Pharmacology of anticancer drugs

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Anticancer drugs

Definition:

- drugs used in therapy of all types of cancer disease

synonyms =

- chemoterapeutics, cytostatic or cytotoxic drugs

chemoprotective substances – protect somatic cells against toxic effect of chemoterapeutics (mesna, AcCys, dexrazoxane etc.)

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Carcinogenesis

- !! multistage process !!
- process of transformation of somatic cell to malignant
- 3 phases:

initiation

carcinogens, mutagens and mutation

promotion

expansion of cells

progression

final transformation to malignancy

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Carcinogenesis

Factors related to tumours

- exogenic: tobacco, ethanol, infections, diet, radiation

  International Agency for Research on Cancer (IARC) http://www.iarc.fr
- endogenic: genetic predisposition (*Xeroderma pig.*)

  defects of immune system

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Tumors

Types of tumours:

1. *Benign*

- multiplication of differenciated cells, danger of localization and size

2. *Malignant*

- invasivness, dedifferentiation, metastasis, uncontrolled proliferation

3. *Transitional states*

- characteristics of 1. and 2.

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Characteristics of malignant cell

Uncontrolled proliferation

- the clonal expansion, defect in proliferation controlling mechanisms
- speed of proliferation, cell cycle, apoptosis
- mechanisms: extracellular signals, receptors, intracellular signaling pathways, intracelular signals

Dediferentiation and loss of function

- ↓degree of differentiation = ↑speed of proliferation

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Characteristics of malignant cell

Invasiveness

- proteolytic enzymes, angiogenesis

Metastases

- secondary tumours

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Anticancer treatment

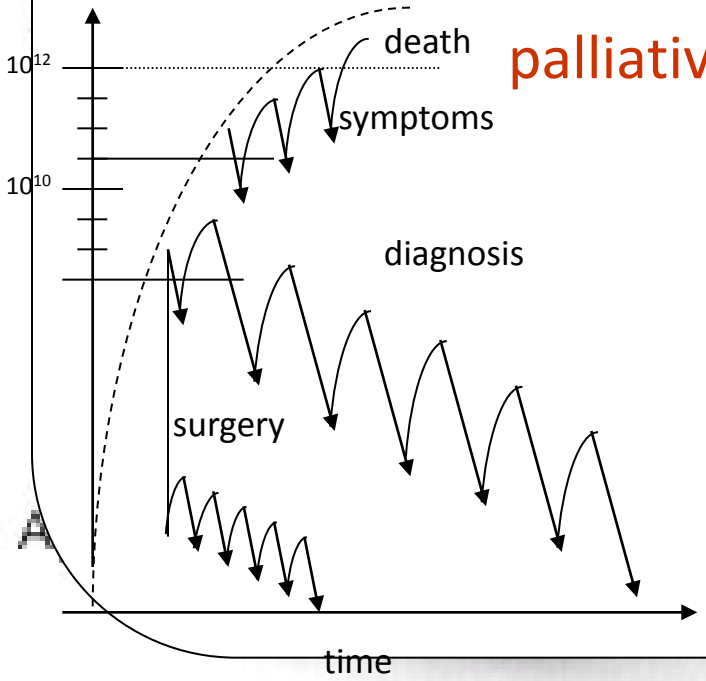
Surgical excision

Radiation: ionizing radiation

Chemotherapy: curative

palliative: adjuvant

neoadjuvant



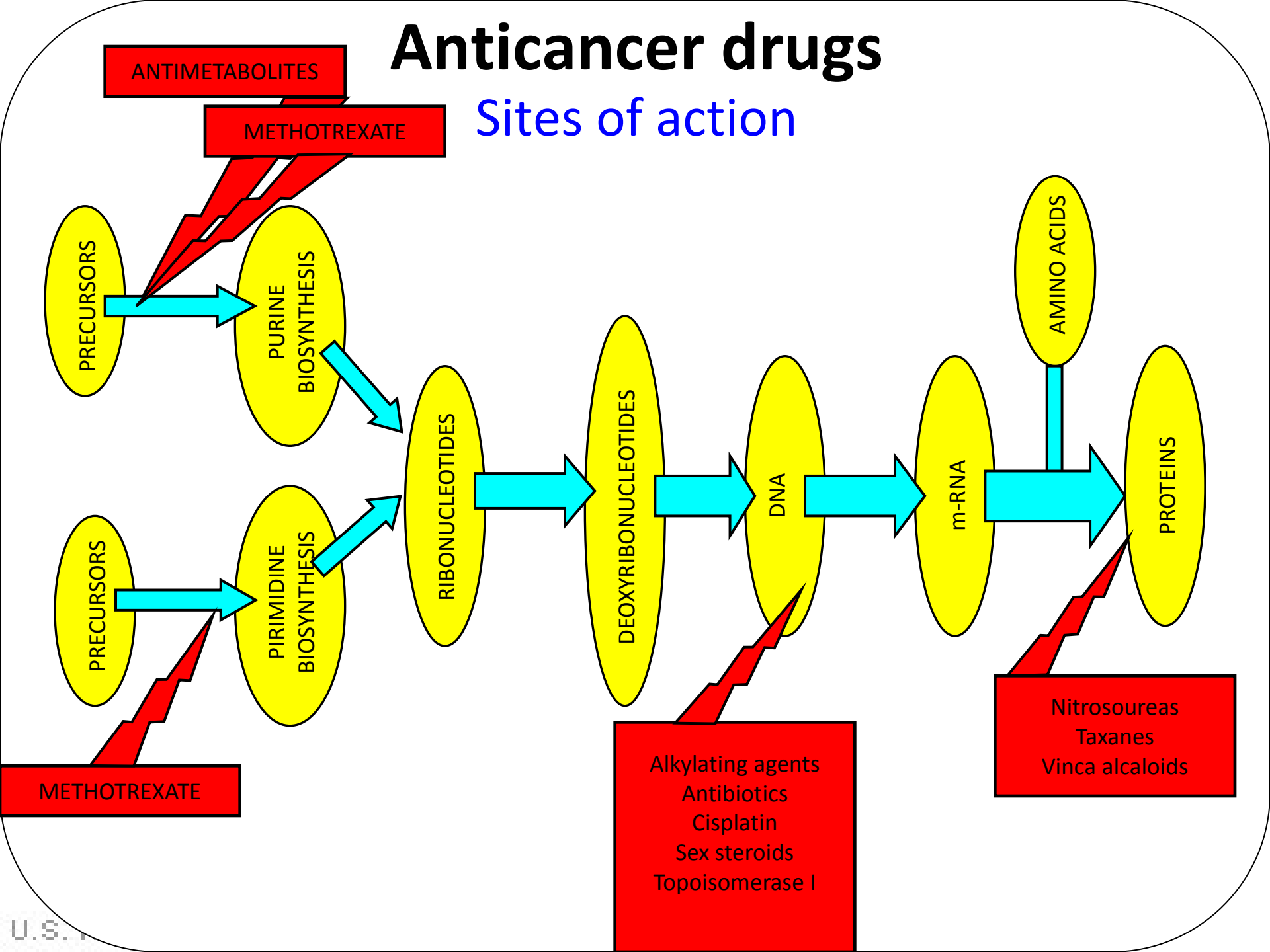
Anticancer drugs

Sites of action

1. interference with DNA (RNA) : alkylating and intercalating agents, inhibitors of topoisomerase, radiomimetics
2. antimetabolites: pyrimidine and purine analogues, folate antagonists
3. interference with microtubules
4. hormones
5. others

Anticancer drugs

Sites of action

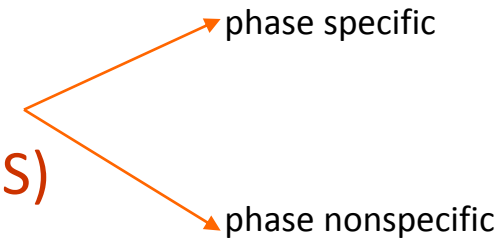


Anticancer drugs

Classification

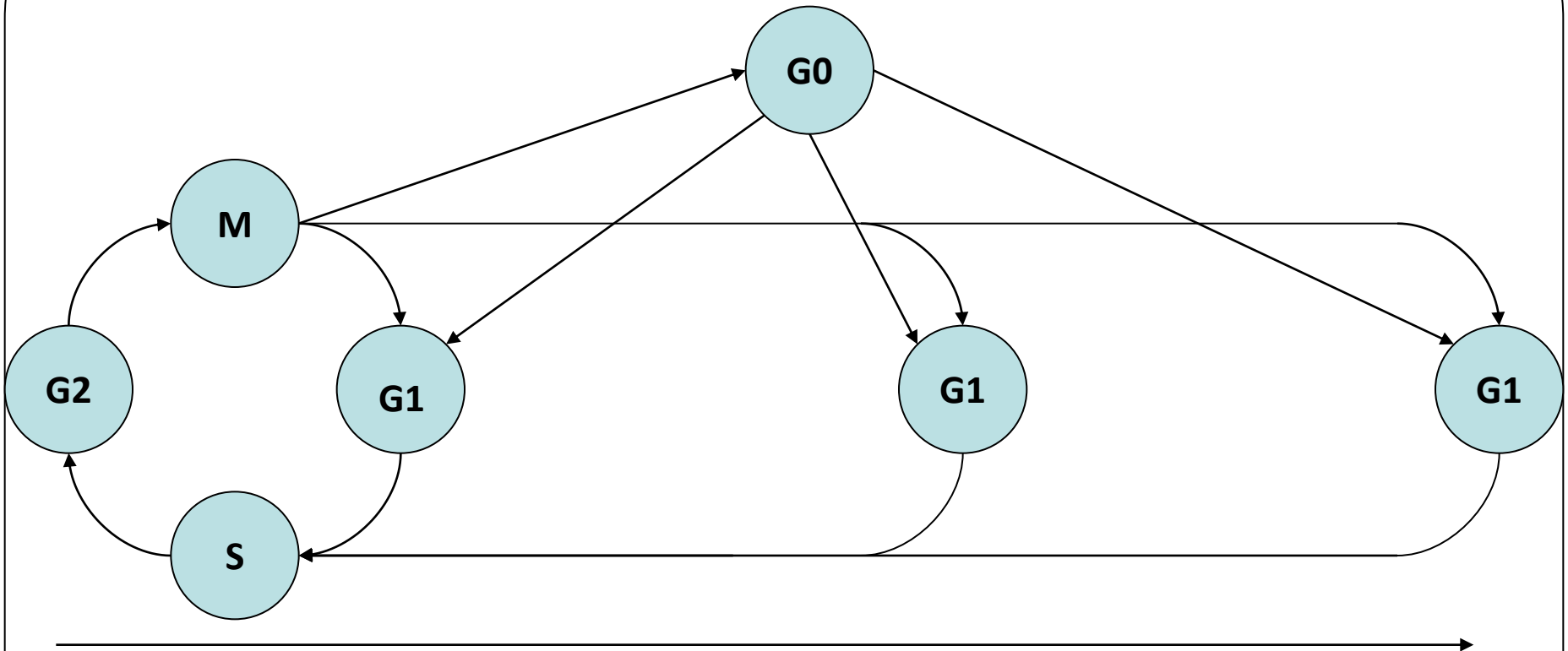
with regard to:

1. the cell cycle: cell cycle specific (CCS)
   cell cycle nonspecific (CCNS)



2. chemical structure
3. principle of action

Anticancer drugs



fast proliferating cells – mid.speed of proliferation – slow proliferating cells

stem cells, germ-cells-- hair foliculs, skin cells -- liver, kidneys

Burkitt‘s carcinom -- acute leukemia -- Ca of colon

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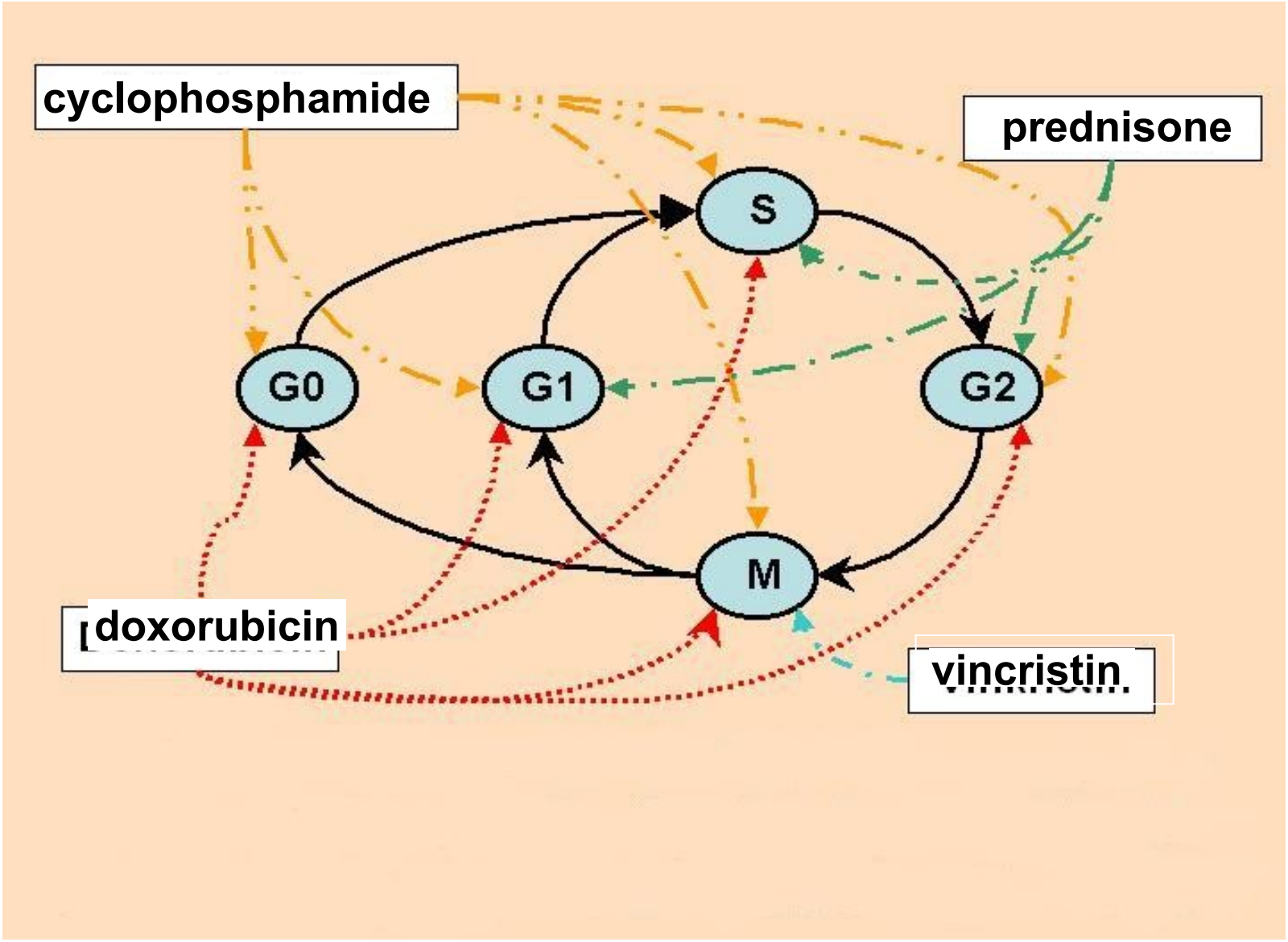


Anticancer drugs

Adverse effects

Early

- nausea, vomitus
- fever
- sweating
- allergic reaction

Retarded

- myelotoxicity
- GIT toxicity
- secondary malignity
- alopecia
- local toxicity
- development of resistance
- reproductive toxicity

Anticancer drugs

Anticancer drugs

Classification

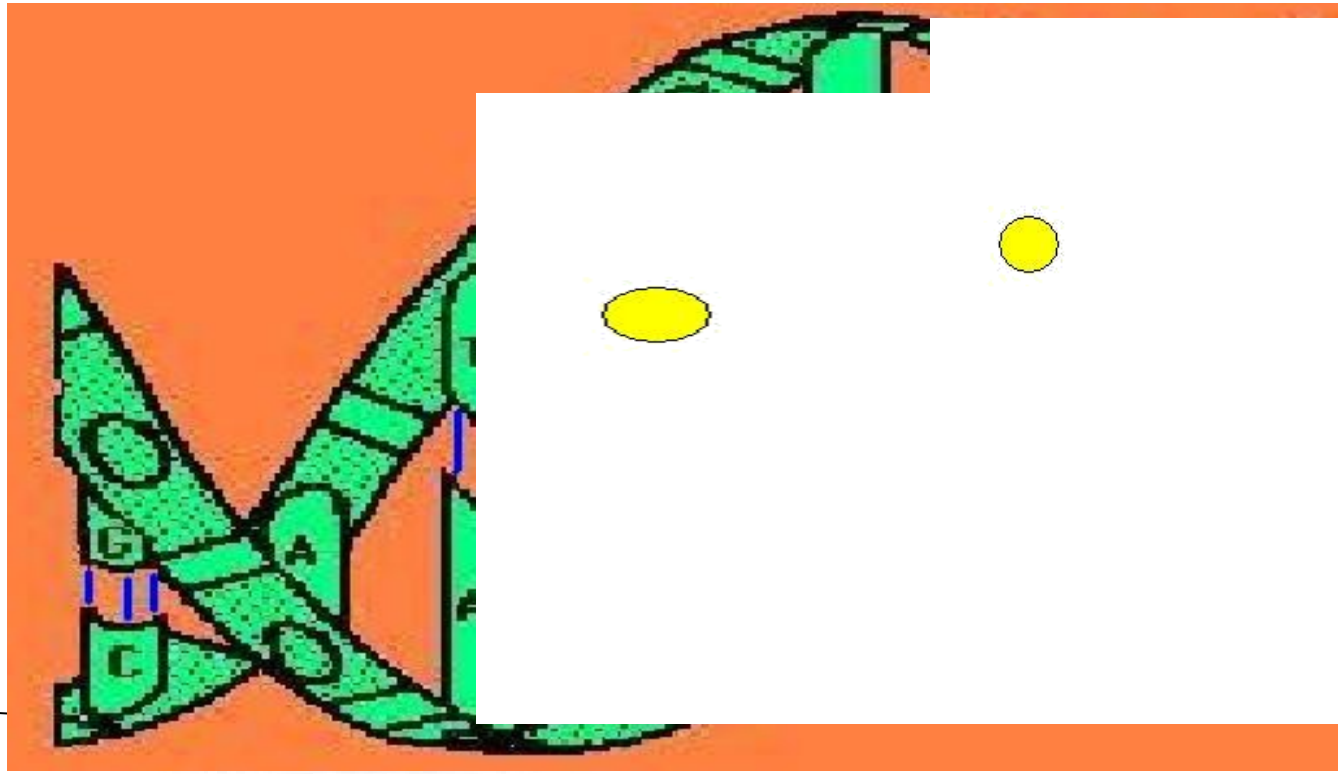
with regard to: principle of action

1. alkylating agents and related compounds
2. intercalating agents
3. antimetabolites
4. inhibitors of topoisomerases I and II
5. hormones
6. miscellaneous agents

Anticancer drugs

1. Alkylating agents and related compounds

Principle of action



Anticancer drugs

1. Alkylating agents and related compounds

Principle of action: covalent bounds to cell structures (DNA)

Adverse effects: myelotoxicity, vomitus, second. malignity

Members: nitrogen mustards: cyclophosphamide, ifosfamide, chlorambucil, melphalan

acrolein

phosphoramide

nitrosoureas: carmustine (BCNU), lomustine (CCNU), streptozocine

platin complexes: cisplatin, carboplatin, oxaliplatin

procarbazine, dacarbazine

busulphan

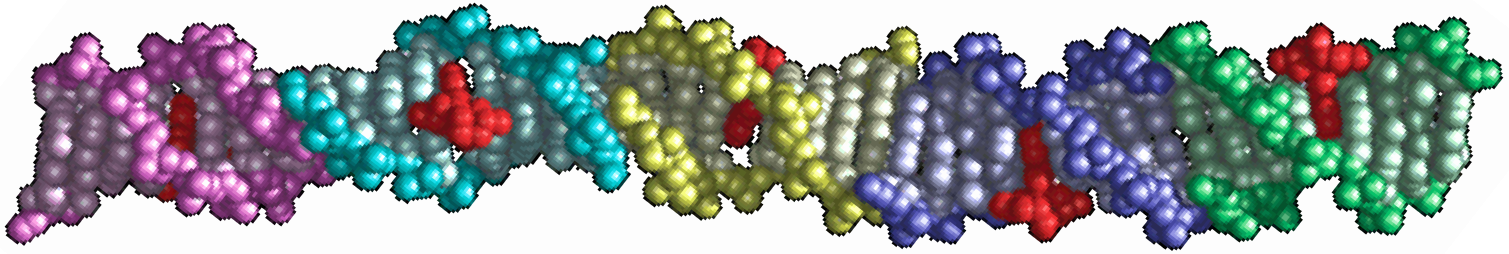
Anticancer drugs

2. Intercalating agents

Principle of action: n[illegible]nds

Adverse effects

Members: anth[illegible]ycin), daunorubicin (daunor[illegible]



Anticancer drug

3. Inhibitors of topoisome

Principle of action

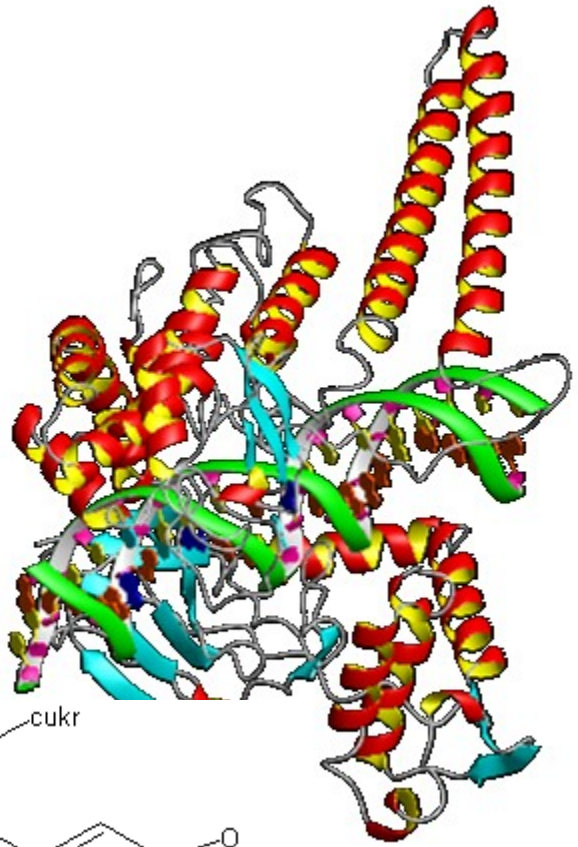
Adverse effects

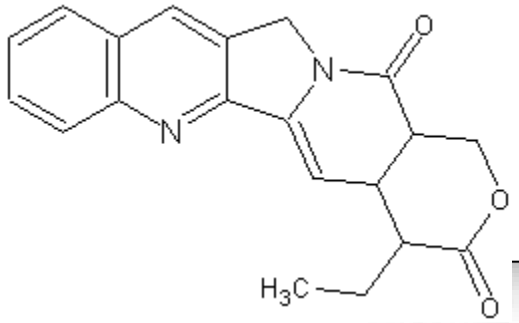
Members: Topoisomerase I

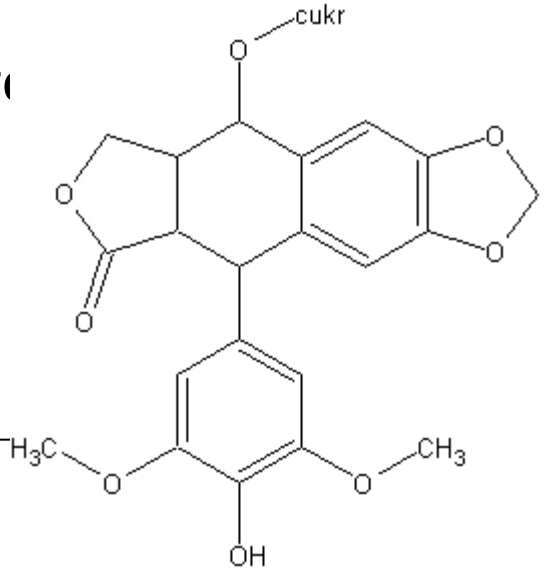
irinotecan, topotecan

Topoisomerase II

etoposid, teniposid (fr







Anticancer drugs

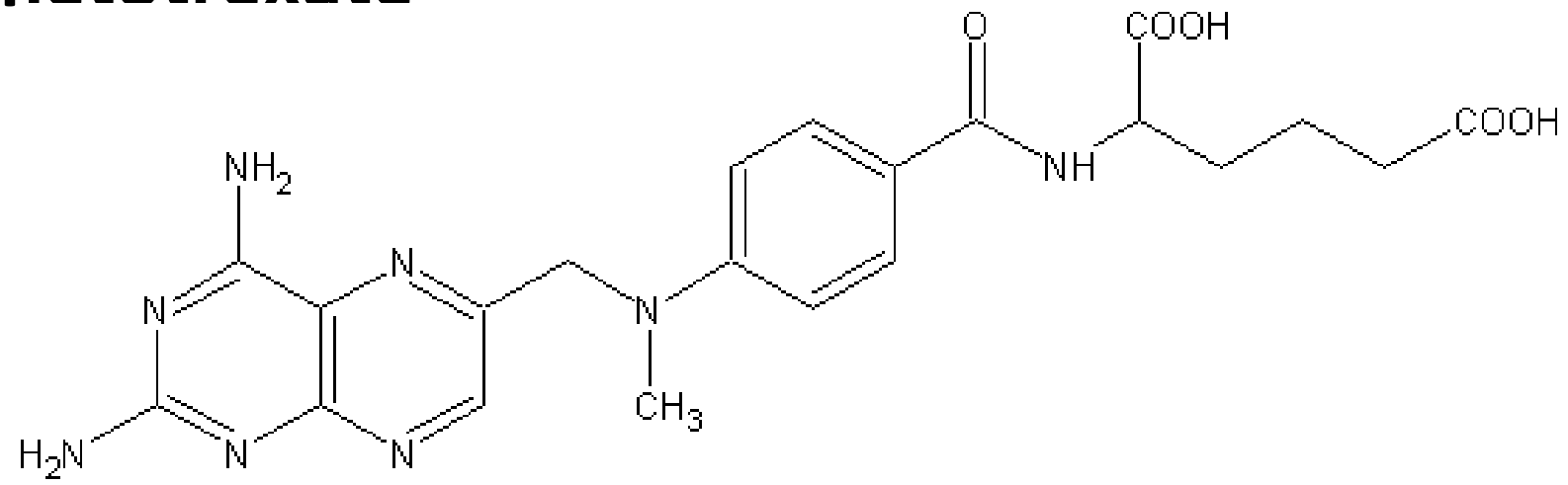
3. Inhibitors of topoisomerases

Anticancer drugs

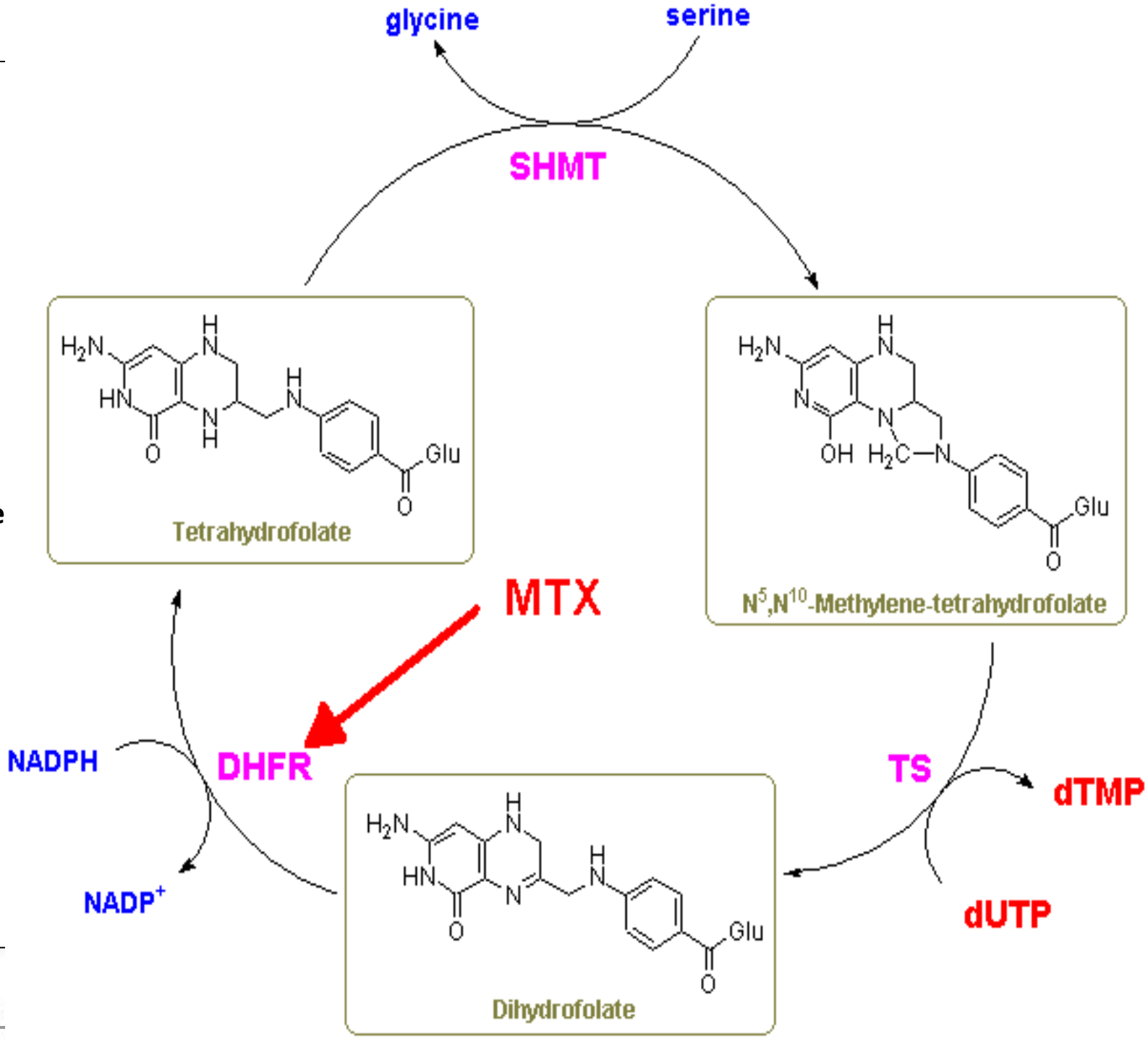
4. Antimetabolites

1. Folate antagonists

metotrexate



MTX- methotrexate
DHFR- dihydrofolate reductase
SHMT- serin $OHCH_3$transferase
TS-thymidylate syntase



Anticancer drugs

4. Antimetabolites

1. Folate antagonists

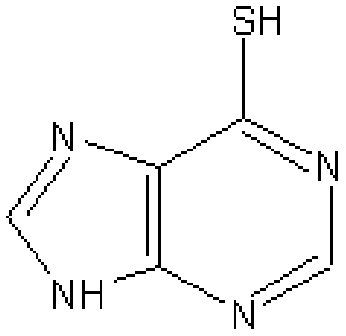
Principles of action

Adverse effects: nephrotoxicity, hepatotoxicity

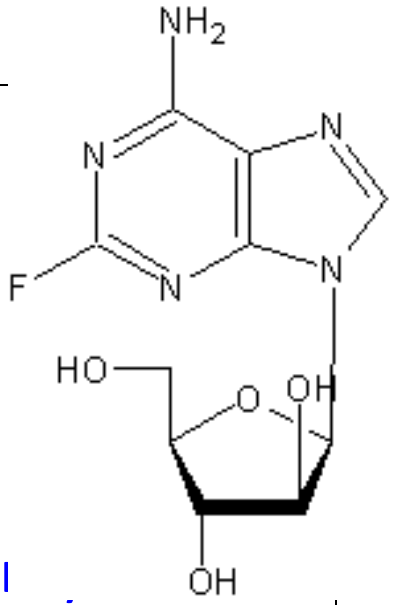
Members**:** **metotrexate (MTX), trimetrexate**

leucovorin (folinic acid) – antagonist of MTX

- immunosuppressive therapy



Anticancer drugs



4. Antimetabolites

2. Purine analogues

Principles of action: antagonism of purine bases and e
defect of transcription and replication of NA

+ functionaless proteins

Adverse effects: nephrotoxicity, myelosuppression

Members: 6-mercaptopurin, 6-thioguanin, azathioprin (immunosupression), fludarabine, cladribine, pentostatin

- ↑of effect by inactivating xantinoxidase

Anticancer drugs

4. Antimetabolites

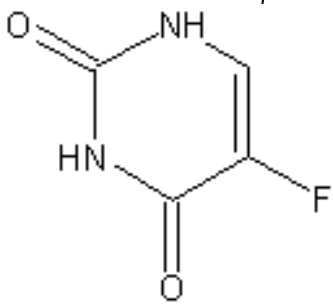
3. Pyrimidine analogues

Principle of action: incorporation to DNA or inhibition of replication enzymes

Adverse effects: myelosuppression, myelotoxicity

cytarabine,5-fluorouracil, gemcitabine, **floxuridine**, tegafur

- synergisms of flourouracil and MTX



Anticancer drugs

Inhibitors of mitosis

Principle of action: interaction with mitotic spindle

Vinca alkaloids (from periwinkle plant)

Adverse effects: neurotoxicity, myelotoxicity

- **vincristine, vinblastine, vindesine, vinorelbine**
- M phase specific

Taxanes (from Pacific yew)

Adverse effects: neurotoxicity, bradycardia, granulocytopenia

- **docetaxel, paclitaxel**

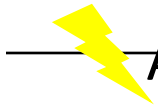
Anticancer drugs

Inhibitors of mitosis

Anticancer drugs

Inhibitors of protein synthesis

Asparaginase – cristantaspase

Principle of action: Asn  Asp and NH_3

Adverse effects: allergic reaction, neurotoxicity, hepatotoxicity, pancreatitis

- !! IS NOT myelosuppresive and not toxic for GIT !!

Anticancer drugs

5. Hormons and hormon antagonists

Androgens

Antiandrogens

Oestrogens

Antioestrogens

Gestagens

Inhibitors of gonadoliberin

Inhibitors of aromatases

Glucocorticoids

Octreotid

Estramustin, prednimustin

Anticancer drugs

5. Hormons and hormon antagonist

Androgens

Principle of action: antagonism of oestrogens

Adverse effects: retention of Na^+, hepatotoxicity, virilisation

- **testosterone, fluoxymesterone**
- combinations with antioestrogens

Antioestrogens

Principle of action:

Adverse effects: flush syndrome, nausea

- **tamoxifen**

Anticancer drugs

5. Hormons and hormon antagonists

Antiandrogens

Principle of action: antagonism of androgens

Adverse effects: gynecomastia

cyproteron, **flutamid**, nilutamid, bikalutamid

Oestrogens

Principle of action

Adverse effects: gynecomastia, trombembolia, retention of Na^+

- ethinylestradiol

Anticancer drugs

5. Hormons and hormon antagonists

Inhibitors of gonadoliberin (gonadotrophin – releasing hormone)

Principle of action: ↓ releasing of sex hormones

Adverse effects: flush s., myalgia, osteoporosis

leuprolid acetate, goserelin, buserelin

Inhibitors of aromatases

Principle of action: inhibition of aromatases

Adverse effects: swellings, myalgia, artralgia

aminoglutethimide, anastrozole

Anticancer drugs

5. Hormons and hormon antagonist

Glucocorticoids

Principle of action: inhibition of lymphocyte proliferation

Adverse effects:

prednisone, dexametazone

symptomatic treatment - swellings

Anticancer drugs

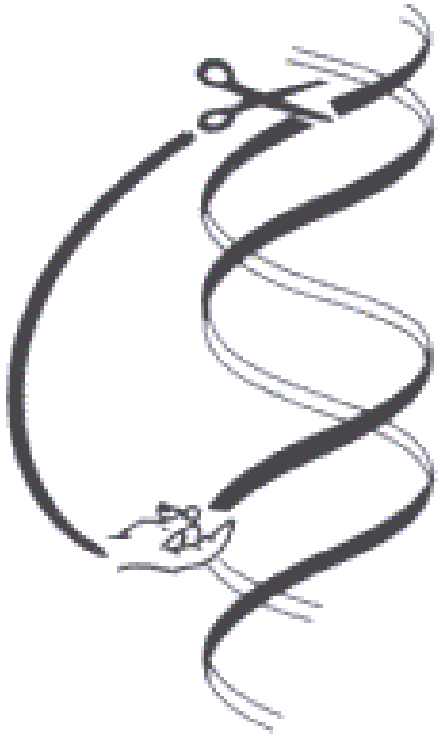
6. Others

Radiomimetics

Principle of action: production of ROS

Adverse effects: pulmonary fibrosis,hyper
reactions

- **bleomycin**
- low myelotoxicity



Anticancer drugs

6. Others

Radioisotopes

- i.e. ^{131}I in therapy of cancers of thyroid gland

Immunomodulators and others

- monoclonal antibodies
- inhibitors of angiogenesis
- interferons