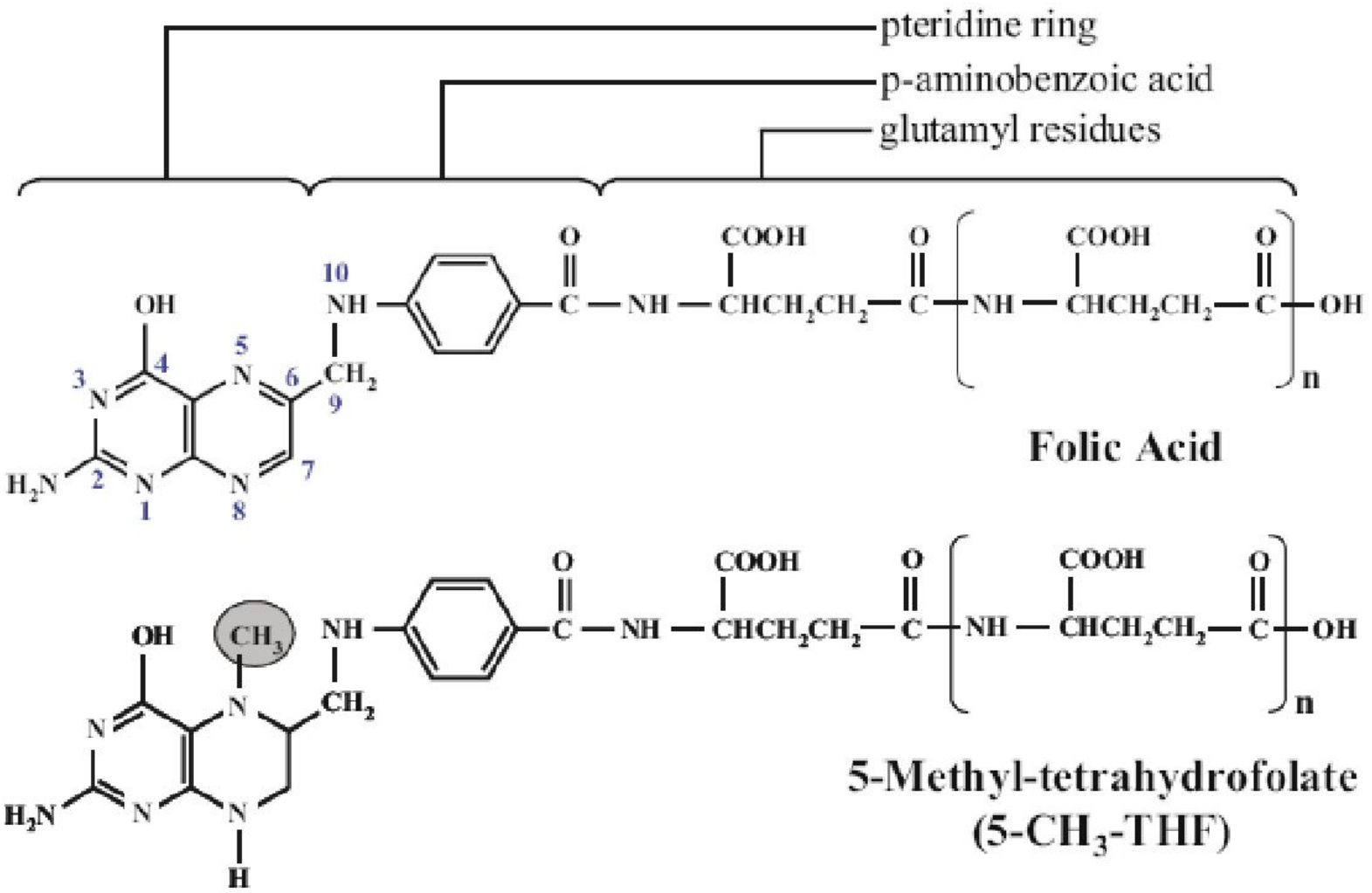
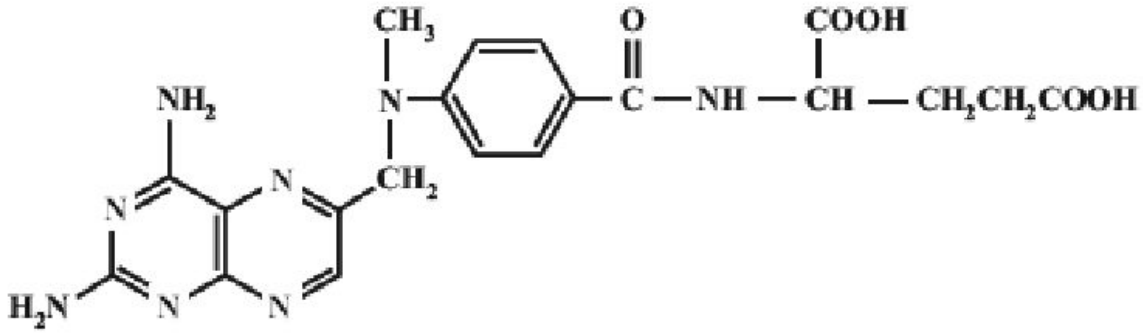
ANTIFOLATI

FOLATES

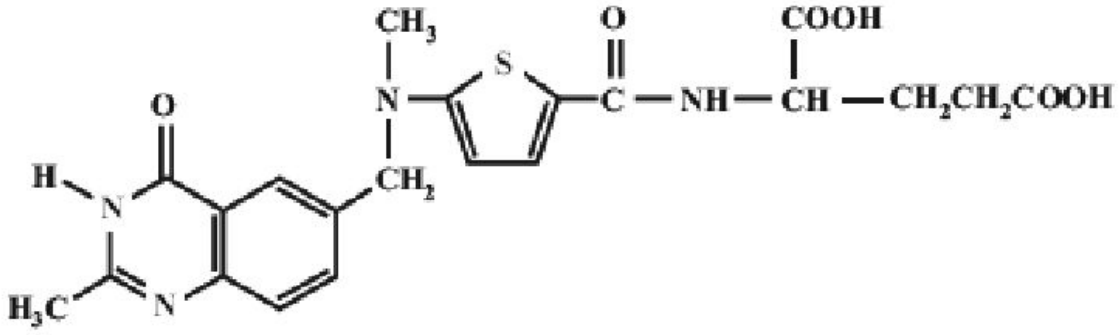

pteridine ring
p-aminobenzoic acid
glutamyl residues
Folic Acid
5-Methyl-tetrahydrofolate
(5-CH3-THF)

ANTIFOLATI

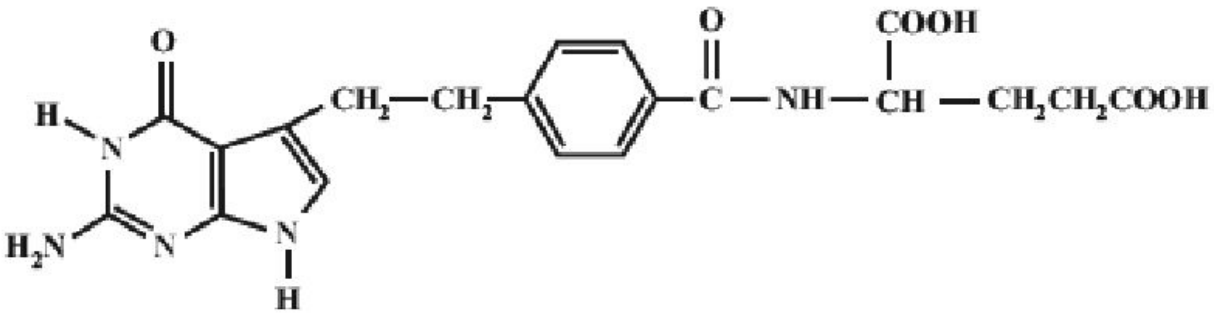
ANTIFOLATES



Methotrexate

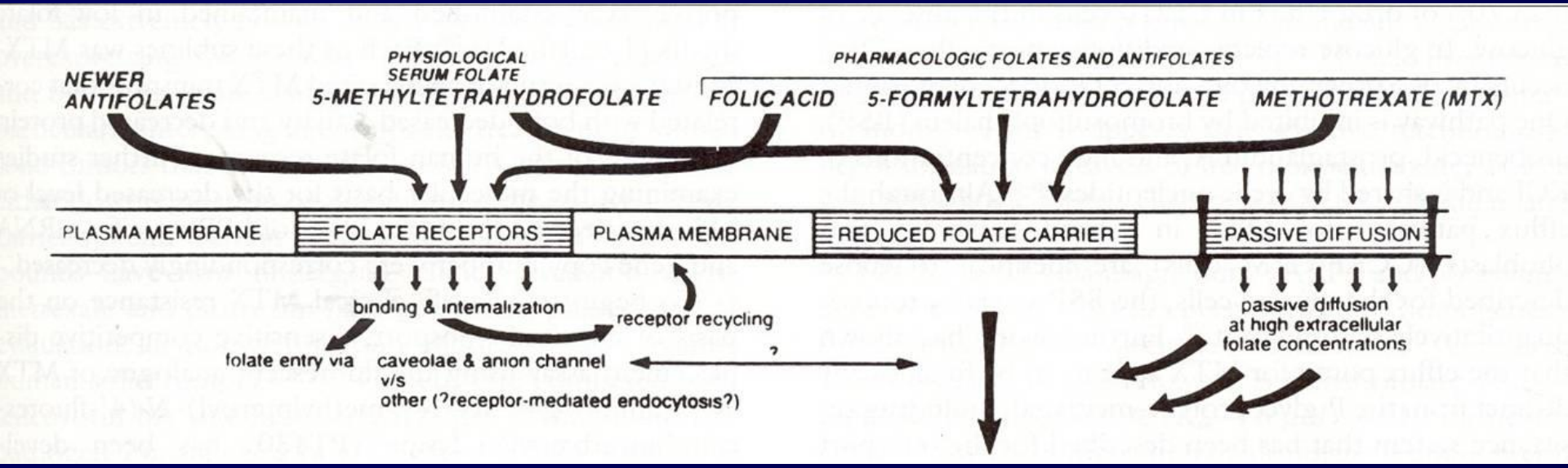


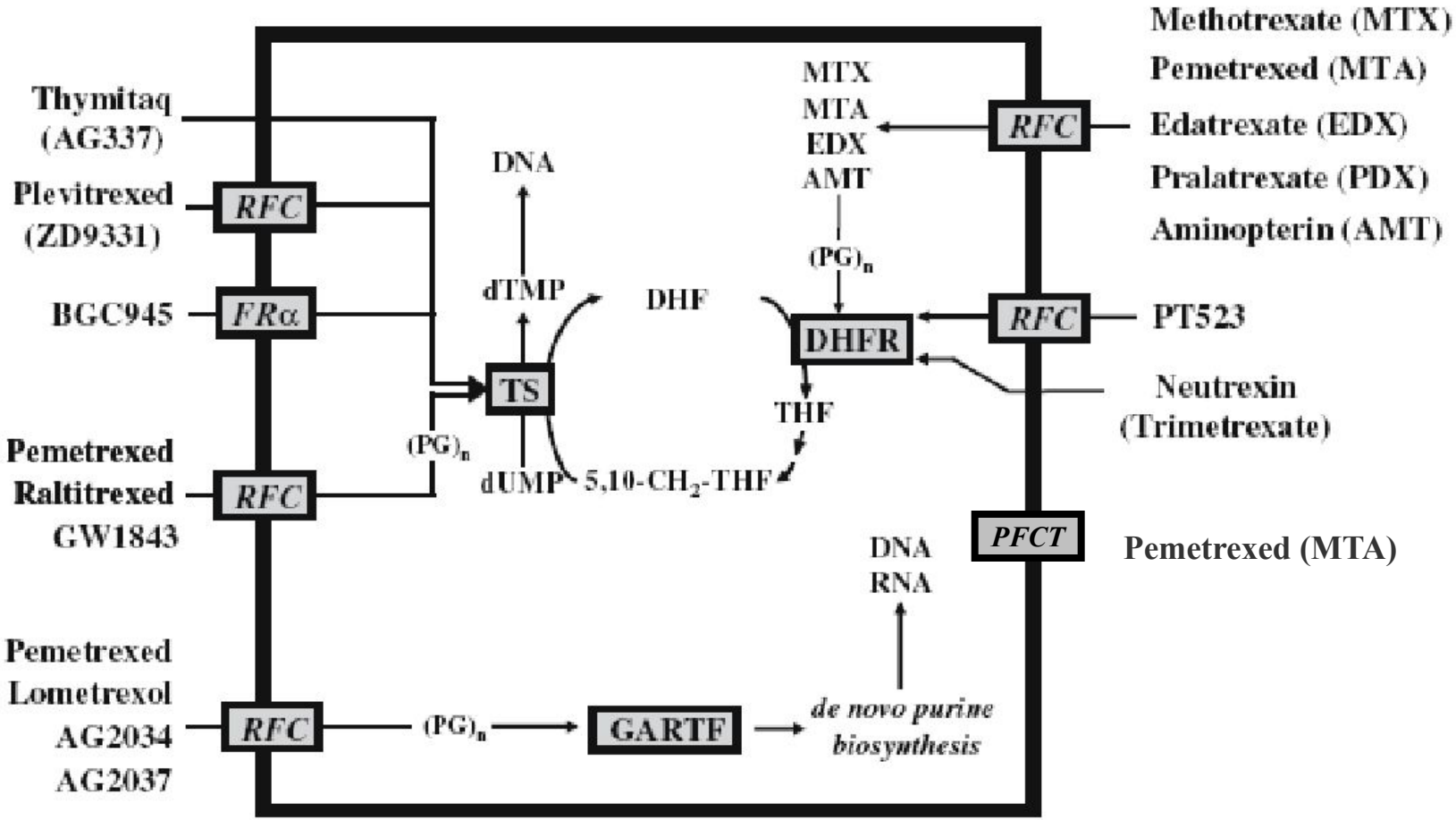
Pemetrexed

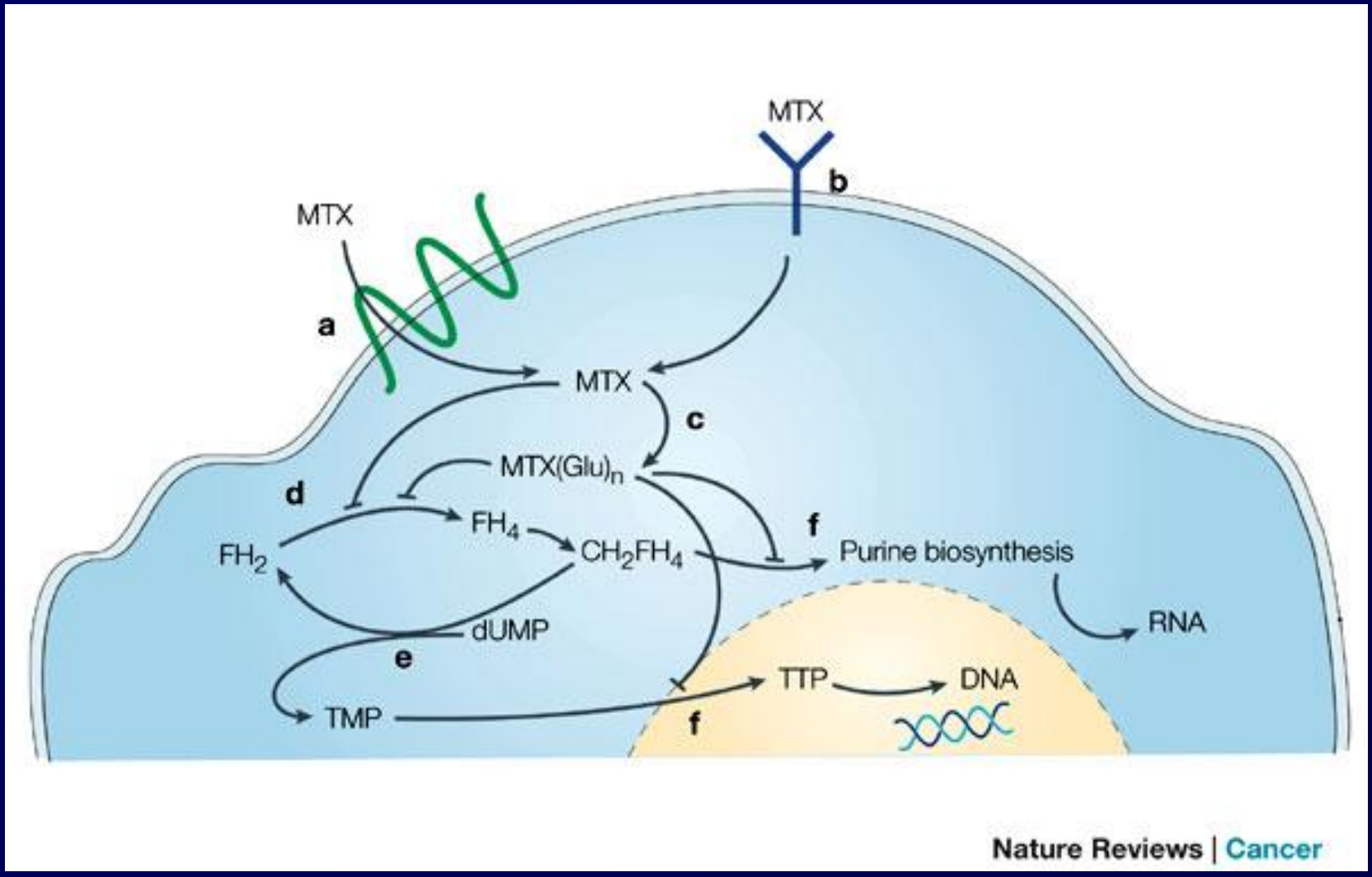


Raltitrexed

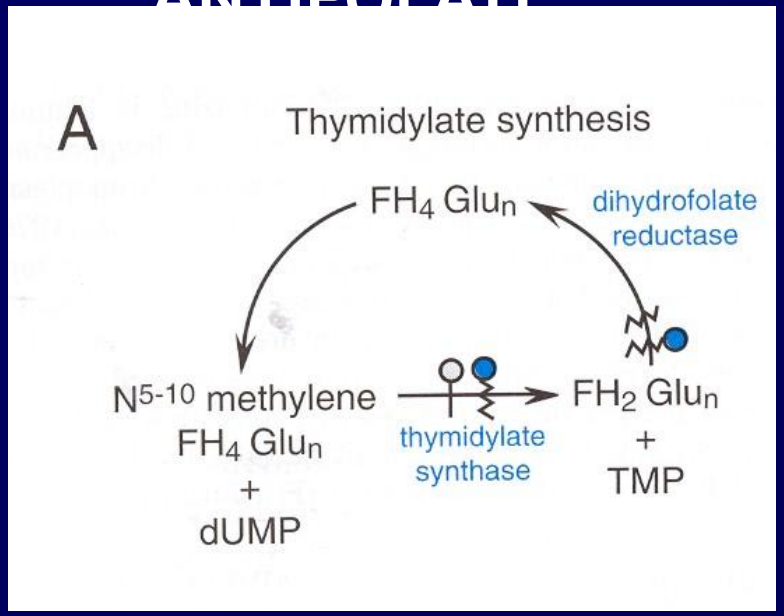
MECCANISMI DI TRASPORTO DEI FOLATI




Methotrexate (MTX)
Pemetrexed (MTA)
Edatrexate (EDX)
Pralatrexate (PDX)
Aminopterin (AMT)
Thymitaq (AG337)
Plevitrexed (ZD9331)
BGC945
Pemetrexed Raltitrexed GW1843
Pemetrexed Lometrexol AG2034 AG2037
RFC
FRα
PFCT
MTX
MTA
EDX
AMT
DNA
dTMP
DHF
TS
DHFR
THF
dUMP
5,10-CH2-THF
(PG)n
PT523
Neutrexin (Trimetrexate)
DNA
RNA
GARTF
de novo purine biosynthesis


MTX
b
MTX
a
MTX
c
MTX(Glu)n
d
FH4
FH2
CH2FH4
f
Purine biosynthesis
RNA
dUMP
e
TTP
DNA
TMP
f
Nature Reviews | Cancer

MECCANISMO D'AZIONE DEGLI ANTIFOLATI



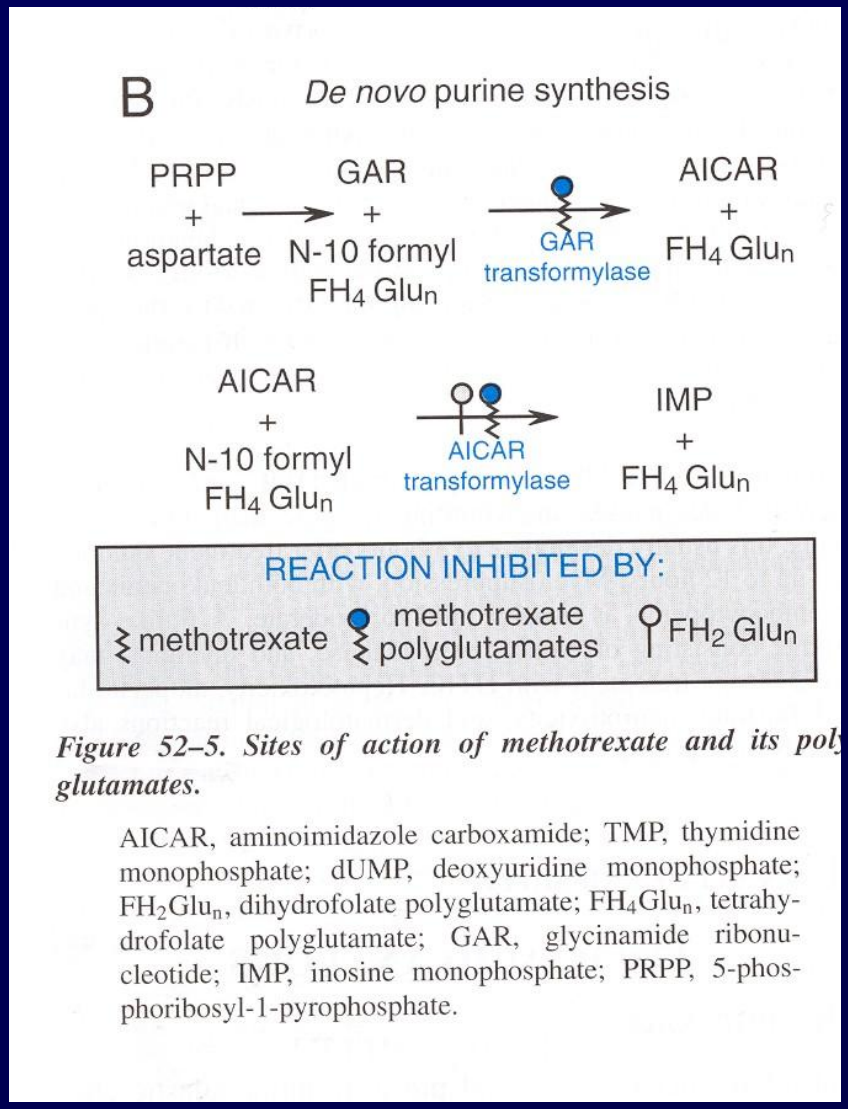
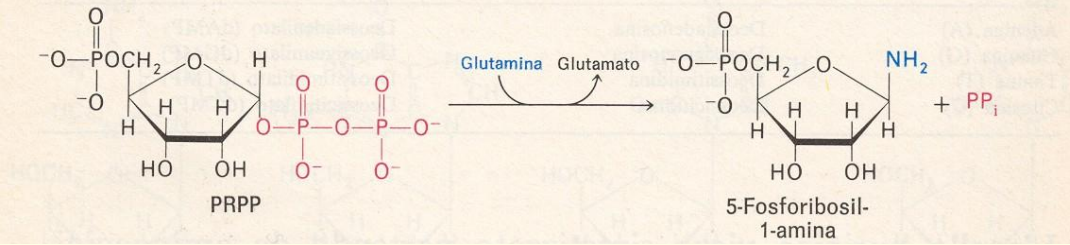


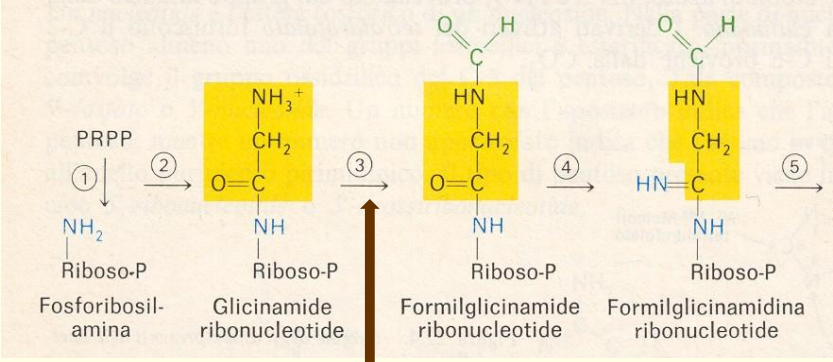
Figure 52–5. Sites of action of methotrexate and its poly glutamates.

AICAR, aminoimidazole carboxamide; TMP, thymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2Glu_n, dihydrofolate polyglutamate; FH_4Glu_n, tetrahydrofolate polyglutamate; GAR, glycinamide ribonucleotide; IMP, inosine monophosphate; PRPP, 5-phosphoribosyl-1-pyrophosphate.

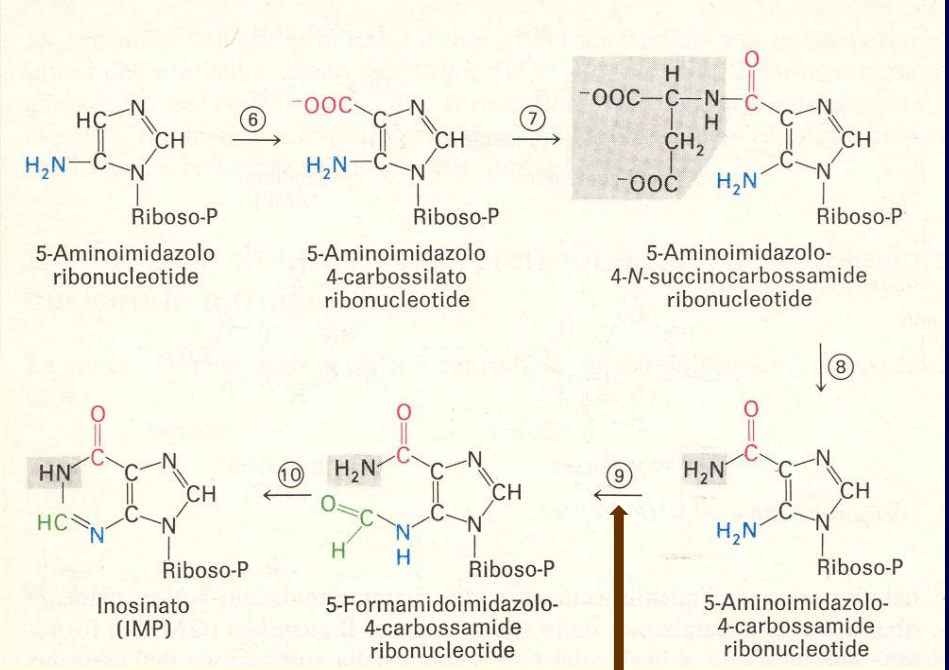
	INIBISCE
MTX	Diidrofolato reduttasi
$MTX(Glu_n)$	Diidrofolato reduttasi Timidilato sintetasi AICAR transformilasi GAR transformilasi
$FH_2(Glu_n)$	Timidilato sintetasi AICAR transformilasi GAR transformilasi

BIOSINTESI DELLE BASI PURINICHE





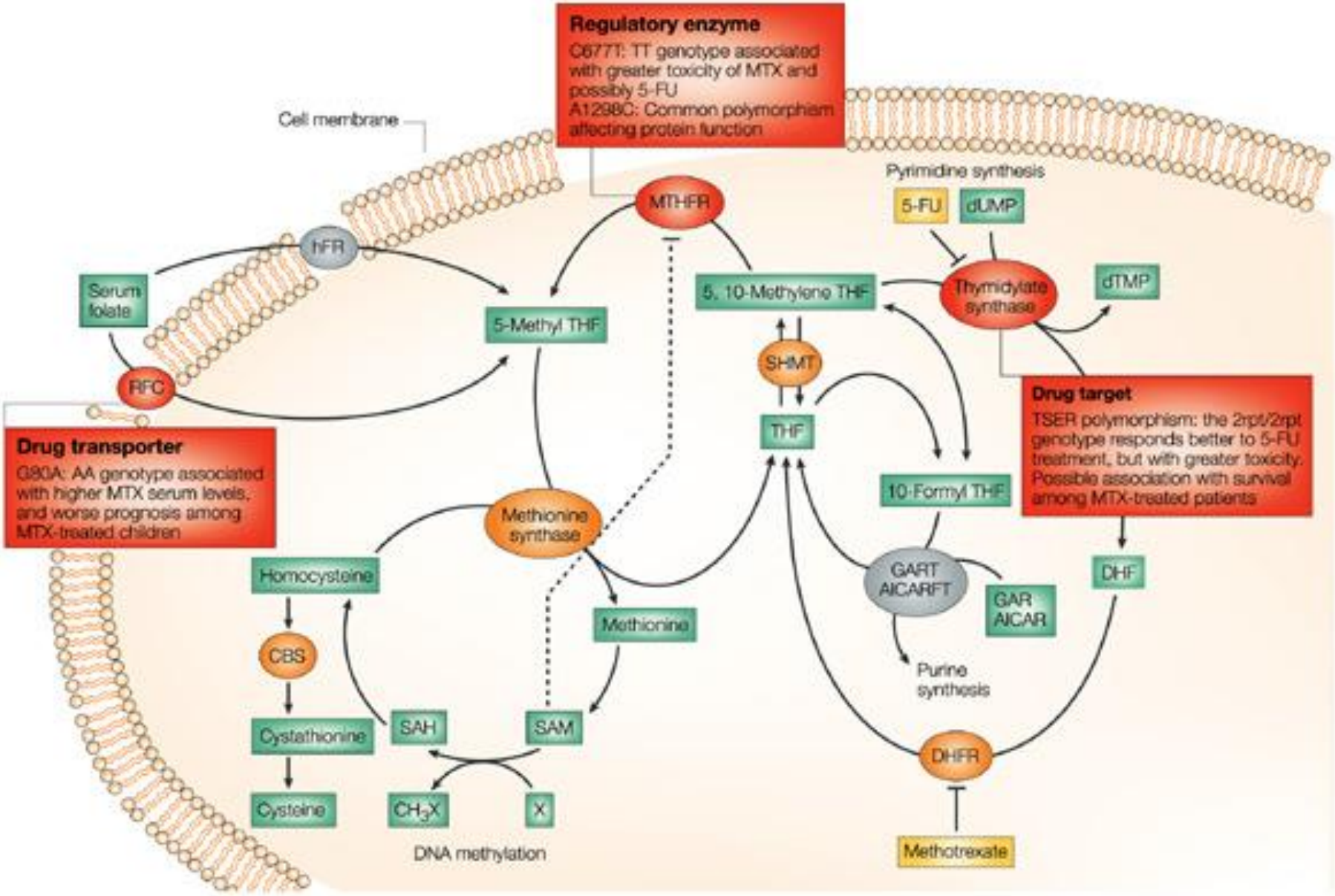
METENILTETRAIDROFOLATO



N^{10}-FORMILTETRAIDROFOLATO

EFFETTI COLLATERALI DEGLI ANTIFOLATI

- mielosoppressione, trombocitopenia
- polmonite
- fibrosi epatica e cirrosi
- embriotossicità


Regulatory enzyme
C677T: TT genotype associated with greater toxicity of MTX and possibly 5-FU
A1298C: Common polymorphism affecting protein function
Cell membrane
MTHFR
Pyrimidine synthesis
5-FU
dUMP
hFR
Serum folate
5-Methyl THF
5, 10-Methylene THF
Thymidylate synthase
dTMP
SHMT
RFC
THF
Drug target
TSER polymorphism: the 2rpt/2rpt genotype responds better to 5-FU treatment, but with greater toxicity. Possible association with survival among MTX-treated patients
Drug transporter
G80A: AA genotype associated with higher MTX serum levels, and worse prognosis among MTX-treated children
10-Formyl THF
Methionine synthase
Homocysteine
GART AICARFT
GAR AICAR
DHF
Methionine
CBS
Purine synthesis
Cystathionine
SAH
SAM
DHFR
Cysteine
CH_3X
X
DNA methylation
Methotrexate

ASPETTI FARMACOGENETICI

SNP a livello del gene che codifica per MTHFR

Diverso numero di sequenze ripetute a livello di TSER

SNP a livello del gene che codifica per RCF

MECCANISMI DI RESISTENZA AGLI ANTIFOLATI

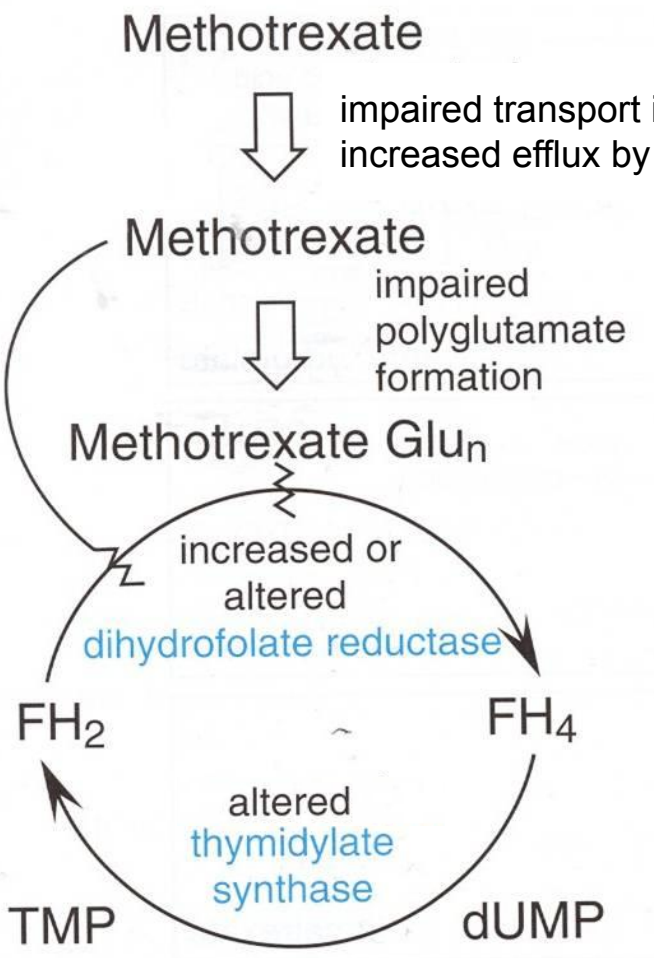
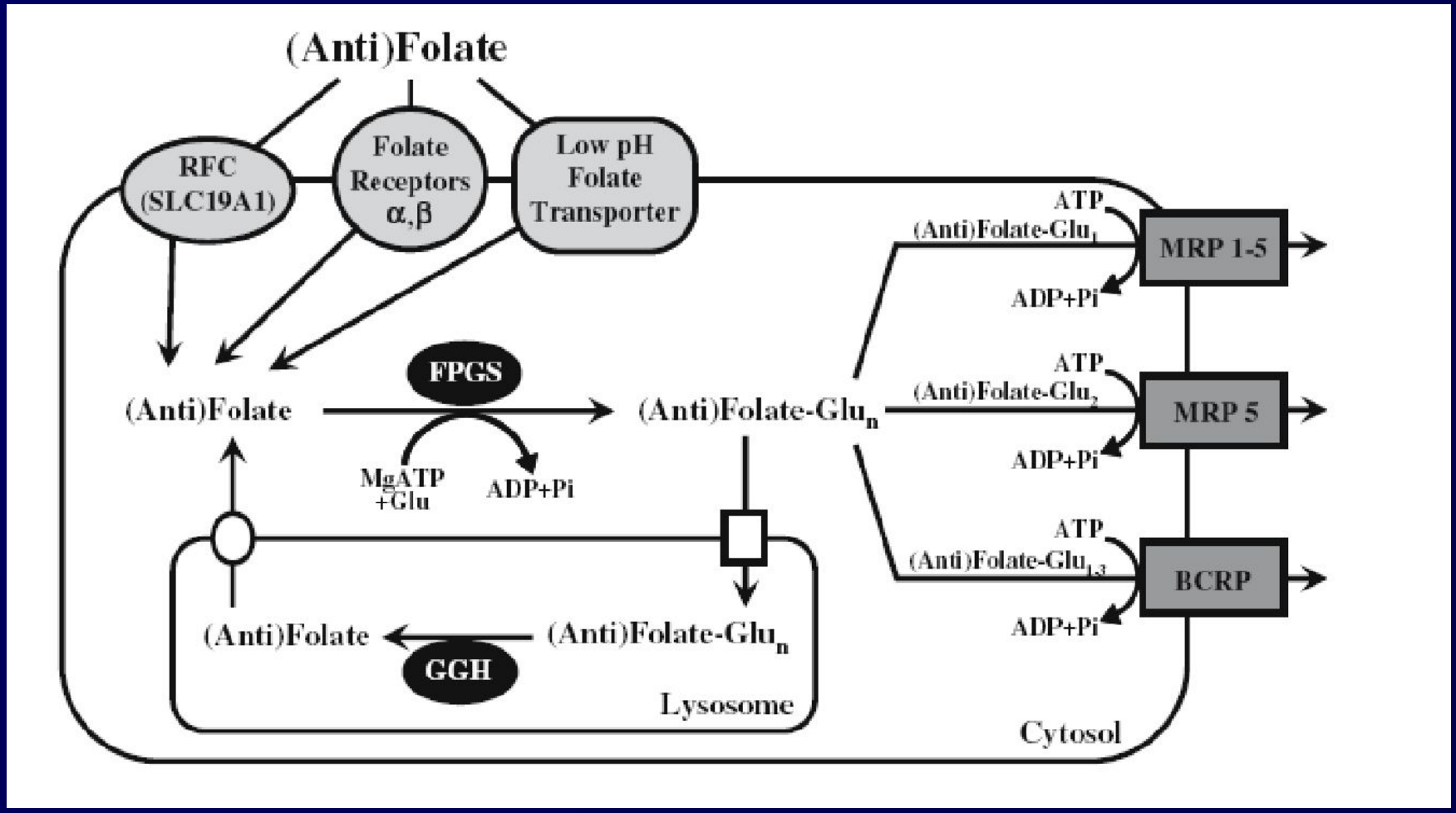


Figure 52–7. Mechanisms of tumor cell resistance to methotrexate.

TMP, thymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2, dihydrofolate; FH_4, tetrahydrofolate; Glu_n, polyglutamate.


(Anti)Folate
RFC
(SLC19A1)
Folate
Receptors
α,β
Low pH
Folate
Transporter
ATP
(Anti)Folate-Glu1
MRP 1-5
ADP+Pi
FPGS
(Anti)Folate
(Anti)Folate-Glun
ATP
(Anti)Folate-Glu2
MRP 5
ADP+Pi
MgATP
+Glu
ADP+Pi
ATP
(Anti)Folate-Glu1-3
BCRP
ADP+Pi
(Anti)Folate
(Anti)Folate-Glun
GGH
Lysosome
Cytosol

MECCANISMI DI RESISTENZA AGLI ANTIFOLATI

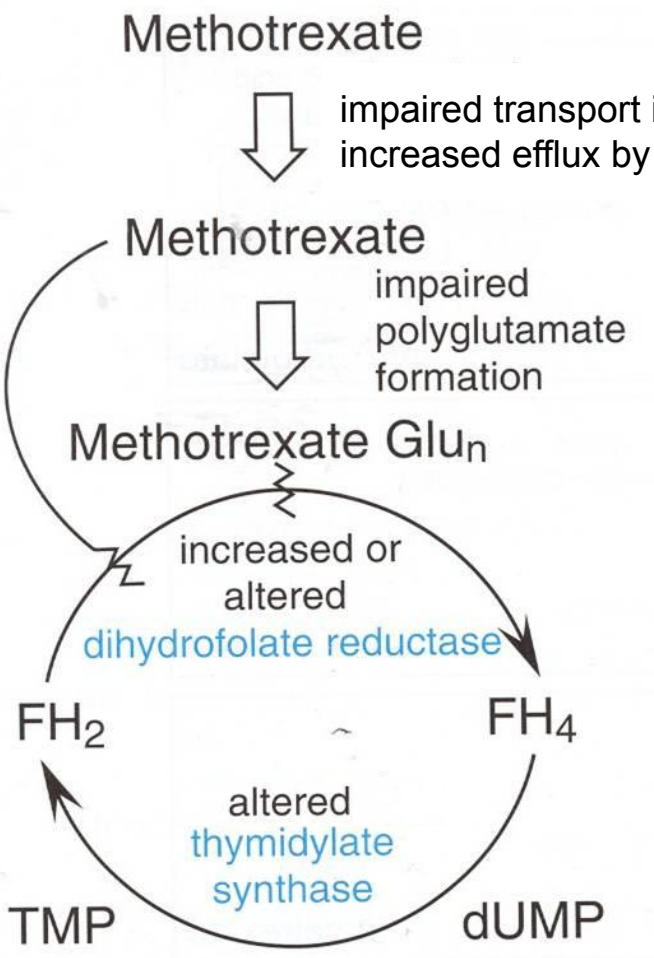
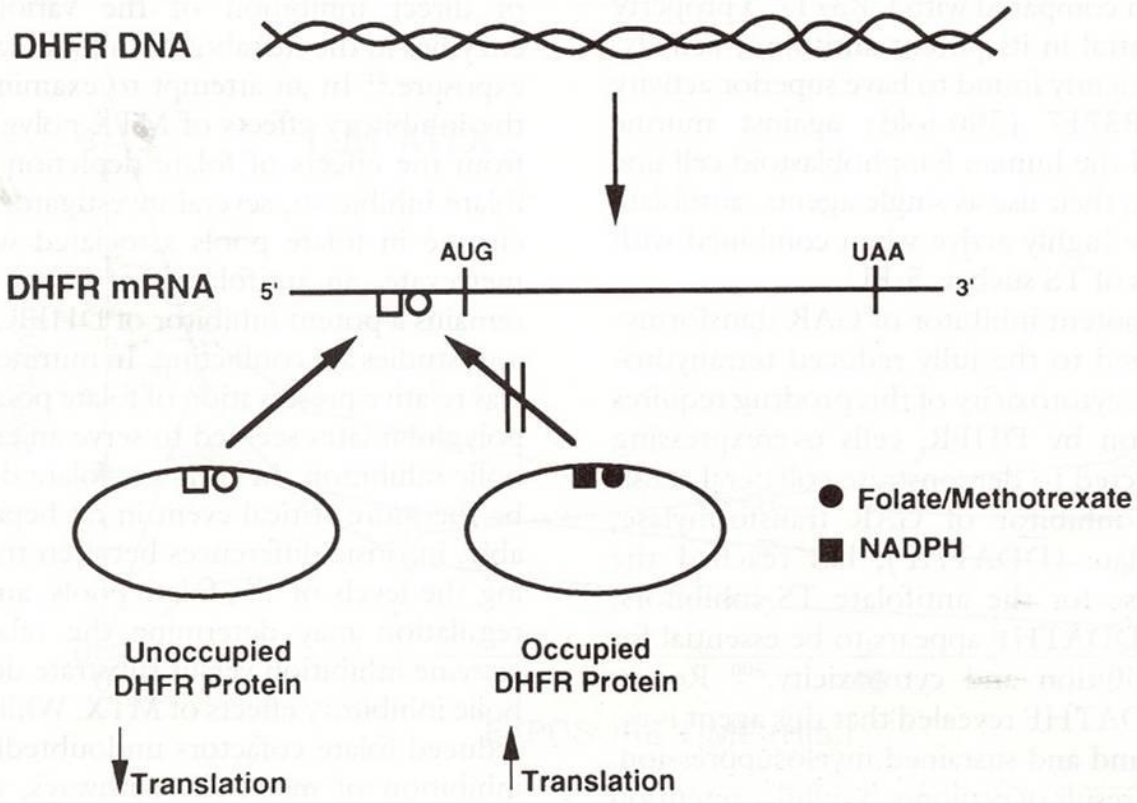


Figure 52–7. Mechanisms of tumor cell resistance to methotrexate.

TMP, thymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2, dihydrofolate; FH_4, tetrahydrofolate; Glu_n, polyglutamate.

Figure 6-6. Proposed model for autoregulatory control of DHFR mRNA translation by DHFR protein.



MECCANISMI DI RESISTENZA AGLI ANTIFOLATI

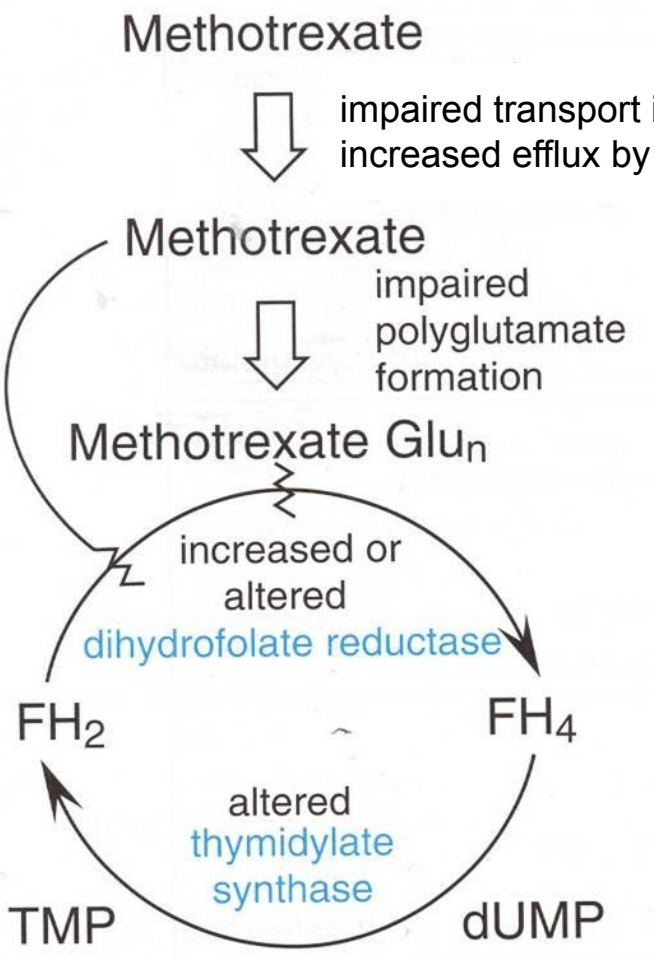
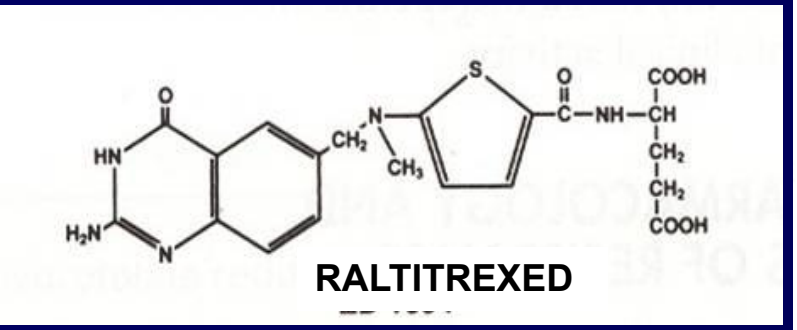


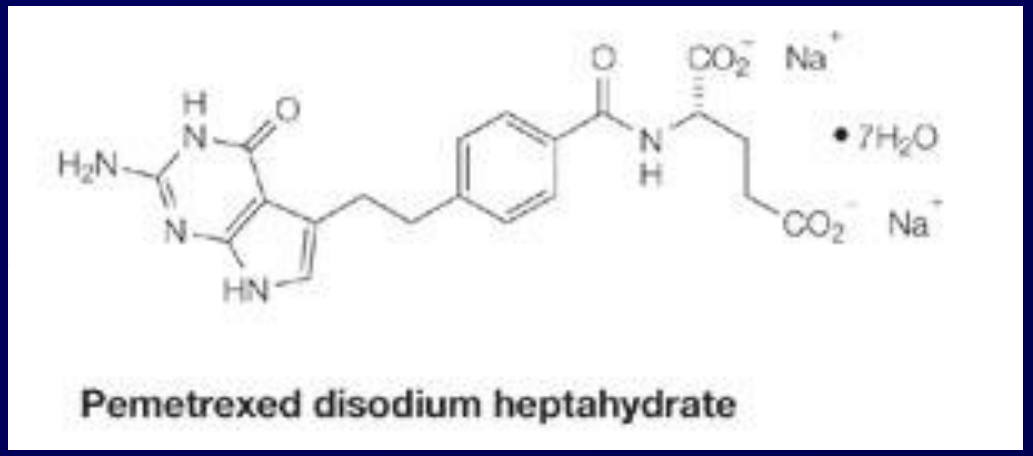
Figure 52–7. Mechanisms of tumor cell resistance to methotrexate.

TMP, thymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2, dihydrofolate; FH_4, tetrahydrofolate; Glu_n, polyglutamate.

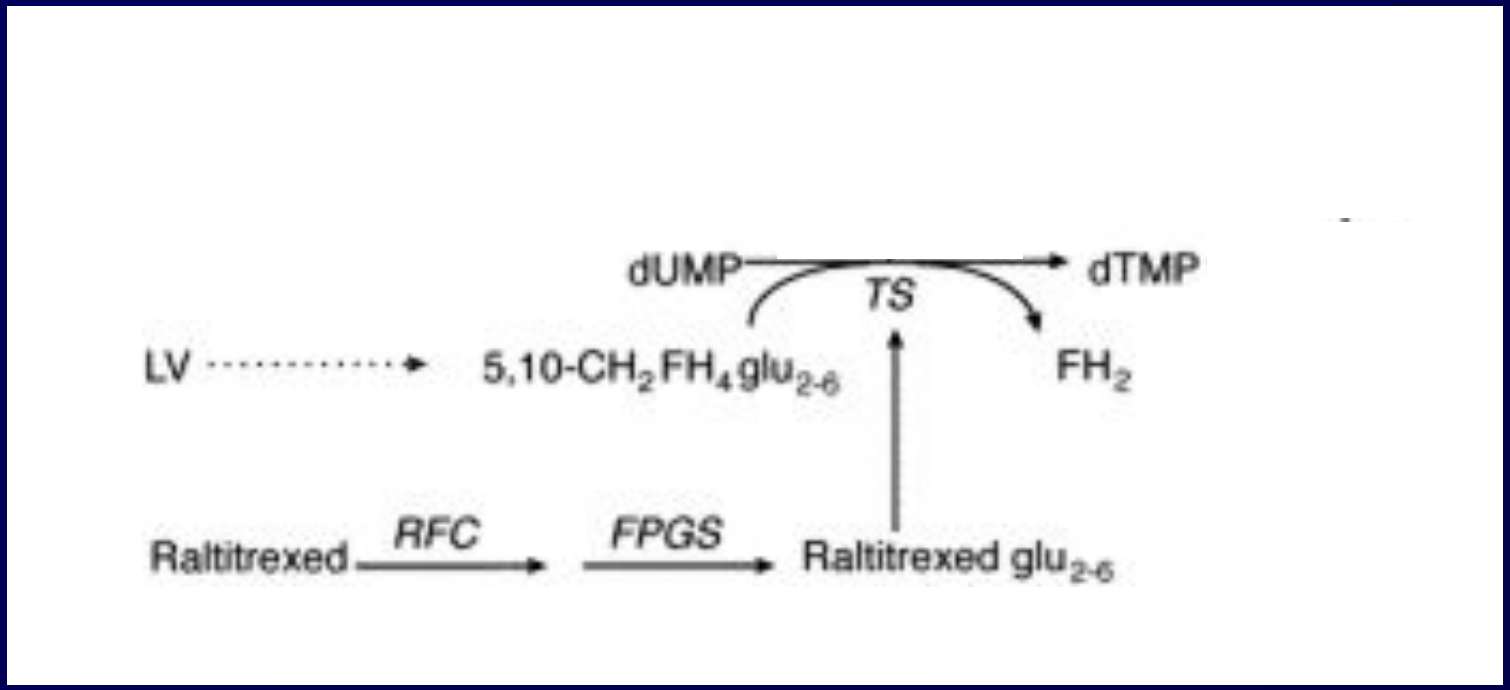
NUOVI ANTIFOLATI



RALTITREXED



Pemetrexed disodium heptahydrate

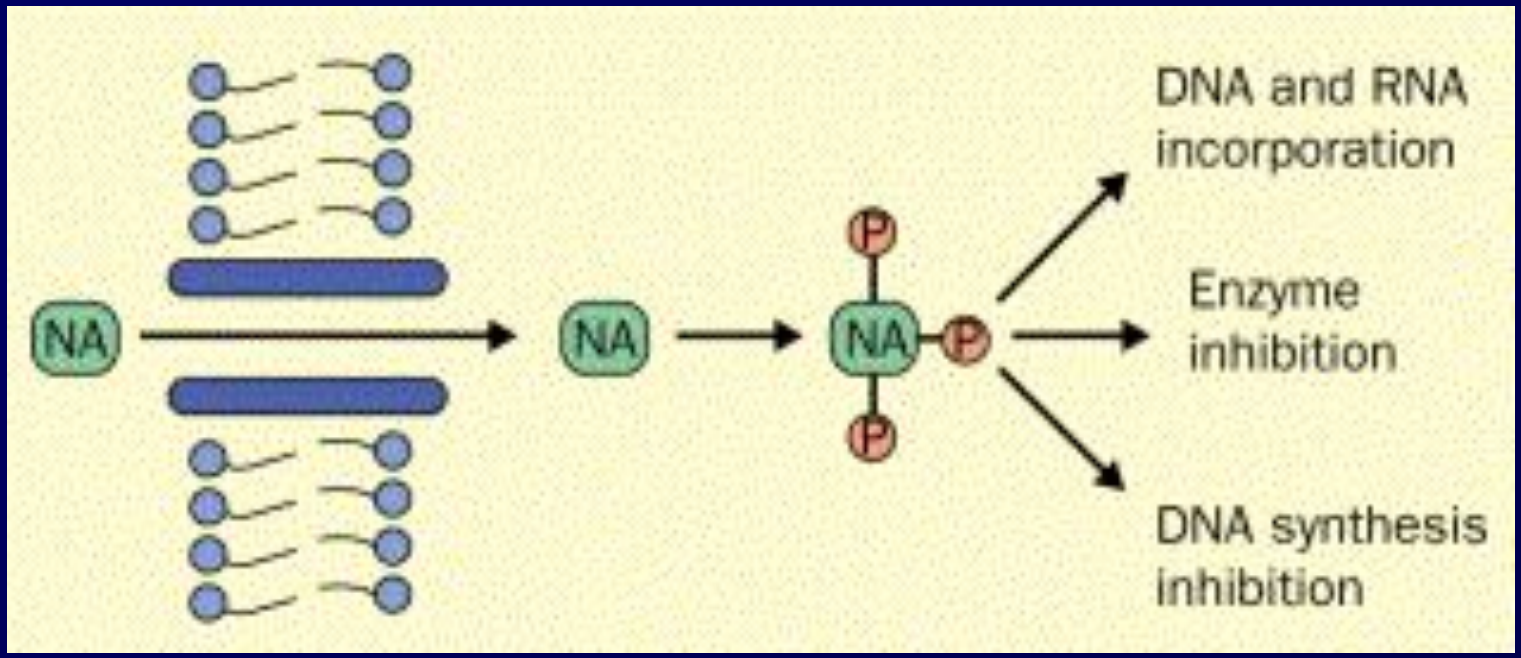


ANALOGHI DELLE NUCLEOBASI

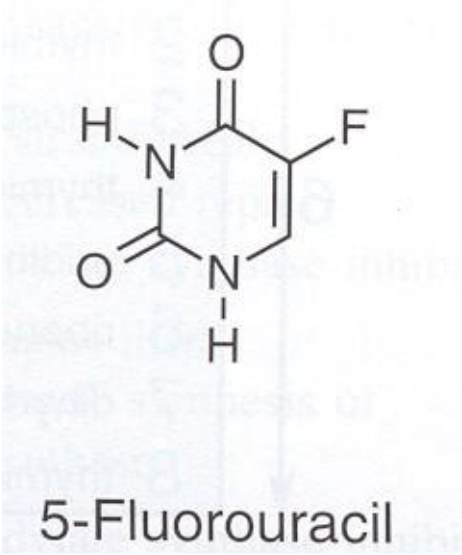
E

DEI NUCLEOSIDI

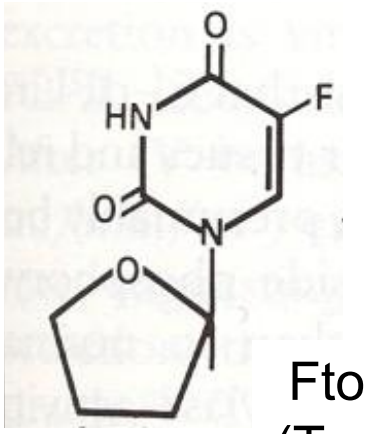
ANALOGHI DELLE NUCLEOBASI E DEI NUCLEOSIDI



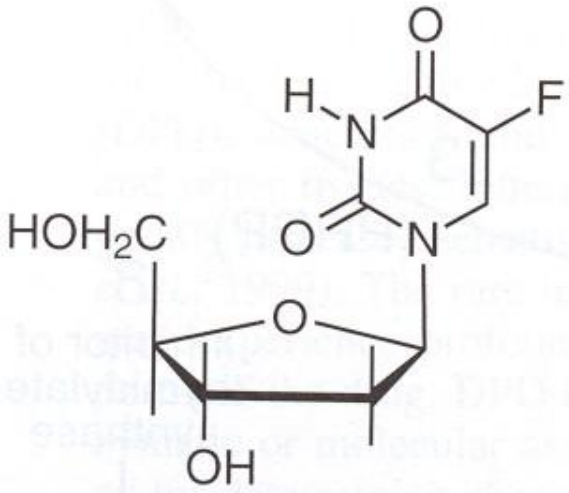
FLUOROPIRIMIDINE



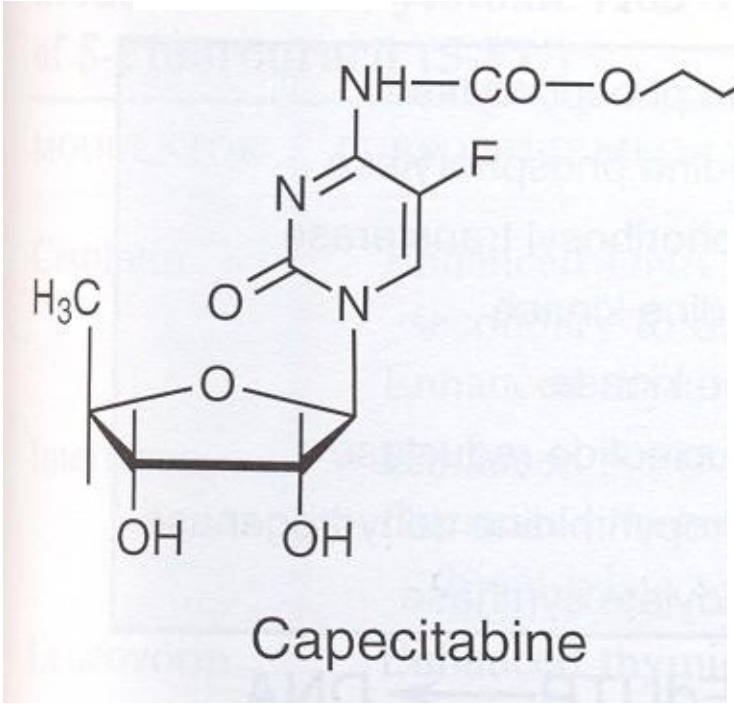
5-Fluorouracil



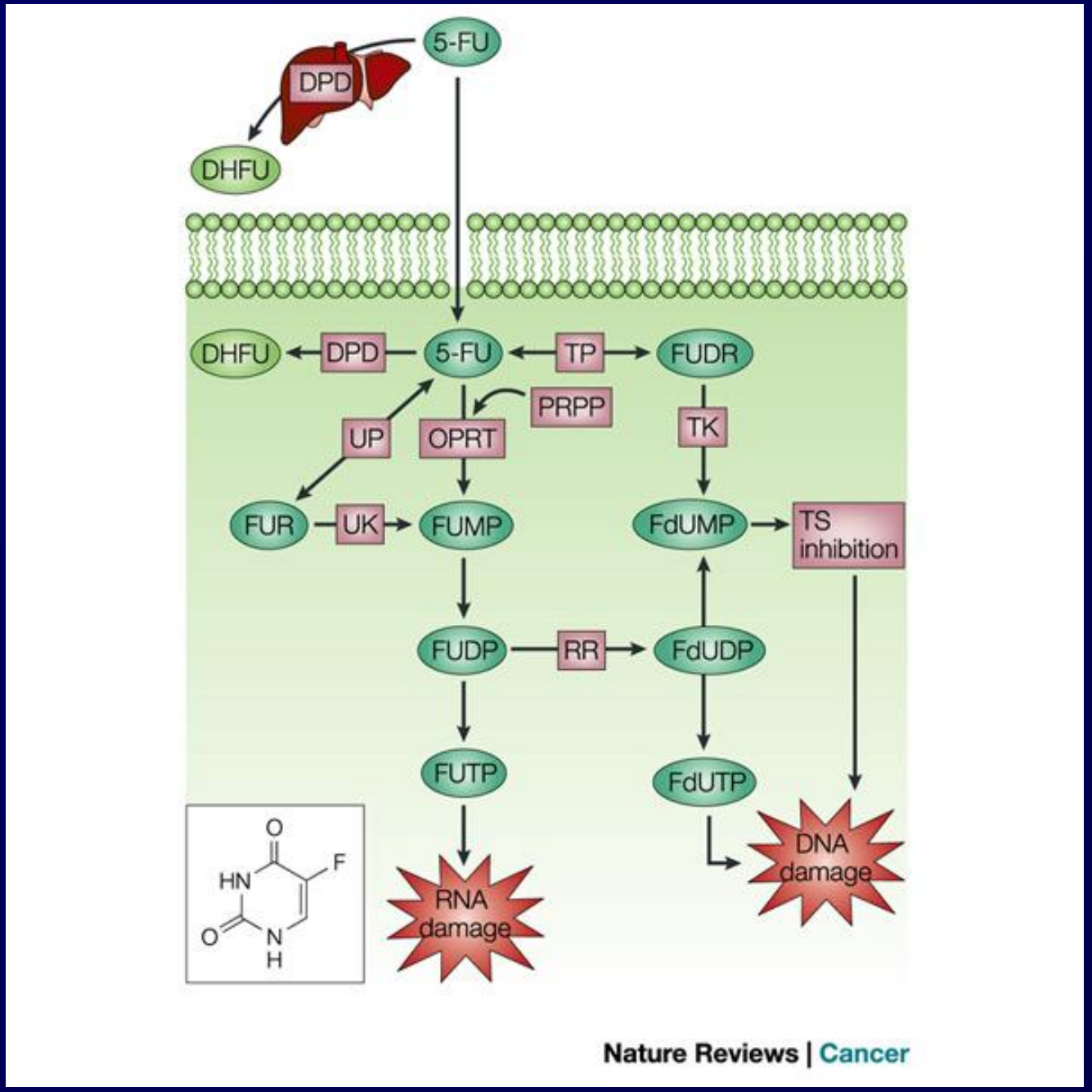
Ftorafur
(Tegafur)



5-Fluorodeoxyuridine
(floxuridine)



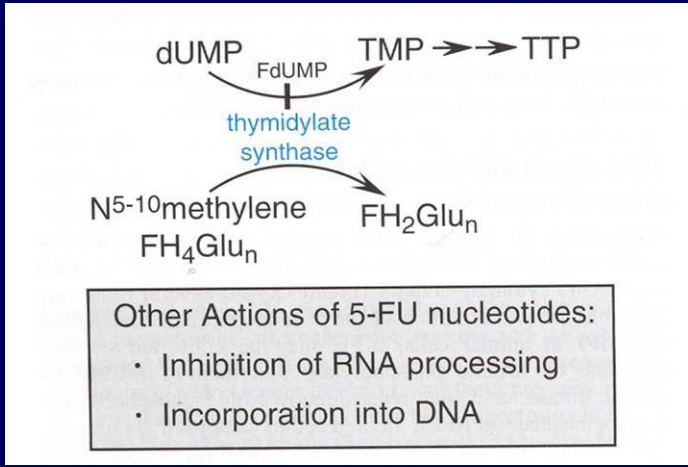
Capecitabine

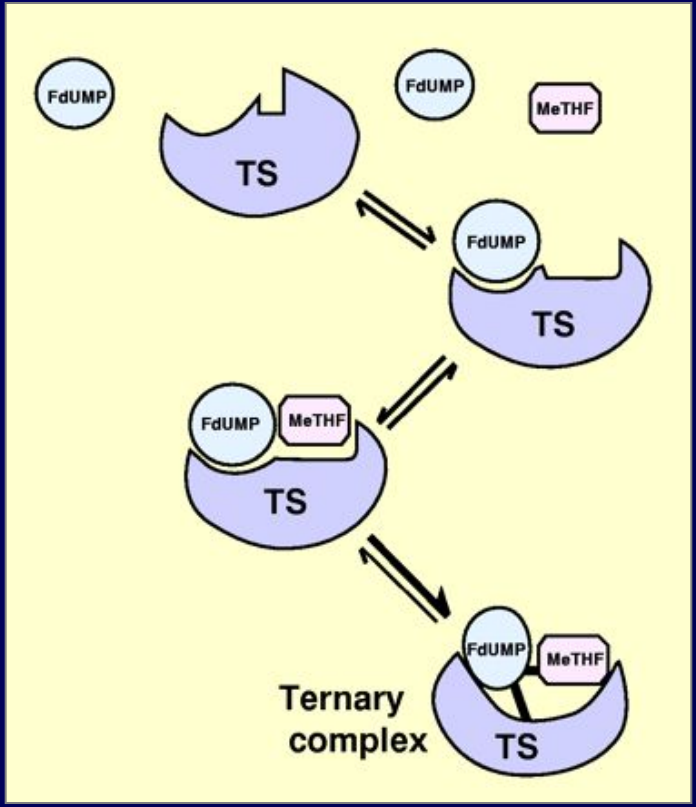

5-FU
DPD
DHFU
DHFU
DPD
5-FU
TP
FUDR
PRPP
UP
OPRT
TK
FUR
UK
FUMP
FdUMP
TS inhibition
FUDP
RR
FdUDP
FUTP
FdUTP
HN
O
F
O
N
H
RNA damage
DNA damage
Nature Reviews | Cancer

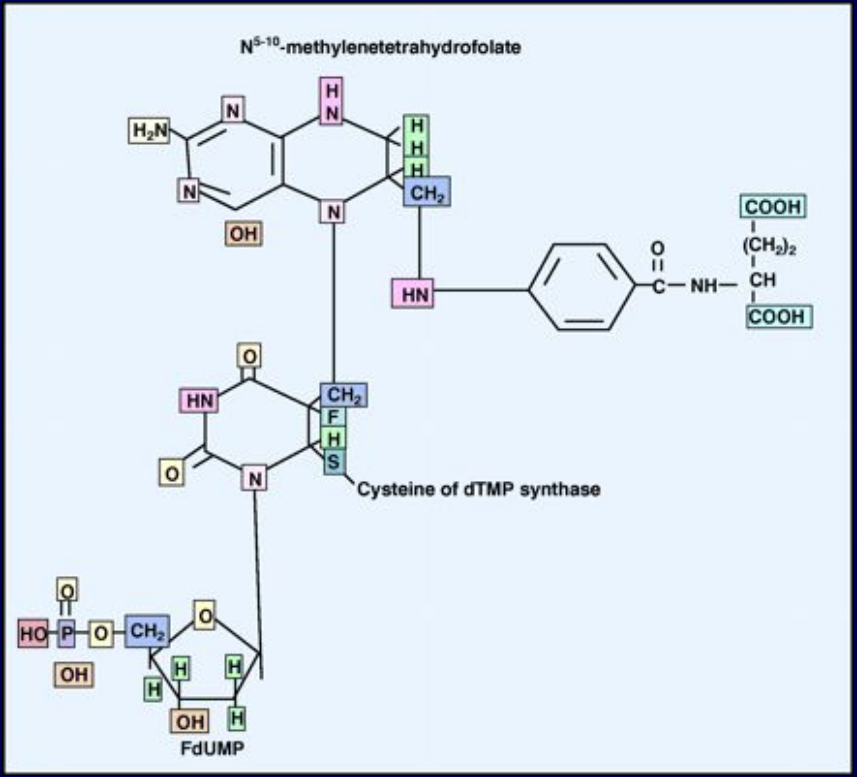
MECCANISMI D'AZIONE DEL 5-FLUOROURACILE

1) Inibizione della timidilato sintasi

MECCANISMI D'AZIONE DEL 5-FLUOROURACILE

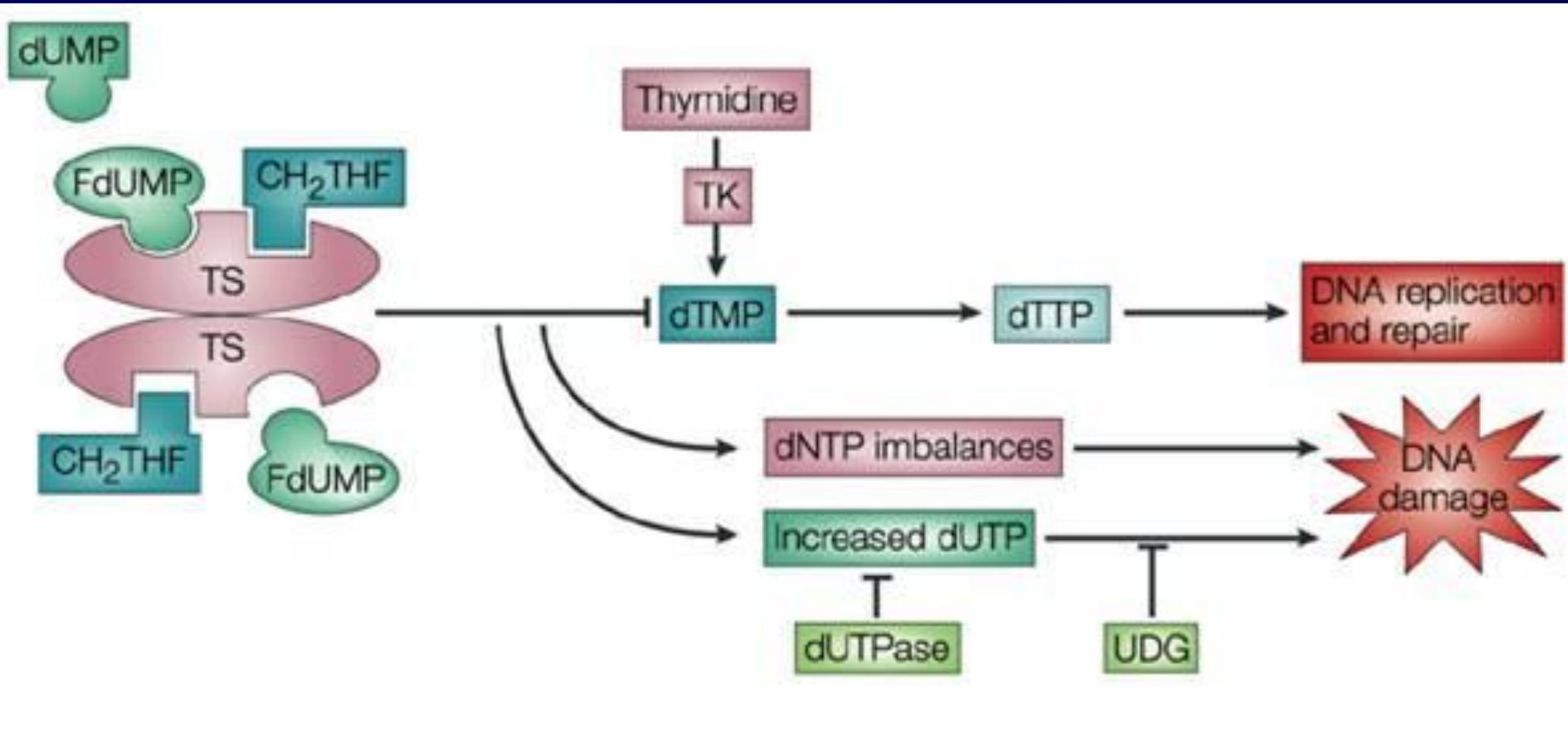






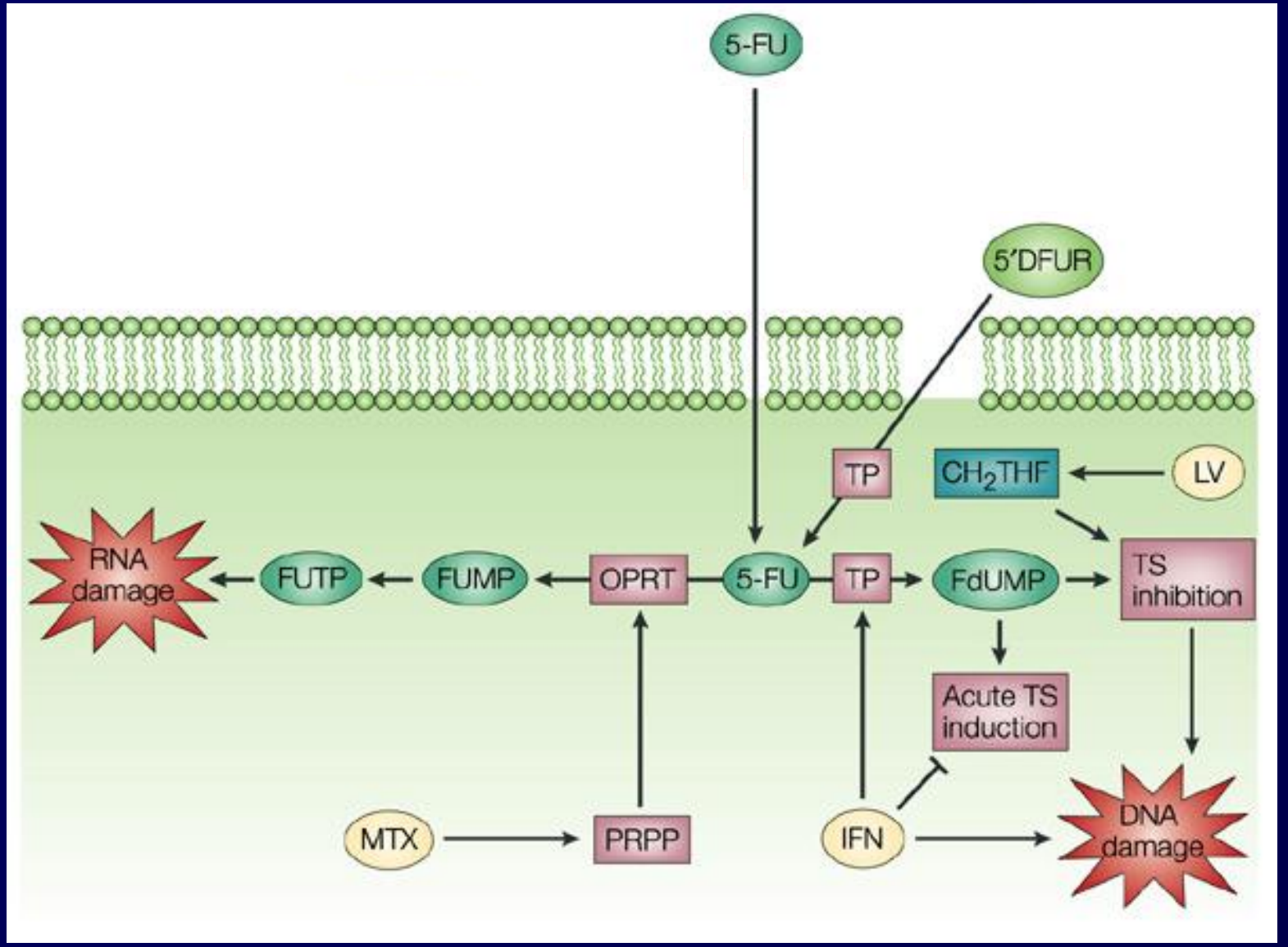
MECCANISMI D'AZIONE DEL 5-FLUOROURACILE

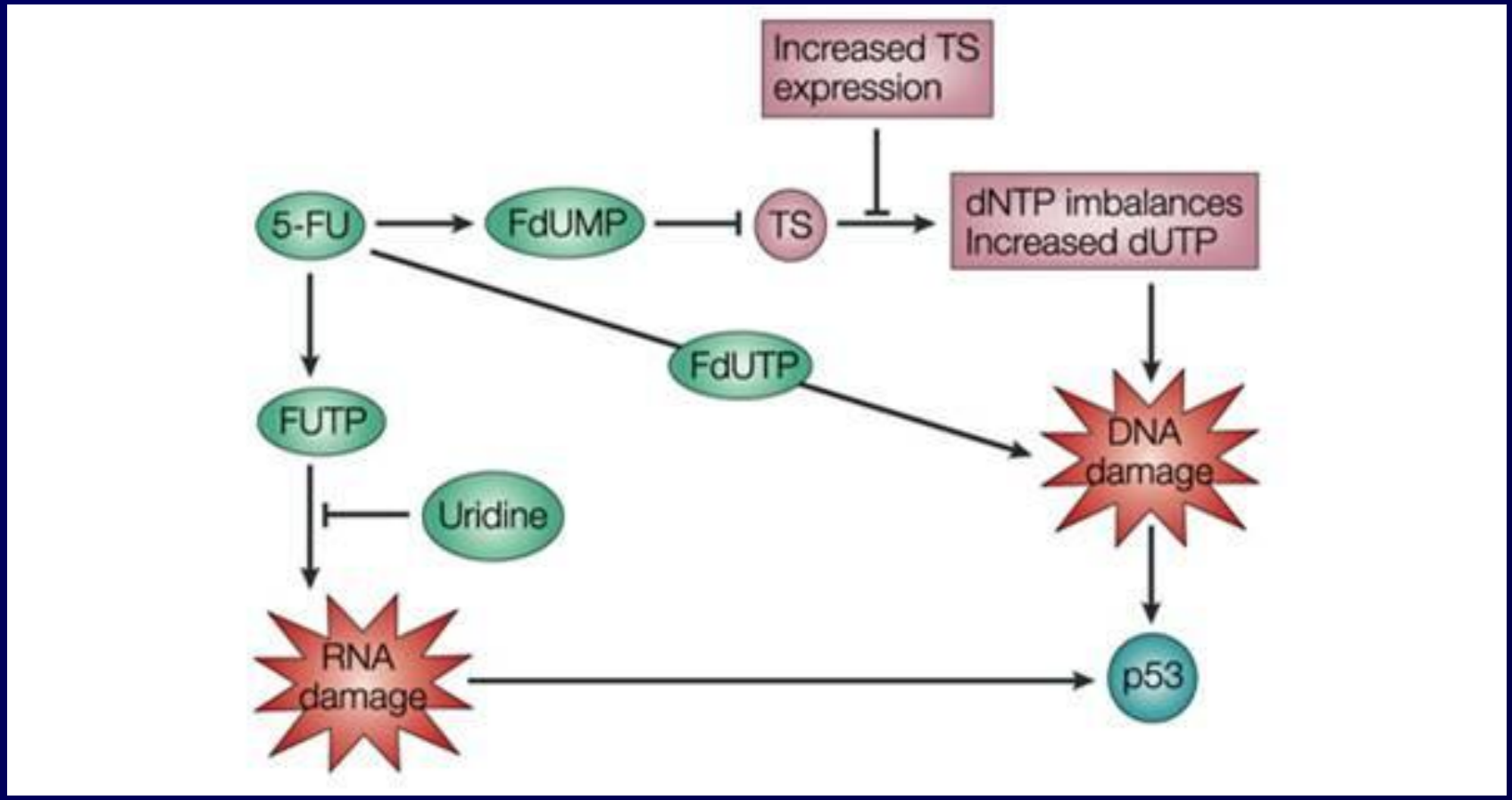
1) Inibizione della timidilato sintasi
2) Incorporazione di FUTP nel RNA


dUMP
FdUMP
CH_2THF
TS
TS
CH_2THF
FdUMP
Thymidine
TK
dTMP
dTTP
DNA replication and repair
dNTP imbalances
Increased dUTP
DNA damage
dUTPase
UDG

MECCANISMI D'AZIONE DEL 5-FLUOROURACILE

1) Inibizione della timidilato sintasi
2) Incorporazione di FUTP nel RNA
3) Incorporazione di FdUTP nel DNA


5-FU
5′DFUR
TP
CH2THF
LV
RNA damage
FUTP
FUMP
OPRT
5-FU
TP
FdUMP
TS inhibition
Acute TS induction
MTX
PRPP
IFN
DNA damage


Increased TS expression
5-FU
FdUMP
TS
dNTP imbalances Increased dUTP
FdUTP
FUTP
DNA damage
Uridine
RNA damage
p53

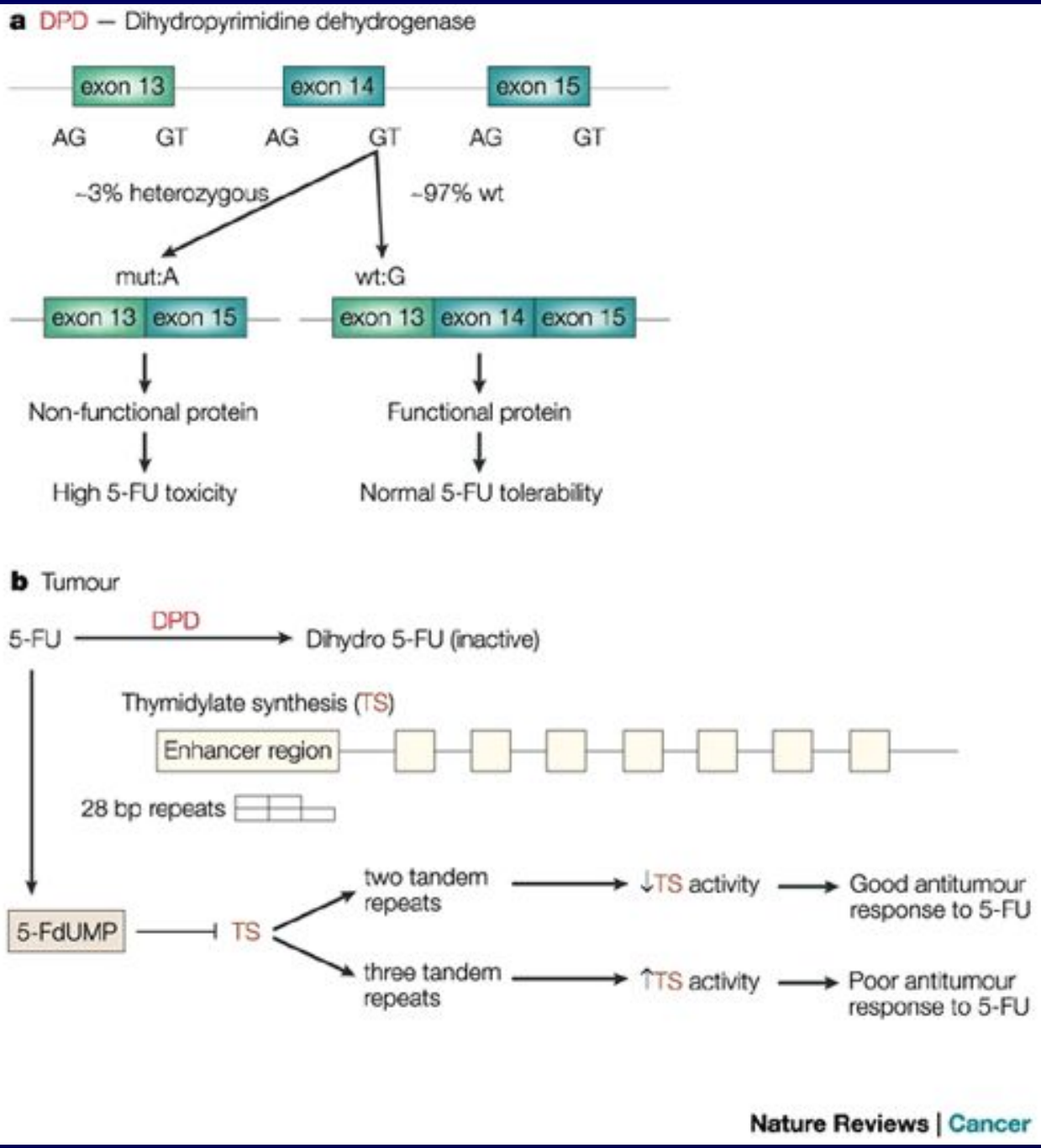
EFFETTI TOSSICI DEL 5FU

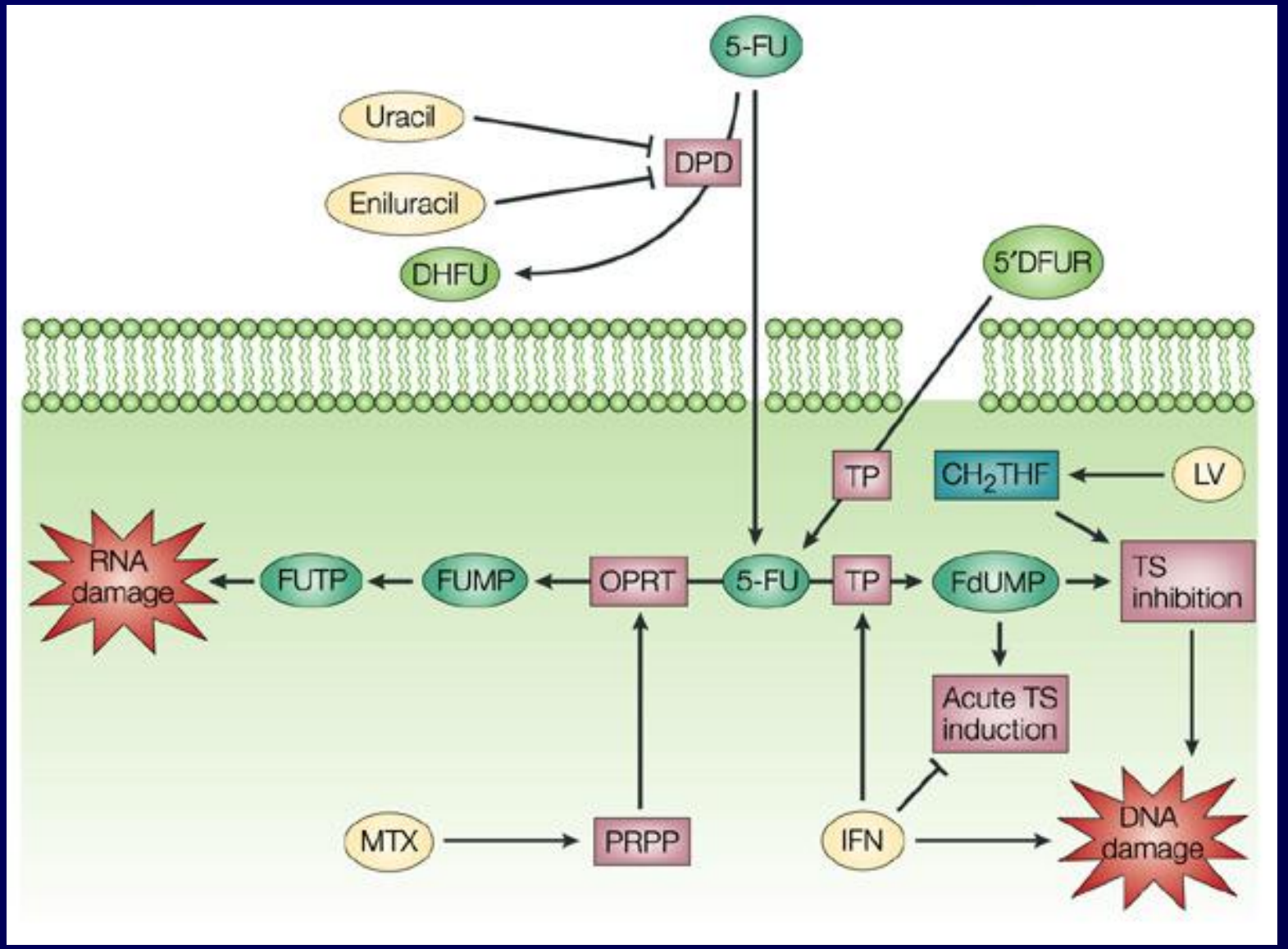
- EFFETTI GI: anoressia e nausea; stomatite e diarrea
- MIELOSOPPRESSIONE
- MANIFESTAZIONI NEUROLOGICHE
- TOSSICITÀ CARDIACA
- MANIFESTAZIONI CUTANEE

HAND-FOOT SYNDROME

MECCANISMI DI RESISTENZA AL 5FU

- PERDITA O ↓ ATTIVITÀ DEGLI ENZIMI ATTIVATORI
- ↓ PIRIMIDINA MONOFOSFATO CHINASI
- ↑ LIVELLI DELL'ENZIMA DEGRADATIVO DPD
- PRODUZIONE DI FORME ALTERATE DI TS


a DPD — Dihydropyrimidine dehydrogenase
exon 13
exon 14
exon 15
AG
GT
AG
GT
AG
GT
~3% heterozygous
~97% wt
mut:A
wt:G
exon 13
exon 15
exon 13
exon 14
exon 15
Non-functional protein
Functional protein
High 5-FU toxicity
Normal 5-FU tolerability
b Tumour
5-FU
DPD
Dihydro 5-FU (inactive)
Thymidylate synthesis (TS)
Enhancer region
28 bp repeats
5-FdUMP
TS
two tandem repeats
↓TS activity
Good antitumour response to 5-FU
three tandem repeats
↑TS activity
Poor antitumour response to 5-FU

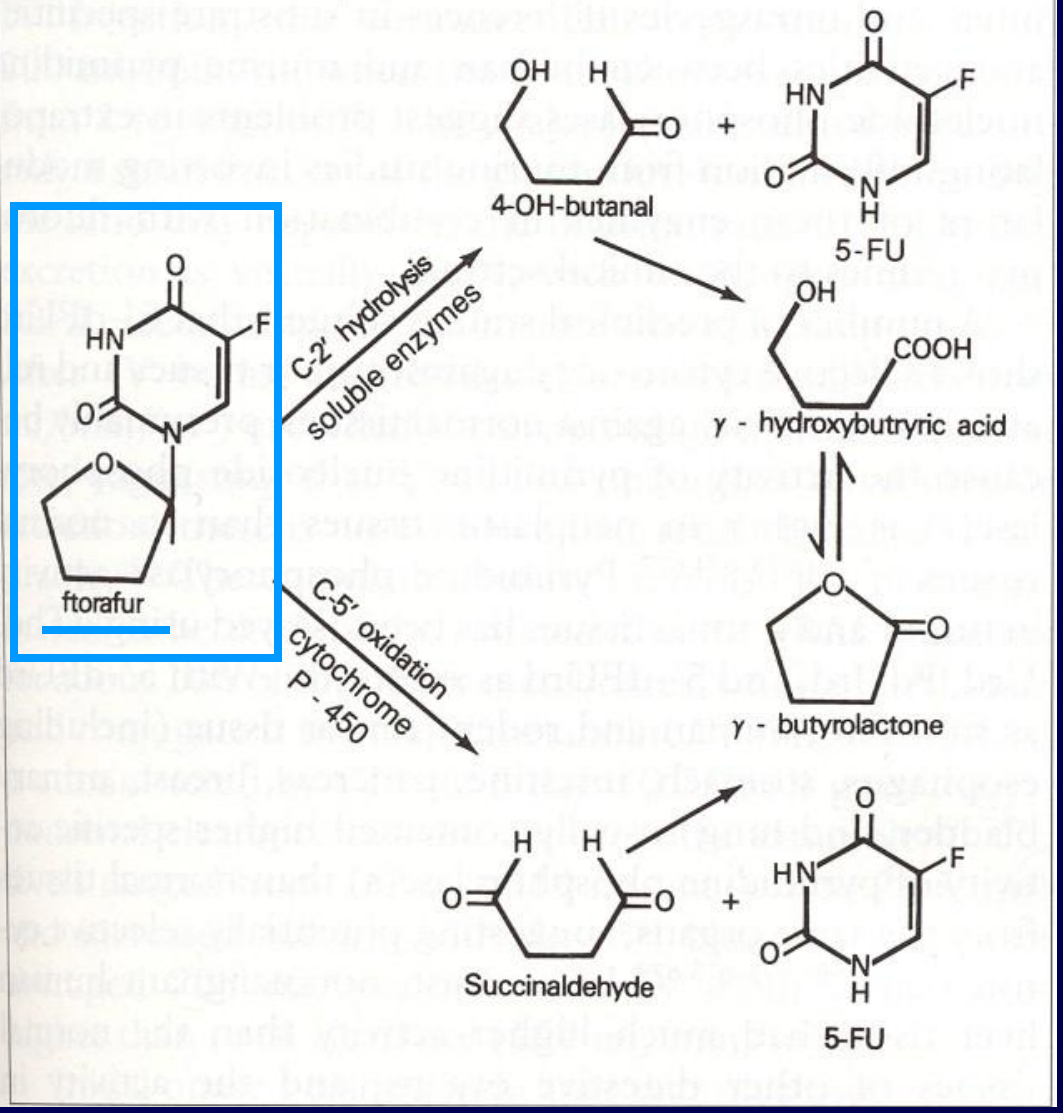

5-FU
Uracil
DPD
Eniluracil
DHFU
5'DFUR
TP
CH2THF
LV
RNA damage
FUTP
FUMP
OPRT
5-FU
TP
FdUMP
TS inhibition
Acute TS induction
MTX
PRPP
IFN
DNA damage

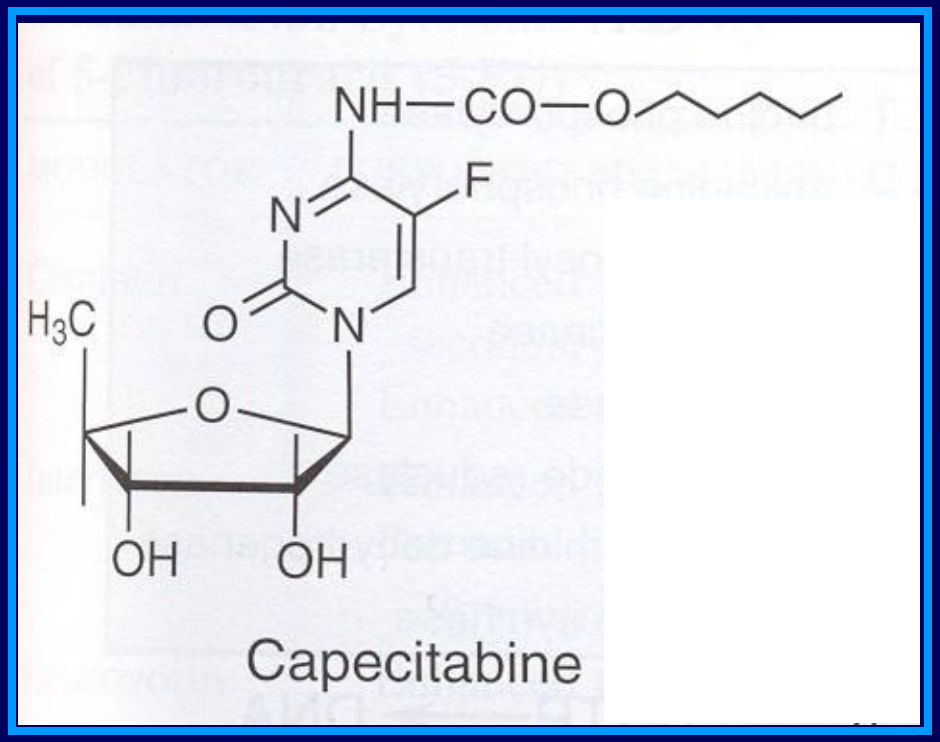
TRATTAMENTI COMBINATI CONTENENTI FLUOROPIRIMIDiNE

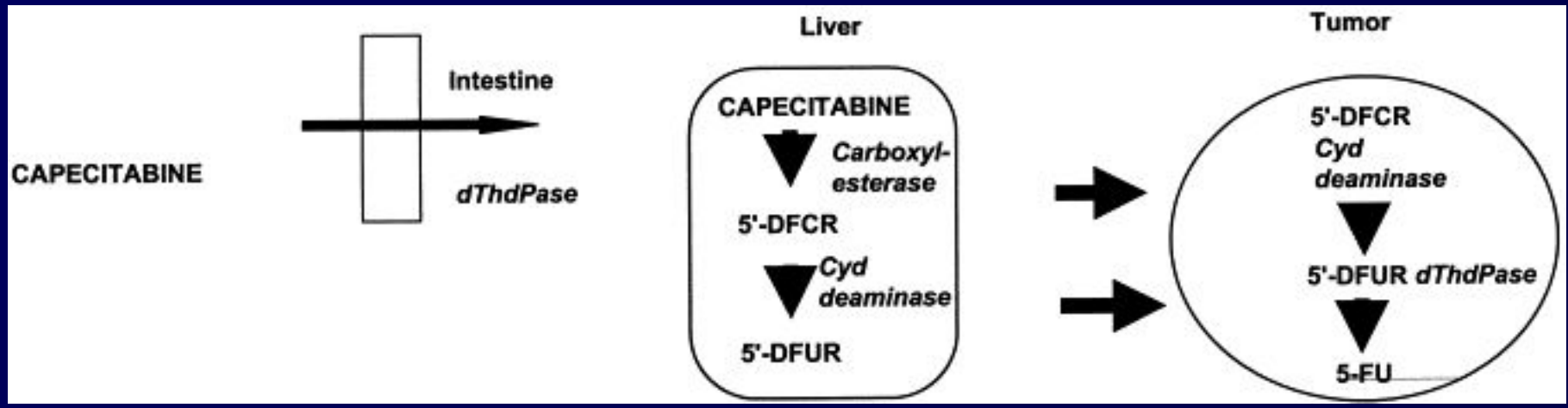
UFT: ftorafur (profarmaco del 5FU)
uracile (inibitore della DPD)

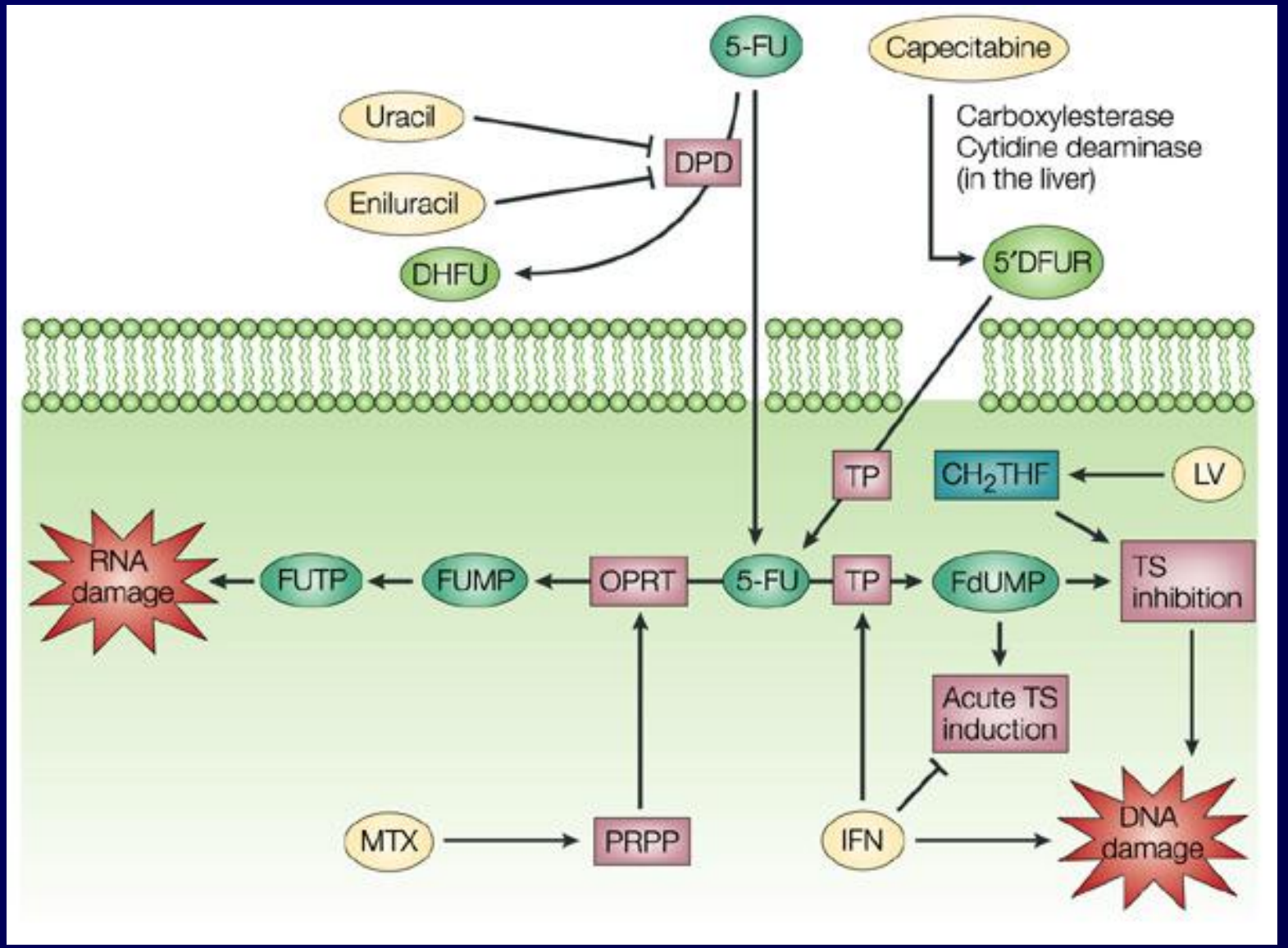
S1: ftorafur (profarmaco del 5FU)
5-cloro-2,4-diidrossipiridina (inibitore della DPD)
potassio oxonato (inibitore della fosforibosil-pirofosfato transferasi, riduce i sintomi intestinali)

Figure 7-18. Metabolism of ftorafur.

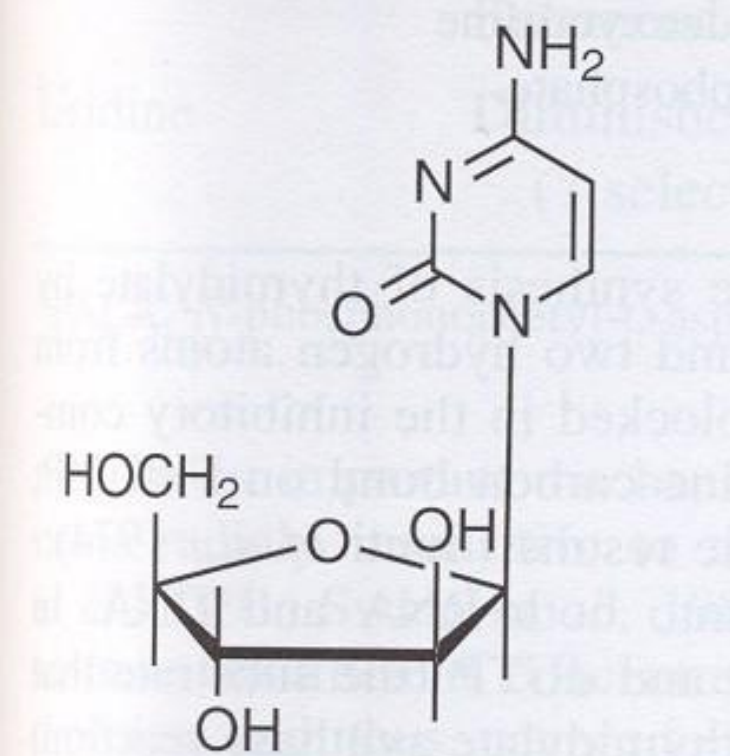



NH—CO—O
F
N
O
N
H_3C
O
OH
OH
Capecitabine


CAPECITABINE
Intestine
dThdPase
Liver
CAPECITABINE
Carboxyl-esterase
5'-DFCR
Cyd deaminase
5'-DFUR
Tumor
5'-DFCR
Cyd deaminase
5'-DFUR dThdPase
5-FU


5-FU
Capecitabine
Uracil
DPD
Eniluracil
DHFU
Carboxylesterase
Cytidine deaminase
(in the liver)
5'DFUR
TP
CH2THF
LV
RNA damage
FUTP
FUMP
OPRT
5-FU
TP
FdUMP
TS inhibition
Acute TS induction
MTX
PRPP
IFN
DNA damage

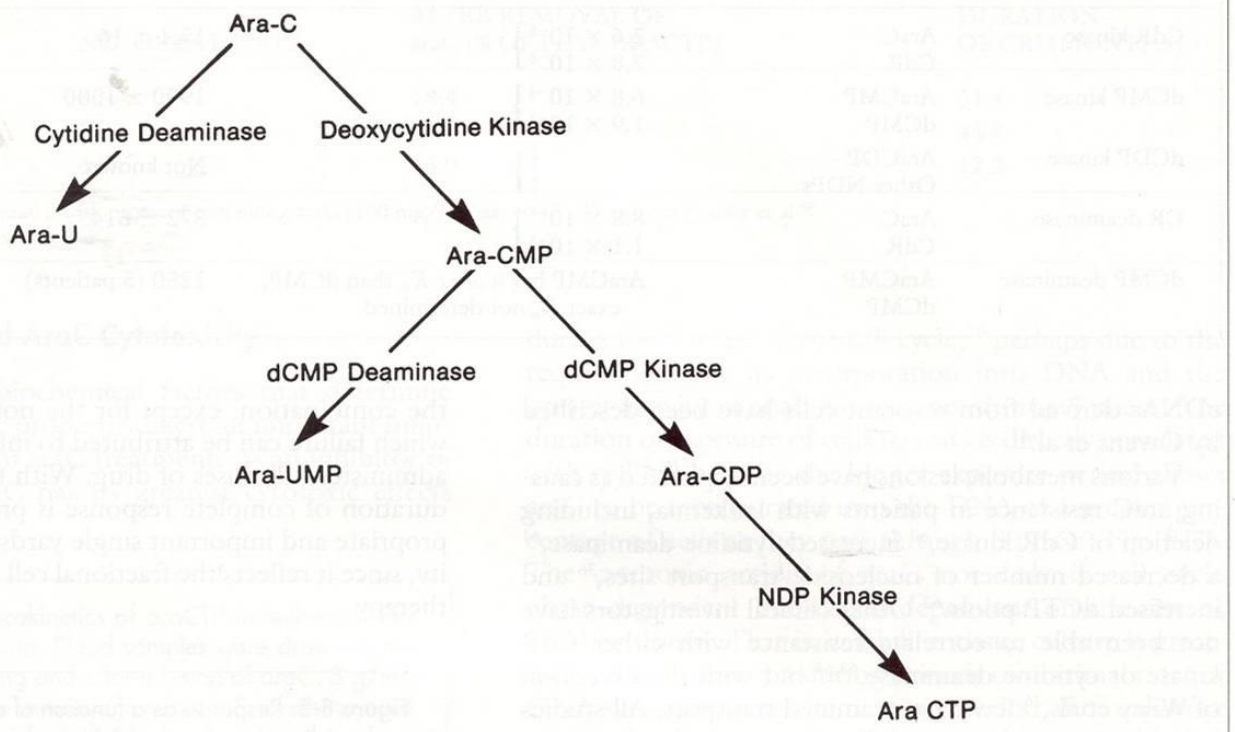
ANALOGHI DELLA CITOSINA



Cytosine arabinoside
(cytarabine; AraC)

PATHWAYS PER L'ATTIVAZIONE/DEGRADAZIONE DI AraC

Figure 8-4. Metabolism of arabinosyl cytosine by tumor cells. The conversion of araUMP to a triphosphate has not been demonstrated in mammalian cells. d = deoxyribose; MP = monophosphate; DP = diphosphate; TP = triphosphate; NDP = nucleoside diphosphate.



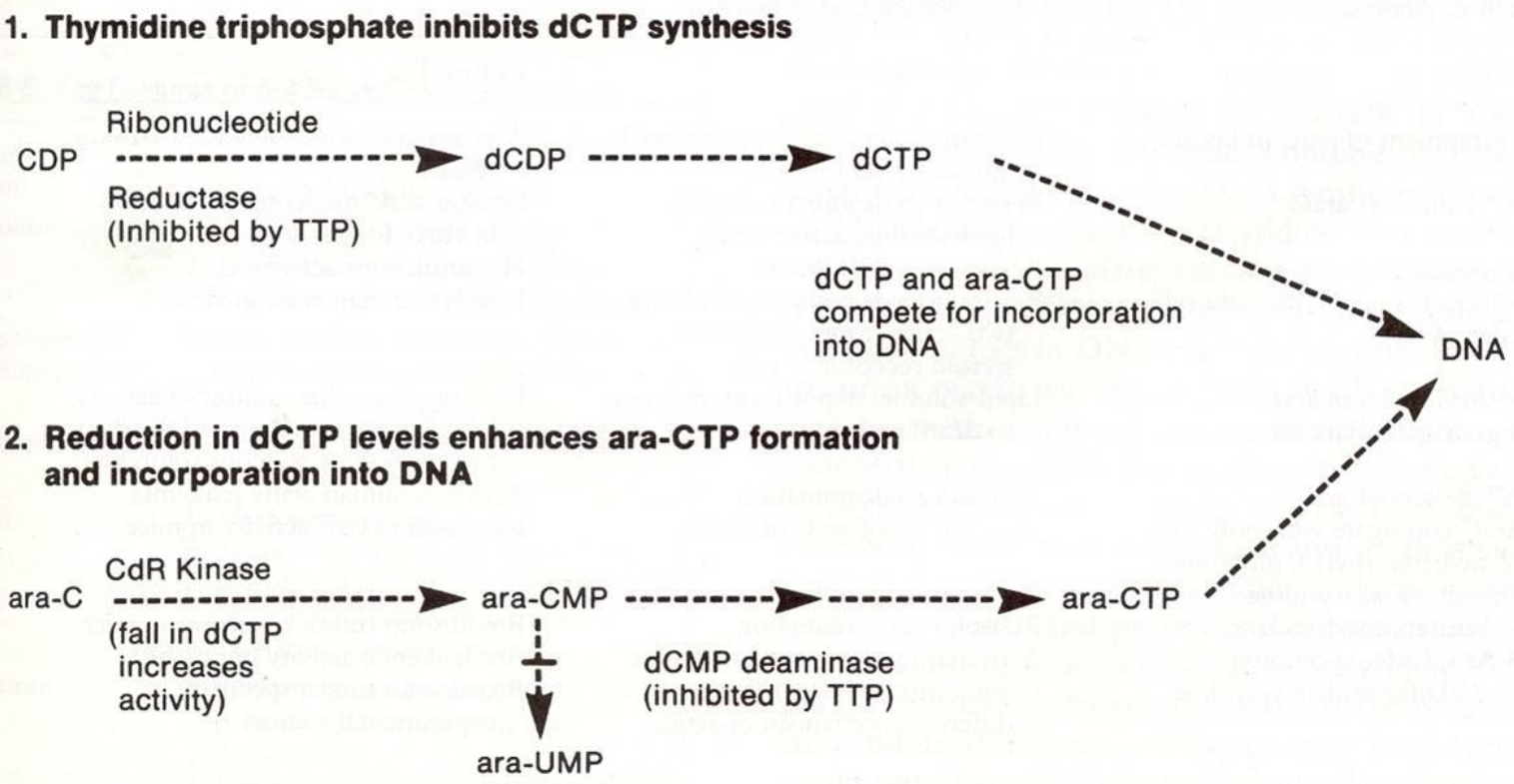
MECCANISMO D'AZIONE di AraC

- competizione con dCTP per l'incorporazione nel DNA
- inibizione della DNA polimerasi:
  - blocco dell'allungamento della catena di DNA
  - blocco della sintesi riparativa di DNA
- ripetizione di segmenti di DNA
  - aumentata possibilità di ricombinazione, crossover e amplificazione genica
- competizione con CDP-colina
  - inibizione della sintesi di glicoproteine e glicolipidi di membrana
- inibizione del trasferimento di galattosio, *N*-acetilglucosamina e acido sialico alle glicoproteine di membrana
- inibizione della sintesi di acido CMP-neuraminico

MECCANISMI DI RESISTENZA AGLI ANALOGHI DELLA CITOSINA

- ALTERAZIONE DELLE ATTIVITÀ RELATIVE DEGLI ENZIMI ATTIVATORI O DEGRADATIVE
- ALTERAZIONI A CARICO DEI TRASPORTATORI DI MEMBRANA
- ESPANSIONE DEL POOL CELLULARE DI dCTP
- SOVRAESPRESSIONE DEL GENE ANTIAPOPTOTICO *bcl-2*
- FOSFORILAZIONE DI FATTORI DI TRASCRIZIONE E/O FATTORI DI RISPOSTA A DANNI A CARICO DEL DNA

ure 8-9. Interactions of thymidine and arabinosyl cytosine.

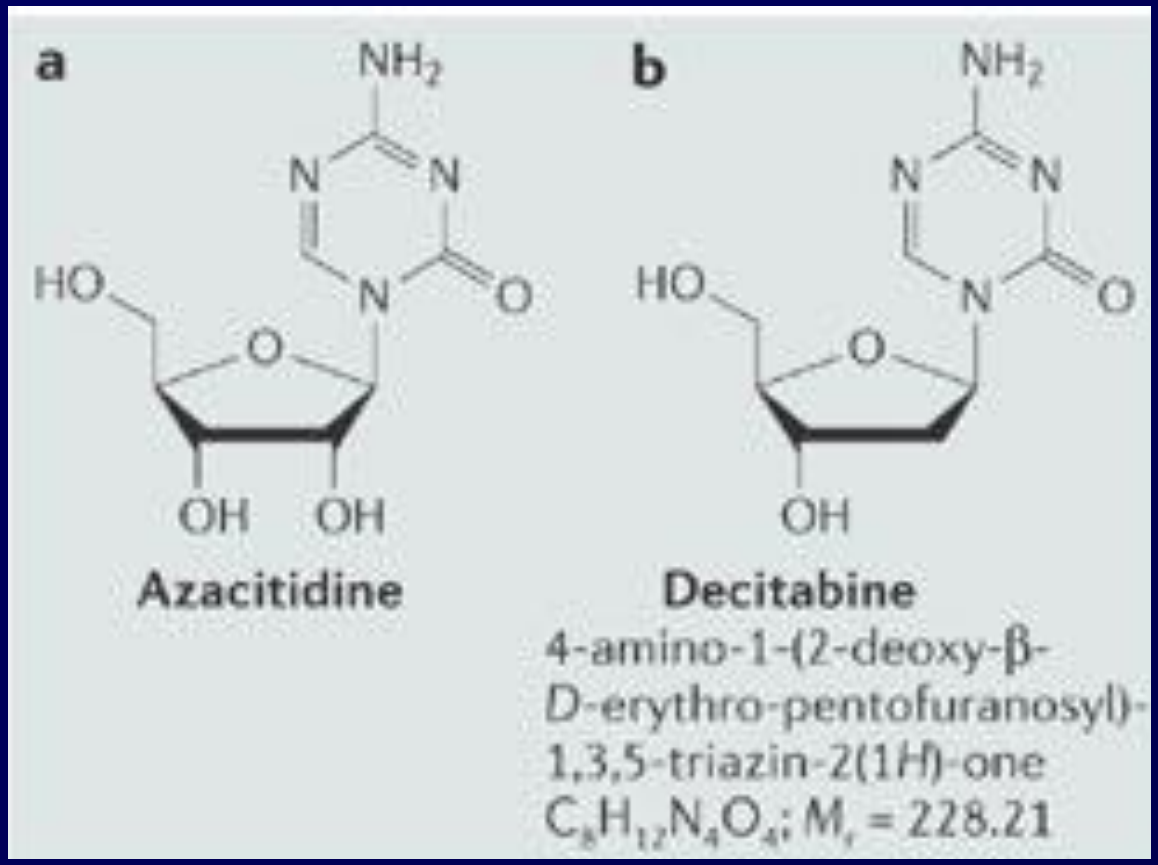


EFFETTI TOSSICI DEGLI ANALOGHI DELLA CITOSINA

- MIELOSOPPRESSIONE
- EFFETTI GI
- MUCOSITE
- LIEVE DISFUNZIONE EPATICA (reversibile)
- POLMONITE

STOMATITE
DA AraC

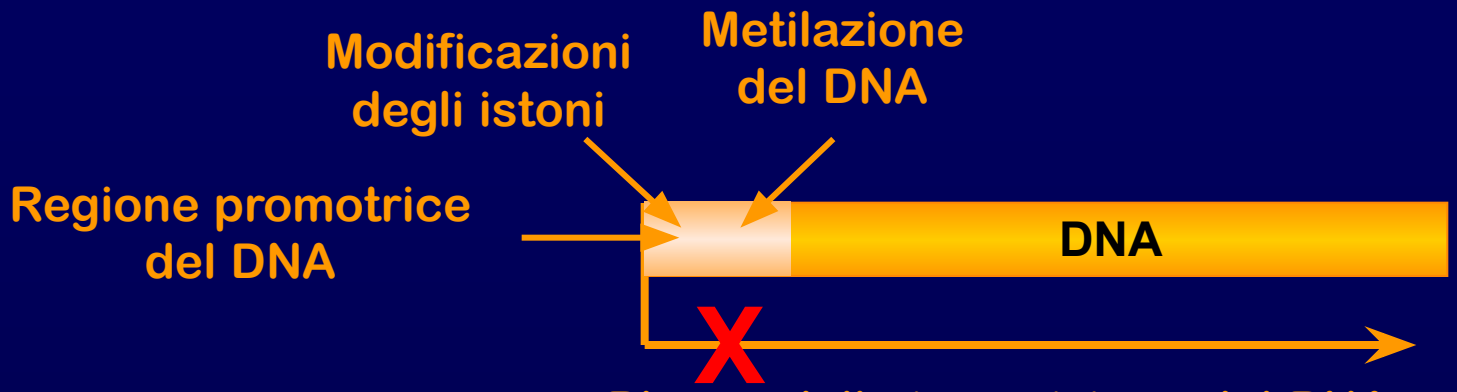
ANALOGHI DELLA CITOSINA

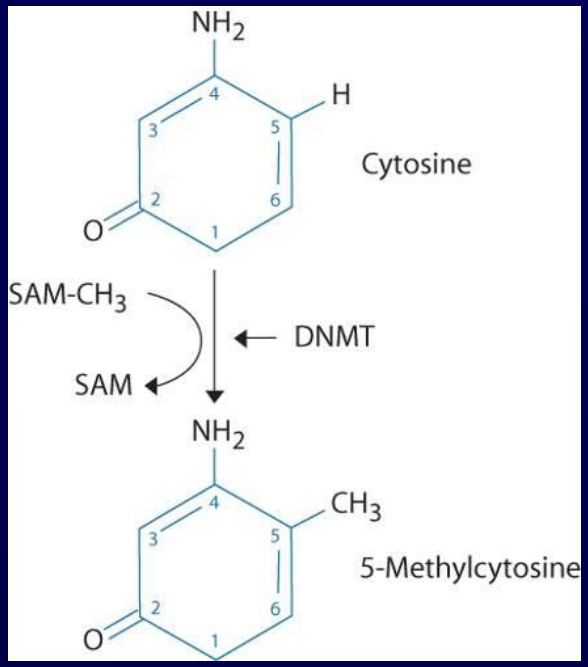


inibitori della metilazione del DNA

approvati per la terapia delle sindromi mielodisplastiche

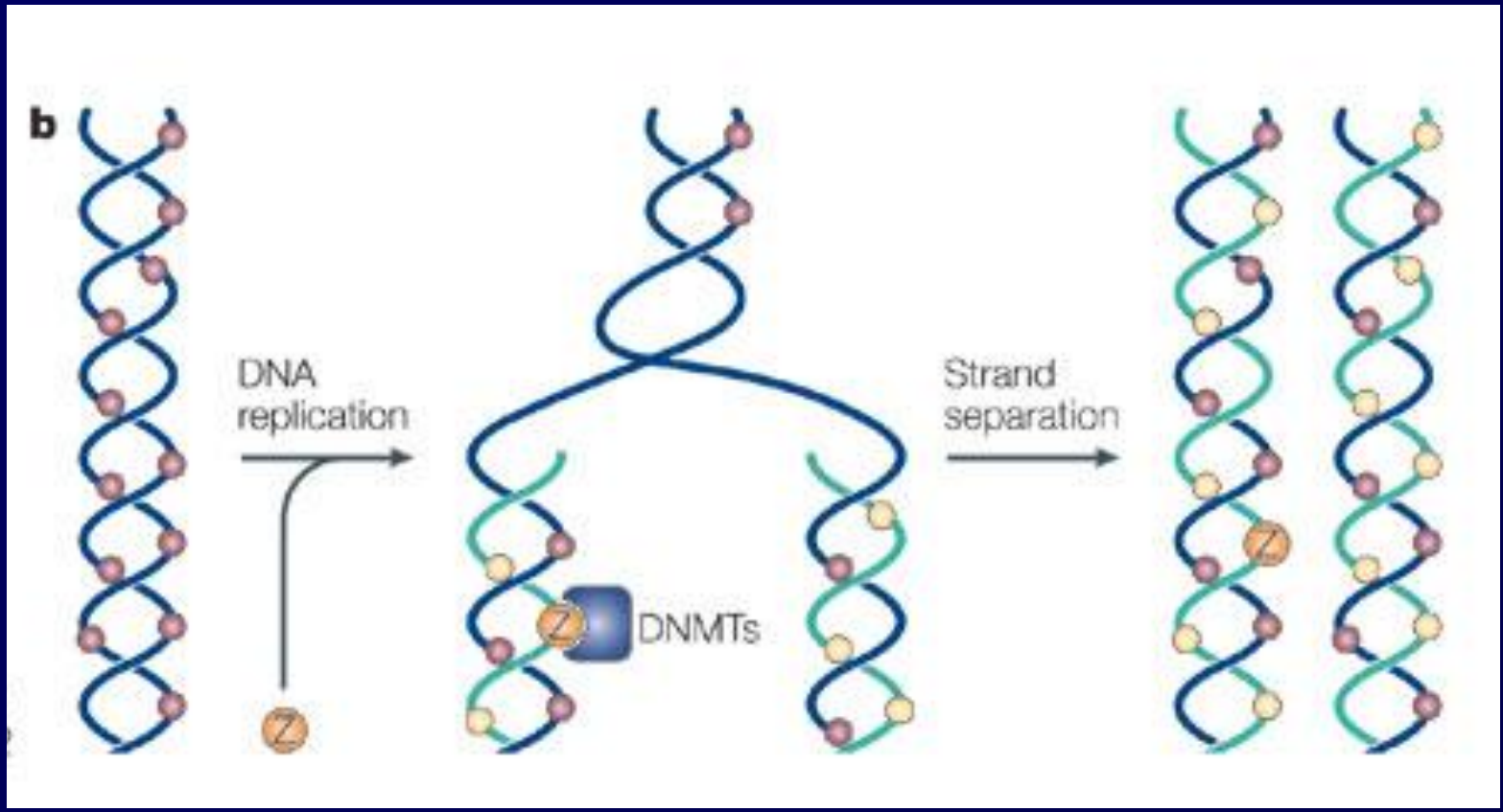
Modificazioni Epigenetiche e Cancro



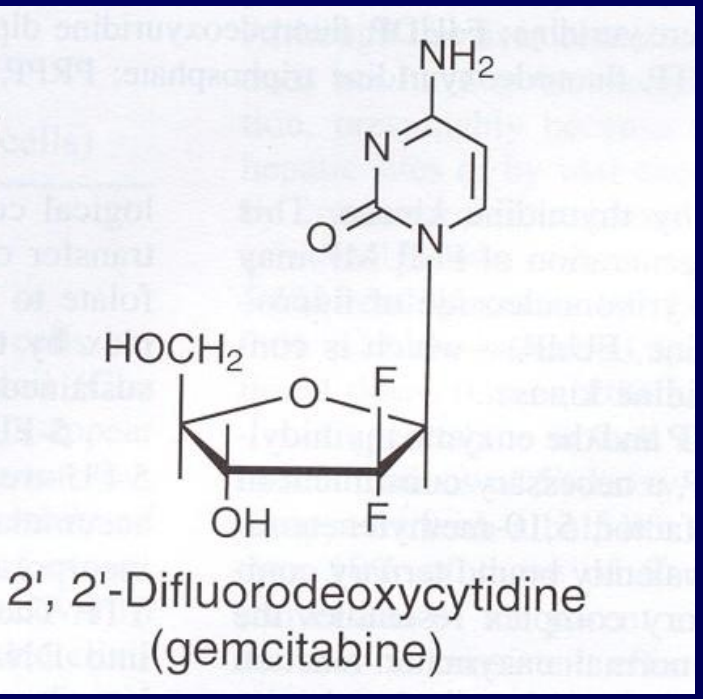


Metilazione del DNA

METILAZIONE DEL DNA



ANALOGHI DELLA CITOSINA



2', 2'-Difluorodeoxycytidine
(gemcitabine)

competizione tra dFdCTP e dCTP

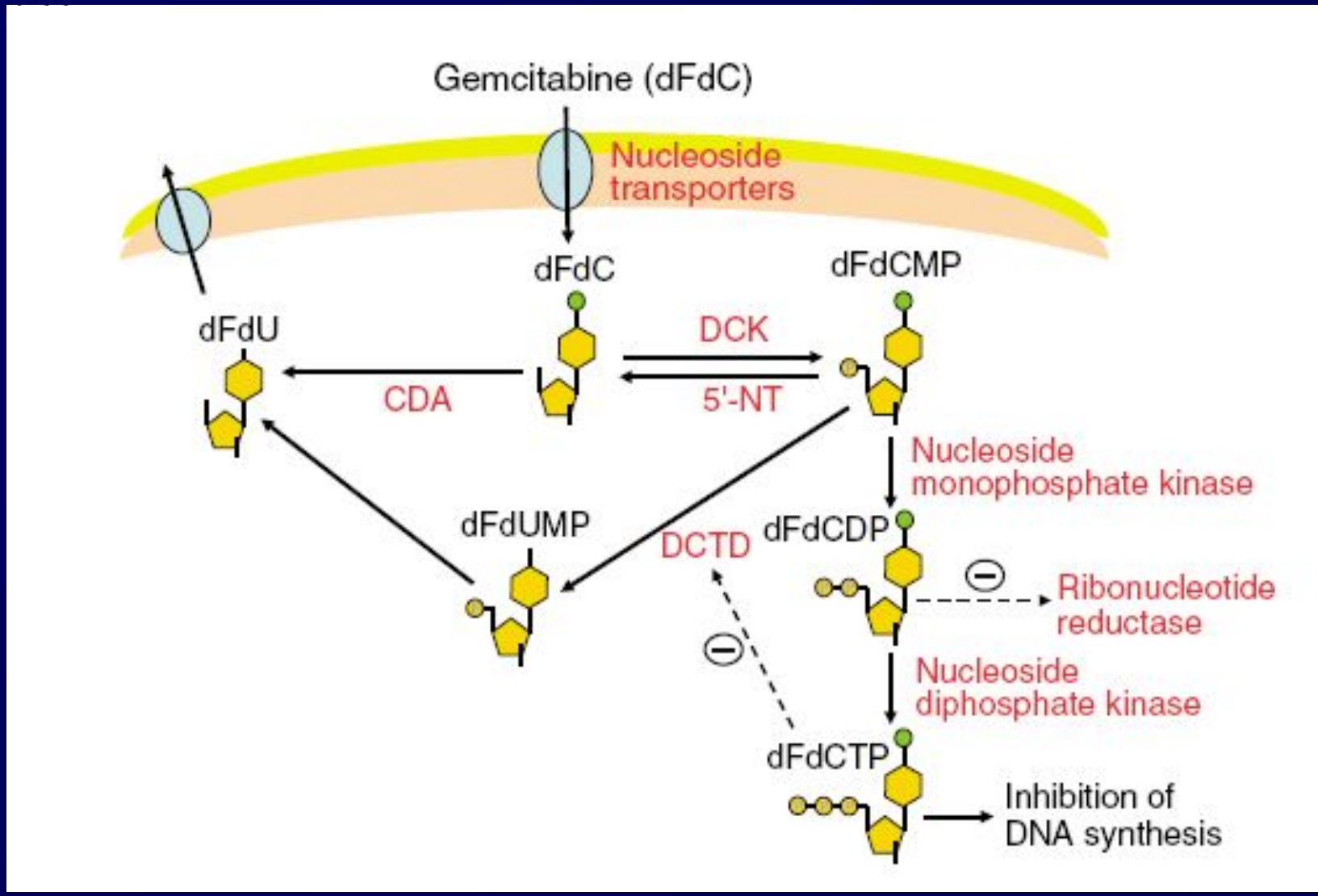
- inibizione DNA polimerasi

inibizione della ribonuclotide reduttasi

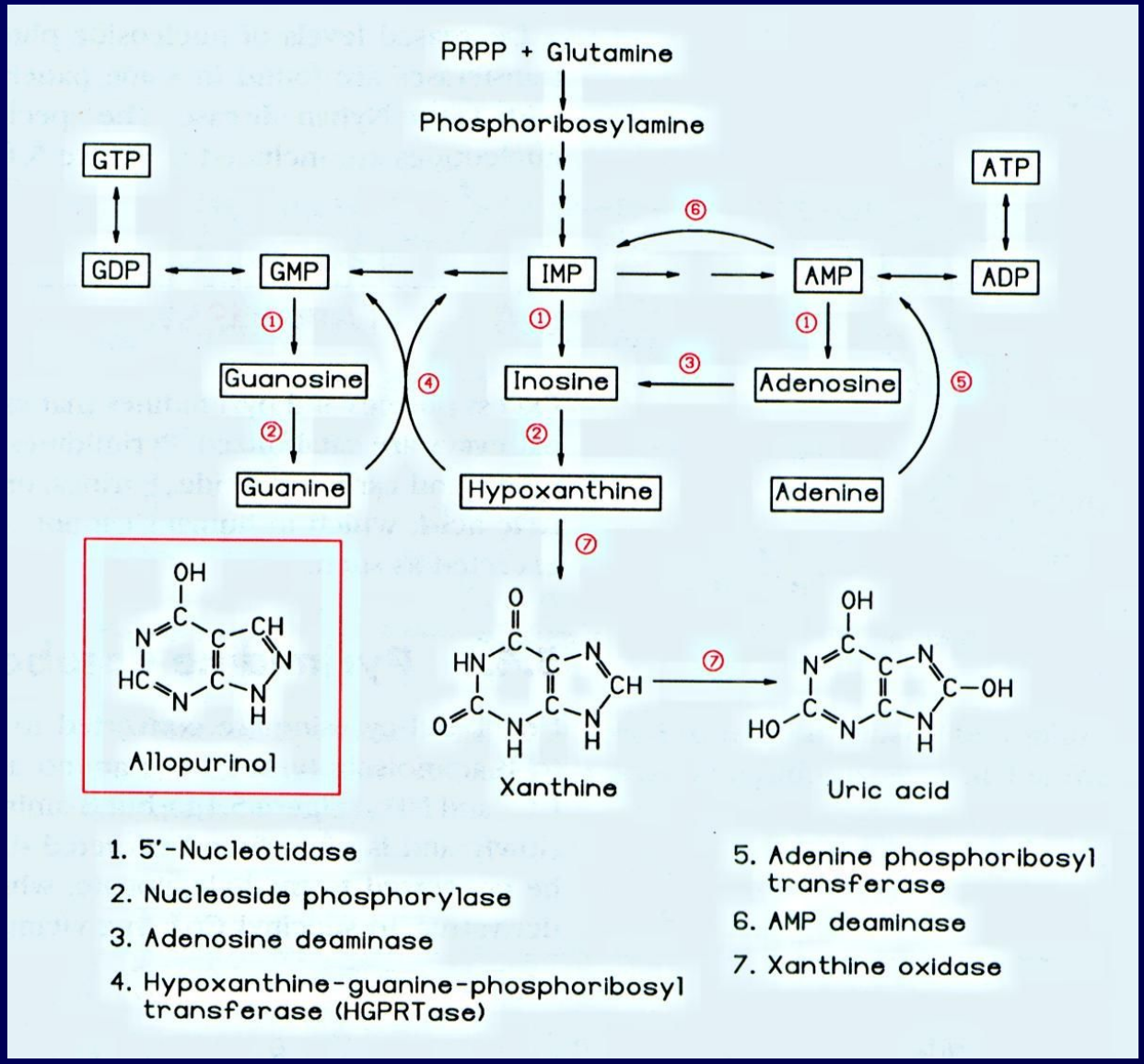
incorporazione di dFdCTP nel DNA

- Blocco dell'allungamento della catena dopo l'incorporazione di un ulteriore nucleotide elusione dei sistemi di riparazione del DNA

attiva anche su cellule in fase non-S

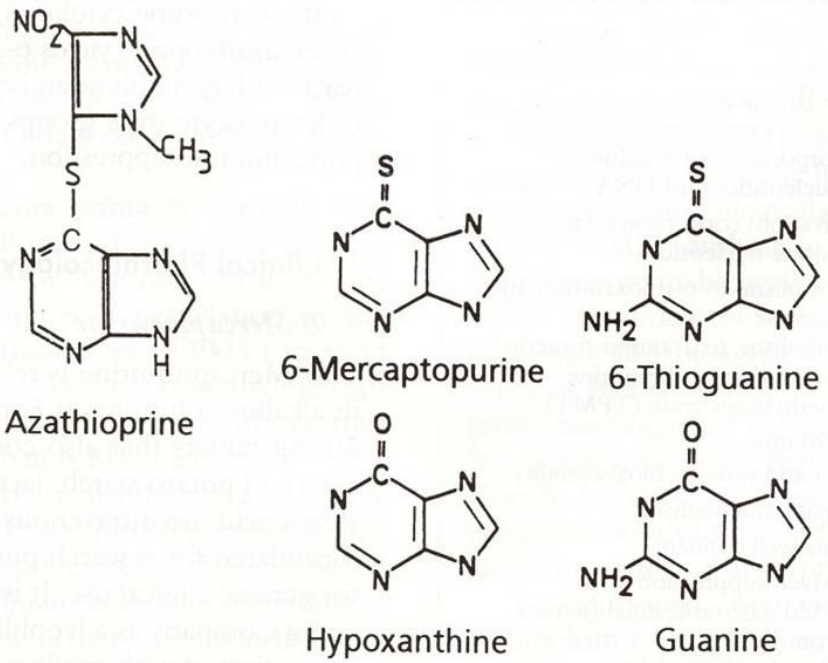

Gemcitabine (dFdC)
Nucleoside transporters
dFdC
dFdCMP
dFdU
DCK
CDA
5'-NT
Nucleoside monophosphate kinase
dFdUMP
DCTD
dFdCDP
Ribonucleotide reductase
Nucleoside diphosphate kinase
dFdCTP
Inhibition of DNA synthesis

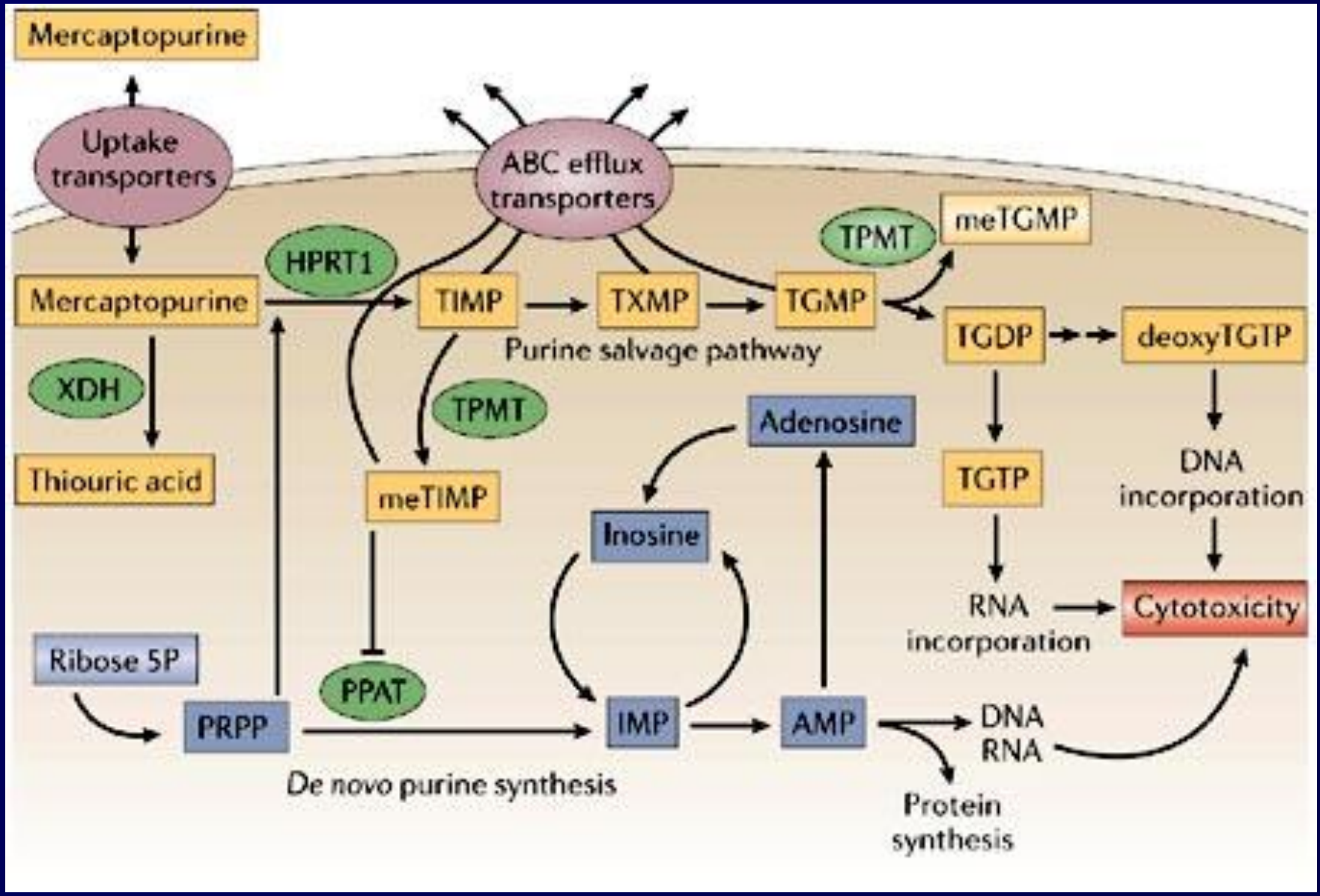
VIA DI RECUPERO DELLE BASI PURINICHE

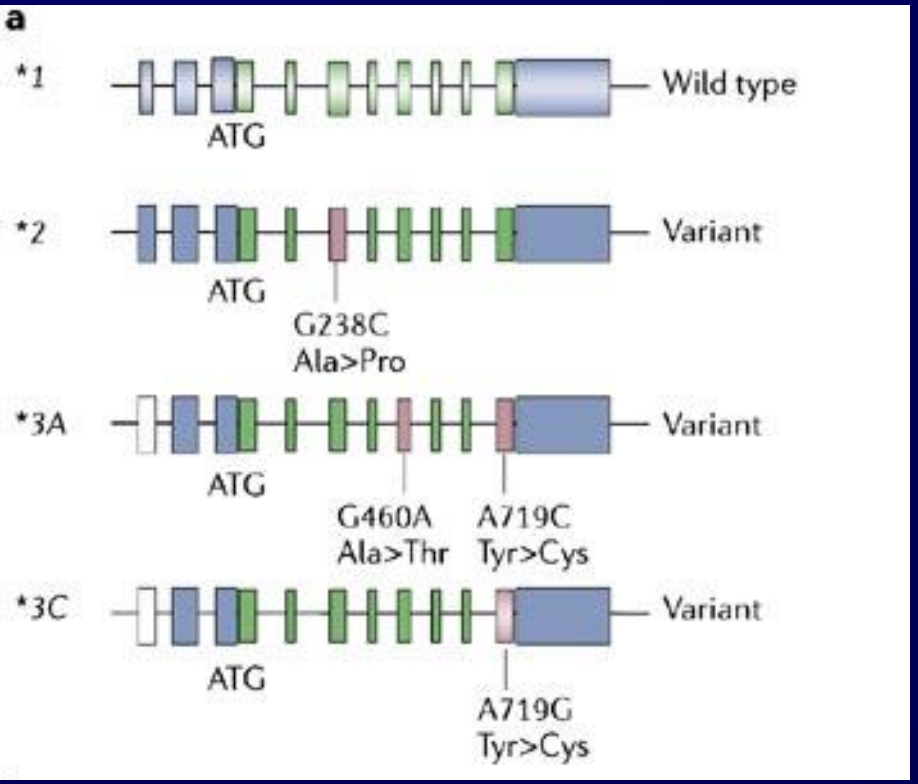


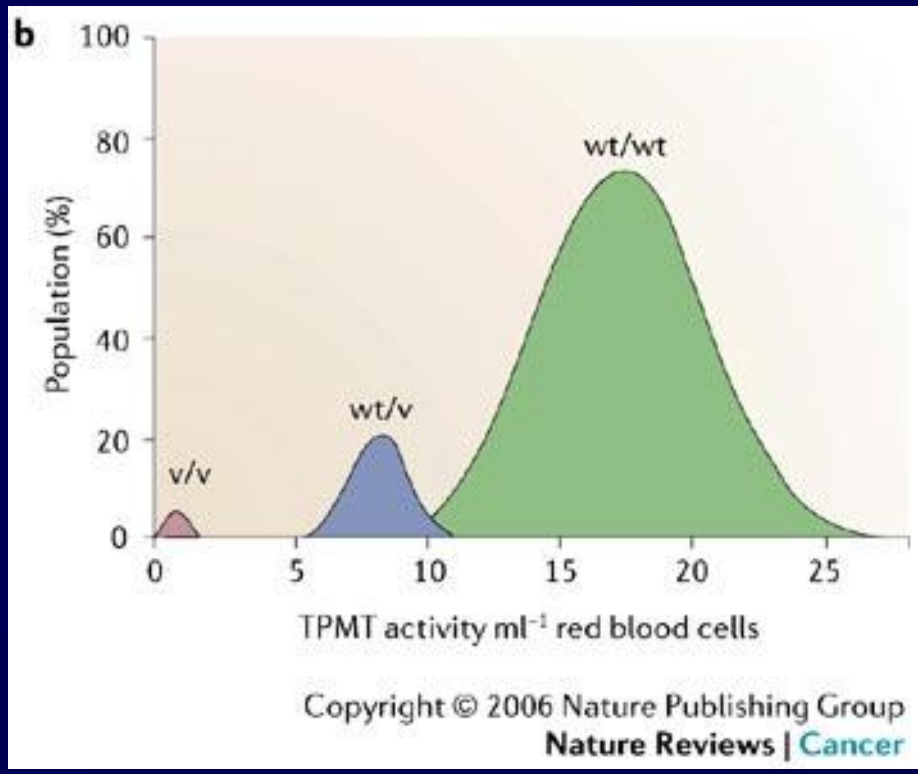
ANALOGHI DELLA GUANINA

Figure 9-1. Structure of the naturally occurring purine guanine and related antineoplastic agents 6-mercaptopurine, 6-thioguanine, and azathioprine.




Mercaptopurine
Uptake transporters
ABC efflux transporters
HPRT1
Mercaptopurine
TIMP
TXMP
TGMP
TPMT
meTGMP
TGDP
deoxyTGTP
Purine salvage pathway
XDH
Thiouric acid
TPMT
meTIMP
Adenosine
Inosine
TGTP
DNA incorporation
RNA incorporation
Cytotoxicity
Ribose 5P
PPAT
PRPP
IMP
AMP
DNA
RNA
De novo purine synthesis
Protein synthesis





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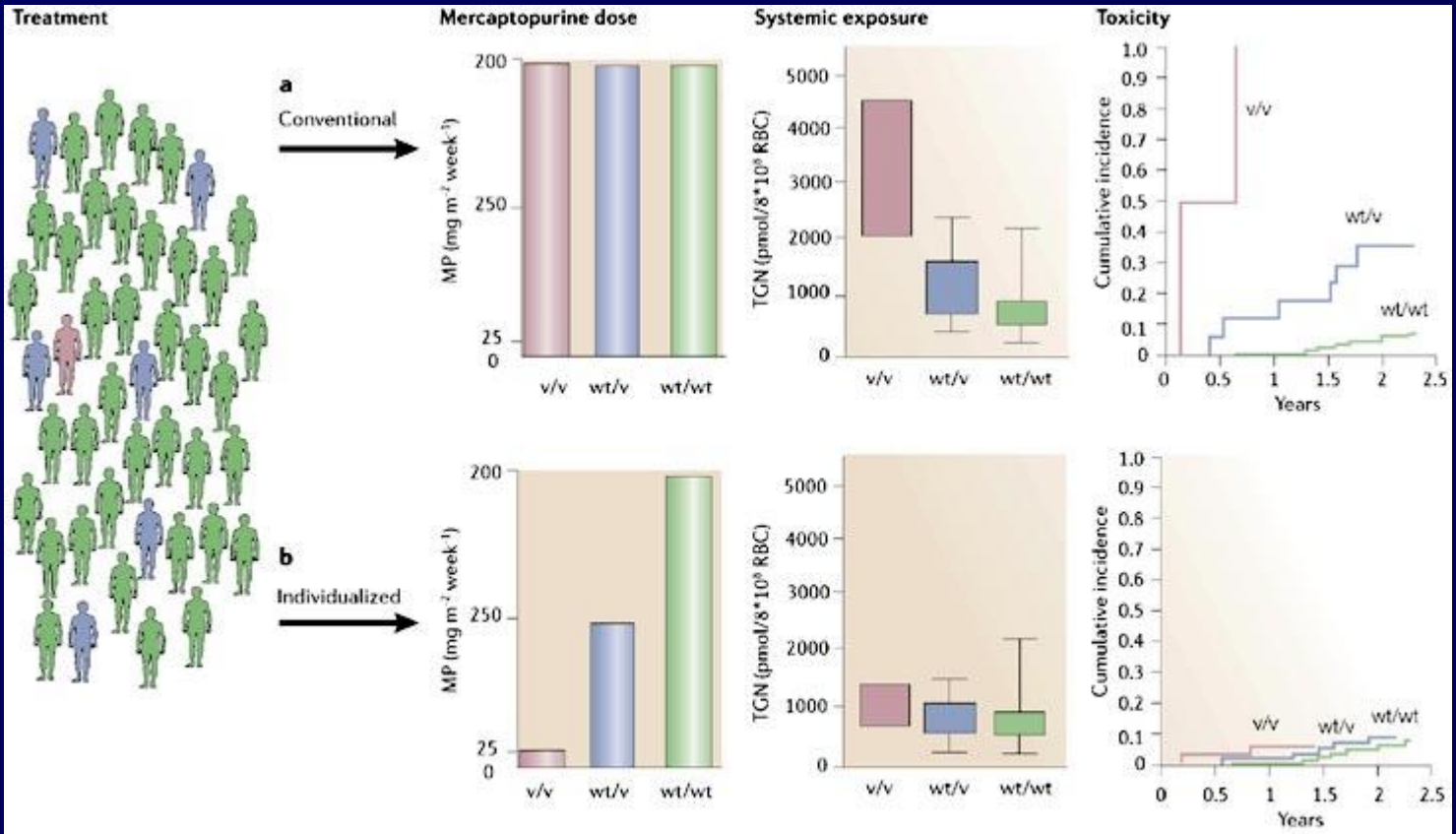
Treatment
Mercaptopurine dose
Systemic exposure
Toxicity
a
Conventional
b
Individualized
MP (mg m⁻² week⁻¹)
TGN (pmol/8*10⁸ RBC)
Cumulative incidence
Years
v/v
wt/v
wt/wt
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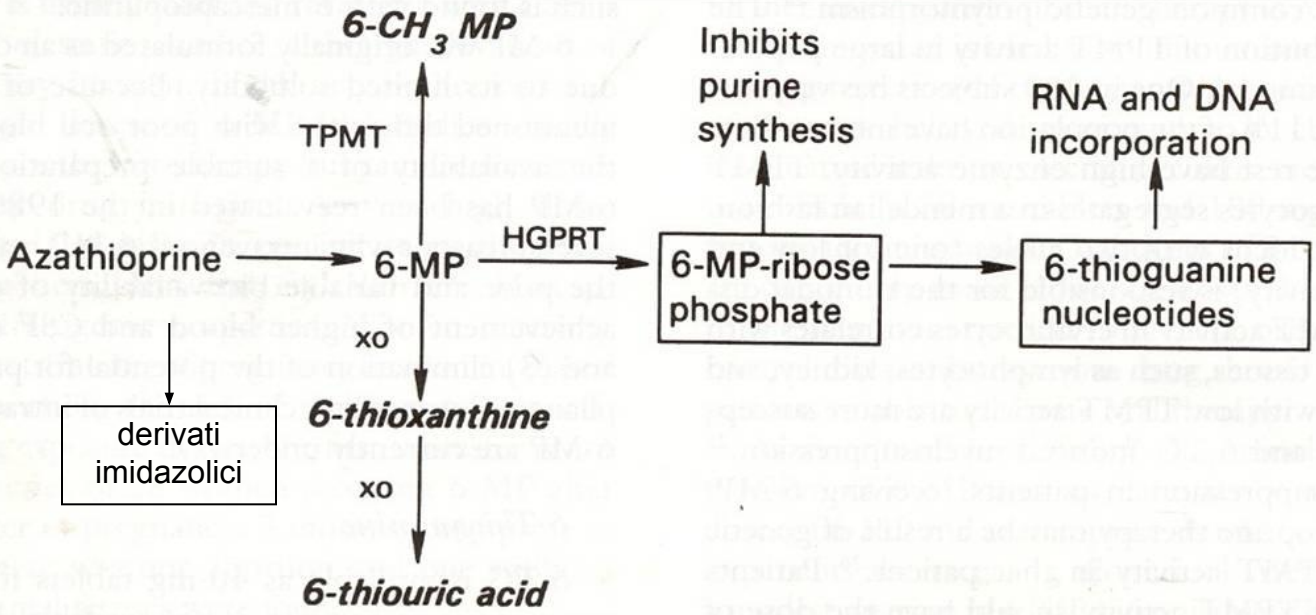
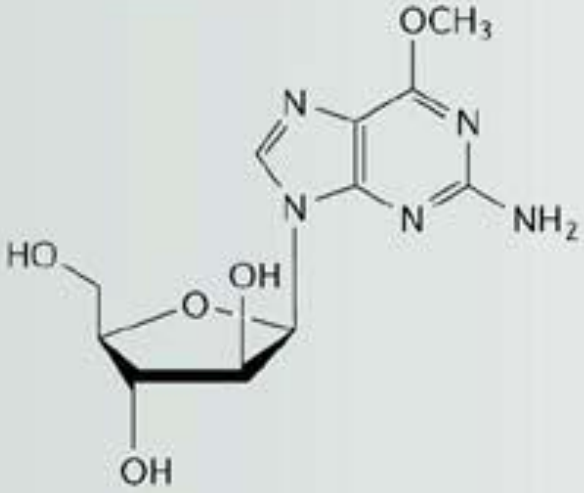
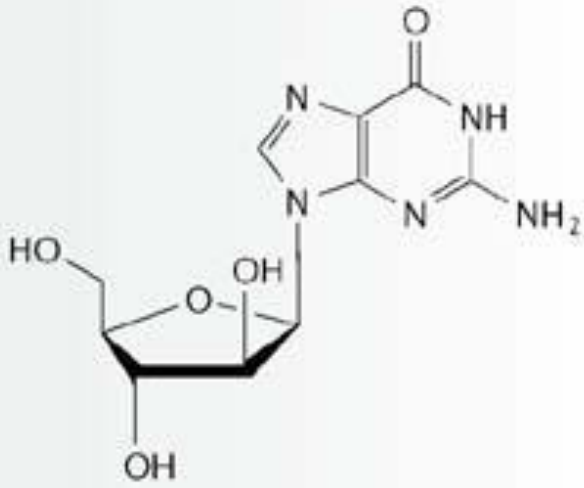
Figure 9-2. Mechanism of activation and catabolism of azathioprine and 6-mercaptopurine. Active metabolites are indicated by surrounding boxes. Inactive (or less active) metabolites are indicated by italic print. TPMT = thiopurine methyltransferase; xo = xanthine oxidase; HGPRT = hypoxanthine-guanine phosphoribosyltransferase.





Adenosine deaminase



Nelarabine

2-amino-9-α-D-arabinofuranosyl-6-methoxy-9*H*-purine;
$C_{11}H_{15}N_5O_5$; M_r = 297.27; CAS number: 121032-29-9

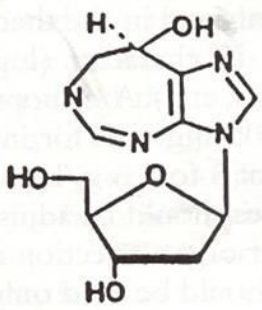
ara-G

MECCANISMI DI RESISTENZA AGLI ANALOGHI DELLA GUANINA

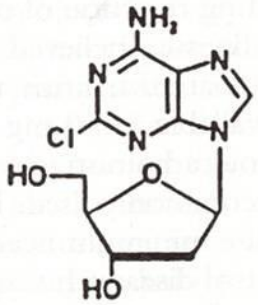
- PERDITA O ↓ ATTIVITÀ DELL' ENZIMA HGPRT
- ↓ TRASPORTO ATTRAVERSO LA MEMBRANA PLASMATICA
- ↑ DELLA VELOCITÀ DI DEGRADAZIONE
- ALTERATA EFFICIENZA DEGLI ENZIMI CHE RIPARANO IL DNA
- ↑ DELL'ATTIVITÀ DELLA MRP5

ANALOGHI DELL' ADENOSINA

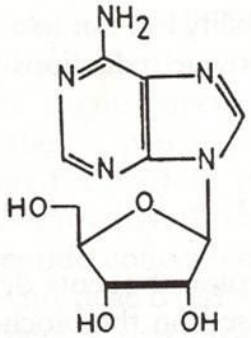
Figure 9-3. Structure of adenosine and the adenosine analogues fludarabine (9-β-arabinofuranosyl-2-fluoroadenosine monophosphate, F-araAMP), pentostatin (2-deoxycoformycin), and cladribine (2CdA, 2-chlorodeoxyadenosine).



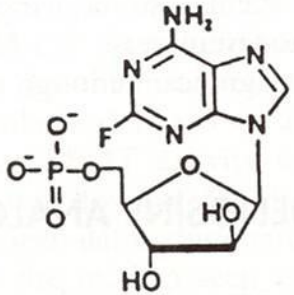
pentostatin



cladribine



adenosine



fludarabine phosphate

Deficit o inibizione dell'enzima adenosina deaminasi (ADA)

↓

Accumulo di dAdenosina e dATP

↓

Inibizione a feedback della ribonucleotide reduttasi

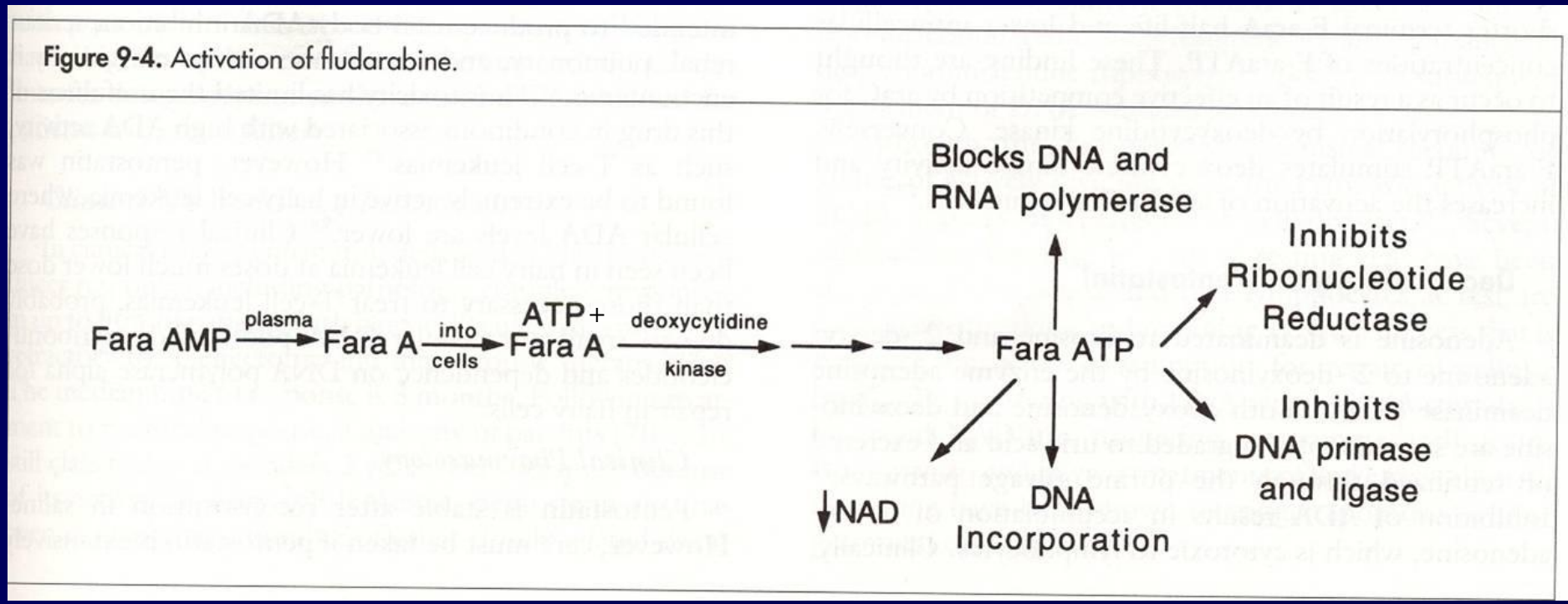
+

Inibizione della S-adenosil-omocisteina idrolasi

Inibizione sintesi e riparazione del DNA

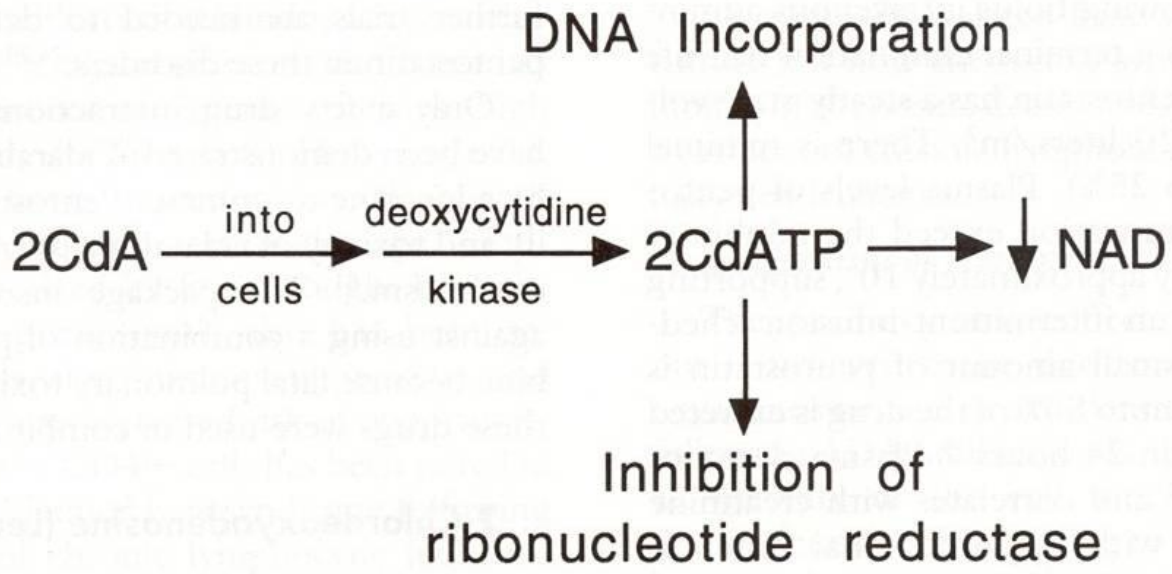
Inibizione delle reazioni di metilazione

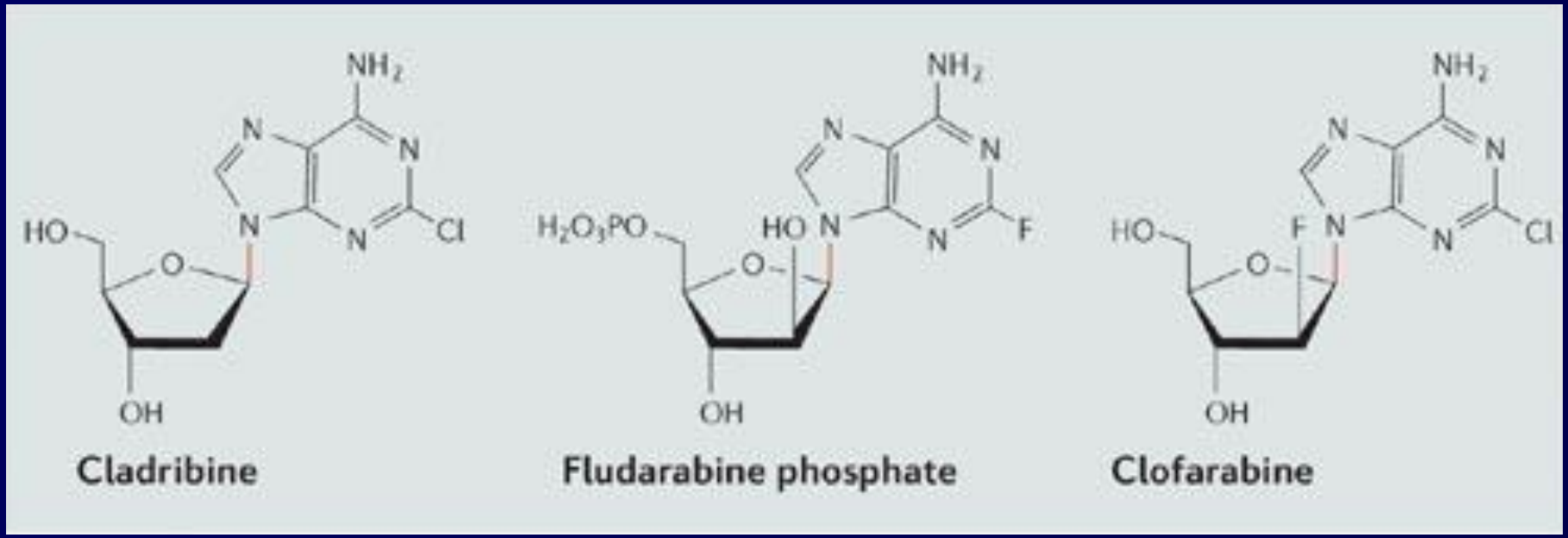
DERIVATI DELLA DESOSSIADENOSINA

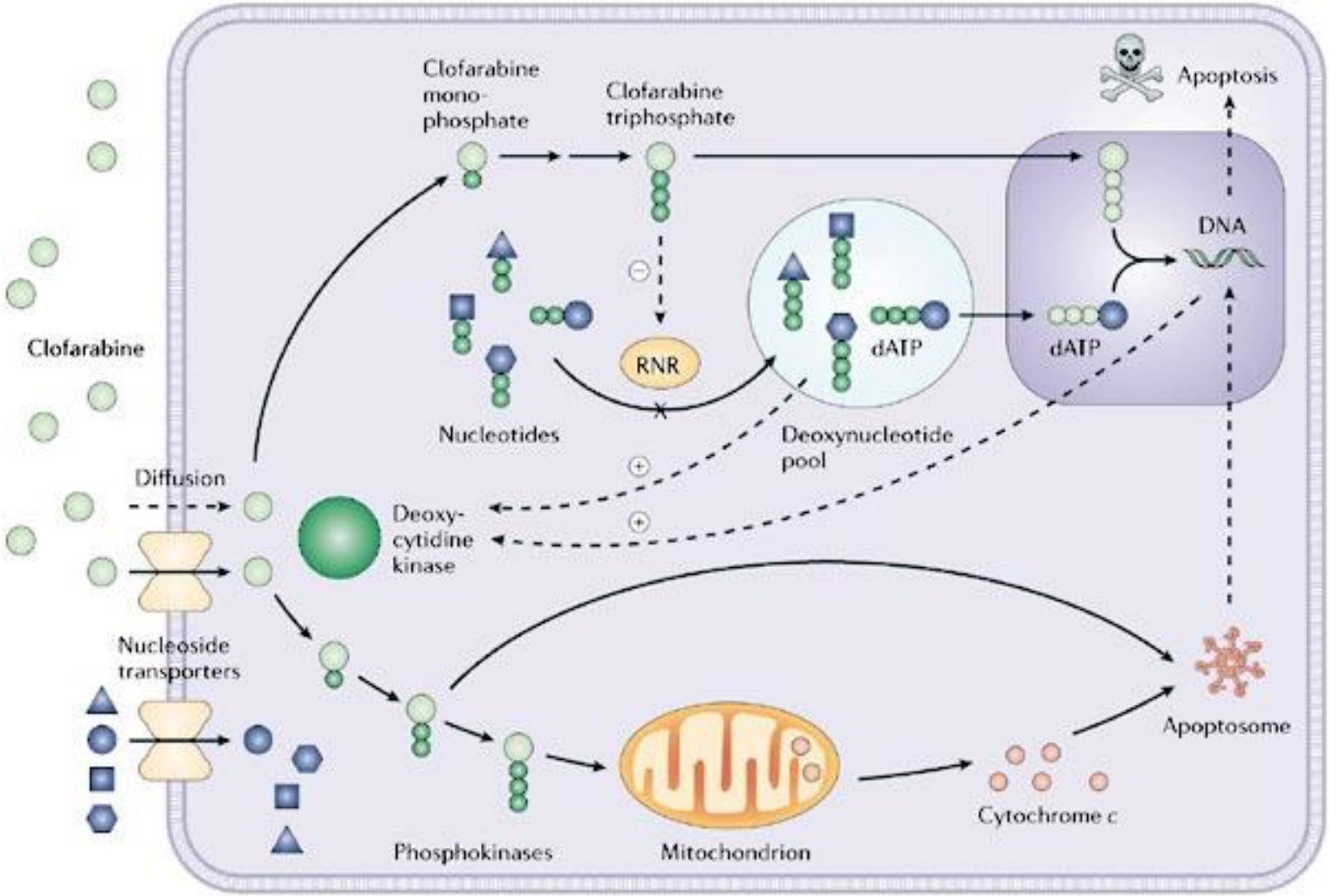


DERIVATI DELLA DESOSSIADENOSINA

Figure 9-5. Activation of 2-chorodeoxyadenosine (2CdA or clodribine).




NH2
N
N
N
N
Cl
HO
O
OH
Cladribine
NH2
N
N
N
N
F
H2O3PO
HO
O
OH
Fludarabine phosphate
NH2
N
N
N
N
Cl
HO
F
O
OH
Clofarabine


Clofarabine
Clofarabine mono-phosphate
Clofarabine triphosphate
Apoptosis
DNA
RNR
dATP
dATP
Nucleotides
Deoxynucleotide pool
Diffusion
Deoxy-cytidine kinase
Nucleoside transporters
Apoptosome
Phosphokinases
Mitochondrion
Cytochrome c

Parameter	Clofarabine	Fludarabine	Cladribine
Phosphorylated by dCK	++++	+	++++
dCK rate-limiting enzymatic step	No	Yes	No
Major metabolites in cells	MP and TP	TP	MP and TP
Ribonucleotide reductase inhibition	++++	++	++++
Inhibition DNA chain elongation	++++	++++	++
Inhibition RNA synthesis	+	++++	No
Mitochondrial release cytochrome *c*	++++	++	++++
Cellular elimination (CEM cells)	Slow	Not tested	Rapid

CEM, acute lymphocytic leukaemia cells; dCK, deoxycytidine kinase; MP, monophosphate; TP, triphosphate.

CARATTERISTICHE DEI DERIVATI DELLA DESOSSIADENOSINA

- Resistenza alla adenosina deaminasi
- Attività anche su cellule non proliferanti
  - inibizione della riparazione del DNA
  - alterazioni mitocondriali
  - attivazione diretta del programma apoptotico
- Mielosoppressione ed effetto immunosoppressivo

Drug	Main uses	Doses	Main adverse effects
Purine analogues			
Fludarabine	Chronic lymphocytic leukaemia	25 mg/m^2 daily intravenously over 30 min for 5 days; repeat every 28 days	Myelosuppression, opportunistic infections, neurotoxicity
Cladribine	Hairy-cell leukaemia; non-Hodgkin lymphoma	4 mg/m^2 daily by continuous intravenous infusion for 5 consecutive days	Myelosuppression, rash, septicaemia, fever
Pyrimidine analogues			
Cytarabine	Acute myelogenous and lymphoblastic leukaemias	Conventional dose — 100–200 mg/m^2 intravenously on days 1 to 7	Conventional dose — myelosuppression, vomiting, stomatitis
		High-dose — 3 g/m^2 intravenously over 1–3 h every 12 h for 12 doses	High dose — neurotoxicity, pericarditis
Gemcitabine	Pancreatic, lung, breast, and bladder cancers	1 g/m^2 intravenously over 30 min once a week for 3 consecutive weeks every 4 weeks	Mild myelosuppression, nausea and vomiting, and skin rashes
Fluoropyrimidines			
Fluorouracil	Gastrointestinal, pancreatic, head and neck, renal, skin, prostate, and breast cancers	Mayo regimen — 450–600 mg/m^2 intravenous bolus on days 1–5 every 4 weeks	Bolus — myelosuppression, stomatitis, nausea and vomiting, diarrhoea, angor pectoris
		Roswell Park regimen — 450–600 mg/m^2 intravenous bolus weekly	
		Infusion — 200–400 mg/m^2 daily continuously	Infusion — hand foot syndrome
Capecitabine	Relapsed breast and colorectal cancers	2·5 g/m^2 daily by mouth; 2 weeks on drug, 1 week of rest	Hand-foot syndrome, diarrhoea, nausea and vomiting

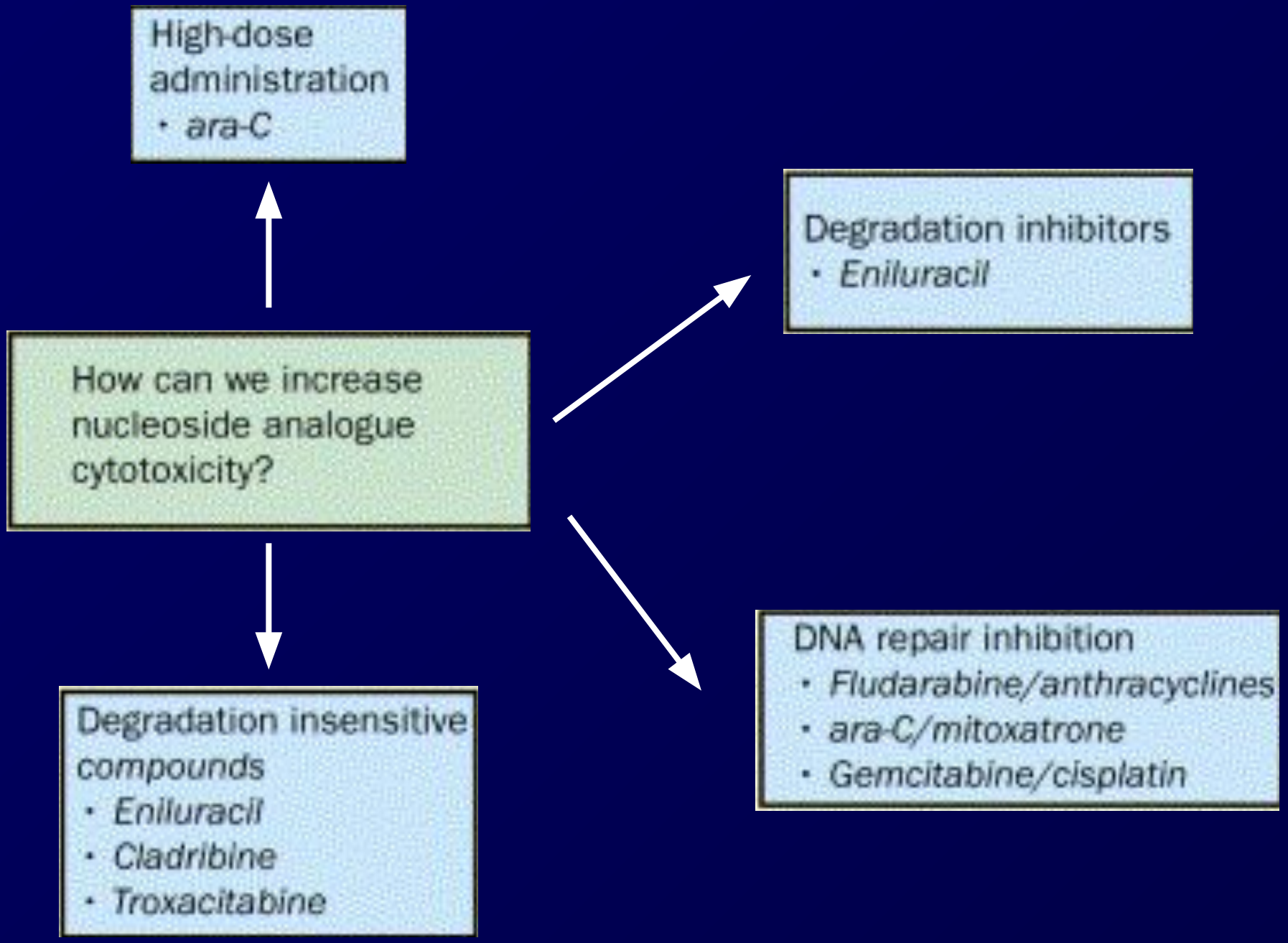
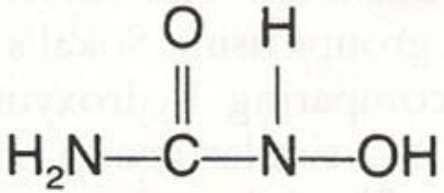

High-dose administration
• ara-C
How can we increase nucleoside analogue cytotoxicity?
Degradation inhibitors
• Eniluracil
DNA repair inhibition
• Fludarabine/anthracyclines
• ara-C/mitoxatrone
• Gemcitabine/cisplatin
Degradation insensitive compounds
• Eniluracil
• Cladribine
• Troxacitabine

Figure 10-1. Structure of hydroxyurea.



MECCANISMI D'AZIONE DELLA IDROSSIUREA

- effetto scavenger sul radicale libero tirosinico presente nel sito attivo
- liberazione di NO

MECCANISMI DI RESISTENZA ALLA IDROSSIUREA

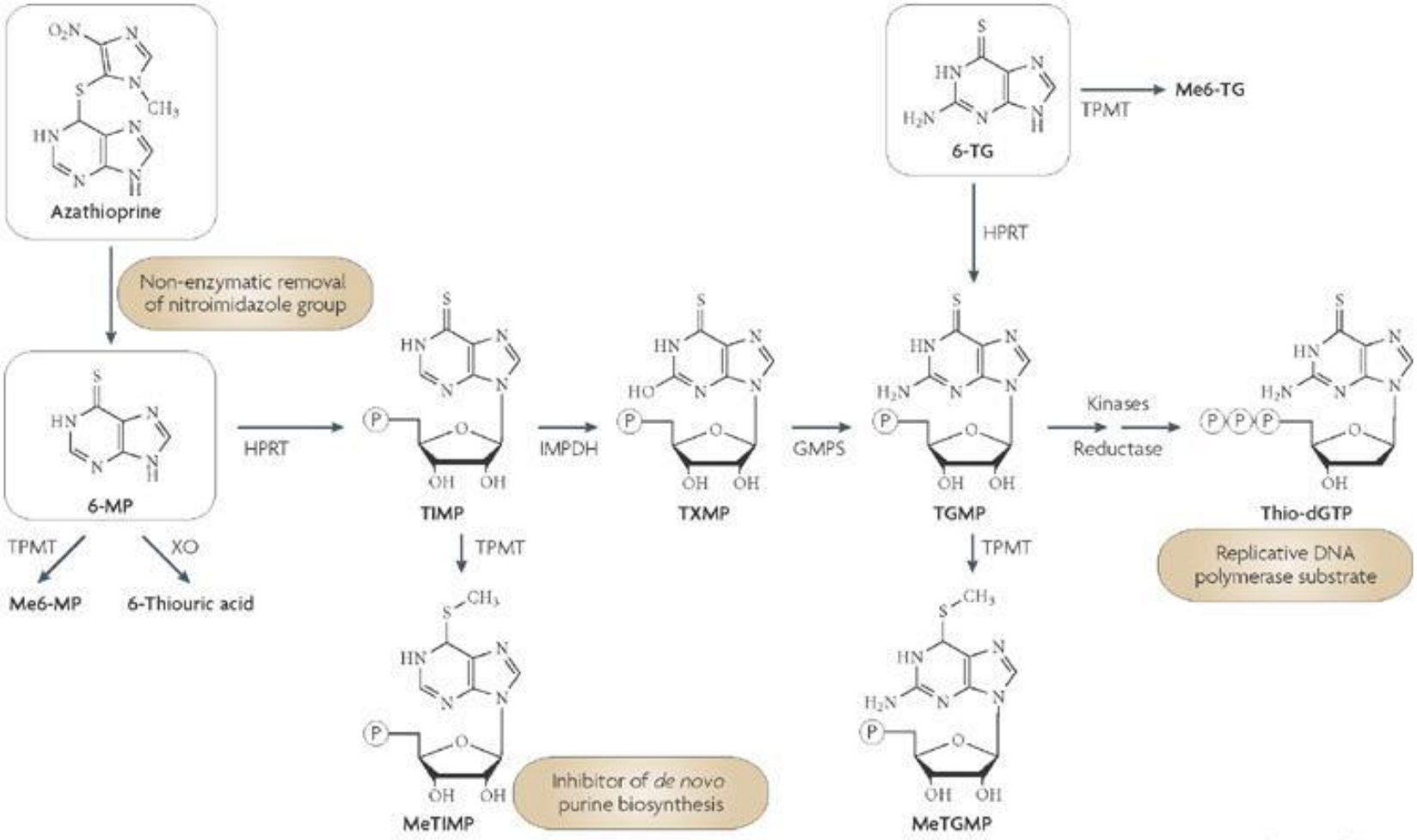
- ↑ DEI LIVELLI DI RIBONUCLEOTIDE REDUTTASI
- PRODUZIONE DI FORME ALTERATE DELL'ENZIMA

IMPIEGO DELLA IDROSSIUREA IN PATOLOGIE NON NEOPLASTICHE

- ANEMIA FALCIFORME
- INFEZIONE DA HIV
- TROMBOCITEMIA
- POLICITEMIA VERA

EFFETTI TOSSICI DEGLI ANALOGHI DELLA IDROSSIUREA

- MIELODEPRESSIONE
- EFFETTI GI E DERMATOLOGICI
- ↑ RISCHIO DI INSORGENZA DI LEUCEMIE SECONDARIE
- EFFETTO TERATOGENO


Azathioprine
Non-enzymatic removal of nitroimidazole group
6-MP
HPRT
TIMP
IMPDH
TXMP
GMPS
TGMP
Kinases
Reductase
Thio-dGTP
Replicative DNA polymerase substrate
TPMT
Me6-MP
XO
6-Thiouric acid
TPMT
MeTIMP
Inhibitor of de novo purine biosynthesis
6-TG
TPMT
Me6-TG
HPRT
TPMT
MeTGMP
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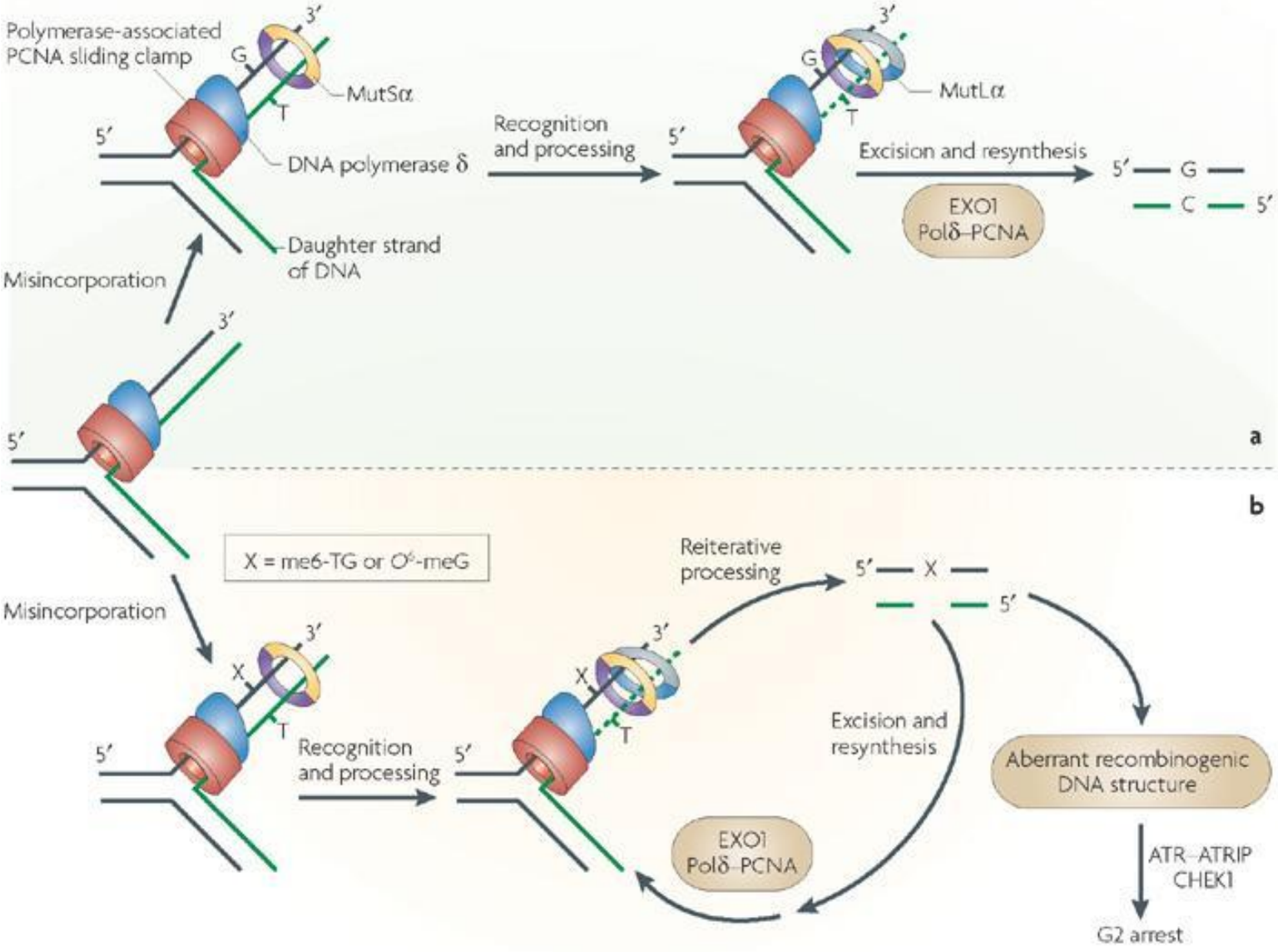
Polymerase-associated PCNA sliding clamp
3′
G
T
MutSα
5′
DNA polymerase δ
Daughter strand of DNA
Misincorporation
Recognition and processing
MutLα
Excision and resynthesis
EXO1
Polδ–PCNA
5′ G
C 5′
a
b
X = me6-TG or O⁶-meG
Misincorporation
X
Recognition and processing
Reiterative processing
5′ X
5′
Excision and resynthesis
Aberrant recombinogenic DNA structure
ATR–ATRIP
CHEK1
G2 arrest
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