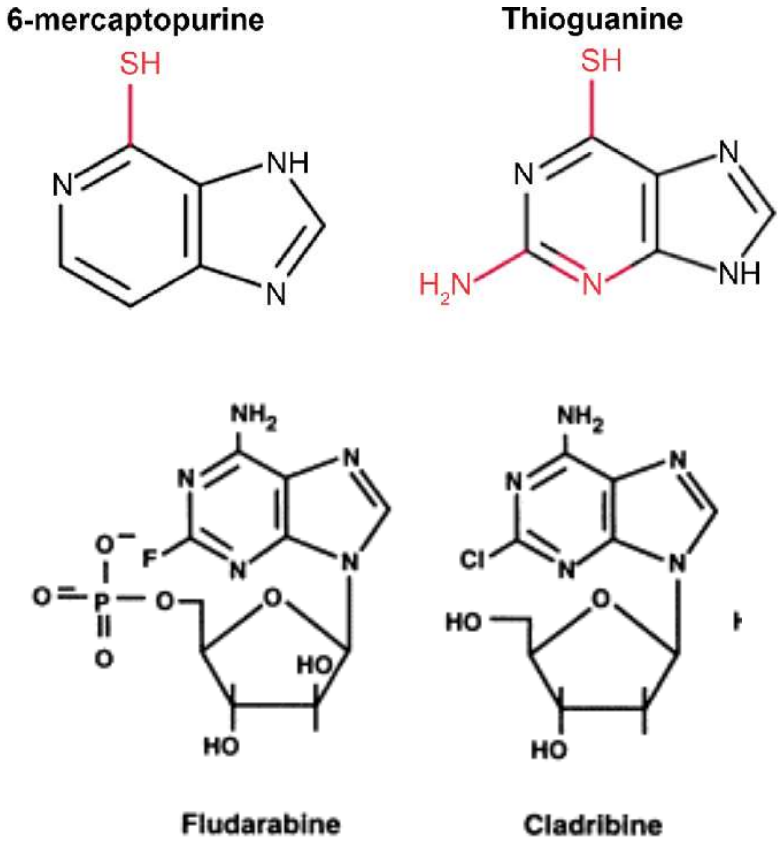


Methotrexate

Antimetabolites

- Purine analogues

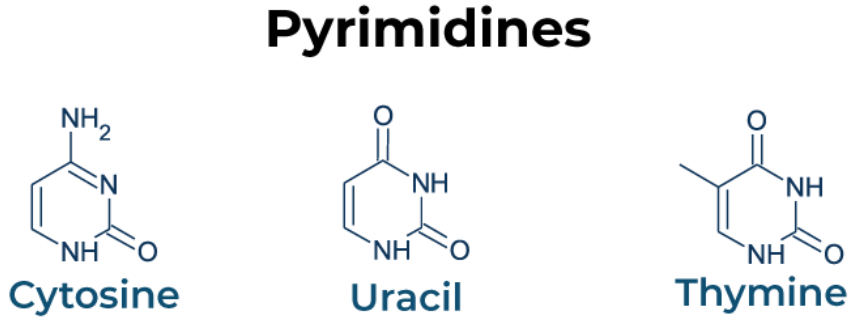




- Become incorporated into DNA in place of normal purine nucleotides
- Inhibit DNA replication, transcription and repair
- Results in cell death
- Most active in S phase

Antimetabolites

- Pyrimidine analogues



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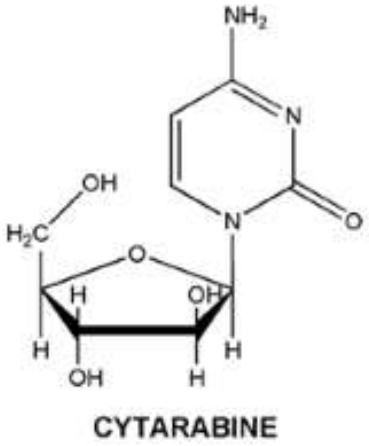
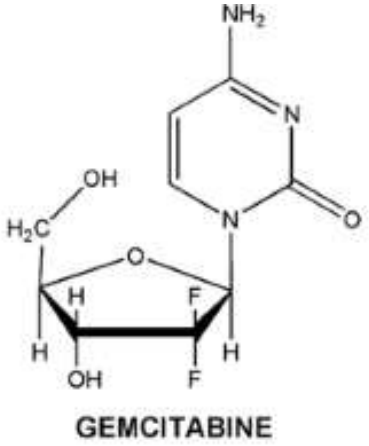
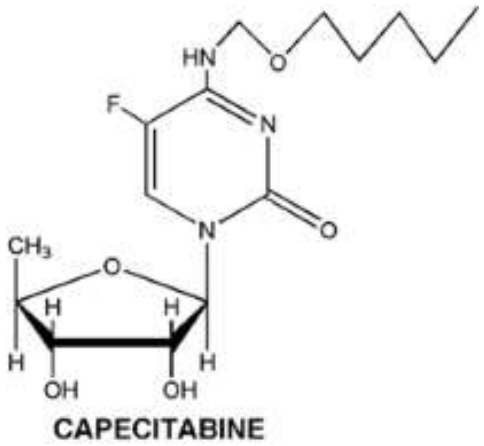
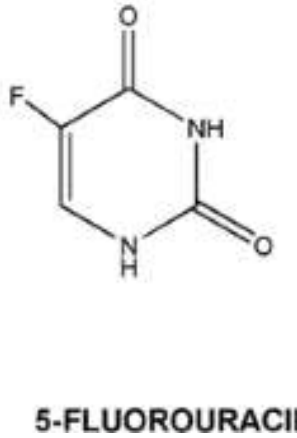
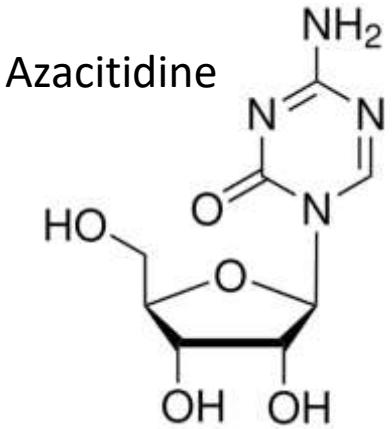






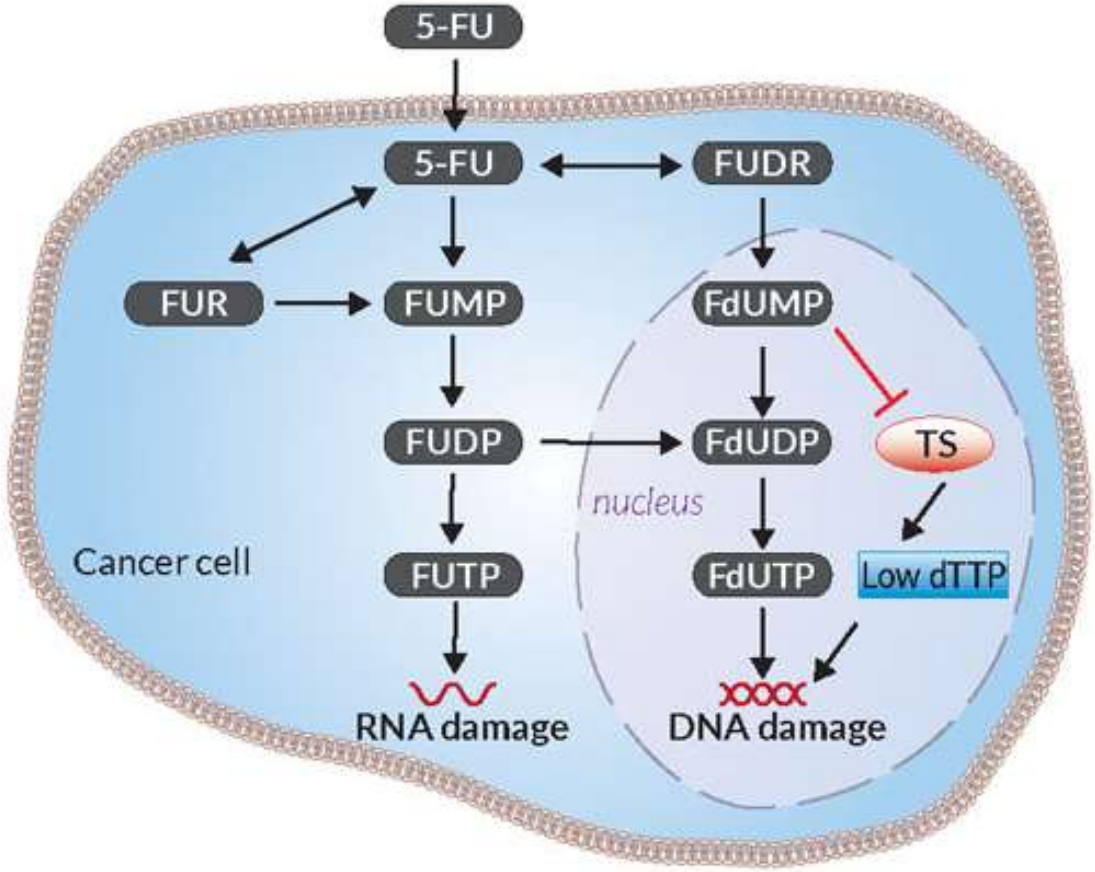




Antimetabolites

- Fluorouracil

- Inhibits thymidylate synthetase → decreased thymidine (thymine) production)
- FdUTP is incorporated into DNA in place of thymine
- FUTP is incorporated into RNA in place of uracil



Fluorouracil

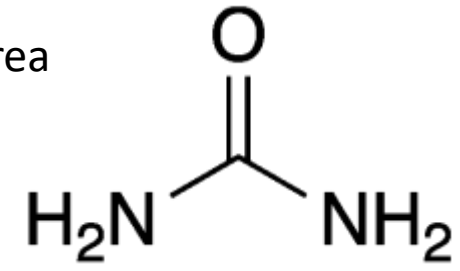
- bolus vs. infusion

	Bolus	Infusion
Dose range	• 400-600mg/m^2 • High peak plasma concentrations (0.1-1 mmol/L) followed by rapid decline	• 2400mg/m^2 over 46h • 3200mg/m^2 over 48h • 4000mg/m^2 over 96h • Prolonged plasma concentrations >1 µmol/L
Cytotoxic effects	• Due to incorporation of FUTP into RNA • Concentration dependent • Cell cycle non-specific	• Due to inhibition of thymidylate synthase • Cell cycle specific (S phase) • Enhanced by leucovorin

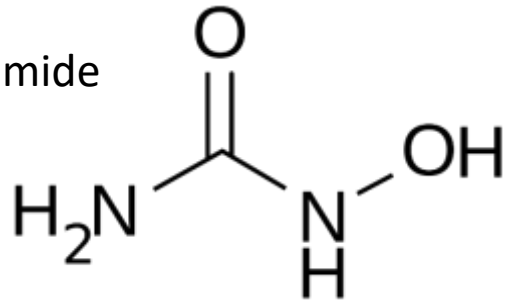
Antimetabolites

- Ribonucleotide reductase inhibitors

Urea



Hydroxycarbamide



- Hydroxycarbamide (hydroxyurea)
  - Structural analogue of urea
  - Inhibits ribonucleotide reductase – enzyme responsible for converting ribonucleotides to deoxyribonucleotides (required for DNA synthesis and DNA repair)
  - Results in accumulation of DNA strand breaks → apoptosis

Folate antagonists

Methotrexate

Pemetrexed

Purine analogues

Mercaptopurine

Thioguanine

Fludarabine

Cladribine

Pyrimidine analogues

Fluorouracil

Capecitabine

Cytarabine

Gemcitabine

Azacitidine

Ribonucleotide reductase inhibitors

Hydroxyurea

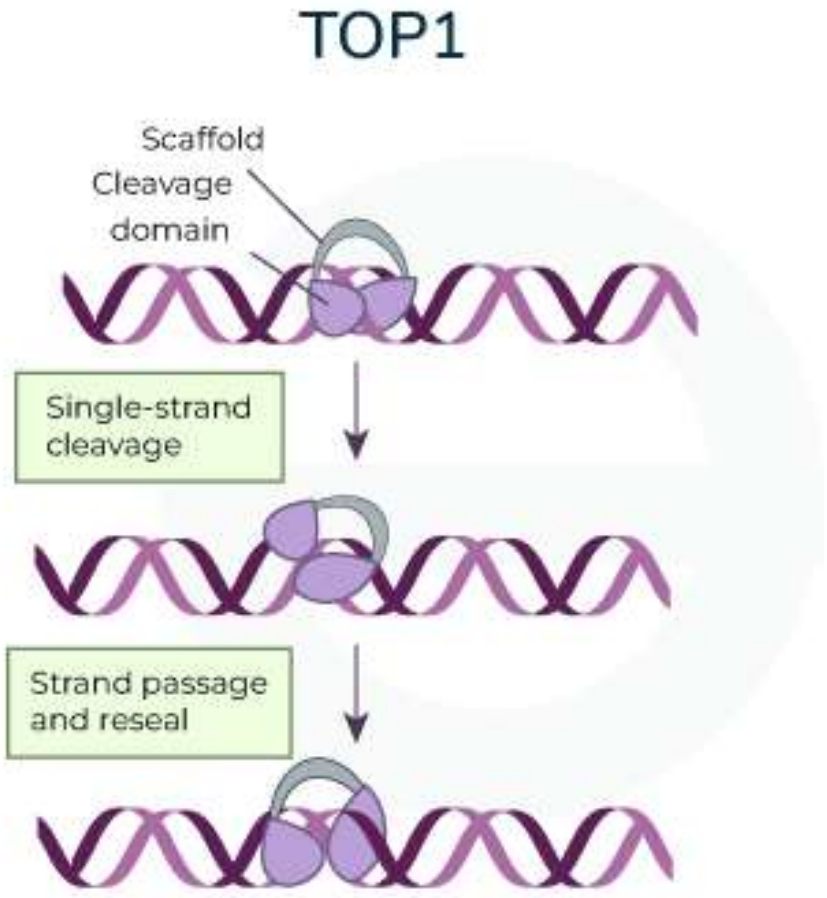
Gemcitabine

Fludarabine

Topoisomerase I inhibitors

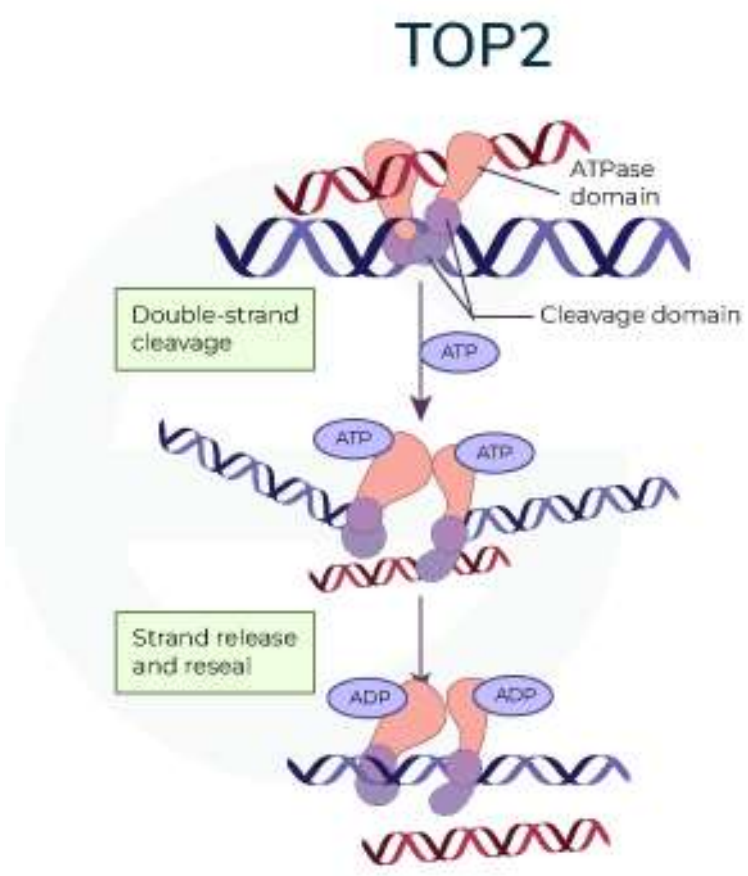
- Irinotecan, topotecan

- Inhibition of topoisomerase I
  - Binds to topoisomerase I
  - Stabilises the “cleavable complex”
  - Inhibits re-ligation / resealing of DNA strand
- Accumulation of cleavable complexes and single strand DNA breaks → cell death
- Cell cycle activity
  - S phase cytotoxicity
  - G2/M phase cell cycle arrest



Topoisomerase II inhibitors

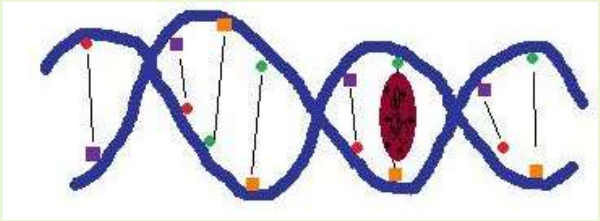
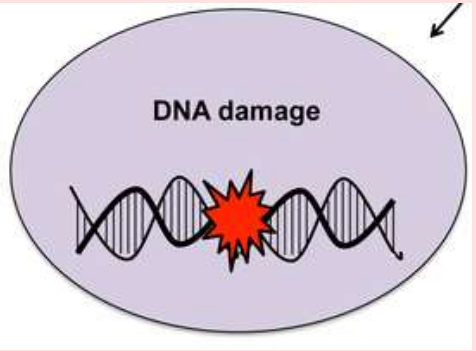
- Etoposide



- Form complexes with topoisomerase II and DNA
  - Induces double-stranded DNA breaks
  - Prevents repair of DNA
- Inhibition of DNA replication → cell death
- Most active in S phase of cell cycle

Antitumour antibiotics

- Anthracyclines, Mitoxantrone

Intercalation	Topoisomerase II inhibition	Formation of ROS
		
→ Inhibits DNA / RNA synthesis	→ Fragmentation of DNA	→ Cleaves DNA and cell membranes

- Non-cell cycle specific
  - Most active in S phase

Other antitumour antibiotics

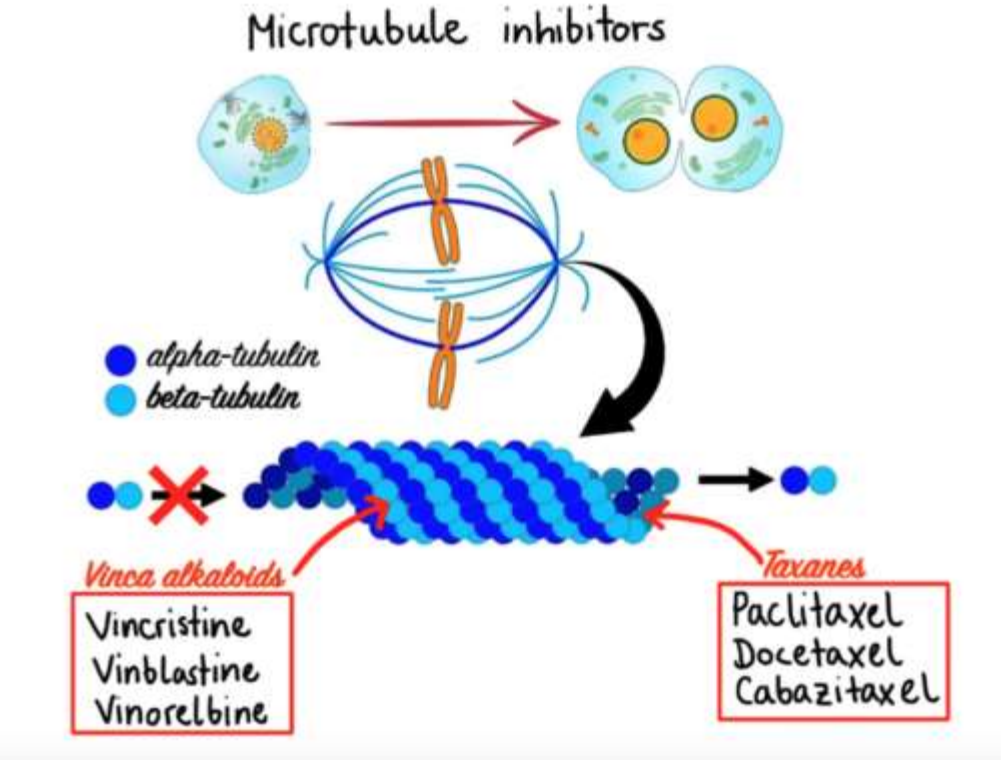
Bleomycin	• Derived from *Streptomyces verticillus* • Binds to DNA via DNA binding site • Iron binding site becomes oxidised • Formation of ROS → DNA strand breakage

Mitomycin	• Derived from *Streptomyces caespitosus*
	• Alkylating agent
	  • Cross linking of DNA strands
	  • Inhibition of DNA synthesis

Dactinomycin	• Derived from *Streptomyces parvullus* • Intercalates between nucleotide base pairs → inhibits DNA synthesis • Produces free radicals → DNA strand breakage

Tubulin / microtubule inhibitors

- Plant derivatives
- Inhibit or arrest cell division by disrupting microtubule function
- Work in the M phase of the cell cycle
  - Cell cycle specific agents



Tubulin inhibitors

- Vinka alkaloids

- Extracted from periwinkle – *Caranthus roseus*
- Bind to tubulin → prevent microtubule formation

- Examples
  - Vincristine
  - Vinorelbine
  - vinblastine

Tubulin inhibitors

- Taxanes

Originally isolated from the bark of the yew tree (*Taxus baccata*)

Bind to and stabilise microtubules

- Prevent breakdown of microtubules → cell arrest in M phase → apoptosis

- Examples
  - Paclitaxel
  - Docetaxel

Tubulin inhibitors

- Epithilones

- Eribulin
  - Interferes with the growth of microtubules (interrupts the formation of mitotic spindles)
- Eribulin is a synthetic analogue of halichondrin B
  - Isolated from Japanese sea sponge *Halichondria okadai*

Determinants of cytotoxicity

- cell cycle specific agents

- Cells must be actively dividing
  - More effective against tumours with a high growth fraction
- Schedule dependent
  - Increased activity if given as continuous infusion or repeated dosing
- Threshold concentration for cytotoxic effects
  - Greater effect with continued exposure above a threshold concentration

Determinants of cytotoxicity

- cell cycle non-specific agents

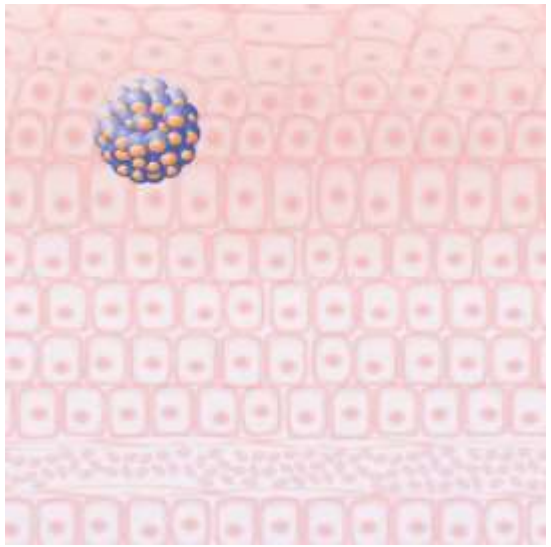
- Active at all phases of the cell cycle
  - Alkylating agents can alkylate non-dividing cells, but they only cause cell death when the cells are stimulated to divide
- Dose dependent
  - Linear dose-response relationship (higher dose = greater cell kill)
- Can reduce toxicity if given as a continuous infusion or "fractionated doses"

Multi-drug regimens

- Individual therapeutic activity
- Different cytotoxic mechanisms → synergistic effects
- Different adverse effects → allows optimal doses
- Overcome resistance

Cyclical administration of chemotherapy

- Fractional cell kill hypothesis
  - Each dose of cytotoxic drug kills a proportion of cells (independent of tumour size / disease burden)
- Cycle length may depend on
  - Rate of regrowth of the tumour
  - Rate of recovery of normal healthy cells (bone marrow)



Limitations of chemotherapy

- Poor oral bioavailability
- Lack of specificity for tumour cells
- Relative lack of activity against non-cycling tumour cells
- Limited penetration into solid tumours or sanctuary sites
- Development of common mechanisms for tumour resistance


QUIZ TIME

Which of the following is CORRECT regarding taxanes?

a) They are plant alkaloids derived from the periwinkle plant
b) They inhibit microtubule assembly
c) They are mainly active in the S phase of the cell cycle
d) They stabilise microtubules and prevent their breakdown

Which of the following is CORRECT regarding taxanes?

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What is the primary function of topoisomerase II in DNA replication?

a) Promoting DNA unwinding during replication
b) Stabilizing microtubule formation
c) Relaxing supercoils by cleaving two DNA strands and re-ligating them
d) Cleaving one DNA strand to relieve tension

What is the primary function of topoisomerase II in DNA replication?

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Which phase of the cell cycle is predominantly affected by antimetabolite chemotherapy agents?

a) G1 phase
b) S phase
c) M phase
d) G2 phase

Which phase of the cell cycle is predominantly affected by antimetabolite chemotherapy agents?

a) G1 phase

b) S phase

c) M phase

d) G2 phase

What is NOT a key effect of anti-tumour antibiotics like anthracyclines on DNA structure?

a) Preventing DNA unwinding by helicase
b) Formation of reactive oxygen species
c) Inhibiting relaxation of supercoils
d) Intercalation between base pairs of DNA

What is NOT a key effect of anti-tumour antibiotics like anthracyclines on DNA structure?

a) Preventing DNA unwinding by helicase
b) Formation of reactive oxygen species
c) Inhibiting relaxation of supercoils
d) Intercalation between base pairs of DNA

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a) Inhibiting topoisomerase
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c) Inhibiting nucleic acid metabolism
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