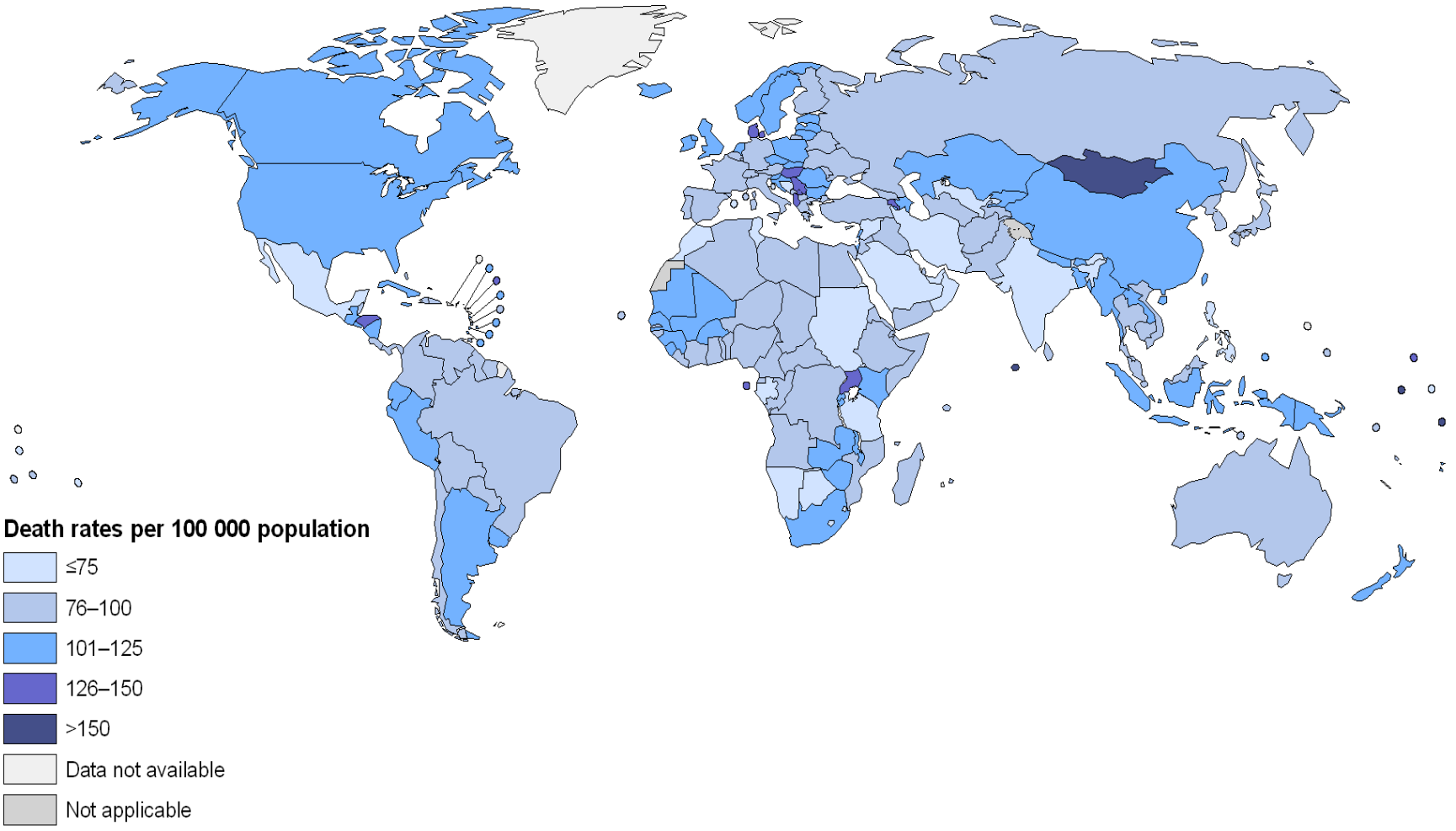
Chemotherapy of Neoplastic diseases (Anticancer drugs)

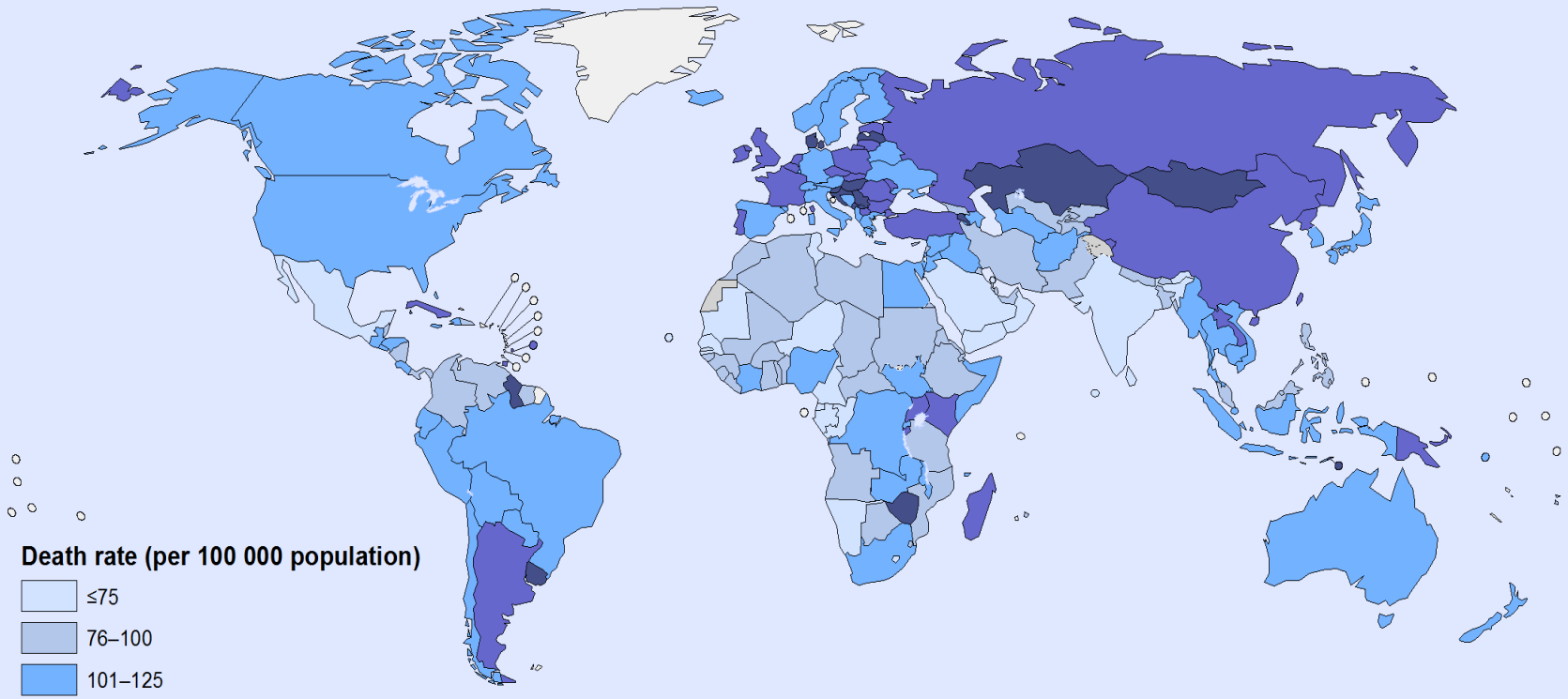
Cancer, death rates per 100 000 population, age standardized
Females, 2008



Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Cancer mortality: age-standardized death rate per 100 000 population, both sexes, 2012



Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Definition: The word **cancer means crab**, since it sticks to the part stubbornly like crab.

Cancer is defined as a mass of the tissue formed as a result of abnormal, excessive, uncoordinated, autonomous, and purposeless proliferation of body's own cells.

Pathogenesis of Cancer

1. Uncontrolled proliferation
2. Dedifferentiation and loss of function
3. Invasiveness
4. Metastasis.

Types of cancer genes

Type of gene	Normal function	Mutated function	Types of proteins
Oncogene	Promotes division	Promotes division - abnormal time or cell type	Growth factors
Tumor suppressor gene	Suppresses cell division	Fails to suppress division	Checkpoint molecules
DNA repair gene mutation	Repair DNA mutations	Fail to repair DNA mutations	Enzymes for mismatch or excision repair

Proto-oncogenes & tumor suppressor genes

Proto-oncogenes 1-hit GAIN of function		Tumor suppressor genes 2-hit LOSS of function	
RAS (GTP binding protein)	• Cholangiocarcinoma • Pancreatic adenocarcinoma	***BRCA1 & 2*** (DNA repair genes)	• Breast & ovarian cancer
MYC (Transcription factor)	• Burkitt lymphoma	***APC/β-catenin*** (WNT signaling pathway)	• Colon, gastric & pancreatic cancer • Familial adenomatous polyposis
ERBB1 (EGFR) (Receptor tyrosine kinase)	• Lung adenocarcinoma	**TP53** (Genomic stability)	• Most cancers • Li-Fraumeni syndrome
ERBB2 (HER2) (Receptor tyrosine kinase)	• Breast cancer	**RB** (G_1/S transition inhibitor)	• Retinoblastoma • Osteosarcoma
ABL (Nonreceptor tyrosine kinase)	• Chronic myelogenous leukemia	**WT1** (Urogenital differentiation)	• Wilms tumor
BRAF (RAS signal transduction)	• Hairy cell leukemia • Melanoma	**VHL** (Ubiquitin ligase component)	• Renal cell carcinoma • Von Hippel-Lindau syndrome

THE GENESIS OF A CANCER CELL

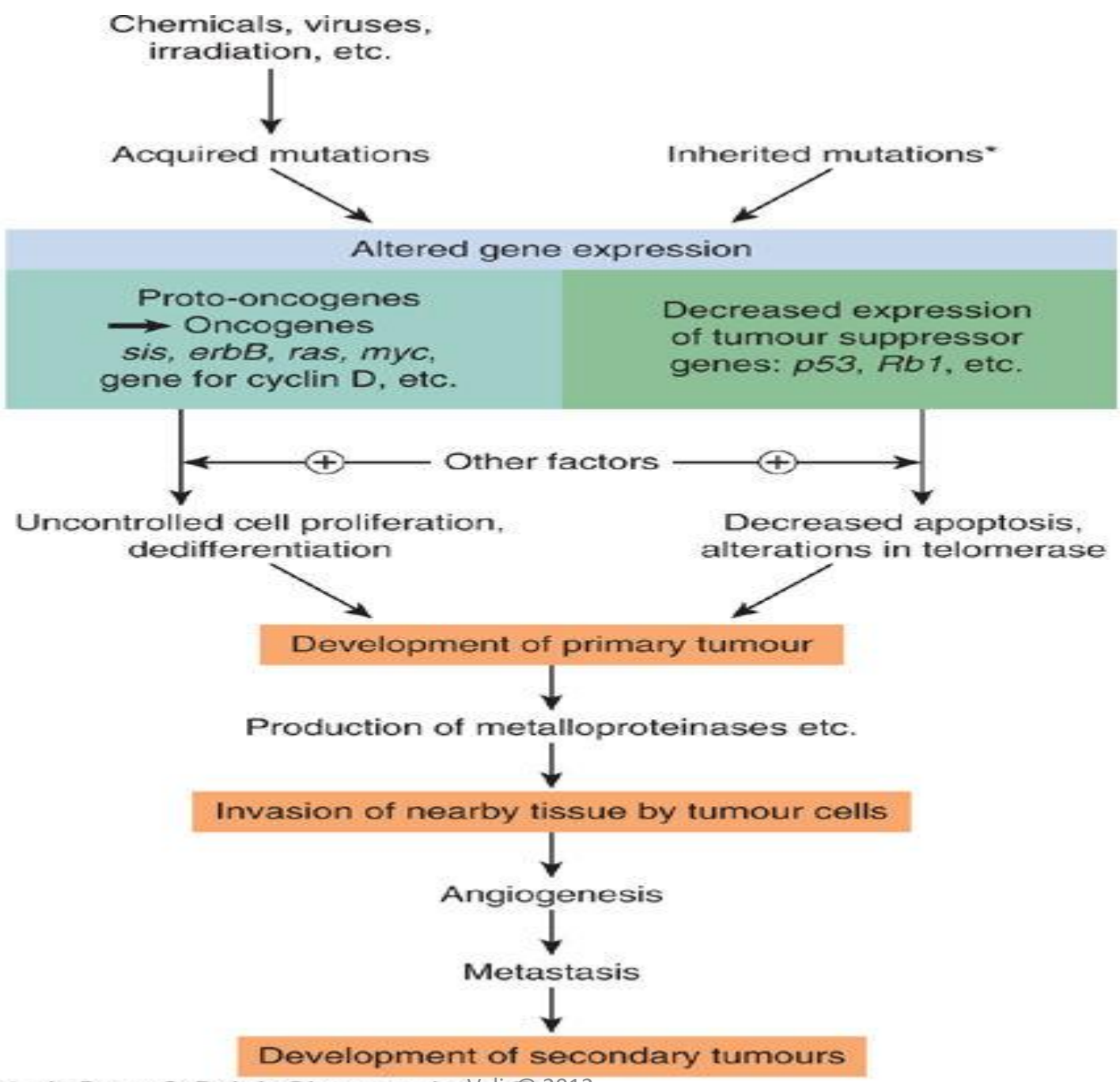
1. A normal cell turns into a cancer cell because of one or more mutations in its DNA.

i) Which can be inherited, e.g. defective copy of either of the tumor suppressor genes ***BRCA1*** and ***BRCA2*** increased risk of breast cancer. OR

ii) Which can be inherited acquired usually through exposure to viruses or *carcinogens* (e.g. tobacco products, asbestos).

2. Proto-oncogenes are genes that normally control cell division, apoptosis and differentiation but which can be converted to oncogenes that induce malignant change by viral or carcinogen action.

3. The inactivation of *tumour suppressor genes* (antioncogenes) and mutations of these genes are involved in many different cancers.



Types of tumors

1. Carcinoma- Epithelial origin

2. Sarcoma- Mesenchymal origin

3. Undefferntiated malignant tumors

Classification of tumors

A. Carcinoma

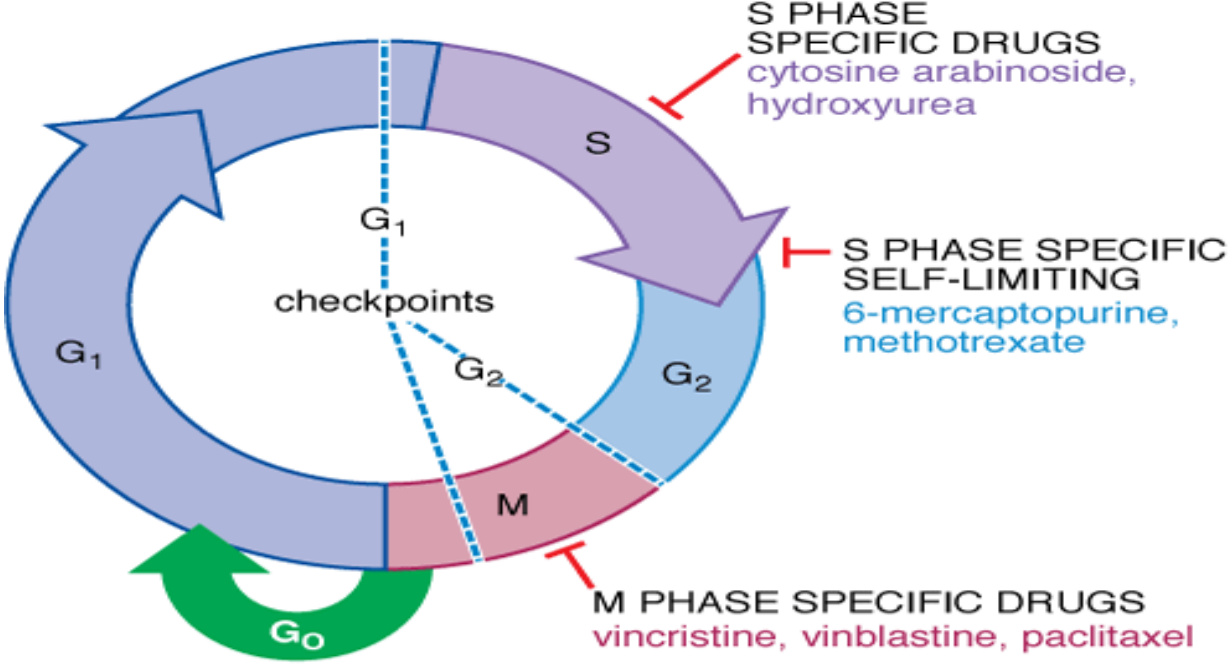
1. Squamous cell carcinoma
2. Transitional cell carcinoma
3. Glandular epithelium – Adenocarcinoma
4. Basal cell carcinoma
5. Melanoma
6. Hepatoma
7. Choriocarcinoma

B. Sarcoma

1. Adipose tissue- Liposarcoma
2. Adult fibrous tissue- Fibrocarcinoma
3. Cartilage- Chondrosarcoma
4. Bone- Osteosarcoma
5. Haematopoietic cells- Leukaemias
6. Nerve cells- Neuroblastoma
7. Lymphoid tissue- Malignant lymphomas

C. Mixed tumors

Salivary gland – Malignant mixed salivary tumor



The cell life cycle

1. a phase that precedes DNA synthesis **(G_1)**
2. a DNA synthetic phase **(S)**
3. an interval following the termination of DNA synthesis **(G_2)**
4. the mitotic phase **(M)** in which the cell, containing a double complement of DNA, divides into two daughter G_1 cells
5. a probability of moving into a quiescent state **(G_0)** and failing to move forward for long periods of time

Principles of Combination Therapy for cancer

1. Each drug should be active when used alone against the particular cancer.
2. The drugs should have different mechanisms of action.
3. Cross-resistance between drugs should be minimal.
4. The drugs should have different toxic effects.
5. Drugs with known synergistic biochemical interactions.
6. Kinetic scheduling : On basis of cell cycle specificity or non-specificity of the drugs.
7. Generally, Cell cycle non-specific drugs are used initially in short courses (pluses) and then cell cycle specific drugs are given to improve cell killing.

Cell cycle specific drugs

G1: Vinblastine

S: Mtx, 6-TG, 6-MP, 5-FU, Mitomycin

G2: Daunorubicin, Belomycin, Etoposide, Topotecan

M: Vincristine, Vinblastine, Paclitaxel, Docetaxel

Cell cycle non-specific drugs

Kill resting as well as dividing cells e.g. Nitrogen mustard, Cyclophosphamide, Cholrambucil, Carmustine, L-asparginase, Cisplatin, Actinomycin D.

Classification of Anticancer drugs

A) Drug acting directly on cells (Cytotoxic drugs)

1. Alkylating agents

Nitrogen mustards: Mechlorethamine, Cyclophosphamide, . Ifosfamide, Chlorambucil, Melphalan

Ethylenimine: Thio-TEPA

Alkyl sulfonate: Busulfan

Nitrosureas: Carmustine (BCNU), Lomustine (CCNU)

Triazine: Dacarbazine (DTIC)

2. Antimetabolites

Folate antagonist: Methotrexate (Mtx)

Purine antagonist: 6-Mercaptopurine (6-MP), 6-Thioguanine (6TG) Azathoprine, Fludarabine

Pyrimidine antagonist: 5-Fluorouracil (5-FU)

3. Natural Compounds

Vinca alkaloids: Vincristine (Oncovin), Vinblastine

Taxanes: Paclitaxel, Docetaxel

Epipodophyllo toxin: Etoposide

Camptothecin analogues: Topotecan, Irinotecan

4. Antibiotics: Actinomycin D, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin

5. Protein tyrosine kinase inhibitors: Imatinib Dasatinib, Nilotinib,Gefitinib, Erlotinib, Sorafenib, Sunitinib

6. Miscellaneous: Hydroxyurea, Procarbazine, L-Asparaginase, Cisplatin, Carboplatin

B. Drugs altering hormonal milieu

1. *Glucocorticoids:* Prednisolone and others
2. *Estrogen :* Fosfestrol, Ethinylestradiol
3. *Selective estrogen receptor modulators:* Tamoxifen, Toremifene
4. *Selective estrogen receptor down regulator:* Fluvestrant
5. *Aromatase Inhibitors:* Letrozole, Anastrozole, Exemestane
6. *Antiandrogen:* Flutamide, Bicalutamide
7. *5-α reductase inhibitor:* Finasteride, Dutasteride
8. *GnRH analogues:* Nafarelin, Triptorelin
9. *Progestins:* Hyrdroxyprogesterone acetate, etc.

C. Monoclonal antibodies: Panitumumab, Trastuzumab Rituximab, Aalemtuzumab, Bevacizumab

Resistance to Anticancer Drugs

1. Increased DNA Repair:

Alkylating agents and cisplatin

2. Formation of Trapping Agents:

Some tumor cells increase their production of thiol trapping agents (eg, glutathione), which interact with anticancer drugs that form reactive electrophilic species. Alkylating agent eg. bleomycin, cisplatin, and the anthracyclines.

3. Changes in Target Enzymes

4. Changes in the drug sensitivity of a target enzyme Methotrexate.

5.Decreased Activation of Prodrugs: Eg. Purine Antimetabolites (Mercaptopurine, Thioguanine) and The Pyrimidine Antimetabolites (Cytarabine, Fluorouracil)

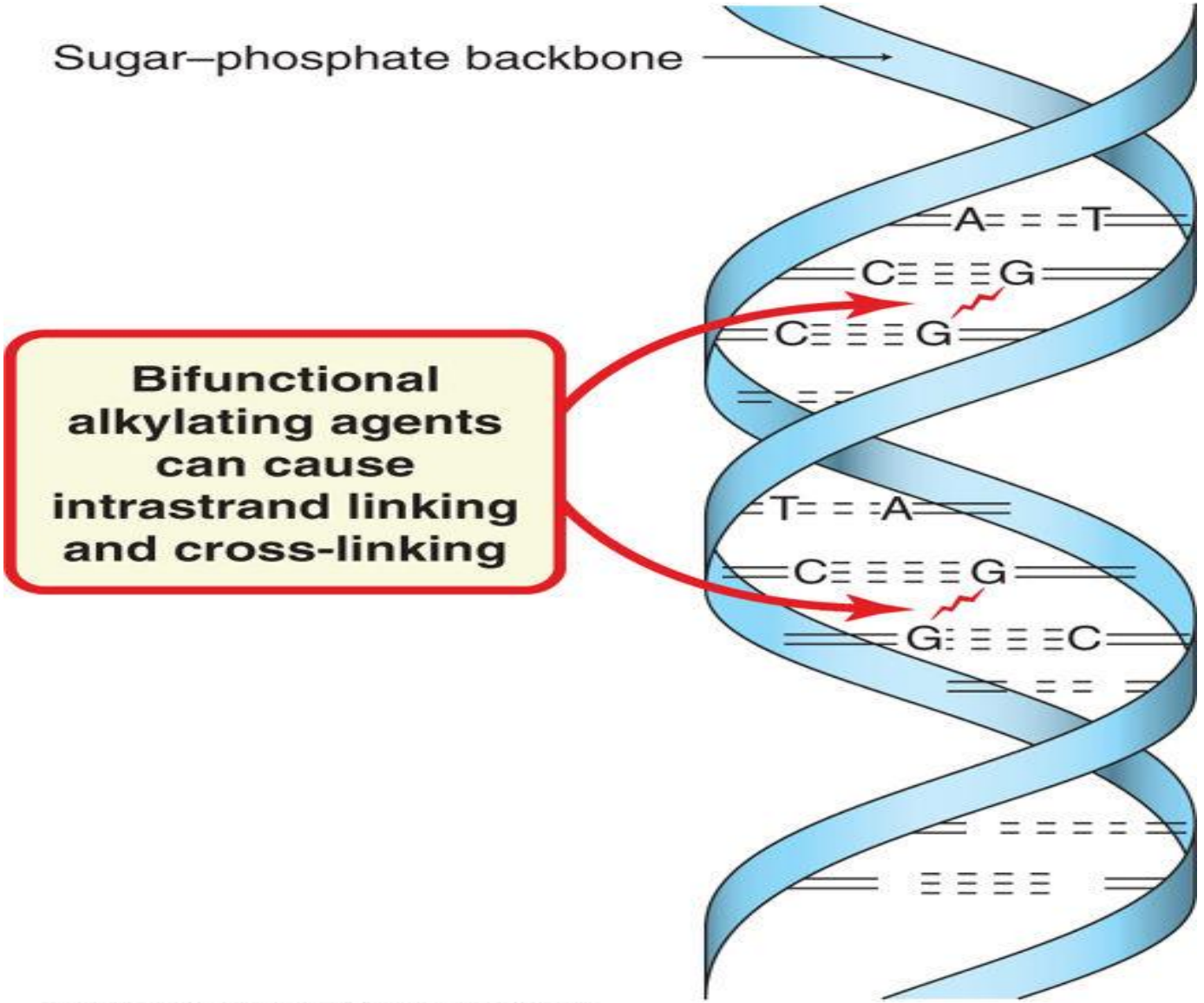
6. Inactivation of Anticancer Drugs

Eg: Purine and Pyrimidine antimetabolites.

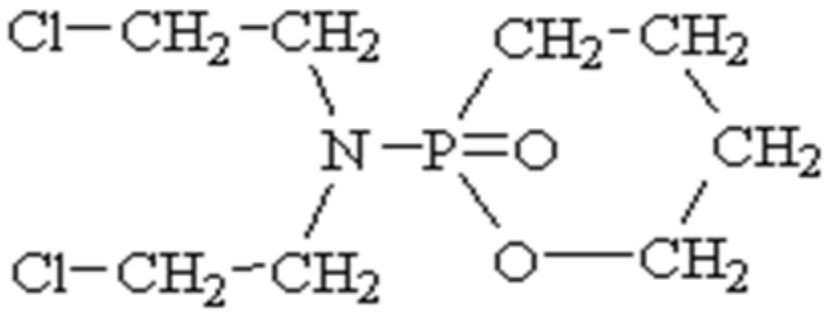
7. Decreased Drug Accumulation (Efflux of drug)

This form of multidrug resistance involves the increased expression of a normal gene (*MDR1*) for a cell surface glycoprotein (P-glycoprotein).

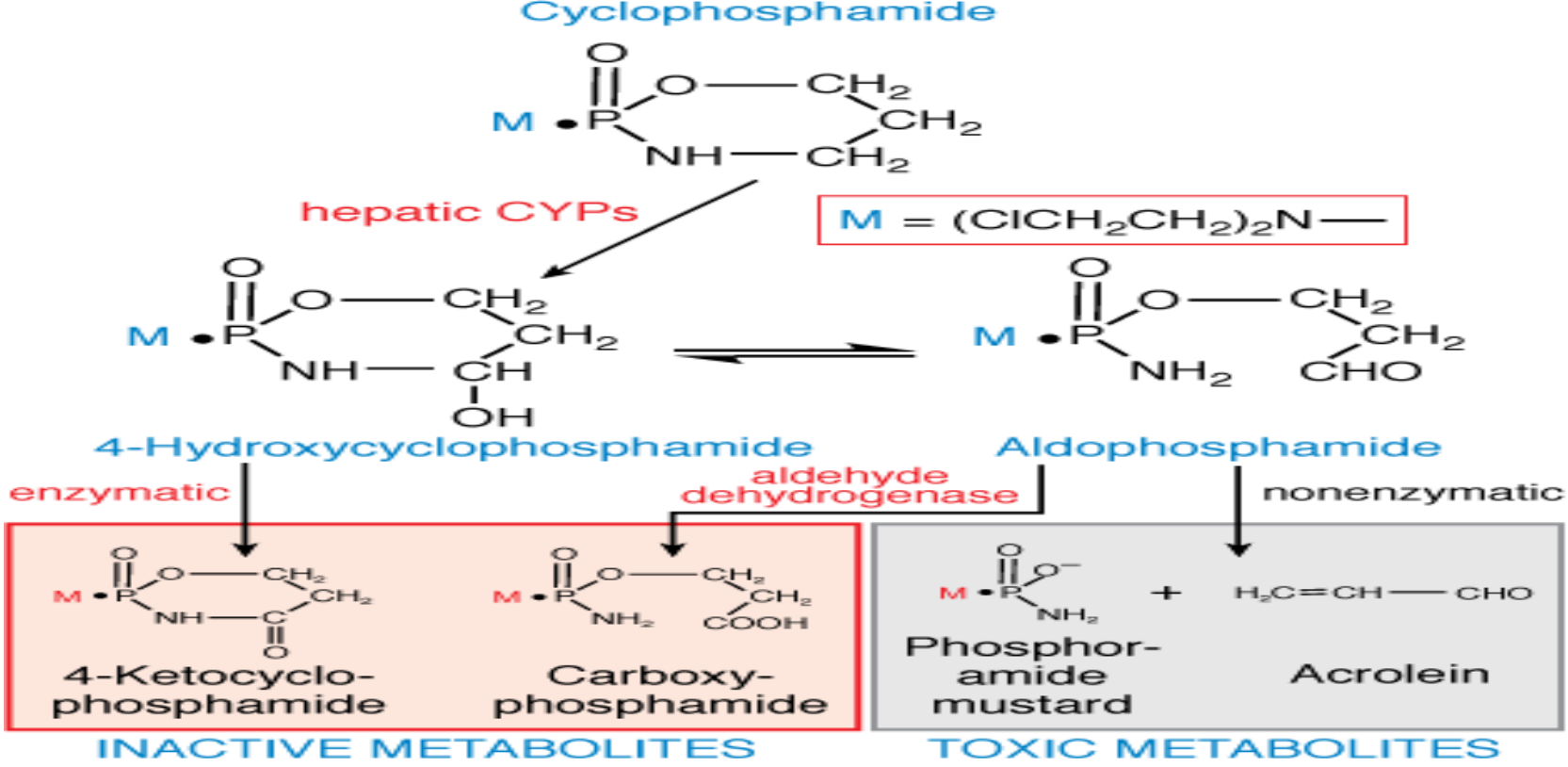
Pharmacology of Alkylating agent



Pharmacology of Cyclophospamide



Cyclophosphamide



Mechanism of action

1. They form reactive molecular species that **alkylate nucleophilic groups on DNA bases**, particularly the **N-7 position of guanine.**
2. This leads to cross-linking of bases, abnormal base-pairing, and DNA strand breakage.

Uses

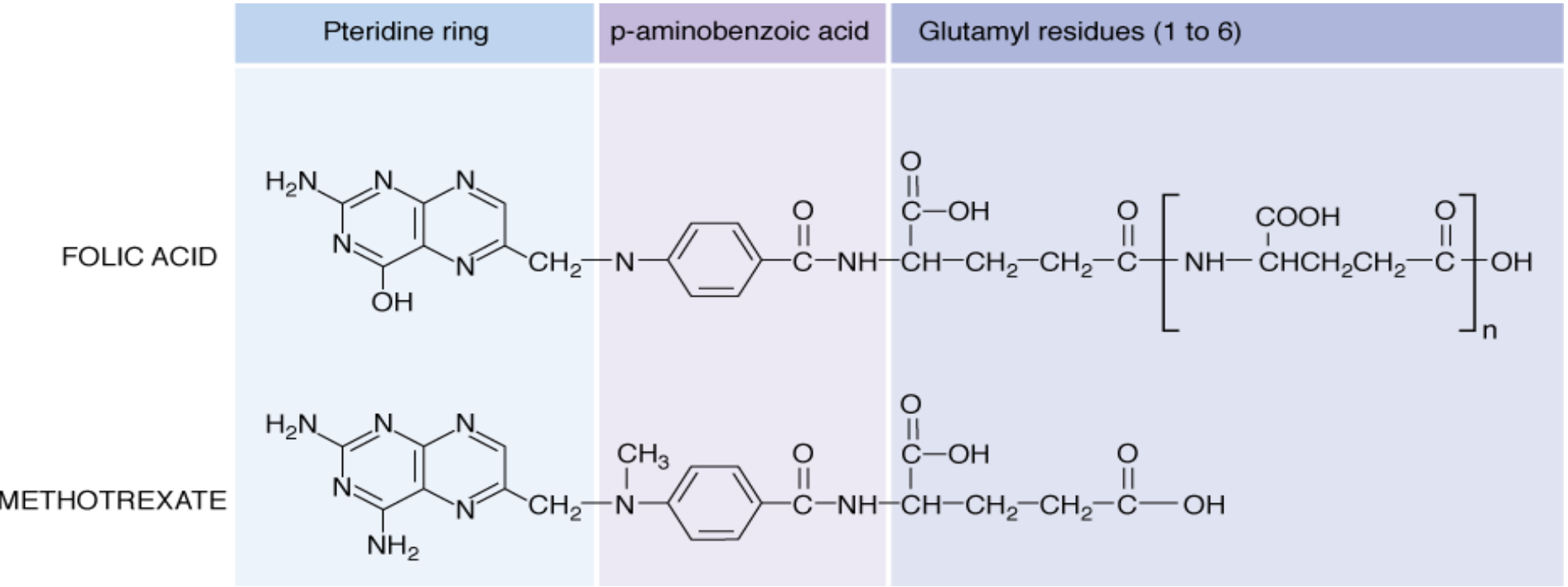
Uses of cyclophosphamide include leukemia, non-Hodgkin's lymphoma, breast and ovarian cancers, and neuroblastoma.

Brands

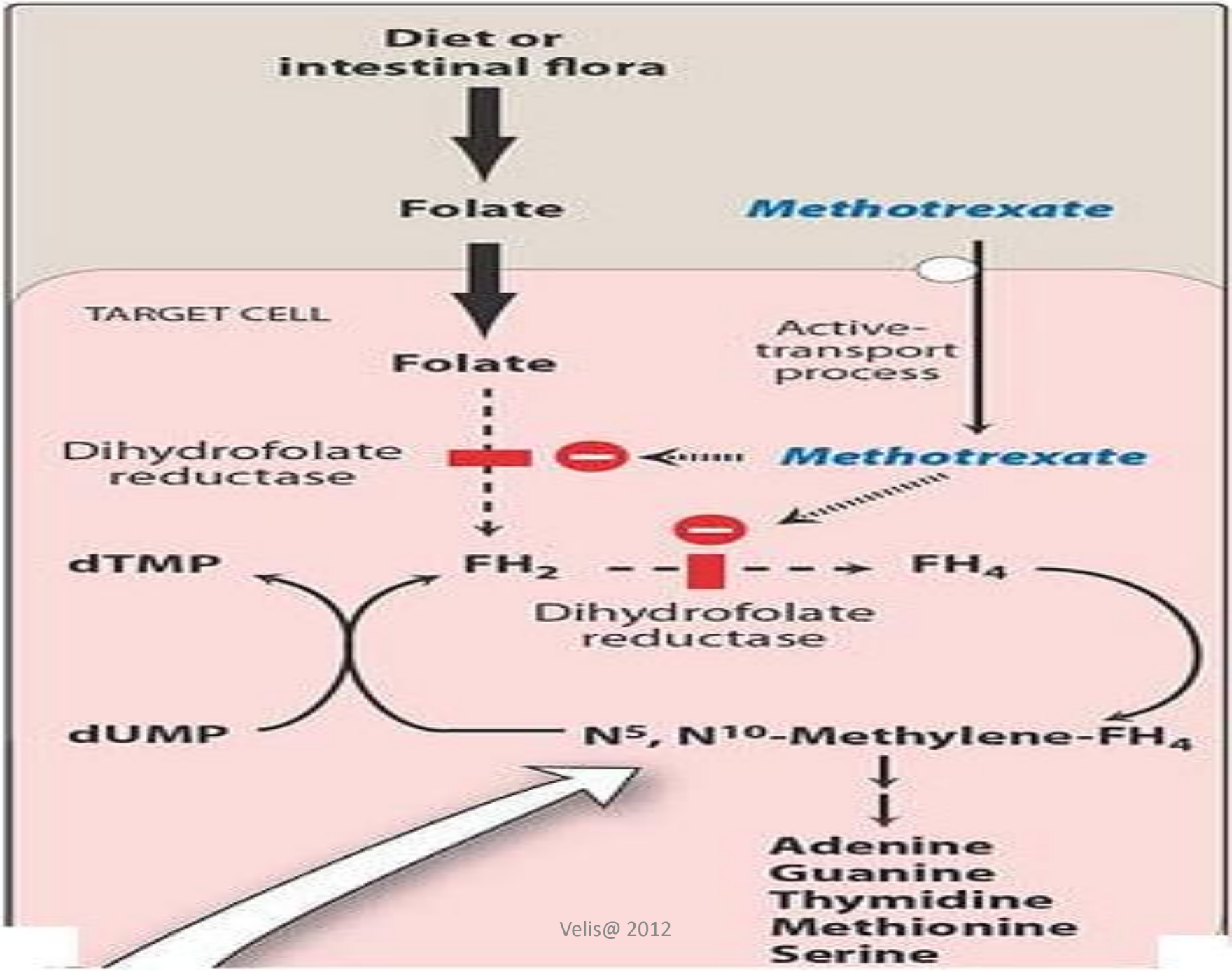
ENDOXAN, CYCLOXAN 50mg tab, 200, 500, 1000mg inj.

Pharmacology of Antimetabolites

Methotrexate (Mtx)



1. Methotrexate is an inhibitor of **dihydrofolate reductase.**
2. This action leads to a decrease in the synthesis of thymidylate, purine nucleotides, and amino acids and thus interferes with nucleic acid and protein metabolism .
3. The formation of polyglutamate derivatives of methotrexate appears to be important for cytotoxic actions.


Diet or intestinal flora
Folate
Methotrexate
TARGET CELL
Folate
Active-transport process
Dihydrofolate reductase
Methotrexate
dTMP
FH_2
FH_4
Dihydrofolate reductase
dUMP
N^5, N^{10}-Methylene-FH_4
Adenine
Guanine
Thymidine
Methionine
Serine

Uses

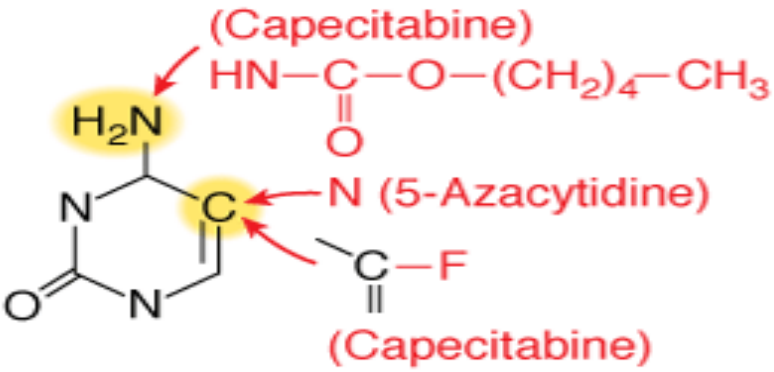
1. Methotrexate is effective in choriocarcinoma, acute leukemias, non-Hodgkin's and primary central nervous system lymphomas, and a number of solid tumors, including breast cancer, head and neck cancer, and bladder cancer.
2. Methotrexate is used also in rheumatoid arthritis psoriasis and ectopic pregnancy.

Brands

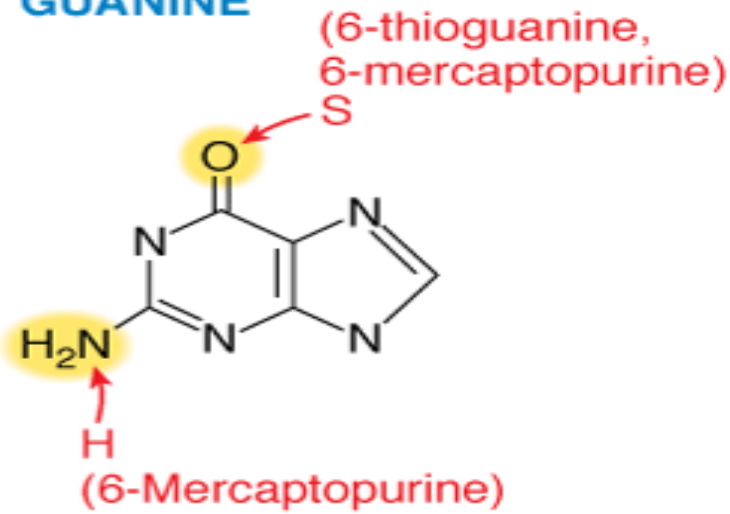
NEOTREXATE 2.5mgtab, 50mg/2ml inj

Modification of Base

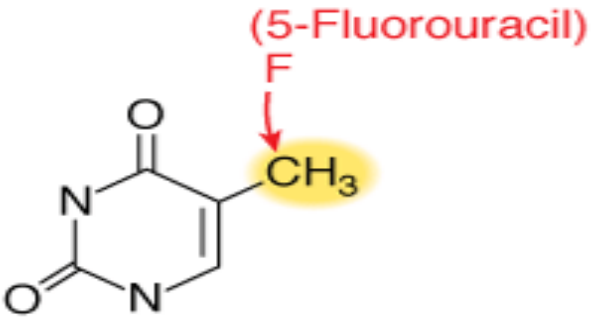
CYTOSINE



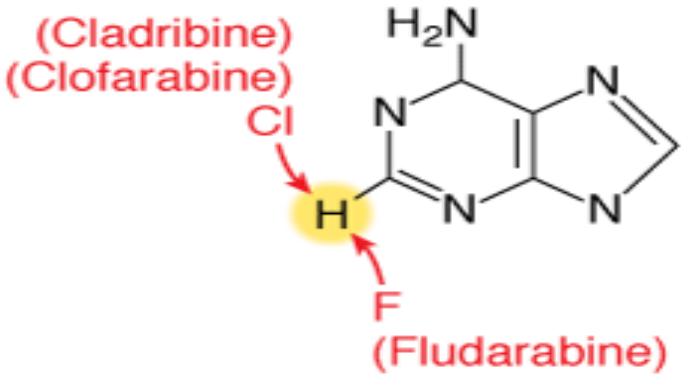
GUANINE



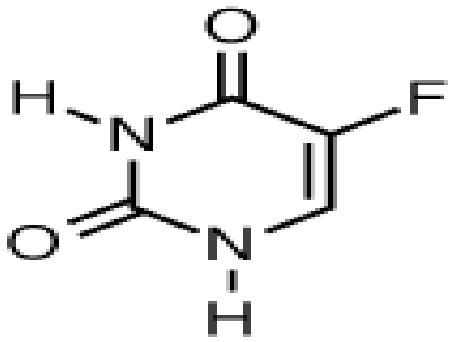
THYMINE



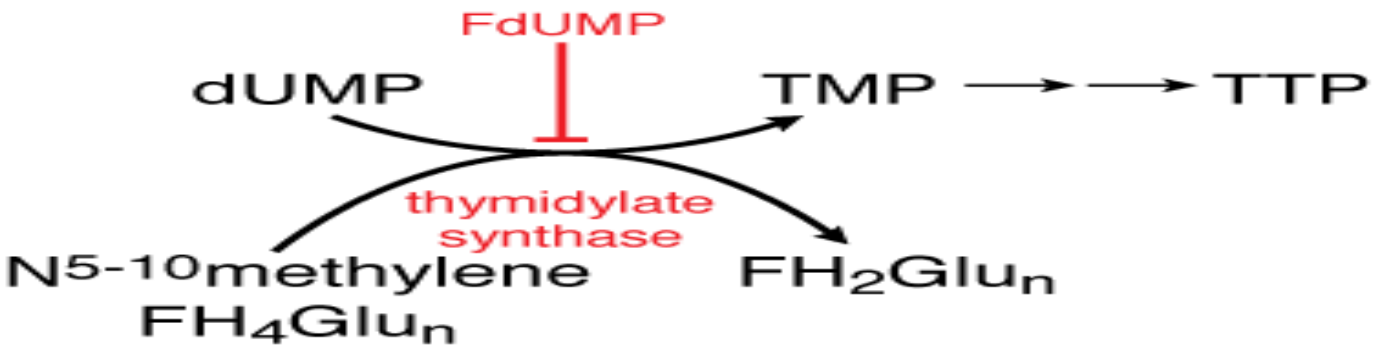
ADENINE



5- Fluorouracil (5-FU)



5-FLUOROURACIL
(5-FU)



Other actions of 5-FU nucleotides:
- Inhibition of RNA processing
- Incorporation into DNA

Mechanism of action

1. Fluorouracil is converted in cells to **5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP)**, which inhibits **thymidylate synthase and leads to "thymineless death" of cells.**
2. Incorporation of FdUMP into DNA inhibits DNA synthesis and function .
3. While incorporation of 5-fluorouridine-5'-triphosphate (FUTP), another 5-FU metabolite, into RNA interferes with RNA processing and function.

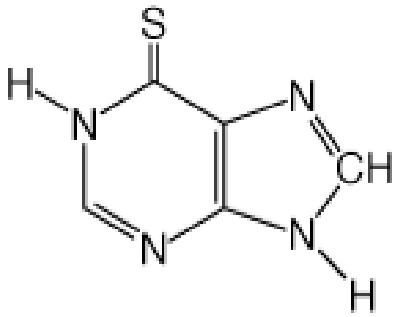
Uses

Fluorouracil is used in bladder, breast, colon, anal, head and neck, liver, and ovarian cancers. The drug can be used topically for keratoses and superficial basal cell carcinoma.

Brands

FLURACIL, FIVE FLURO 250mg cap and 250 mg/5ml, iv inj.

Mercaptopurine (6-MP) and Thioguanine (6-TG)



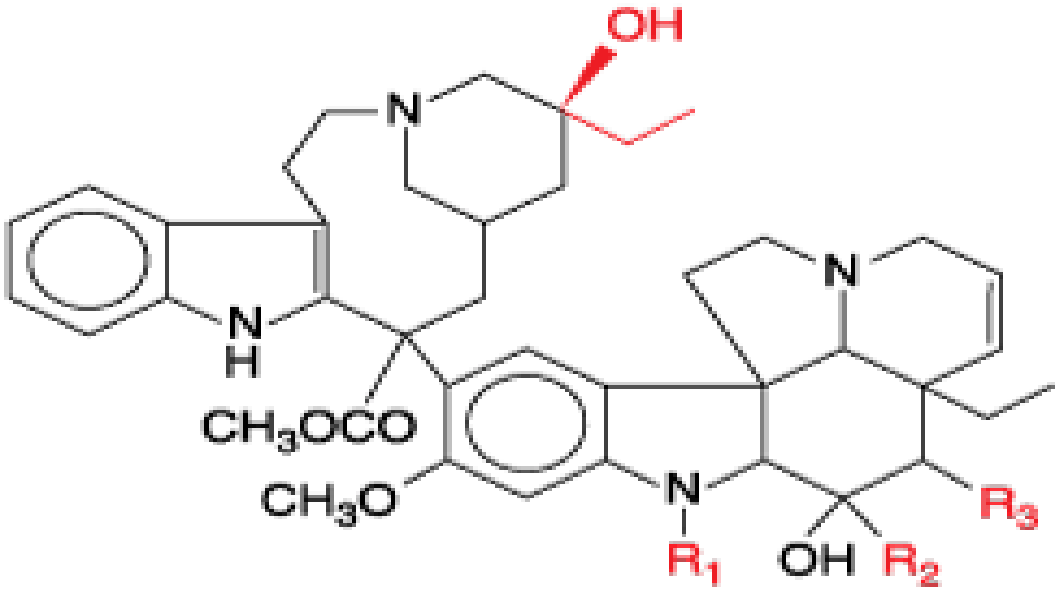
MERCAPTOPURINE

Mechanisms of Action

Mercaptopurine and thioguanine are purine antimetabolites. Both drugs are activated by hypoxanthine-guanine phosphoribosyl transferases (HGPRTases) to toxic nucleotides that inhibit several enzymes involved in purine metabolism

Uses: Purine antimetabolites are used mainly in the acute leukemias and chronic myelocytic leukemia.

Pharmacology of Vinca alkaloids



The vinca alkaloids are derived from the Madagascar periwinkle plant *Catharanthus roseus*.

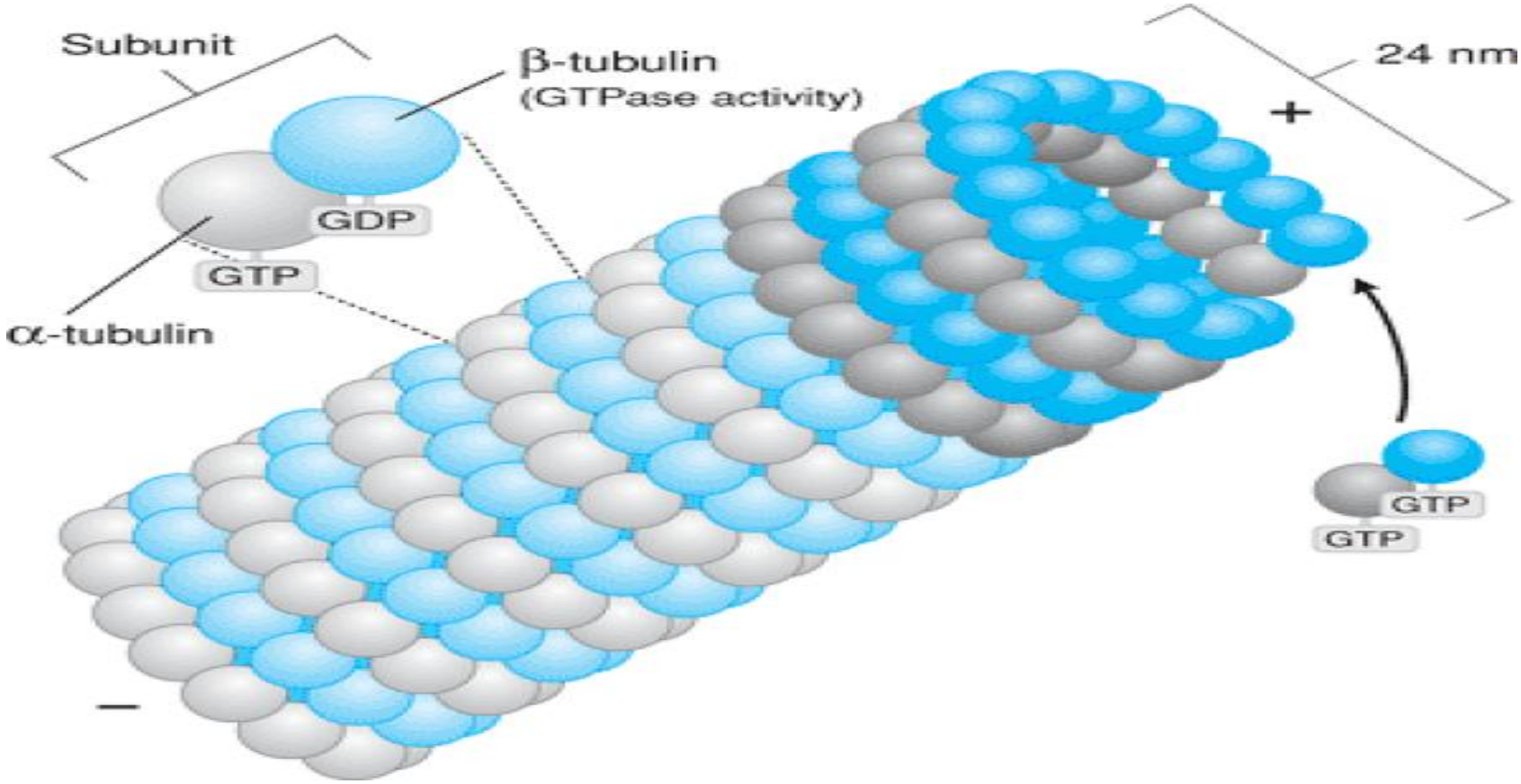
Vincristine,

Vinblastine

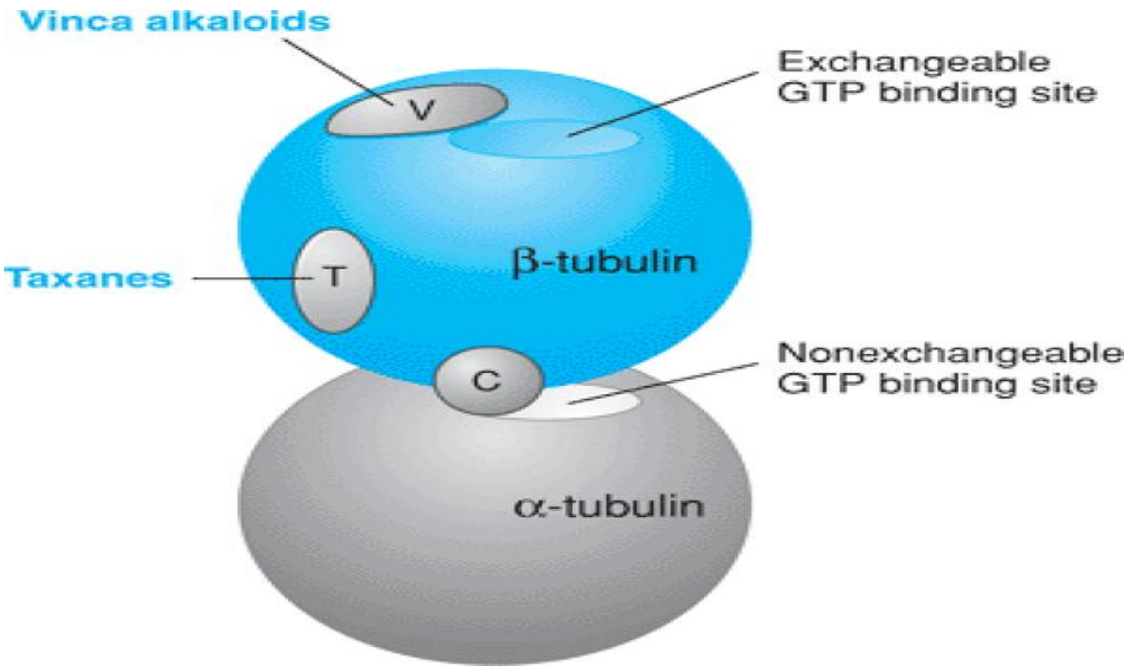
Vinorelbine and

Vindesine

Mechanism of action of Vincristine (oncovin)



The **vinca alkaloids** block the formation of the mitotic spindle by preventing the assembly of tubulin dimers into microtubules. They act primarily in the **M phase** of the cancer cell cycle.



1. Vinca alkaloids bind to ß-tubulin on a portion of the molecule that overlaps with the GTP-binding domain.
2. The binding of vinca alkaloids to ß-tubulin at the (+) end of microtubules inhibits tubulin polymerization and thereby prevents microtubule extension.
3. Because microtubules must constantly add tubulin to maintain stability (i.e., they must retain a GTP-bound tubulin cap), inhibition of tubulin addition eventually leads to the depolymerization of existing microtubules.

Uses

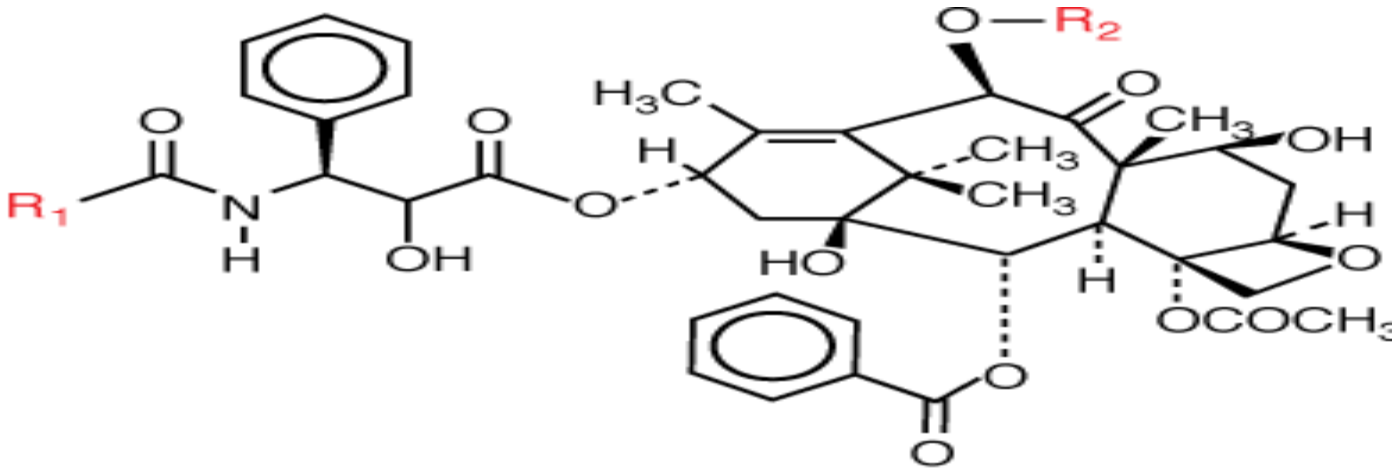
1. Vincristine is used in acute leukemias, lymphomas, Wilms' tumor, and neuroblastoma.
2. Vinblastine is used for lymphomas, neuroblastoma, testicular carcinoma, and Kaposi's sarcoma.
3. Vinorelbine is used in non-small cell lung cancer and breast cancer.

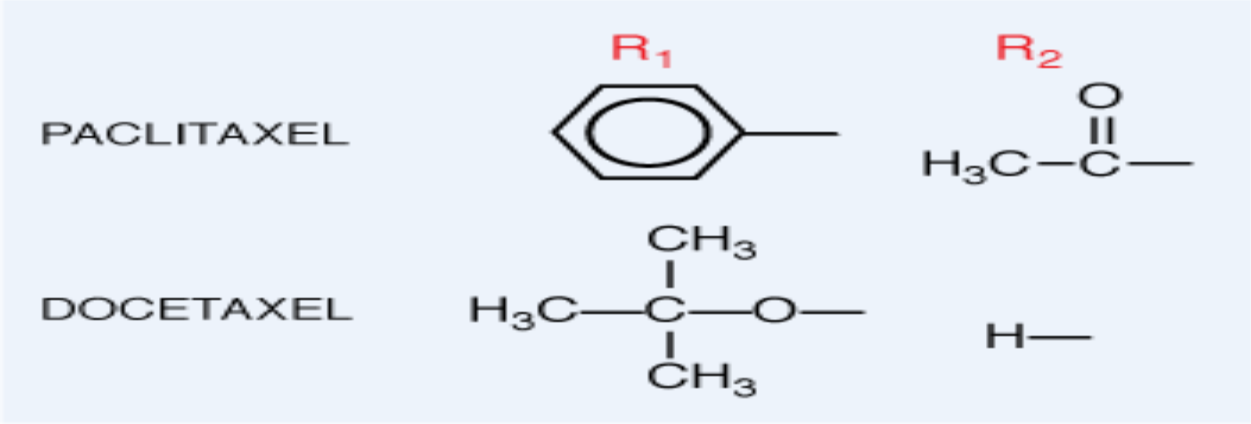
Brands

VINCRISTIN, CYTOCRISTIN 10mg/vial inj.

Taxanes

The first compound of this series, paclitaxel (TAXOL, others), was isolated from the bark of the Western yew tree in 1971





Mechanism of action

1.Paclitaxel and docetaxel interfere with the mitotic spindle. They act differently from vinca alkaloids, since they prevent microtubule *disassembly* into tubulin monomers.

2. They **enhance polymerization of tubulin.**

3. The microtubules are **stabilized** and their **depolymerization** is prevented

4. Abnormal bundles of microtubles are produced throughout the cell.

Uses: Approved indications of paclitaxel are metastatic ovarian and breast carcinom.

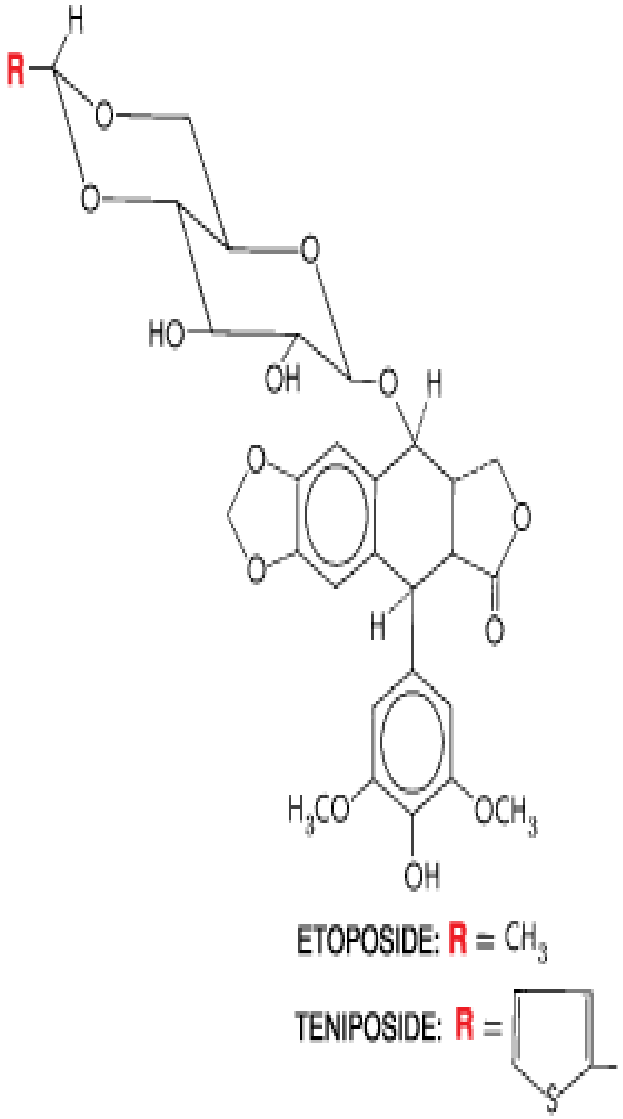
Brands: INTAXEL, PAXTAL 30mg in 5ml cremophor emulsion per vial

Epipodophyllotoxins

Etoposide : It is a semisynthetic derivative of podophyllotoxin a plant glycoside

Mechanisms of action

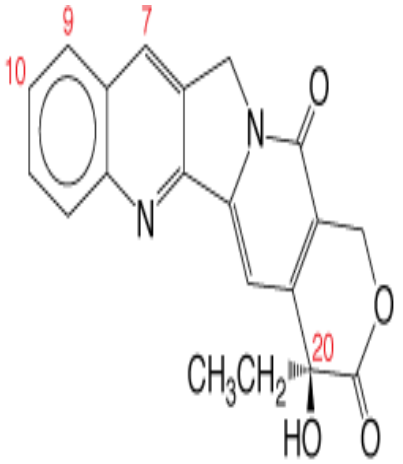
1. Etoposide, a semisynthetic derivative of podophyllotoxin, induces DNA breakage through its inhibition of **topoisomerase-II**
2. Resealing of DNA strand is prevented
3. The drug is most active in the late S and early G_2 phases of the cell cycle.
4. Teniposide is an analog with very similar pharmacologic characteristics.



Uses: These agents are used in combination drug regimens for therapy of lymphoma, and lung, germ cell, and gastric cancers.

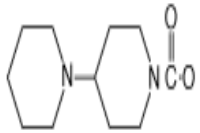
Camptothecin Analogs

The lead compound in this class, camptothecin, was isolated from the Chinese tree *Camptotheca acuminata* in 1966..



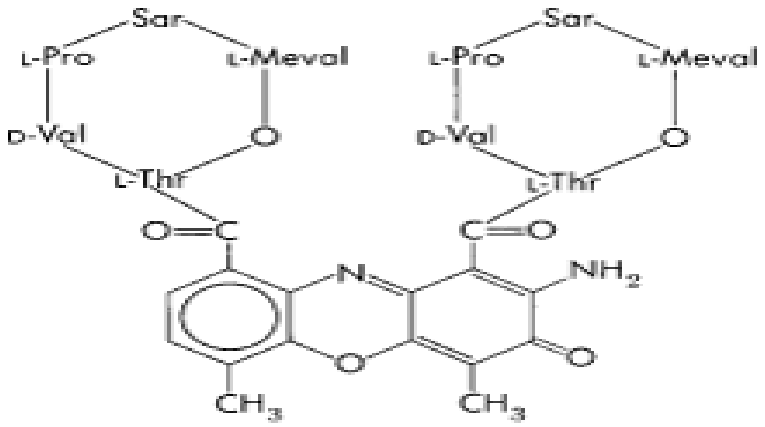
Mechanism of action

1. The 2 camptothecins, **topotecan** and **irinotecan** , produce DNA damage by inhibiting topoisomerase I. They damage DNA by inhibiting an enzyme that cuts and relegates single DNA strands during normal DNA repair processes.
2. The camptothecins are potent, cytotoxic antineoplastic agents that target the nuclear enzyme topoisomerase I.

	C-10	C-9	C-7
Camptothecin	H	H	H
Topotecan	OH	$(CH_3)_2NHCH_2$	H
Irinotecan		H	CH_2CH_3
SN-38	OH	H	CH_2CH_3

Uses: Topotecan is used as second-line therapy for advanced ovarian cancer and for small cell lung cancer. Irinotecan is used for metastatic colorectal cancer.

Pharmacology of Anticancer antibiotics
Dactinomycin (Actinomycin D)



Mechanism of action

The anthracyclines (**doxorubicin** , **daunorubicin**, **idarubicin** , **epirubicin** , **mitoxantrone**) intercalate between base pairs, inhibit topoisomerase II, and generate free radicals. They block the synthesis of RNA and DNA and cause DNA strand scission. Membrane disruption also occurs. Anthracyclines are CCNS drugs.

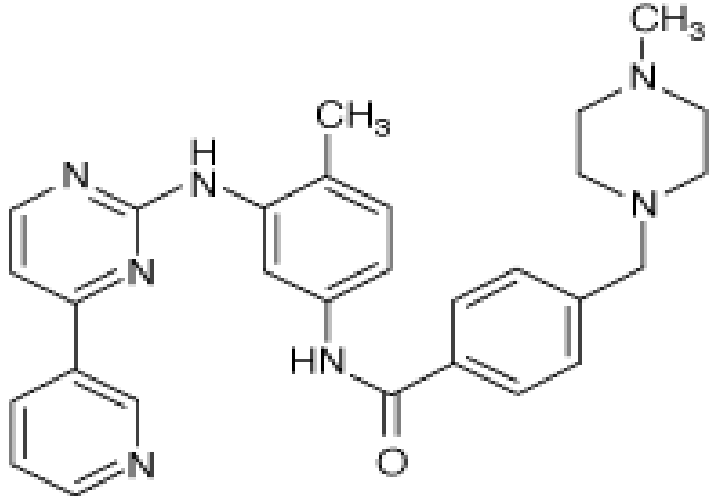
Uses

1. The most important clinical use of dactinomycin is in the treatment of rhabdomyosarcoma and Wilms tumor in children,
2. Ewing, Kaposi, and soft-tissue sarcomas also respond.
3. Dactinomycin and methotrexate form a curative therapy for choriocarcinoma.

Brands

DDACMOZEN 0.5 mg/vial inj.

Protein tyrosine kinase inhibitors:



Imatinib

Mechanism of action

1. It inhibits the **tyrosine kinase activity** a protein product of the ***bcr-abl*** **oncogene** that is commonly expressed in chronic myelogenous leukemia (CML).
2. In addition to its activity in CML, imatinib is effective for treatment of gastrointestinal stromal tumors that express the c-*kit* tyrosine kinase, which is also inhibited.

Uses: Chronic myeloid leukaemia

Brands: IMATIB-α, SHANTINAB 100mg cap.

Platinum Coordination Complexes

The platinum coordination complexes have broad antineoplastic activity and have become the foundation for treatment of ovarian, head and neck, bladder, esophagus, lung, and colon cancers

Mechanism of Action

1. Cisplatin, carboplatin, and oxaliplatin enter cells by an active Cu^{2+} transporter, CTR1, and in doing so rapidly degrade the transporter.
2. Inside the cell, the chloride, cyclohexane, or oxalate legends of the three analogs are displaced by water molecules, yielding a positively charged and highly reactive molecule.
3. The activated platinum complexes can react with electron-rich molecules, such as sulfhydryls, and with various sites on DNA, forming both intrastrand and interstrand cross-links.
4. The N-7 of guanine is a particularly reactive site, leading to platinum cross-links between adjacent guanines (GG intrastrand cross-links) on the same DNA strand; guanine–adenine cross-links also form and may contribute to cytotoxicity.

Miscellaneous compounds

A) Hydroxyurea (HU)

1. This drug has unique and surprisingly diverse biological effects as an anti-leukemic drug, radiation sensitizer.

2. HU inhibits the enzyme **ribonucleoside diphosphate reductase**, which catalyzes the reductive conversion of ribonucleotides to deoxyribonucleotides, a rate-limiting step in the biosynthesis of DNA.

3. The drug is specific for the S phase of the cell cycle.

4. Because cells are highly sensitive to irradiation at the G_1–S boundary, HU and irradiation cause synergistic antitumor effects

B) L-Asparaginase (L-ASP)

The enzyme is purified from ***Escherichia coli*** proved to have dramatic antitumor activity against malignant lymphoid cells.

Mechanism of Action

1. Most normal tissues are able to synthesize L-asparagine in amounts sufficient for protein synthesis, but lymphocytic leukemias lack adequate amounts of **asparagine synthetase,** and derive the required amino acid from plasma.
2. L-ASP, by catalyzing the hydrolysis of circulating **asparagine to aspartic acid and ammonia,** deprives these malignant cells of asparagine, leading to cell death.
3. L-ASP is used in combination with other agents, including methotrexate, doxorubicin, vincristine, and prednisone for the treatment of ALL and for high-grade lymphomas.

Drugs altering hormonal milieu

A) Glucocorticoids (Prednisolone and Dexamethasone)

1. Act through their binding to a specific **physiological receptor that translocates to the nucleus and induces anti-proliferative and apoptotic responses in sensitive cells.**
2. Because of their lympholytic effects and their ability to suppress mitosis in lymphocytes, glucocorticoids are used as cytotoxic agents in the treatment of acute leukemia in children and malignant lymphoma in children and adults.

B) Estrogens (Fosfestrol, Ethinylestradiol) and Androgens

1. These agents are of value in certain neoplastic diseases, notably those of the **prostate and mammary gland**, because these organs are dependent on hormones for their growth, function, and morphological integrity.
2. By changing the hormonal environment of such tumors, it is possible to alter the course of the neoplastic process.
3. High doses of estrogen have long been recognized as effective treatment of breast cancer.

C) Selective Estrogen-Receptor Modulators (SERM)

SERMs bind to the ER and exert either estrogenic or anti-estrogenic effects, depending on the specific organ.

Tamoxifen

1. Tamoxifen was first synthesized in 1966 was found to induce ovulation and proved to have anti-proliferative effects on estrogen-dependent breast cancer cell lines.

Mechanism of Action

1. Tamoxifen is a competitive inhibitor of **estradiol binding to the ER.**
2. Tamoxifen is prescribed for the prevention of breast cancer in high-risk patients, for the adjuvant therapy of early-stage breast cancer, and for the therapy of advanced breast cancer.

Selective Estrogen Receptor Downregulators: SERDs, also termed "pure anti-estrogens,"

Fulvestrant

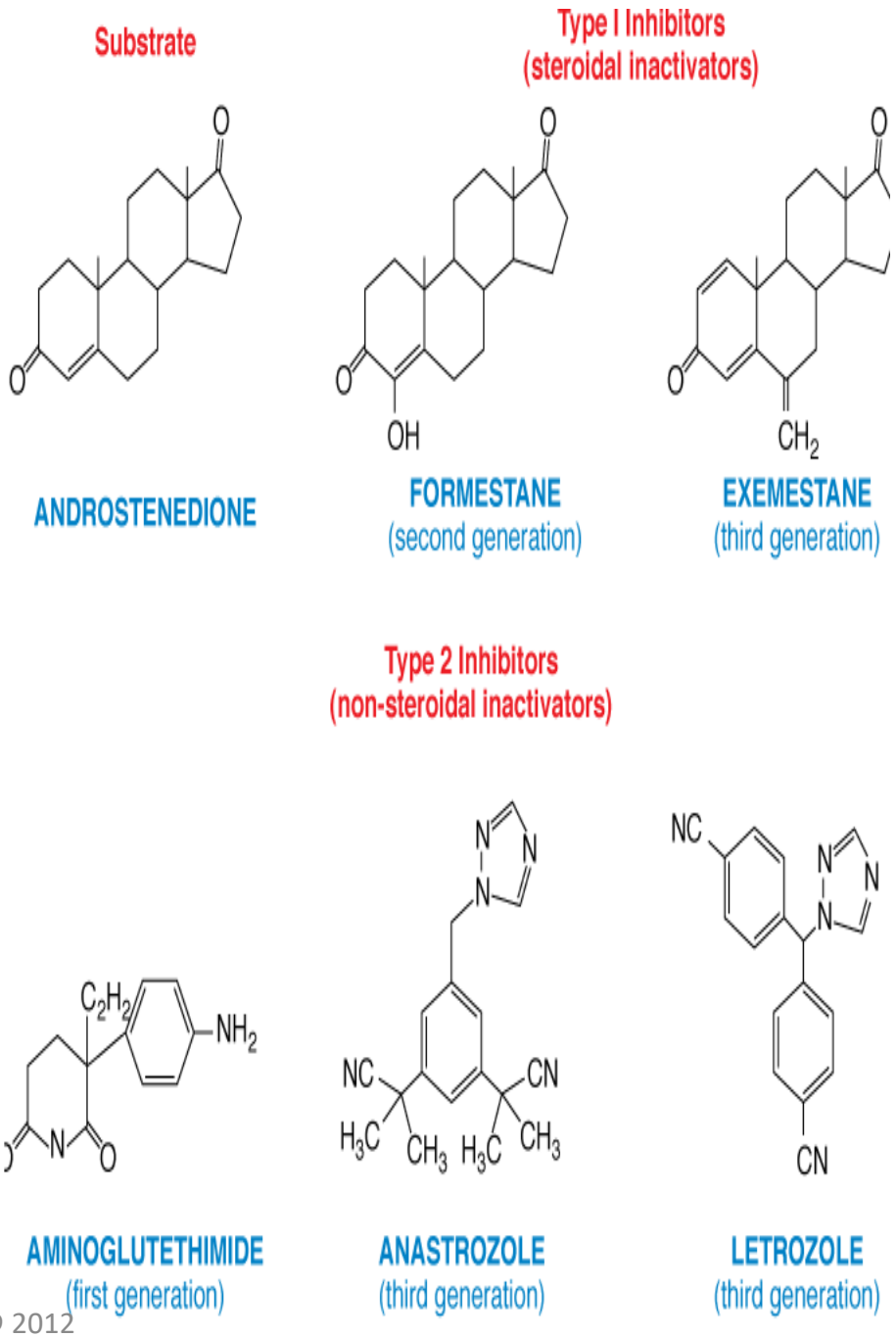
1. Is the first agent approved by the U.S. FDA in the class of ER downregulators. Fulvestrant is approved for postmenopausal women with hormone receptor–positive metastatic breast cancer that has progressed on tamoxifen.

Mechanism of Action

1. Fulvestrant is a steroidal anti-estrogen that binds to the ER with an affinity >100 times that of tamoxifen.
2. The drug inhibits the binding of estrogen but also alters the receptor structure such that the receptor is targeted for proteasomal degradation; fulvestrant also may inhibit receptor dimerization.
3. Fulvestrant reduces the number of ER molecules in cells, both *in vitro* and *in vivo;* as a consequence of this ER downregulation, the drug abolishes ER-mediated transcription of estrogen-dependent genes

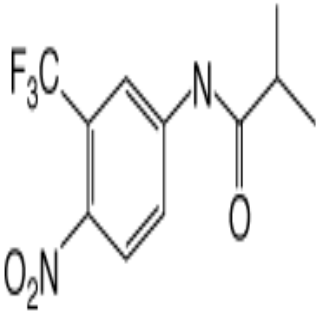
Aromatase Inhibitors

1. Aromatase inhibitors block the function of the **aromatase enzyme that converts androgens to estrogens.**
2. The aromatase enzyme is responsible for the conversion of adrenal androgens and gonadal androstenedione and testosterone to the estrogens, estrone (E1) and estradiol (E2), respectively.
3. In postmenopausal women, AIs can suppress most peripheral aromatase activity, leading to profound estrogen deprivation. This strategy of estrogen deprivation of ER^+ breast cancer

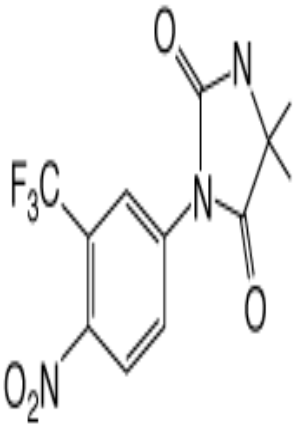


Anti-Androgens

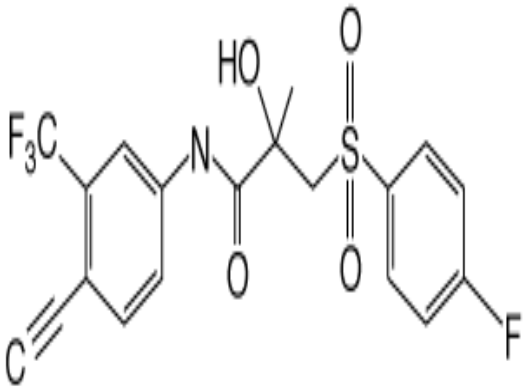
1. Anti-androgens bind to ARs and competitively inhibit the binding of testosterone and dihydrotestosterone.
2. The nonsteroidal anti-androgens are taken orally and inhibit ligand binding and consequent AR translocation from the cytoplasm to the nucleus.
3. Currently, anti-androgen monotherapy is not indicated as first-line treatment for patients with advanced prostate cancer.



flutamide



nilutamide



bicalutamide

5-α reductase inhibitor

Finasteride and **Dutasteride** inhibit conversion of testosterone to dihydrotestosterone in prostate .Used for palliative effect in advanced carcinoma of prostate.

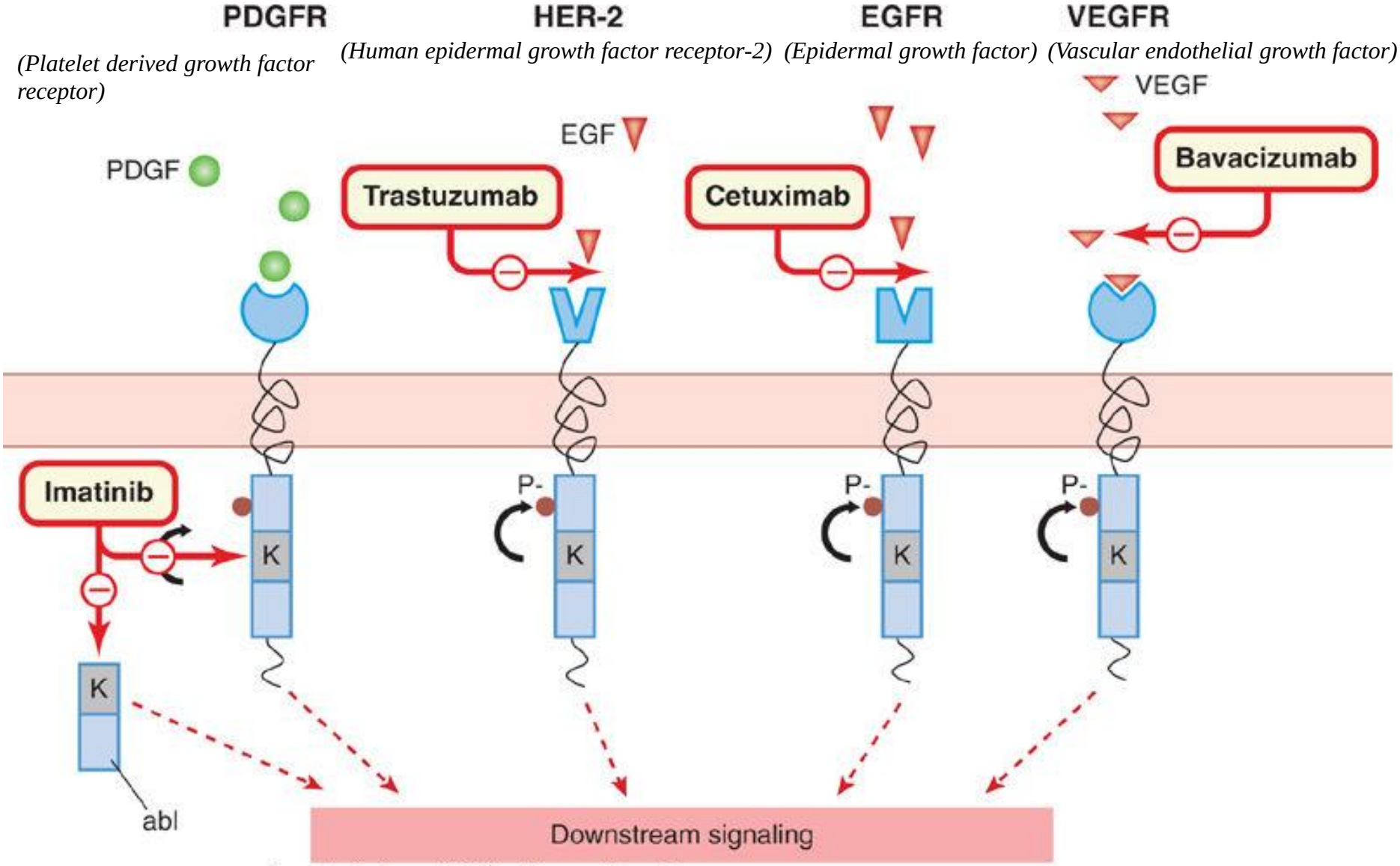
GnRH analogues

Nafarelin and **Triptorelin** indirectly inhibit estrogen and androgen secretion by suppression of FSH and LH release from pituitary. Used in advanced estrogen/androgen dependent carcinoma of breast/prostate.

Progestins

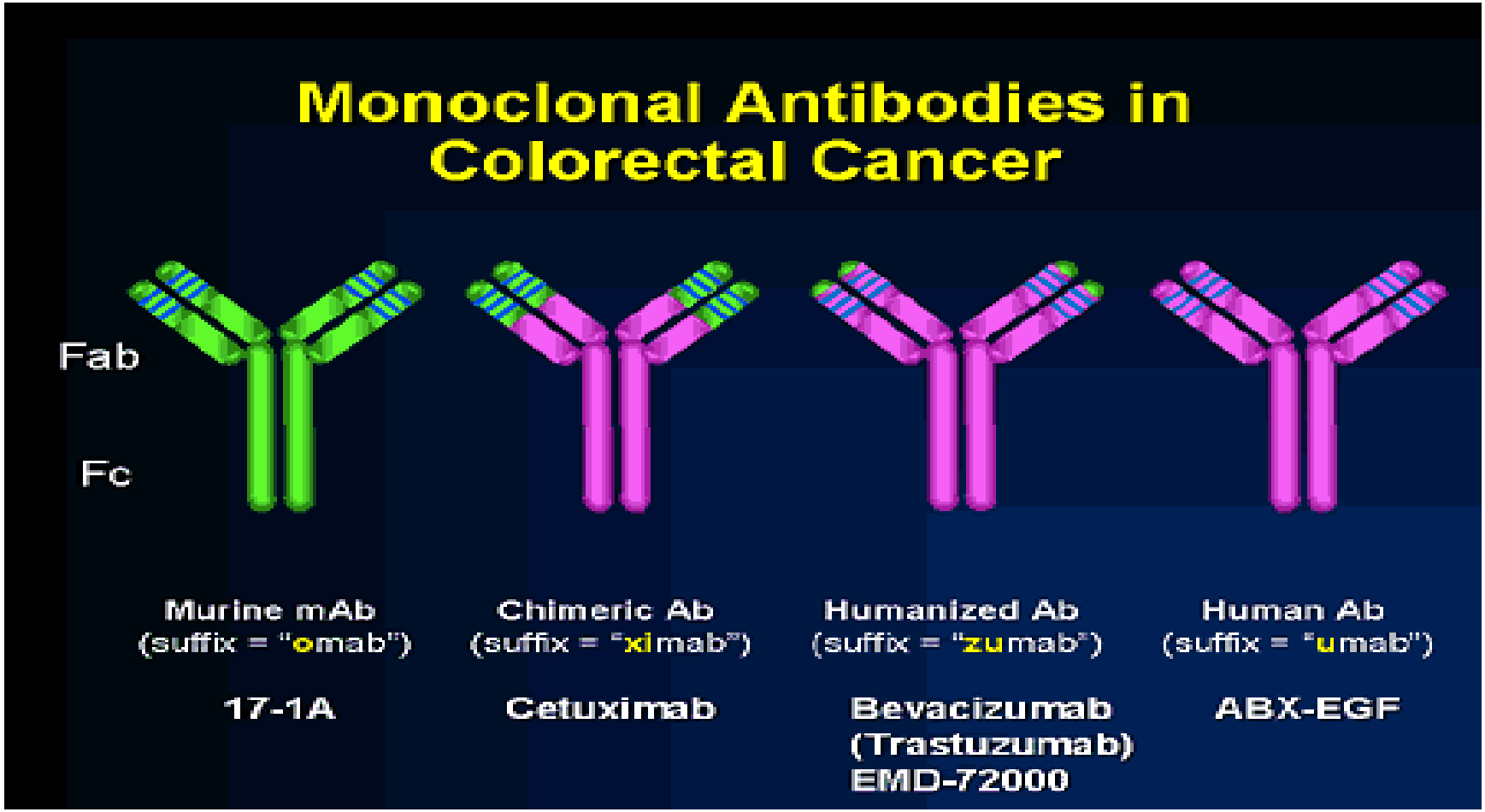
Hyrdroxyprogesterone acetate, etc.

Used for temporary remission in advanced, recurrent metastatic endometrial carcinoma.



Intracellular signaling pathways

Monoclonal antibodies are immunoglobulins, of one molecular type, produced by hybridoma cells in culture, that react with defined target proteins expressed on cancer cells.



Rituximab Rituximab is a monoclonal antibody that is licensed (in combination with other chemotherapeutic agents) for treatment of certain types of ***lymphoma***. It lyses B lymphocytes by binding to the **calcium channel-forming CD20 protein and activating complement.** It also sensitizes resistant cells to other chemotherapeutic drugs. It is effective in 40-50% of cases when combined with standard chemotherapy.

Alemtuzumab is another monoclonal antibody that **lyses B lymphocytes,** and is used in the treatment of resistant chronic lymphocytic leukemia. It may also cause a similar cytokine release reaction to that with rituximab.

Trastuzumab (Herceptin) is a humanised murine monoclonal antibody that binds to an oncogenic protein termed *HER2* (the human epidermal growth factor receptor 2). There is some evidence that, in addition to inducing host immune responses, trastuzumab induces cell cycle inhibitors p21 and p27. Tumour cells, in about 25% of breast cancer patients, over express this receptor and the cancer proliferates rapidly. The drug is often given with a taxane such as docetaxel.

Panitumumab and **Cetuximab**, which bind to epidermal growth factor (EGF) receptors (also over expressed in a high proportion of tumours). They are used for the treatment of colorectal cancer usually in combination with other agents.

Bevacizumab is a humanised monoclonal antibody that is also used for the treatment of colorectal cancer but would be expected to be useful for treating other cancers too. It neutralises *VEGF* (vascular endothelial growth factor), thereby preventing the angiogenesis that is crucial to tumour survival.

General toxicity of cytotoxic drugs

1. Bone marrow Depression
2. Lymphocytopenia
3. Oral cavity
4. GIT: Nausea, vomiting, diarrhoea, Shedding of mucosa, hemorrahage
5. Gonads: Oligozoospermia and impotence
6. Teratogenicity
7. Carcinogenicity
8. Hyperuricaemia
9. Skin: Alopecia, Dermatitis., etc

Management of toxicity of anticancer drugs

1.Toxicity blocking drugs: Folinic acid: Rescues normal cell

2.Cystitis caused by cyclophophamide: Mesna and irrigation of bladder by acetylcysteine

3. Controlling vomiting : Ondansetron a 5-HT_3 antagonist

4. Hyperuricaemia: Allopurinol

5. Hypercalcaemia: Vigorous hydration and i.v bisphosphonates

6. Drugs given in pulses with 2-3 week intervals

7.Selective exposure of tumour to the drug

8. Platelet and or granulocyte transfusion

9. Use of biological response modifiers like GM-CSF/G-CSF for hasten recovery from cytotoxic drug induced myelosuppression.

10. Molgramostim: A colony stimulating factor

11. Bone marrow transplantation

12. Thalidomide: Anxiolytic, antiemetic, adjuvant analgesic/antipyretic

Targeted drugs for cancer

1. *Tyrosine protein kinase inhibitors :* Imatinib, Nilotinib
2. *EGF receptor inhibitors:* Gefitinib, Erlotinib, Cetuximab
3. *Angiogenesis inhibitors:* Bevacizumab, Sunitinib
4. *Proteasome inhibitor:* Bortezomib
5. *Unarmed monoclonal antibody (MAbs):* Rituximab,Trastuzumab
6. Armed (Toxin linked) *MAbs:* Ozogamicin, Gemtuzumab
7. Armed (Radioisotope carrying) *MAbs:* Ibritumomab (^{90}Y), Tositumomab (^{131} I)