Mécanismes d'action des médicaments anticancéreux et des traitements ciblés - Principes et stratégie du traitement des cancers

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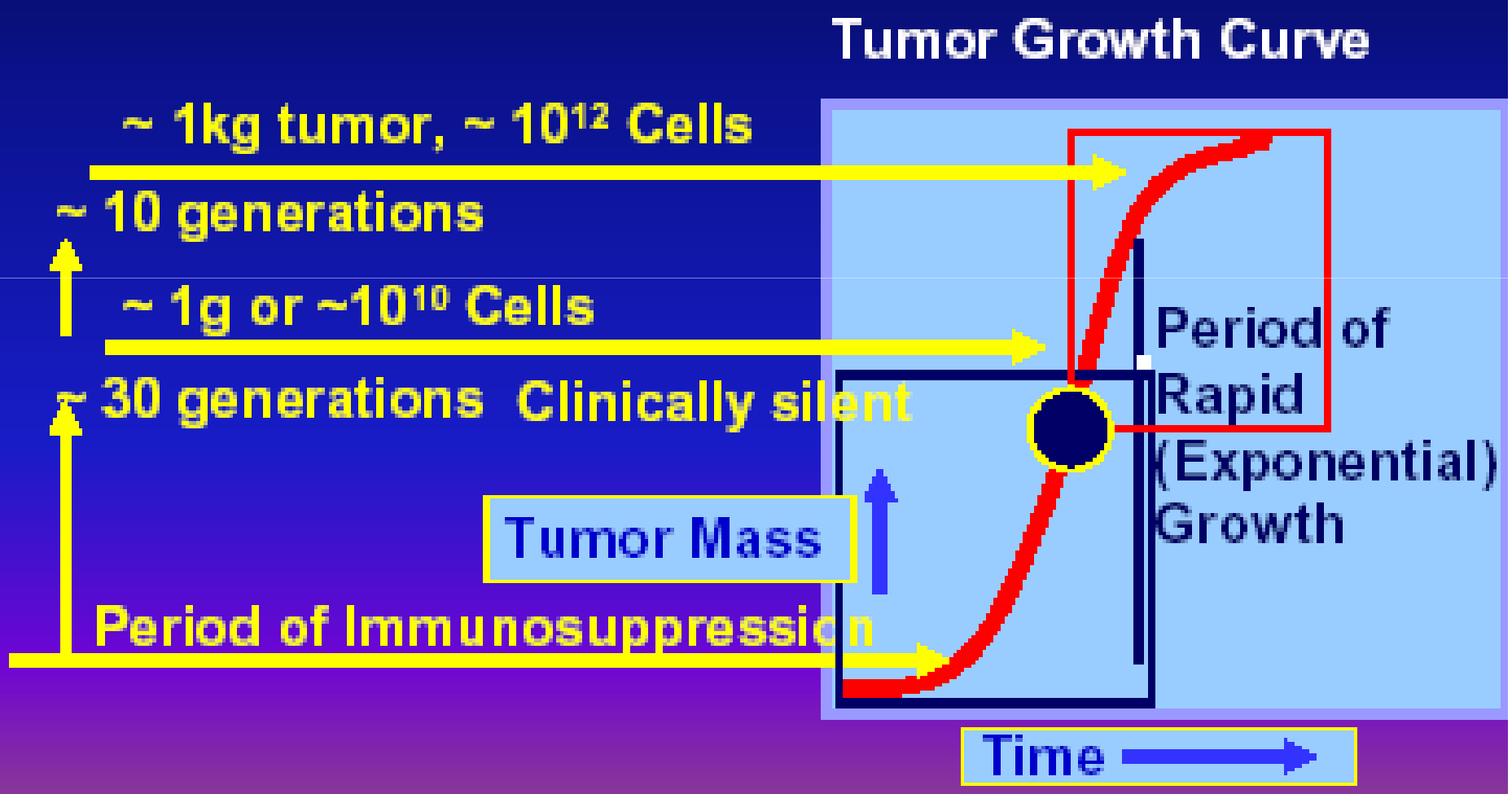
20 Octobre 2013

Cinétique de croissance tumorale:

- une fois détectable la tumeur croit rapidement



Principes et stratégie du traitement

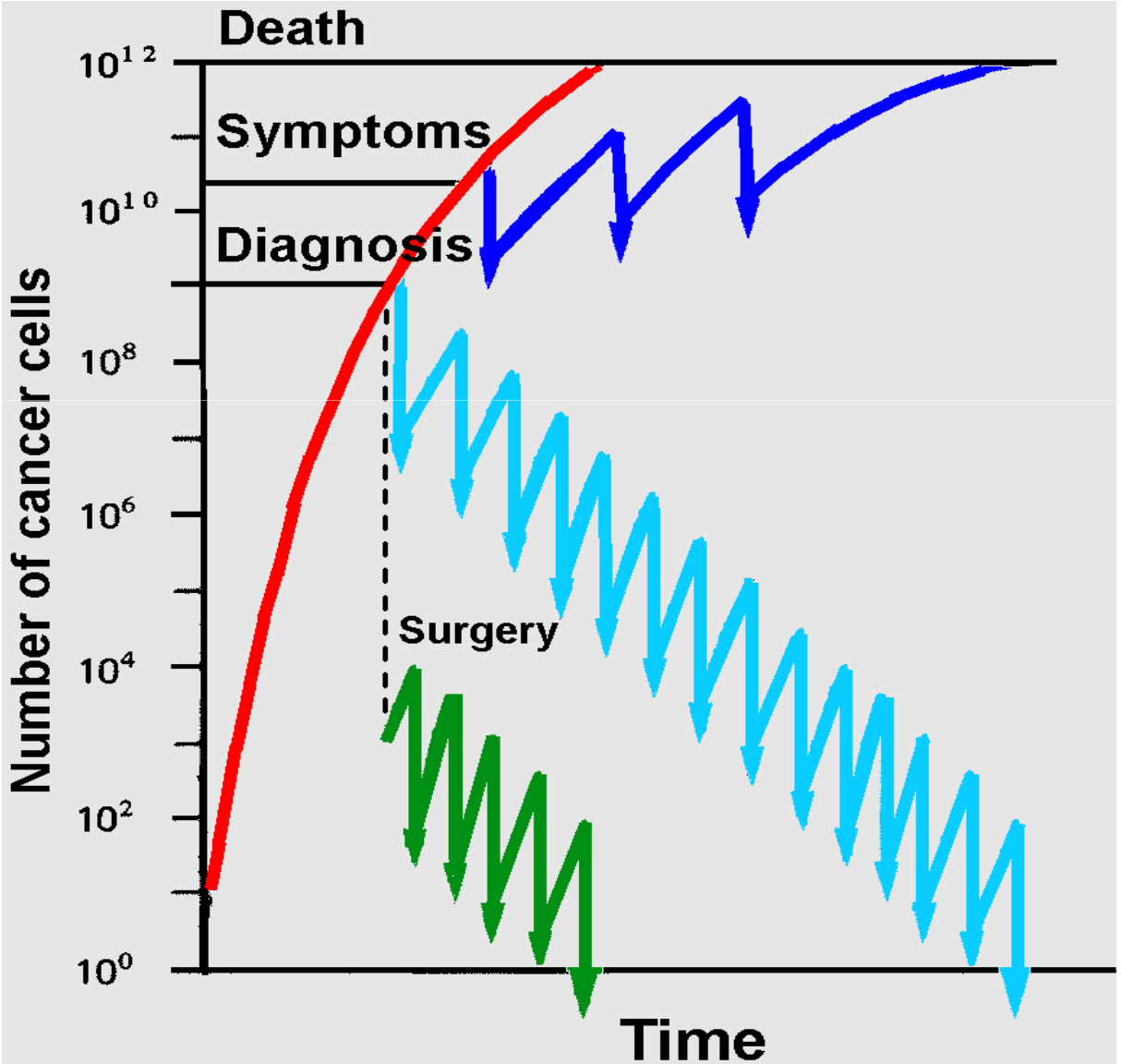
- **Enlever l'ensemble des cellules tumorales avant invasion**
- **Interférer avec la croissance tumorale:**
- **Induire la mort cellulaire par apoptose ou nécrose**
  - **En agissant à l'intérieur des cellules**
  - **En agissant à la surface des cellules**
  - **Par restauration de l'immunité antitumorale**
  - **En agissant sur le microenvironnement tumoral**

Principes

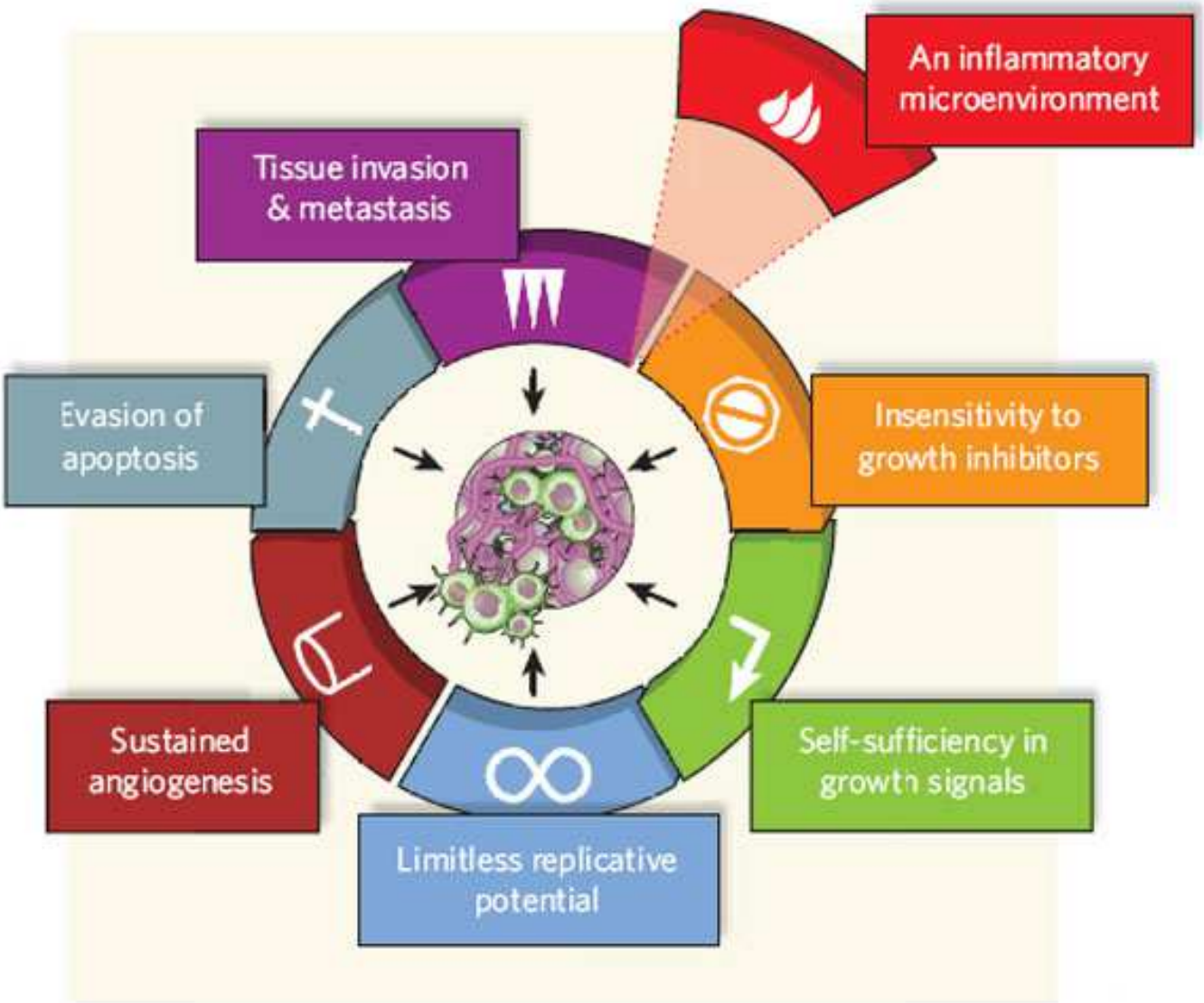
- **Associations thérapeutiques: locale, régionale et générale**
  - **Chirurgie**
  - **Radiothérapie**
  - **médicaments**
- **Combinaisons**
  - **Chimiothérapie classique**
  - **Traitements ciblés**

LOG kill hypothesis

- The example shows the effects of tumor burden, scheduling, initiation/duration of treatment on patient survival.
- The tumor burden in an untreated patient would progress along the path described by the RED LINE –
- The tumor is detected (using conventional techniques) when the tumor burden reaches 10^9 cells
- The patient is symptomatic at 10^{10}-10^{11} cells
- Dies at 10^{12} cells.



Complexité du ciblage thérapeutique des cancers



Addiction tumorale et instabilité génétique

- Démontrée dans certains cancers
  - Leucémies myéloides chroniques
  - Lymphome de Burkitt
- Addiction incomplète la plus fréquente
  - B raf et mélanome
  - C kit et GIST
- Instabilité génétique responsable de la résistance thérapeutique

Thérapeutique

- **Les buts des traitements anticancéreux:**
  - **curatifs (adjuvant, néoadjuvant, métastatique)**
  - **maintient de la qualité et de la durée de vie**
  - **soulagement des symptômes (traitement palliatif)**
  - **essais cliniques de nouveaux traitements**

  A discuter avec le patient et sa famille

Evaluation de la réponse thérapeutique individuelle

1. Réponse complète (CR): disparition complète de toutes les manifestations tumorales
2. Réponse partielle (PR) . Diminution >50% de la taille tumorale sans progression d'autre localisation
ni nouvelle tumeur
3. Maladie stable: pas d'augmentation de la masse tumorale ou diminution < 25%
4. Progression- Augmentation de la masse tumorale >25%, nouvelles lésions ou décès lié à la maladie

Efficacité globale du traitement dans des groupes de patients

- Durée de survie –semaines mois années
- Taux de réponse (% de CR+PR)
- Durée de réponse jusqu'à la progression
- Toxicités- grading du NCI
- Qualité de vie- requis par la FDA pour toutes les nouvelles molécules

Traitements médicamenteux

- **Chimiothérapie « classique »**
  - **Adjuvante**
  - **Neo-adjuvante**
  - **Palliative**
- **Problème de la résistance et de l'échappement tumoral**
- **Thérapie « ciblée »: cible l'addiction tumorale à une anomalie moléculaire**
- **Thérapie personnalisée: adaptée au développement tumoral et à la génétique constitutionnelle**

1945	Nitrogen mustard	
	Mercaptopurine	Premières rémissions complètes en hématologie
	Methotrexate	
1950	Busulfan	Rechutes et résistance
	Cyclophosphamide	
	Chlorambucil	
1960	5Fluoruracil	
	Vinblastin-Vincristin	
	Actinomycin D	Associations médicamenteuses
	L-PAM	
1970	AraC	Multi- drug- resistance (MDR)
	MOPP	Oncogenes- facteurs de croissance et récepteurs
	Bleomycin	Anticorps monoclonaux
1980	Doxorubicin	
	DTIC-CCNU	P glycoprotéine et efflux des médicaments
	Cis Platin	Antioncogènes
	VP16	
1990	Mitoxantrone	Cycle cellulaire et signalisation
		Facteurs de croissance hématopoiétiques (HuR)
	Taxol-Taxotere	Génétique des tumeurs familiales
2000	Oxaliplatine- G-CSF- Erythropoiétine	Ciblage thérapeutique
	Herceptin-Rituximab	
	Glivec	
	Gefitinib- crizotinib- Vemurafenib-anti	
	CTLA4-PD1- PDL1	

Dommages cellulaires provoqués par la chimithérapie cytotoxique

1- blocage de la synthèse des précurseurs de l'ADN

2- Interaction directe avec l'ADN

3- Inhibition de la synthèse de l'ADN

4- Interférence avec la transcription

5- Inhibition de la synthèse des protéines

6- L'effet global est la mort cellulaire par apopotose ou nécrose

Spécificités des traitements anticancéreux

- **Les cytotoxiques ne distinguent pas les cellules cancéreuses des cellules normales**

- **Les cellules cancéreuses sont plus fréquemment impliquées dans la multiplication cellulaire et sont plus sensibles aux effets toxiques des cytotoxiques**

- **La moelle osseuse, l'épithélium digestif et les follicules pileux sont les plus sensibles aux effets toxiques**

Mécanismes de Résistance aux anticancéreux

Mechanism	Drugs or Drug Groups
Change in sensitivity (or ↑ level) or ↓ binding affinity of target enzymes or receptors	**Etoposide, methotrexate, vinca alkaloids, estrogen & androgen receptors**
Decreased drug accumulation via ↑ expression of glycoprotein transporters, or ↓ permeability	**Methotrexate, alkylating agents, dactinomycin**
Formation of drug-inactivating enzymes	***Purine & pyrimidine antimetabolites***
Production of reactive chemicals that "trap" the anticancer drug	**Alkylators, bleomycin, cisplatin. doxorubicin**
Increased nucleic acid repair mechanisms	**Alkylating agents, cisplatin**
Reduced activation of pro-drugs	***Purine & pyrimidine antimetabolites***

Resistance aux médicaments

- Increased expression of MDR-1 gene for a cell surface P-glycoprotein
- MDR-1 gene is involved with drug efflux
- Drugs that reverse MDR : verapamil, quinidine, cyclosporine
- MDR increases resistance to natural drug products including the anthracyclines, *vinca* alkaloids, and epipodophyllotoxins

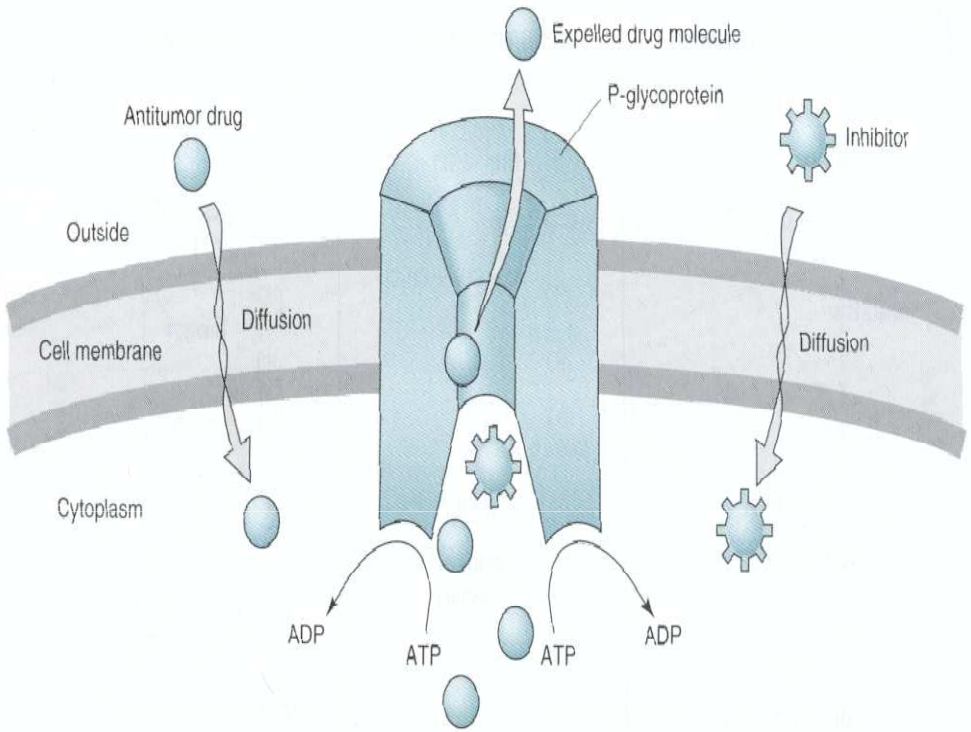


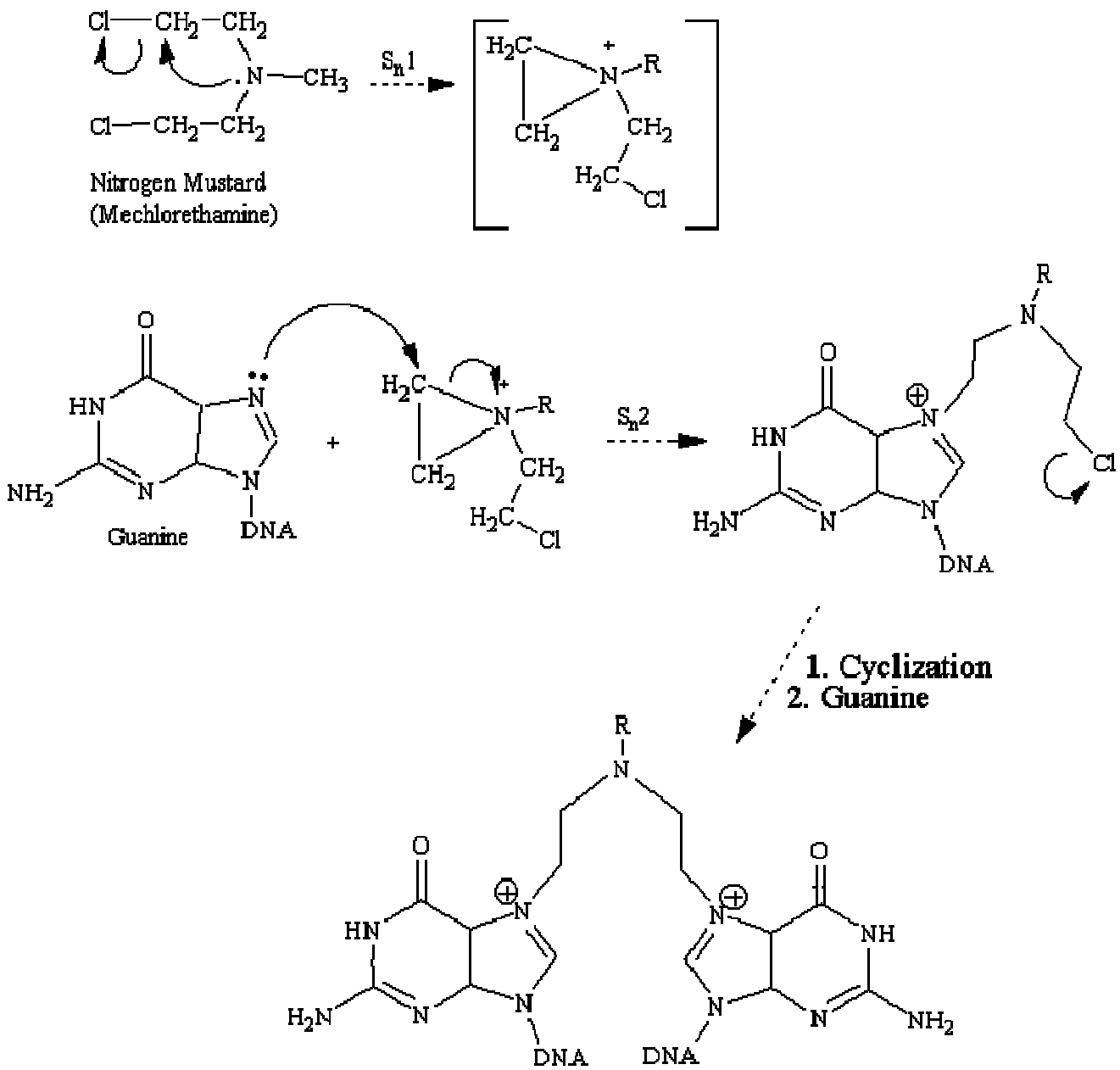
Figure 55–3. Schematic concept of the P-glycoprotein drug transport molecule responsible for multidrug resistance in cancer cells. ATP is used to drive the efflux process. The protein consists of 12 transmembrane domains with two ATP binding sites, only one of which must be occupied for drug transport to occur. Verapamil, quinidine, cyclosporine, and certain other drugs are able to inhibit transport at concentrations as low as 3 μmol/L, probably by acting as competitive substrates.

Les agents alkylants

-Sont responsables de la production d'ions très réactifs chargés positivement

- Ces ions forment des liaisons covalentes avec des régions electrophiles sur des molécules biologiques (Nucléotides, protéines AA)

- La liaison de ces alkylants fonctionnels au DNA est la cause de la mort (mutagenese, apoptose)


Nitrogen Mustard
(Mechlorethamine)
Sn1
Guanine
DNA
Sn2
1. Cyclization
2. Guanine

Agents alkylants

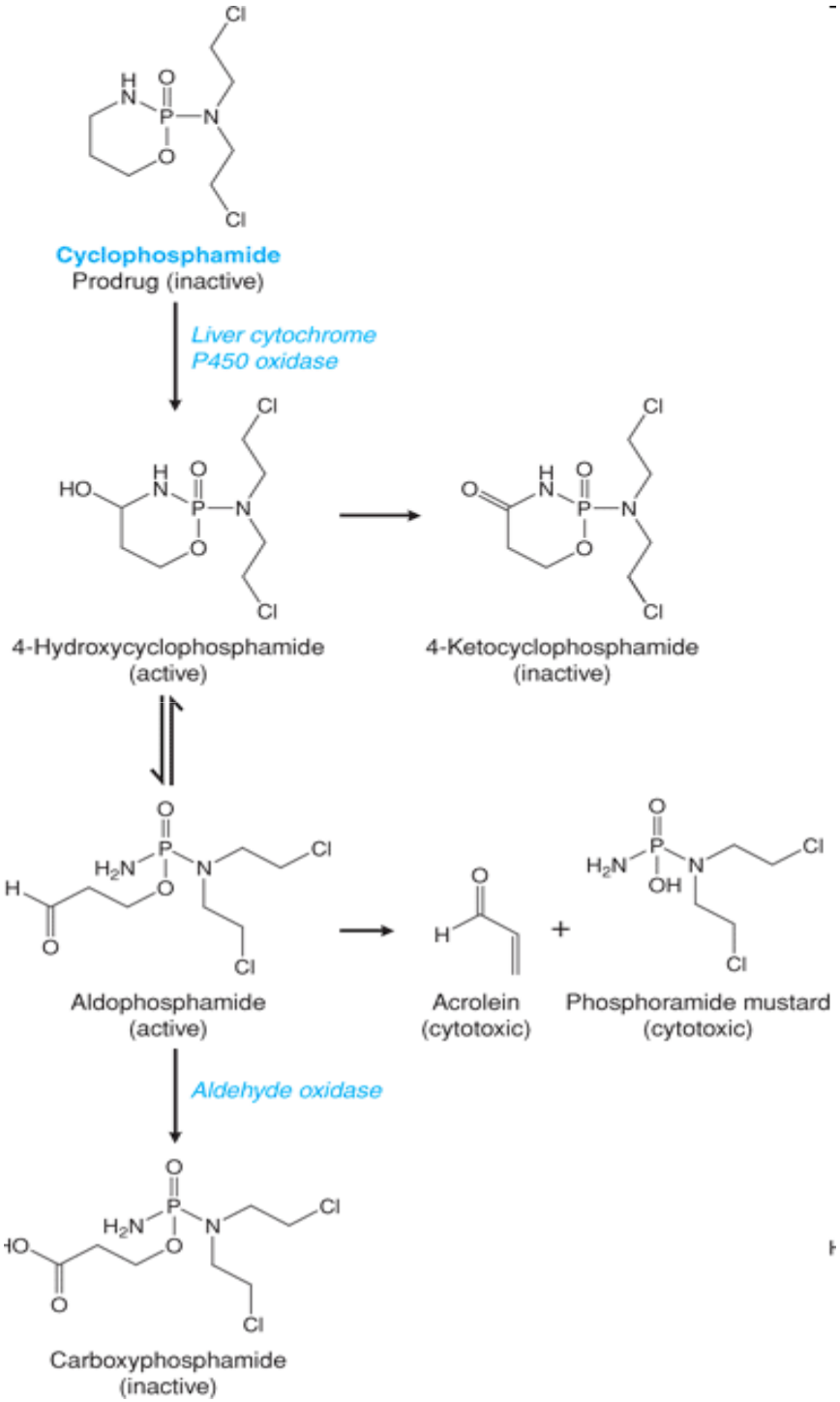
- **Cyclophosphamide**
- **Cisplatine**
- **Procarbazine**
- **Busulfan**
- **Mechlorethamine**

Utilisation clinique

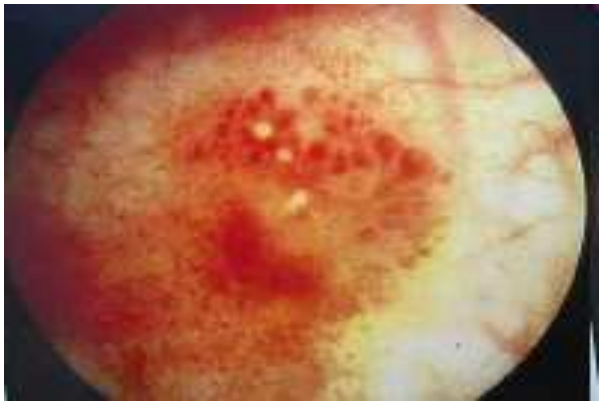
- **Lymphomes Non-Hodgkiniens**
- **Cancers du sein**
- **Cancers de l’ovaire**
- **Neuroblastome**

Toxicités associées aux alkylants

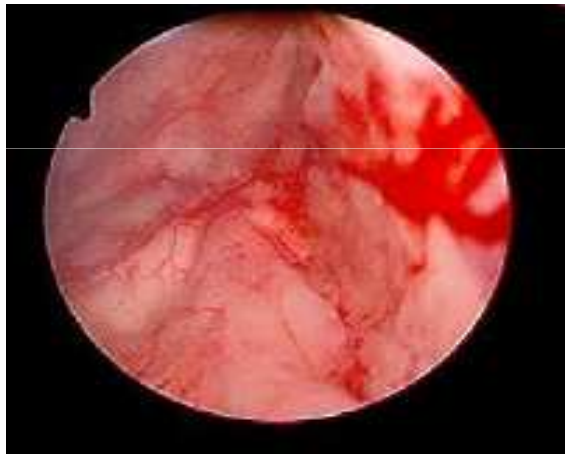
Nausées vomissements
Myélosuppression
Alopécie
Stérilité infertilité
Second cancer; leucémie secondaire
Cystite hémorragique
Neurotox
Nephrotox
Déficit immunitaire
SIADH


Cyclophosphamide
Prodrug (inactive)
Liver cytochrome
P450 oxidase
4-Hydroxycyclophosphamide
(active)
4-Ketocyclophosphamide
(inactive)
Aldophosphamide
(active)
Acrolein
(cytotoxic)
Phosphoramide mustard
(cytotoxic)
Aldehyde oxidase
Carboxyphosphamide
(inactive)

Effets secondaires



- Acroleine
- Cystite hémorragique
  - Hematurie- douleurs
  - Cyctoscopie
- Prévenue et traitée par MESNA (mercaptoethanesulfonate)
- Rarement responsible de SIADH et



Tox pulmonaire

Autres alkylants

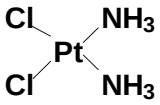
- Méchlorétamine: Hodgkin- très vésicant-instable
- Ifosfamide: plus actif, cancer testiculaire, poumon, lymphome, sarcome- neurotoxicité
- Chlorambucil- LLC- myelotox- tox pulmonaire
- Procarbazine MA: Voie orale, maladie de Hodgkin
- Nitrosourées: carmustine- lymphomes-tumeurs cérébrales, toxicité médullaire

source
http://www.extravasation.org.uk/CEG.htm

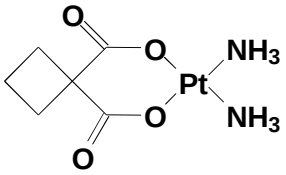
Cisplatine

- **Dérivé du Platine**
- **Même MA que le ciclophosphamide**
- ****Cancer du testicule**
- **Utilisé aussi pour les Ca de la vessie, poumon, ovaire ORL**
- **Carboplatine a un profil de sécurité meilleur mais pas les meme indications**
- **Effets secondaires**
  - **Nephrotoxicité- prévention**
  - **Ototoxicité**
  - **Névrite périphérique**
  - **Nausées et vomissements sévères**
  - **Toxicité médullaire**

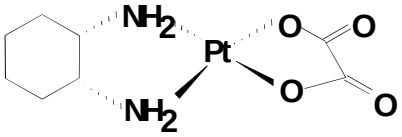
Strategies pour améliorer les thérapeutiques



CISPLATINE



CARBOPLATINE

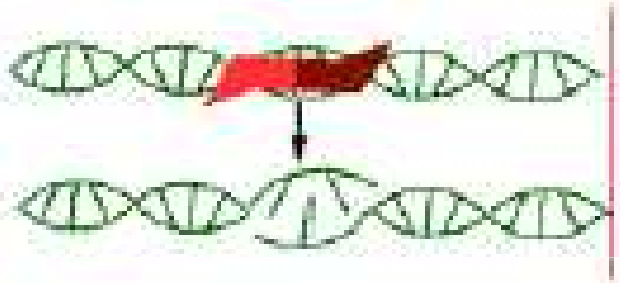


Oxalato 1,2-trans-L-diaminocyclohexane platinium (OXALIPLATINE®)

Cibles et toxicité- mécanismes d'action- différents

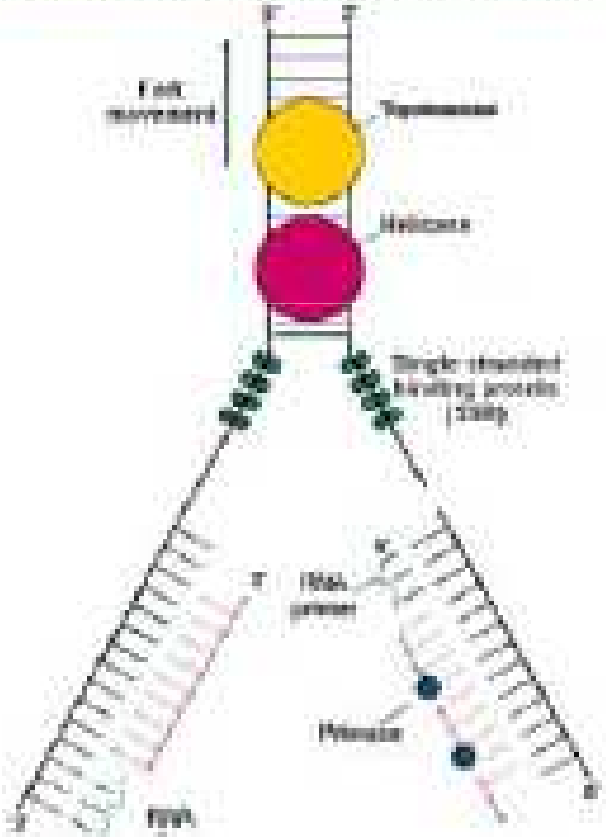
Anthracyclines

1) Anthracyclines act as intercalators by sliding their planar ring structure perpendicularly between the nucleotide pairs of the DNA helix.



2) Anthracyclines complex with nuclear enzymes helicases that dissociate duplex DNA into single strands.

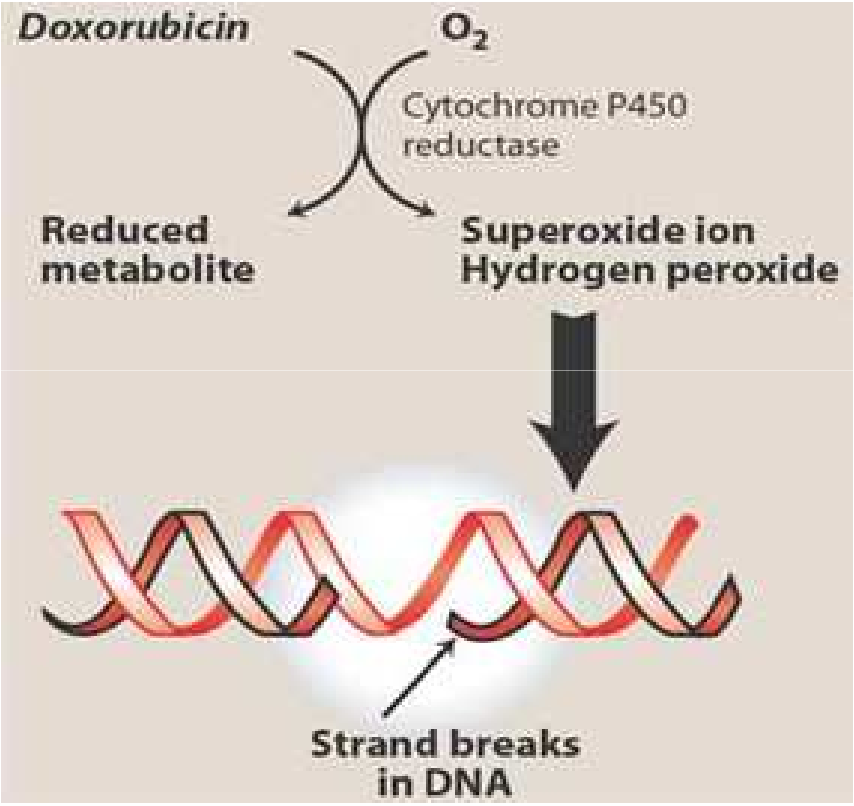
3) Anthracyclines form complex with topoisomerase II



Antibiotiques Anticancer

- Anthracyclines:
  - Doxorubicine (Adriamycin)
  - 4’épi- adriamycine
  - Daunorubicine
- Bleomycine
- Dactinomycine

Doxorubicin & Daunorubicin



- These drugs intercalate between base pairs, inhibit topoisomerase II and also generate free radicals
- They block RNA and DNA synthesis and cause strand scission
- *These are CCNS drugs
- Used as a component in ABVD regimen in Hodgkin's lymphoma

Evènements indésirables

- **Toxicité cardiaque- cardiomyopathie dilatée- tox cumulative**
- **Toxicité médullaire**
- **Alopécie**
- **Rappel radiothérapie**
- **Mucite**
- **Nausées vomissements**
- **Alopécie**
- **Causticité**

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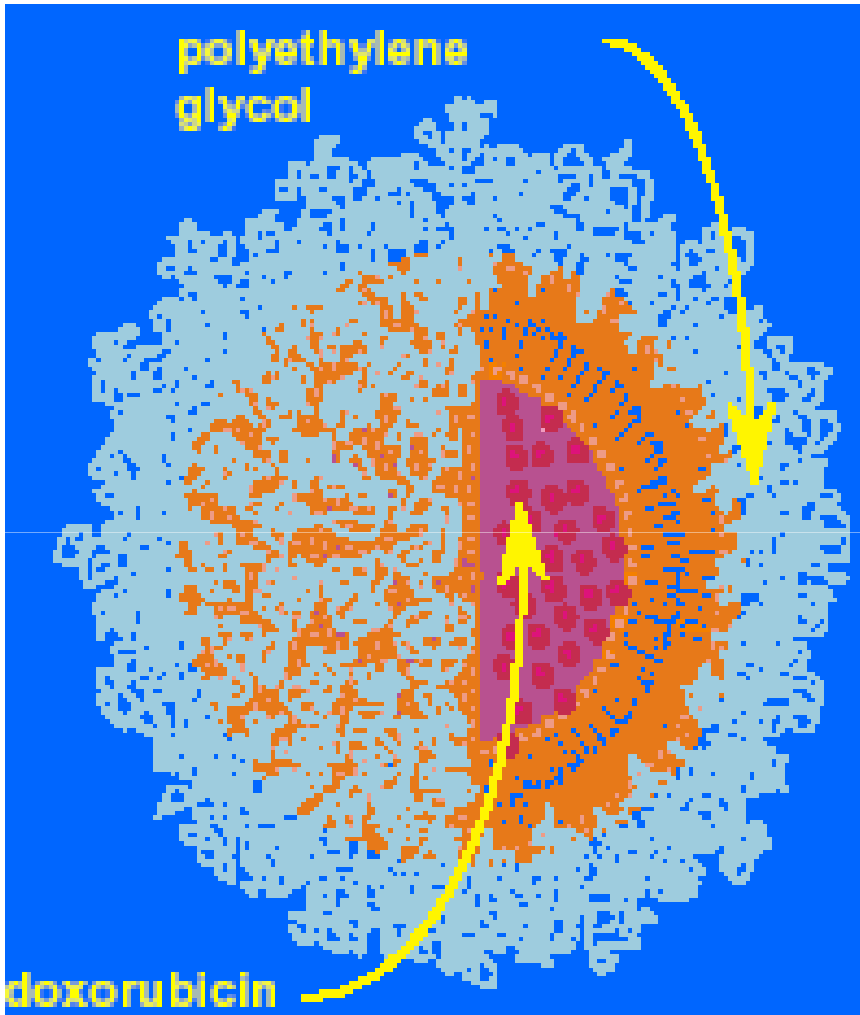


Structure of Doxil® (Caelyx®)

- surface-grafted PEG
- evades MPS cells, long-circulating
- drug stays in liposome and accumulates in solid tumors via 'passive targeting'
- released drug kills tumor cells

Antimetabolites

Les antimétabolites sont des analogues structuraux de substances biologiquement impliquées dans la fonction cellulaire

Ils vont interférer avec la synthèse des acides nucléiques en s'incorporant frauduleusement

ou

En inhibant de manière spécifique des enzymes critiques de la synthèse des acides nucléiques

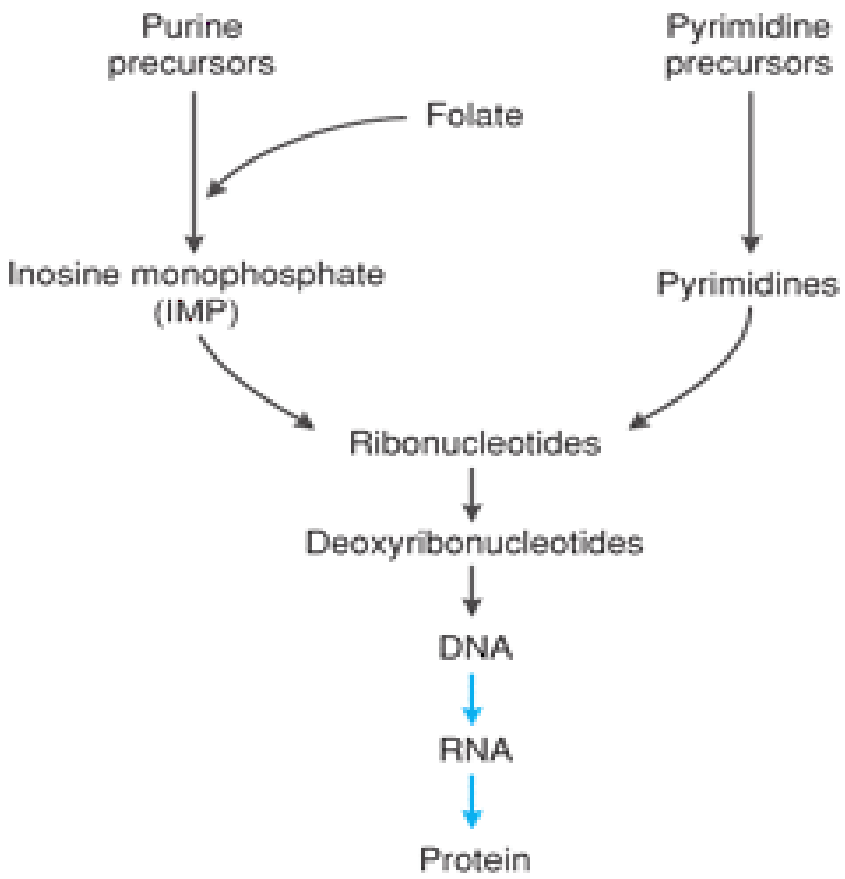
Ils sont cycle spécifique – Phase S

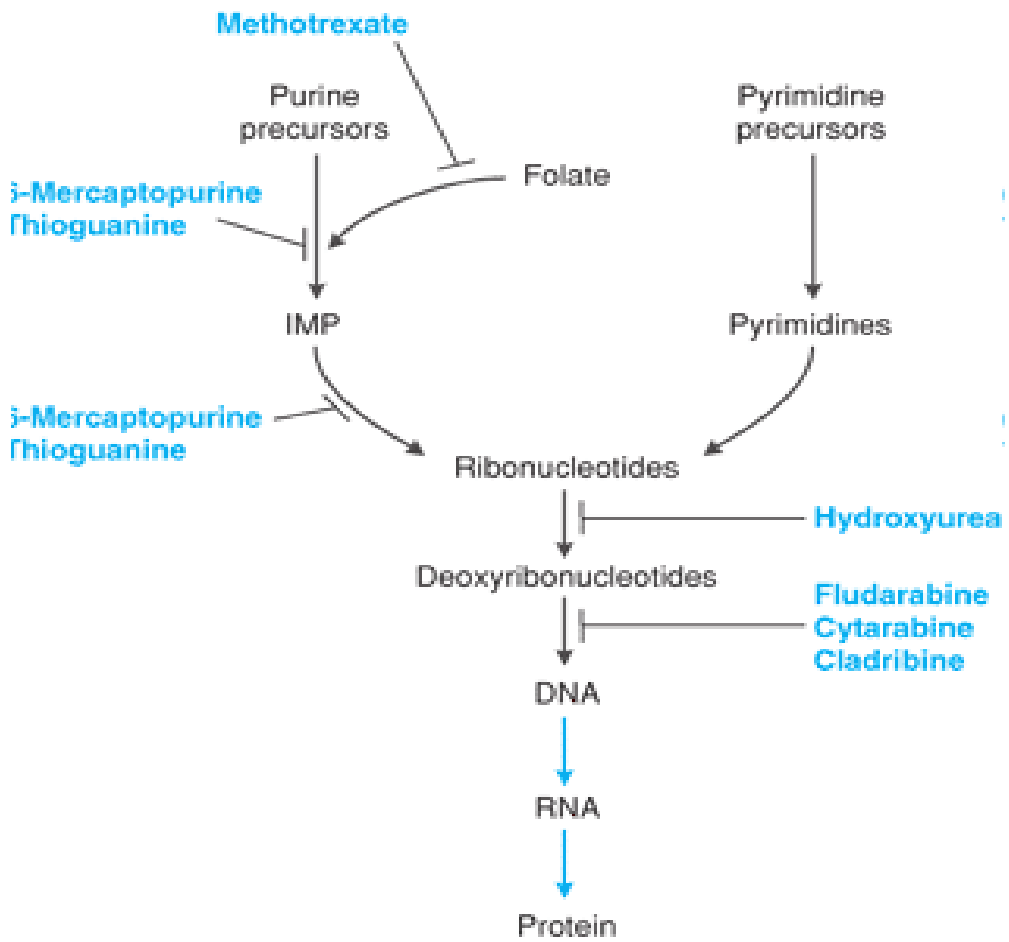
Legend
Drug Class
Sub-class
Prototype Drug

Antimetabolites

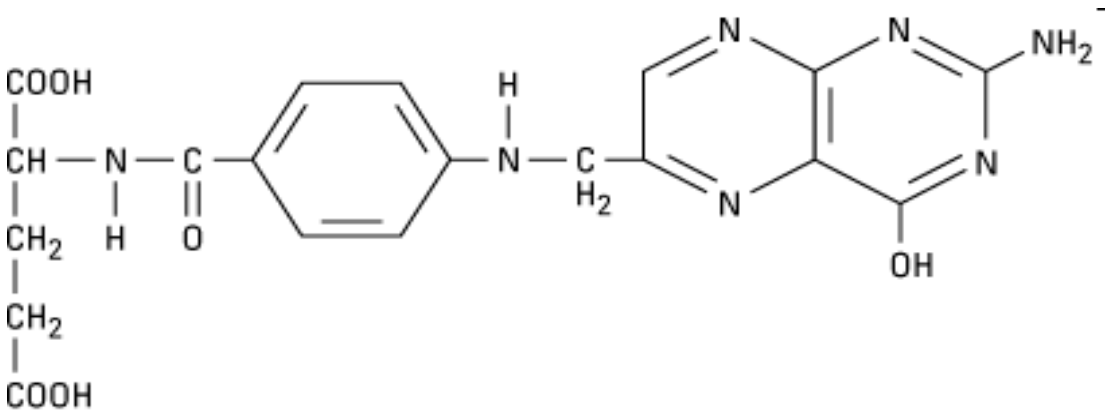
- **Folic Acid Analogs**
  - Methotrexate
  - Trimetrexate
  - Pemetrexed
- **Purine Analogs**
  - Mercaptoguanine
  - **Thioguanine**
  - **Fludarabine Phosphate**
  - **Cladribine**
- **Pyrimidine Analogs**
  - Fluorouracil
  - **Cytarabine**
  - **Gemcitabine**
  - **Capecitabine**

Antimetabolits: sites of drug action

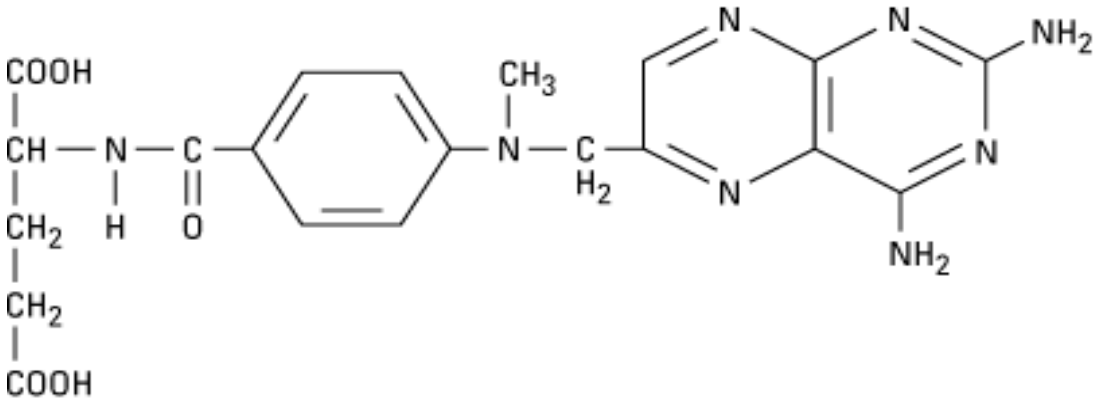




Methotrexate



Folic acid



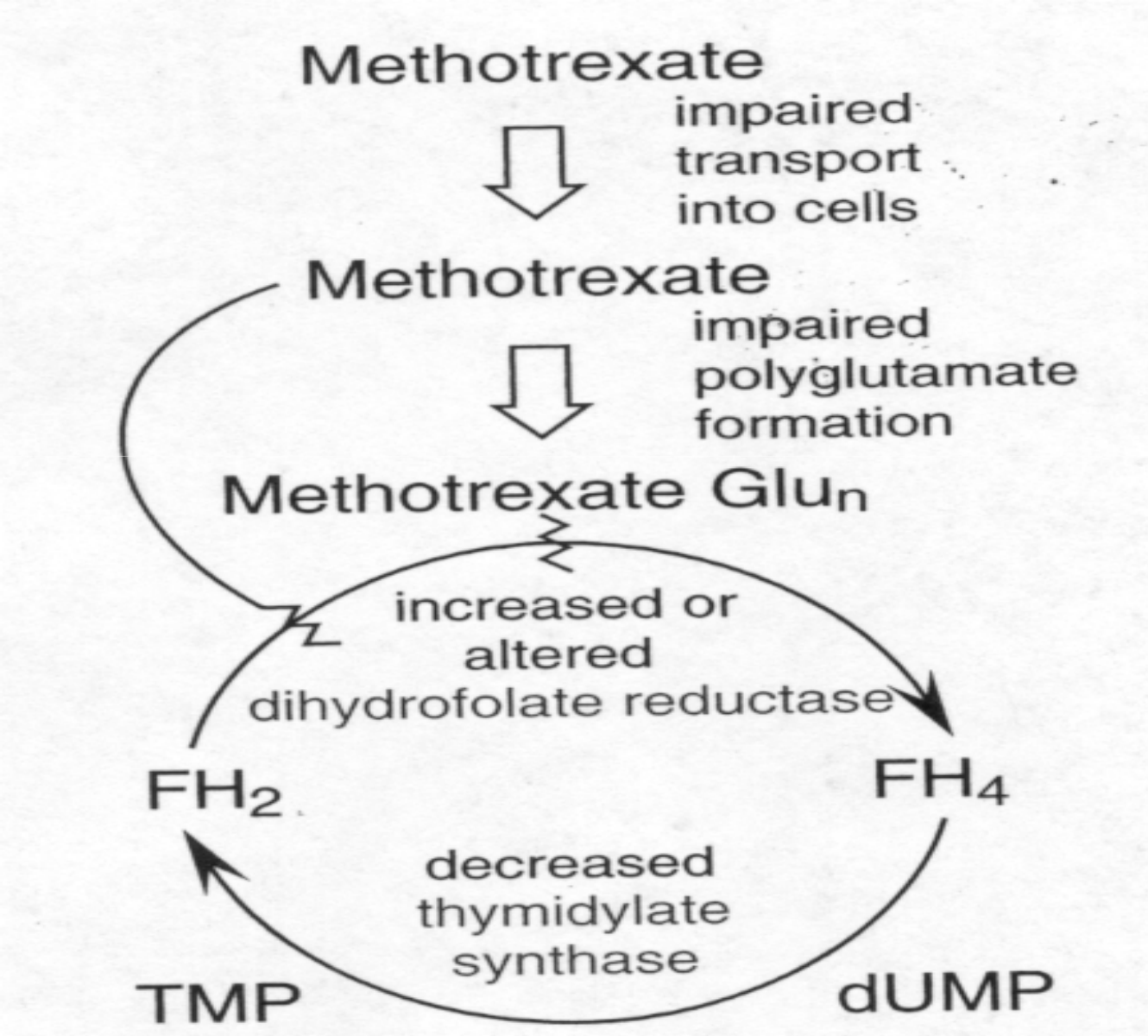
Methotrexate

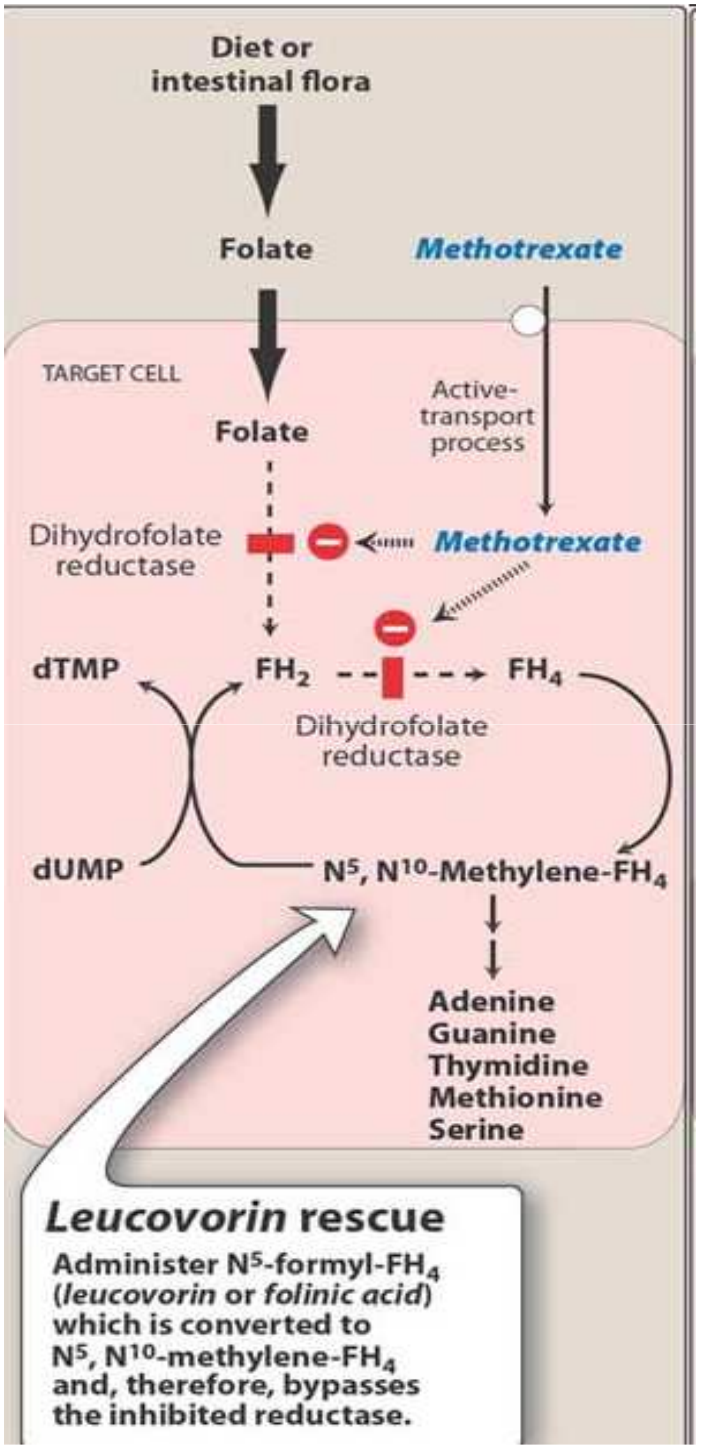
Methotrexate (MTX)

- MTX is a folic acid analog that binds with high affinity to the active catalytic site of dihydrofolate reductase (DHFR)
- Thus it interferes with the synthesis of tetrahydrofolate (THF)
- THF serves as the key one-carbon carrier for enzymatic processes involved in de novo synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine.
- Inhibition of these various metabolic processes thereby interferes with the formation of DNA, RNA, and key cellular proteins.

Mechanism of Resistance

1. Decreased drug transport
2. Altered DHFR
3. Decreased polyglutamate formation
4. Increased levels of DHFR





Leucovorin Rescue

Mechanism of action of methotrexate and the effect of administration of leucovorin.

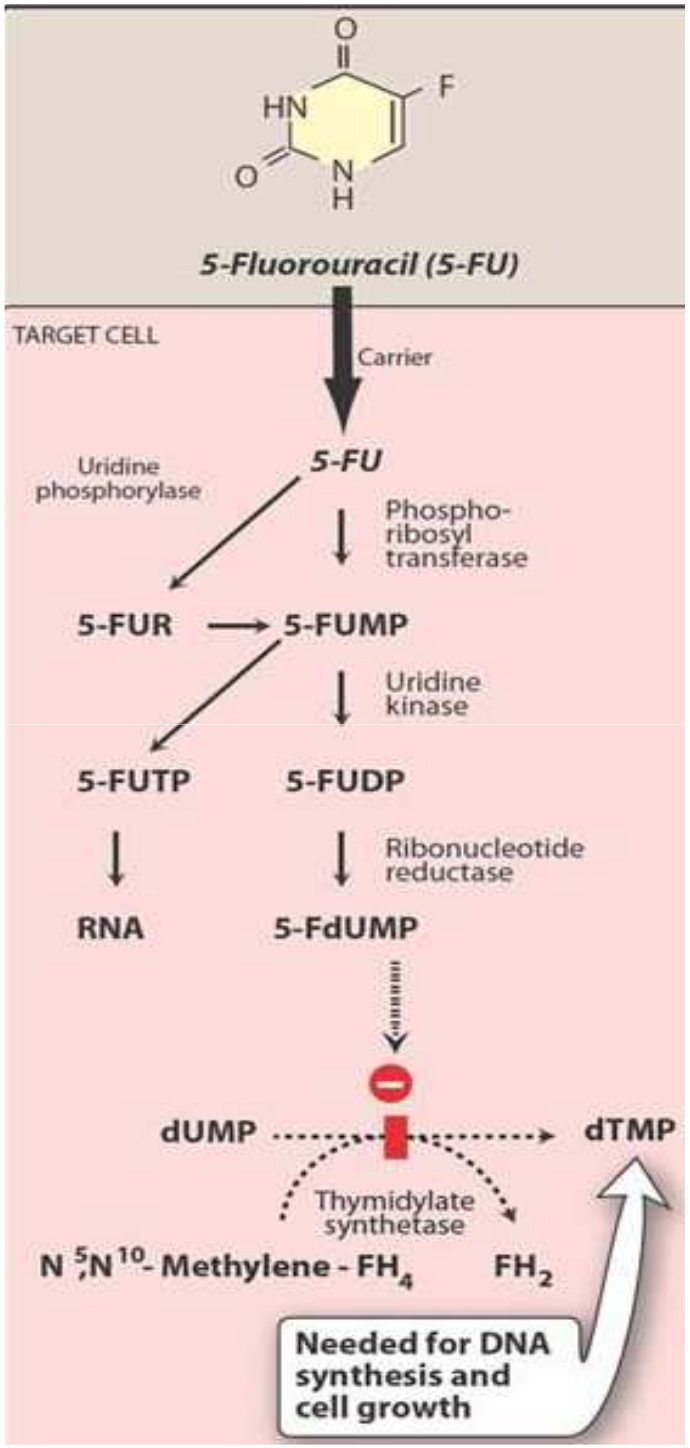
- FH2 = dihydrofolate
- FH4 = tetrahydrofolate
- dTMP = deoxythymidine monophosphate
- dUMP = deoxyuridine mono phosphate.

Effets secondaires

- **Toxicité médullaire**
- **Mucite**
- **Anémie par carence en folates**
- **Antidote: acide folinique (rescue-dose dépendant)**

Cytarabine (Ara-C)

- Cytarabine arabinoside is a pyrimidine antimetabolite
- The drug is activated by kinases to AraCTP
  - This acts as an inhibitor of DNA polymerase
- ***of all antimetabolites, this is the most specific for S phase of tumor cell cycle
- It is an important component in acute lukemia regimens
- ADR: at high doses cause neurotoxicity (cerebellar dysfunction and peripheral neuritis)
  - Hand-foot syndrome***



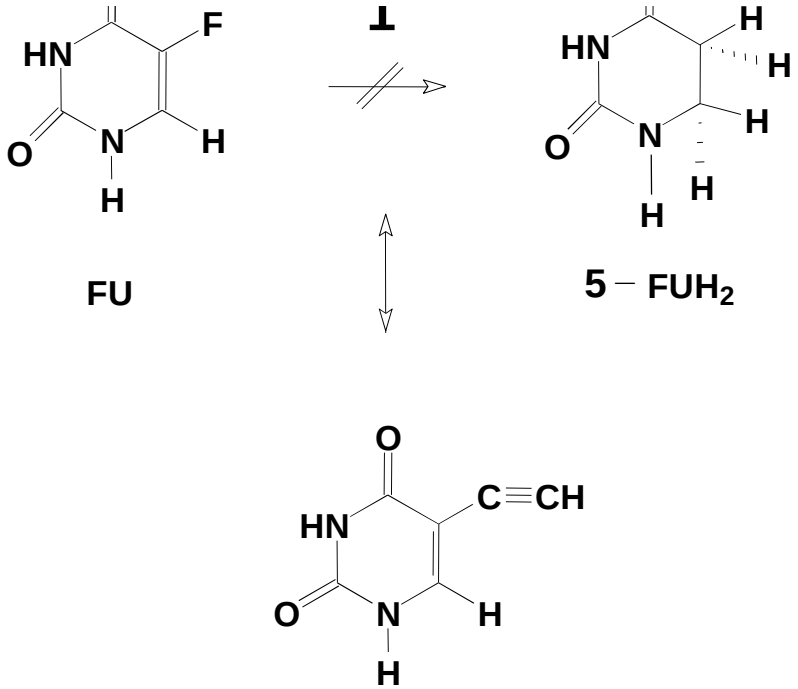
5-FU

Mechanism of the cytotoxic action of 5-FU

- 5-FU is converted to 5-FdUMP, which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase.
- 5-FU = 5-fluorouracil
- 5-FUR = 5-fluorouridine
- 5-FUMP = 5-fluorouridine monophosphate
- 5-FUDP = 5-fluorouridine diphosphate
- 5-FUTP = 5-fluorouridine triphosphate
- dUMP = deoxyuridine monophosphate
- dTMP = deoxythymidine monophosphate
- 5-FdUMP = 5-fluorodeoxyuridine monophosphate.

Stratégies pour améliorer les thérapeutiques

A



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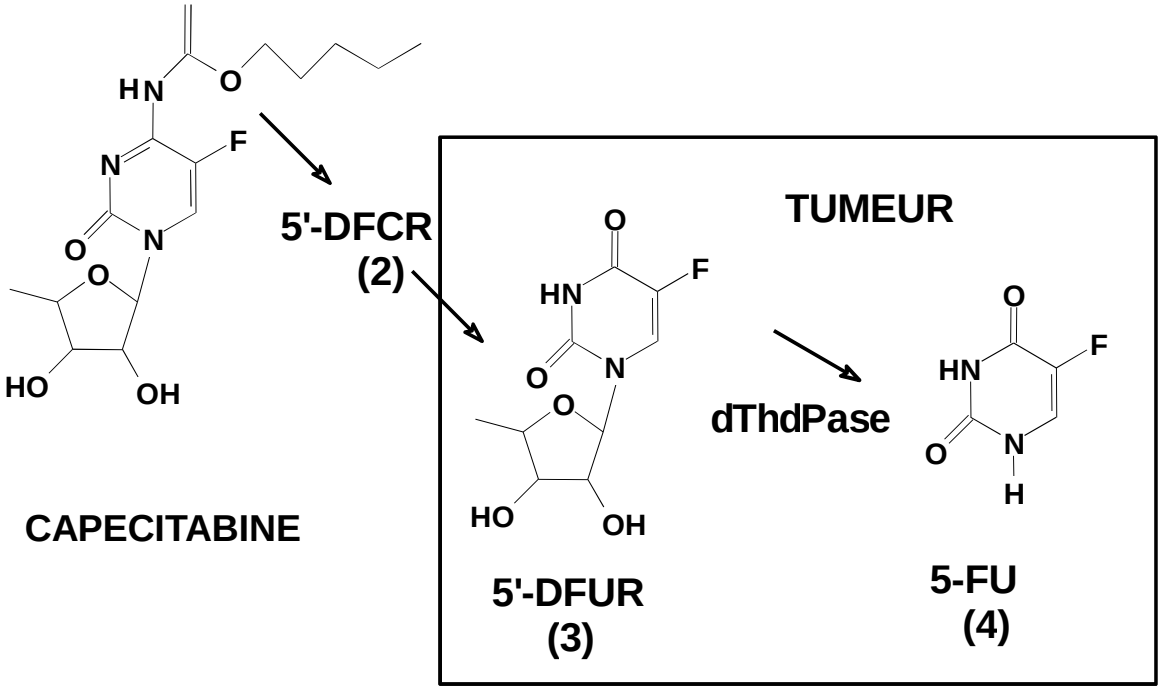
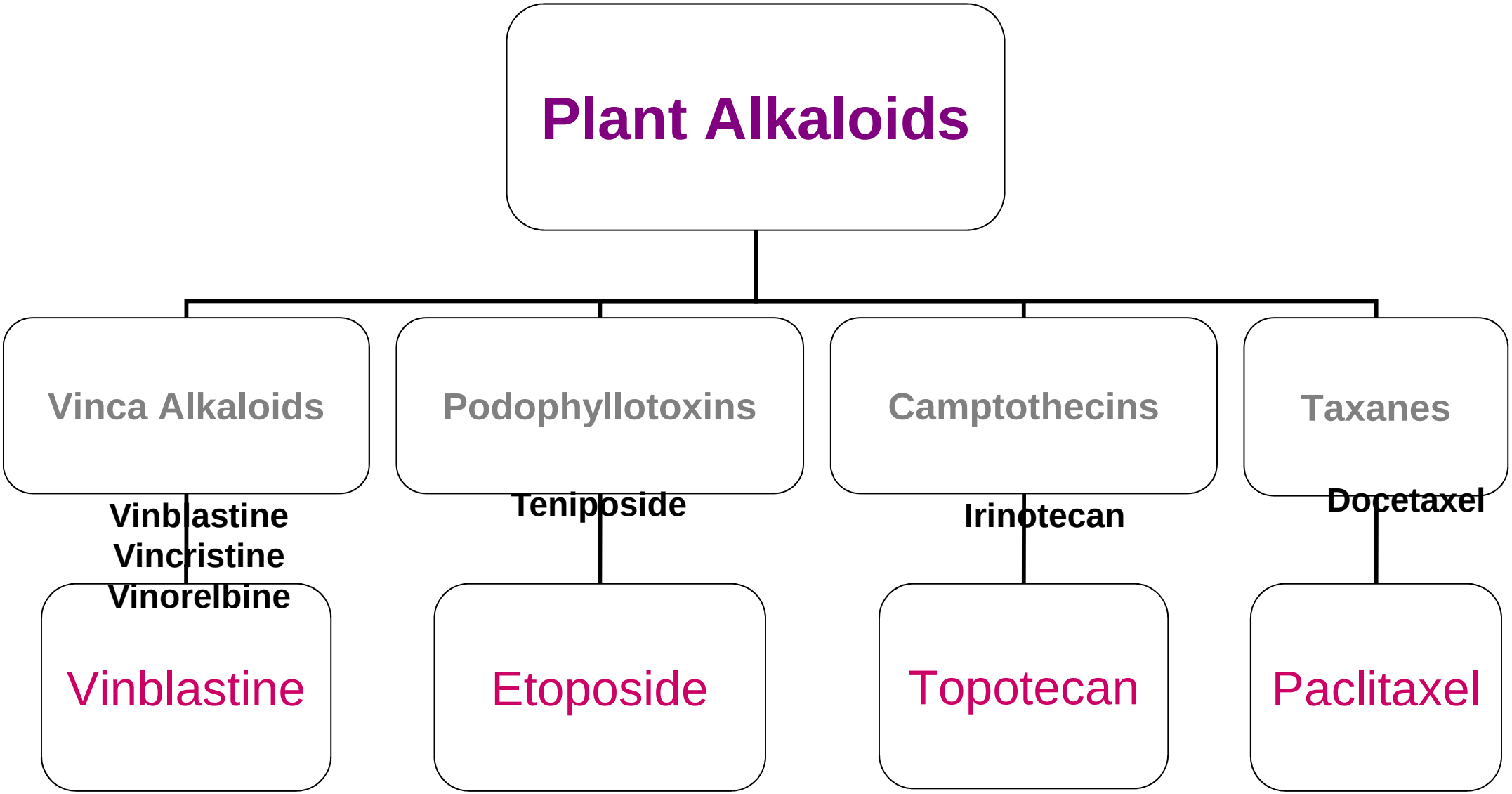
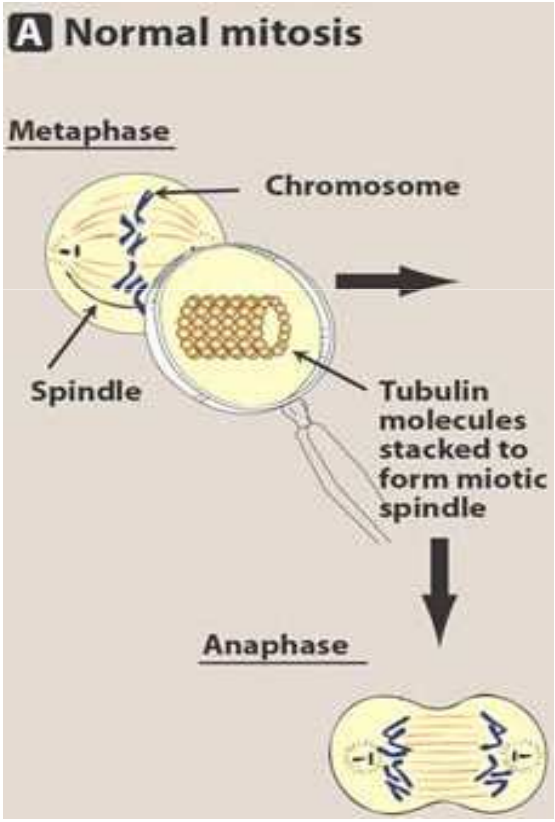


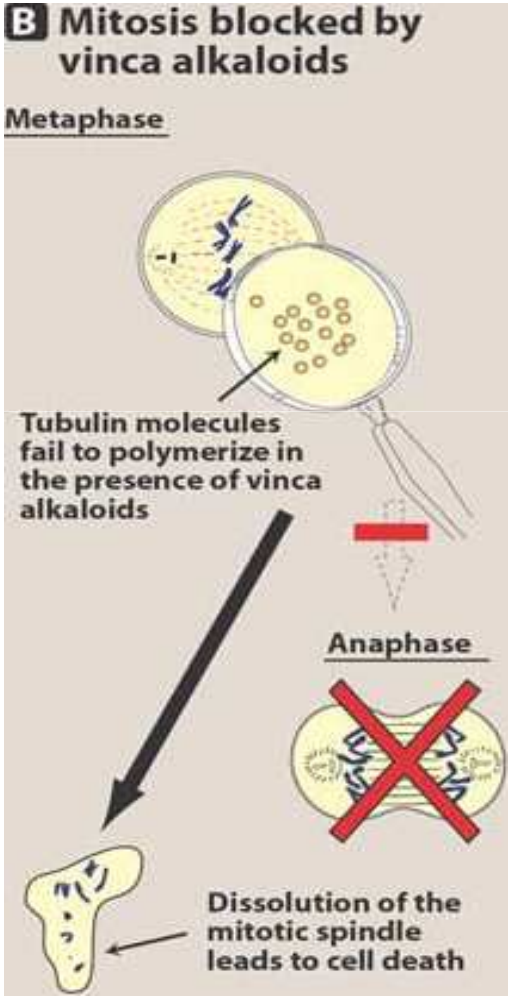
Nombreux médicaments adaptés à la forme orale:
Taxanes, Vinorelbine, Inhibiteurs de TOPO-1…

le pari
Jeudi 16 decembre 2004
Hôtel Hilton
Arc de triomphe
AMGEN

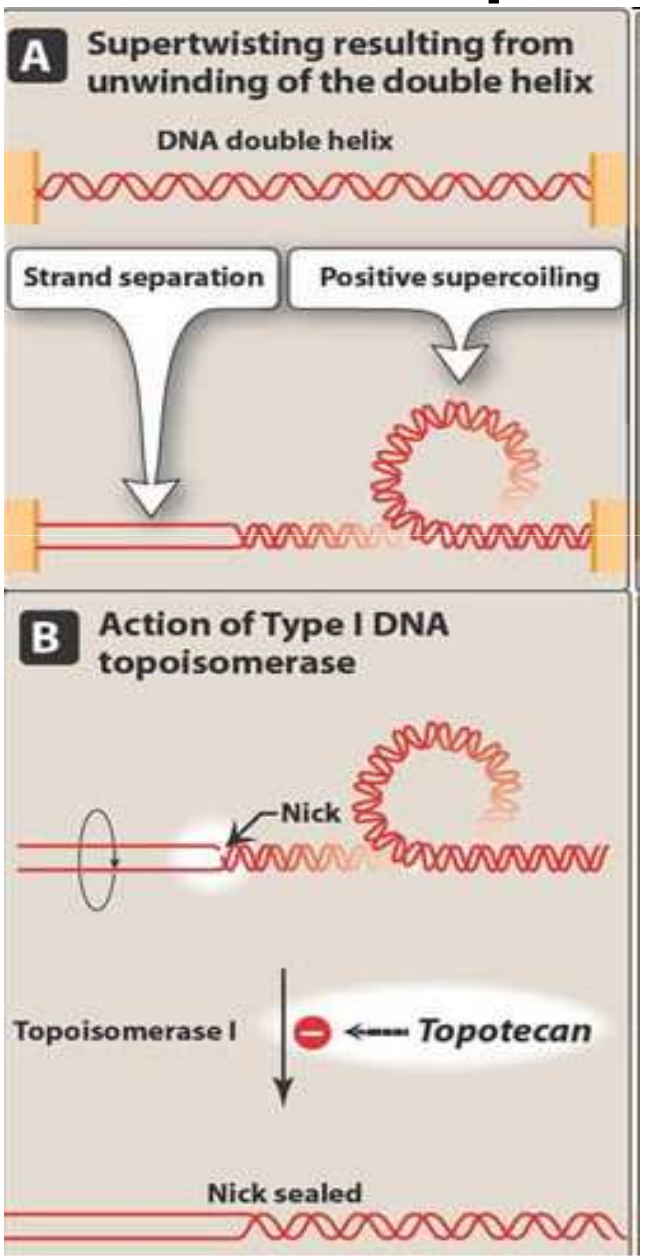

Plant Alkaloids
Vinca Alkaloids
Podophyllotoxins
Camptothecins
Taxanes
Vinblastine
Vincristine
Vinorelbine
Teniposide
Irinotecan
Docetaxel
Vinblastine
Etoposide
Topotecan
Paclitaxel

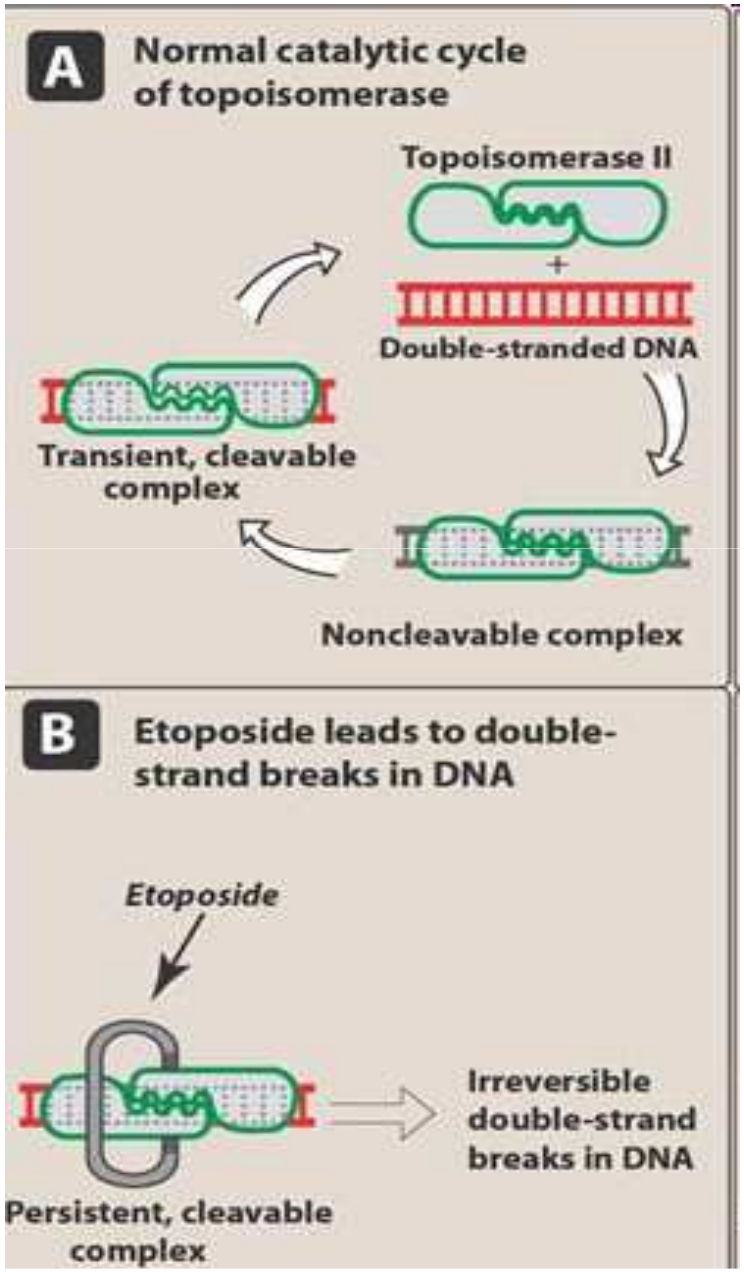
Alcaloides de la Vinca(Vinblastine, vincristine)





Topoisomerase inhibitors



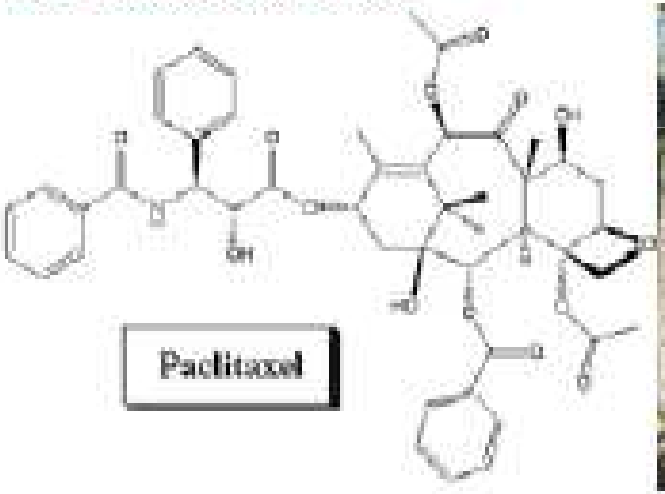


Taxanes

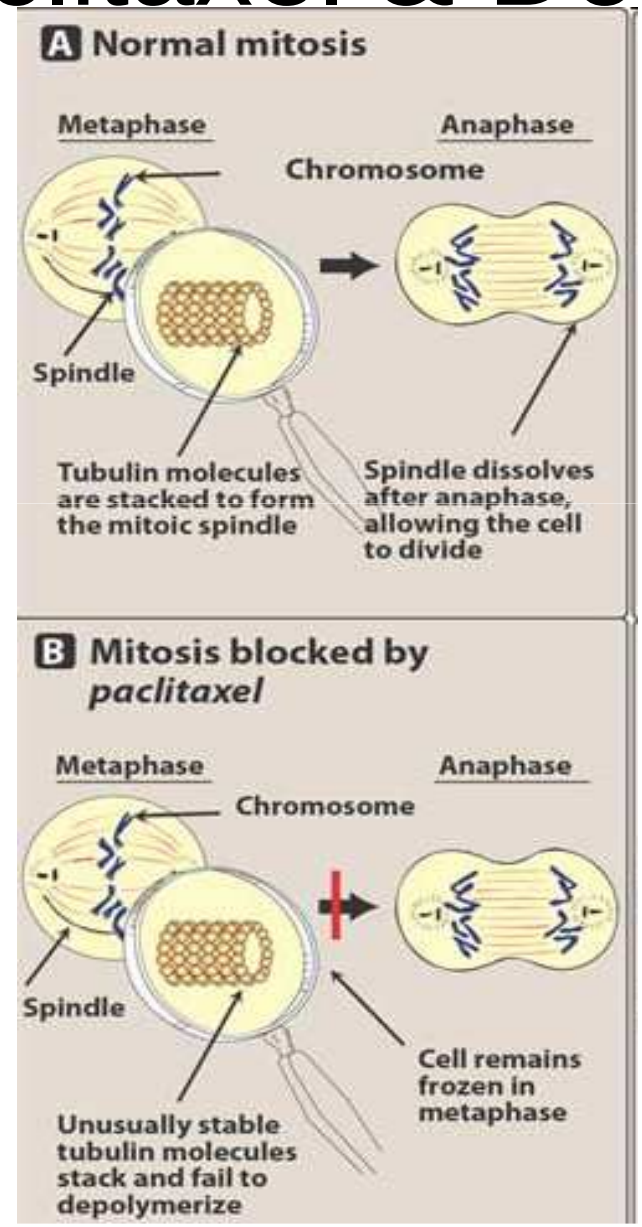
Paclitaxel (Taxol)

-Derived from bark of Pacific yew (*Taxus brevifolia*) or semisynthetically derived from *T. baccata*

The taxane & oxetane ring and the ester side chain are necessary for the cytotoxic effect

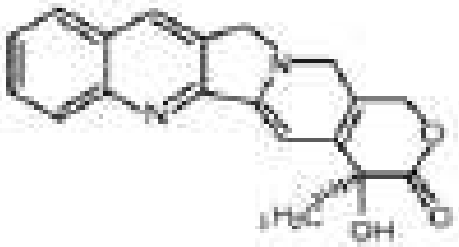


Paclitaxel & Docetaxel



Camptothecin
Topotecan (Hycamtin) and Irinotecan(Camptosar)

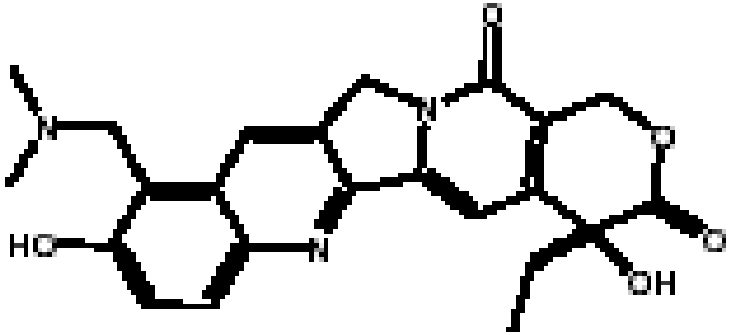
Camptotheca acuminata



Camptothecin

Inhibits topoisimerase I preventing resealing of the single strand breaks. This occurs in the S phase.

Topotecan



Topotecan

- Used in the treatment of small cell lung cancer and metastatic ovarian cancer who have failed first line treatment

- After administration, the lactone moiety hydrolyses to hydroxy-acid form (physiological pH)

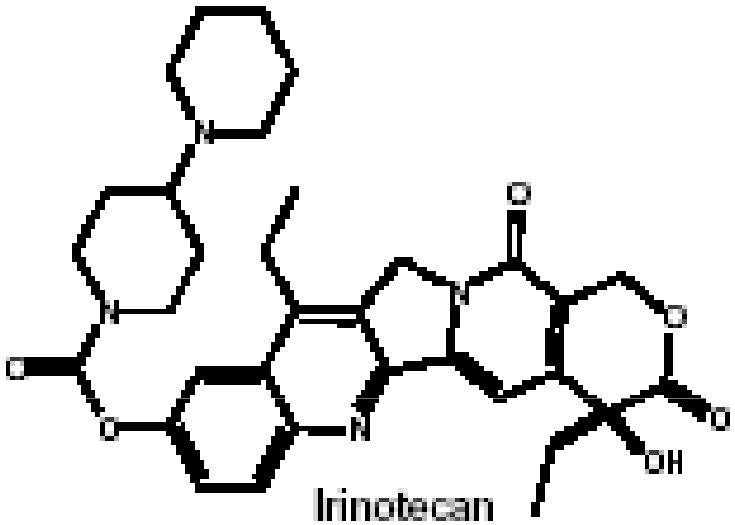
- Myelosuppression is the dose-limiting toxicity

Irinotecan

- Used to treat metastatic carcinoma of colon and rectum refractory to 5-fluoro uracil

- After administration, it is converted to an active metabolite (SN-38 in the liver)

- SN-38 undergoes conjugation to form inactive glucuronide



- Irinotecan half-life 6 hours and SN-38 is 10 hours

- Severe diarrhea is the dose-limiting toxicity, dehydration + electrolyte imbalance)

Problèmes généraux avec les anticancéreux

- Ils sont pour l’essentiel antiprolifératifs et endommagent l’ADN et initient l’apoptose
- Ils agissent préférentiellement sur les cellules qui prolifèrent rapidement
- Cela est responsable de toxicités sévères
- Ils ont en commun de nombreuses toxicités

Effets secondaires des anticancéreux chez les humains

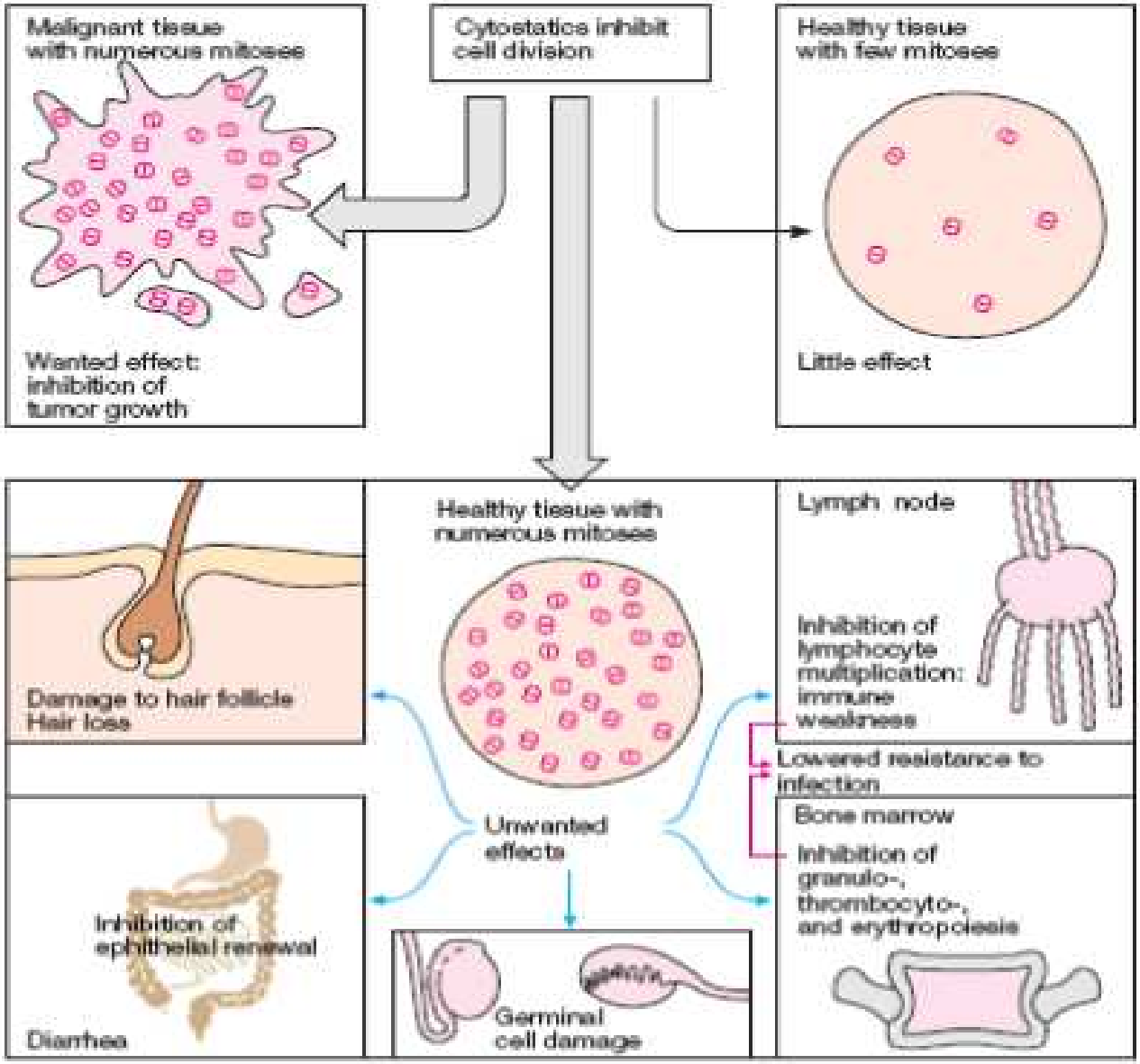
Tissue	Undesirable Effects
Bone marrow	Leukopenia and resulting infections
	Immunosuppression
	Thrombocytopenia
	Anemia
GI tract	Oral or intestinal ulceration
	Diarrhea
Hair follicles	Alopecia
Gonads	Menstrual irregularities, including premature menarche; impaired spermatogenesis
Wounds	Impaired healing
Fetus	Teratogenesis (especially during first trimester)

Toxicités spécifiques de médicaments

Toxicité	médicament
Renale	Cisplatine,* methotrexate
Hepatique	6-MP, busulfan, cyclophosphamide
Pulmonaire	Bleomycine,* busulfan, procarbazine
Cardiaque	Doxorubicine, daunorubicine
Neurologique	Vincristine,* cisplatine, paclitaxel
Immunosuppression	Cyclophosphamide, cytarabine, dactinomycine, methotrexate
Autres	Cyclophosphamide (cystite); procarbazine (leucémie); asparaginase* (pancreatite)

Chemotherapeutic agents are much more toxic to tissues that have a high growth fraction than to tissues that have a low growth fraction.

- Proliferating cells are especially sensitive to chemotherapy because cytotoxic drugs usually act by disrupting DNA synthesis or mitosis, cellular activities that only proliferating cells carry out.
- Unfortunately, toxicity to the anticancer agents is to any rapidly dividing cells. (e.g. bone marrow, hair follicles, sperm forming cells).



Agents hormonaux

- **Glucocorticoides**
- **Antagonistes des hormones sexuelles**
- **Analogues de la GnRH**
- **Inhibiteurs de l’Aromatase**

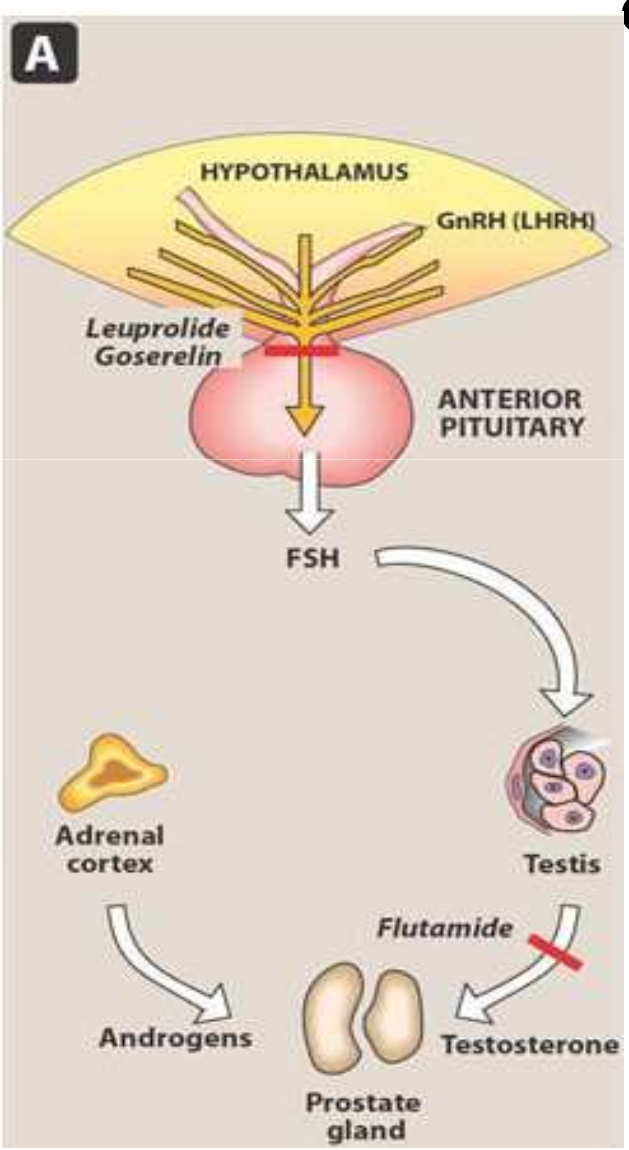
Tamoxifene

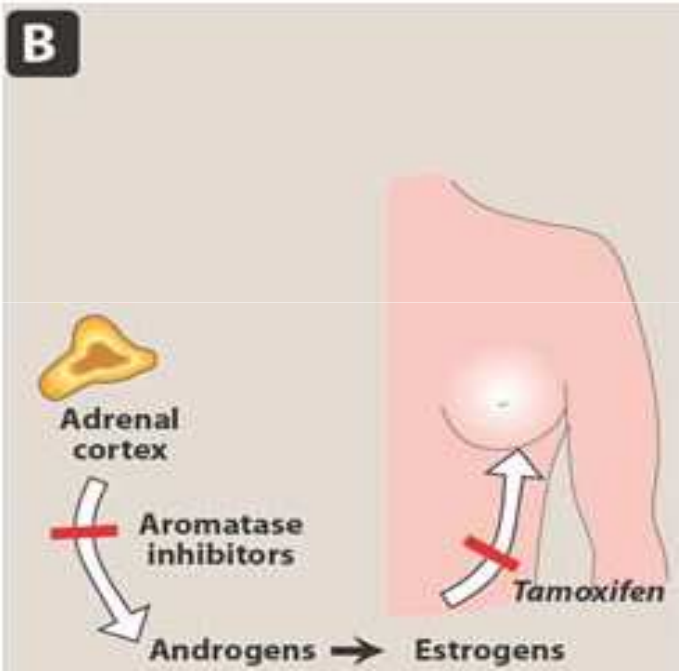
- Bloque la liaison des estrogènes au récepteurdans les tissus cibles (sein)

EI:

- Cancer de l’endomètre, flushes, thrombose veineuse

Mécanisme d'action des antihormones





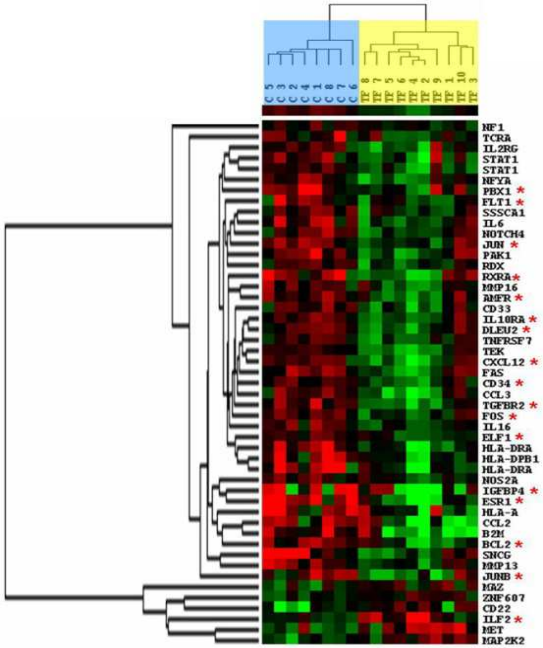
Les thérapies ciblées dans les Cancers

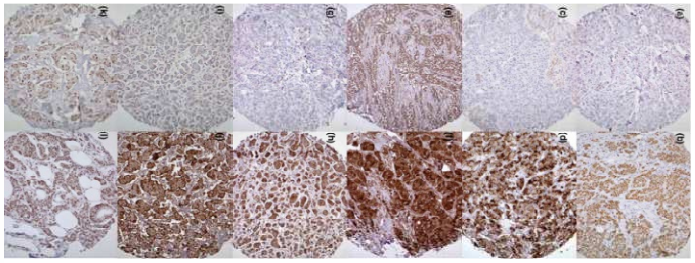
Qu’est ce qui est ciblé?

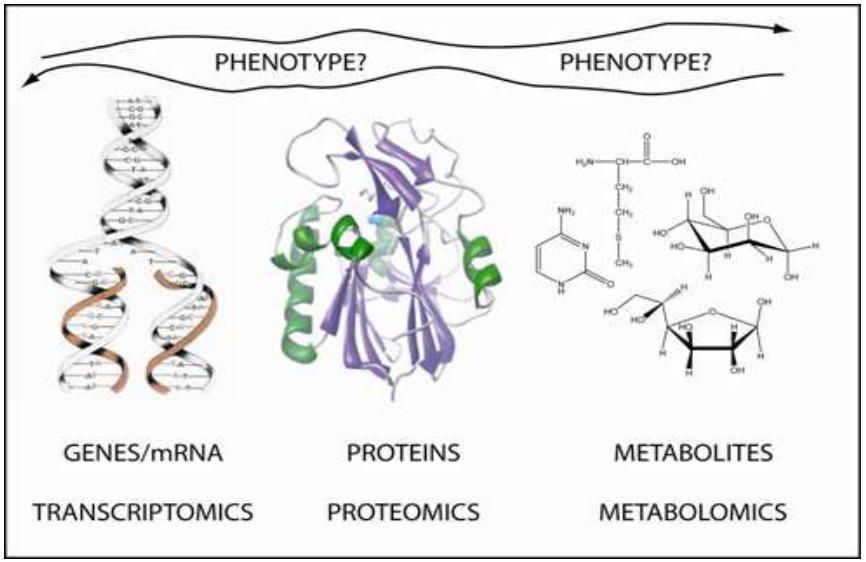
- Une caractéristique spécifique de la pathologie
  - dans le tissu pathologique
  - Dans son environnement

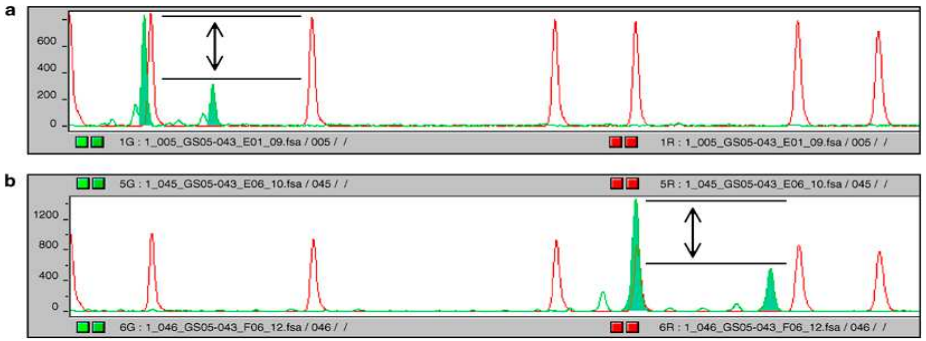
- Un sous groupe spécifique de pathologie
- Une molécule altérée responsable de la pathologie
- Les traitements sont à priori actif sur le tissu tumoral et peu sur les tissus sains (spécifiques)

Comment identifier les caractéristiques des tumeurs: des outils pour des cibles

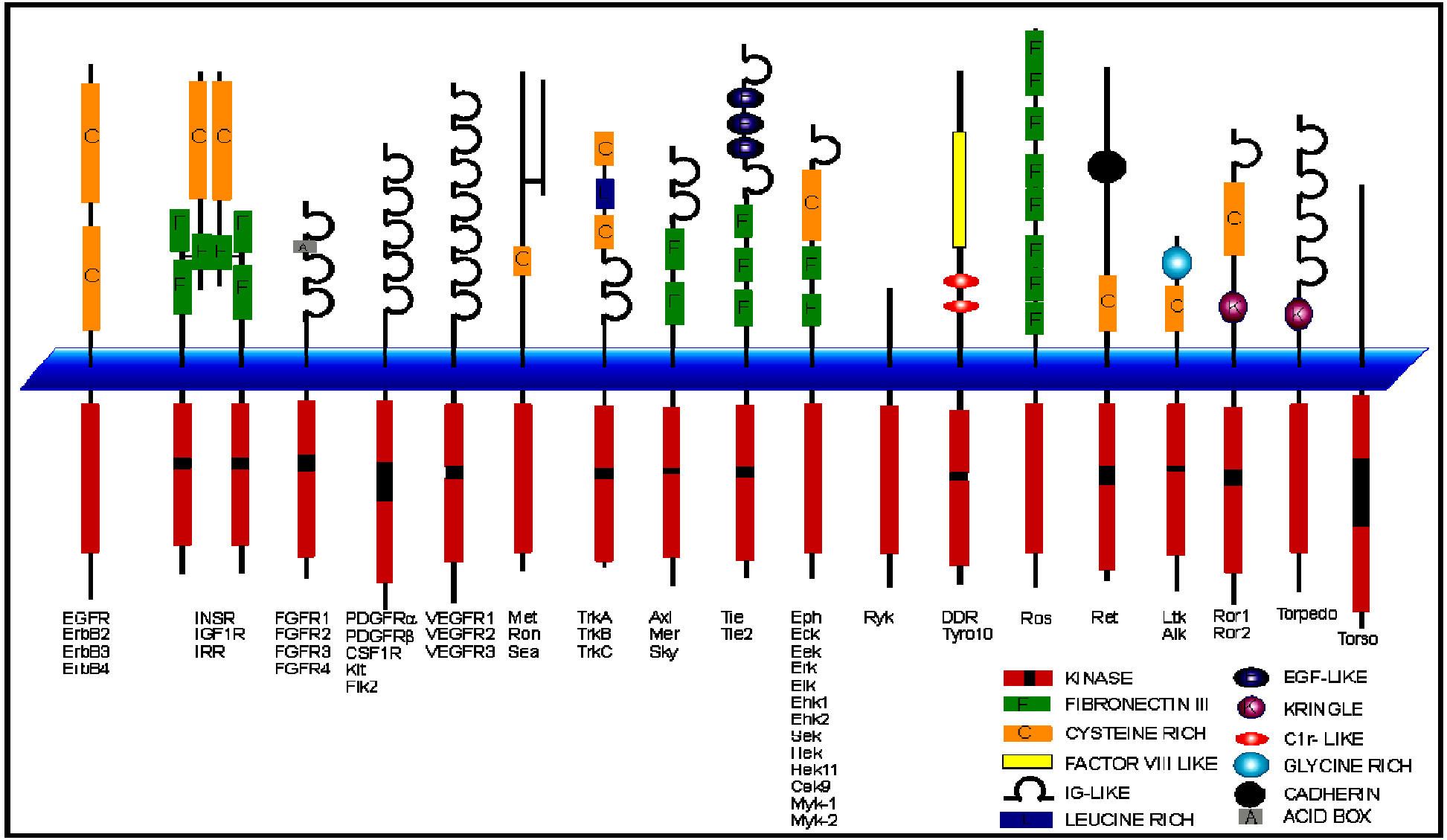


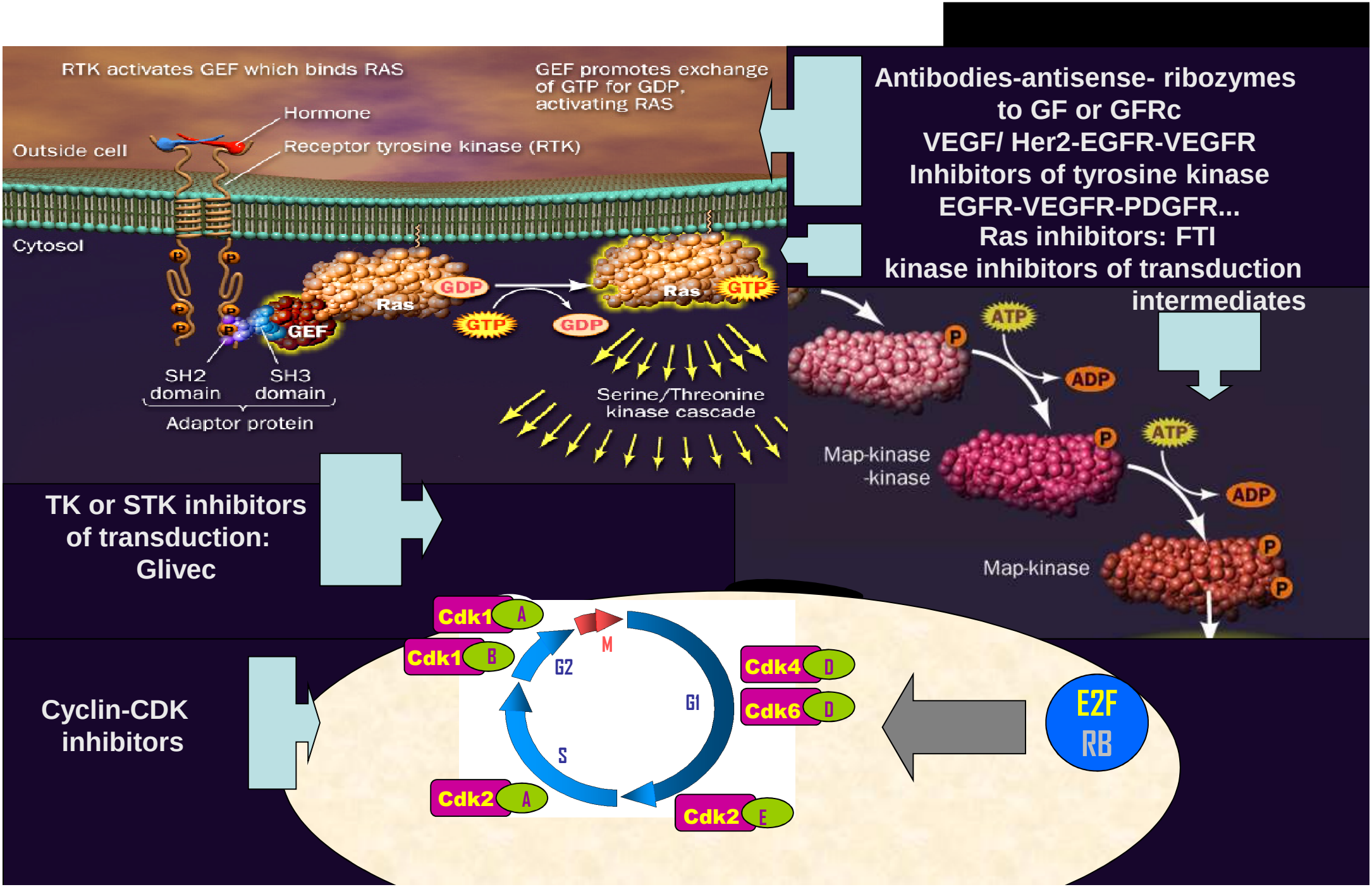






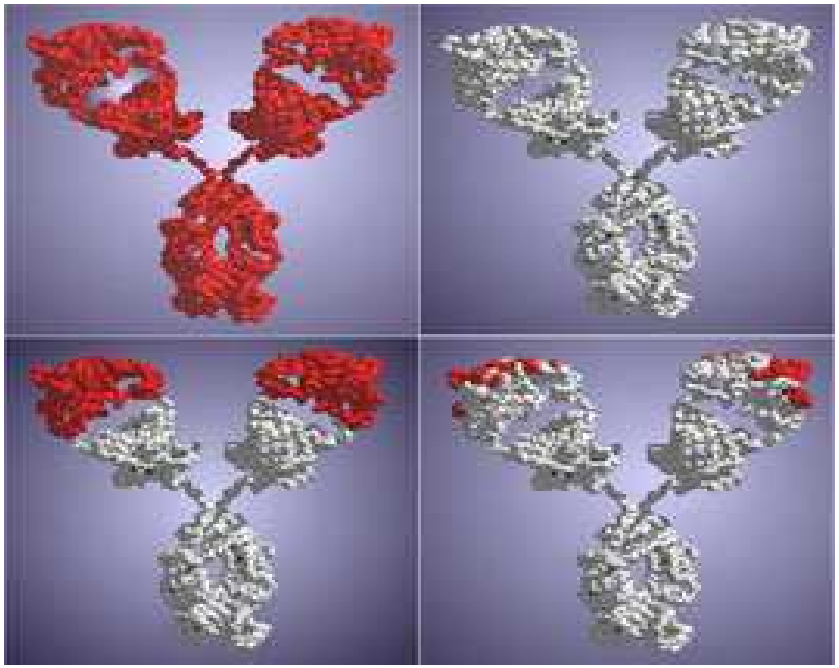
Les récepteurs membranaires à Tyrosine kinase




RTK activates GEF which binds RAS
GEF promotes exchange of GTP for GDP, activating RAS
Hormone
Outside cell
Receptor tyrosine kinase (RTK)
Cytosol
Ras
GDP
GTP
GEF
SH2 domain
SH3 domain
Adaptor protein
Serine/Threonine kinase cascade
Antibodies-antisense- ribozymes to GF or GFRc
VEGF/ Her2-EGFR-VEGFR
Inhibitors of tyrosine kinase
EGFR-VEGFR-PDGFR...
Ras inhibitors: FTI
kinase inhibitors of transduction intermediates
ATP
ADP
P
Map-kinase -kinase
Map-kinase
TK or STK inhibitors of transduction: Glivec
Cyclin-CDK inhibitors
Cdk1 A
Cdk1 B
Cdk4 D
Cdk6 D
Cdk2 A
Cdk2 E
G2
M
G1
S
E2F
RB

Comment cibler les tyrosine-kinases?

Murin **Humain**



Chimerique **Humanisé**

Anticorps monoclonaux

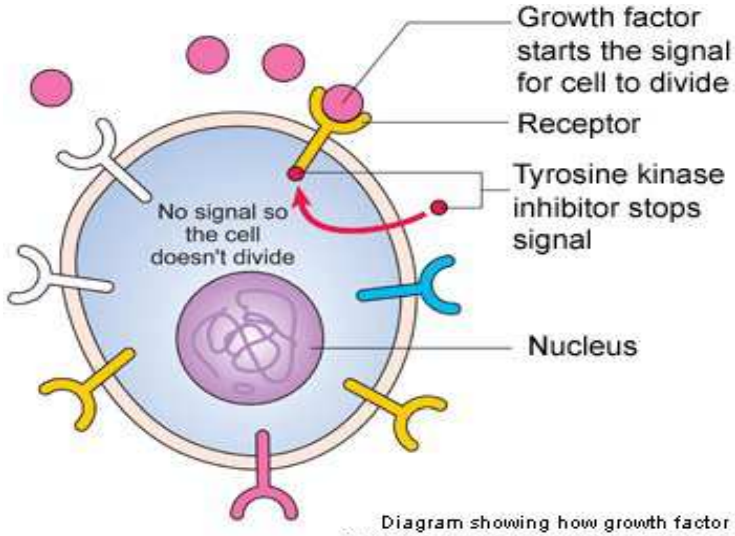
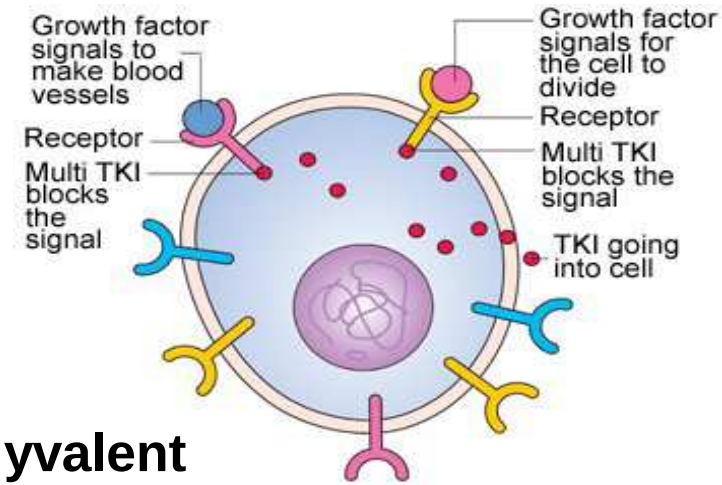


Diagram showing how growth factor inhibitors stop the signal inside the cell
Copyright © CancerHelp UK

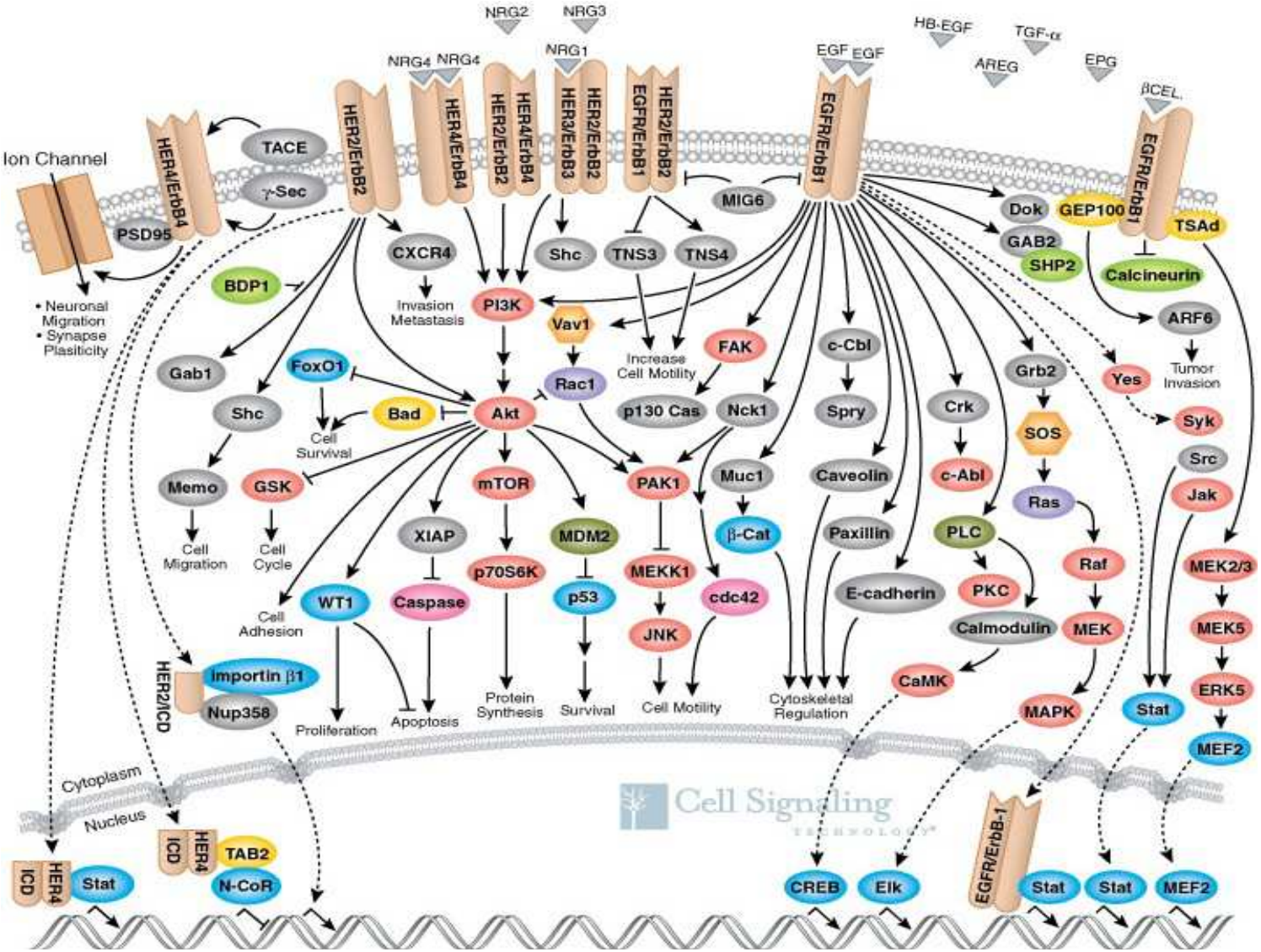
Spécifique



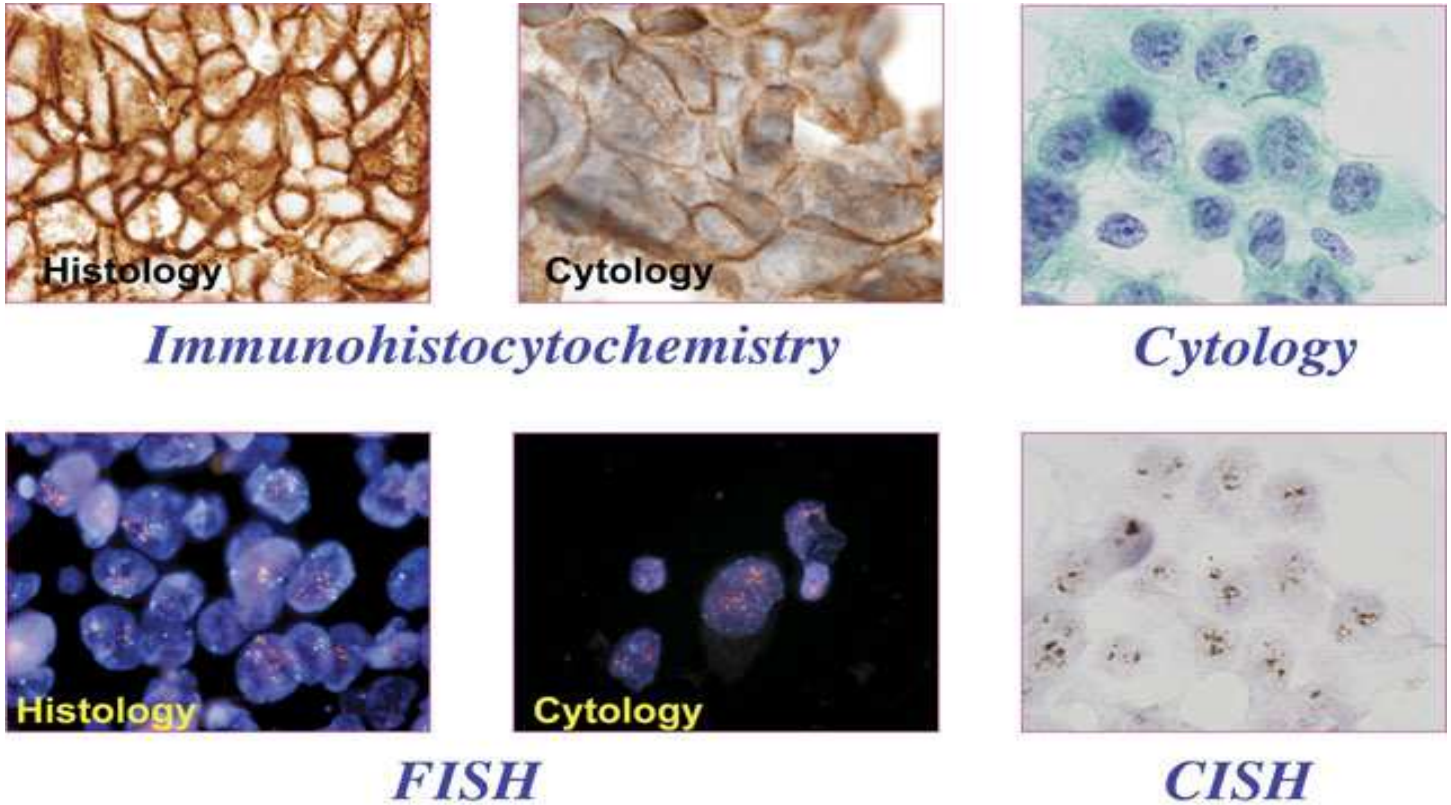
TKI

Polyvalent

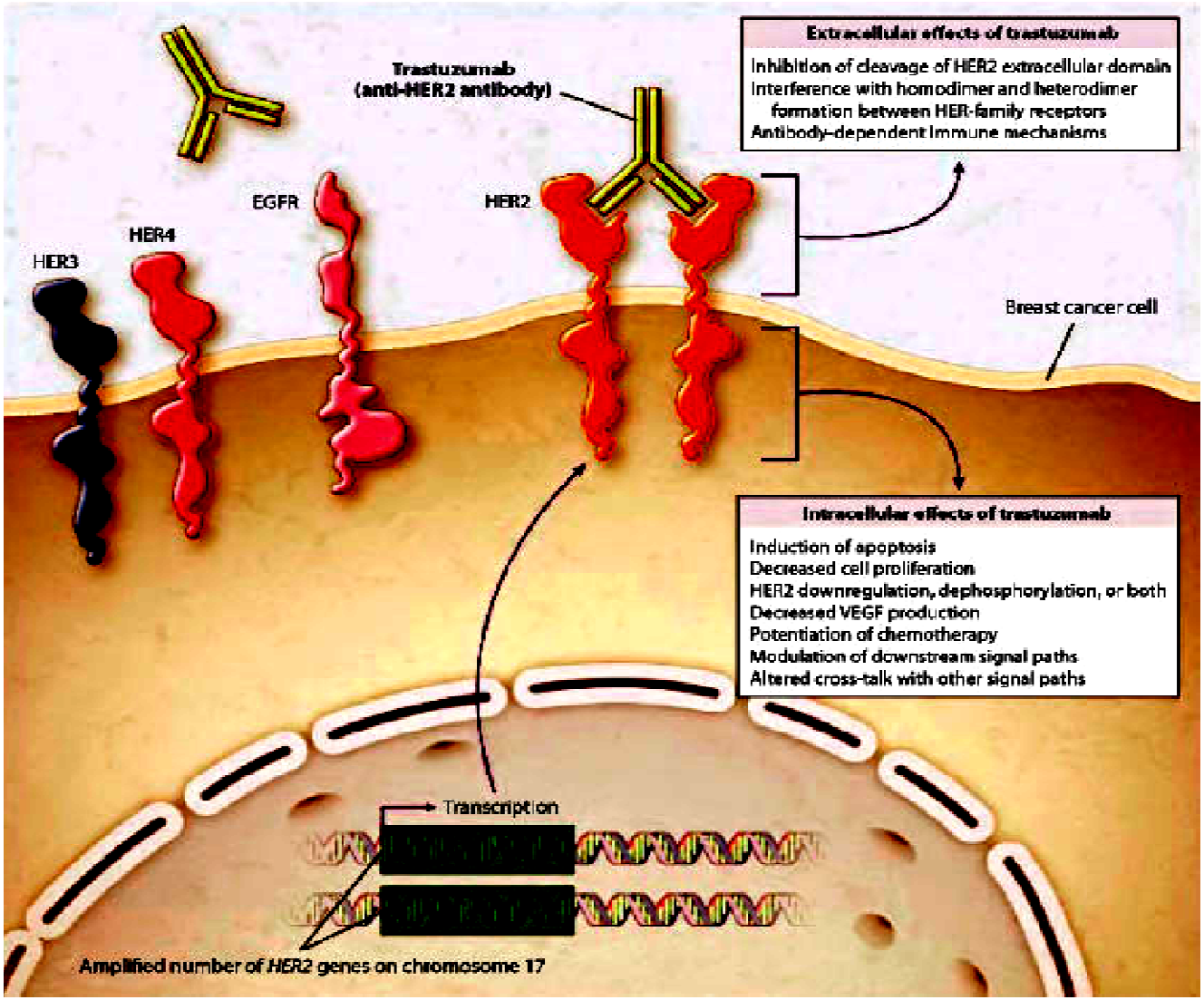
La famille erb



Cancers du sein HER2 positifs

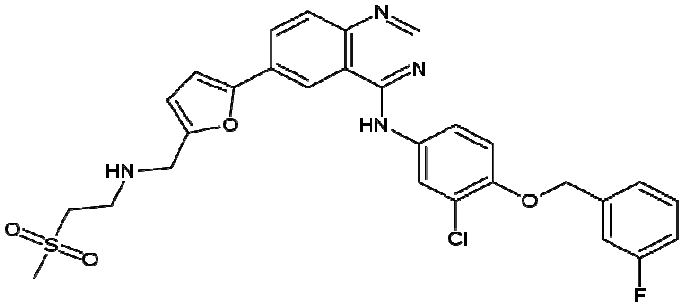


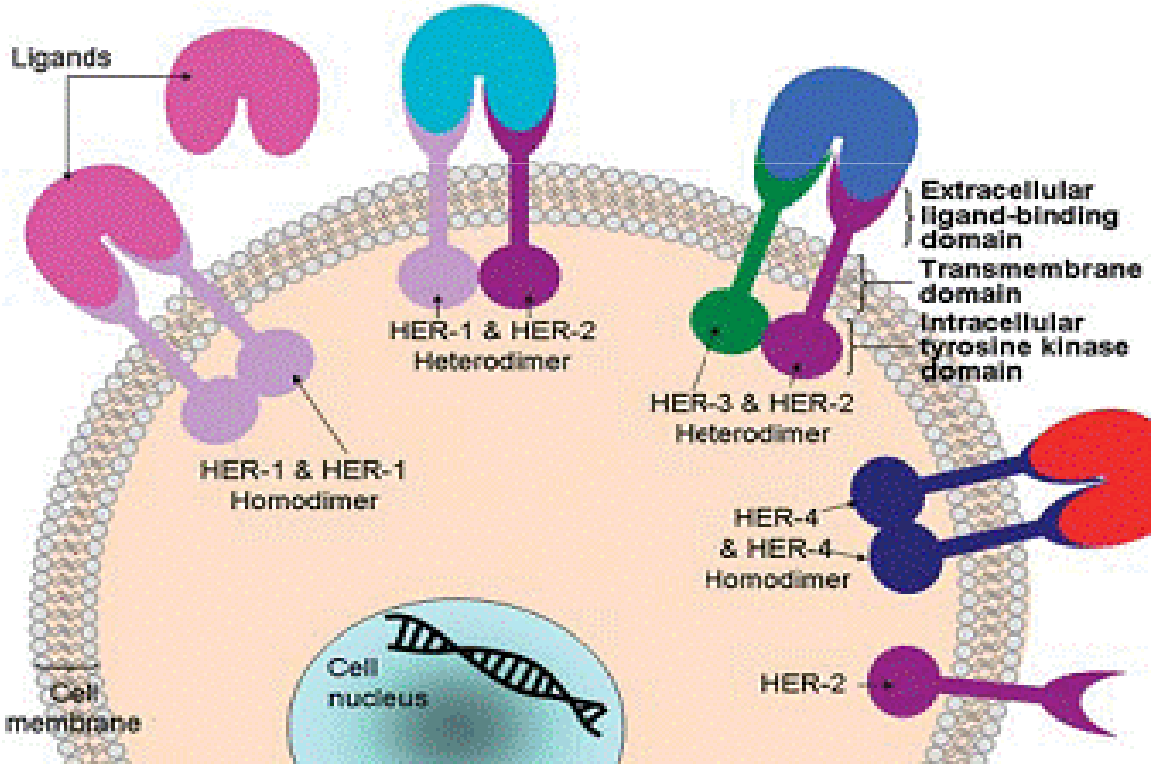
Trastuzumab- Herceptin



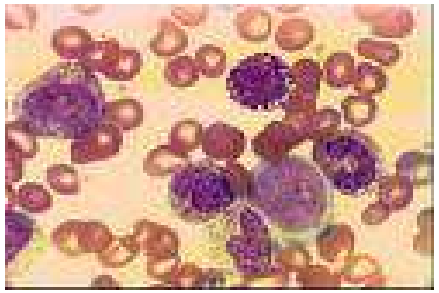
Inhibiteur de kinase bispécifique

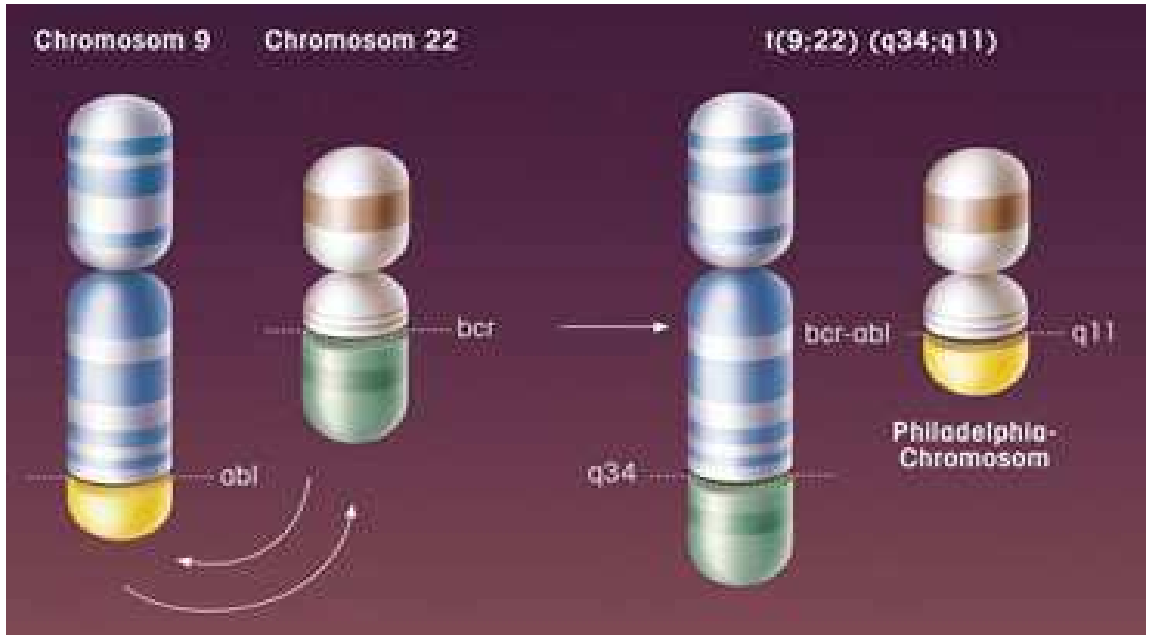
- Lapatinib: inhibe HER1 et HER2





La leucémie myéloide chronique (LMC)



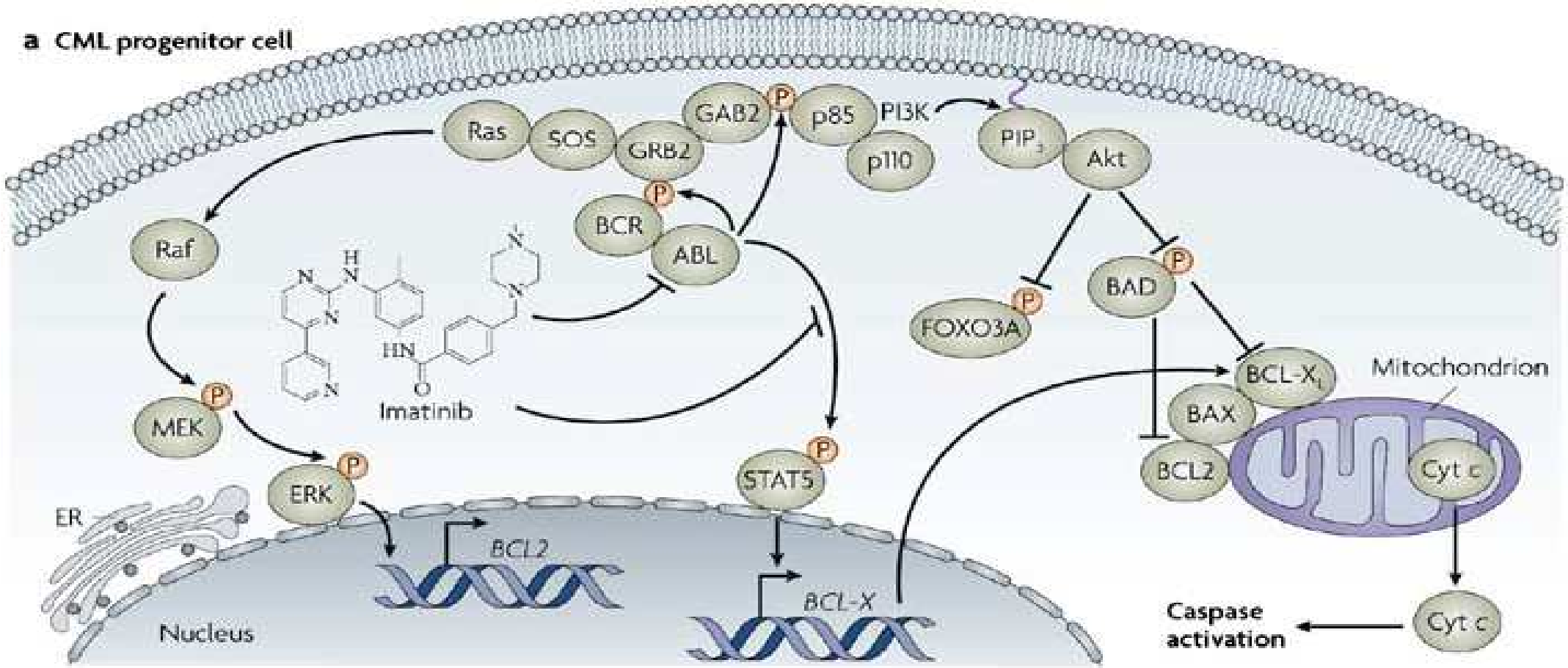


15 à 20% des Leucémies
1 à 2 cas pour 100.000 par an
Après 50 ans
Phase chronique- phase accélérée- phase blastique

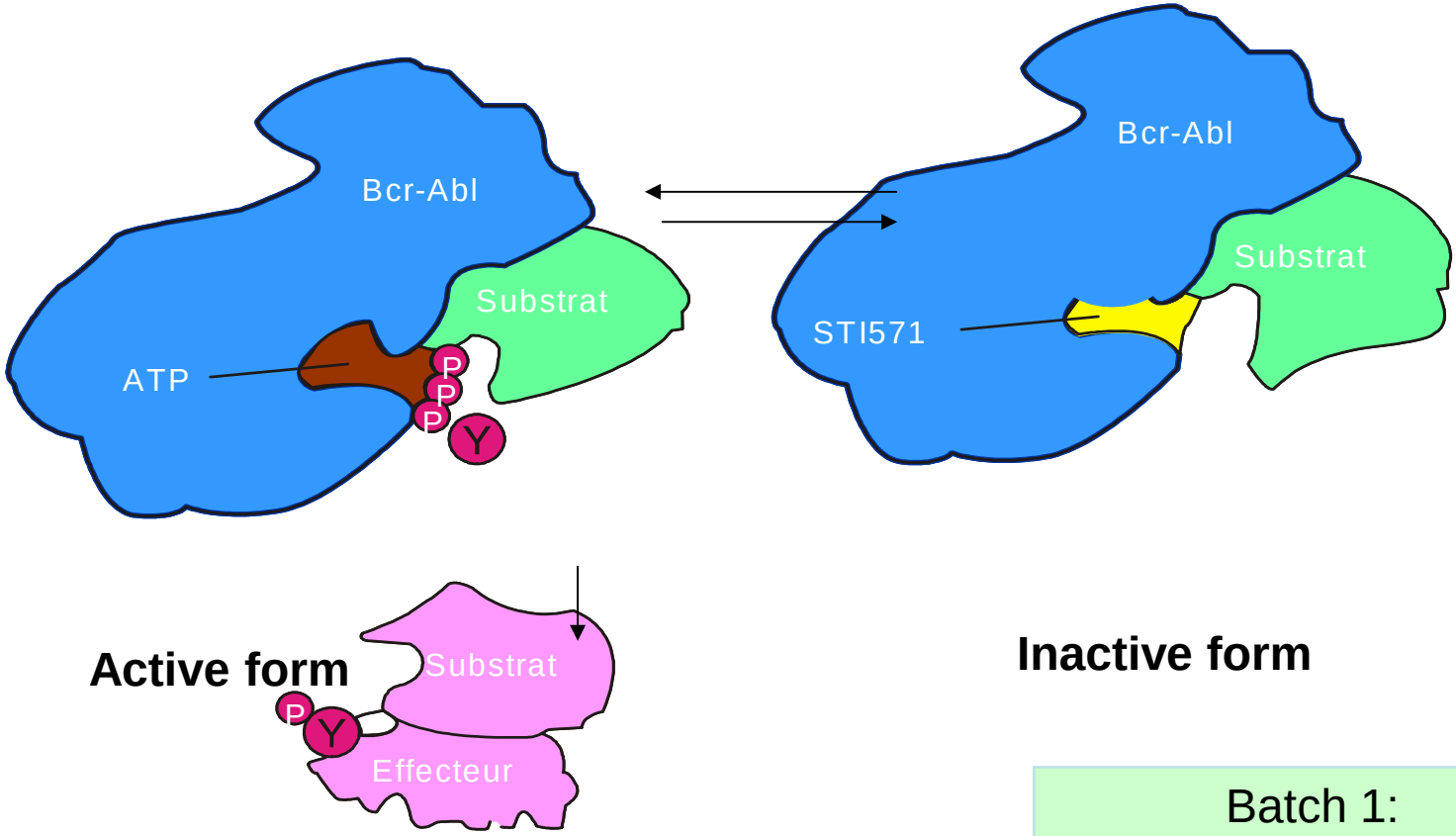
- **La fusion BCR-ABL active l'activité Kinase d'ABL**
- **Elle est responsable de la leucémie**

Fonction de BCR-ABL

a | Constitutive signalling in CML progenitor cell, through BCR–ABL tyrosine kinase, leads to activation of Ras–ERK (extracellular signal-regulated kinase), phosphatidylinositol 3-kinase (PI3K)–Akt and signal transducer and activator of transcription (STAT5) pathways. Several of these pathways converge on anti-apoptotic mechanisms: the Ras–ERK pathway stimulates the expression BCL2, STAT5 activates BCL-X, and Akt inhibits BCL2-antagonist of cell death (BAD) and forkhead box O3A (FOXO3A). Imatinib blocks all BCR–ABL-dependent phosphorylation and signalling events, leading to reversal of pro-survival effects and activation of apoptosis.

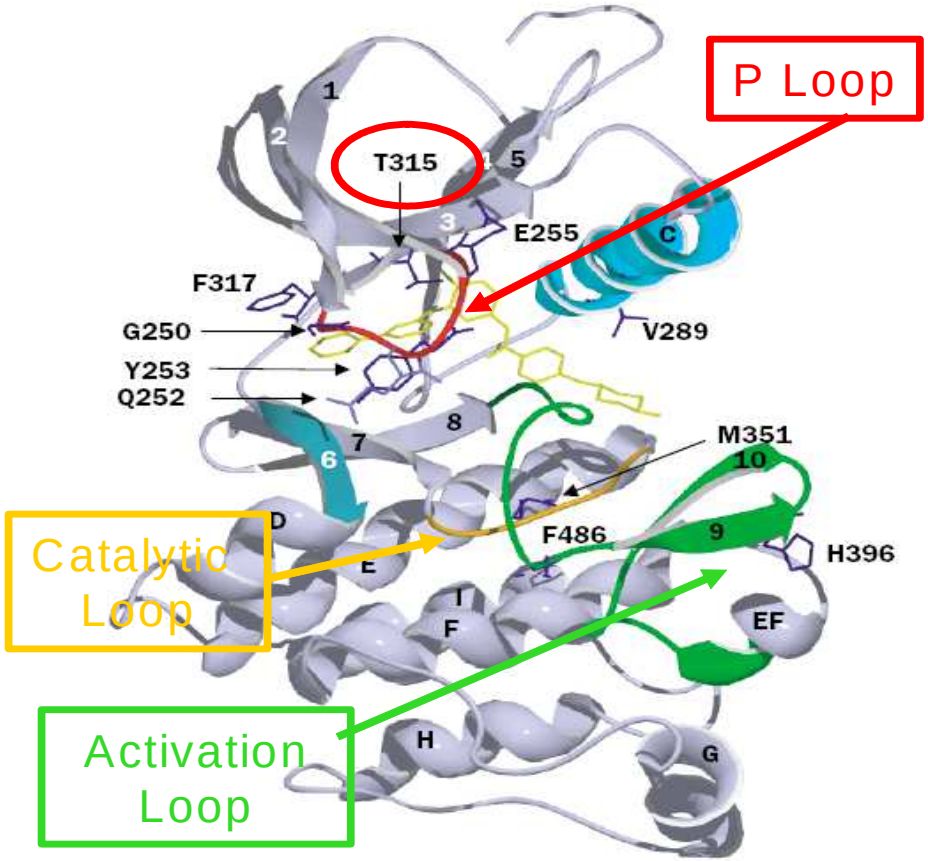


Mécanisme d'action de l'imatinib mésylate (STI571, CGP57148, Glivec®)



Batch 1:
331 mg, 26 August 1992

Résistance à l'imatinib et aux ITKs



0'Hare, Blood 2007

	Ba/F3 cellular proliferation IC_{50} values		
	imatinib (nM)	nilotinib (nM)	dasatinib (nM)
Native Bcr-Abl	260	13	0.8
244M>V	2000	38	1.3
250G>E	1350	48	1.8
252Q>H	1325	70	3.4
253Y>F	3475	125	1.4
253Y>H	>6400	450	1.3
255E>K	5200	200	5.6
255E>V	>6400	430	11
299V>L	540[†]	nd	18[†]
311F>L	480	23	1.3
315T>A	971	61	125[†]
315T>I	>6400	>2000	>200
317F>L	1050	50	7.4
317F>V	350[†]	nd	53[†]
315M>T	880	15	1.1
355E>G	2300[‡]	nd	1.8[§]
359F>V	1825	175	2.2
379V>I	1630	51	0.8
387L>M	1000	49	2
396H>P	850	41	0.6
396H>R	1750	41	1.3

Sensitive — Intermediate sensitivity — Insensitive

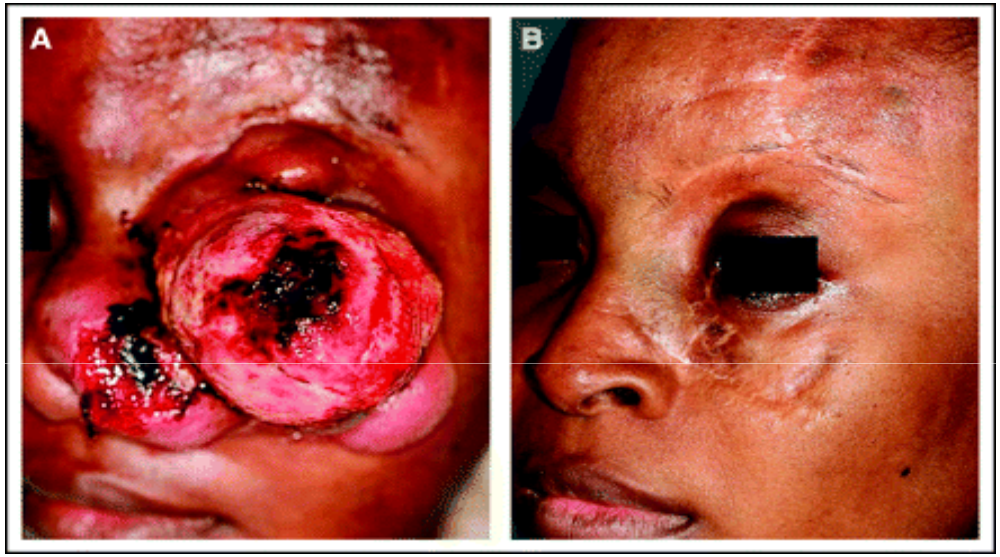
ITK de seconde génération : dasatinib (Sprycel®)

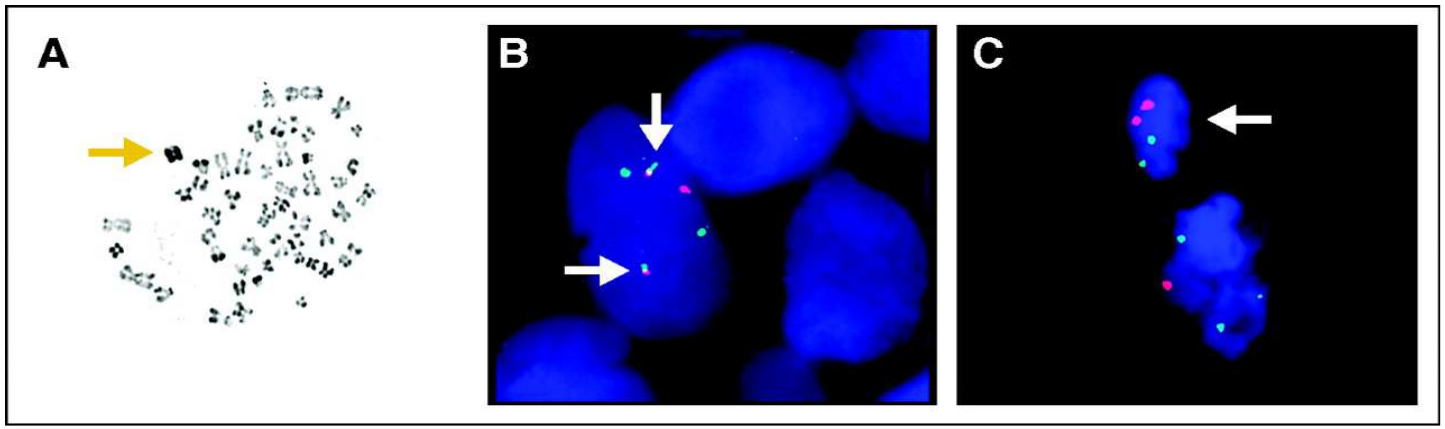
Imatinib et tumeurs stromales (GIST) avec amplification de Kit

- Tumeurs rares au pronostic sévère (40% de survie à 1 an)
- Le gène Kit est activé dans la tumeur
- L’ Imatinib inhibe la kinase Kit
- L’Imatinib augmente la survie globale à 90% à un an, à 65% à 3 ans
- Le type de mutation activatrice est corrélé à la réponse thérapeutique (mut exon 11 de bon pronostic, absence de mut de mauvais pronostic)

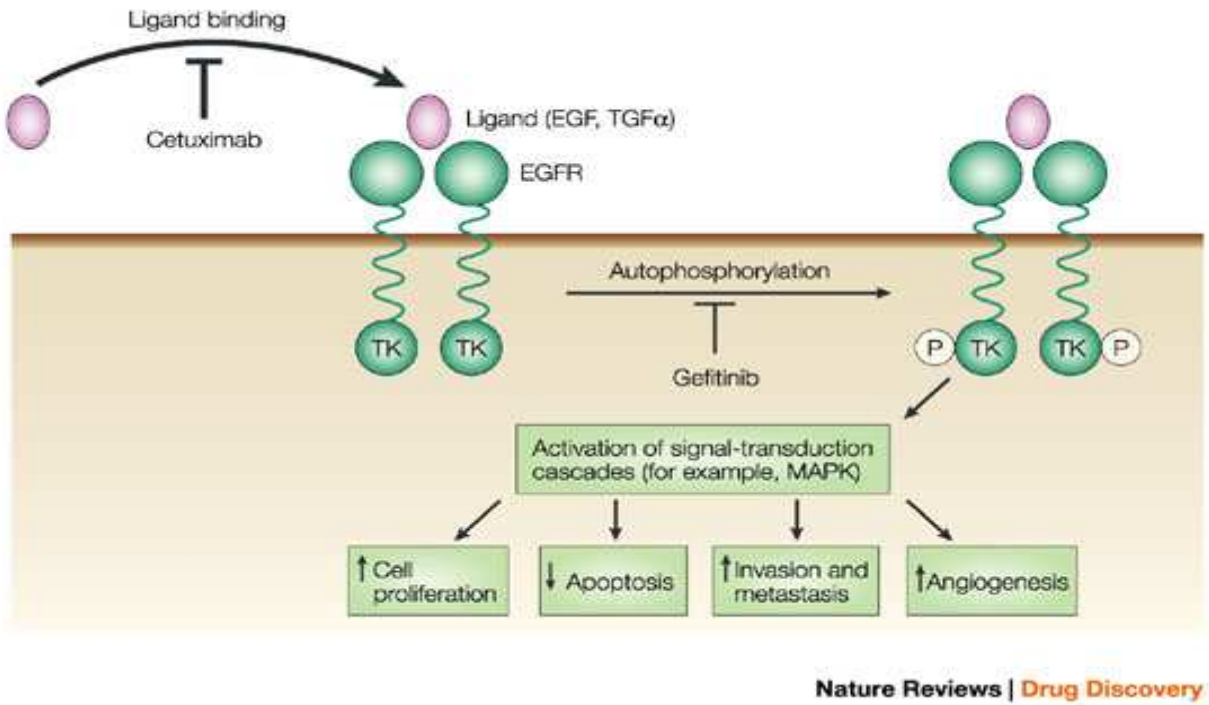
Imatinib et Dermatofibrosarcome de Darrier et Ferrand

- Sarcome sous cutané
- Invalidant et récidivant localement
- Traité par chirurgie
- Résistant à la chimiothérapie
- Présence d'une fusion Coll1-PDGF avec activation de la kinase du PDGFR
- Réponse à l'Imatinib



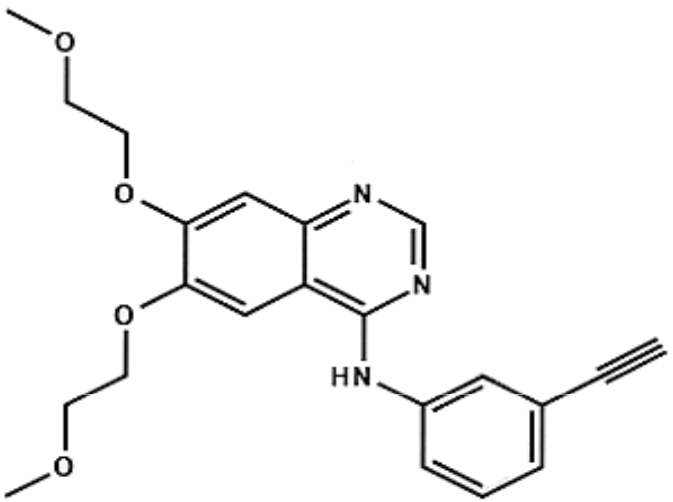


Anticorps anti EGFR: Cetuximab

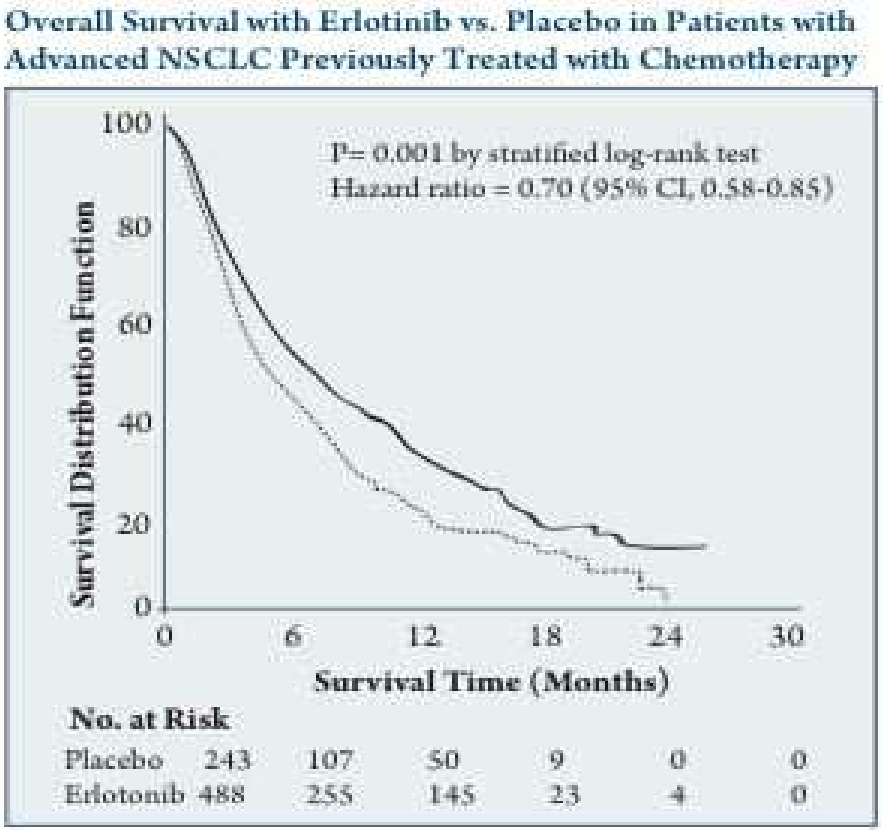


- Anticorps chimérique très affin
  Inhibe la liaison EGF-EGFR
  Bloque l'activité TK
  Bloque la dimérisation du récepteur
  Induit son internalisation
  Est une cible pour l'ADCC (?)

Les inhibiteurs de Tyrosine Kinase spécifiques de l'EGFR: Erlotinib



- Inhibiteur spécifique de la kinase EGFR
- développé dans le cancer du poumon
- actif en monothérapie
- actif préférentiellement chez
- Les femmes
- les non fumeurs
- asiatiques
- adénocarcnomes



Reprinted with permission. Shepherd FA et al 2005.[45]

Inhibiteurs de TK : efficacité et effets secondaires

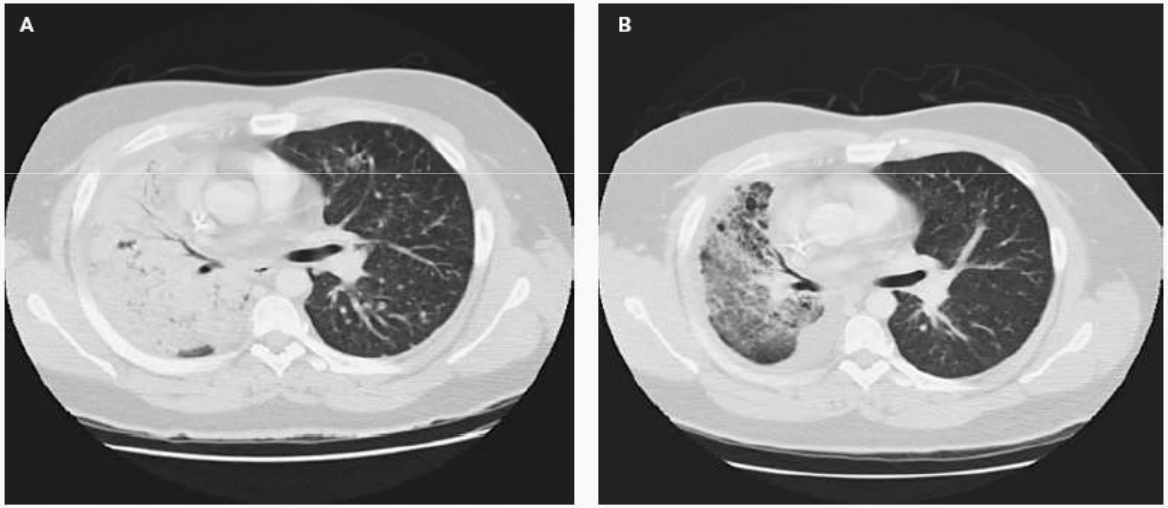
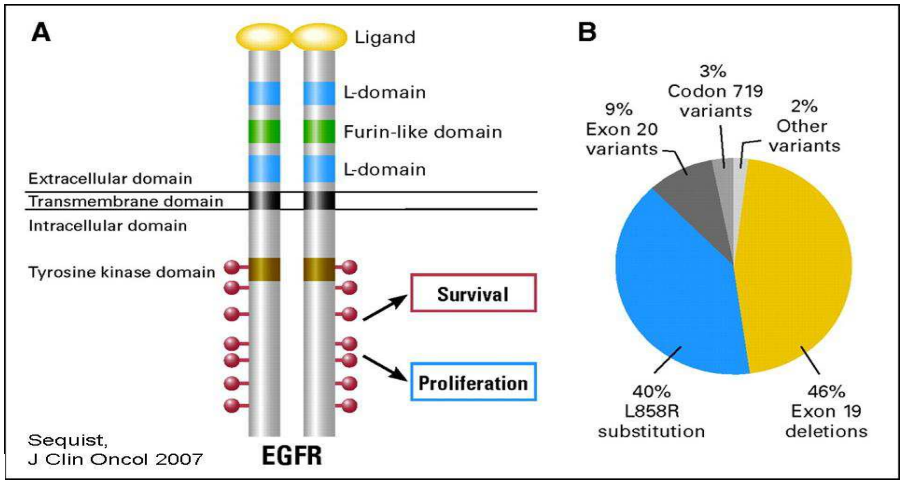
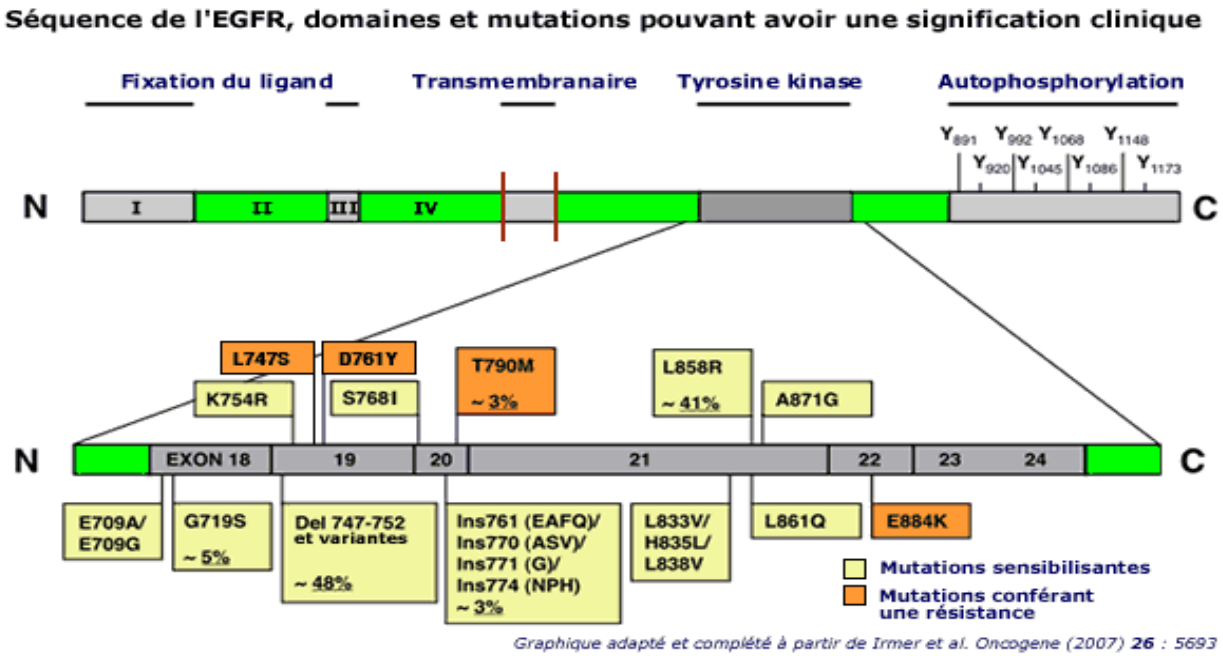


Figure 1. Example of the Response to Gefitinib in a Patient with Refractory Non–Small-Cell Lung Cancer.
A computed tomographic scan of the chest in Patient 6 shows a large mass in the right lung before treatment with gefitinib was begun (Panel A) and marked improvement six weeks after gefitinib was initiated (Panel B).

Efficacité des TKI

- Si mutation du récepteur de l'EGF
  - Délétions
  - Mutations ponctuelles activatrices

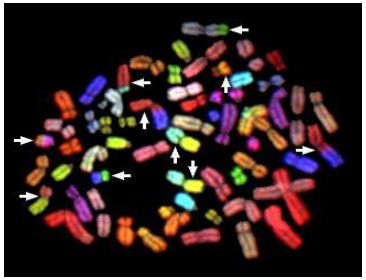




Phase 2 en 1ère intention si mutation
67/428 patients avec mutation
40 patients traités
38/40 ont une réponse: 5 RC, 26 RP, 5 stabilisation)
La réponse est variable selon la mutation
La durée de réponse est > 13 Mois
Paz-Arez, JCO

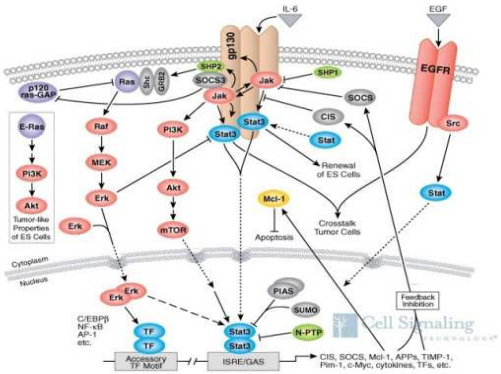
Additional programme for an optimized access to targeted therapies

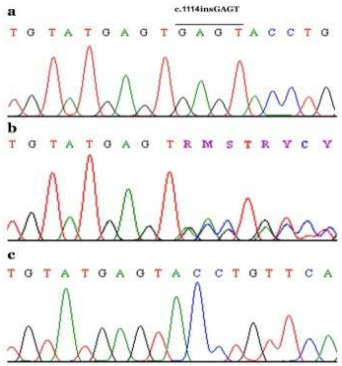
The French programme for the development of molecular genetics hospital-based platforms for cancer



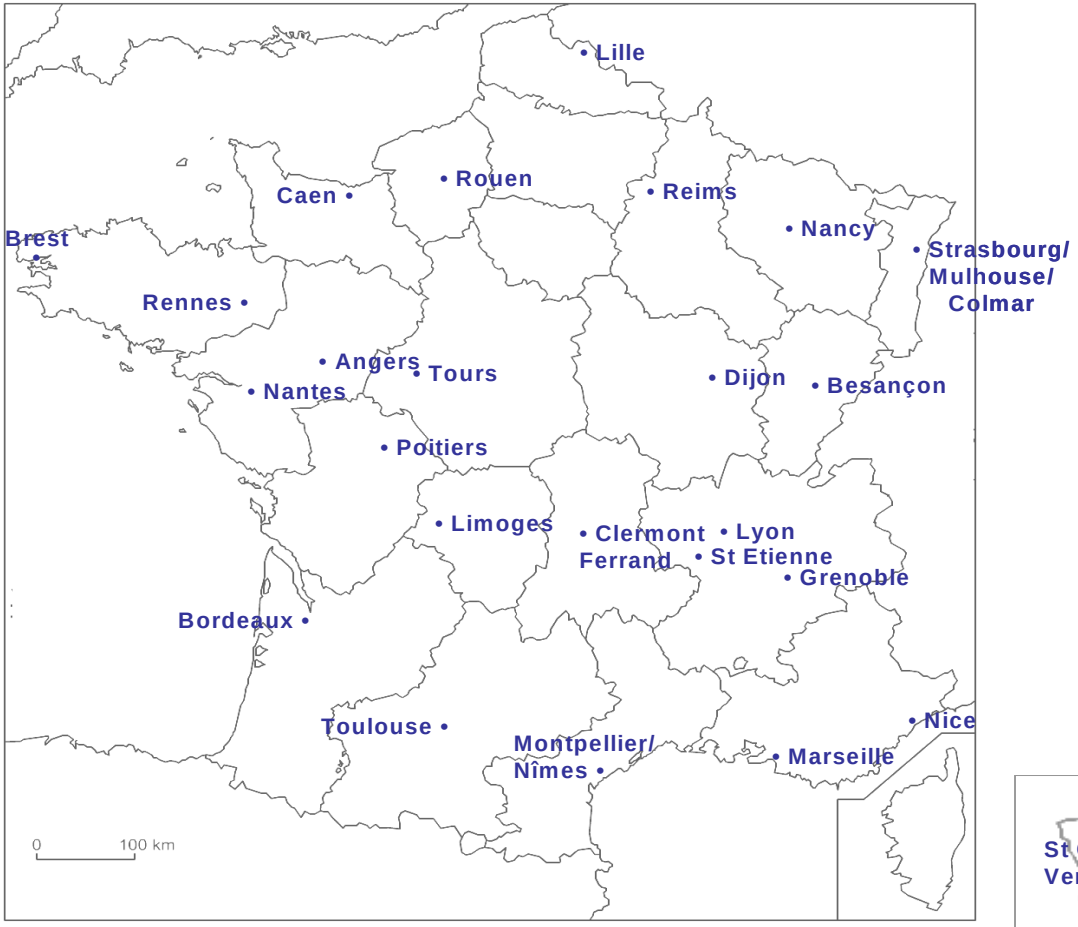
Molecular genetics has become an essential tool to assess :

- Diagnosis
- Tumour classification
- Prediction of response/non response to targeted therapies
- Therapeutic follow-up

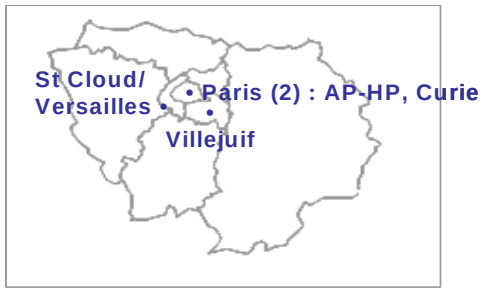




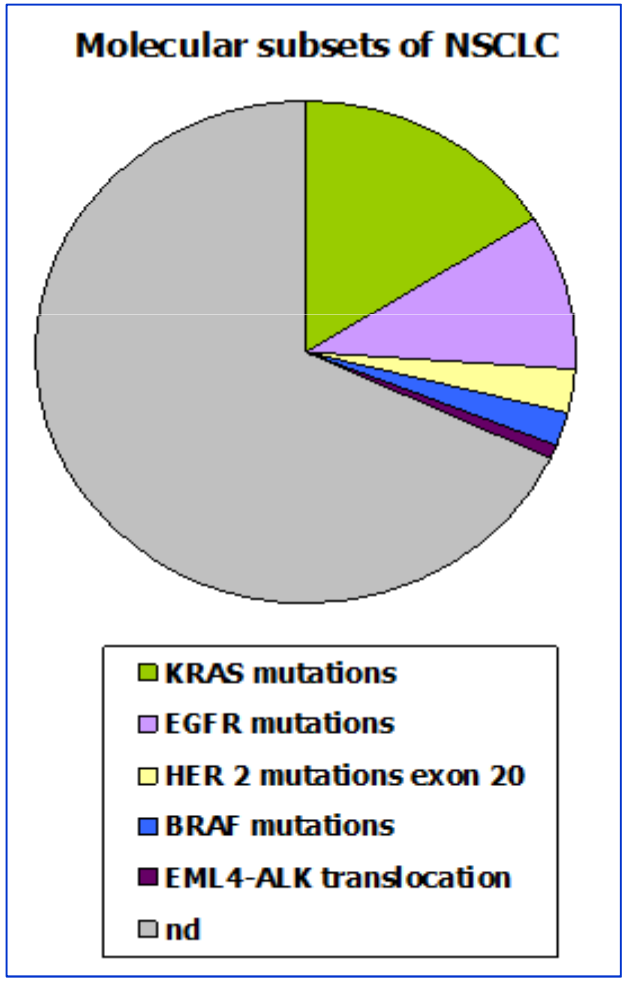
28 regional platforms



- Partnerships between several laboratories located in University hospitals and cancer centres
- Regional or interregional organization according to the number of tests to be performed
- Cooperation between pathologists and biologists



A new approach for rapid access to targeted therapies



Biomarkers for targeted therapies currently evaluated in clinical trials (Phases I to III) :

Cancer	Molecular target
Lung	EGFR mutations
	KRAS mutations
	HER2 exon 20 mutations
	BRAF mutation
	PI3KCA mutations
	EML4-ALK translocation
Colon - rectum	KRAS mutations
	BRAF mutation
	microsatellite instability if < 60 years
Breast	HER2 amplification
	BRCA1/2 germinal mutations
	PI3KCA mutations
Melanoma	BRAF mutation
	cKIT mutation

La modulation médicamenteuse de l’angiogenèse dans les cancers et l’immunothérapie des cancers