



DEBRECENI
EGYETEM

PRINCIPLES of CANCER CHEMOTHERAPY

Ilona Benkő M.D., Ph.D.

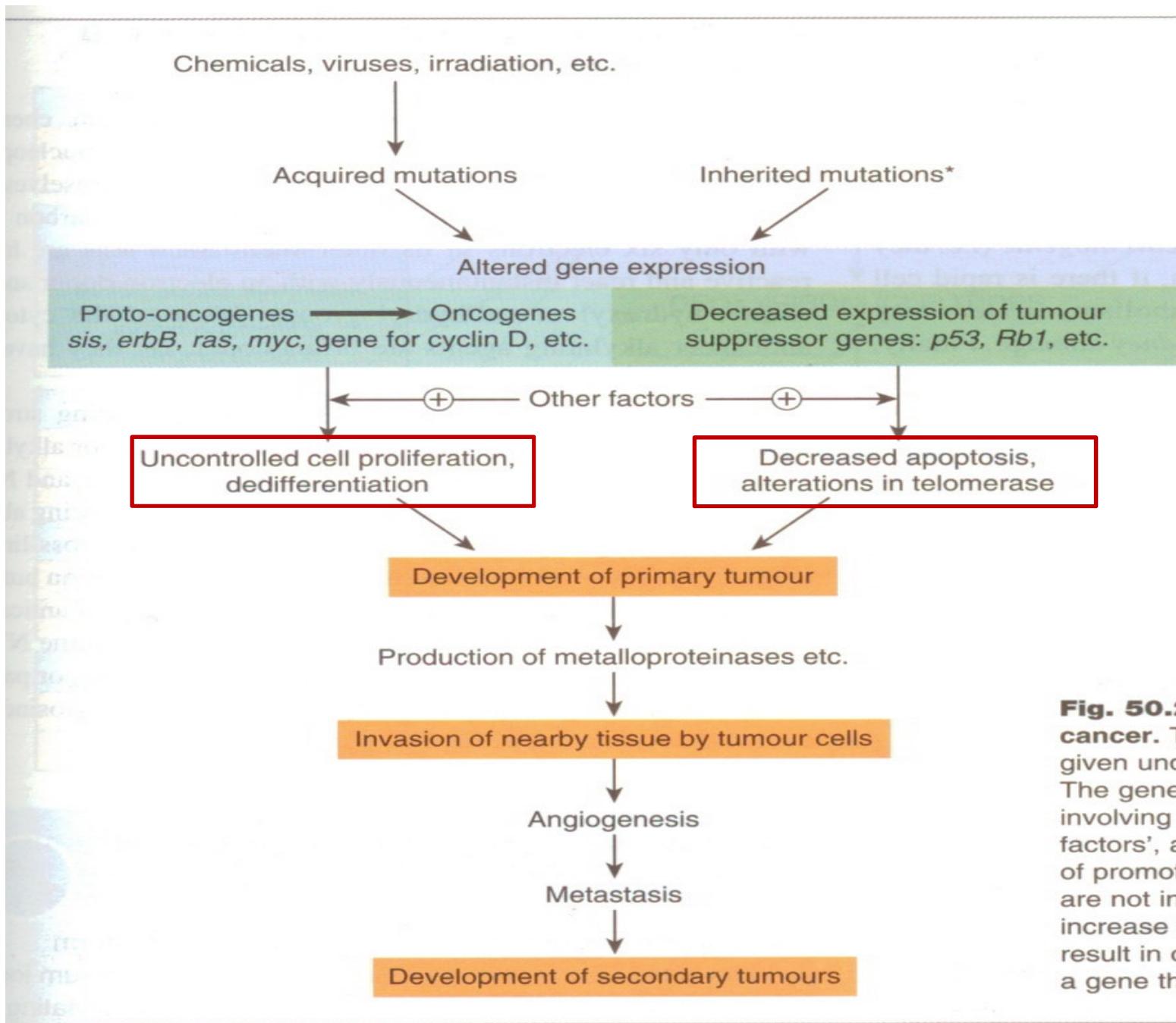
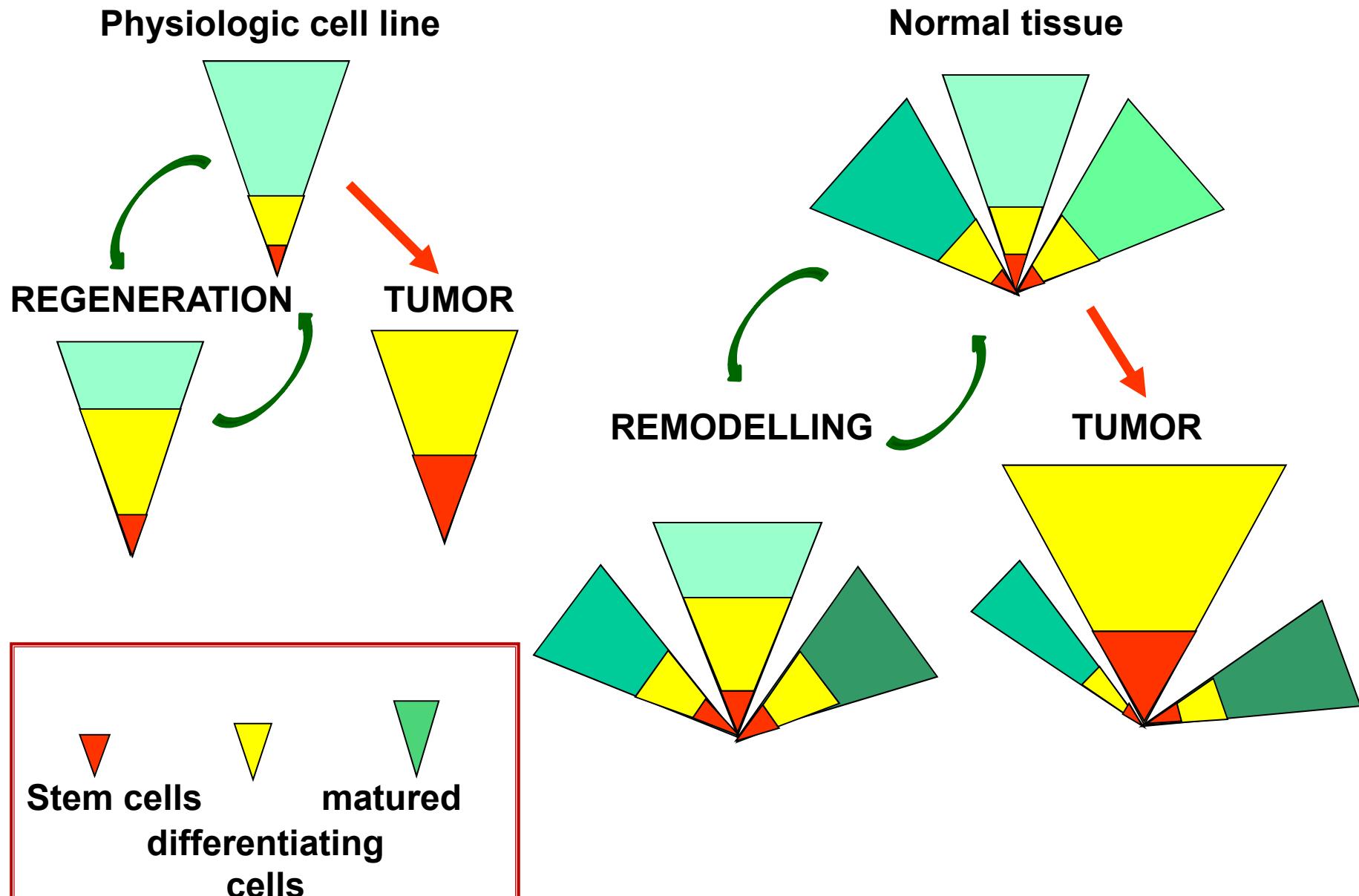


Fig. 50.2
The process of cancer. The diagram shows the given under normal conditions. The genesis of cancer involves mutations in 'proto-oncogenes', as well as 'tumour-suppressor genes'. These changes are not in themselves sufficient to increase the risk of cancer. It is the result in combination with other factors that increases the risk of cancer. A gene that is mutated in one cell may not affect the cell's behaviour unless it is also mutated in another cell.

Stem cells in physiologic and malignant processes



Characteristics of malignant cells

Instabil genetics

More than one tumor cell population

Further mutations result in further tumor cell clones

spontaneous mutation rate: $1:10^5$



Risk for resistance

Little difference between malignant and physiologic cell lines



Anticancer treatment has a high toxicity



Combinative treatment is required



COMBINATION of

SURGERY

Local effect

IRRADIATION

Local effect

CANCER CHEMOTHERAPY

Systemic effect

CANCER CHEMOTHERAPY

1. Antiproliferative treatment

Cytotoxic drugs which kill cancer cells

2. Biological therapy

By the help of planned drug molecules the clue revealed pathological processes are targeted.

Biological effects are expected with these **biological response modifiers**, which are large molecules produced by biotechnology.

1. Cancer chemotherapy

with classical cytotoxic drugs

Cytotoxic drugs kill cancer cells



2. Biological therapy

Biological therapy

reins cancer cells, which survive.



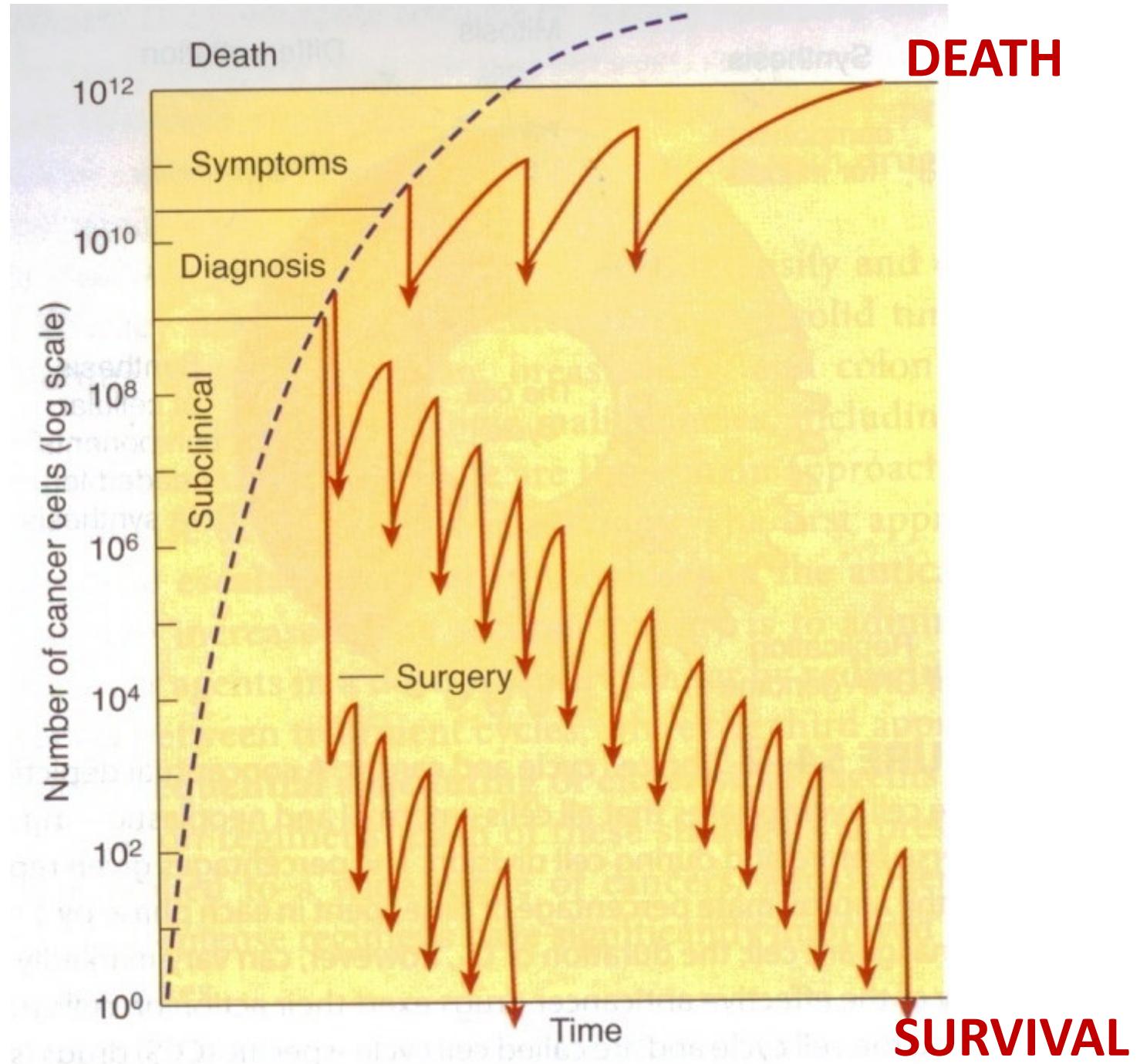
MONOTHERAPY BY BIOLOGICAL DRUGS IS RARELY EFFECTIVE in some special cases for short periods.

e.g. in elderly may be enough

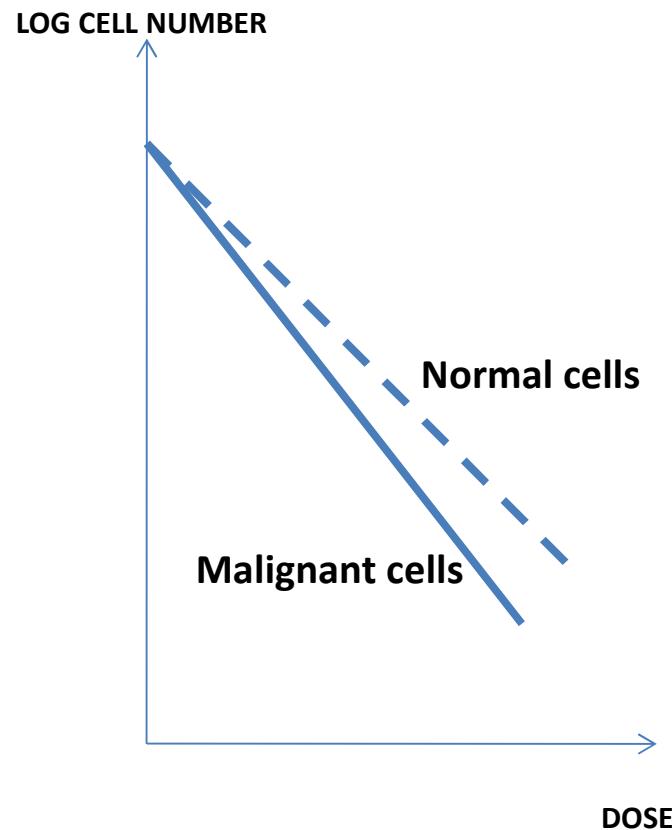
Complex therapy of malignancies

1. Prevention – chemoprevention
2. Influencing tumor cells with combined anticancer therapy
„personalized” therapy e.g. by biological drugs
3. Inhibition of metastases
4. Immunotherapy
5. Prevention and therapy of complications
prophylaxis and therapy of infections – antimicrobial drugs
colony stimulating factors for cytopenias
6. Improving quality of life
therapy of side effects
7. Prevention and therapy of relapses
follow-up for many years

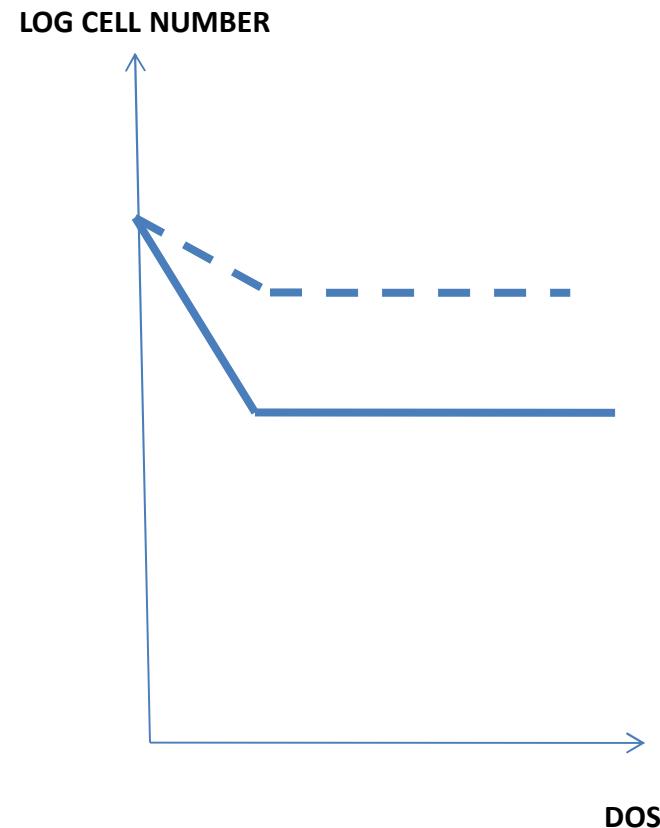
LOG-KILL hypothesis



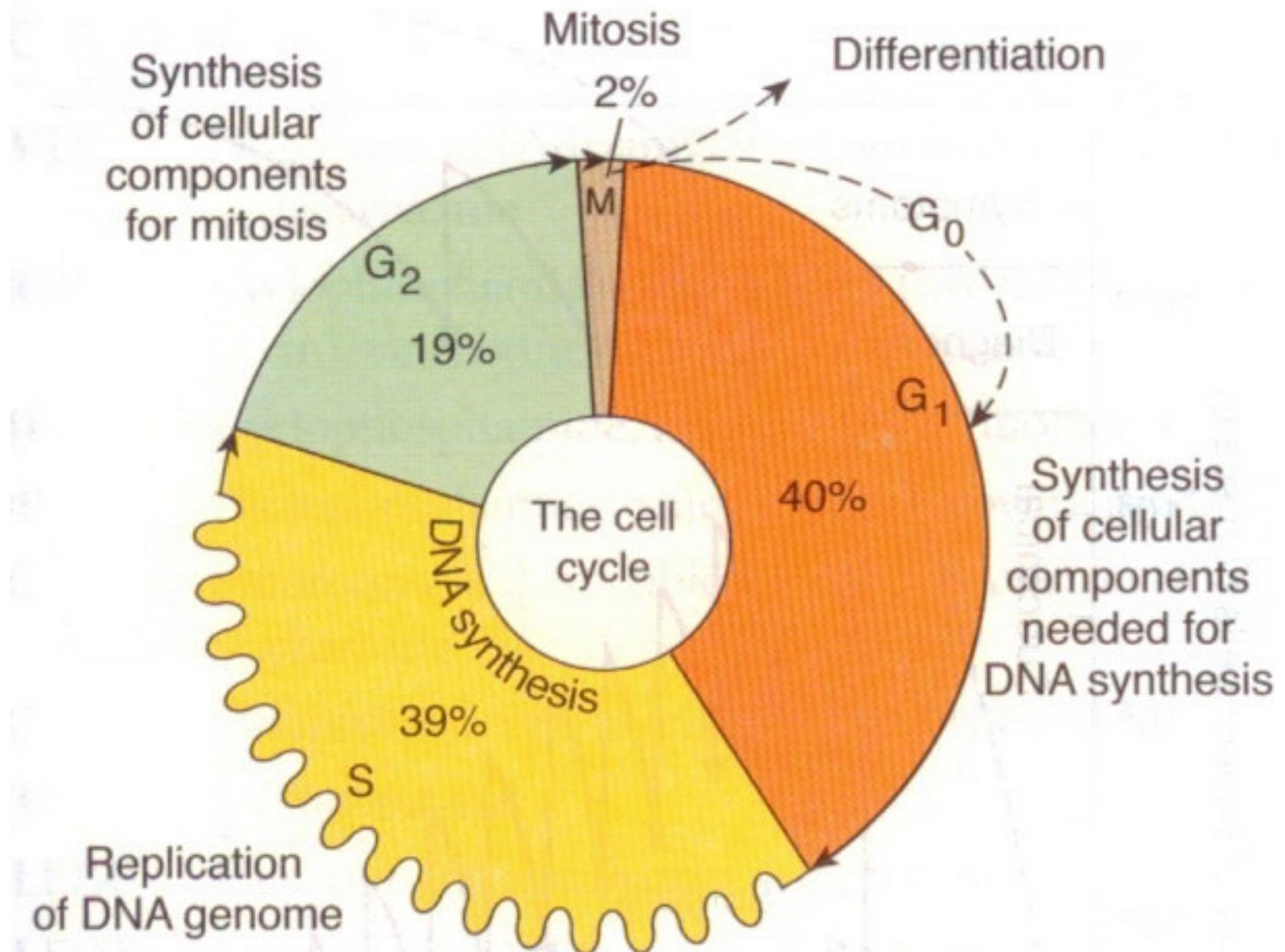
CCNS
Cell cycle non specific drugs



CCS
Cell cycle specific drugs



DOSE-RESPONSE CURVES



Common side effects in cytotoxic cancer chemotherapy and tyrosine kinase inhibitory drugs

DOSE-LIMITING side effect: BONE MARROW SUPPRESSION

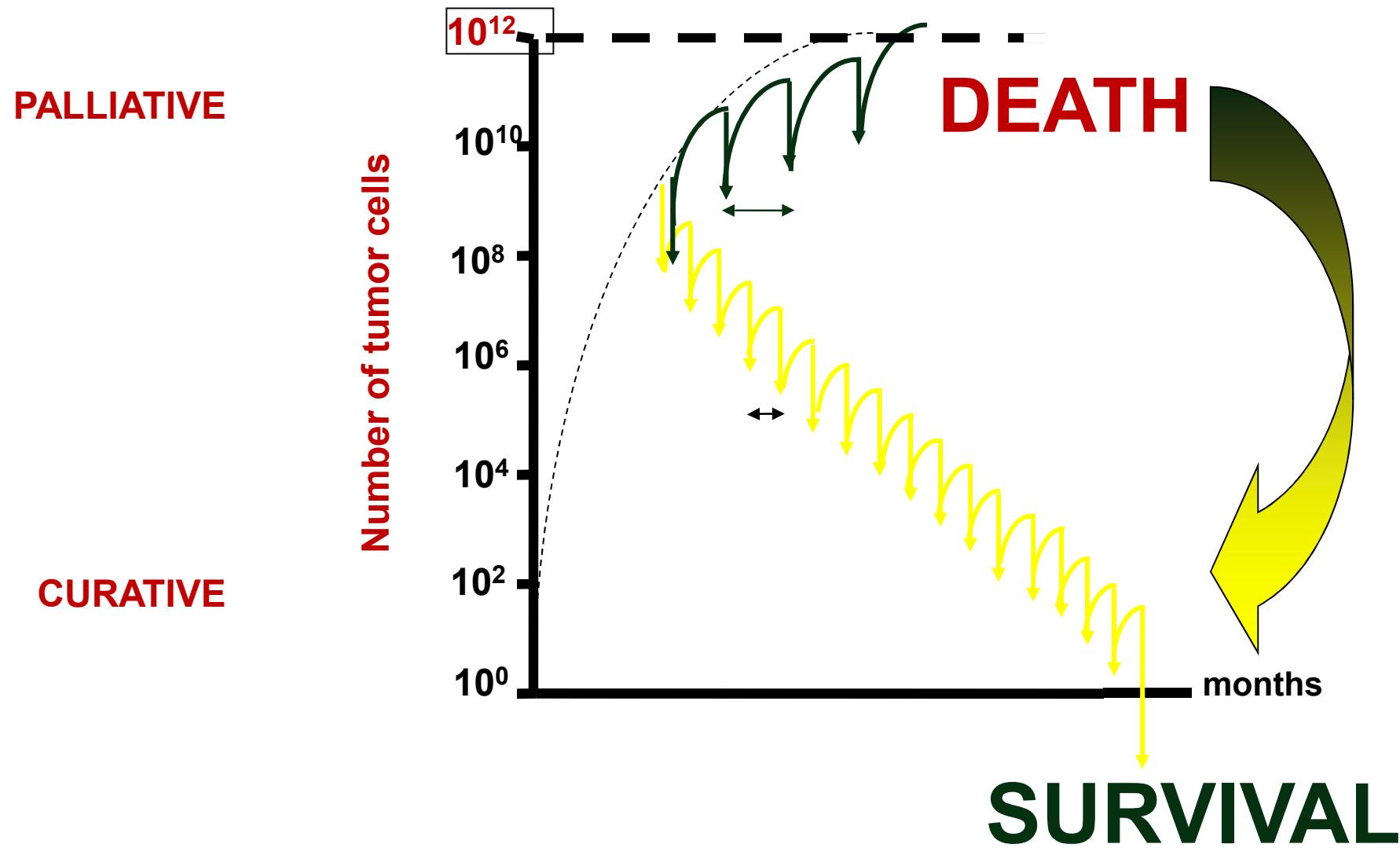
with anemia, neutropenia, lymphopenia, thrombocytopenia
serious infections, sepsis

Mucositis

Damage of gastrointestinal mucosa with nausea, vomitus and diarrhoe

Alopecia

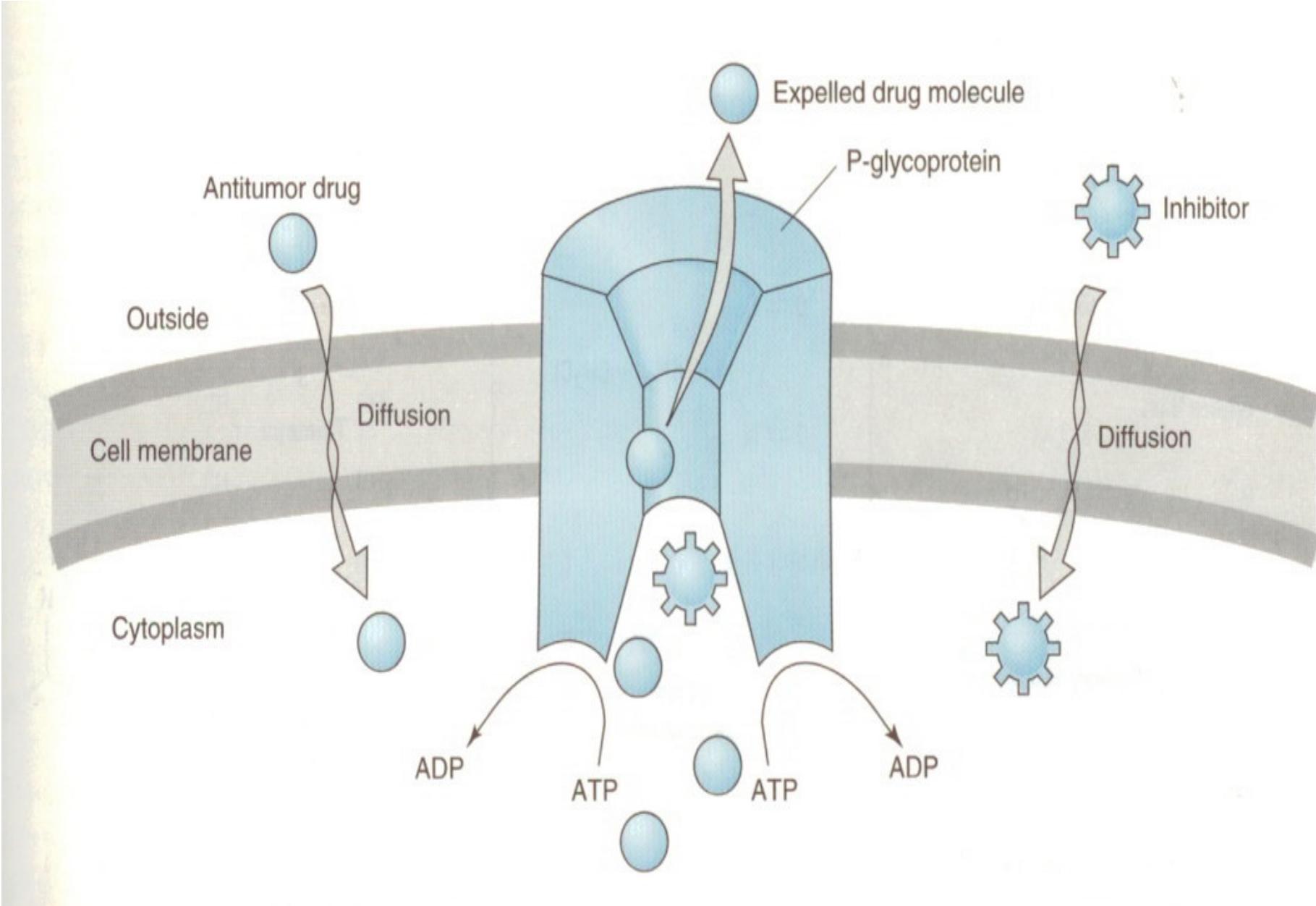
Effect of dose-limiting bone marrow toxicity



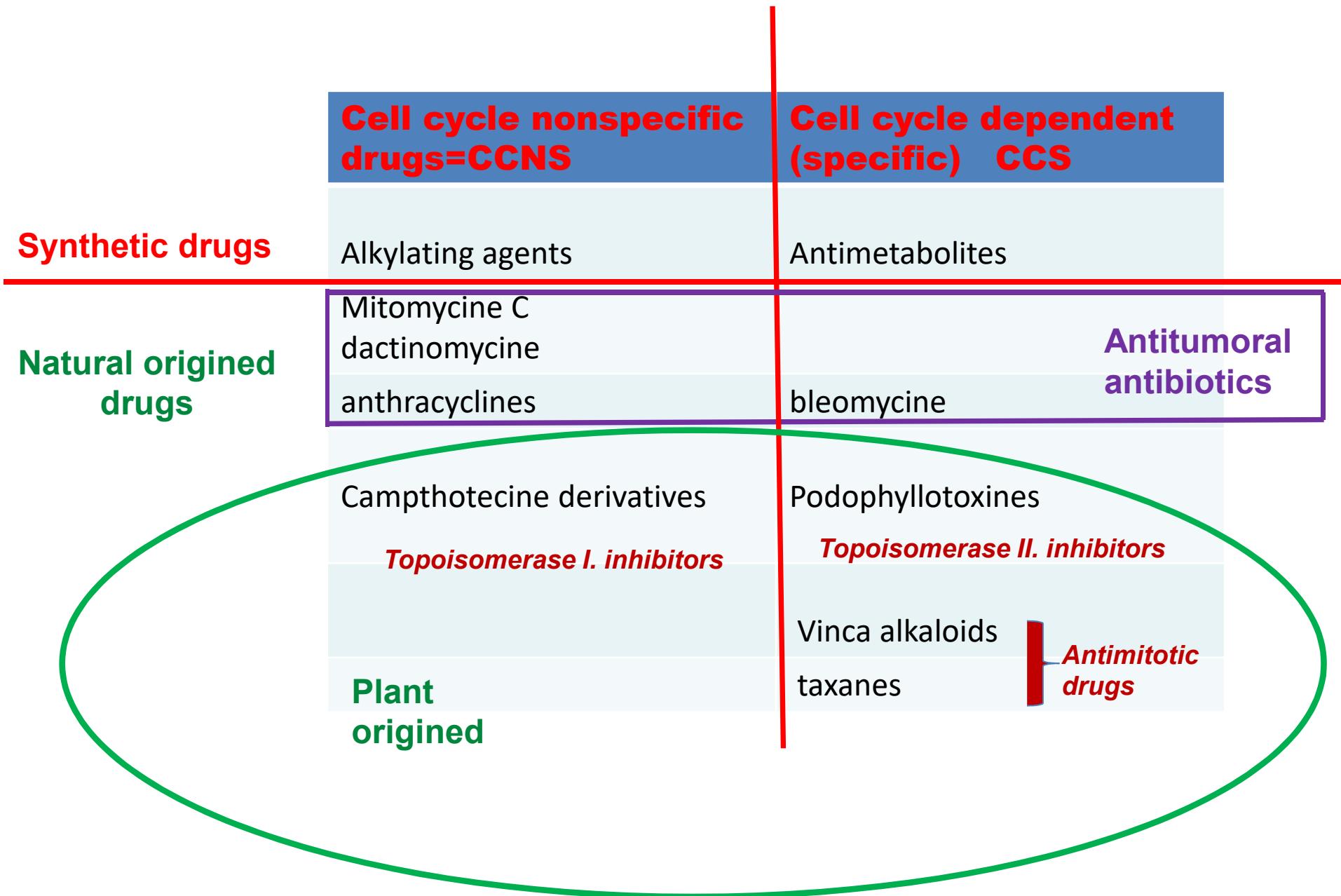
Resistance mechanisms

P-glycoprotein (PGP/MDR1). The physiological role of P-glycoprotein is thought to be the protection of cells against environmental toxins. It functions as a hydrophobic 'vacuum cleaner', picking up drugs as they enter the cell membrane and expelling them. Non-cytotoxic agents that reverse multidrug resistance are being investigated.

- A decrease in the amount of drug taken up by the cell (methotrexate).
- Insufficient activation of the drug (mercaptopurine, fluorouracil, cytarabine). By this it is meant that there may be decreased metabolism of these agents so that they do not enter the pathways where they would normally exert their effects. For example, fluorouracil may not be converted to FDUMP, cytarabine may not undergo phosphorylation; mercaptopurine may not be converted into a 'fraudulent' nucleotide.
- Increase in inactivation (cytarabine, mercaptopurine).
- Increased concentration of target enzyme (methotrexate).
- Decreased requirement for substrate (crisantaspase).
- Increased utilisation of alternative metabolic pathways (antimetabolites).
- Rapid repair of drug-induced lesions (alkylating agents).
- Altered activity of target, for example modified topoisomerase II (doxorubicin).
- Mutations in the *p53* gene and overexpression of the *bcl-2* gene family (several cytotoxic drugs).



Classification of cytotoxic anticancer drugs





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Targets for anticancer drugs

1. DNA
2. DNA synthesis - precursors, enzymes
3. Inhibition of mRNA
4. Inhibition of translation
5. Key enzymes in mitosis
6. Proliferative signals and their receptors or signaling
7. Cell cycle controlling processes
8. Steps of metastasis
9. antitumor immune responses

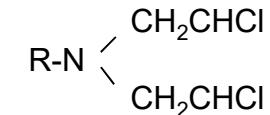
Antiproliferative treatment with cytotoxic drugs

Classification

- 1. Alkylating agents** (e.g., cyclophosphamide)
- 2. Antimetabolites** (e.g., methotrexate, 5-fluorouracil)
- 3. Antitumor antibiotics** (e.g., doxorubicin)
- 4. Antimitotic drugs** (plant alkaloids acting on mitotic proteins, e.g., tubulin, topoisomerase)
 - 4.1. Vinca-alkaloids
 - 4.2. Taxanes
-
- 5. Hormones and hormone-antagonists**
- 6. Miscellaneous**



Alkylating drugs



Mustard derivatives were the first synthetic anticancer drugs
Among them **cyclophosphamide** is the most successful drug even today.

Alkylating agents are the most effective and most toxic group



Narrow therapeutic window

(exception: **cyclophosphamide !!**)

In the most anticancer combination they are the backbone of the therapy even today because of their effectiveness.

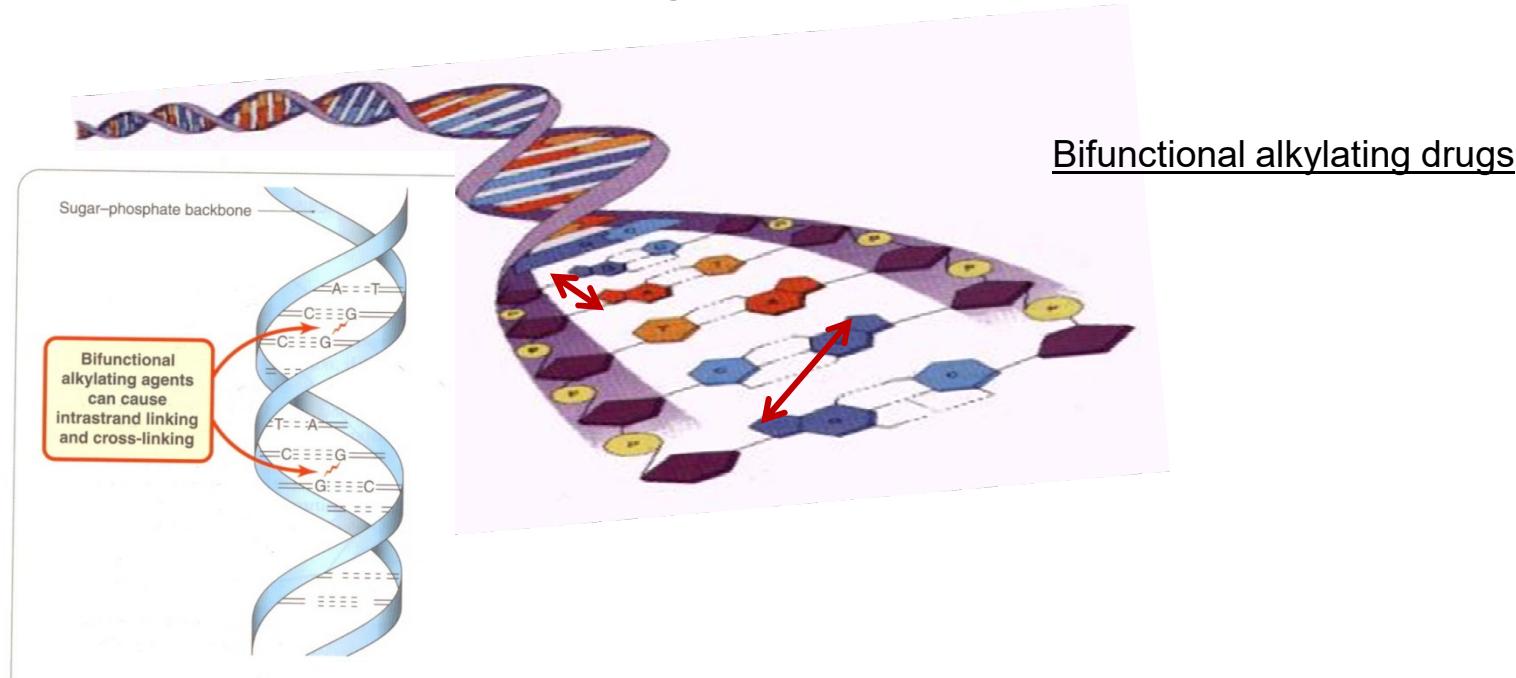
If we are able to manage side effects, they result in the longest survival with complete recovery in the highest probability.

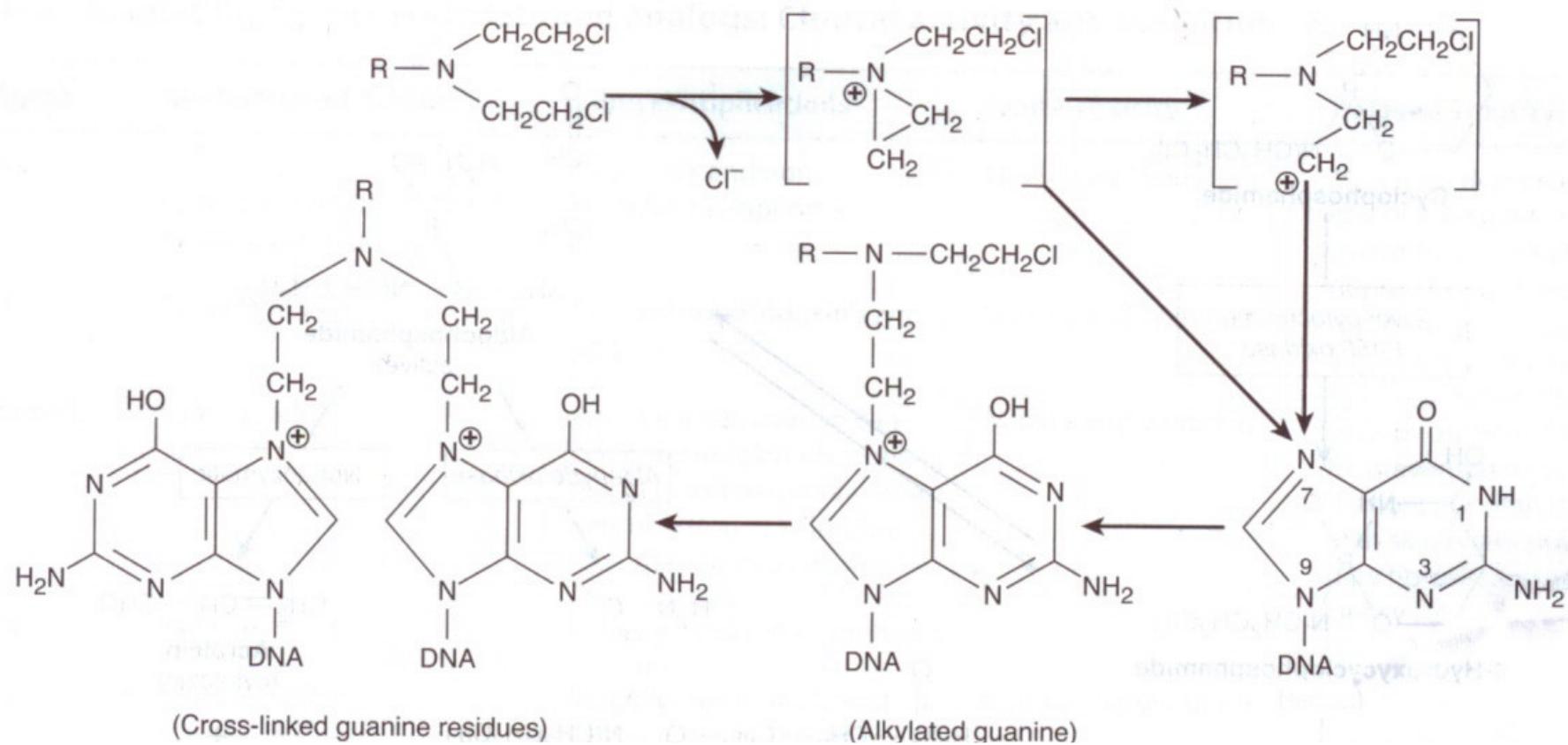


Mechanism of action of alkylating drugs

Covalent, irreversible cross-links between the 2 strip of DNA or within the strip → cell-cycle independent effect

Most frequently they bind to N7 nitrogen of guanine.
Solvolytic formed electrophilic radicals + guanineN7,O6, citosineN3 or adenine N1







Alkylating drugs

1. Nitrogen mustard derivatives

mechlorethane
cyclophosphamid, ifosfamide
melphalane
chlorambucil

2. Nitrosourea derivatives

carmustine, lomustine, semustine

3. Alkylsulfonates

busulfane

4. Etileneimines

tiotepa

5. Triazenes

temozolomide, dacarbazine (antitumor antibiotikum)

6. Others

procarbazine

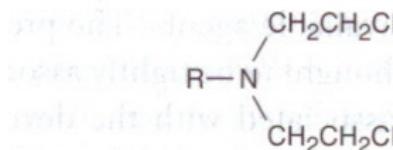
7. Platina derivatives (with very strong complex formation)

cisplatin, carboplatin, oxaliplatin

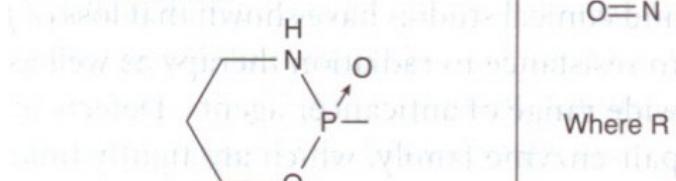
ALKYLATING AGENTS

NITROGEN MUSTARDS

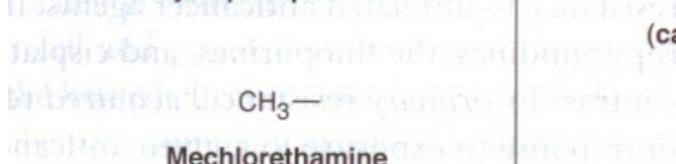
Bis(chloroethyl)amines



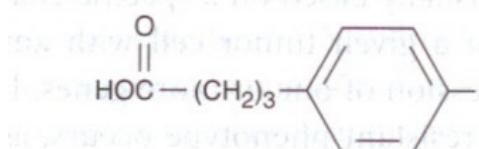
Where R is:



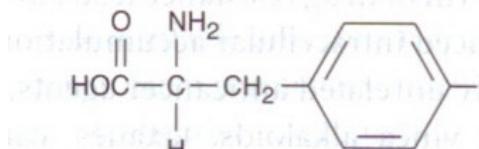
Cyclophosphamide



Mechlorethamine

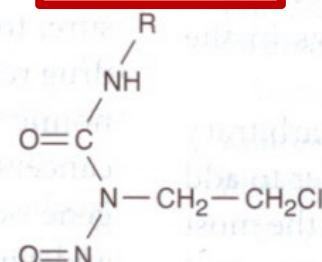


Chlorambucil

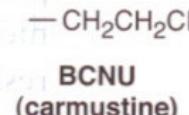


Melphalan

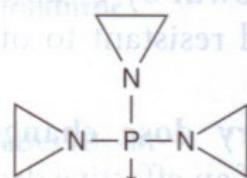
Nitrosoureas



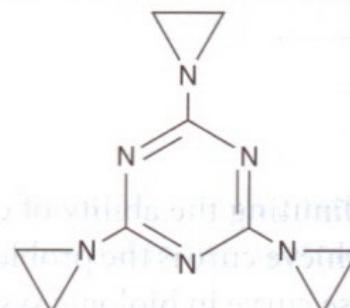
Where R is:



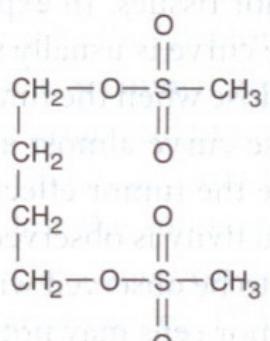
Aziridines



Thiotepa



Alkylsulfonate



Busulfan

Structures of major classes of alkylating agents.

Katzung et al Basic and Clinical Pharmacology textbook



Alkylating drugs

1. Nitrogen mustard derivatives

mechlorethamine

MOPP protocol for Hodgkin disease

M=mechlorethamine+ O=Oncovin (vincristine)+ procarbazine+ prednisolone

melphalan

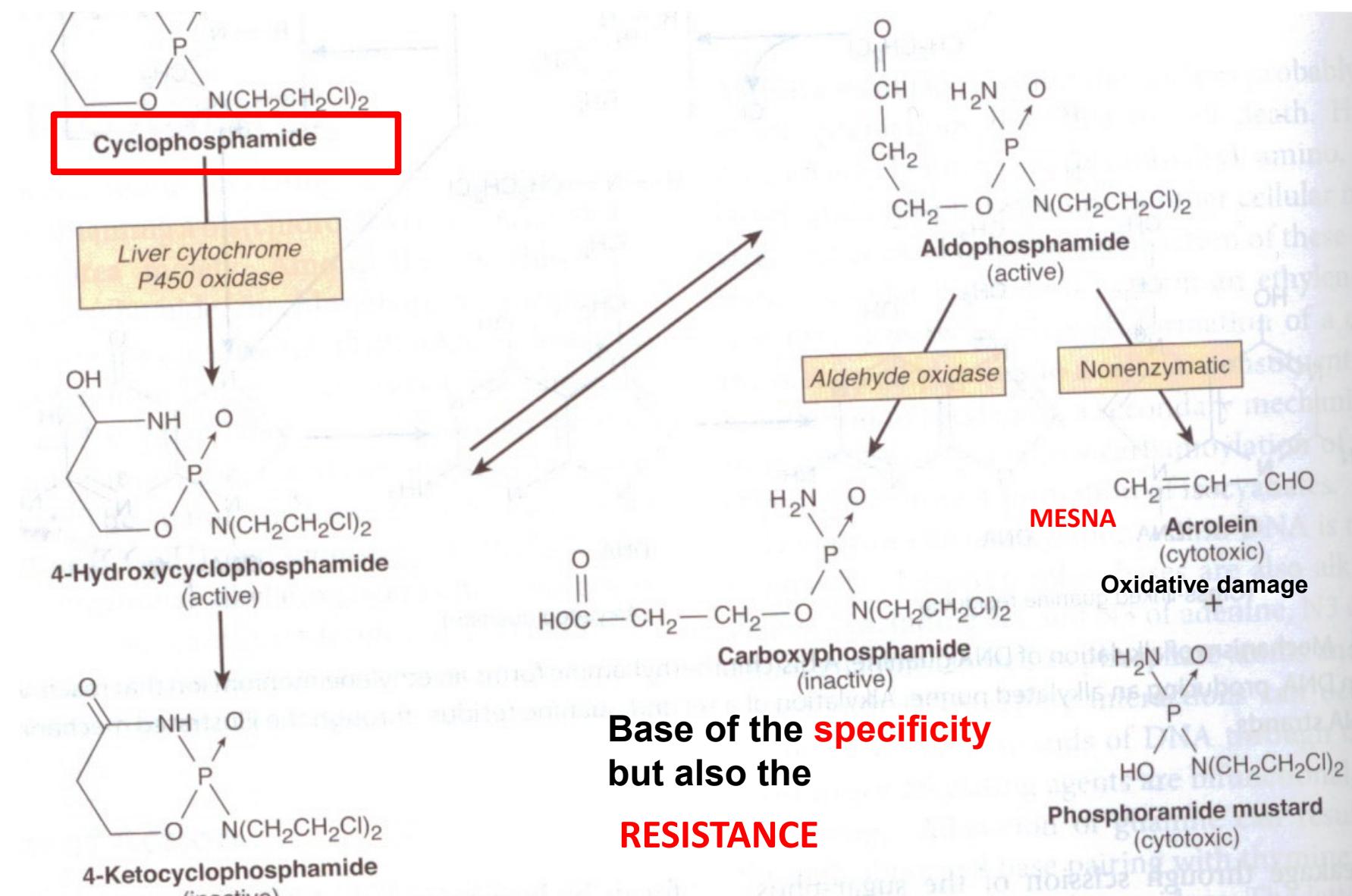
for myeloma multiplex p.o.

chlorambucil

CML p.o. maintenance therapy

cyclophosphamide, ifosfamide

prodrug the active metabolite forming in liver has cytotoxic effect



-5 Cyclophosphamide metabolism.



Nitrozourea derivatives

lomustin (CCNU) , carmustin (BCNU), semustin
streptozotocin, fotemustin, nimustin

Effect: 2-chloretil-diazonium ion
very strong electrophile → alkylation of guanine, cytosine, adenine

Toxicity:

- The most toxic cytotoxic drug group - bone marrow toxicity
- After a single dose of carmustin nadir of neutropenia is 4-6 weeks later and regeneration lasts 2-3 months !
 - Renal toxicity: tubular degeneration, Fanconi syndrome
 - Hepatotoxicity 25 %
 - Lung toxicity: dyspnoe, cyanosis
 - Myelodysplasia
 - Acute lymphocytic leukemia



Nitrozourea derivatives

Clinical use

Active ingredient	Administration	Clinical use
BCNU carmustin	iv	Hodgkin, non-Hodgkin ly
CCNU lomustin	p.o.	Lung cc
Methyl-CCNU	p.o.	Primery brain tu, glioma
streptozotocin	iv.	Insulinoma, carcinoids
fotemustine	iv.	Melanoma brain metastasis



Other alkylating drugs

Active ingredient	Administration	Clinical use	
procarbazine	p.o. within 15 minutes conc in plasma and cerebral fluid are the same in MOPP protokol	Tumor inhibitory effect Monoamino oxidase inhibition cheese reaction – Avoid tiramin containing dishes !!	
dacarbazine	iv. Prodrug, activation in liver	Metilation on DNA RNA and inhibition of protein synthesis	
temozolomide	p.o.	Metilation on DNA	

Spectrum of alkylating drugs

Cyclophosphamide lymphomas and leukemias
breast cc

ovarium cc

Ifosfamide testis tumor
lung cc
sarcomas
cervix cc

Lomustin, carmustin, semustin primary brain tu

Temozolomid és tiotepa glioma

Dacarbazin glioma
melanoma

Busulfan chronic myeloid leukemia **per os !!**

Resistance against alkylating agents

- **Increased activity of DNA repair**

methyl-guanin methyl-transferase (MGMT) in tumor cells, e.g. glioma

Drugs forming methyl adducts: nitrosoureas, procarbazine, temozolomide

- **Increased i.c. Glutation conc**

- **Decreased transport through membrane**

- **Increased elimination**

Cyclophosphamide, iphosphamide - aldehyde oxydase=dehydrogenase

- **MMR not responding**

- **Bcl-2 enhanced expression –apoptosis inhibitory effect**

Specific side effects of alkylating agents

Mutagenicity

**Secondary tumors after about 20 years (leukemias)
in 5 % of patients 4 years after therapy as AML**

Vomitus

Infertility

Haemorrhagic cystitis in cyclophosphamide therapy

Lung fibrosis - busulfan

Bone marrow toxicity (dose limiting effect)

The most frequent reason of death



Serious neutropenia



Life-threatening infections,
Often with opportunist microbes - sepsis

Dose fractioning is required !!

in meantime we have to allow time for regeneration of bone marrow

administration schedule: 1x weekly or monthly as iv.infusion



Platinum derivatives

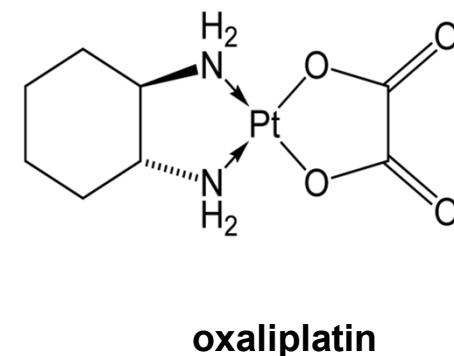
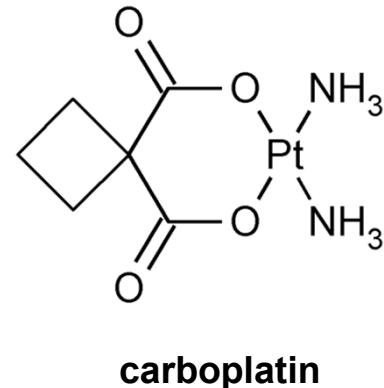
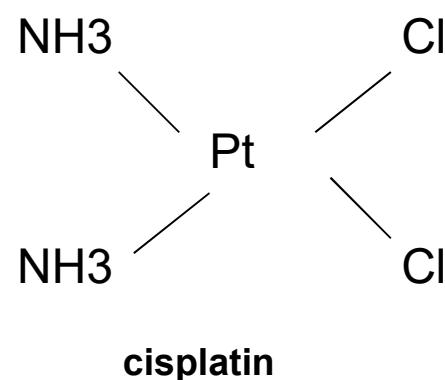
Great improvement in survival in testis and ovary cc

surgery + PVB cisplatin+vincristin+bleomycin



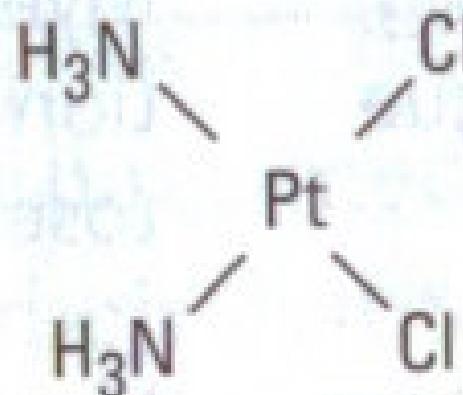
in testis cc survival is 80%, in the group with better prognosis >95 % !

Less possibility for repair in the case of platina-DNA complex than in alkylating drugs, especially in the case of oxaliplatin.



Platinum compounds

Cisplatin
carboplatin



Cisplatin

Alkylating-related agents form a very strong complex with DNA

Specific side effects: haemorrhagic cystitis
vomitus
neurotoxicity especially in the case of carboplatin



Platinum derivatives

Pharmacokinetics:

active transport CTR Cu²⁺ transporter through cell membrane
active ATP requiring MRP1 and ATP7A efflux



RESISTANCE MECHANISMS
Including Multidrug resistance

Distribution: strong protein binding in blood > 90%
T_{1/2} short, accumulation in tissues

High concentration: in liver, kidney and testis
Low pass through BBB

Excretion: kidney

Slow excretion: about 40 % during 5 days

Platinum derivatives

Toxicity:

- **intensive** – common side effects in more serious form, e.g. vomitus, myelotoxicity
- Nephrotoxicity is frequent due to oxidative stress.



Forced diuresis and SH -containing mesna or amifostin decrease the risk of nephrotox

- Neurotoxicity – peripheral neuropatias, damage of sensory nerves
- Ototoxicity
- Lung fibrosis
- Mutagenicity, carcinogenicity >4 years secunder leukemias (AML) 4x risk



Complex-forming drugs with DNA antracyclines

They are used very frequently in protocols – cell-cycle independent drugs

As antitumor antibiotics they are produced by *Streptomyces peucetius*.

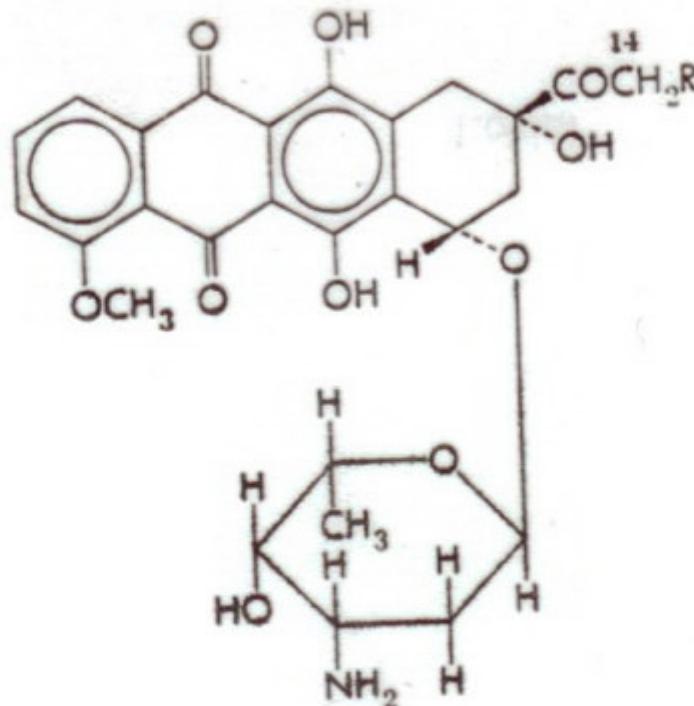
Antracyclines:

doxorubicin=adriamycin
daunorubicin
idarubicin
epirubicin
valrubicin

Yellow, orange or red compounds.

Rigid 4-membered ring structure in one plan.

ANTHRACYCLINES



Daunorubicin: $\text{R} = \text{H}$

Doxorubicin: $\text{R} = \text{OH}$



Complex-forming drugs with DNA antracyclines

- Mode of action:
1. intercalation into DNA base-pairs
 2. topoizomerase II. inhibition
 3. free radical formation
 4. increased apoptosis

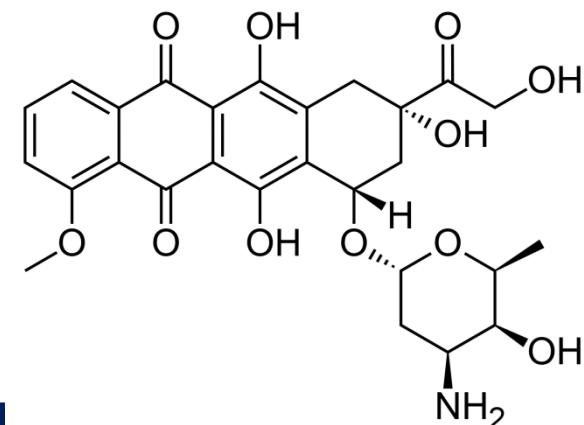


Broad spektrum:

leukemias
breast cc
osteosarcoma

Daunorubicin/idarubicin
Adriamycin/epirubicin

leukemias
+ solid tumors

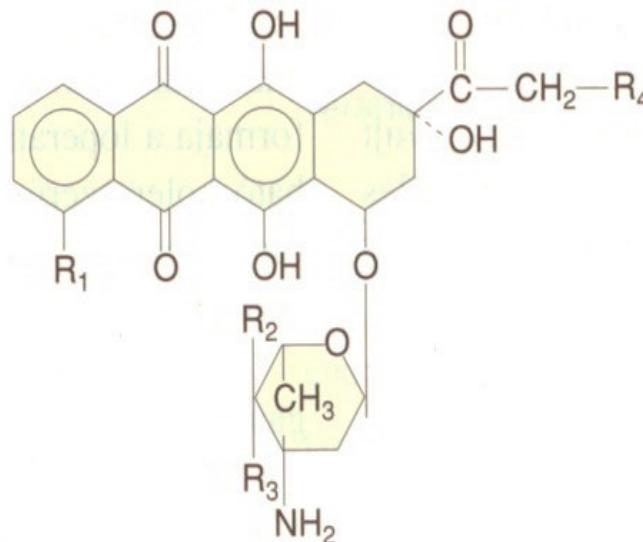


ANTHRACYCLINES

Dose limiting side effects:

Bone marrow suppression

Administration schedule: 1x monthly!



and

cardiotoxicity

Max. 450 mg/m²
cumulated dose

to prevent
cardiotoxicity !

th.:dexrazoxan

	doxorubicin	daunorubicin	epirubicin	idarubicin
R ₁ =	OCH ₃	OCH ₃	OCH ₃	H
R ₂ =	H	H	OH	H
R ₃ =	OH	OH	H	OH
R ₄ =	OH	H	OH	H

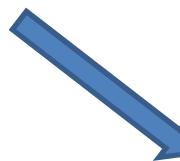
Complex-forming drugs with DNA: antracyclines

Resistance mechanisms:

**ABC transport proteins
detoxificant system at cellular level**



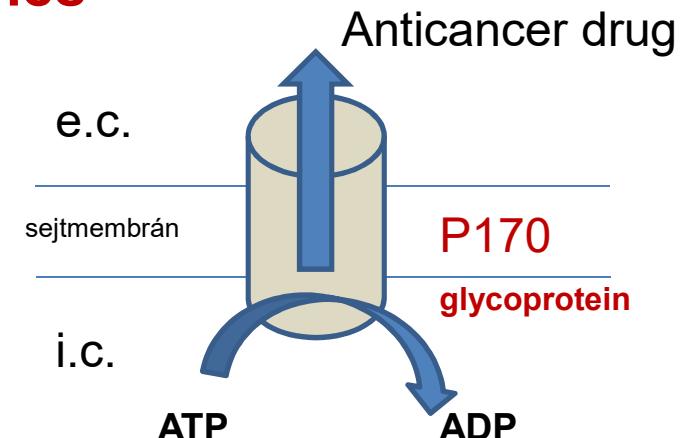
**Protection against cytotoxic agents
In bone marrow**



**in tumor cells
Multi-drog resistance
MDR, MRP**

Substrates for Multi-drog resistance :

In the case of any natural originated polycyclic cytotoxic agents



ANTIMETABOLITES

Antifolate drugs

**methotrexate
raltitrexede**

Pirimidine analogs

**5-fluorouracil and derivatives
cytarabine**

Purine analogs

**cladribine
fludarabine**

**thioguanine
mercaptopurine**

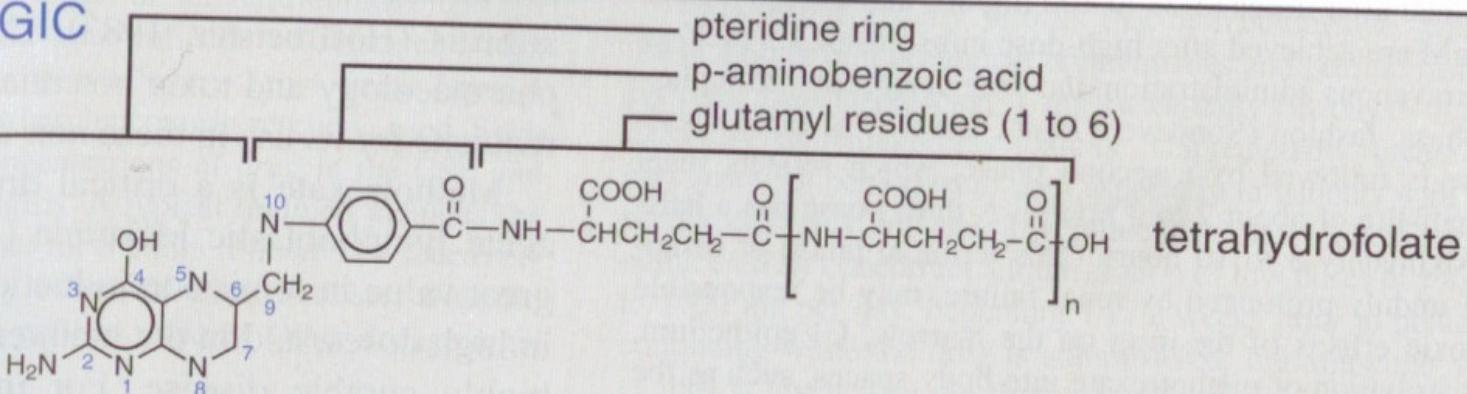
Folate antagonists

Folate antagonists: methotrexate
 from 1940
 antitumor and immunosuppressant drug
 raltitrexede
 trimetrexate
 Trimetrexade is used also in *Pneumocystis carinii* pneumonia

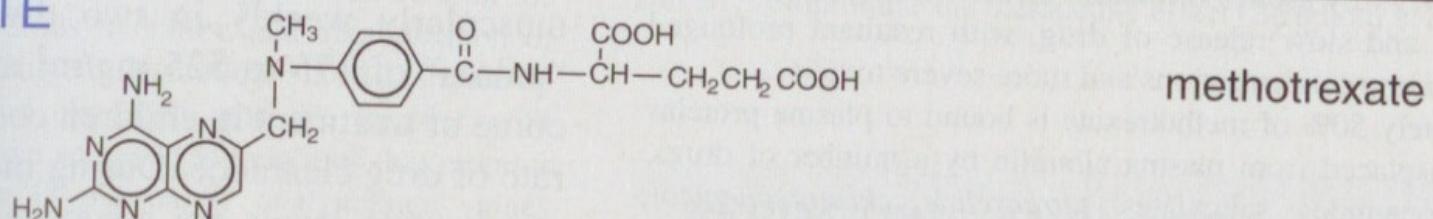
Pharmacokinetics:

- active transport into cells in competition with folic acid
 - exception: trimetrexate, without transporter –quick pass to cells
- Intracellular polyglutamation by folate-glutamate synthase
 - ↓
decreased efflux
- Metabolization:
 - liver by aldehyd dehydrogenase
 -
 - renal toxicity by a metabolite
- intestine bacteria: less active metabolite+glutamin acid

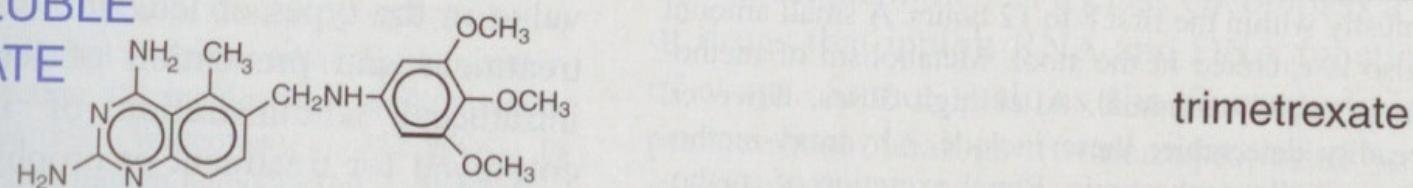
PHYSIOLOGIC FOLATE



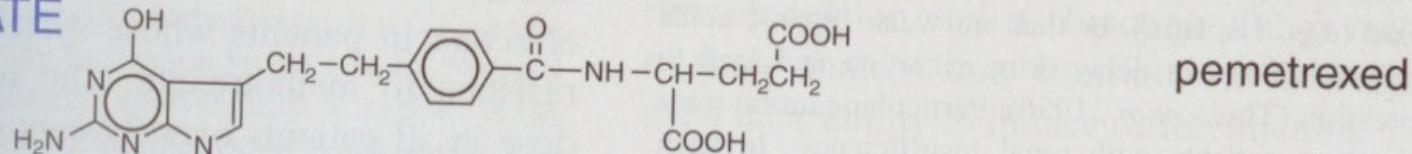
ANTIFOLATE



LIPID SOLUBLE ANTIFOLATE

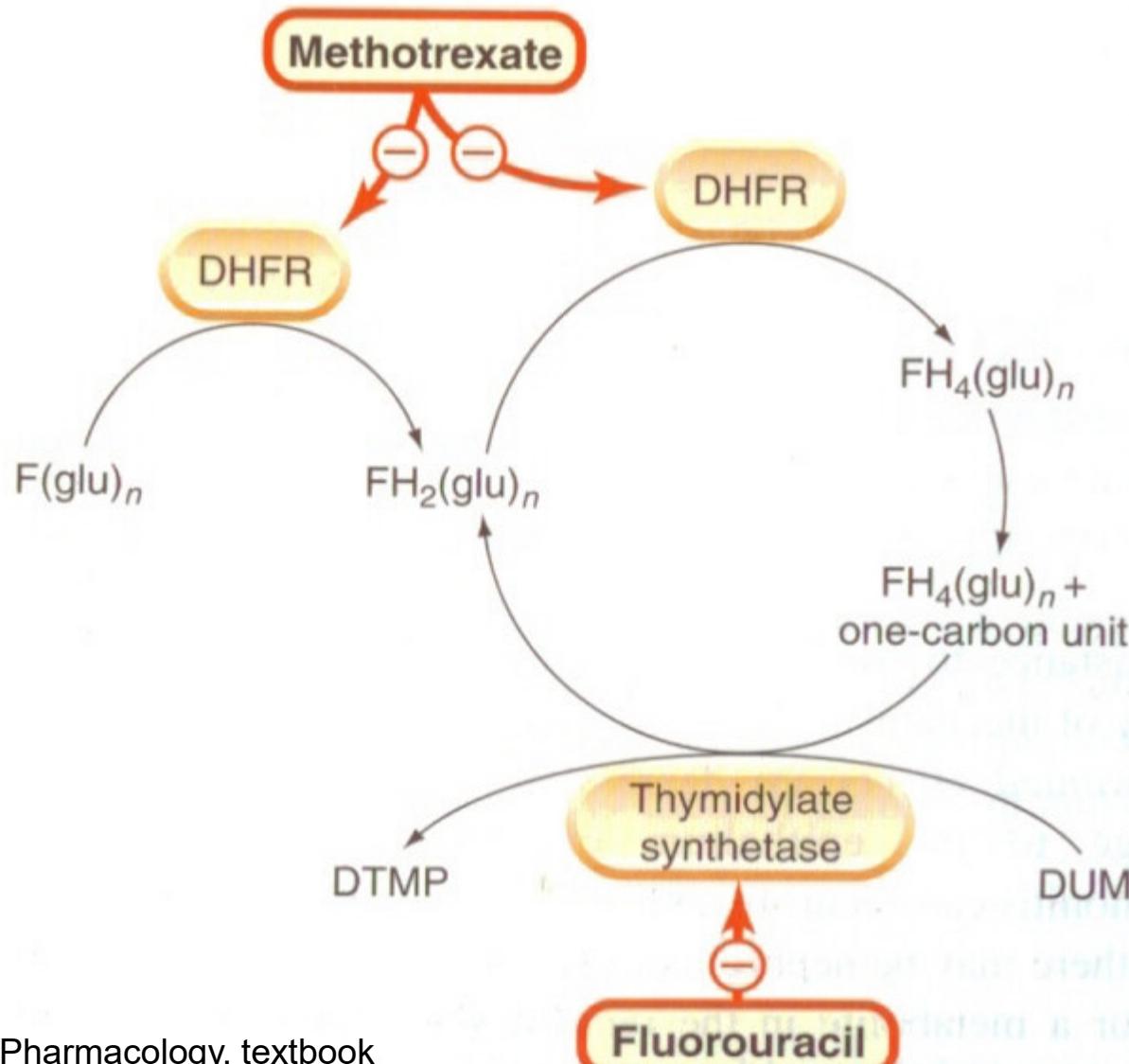


MULTITARGETED ANTIFOLATE

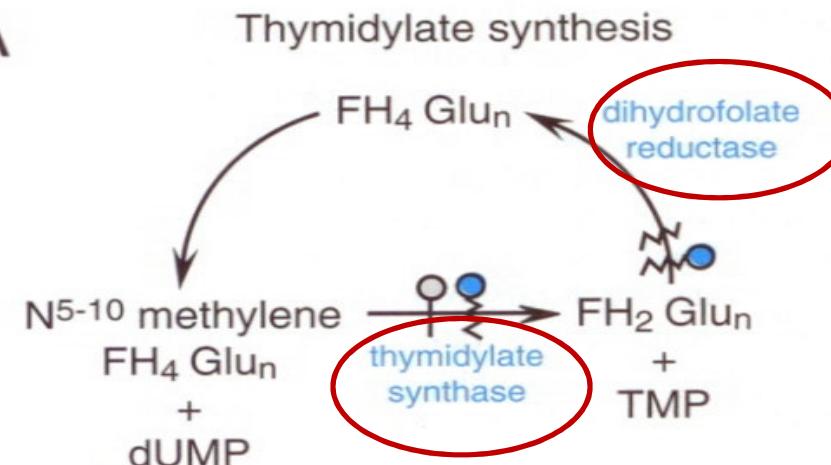


Targets: dihydrofolate reductase (DHFR)

+ thymidylate synthase in the case of the newer drugs



A

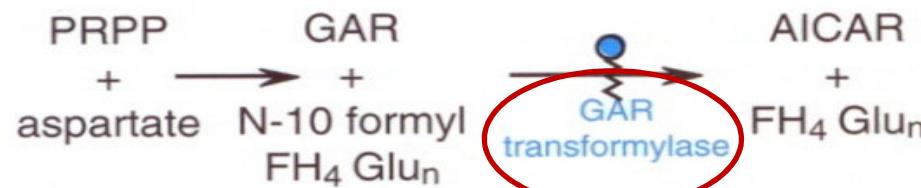


Methotrexate also inhibits other folate dependent enzymes:

B

De novo purine synthesis

Phosphoribosyl transferase



glicinamid ribonucleotid transphormilase

5-aminoimidazole-4-carboxamide ribonucleotide (AICAR)



aminoimidazol carboxamide ribonucleotide=AICAR-transformylase

REACTION INHIBITED BY:

methotrexate

methotrexate
polyglutamates

$\text{FH}_2\text{ Glu}_n$

Folate antagonists

Targets:

dihydrofolate reductase (DHFR) + **tymidilate synthase in the case of the newer drugs**



Pirimidin synthesis

glicinamid ribonukleotid transformilase

+

aminoimidazol carboxamid=AICAR-transformilase

Inhibition of adenosine deaminase



De novo purine synthesis



Immunosuppressive effect

Antiinflammatory effects

Adenosine high plasmakonc.

Chemotaxis inhibition

e.g. Decreased production of TNFalpha and
IFN gamma



Toxicity of Folate antagonists

Besides the common side effects:

- Renal and hepatotoxicity
- Fibrosis in lung
- Neurotoxicity
- Abortion, without teratogenicity during therapy of choriocc.

Well-tolerable in majority of patients,

Even in intratecal administration for prevention

of brain metastasis in leukemias !

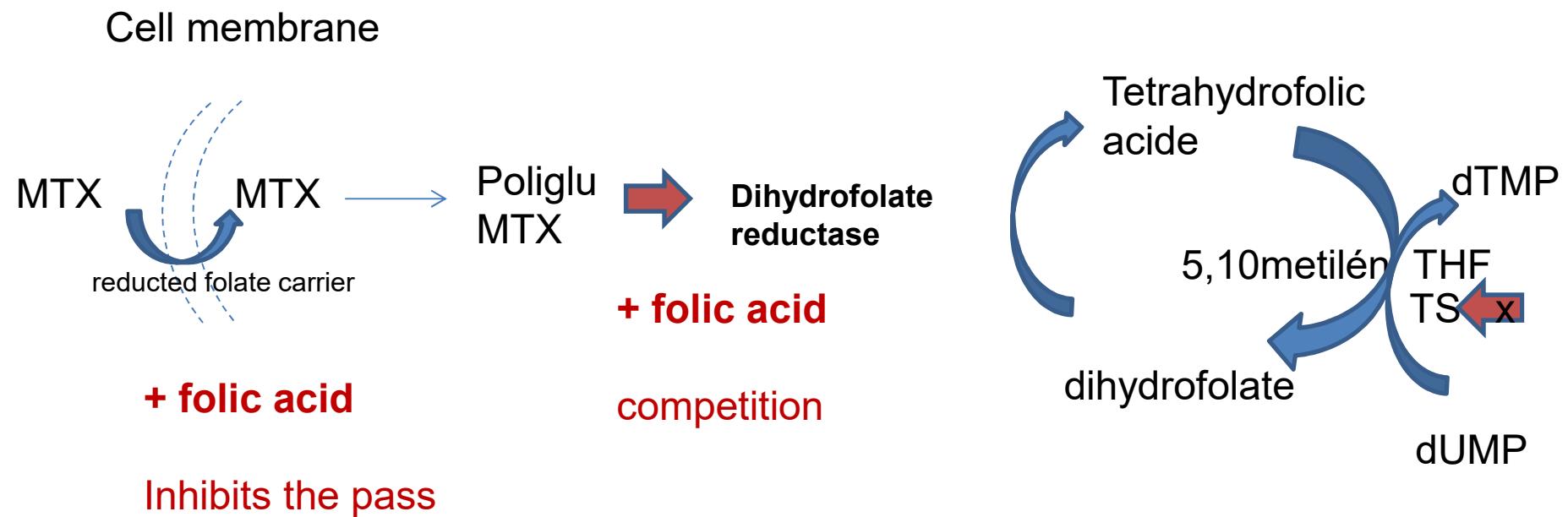
High-dose methotrexate : **leukovorin (folic acid)**

decreases bone marrow toxicity,

B12 vitamin decreases neurotoxicity

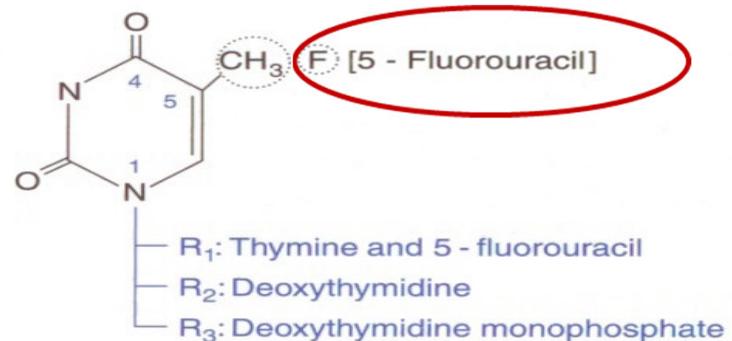
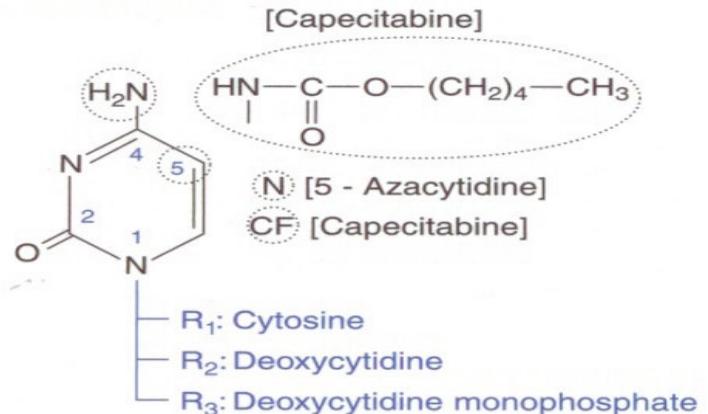


Folic acid- methotrexate interaction

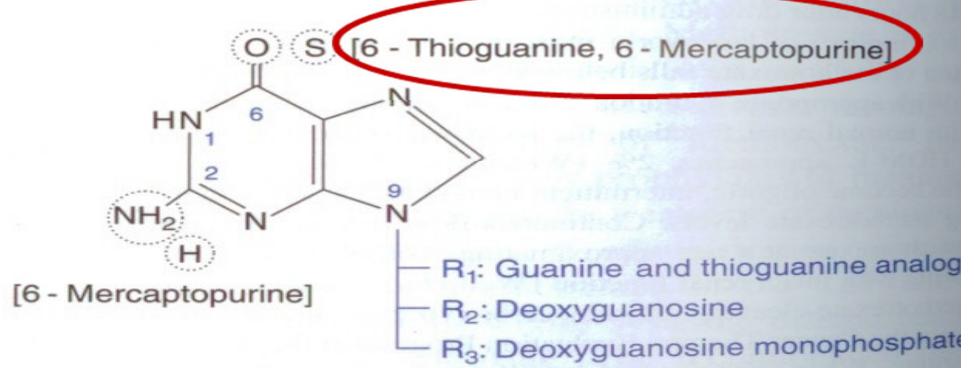
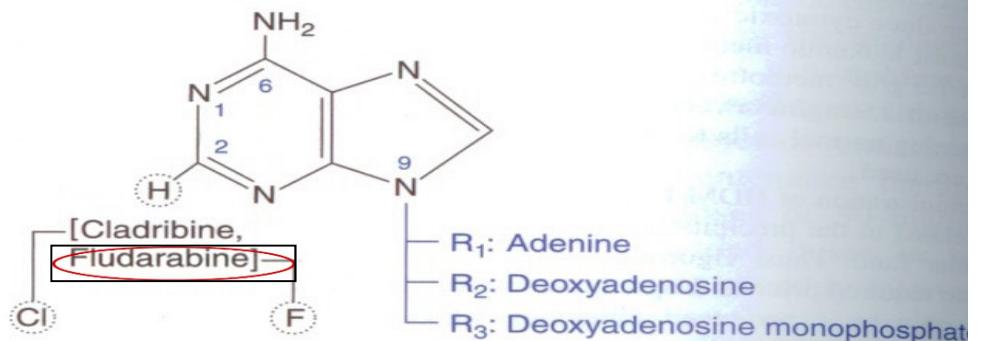


High-dose therapy may be managed by folic acid

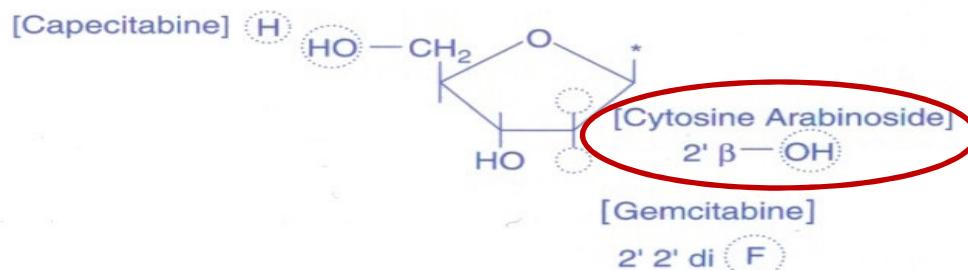
Pyrimidines



Purines



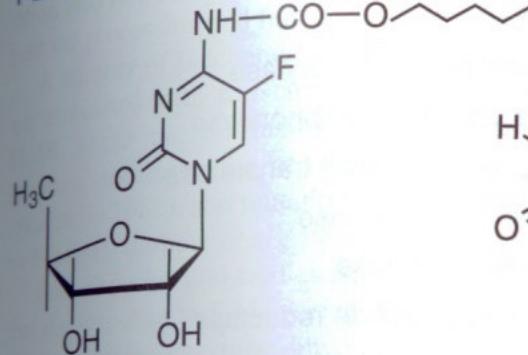
$R_1 = \text{H}$: the base; R_2 = deoxyribose: the deoxynucleoside;
 R_3 = ribose monophosphate/analog: the deoxynucleoside monophosphate/analog



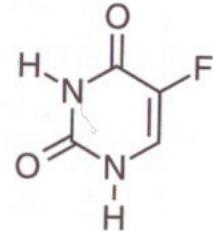


Pyrimidine analogs

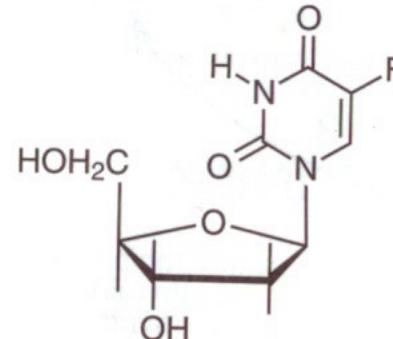
FLUOROURIDYL ANALOGS



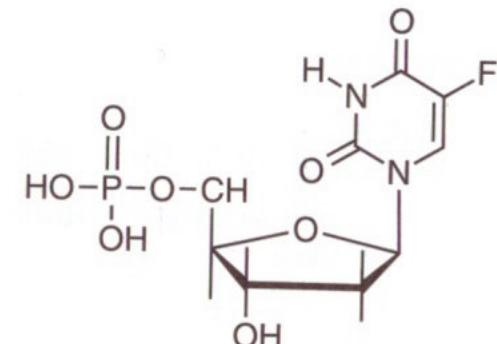
Capecitabine



5-Fluorouracil
(5-FU)

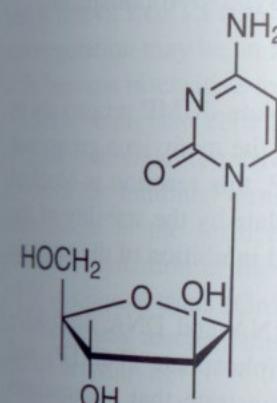


5-Fluorodeoxyuridine
(floxuridine)

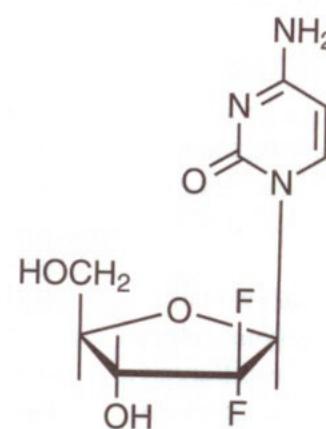
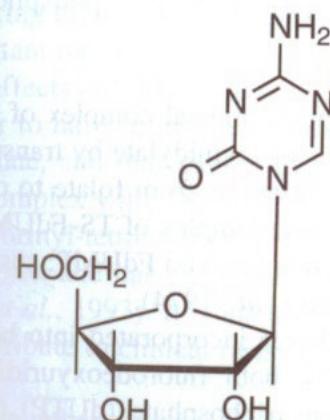


5-Fluorodeoxyuridine
monophosphate
(active metabolite)

CYTIDINE ANALOGS



Cytidine



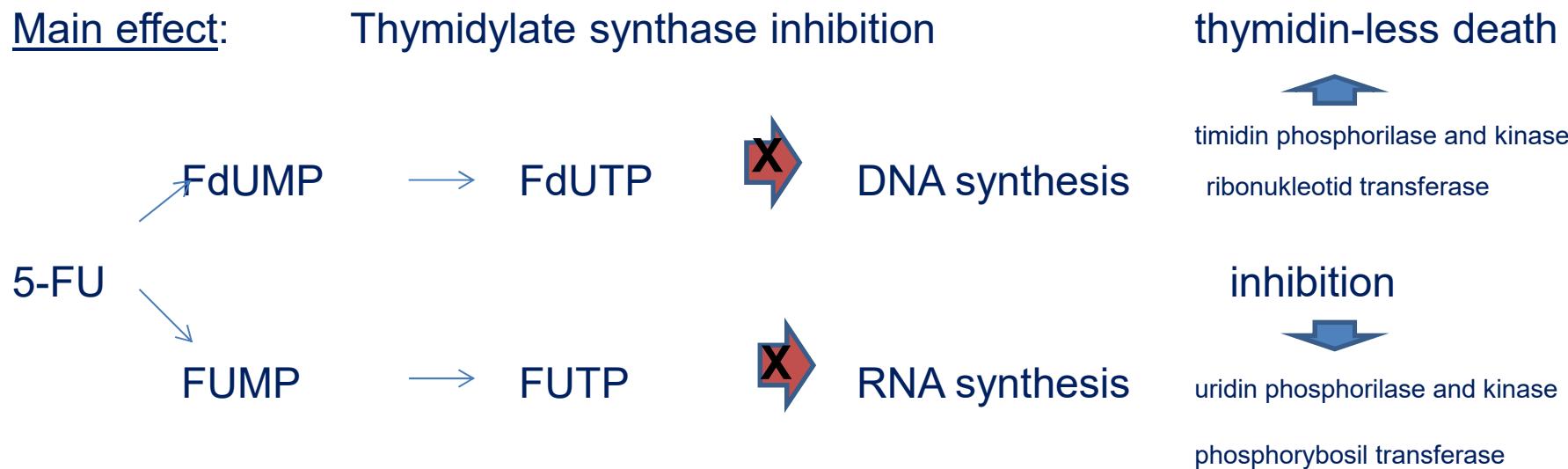


Pyrimidine analogs

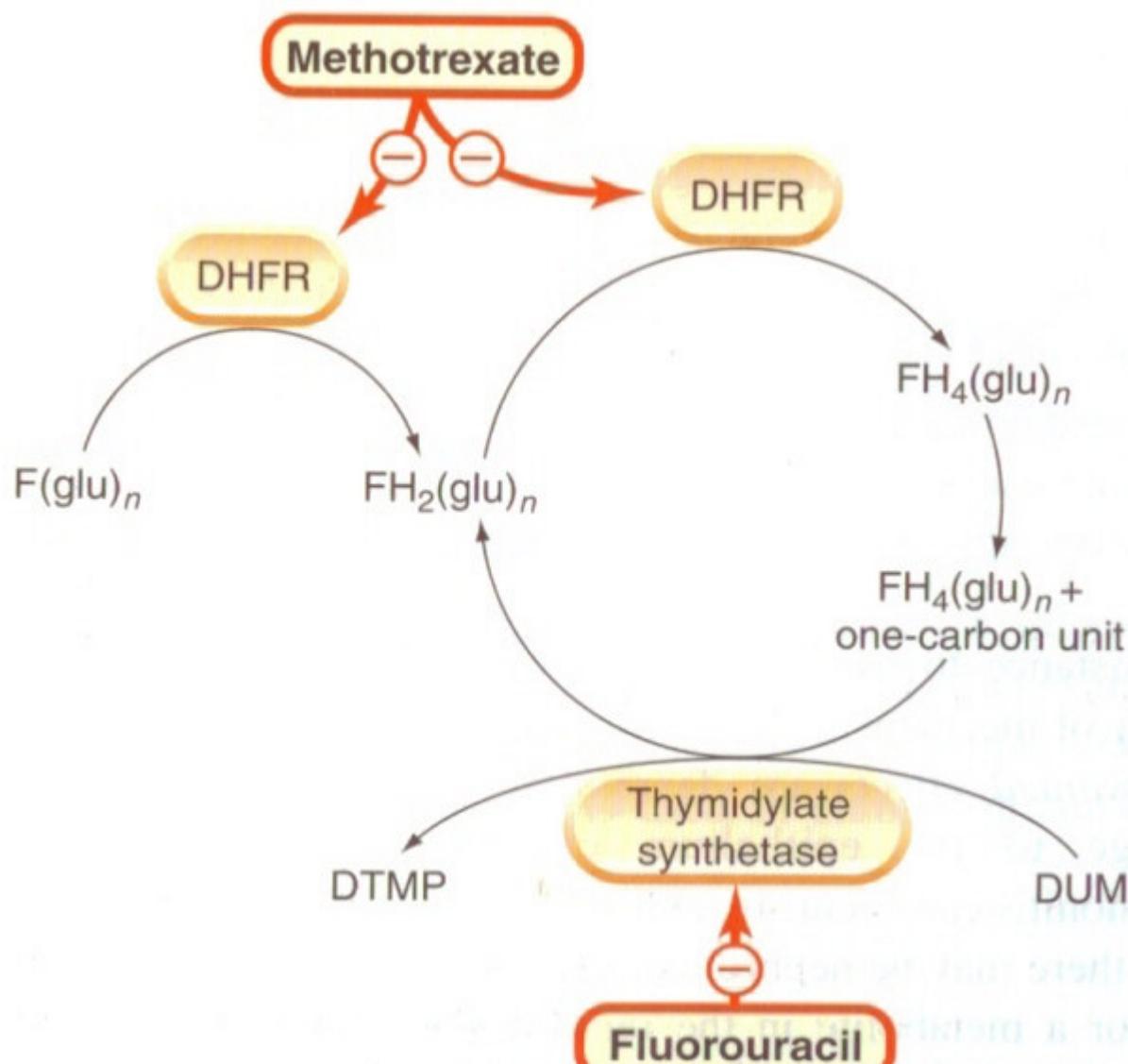
The most important is **5-fluorouracil** and derivatives

5-FU is an exception among antimetabolites.

Much more effectiveness and toxicity than in the case of others because of its mode of action:

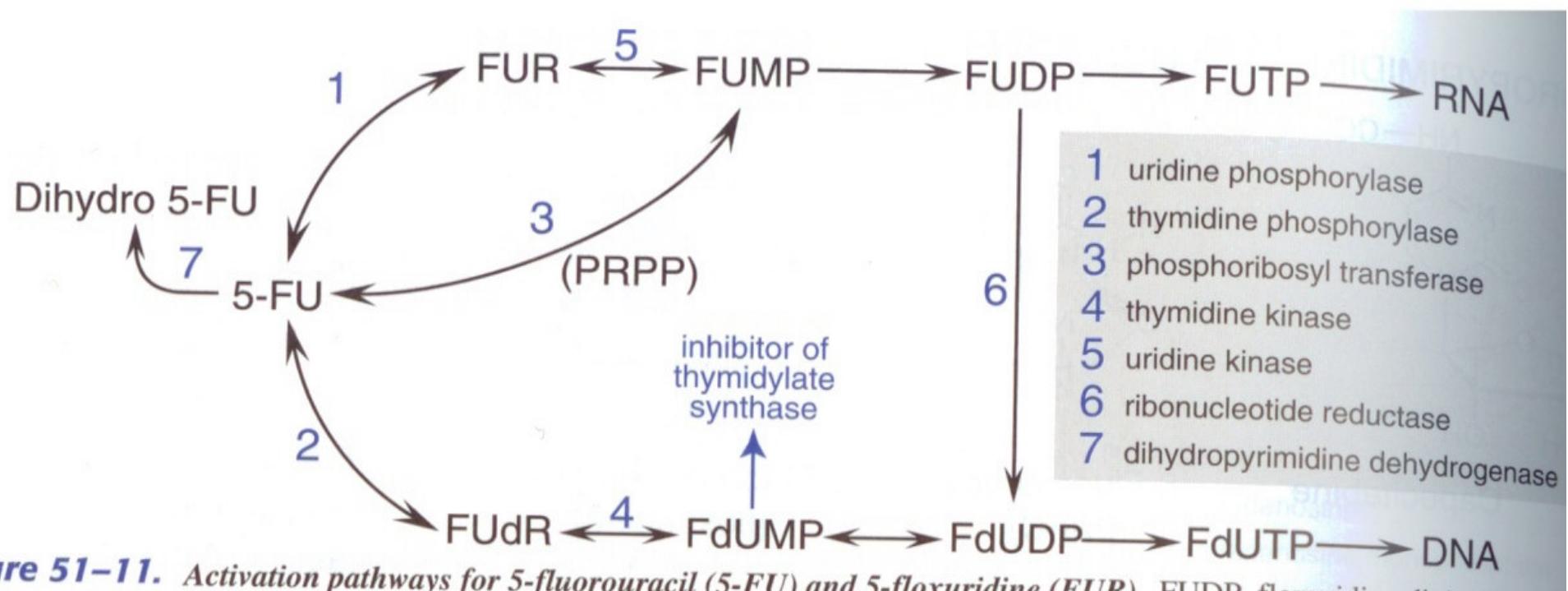


Target for 5-FU: thymidylate synthase



Rang and Dale's Pharmacology, textbook

Fig. 50.8 Simplified diagram of action of methotrexate.



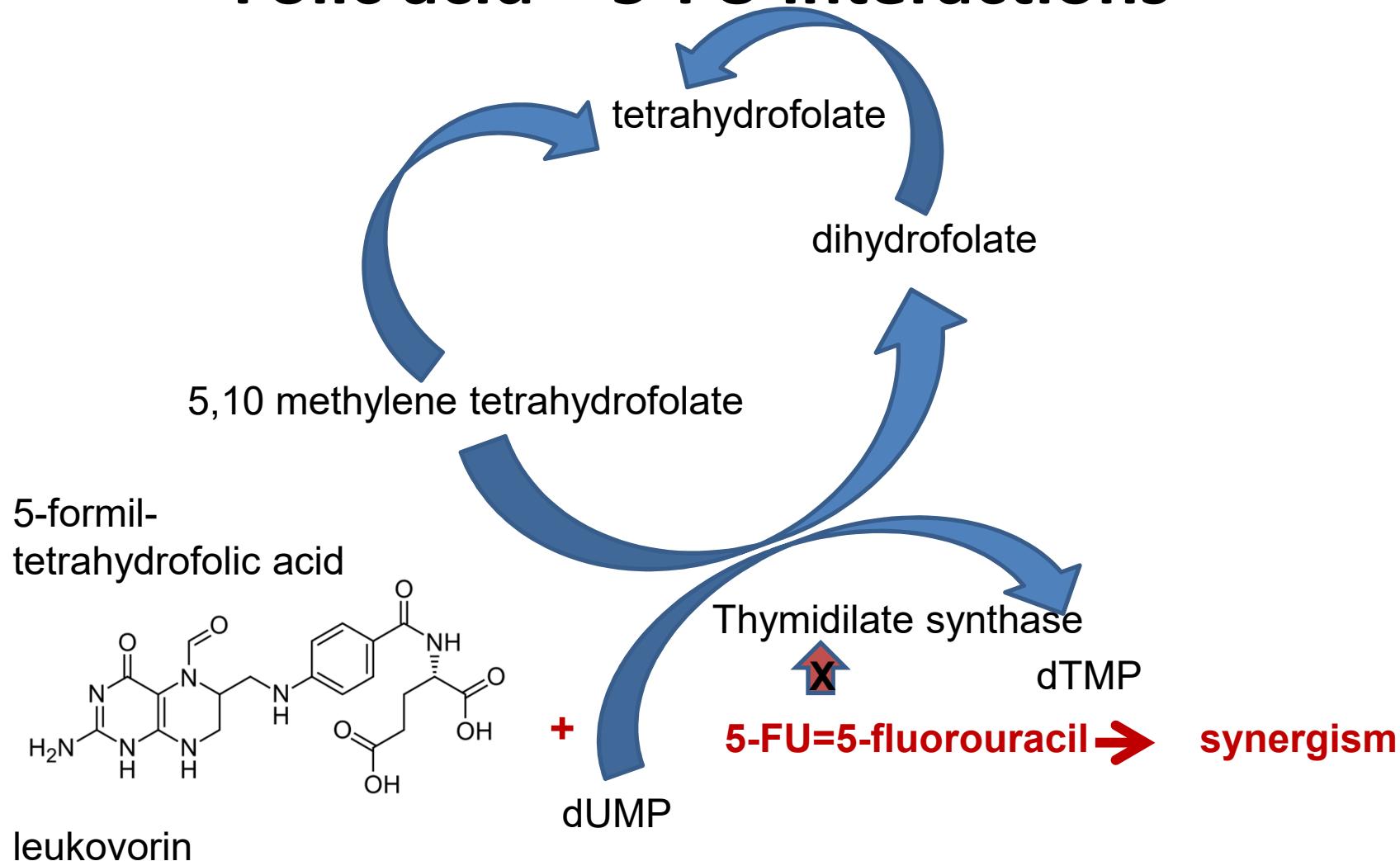


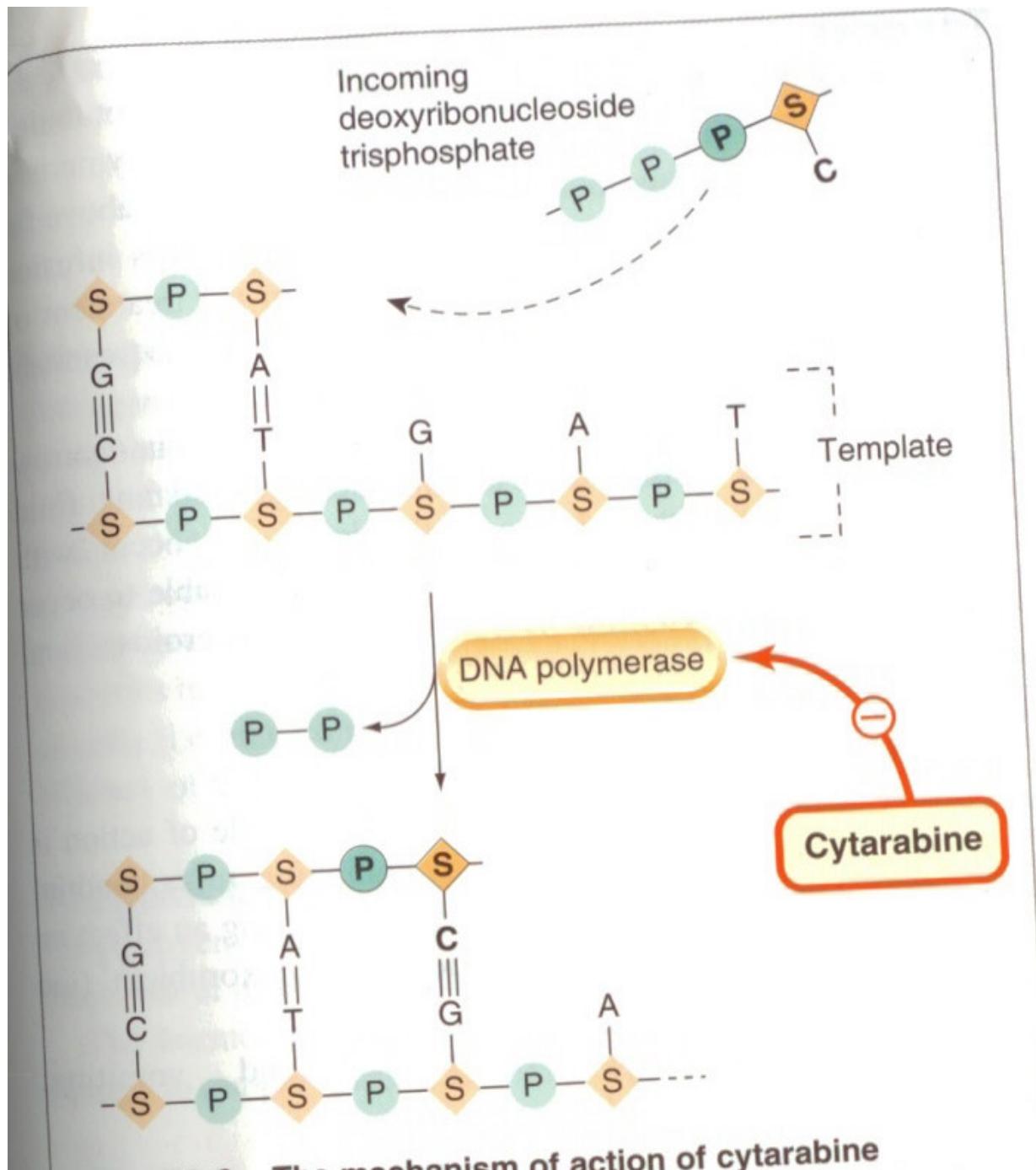
5-FU metabolism and resistance

- DPD=dihidro pyrimidine dehydrogenase inactivates 5-FU in liver and mononuclear blood cells
 - DPD circadian rithm changes conc of 5-FU in plasma 2-3x !!!
 - Increased thymidine kinase results in resistance by salvage mechanism
- Uridine decreases toxicity



Folic acid – 5-FU interactions







Purine analogs

Cladribine

- adenosine deaminase breaks it quickly

Fludarabine

- adenosine deaminase resistant
- DNA polymerase inhibition

spektrum: CLL, Hodgkin

Mercaptopurine

- p.o. Good absorption

ALL

Thioguanine

- bad absorption only iv.

AML

xantine oxydase in metabolism

Besides the common side effects:

gout attack

allopurinol prevention

TERMÉSZETES EREDETŰ TUMORELLENES SZEREK

Streptomyces gombákból		növényekből	
antibiotics to cancer cells	<p>alkilálók: mitomycin C</p> <p>DNS-sel komplexképzők: dactinomycin = actinomycin D plicamycin anthracyclinek: daunorubicin doxorubicin</p>	Vinca alkaloidok	<p>microtubulus összeszerelődését gátlók: vincristine vinblastine</p> <p>microtubulusokat stabilizáló anyagok: paclitaxel docetaxel</p>
		Taxus brevifolia alkaloidok	
		podophyllotoxinok	<p>topoisomerase II. gátlók: etoposid teniposid</p> <p>topoisomerase I. gátlók: camptothecin topotecan</p>
Sejtciklus független szerek		Camptotheca alkaloidok	

Sejtciklus függő szerek



Sejtciklus független szerek



Camptotheca alkaloidok

topoisomerase I. gátlók:
camptothecin
topotecan



TOPOIZOMERASE inhibitors

Camptotecine analogs

mechanism: TOPOIZOMERASE I inhibition



Camptotheca acuminata

cell cycle independent

clinical use:

topotecan

ovarium cc, lung cc

irinotecan

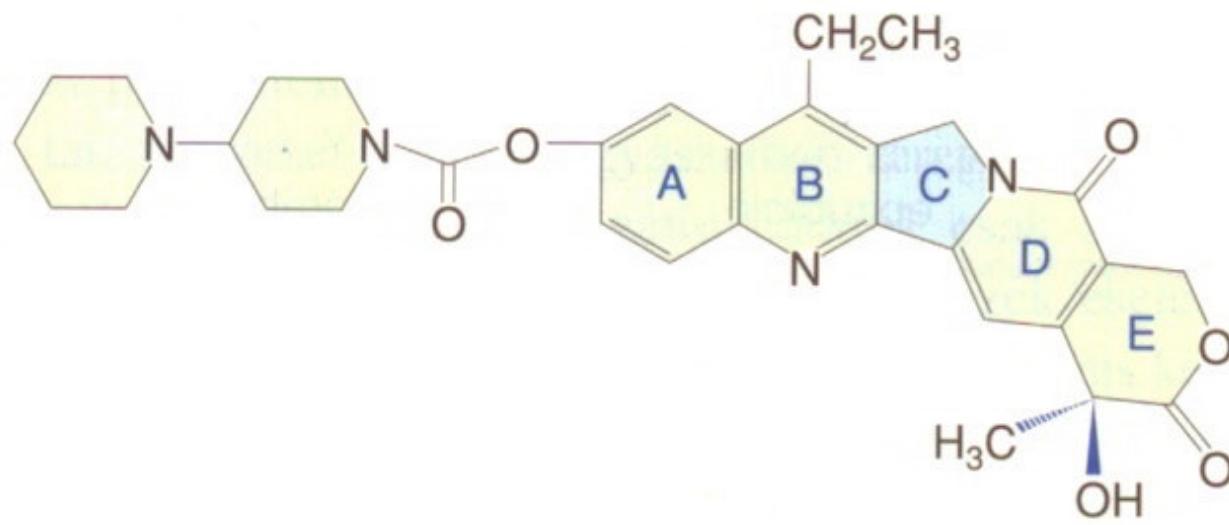
colon cc

Side effects:

serious GI toxicity, maybe even choleriform diarrhoea
serious neutropenia 20% of the patients !!

TOPOIZOMERASE I. INHIBITORS

Camptothecine derivatives



irinotecan

topotecan



Antimitotic drugs

mechanism:

tubulin synthesis

→ mitotic spindle →



Taxus brevifolia

break

Vinca alkaloids

often in combination with alkylating drugs

Vincristine, vinblastine



Vinca rosea

taxanes

paclitaxel, docetaxel

pharmacokinetics: in high doses
zero-ordered
CYP3A4, CYP2C8

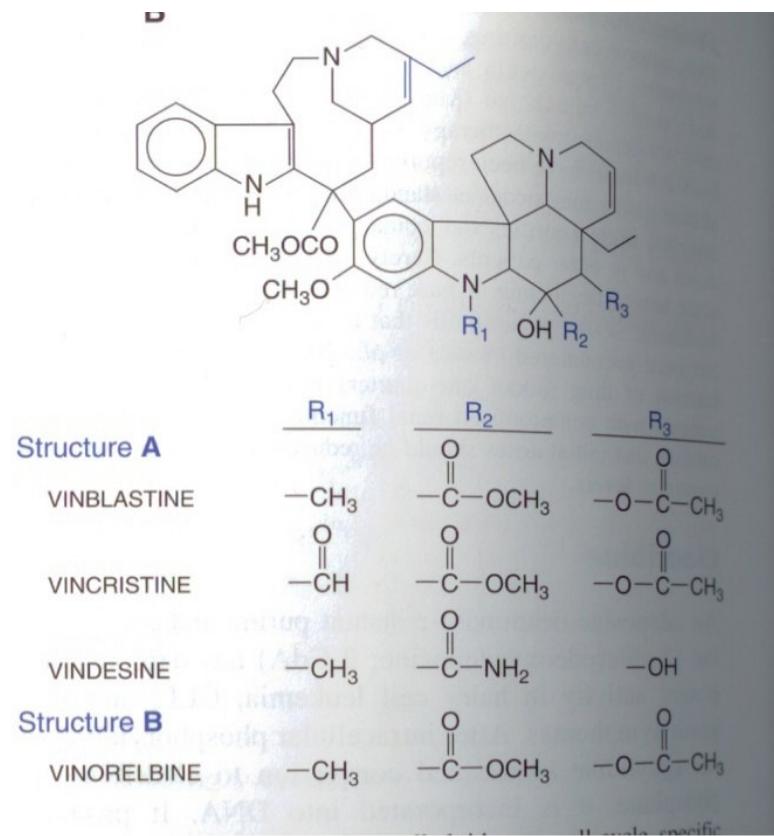
spektrum: leukemias
 Wilms tu, testis, vesicle tu

brest, ovary, lung, GI,
head-neck tu

Toxicity: neurotoxicity,
 paclitaxel hypersensitive reactions

Vinca alkaloids

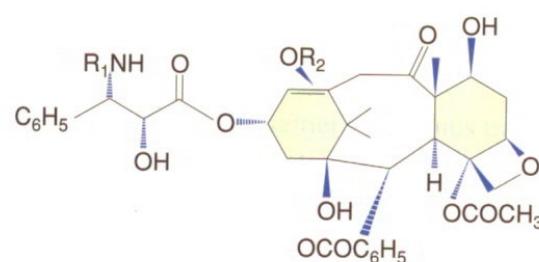
Characteristic side effects: neurotoxicity



Vincristin spectrum:

leukemias
lymphomas, Hodgkin and non-Hodgkin
sarcomas
head-neck tu

TAXANs



taxotere: $R_1 = -COOC(CH_3)_3$; $R_2 = H$

taxol: $R_1 = -COOC_6H_5$; $R_2 = COOCH_3$

Paclitaxel: pharmacokinetics non-linear/zero-ordered

Docetaxel Clearance constant lower toxicity

Side effect: besides the common:
neurotoxicity

hyperallergy bronchus contraction
bradycardia

docetaxel water retention - ascites, pleural fluid !

Epipodophyllotoxines



American indians used as anthelmintics
very toxic, today only for anticancer th
as semisynthetic compounds.

etiposide, teniposide
pass through blood-brain barrier 1-10 %

Podophyllum peltatum

mechanism: topoisomerase II inhibition
binds to mitotic spindle, but in therapeutic doses
there is no inhibitory effect

Cell cycle specific in S phase

Clinical use:

testis tu , lung cc Hodgkin,non-Hodgkin lymphoma

Toxicity: the common+ hepatotoxicity

Thyrosine kinase inhibitors

Antiproliferative treatment by affecting the signaling pathways of growth factors

Prototype: imatinib (Gleevec)

New members: erlotinib, gefitinib

Side effects are similar to the side effects of the classical antiproliferative drugs

BONE MARROW TOXICITY



Cytotoxic therapy with tyrosine kinase inhibitors

Inhibition of signaling

➤ Non specific: imatinib, erlotinib, dasatinib, nilotinib

First for CML, today for many other tumors .

Side effects: remarkable bone marrow toxicity

➤ Gene therapy with tyrosine kinase inhibitory antisense molecules:
oligonucleotids against mRNA

➤ Serin/threonin kinase inhibitors: flavopiridol

In many vegetables and fruits -flavonoid

influences cyclin dependent kinase, cell cycle and apoptosis.

Moderate effect

flavopiridol synthetic flavonoid – CLL th in human II.phase

mechanism: inhibition of cyclin dependent kinase, apoptosis induction

[Mini Rev Med Chem.](#) 2012 Jun;12(7):632-49.

Antiproliferative therapy with hormones and their receptors

➤ Glucocorticoid therapy if there are receptors on cells of acute lymphoid leukemia

Glucocorticoid sensitivity is good prognostic factor

➤ Breast tumors - decrease estrogenic effects

➤ Antiestrogenes tamoxifene, fitoestrogenes

NOT RECOMMENDED they are partial agonists !

Maybe even proliferation of malignant cells

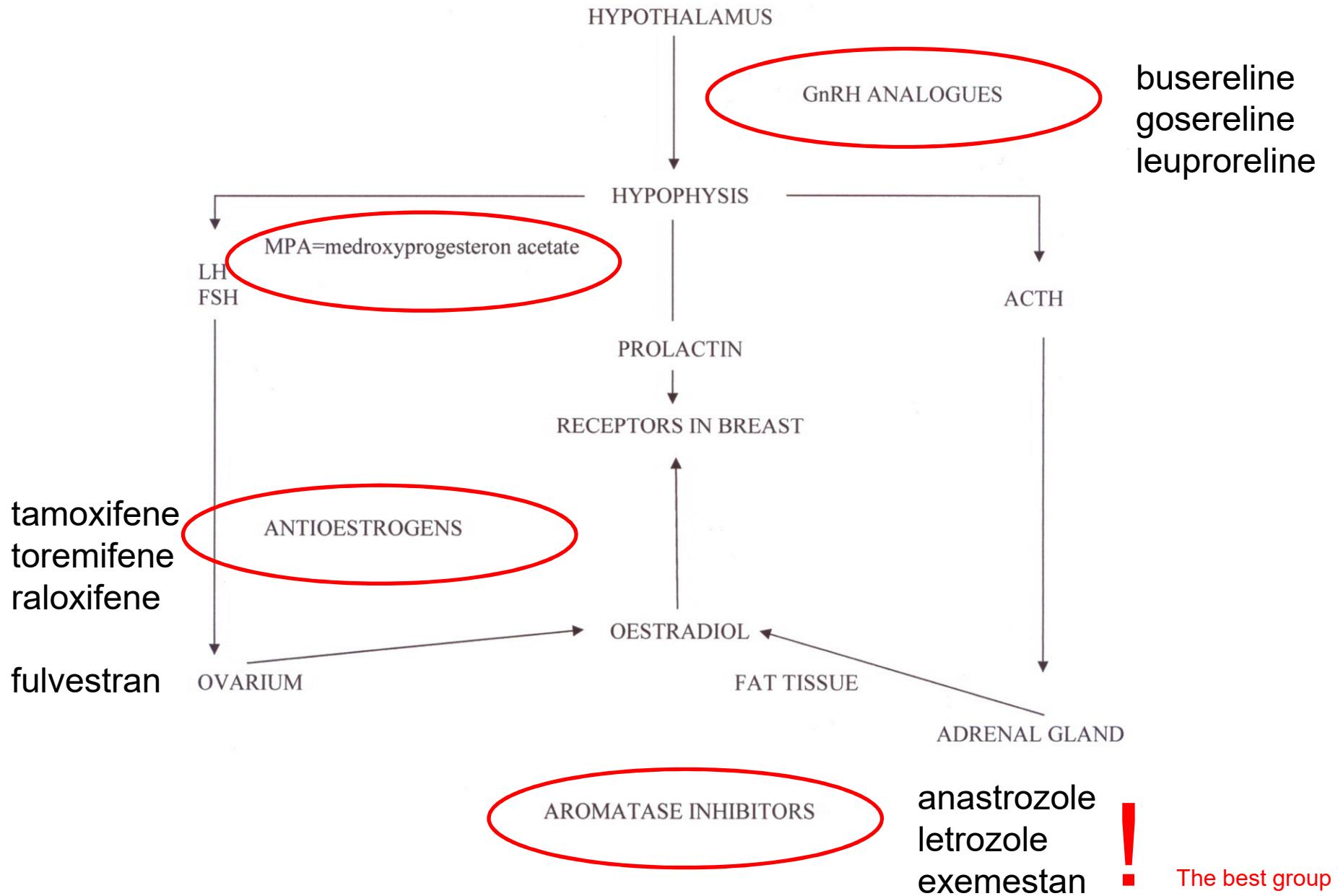
➤ SERM : raloxifen antagonist, in the bone against osteoporosis (inhibits osteoclasts)

➤ Aromatase inhibitors the best tolerable group, e.g. anastrozole, letrozole

➤ Prostate tumors - chemical castration !!

If there are metastases - testosterone receptor antagonists, e.g. flutamide

Hormonal therapy in breast cancer



Selective estrogen receptor modulators (SERMs)

A characteristic that distinguishes these substances from pure receptor agonists and antagonists is that their action is different in various tissues, thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues

Raloxifene:

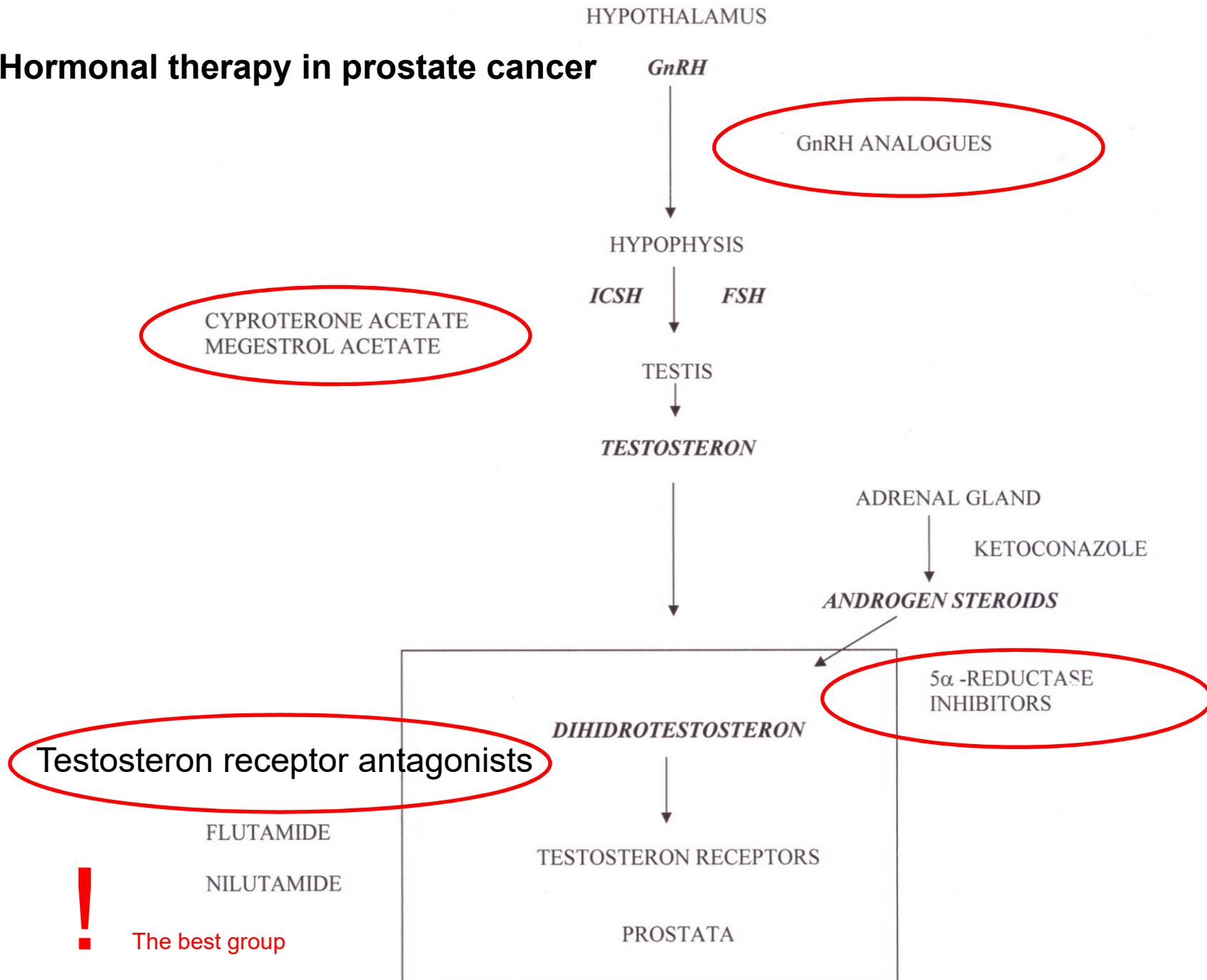
agonist at bone

+

antagonist at breast and uterus

Therapeutic use: breast cc, osteoporosis

Hormonal therapy in prostate cancer





DEBRECENI
EGYETEM

BIOLOGICAL THERAPY in ONCOLOGY

Ilona Benkő M.D., Ph.D.

CANCER CHEMOTHERAPY

Biological therapy

Biological therapy uses living organisms to obtain large molecules which may control cancer cells. Recombinant DNA technology is used often to produce these drugs.

Some types of biological therapy exploit the immune system's natural ability to detect and eliminate of cancer cells, whereas other types target cancer cells directly.

Classification of drugs for anticancer biological therapy:

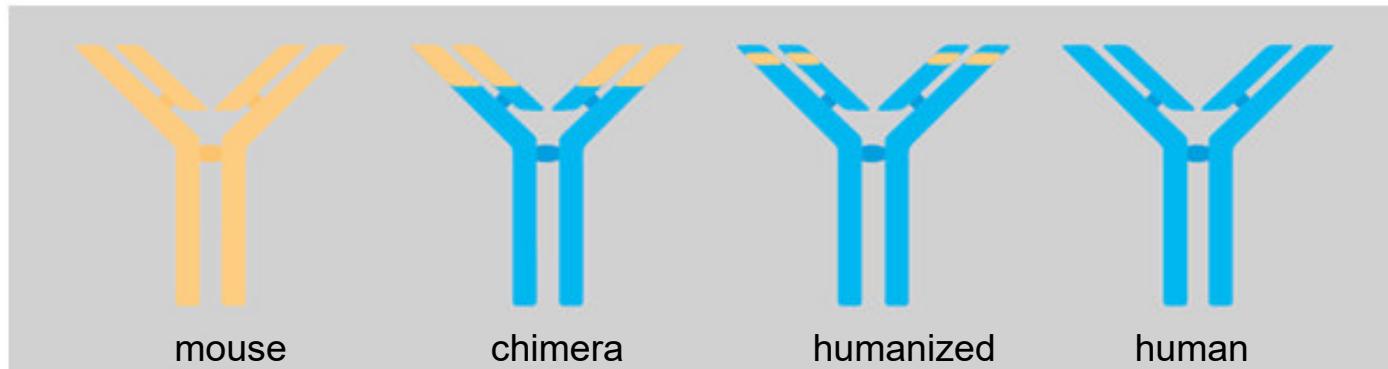
1. Monoclonal antibodies
2. Cytokines
3. Gene therapy
4. Therapeutic vaccines
5. Miscellaneous

Production of monoclonal antibodies

Monoclonal antibodies are produced by mice frequently.

At the beginning mouse antibodies were used. IMMUNE responses were generated !!

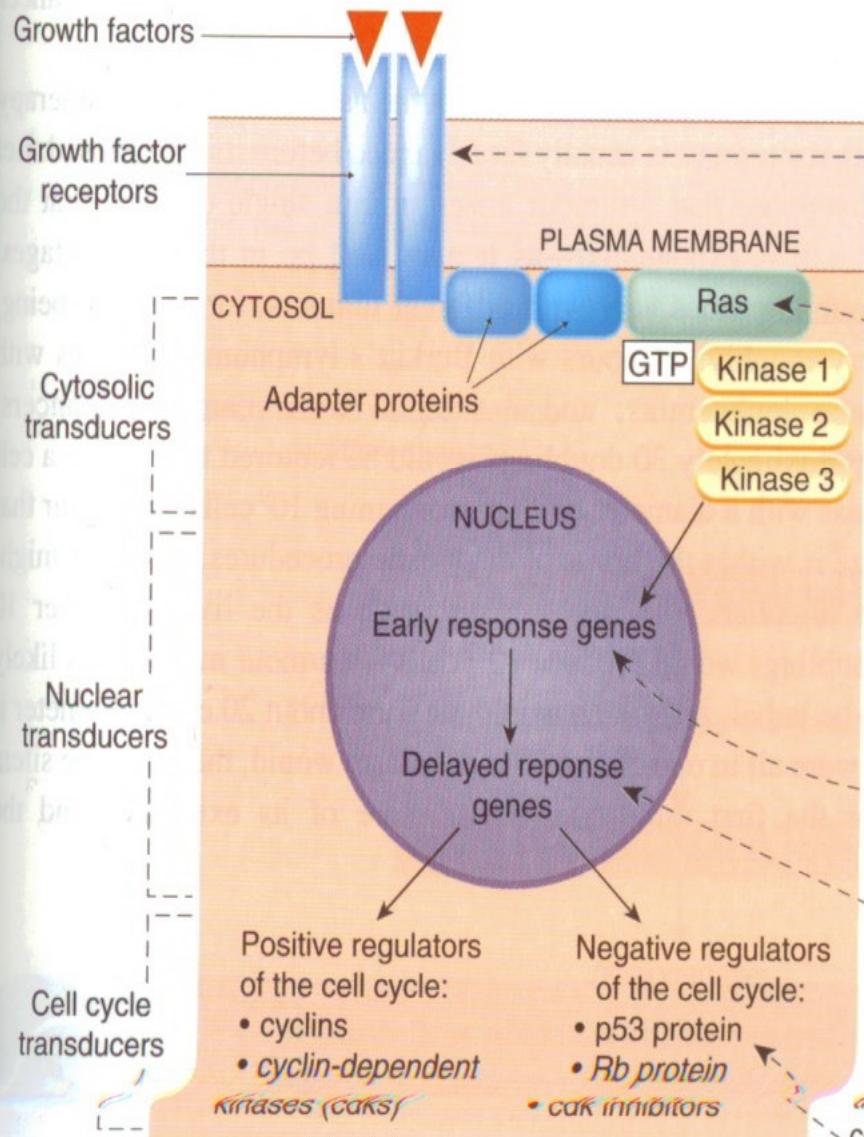
Less antibody formation is seen if monoclonal antibodies bring human parts.



Transgenic mice produce human monoclonal antibodies are obtained.

First Human gene transfer into mice then the cells originated from the mouse spleen are fused with , e.g. myeloma cells in vitro. These cells produce desirable monoclonal antibodies permanently .

Drugs for biological therapy are in the red box



Proto-oncogene	Proto-oncogene products	Cancer	Anticancer drugs
Genes for growth factors e.g. for IGF	Growth factors e.g. IGF	Prostate, breast, colorectal, etc.	Research in progress.
Gene for EGF receptors (e.g. c-erbB)	Her2*, (a receptor tyrosine kinase)	Breast	Inhibited by trastuzumab, cetuximab
Gene for PDGF (c-sis)	PDGF (a receptor tyrosine kinase)	Chronic myeloid leukaemia	Inhibited by imatinib (aka Gleevec)
c-ras	Ras proteins	30% of all tumours	Ras inhibitors in clinical trial
abl	Abl tyrosine kinase (cytoplasmic)	Chronic myeloid leukaemia	Inhibited by imatinib (aka Gleevec)
c-src	Cytoplasmic tyrosine kinase	Breast, pancreas, bone	
Genes for JAK, Lck		Leukemias	Research in progress.
c-jun/c-fos c-myc	Transcription factors (Jun, Fos, Myc)	Colorectal	
	Lung, neural tissue		

Mutation of the delayed response nuclear proto-oncogenes... can alter expression of the regulators of the cell cycle, e.g. more than 50% of *human tumours have mutations of* *the tumour suppressor gene that codes for p53 protein*

Trastuzumab (Herceptin®)

- humanized monoclonal AB
- Pharmacodynamics:
 - inhibitsHER2/neu**
 - prevents activation of receptor kinase
 - blockade of angiogenetic effect, and tumor growth
- Pharmacokinetics:
 - i.v. infusion
 - t_{1/2}: 5.8 days
 - combination with chemotherapeutics (paclitaxel)
- Adverse effects:
 - cardiac failure!, LVF (20% of patients)
 - cardiomyopathy
- Therapeutic application:
 - metastatic breast cancer (overexpressesHER2/neu)

Cetuximab(Erbitux®)

- chimerized monoclonal AB
- Pharmacodynamics:
 - inhibitsEGFR**
 - prevents activation of receptor kinase, dimerization
 - blockade of cell growth
- Pharmacokinetics:
 - i.v. infusion
 - combination with chemotherapeutics(5-FU)
- Adverse effects:
 - hypersensitive reactions
- Therapeutic application:
 - squamous cell carcinoma of head and neck(HNSCC)
 - metastatic colon cancer(EGFR+)

Some FDA-approved monoclonal antibodies in oncology

For solid tumors			targets
trastuzumab	Herceptin	humanised IgG1	HER2
cetuximab	Erbix	murine IgG1	EGFR Erb1
panitumab	Vectibix	human IgG2	EGFR Erb1
bevacizumab	Avastin	„	VEGF
for hematologic malignant diseases			
rituximab	Mabtera	chimera murine /human	CD20
alemtuzumab	Campath	humanised IgG1	CD52
ofatumumab	Arzerra	human IgG1	CD20
Monoclonal antibodies in conjunction with radioisotopes for hematologic malignant diseases			
90Y-ibritumomab	tiuxetan , Zevalin	murine IgG1	CD20
131I-tositumomab	Bexxar	murine IgG2	CD20

bevacizumab(Avastin®)

Humanized IgG1 immunoglobulin

Effect: as anti-VEGF-A inhibits angiogenesis



reduces tu growth + inhibits metastasis formation

Administration: as an infusion

Toxicity:

➤ bleeding in lung life-threatening in 2 % of the patients

Contraindication: bleeding disorders, hemoptysis, brain metastasis

➤ Hypertension endothel NO decreases

➤ Tromboembolic complications in 3-4 % of the patients

Clinical use: Therapy resistant tumors even with metastasis !!

➤ renal tumor

➤ Colon carcinoma breast tu. with metastasis

➤ Lung cc

New monoclonal antibodies under investigation

nivolumab, pembrolizumab

PD-1 checkpoint inhibitors

against programmed cell death receptor

Effects in human phases: lung cc
melanoma
renal cc

Durable beneficial effects in the 25-30 % of patients

Toxicity: autoimmun reactions

onset is very variable, even 6 month after therapy

Serious side effects in the 20% of the patients :
leukopenia, lymphopenia, hepatotoxicity

Adverse effects of monoclonal antibody therapy

- Autoantibody formation
- Cross reactions with own antigens
- Delayed type allergic responses
- Neuritis
- Demyelinization - even leukoencephalitis
- Immunosuppression with infections

BIOLOGICAL THERAPY WITH CYTOKINES

CYTOKINES

glycoproteins

Physiological functions:

cell to cell communications and control

control of cell cycle, proliferation, differentiation and survival

Classification

growth factors

colony stimulating factors

interleukins

interferons

chemokines

Cytokines with antitumor effects

Interferon – alpha

The IFN- α proteins are produced by leukocytes.

They are mainly involved in innate immune response against viral infection.

At least 13 subtypes

Complex anticancer effect:

stimulation of host-mediated antitumor mechanisms

antiproliferative effect

Clinical use:

hairy cell leukemia, melanoma, follicular non-Hodgkin's lymphoma

IL-2

Frequent serious side effects !!

Common side effects in cytokine therapies

Acute :

flu-like syndrome

capillary leak syndrome with generalized edema – pulmonary edema

Sweet's syndrome due to immuncomplex formation

Delayed type serious allergic reactions

**Stevens Johnson sy
exfoliative dermatitis**

GENE THERAPY

1. Antisense therapy against the mutated oncogenes

Targets: **DNA**
 mRNA

2. Replaced the mutated tumor suppressor gene that produces a nonfunctional protein with a normal version of the gene. Because tumor suppressor genes (e.g., *P53*) play a role in preventing cancer, restoring the normal function of these genes may inhibit cancer growth or promote cancer regression.

Vaccines against tumors under investigation

rindopepitum (CDX-110)

effectiveness in gliomas in recidiva

Mechanism of action:

rindopepitum is a peptide which consist of 14 amino acids
enhancement of immune reaction against EGFRvIII

EGFRvIII the epidermal growth factor III. mutant variant

glioblastomas are rich in EGFRvIII

In vivo experiments, increase of antibodies against tumor was observed in mice,
rabbits and macaco monkeys