MUNI
PHARM

CANCER CHEMOTHERAPY
OVERVIEW OF ANTICANCER DRUGS

Assoc. Prof. PharmDr. Peter Kollár, Ph.D.
Department of Pharmacology and Toxicology
Faculty of Pharmacy MU

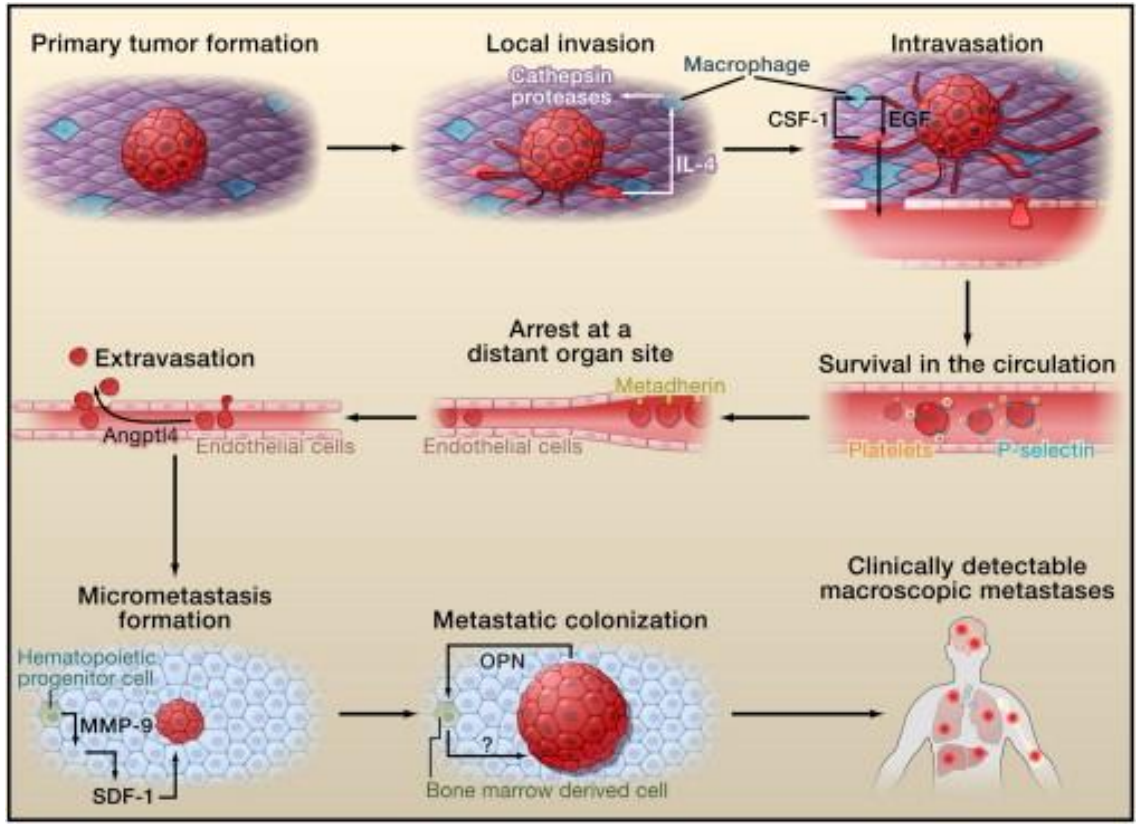
Tumor Cells

Characterized by:

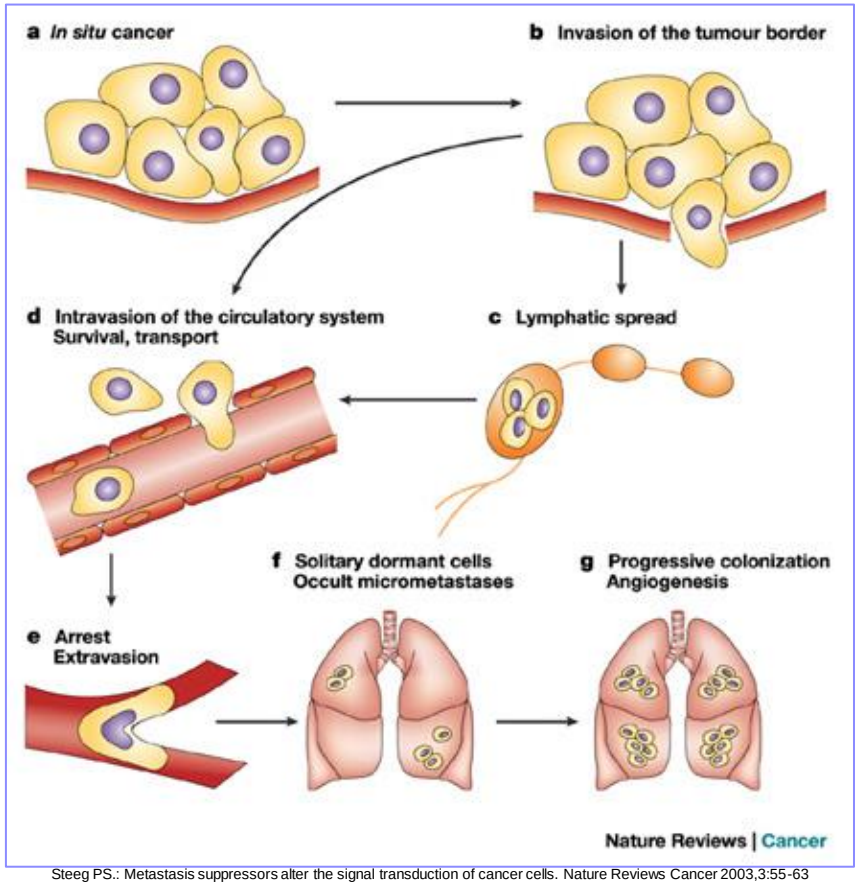
- Persistent, uncontrolled cell proliferation
- Loss of function
- Invasive growth
- Metastases
  - tumor may shed cells into the circulation
  - most circulating tumor cells die
  - part adhere to endothelium, penetrate into surrounding tissues, generating independent tumors (metastases)

MUNI PHARM

Process of Metastasis



Valastyan S., Weinberg RA.: Tumor Metastasis: Molecular Insights and Evolving Paradigms. Cell 2011,147(2):275–292

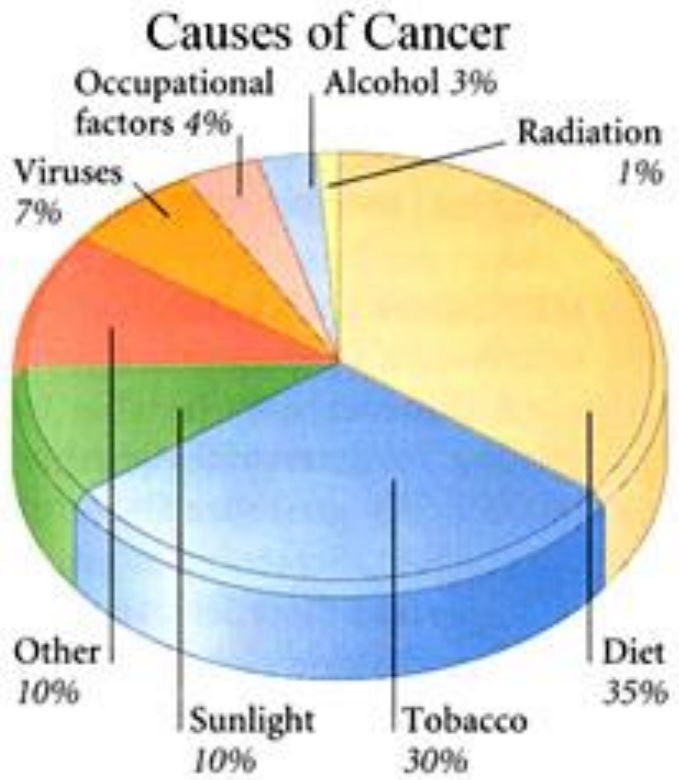


Steeg PS.: Metastasis suppressors alter the signal transduction of cancer cells. Nature Reviews Cancer 2003,3:55-63

MUNI PHARM

Etiology of Cancer

- Genetics
- Viruses
- Occupational and environmental carcinogens
- Radiation



http://forum.facmedicine.com/oncology/6933-understanding-cancer-series-part-24-what-causes-cancer.html

MUNI PHARM

Treatment Approaches

– Surgery, radiotherapy, chemotherapy

– Good response to chemotherapy
- Retinoblastoma
- Osteosarcoma
- Testicular cancer
- Hodgkin’s Disease
- Childhood leukemia
- Some lymphomas
- Some early breast cancers

– Bad response to chemotherapy
- Colon
- Lung
- Late stage breast cancer
- Pancreatic cancer

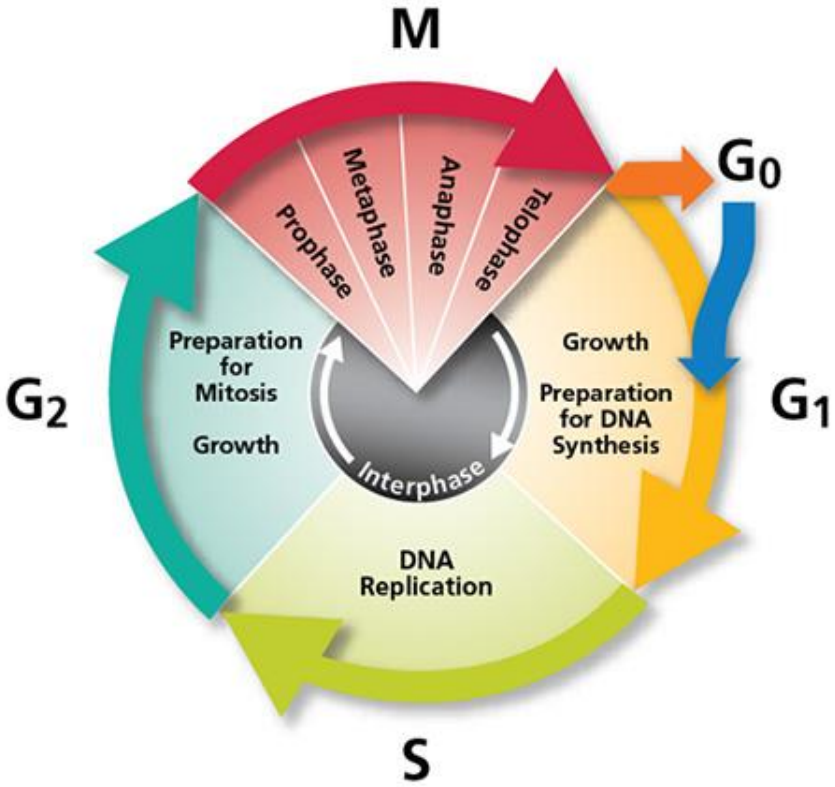
Cell Cycle

Cell Cycle Non-specific (CCNS) Agents

– for large slowly growing tumors (alkylating agents, ATBs, etc.)

Cell Cycle Specific (CCS) Agents

– for rapidly growing tumors (M-phase: taxanes, Vinca alkaloids, S-phase: antiMTBs)



http://www.bdbiosciences.com/research/apoptosis/analysis/index.jsp

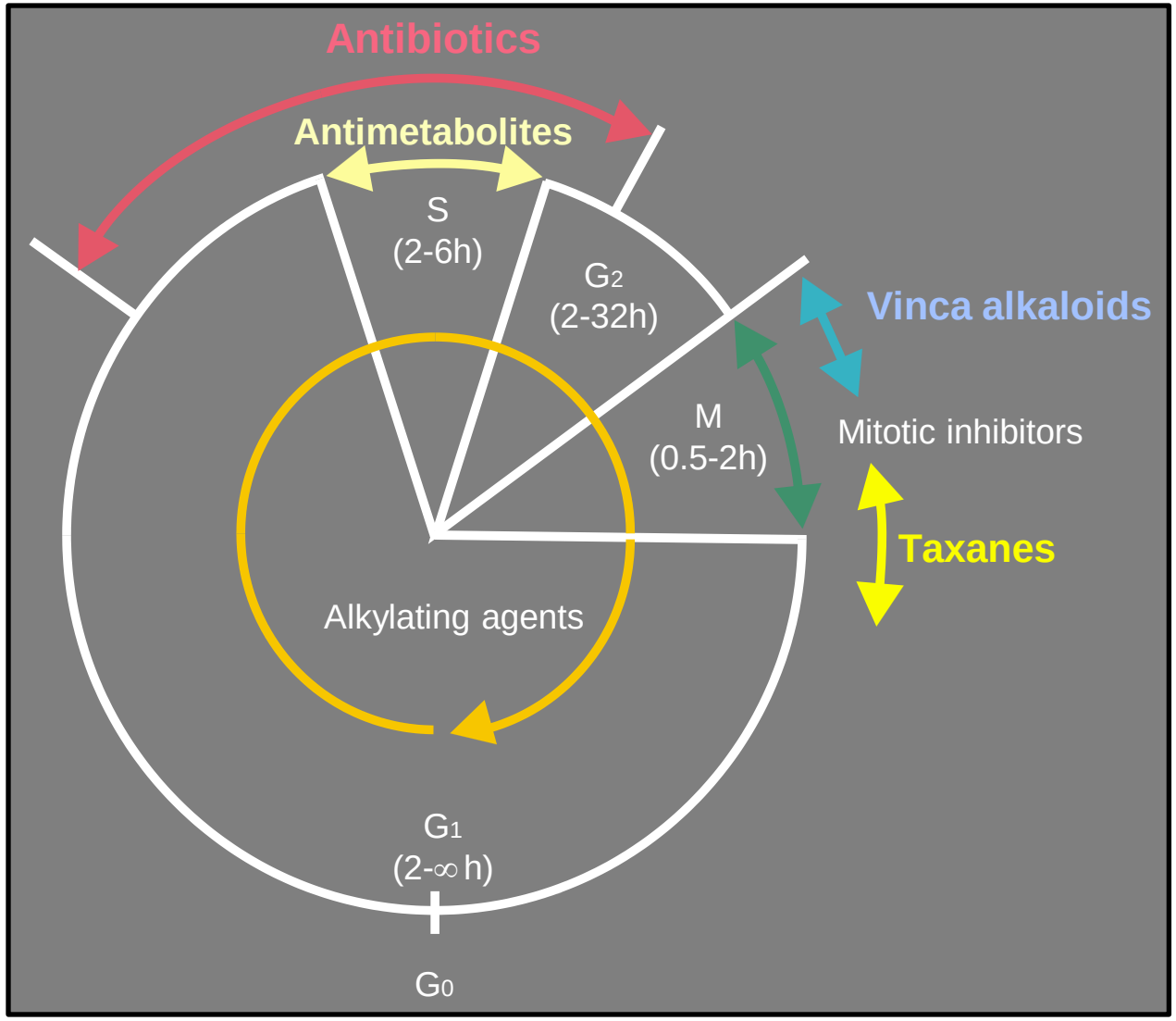
MUNI PHARM

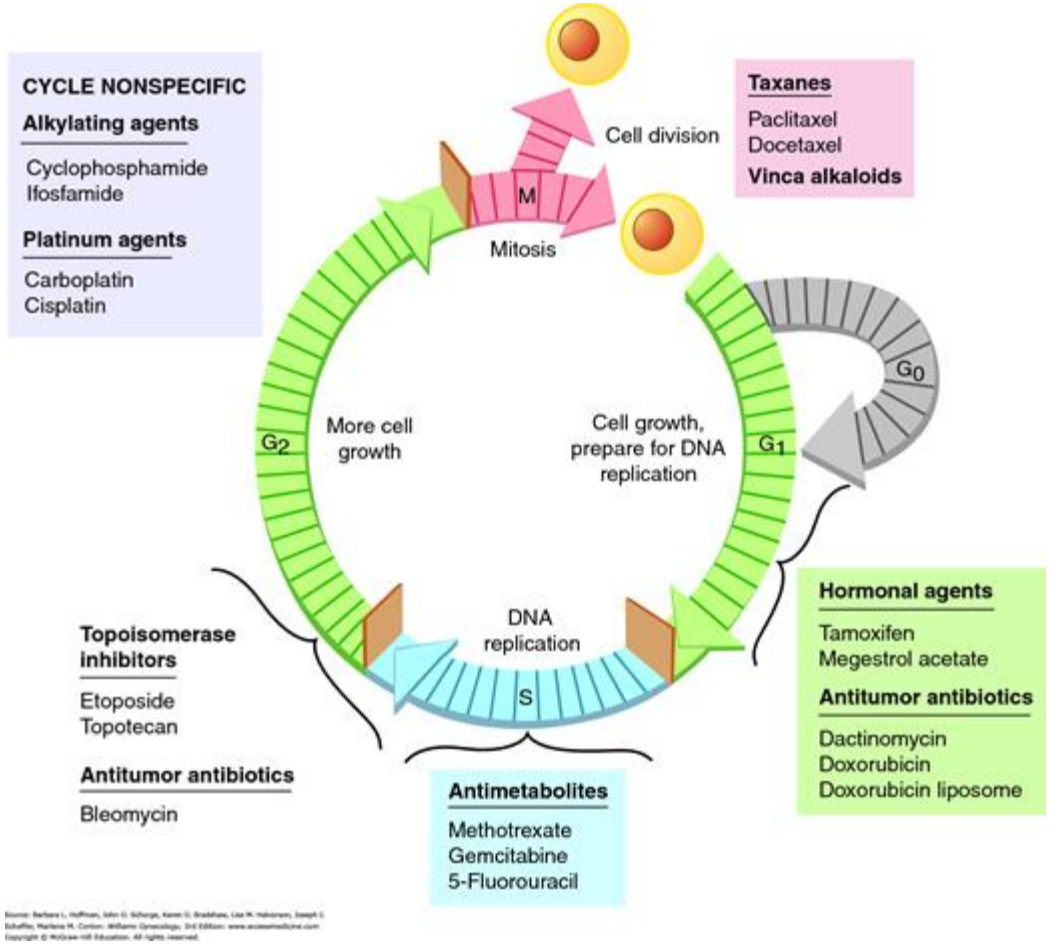
Cell Cycle Specific (CCS) Agents

Cell phase	Description of phase	Chemo drugs effective
G0	Cancer cell resting phase	Refractory to chemotherapy
G1	Interphase Protein and RNA synthesis	L-asparaginase
S	DNA synthesis	Procarbazine Antimetabolites Hydroxyurea Camptothecins
G2	DNA synthesis ceases Protein and RNA synthesis continues Mitotic spindle production	Bleomycin Vinca alkaloids Taxanes
M	Mitosis genetic material segregated into daughter cells	Vinca alkaloids Taxanes

MUNI PHARM

Actions of Cytotoxic Agents within the Cell Cycle





MUNI PHARM

Anticancer Drugs

1) Cytotoxic Drugs

- Alkylating agents
- AntiMTBs
- Antitumor ATBs
- Plant alkaloids (Taxanes, Vinca alkaloids)
- Miscellaneous cytotoxic Dgs

2) Hormones & Hormone Antagonists

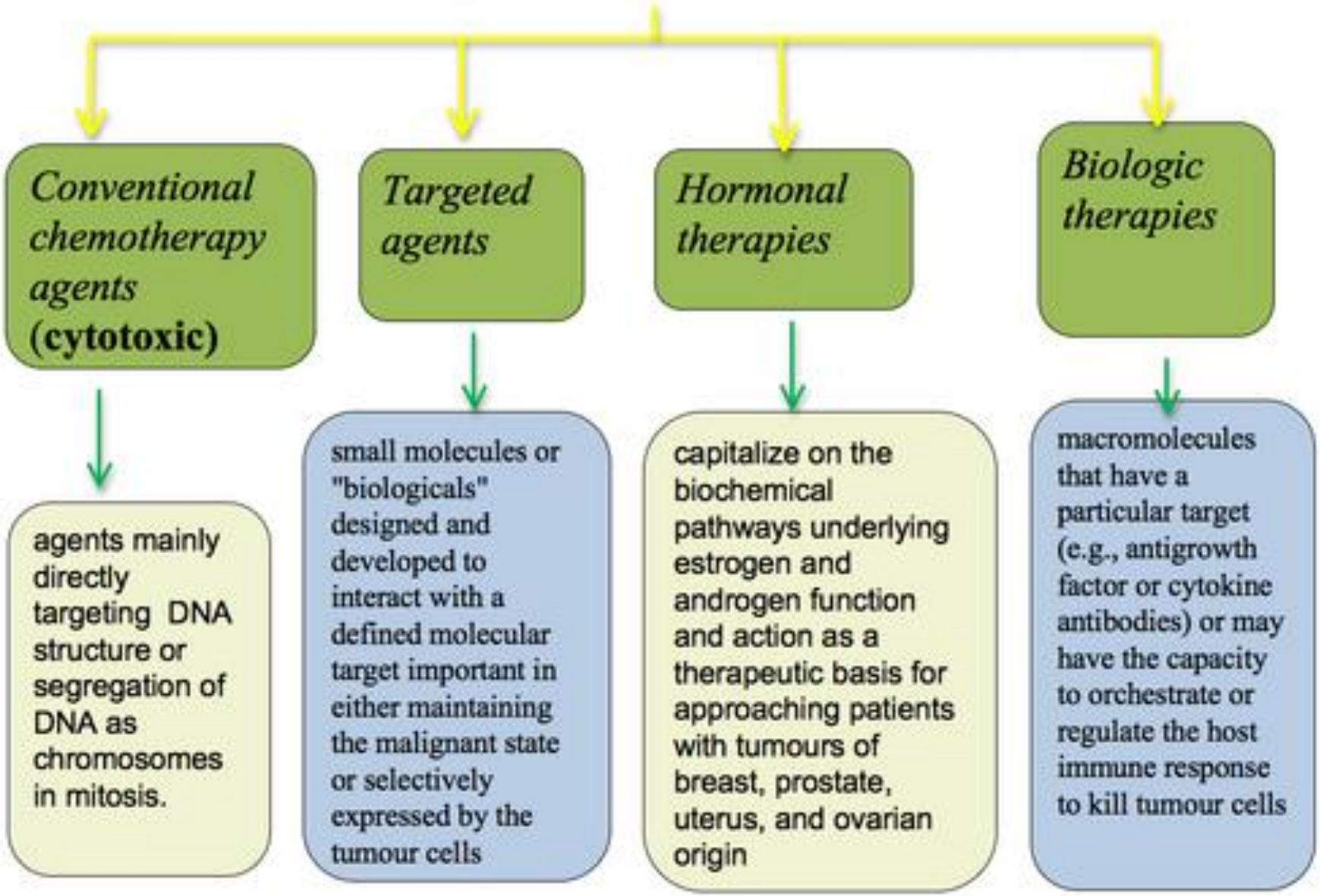
Target specific Rps → only specific cell types → Best-tolerated chemotherapeutics (e.g. tamoxifen)

3) Immunomodulators

- Immunostimulants, incl. INFs & ILs
- Immunosuppressant

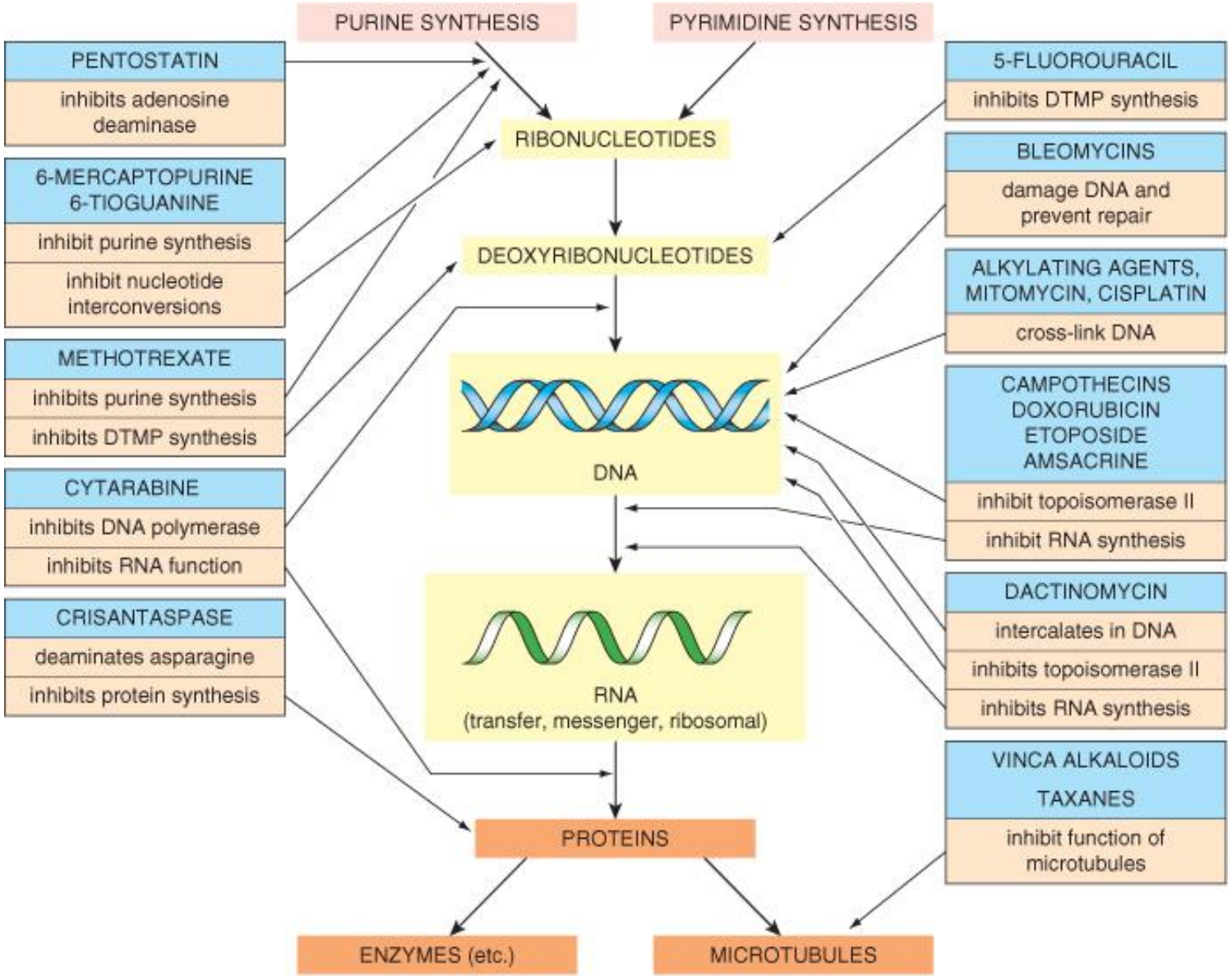
MUNI PHARM

Types of drugs used in cancer treatment



MUNI PHARM

Targets of Cytotoxic Drugs



MUNI PHARM

Classification of Cytotoxic Agents

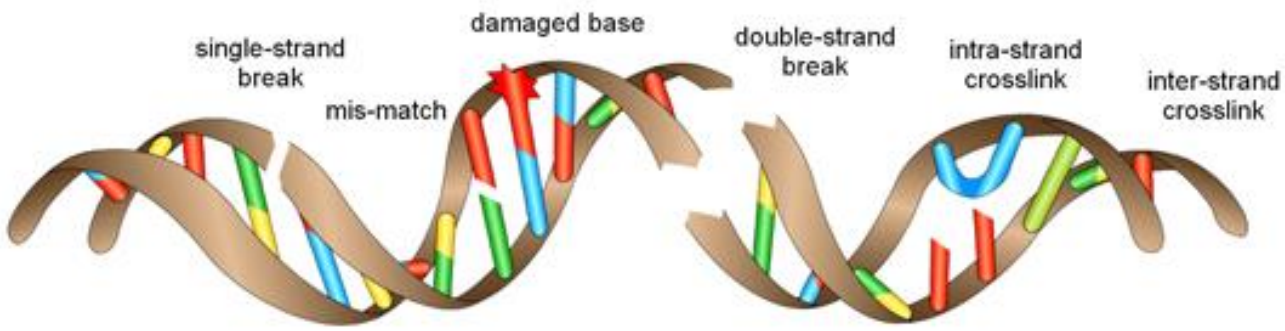
ALKYLATING AGENTS	ANTI-METABOLITES	MITOTIC INHIBITORS	ANTIBIOTICS	OTHERS
BUSULFAN	METHOTREXATE	ETOPOSIDE	BLEOMYCIN	L-ASPARAGINASE
CARMUSTINE	CYTARABINE	TENIPOSIDE	DACTINOMYCIN	HYDROXYUREA
CHLORAMBUCIL	FLOXURIDINE	VINBLASTINE	DAUNORUBICIN	PROCARBAZINE
CISPLATIN	FLUOROURACIL	VINCRISTINE	DOXORUBICIN	
CYCLOPHOSPHAMIDE	MERCAPTOPURINE	VINDESINE	MITOMYCIN-C	
IFOSFAMIDE	PEMETREXED	TAXOIDS	MITOXANTRONE	
MELPHALAN	GEMCITABINE	TAXANES	PLICAMYCIN	
		ANTHRACYCLINES		
		EPOTHILONES		

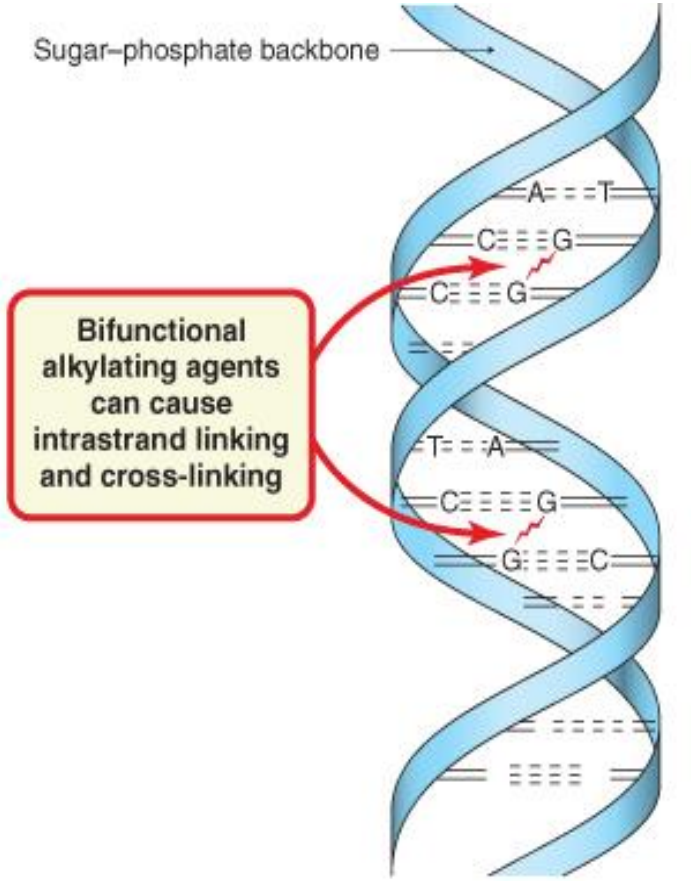
MUNI PHARM

Alkylating Agents

- MoA:

Interact with DNA causing substitution reactions, cross-linking reactions or strand breaks





MUNI PHARM

Alkylating Agents

– Nitrogen mustards

Mechlorethamine, cyclophosphamid, melphalan, chlorambucil

Hodgkin's, Non-Hodgkin's lymphoma, Solid tumors of head, neck, ovaries, breast

– Nitrosoureas

Carmustine, lomustine, semustine

Primary and metastasis tumors of the brain. Hodgkin's ,Non-Hodgkin's lymphoma, Adenocarcinoma of stomach, colon, and rectal cancer, Hepatocarcinoma

– Alkyl sulfonates

Busulfan

Chronic granulocytic leukemia

– Platinum Compounds

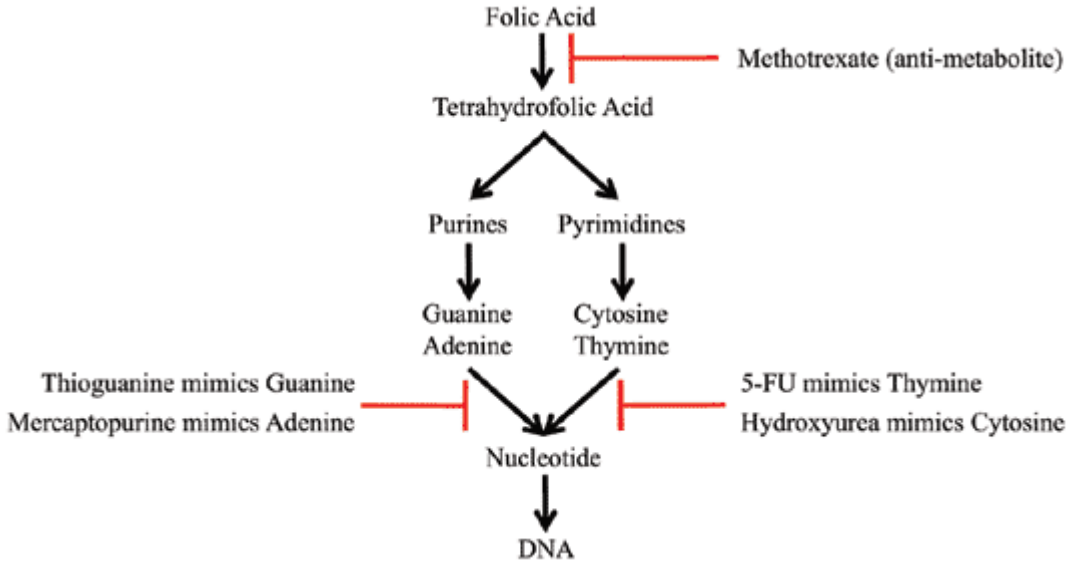
Cisplatin, Carboplatin, Oxaliplatin

Tesicular Ca + carcinoma of ovary, bladder, head, and neck

MUNI PHARM

Antimetabolites

- Similar in structure or function to naturally occurring MTBs involved in NA synthesis
- Either inhibit enzymes involved in nucleic acid synthesis or produce incorrect codes
- Classes:
  1) Folic acid analogues
  2) Purine analogues
  3) Pyrimidine analogues



MUNI PHARM

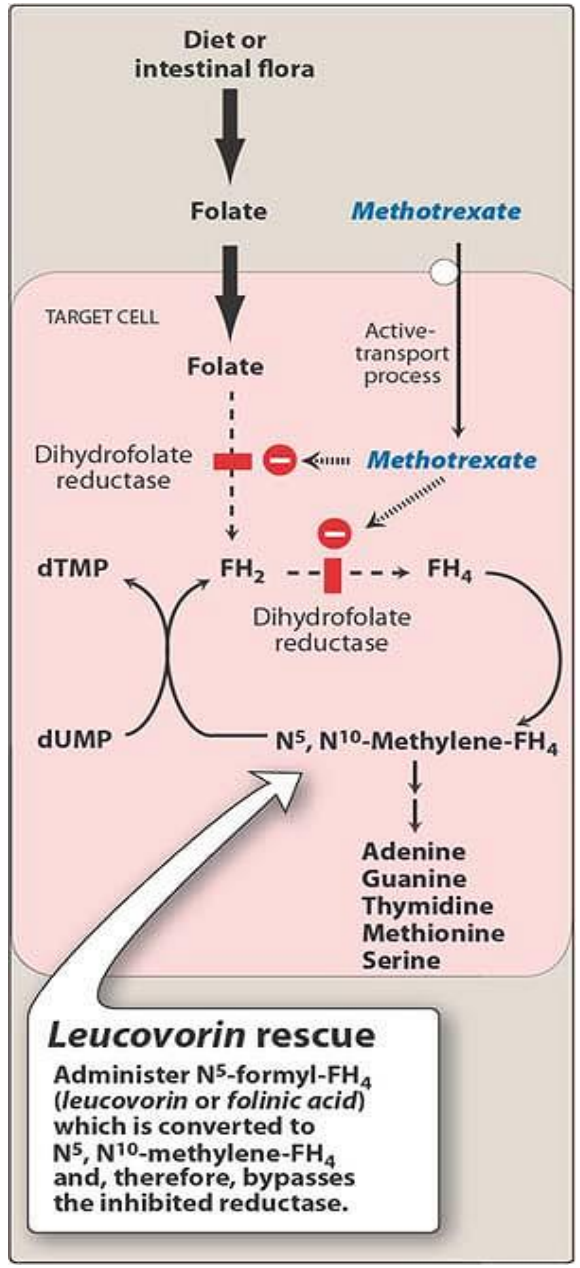
Methotrexate

- High-dose:
  effective against acute lymphocytic leukemia, chorio-carcinoma, Burkitt's lymphoma in children, breast cancer, and head and neck carcinomas (usually in comb. with other Dgs)

- Low-dose:
  effective as a single agent against inflammatory diseases (severe psoriasis, rheumatoid arthritis, Crohn's disease)

- Risk of nephrotoxicity

- TDM needed

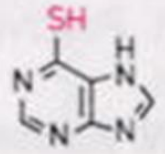


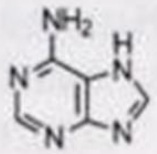
MUNI PHARM

Purine & Pyrimidine Analogues

Incorporation of incorrect structural units for NA

Purine antimetabolite



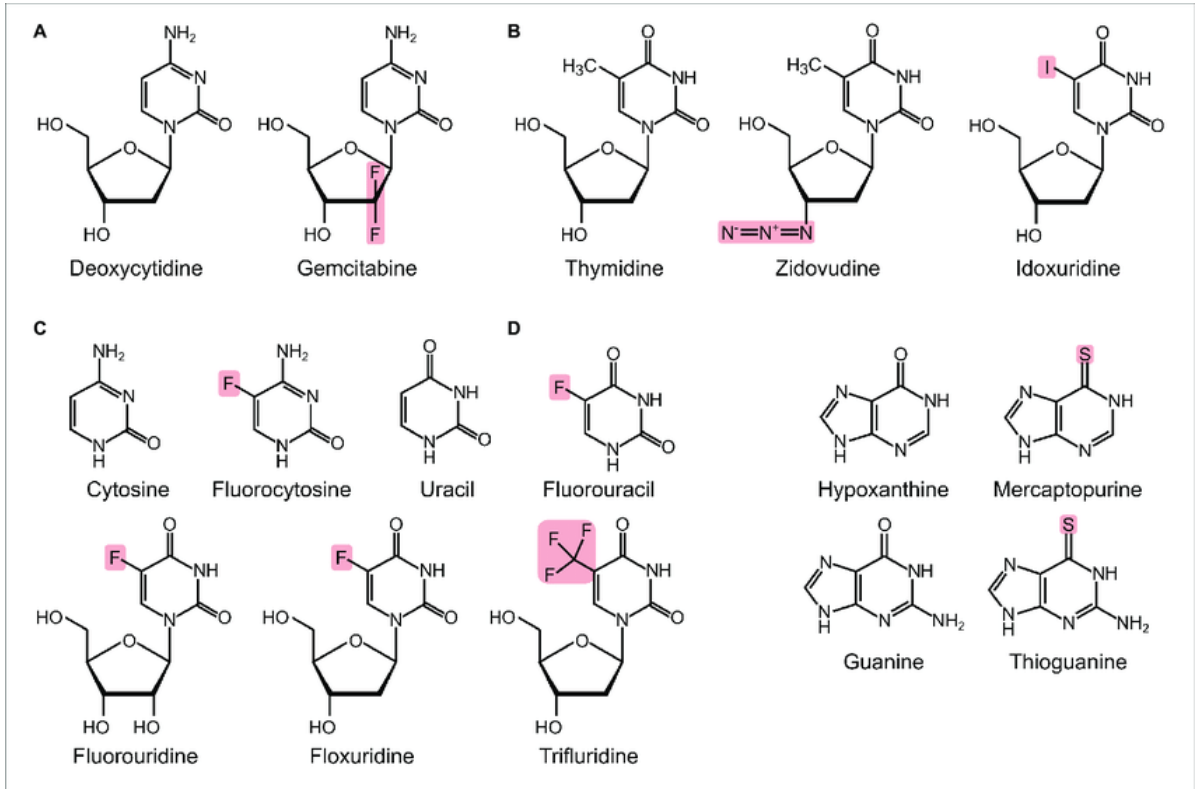


6-merkaptopurin z azathioprinu **instead of** adeninu

Pyrimidine antimetabolite

5-fluorouracil **instead of** uracilu

cytarabin cytosin arabinóza **instead of** cytosin deoxyribózy



MUNI PHARM

Purine Analogues

6−mercaptopurine (6-MP)

- MTBlized by TPMT to nontoxic 6-methyl-MP (polymorphism)
- Acute leukemia in childhood, chronic myelocytic leukemia
- Used also as immunosuppressive agent
- Myelosuppression

Thioguanine

- Acute leukemias and remissions in acute granulocytic leukemias

Fludarabine, pentostatin, cladribine

- Used primarily to treat hairy cell leukemia

MUNI
PHARM

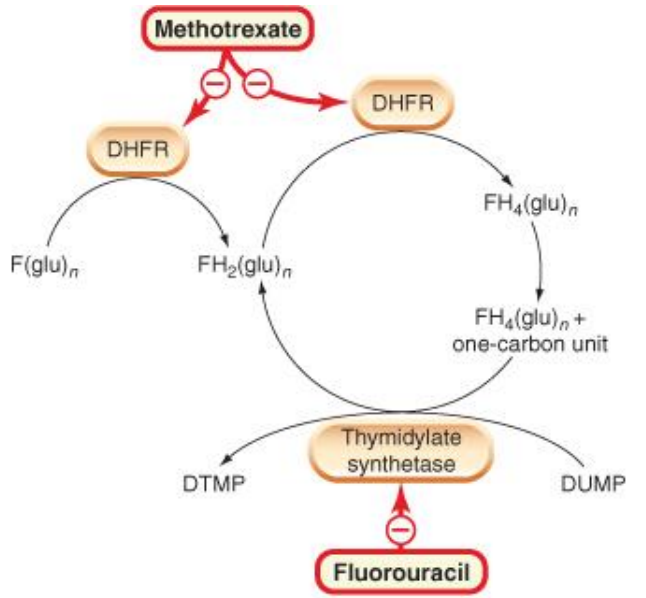
Pyrimidine Analogues

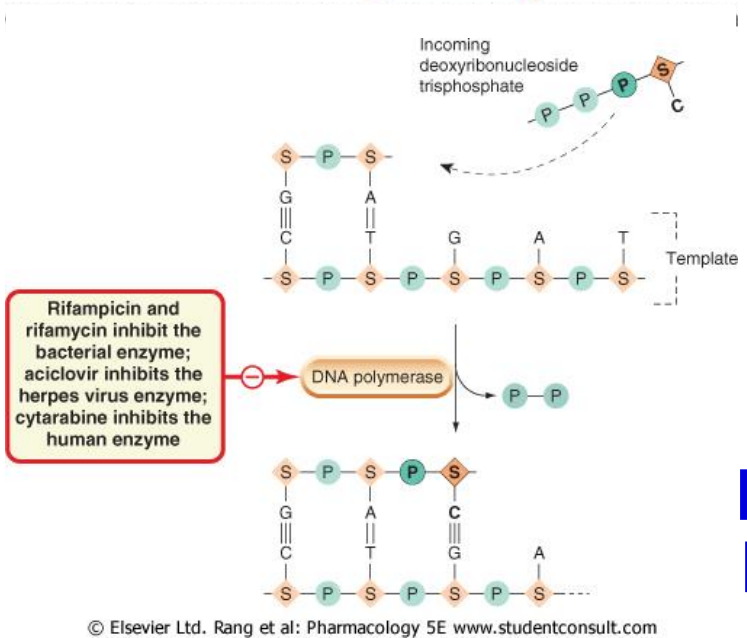
5-fluorouracil (5-FU)

- In combination with other cytostatics to treat cancers of the breast, stomach, colon, rectum, and pancreas
- GIT adverse eff., myelosuppression

Cytarabine

- Acute leukemias
- Adverse eff.: myelosuppression & GIT irritation, neurotoxicity and peripheral neuritis



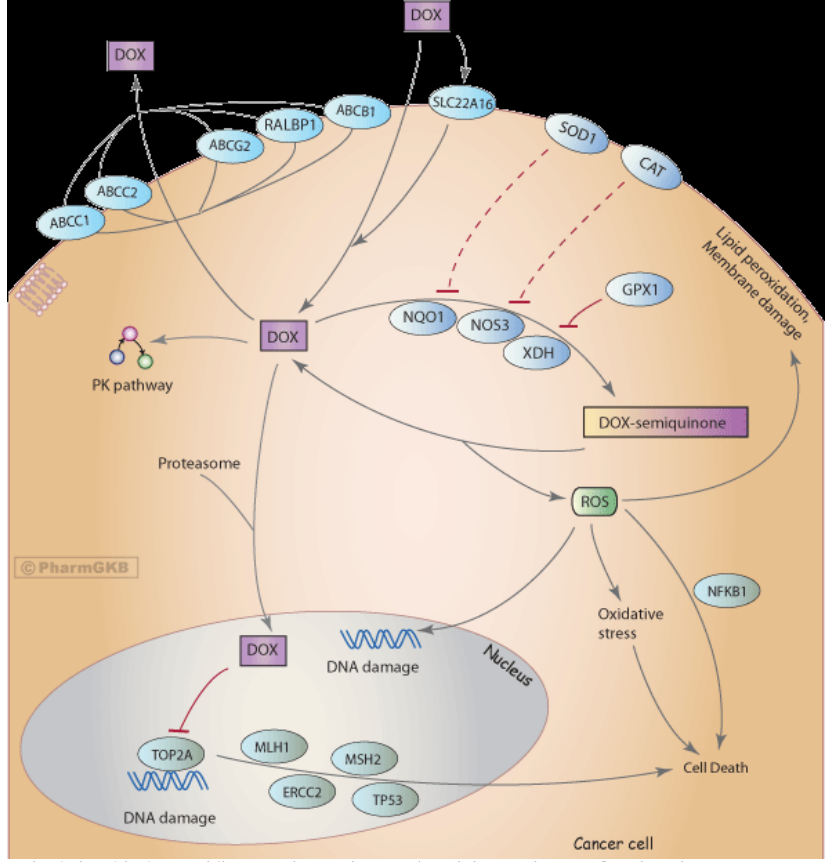


MUNI PHARM

Antitumor Antibiotics

- Group of related antimicrobial compounds produced by Streptomyces species

- Affect structure and function of NAs by:
  - Intercalation between base pairs + inhibition of Topo II (doxorubicin, daunorubicin, idarubicin, epirubicin)
  - DNA strand fragmentation (bleomycin)
  - Cross-linking DNA (mitomycin)



Thorn Caroline F, Oshiro Connie, Marsh Sharon, Hernandez-Boussard Tina, McLeod Howard, Klein Teri E, Altman Russ B. "Doxorubicin pathways: pharmacodynamics and adverse effects" Pharmacogenetics and genomics (2010).

MUNI PHARM

Antitumor Antibiotics

doxorubicin, daunorubicin, idarubicin, epirubicin

- Ca of breast, bone, ovaria, endometrial, lungs, acute lymphocytic leukemia, non−Hodgkin's lymphoma

aktinomycin D

- Wilm’s tumor, melanoma, choriocarcinoma

bleomycin

- Ca of testis, head, neck, skin, esophagus, lungs

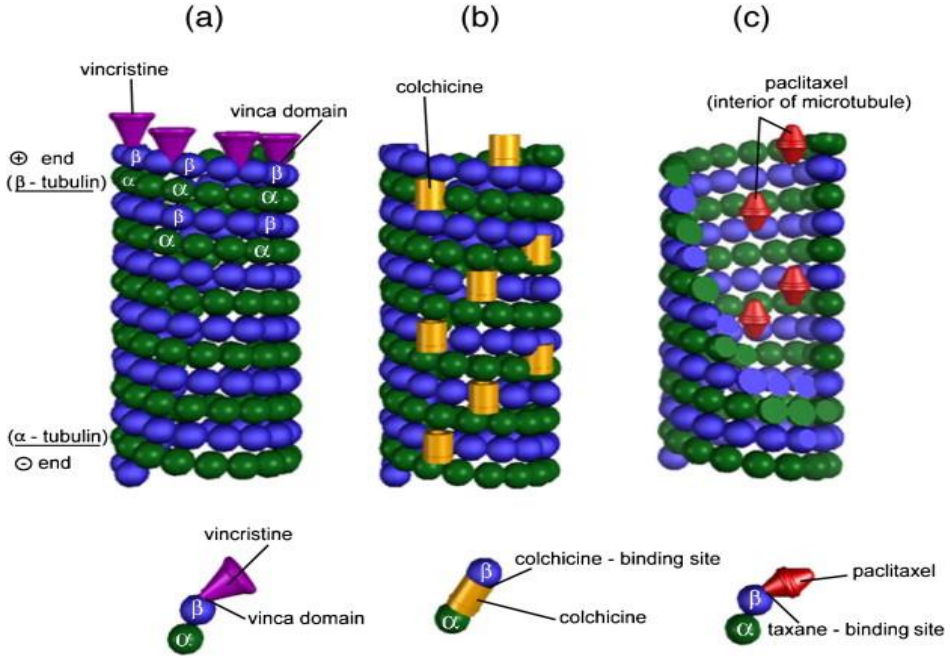
mitomycin

- Activated to form an alkylating agent
- Adenocarcinoma of stomach, pancreas, lungs, colon
- May cause strong myelosuppression

MUNI
PHARM

Plant Alkaloids

- Vinca alkaloids (vincristine, vinblastine, vindesine)
- Taxanes (paclitaxel, docetaxel)
- Podophyllotoxins (etoposide, teniposide)
- Topo I inhibitors from *Camptotheca acuminata* (topotecan, irinotecan)



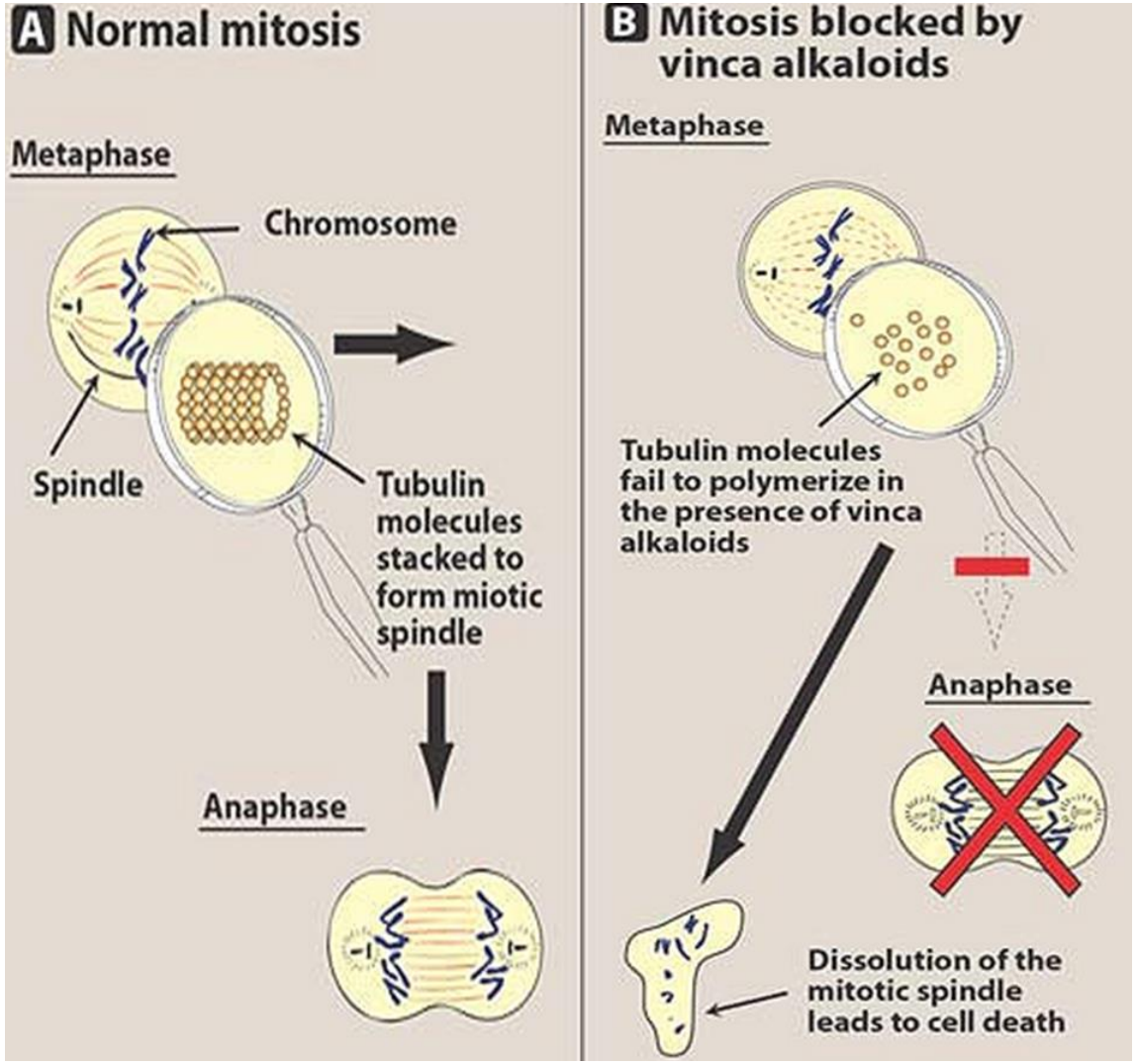
McGrogan BT, Gilmartin B, Carney DN, McCann A.: Taxanes, microtubules and chemoresistant breast cancer. Biochim Biophys Acta 2008;1785(2):96-132.

MUNI PHARM

Vinca Alkaloids

- Prevent assembly of tubulin dimers into microtubules
- Microtubule-destabilizing agents (same as podophyllotoxins and colchicines)

- **I:** Non Hodgkin‘s & Hodgkin's disease, malignant lymphomas and leukemia, testes
- **SE:** Neurotoxicity (VC), bone marrow suppression (VB)

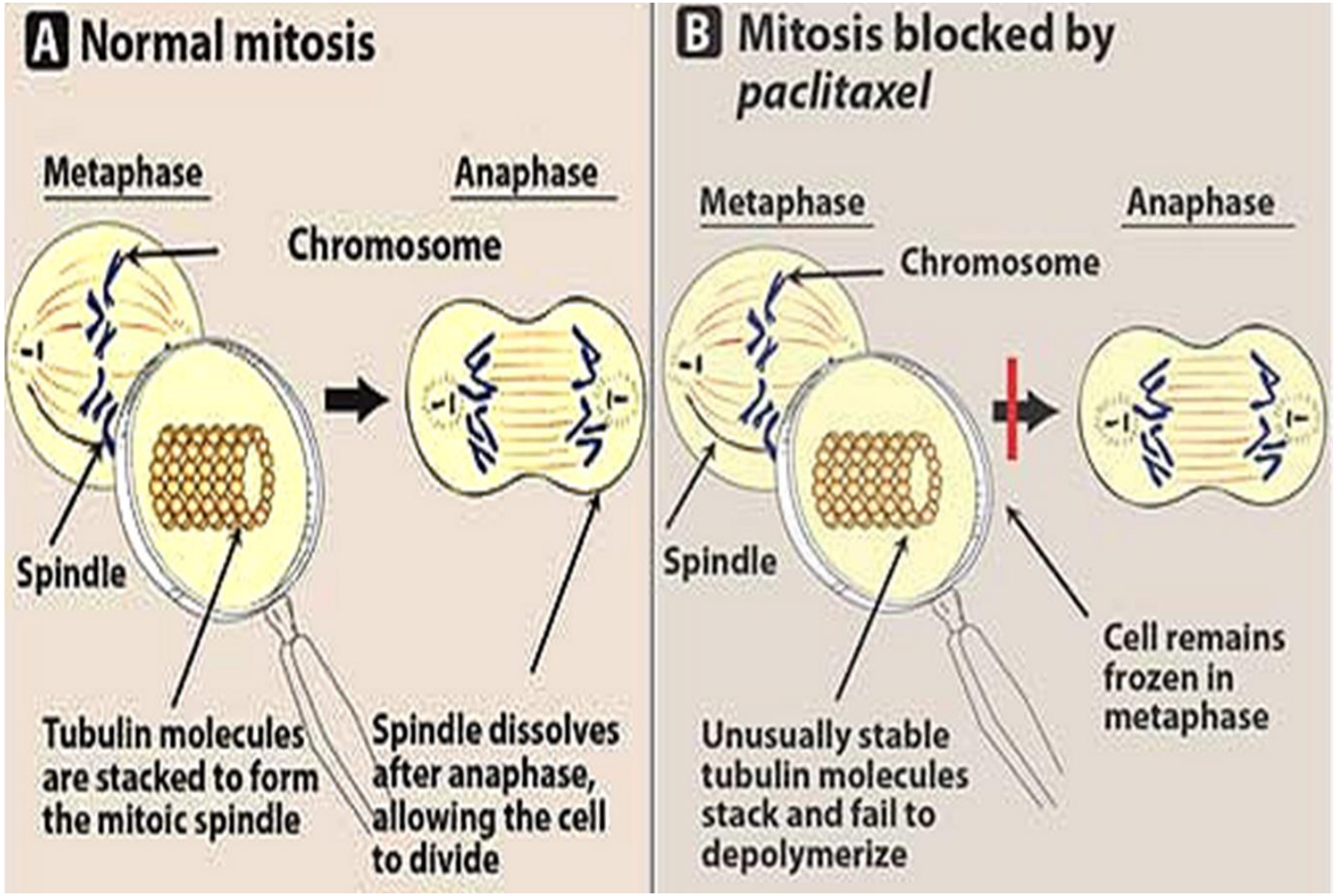


Taxanes

- Act on late G1 and early M-phase
- Microtubule-stabilizing agents

(preventing disassembly into tubulin monomers)

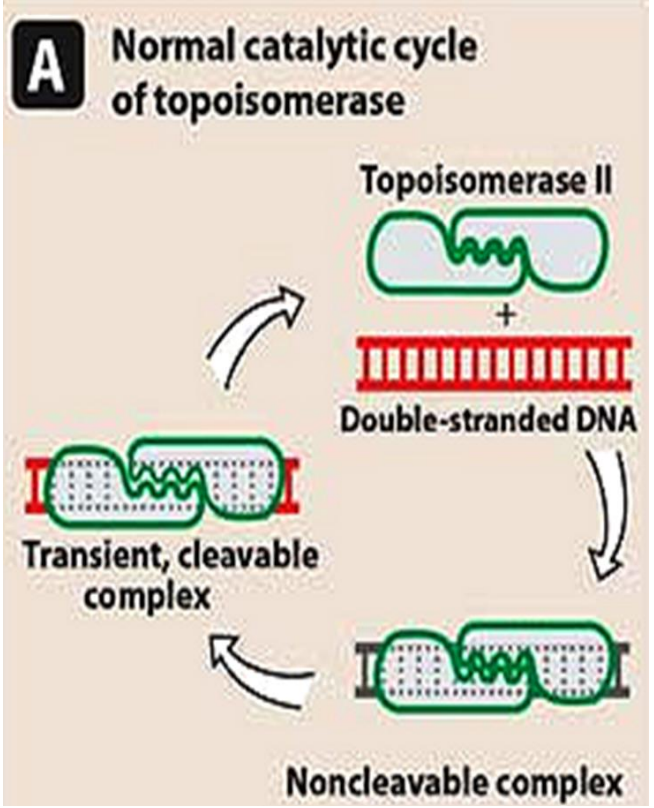
- **I:** Advanced breast and ovarian cancer
- **SE:** Bone marrow suppression and neurotoxicity



Podophyllotoxins

- Topoisomerase II inhibitors (degradation of DNA)
  - E responsible for uncoiling and repairing damaged DNA
- Act on late S and early G2 phase

- **I:** Small cell lung Ca, prostate, testicular Ca (etoposide)
- **SE:** Bone marrow suppression, vomiting, alopecia




May apple (Mandrake) root

Topoisomerase I Inhibitors

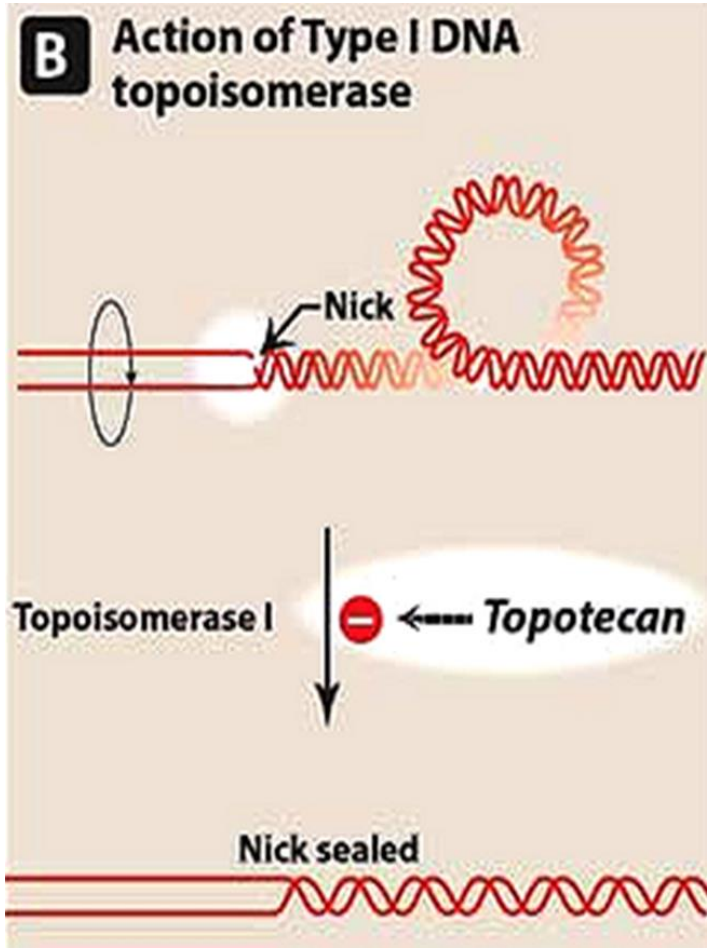
- 1966 - camptothecin - very toxic --

  modification of molecule: topotecan, irinotecan

- Intercalates between DNA bases, thus prevent

  DNA replication

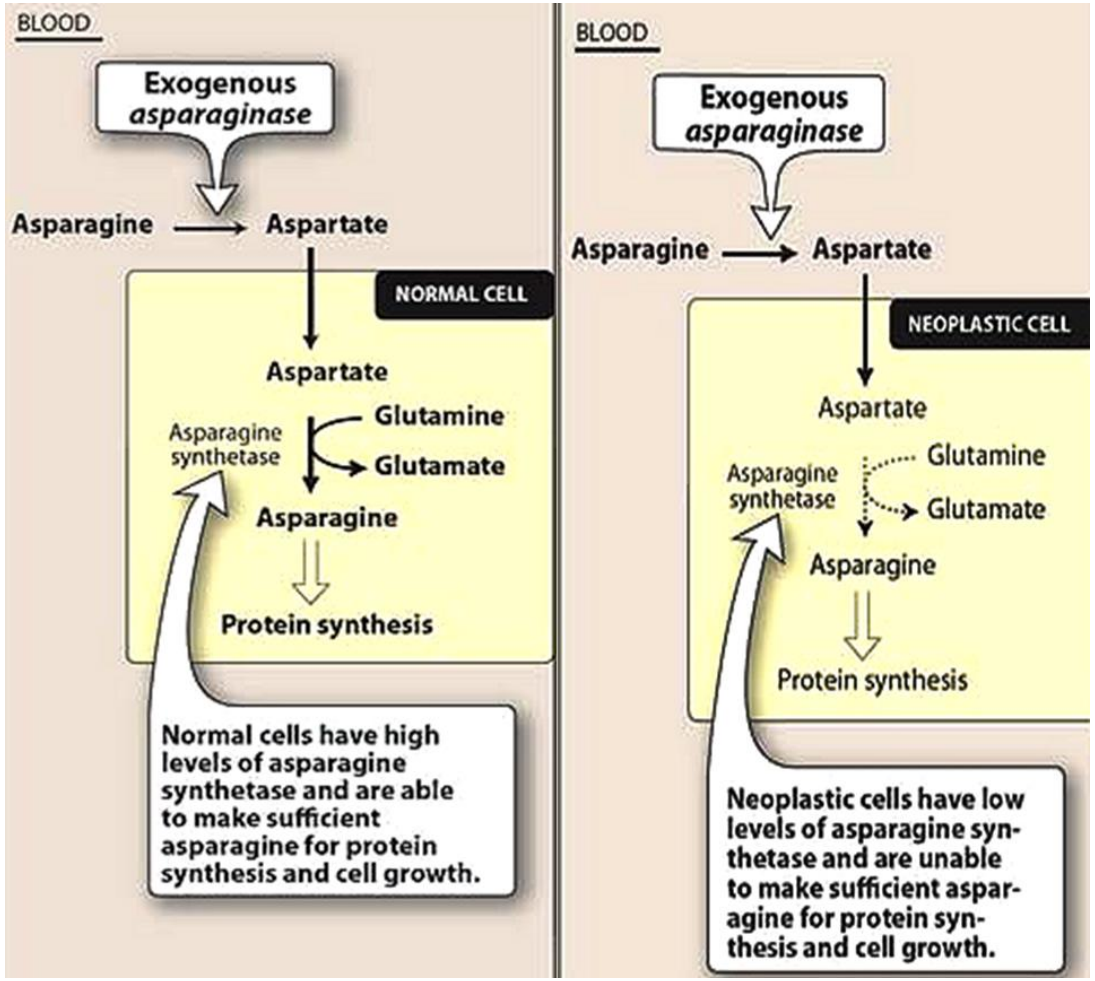
- **I:** Advanced ovarian cancer, colorectal Ca, small cell lung cancer
- **SE:** Myelosuppression, diarrhea




Camptotheca acuminata tree

Miscellaneous Cytotoxic Drugs

- asparaginase
- Depletes serum asparagine (necessary for survival and growth of certain tumors)
- Combination with vincristine & steroids (prednisone or dexamethasone)
- **I:** Leukemias, lymphomas
- **SE:** May cause severe hypersensitivity reactions



MUNI PHARM

Miscellaneous Cytotoxic Drugs

- mitoxantrone
- Intercalates in DNA and inhibits Topo II, thus disrupts

  DNA synthesis and DNA repair

- **I:** Breast Ca, AML, and non-Hodgkin's lymphoma
- **SE:** Cardiotoxicity, vomiting, alopecia

Hormones & Hormone Antagonists

Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone)

- **I:** Leukemias, Hodgskin's disease, other lymphomas
- **SE:** Fluid retention, HT, DM, susceptibility to infection

Sex Hormones (estrogen, progestins, androgens)

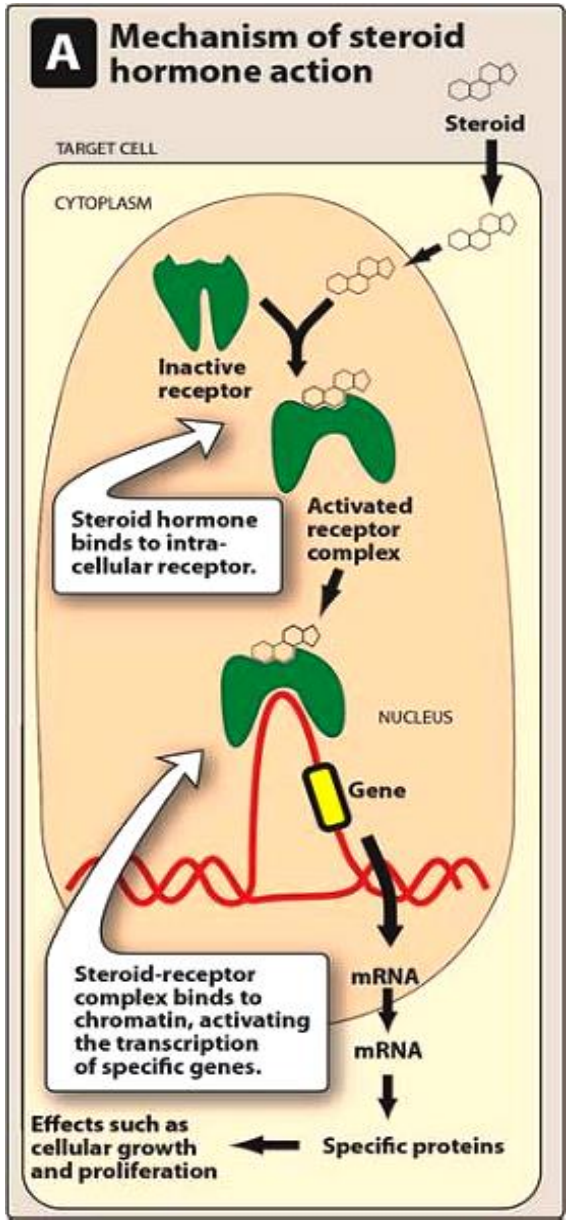
- Hormone-dep. Ca, mainly prostatic tumors

GnRh Analogues (goserelin, leuprolide)

- I: Prostatic Ca

Hormone Antagonists (tamoxifen, flutamide, nilutamide, bicalutamide)

- flutamide: antiandrogen used in prostatic cancer
- tamoxifen: antiestrogen used in breast cancer

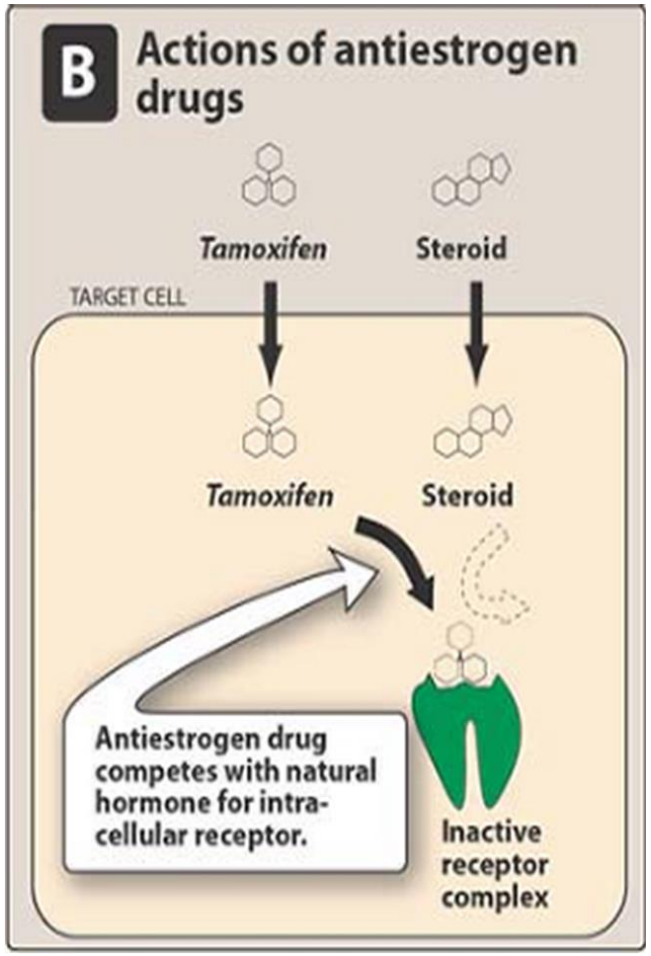


MUNI PHARM

Tamoxifen

- Antagonist of estrogen receptor (ER) selectively in breast tissue (not in bones: no osteoporosis!)
- Prodrug MTBlized by CYP450
- Cytostatic (not toxic) – causes G0 and G1 arrest

- **I:** Early and advanced ER+ breast Ca in both women and men
- **SE:** linked to endometrial Ca (as partial agonist on EM), nausea, vomiting, hot flushes, hypercalcemia

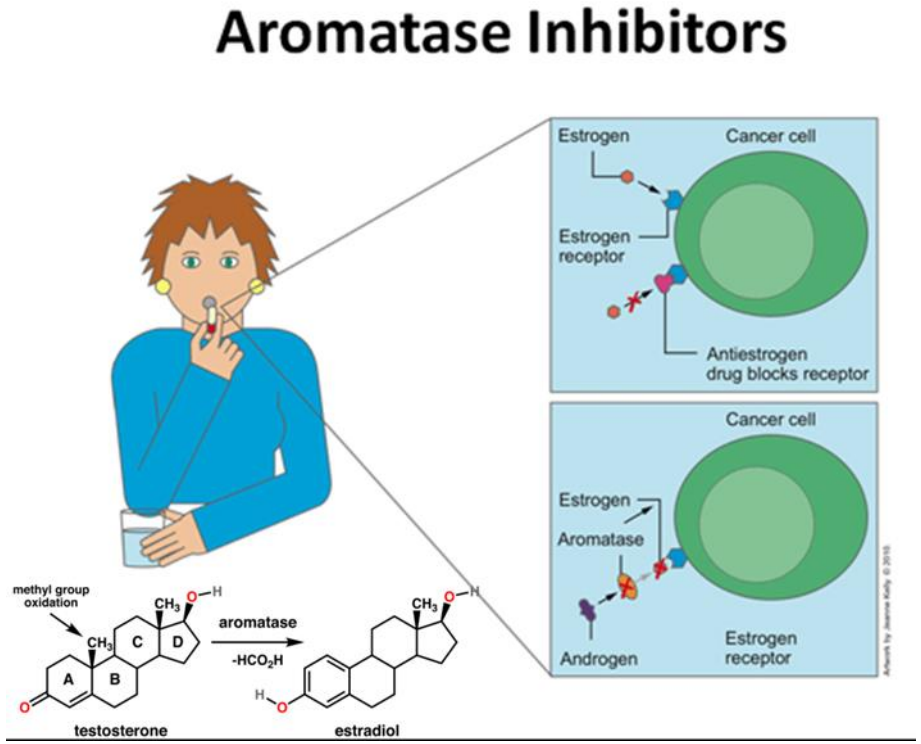


MUNI PHARM

Aromatase Inhibitors

- anastrozole, leterozole
- Ovaries and other tissues produce estrogen under aromatase effect
- **AI**s do NOT block E production by the ovaries, but can block other tissues

- I: breast Ca in post-menopausal women
- SE: GIT, headache, hot flushes



MUNI PHARM

Treatment-associated Problems

Toxicity and Adverse effects

- bone marrow, GIT, hair follicles, reproductive organs

Treatment-induced tumor

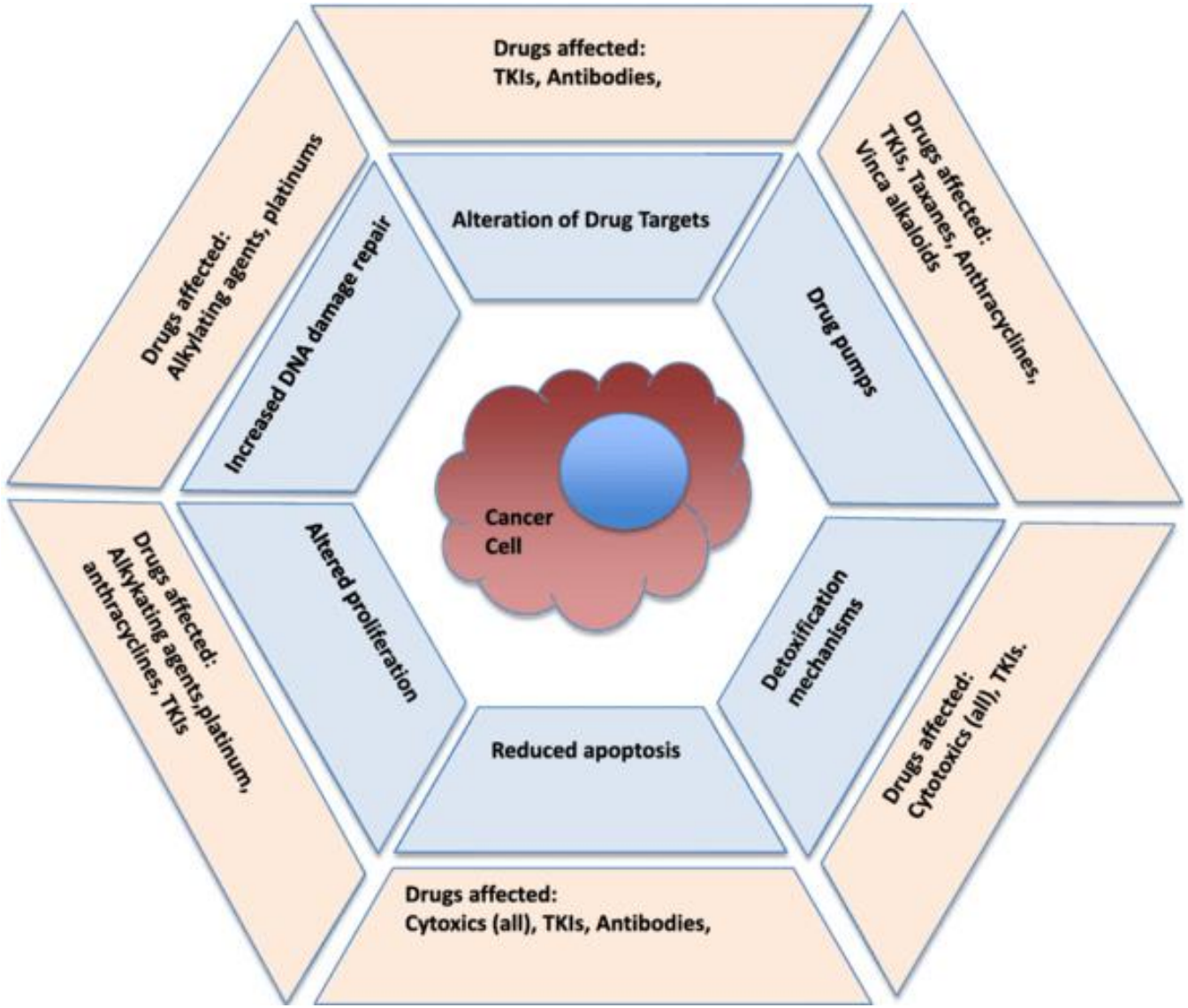
- as potential mutagens they can cause rise of neoplasm several years after the original cancer was treated

Resistance to chemotherapy

- decreased drug uptake by cancer cells
- increased drug remove by cancer cells (P-glycoprotein)
- increased ability to DNA repair by cancer cells
- mutation in the molecule targeted by drug

MUNI
PHARM

Hallmarks of Anticancer Drug Resistance



MUNI PHARM

Myelotoxicity

- Neutropenia, lymfocytopenia, anemia, trombocytopenia
- Increased risk of infection

- Caused by:
  - Alkylating agents, 6-mercaptopurine, vinblastine, etoposide

- Treatment:
  - G-CSF, GM-CSF, erythropoetin

MUNI
PHARM

Toxicity of GIT

- Nausea and vomiting

- Caused by:
  - carmustine, cisPt, cyclophosphamide

- Treatment:
  - Antiemetics (5-HT3 blockers – serotonine antagonists: ondansetron, granisetron, tropisetron) + dexamethasone, metoclopramide

- Mucositis

MUNI PHARM

Nephrotoxicity

- Proximal tubules

- Caused by:
  - cisPt, ifosfamide, carboPt, methotrexate, nitrosoureas

- Treatment:
  - Dose adjustment, TDM

MUNI
PHARM

Neurotoxicity

- Axonal degeneration and impaired neuronal transport

- Caused by:
  - Vinca alkaloids

- Treatment:
  - Decrease dose to maximum tolerated dose, pyridoxine, leucovorin

MUNI
PHARM

Cardiotoxicity

- Acute and chronic

- Caused by:
  - Anthracyclines (doxorubicin, daunorubicin)

- Treatment:
  - dexrazoxane (derivative of EDTA) – chelates iron, and thus decrease the formation of ROS

MUNI
PHARM

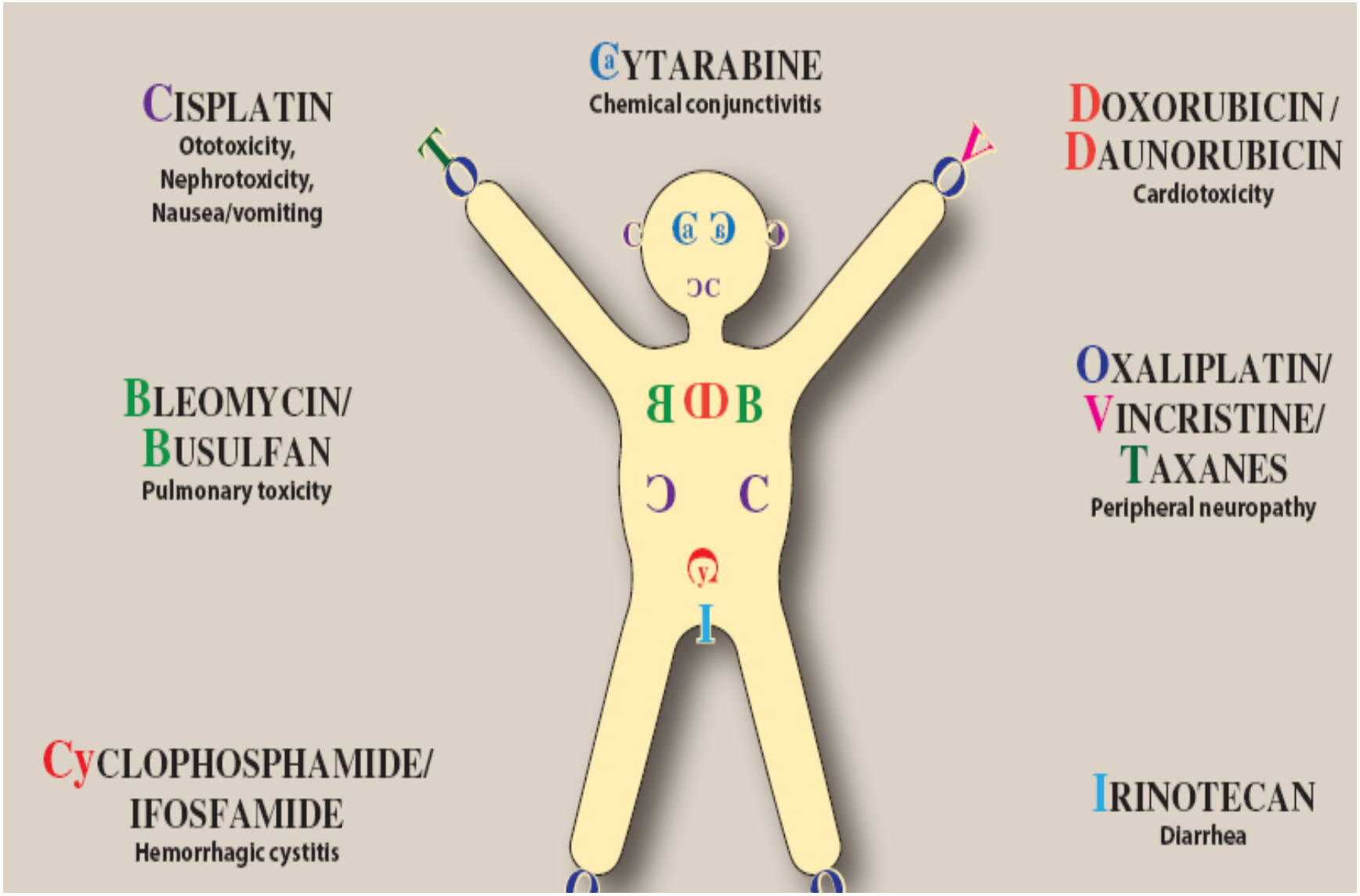
– Infertility
  - Cyclophosphamide, alkylating agents

– Teratogenic Effects
  - Antimetabolites, alkylating agents

– Treatment-induced Tumor
  - Alkylating agents (leukemia)

MUNI
PHARM

Summary of Toxicity of Anticancer Drug



MUNI PHARM

Is this the end?

Not yet…

Targeted therapy

also called

Biological therapy

for cancer!!!

MUNI PHARM

Thank you
for your attention

MUNI PHARM