# Anticancer Drugs

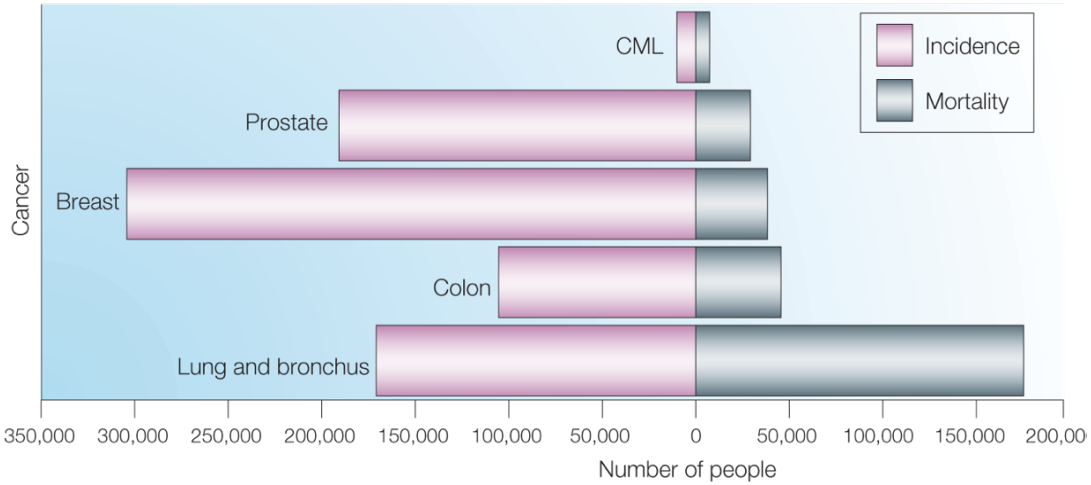
# Some basic Facts about Cancer

- Cancer cells have lost the normal regulatory mechanisms that **control cell growth and multiplication**
- Cancer cell have lost their ability to differentiate (that means to specialize)
- **Benign** cancer cell stay at the same place
- **Malignant** cancer cells invade new tissues to set up secondary tumors, a process known as **metastasis**
- Chemicals causing cancer are called **mutagens**
- Cancer can be caused by chemicals, life style (smoking), and viruses
- genes that are related to cause cancer are called **oncogenes**. Genes that become onogenic upon mutation are called **proto-oncogenes**.

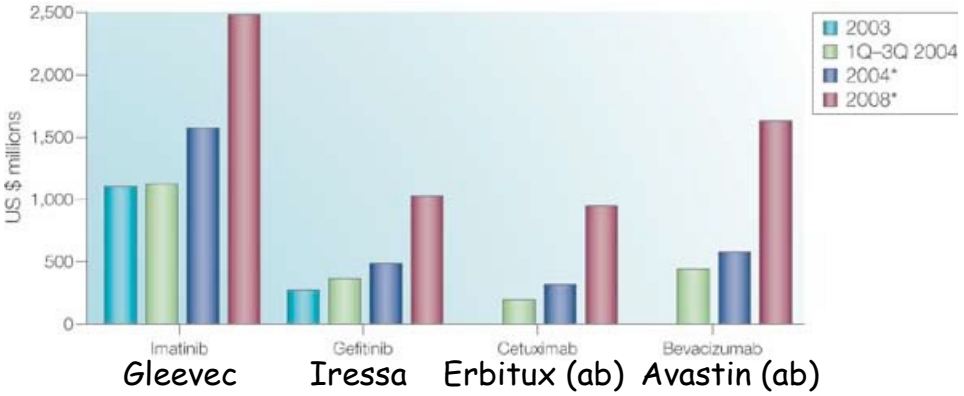
# The Hallmarks of Cancer

- Self-sufficiency in growth signals (e.g. via activation of the H-Ras oncogene)
- Insensitivity to growth inhibitory (anti-growth) signals (lose retinoblastoma suppressor)
- Evasion of programmed cell death (apoptosis) (produce IGF survival factors)
- limitless replicative potential (turn on telomerase)
- sustained angiogenesis (produce VEGF inducer)
- tissue invasion and metastasis (inactivate E-cadherin)
- inactivation of systems that regulate in response to DNA damage (e.g. p53)

# Anti-Cancer Strategies




**Incidence and mortality of selected cancers in the United States in 2002.**

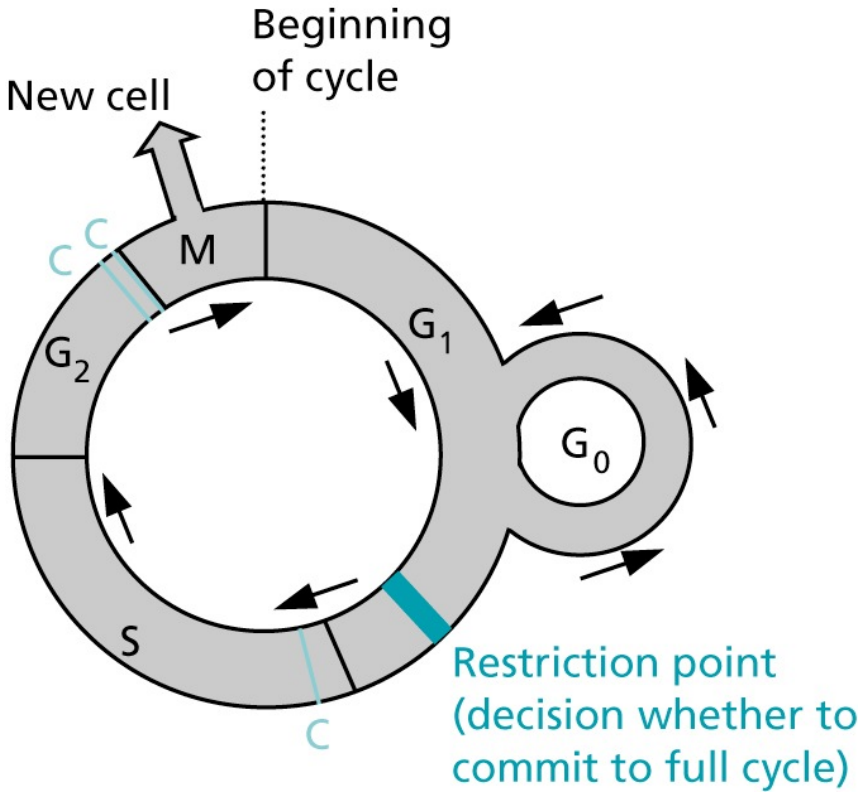



**sales of kinase inhibitors**

Some current and prospective modalities of cancer chemotherapy

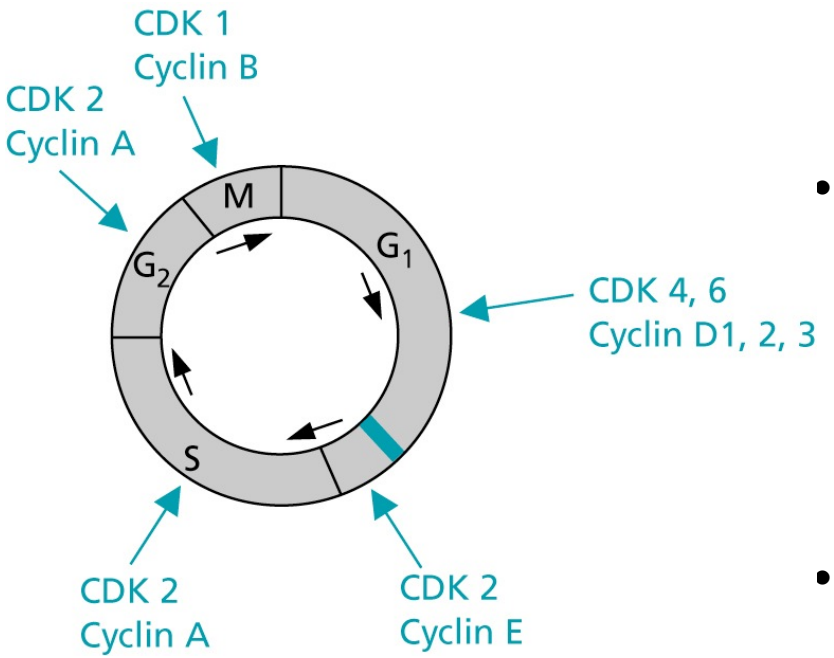
| Category | Function | Examples |
|---|---|---|
| Antimetabolites | Interfere with intermediary metabolism of proliferating cells | Methotrexate, 5-fluorouracil |
| Monoclonal antibodies | Target cancer cells that express specific antigen | Herceptin (Genentech), Zevalin (IDEC Pharmaceuticals/Schering-Plough) |
| Mitosis inhibitors | Target microtubules and associated proteins required in cell division | Taxol |
| Steroid hormones | Block steroid- and hormone-dependent growth of certain tumours | Tamoxifen, flutamide |
| Alkylating/cross-linking agents | Damage DNA and result in death of growing cells | Endoxan, cisplatin, cyclophosphamide |
| Signal-transduction agents | Modulate communication between cells | Gleevec (Novartis), Tarceva (OSI), Iressa (AstraZeneca), LY900003 (ISIS 3521) (Eli Lilly) |
| Angiogenesis inhibitors | Block blood-vessel formation to tumour | Avastin (Genentech) |
| Histone-deacetylase inhibitors | Affect transcription of genes | SAHA (Aton Pharma) |
| Telomerase inhibitors | Affect telomere maintenance required for tumour growth | BIBR1532 (Boehringer Ingelheim) |
| Antitumour antibiotics | Bind DNA to prevent DNA and/or RNA synthesis | Etoposide, doxorubicin |

# Phases of the Cell Cycle




- G1 phase (gap 1): Cell grows in size and prepares to copy its DNA in response to various growth factors
- S phase (synthesis): Replication of DNA, copying of the chromosome
- G2 phase (gap 2): Preparation for cell division. Check copied DNA and repair damaged copies.
- M phase (mitosis): Formation of the mitotic spindle, and separation into two individual cells (cell division).

# Control of Cell Cycle Progression by CDKs




- Progression through the cell cycle is controlled by **cyclin-dependent kinases** (CDKs).
- Binding of cyclin with its associated kinase triggers to move the cell cycle to another phase
- inhibitory proteins are present that can modify the effect of cyclins. These include **p15** and **p16**, that block activity of the cyclin D-CDK complex. Another regulator is p21, that is controlled by the **tumor suppressor protein p53**.
- over-active cyclins or CDKs have been associated with many tumors. Excessive production of cyclins or CDKs or insufficient production of CDK inhibitors leads to disruption of the normal regulation of the cell cycle.

# Cell Death

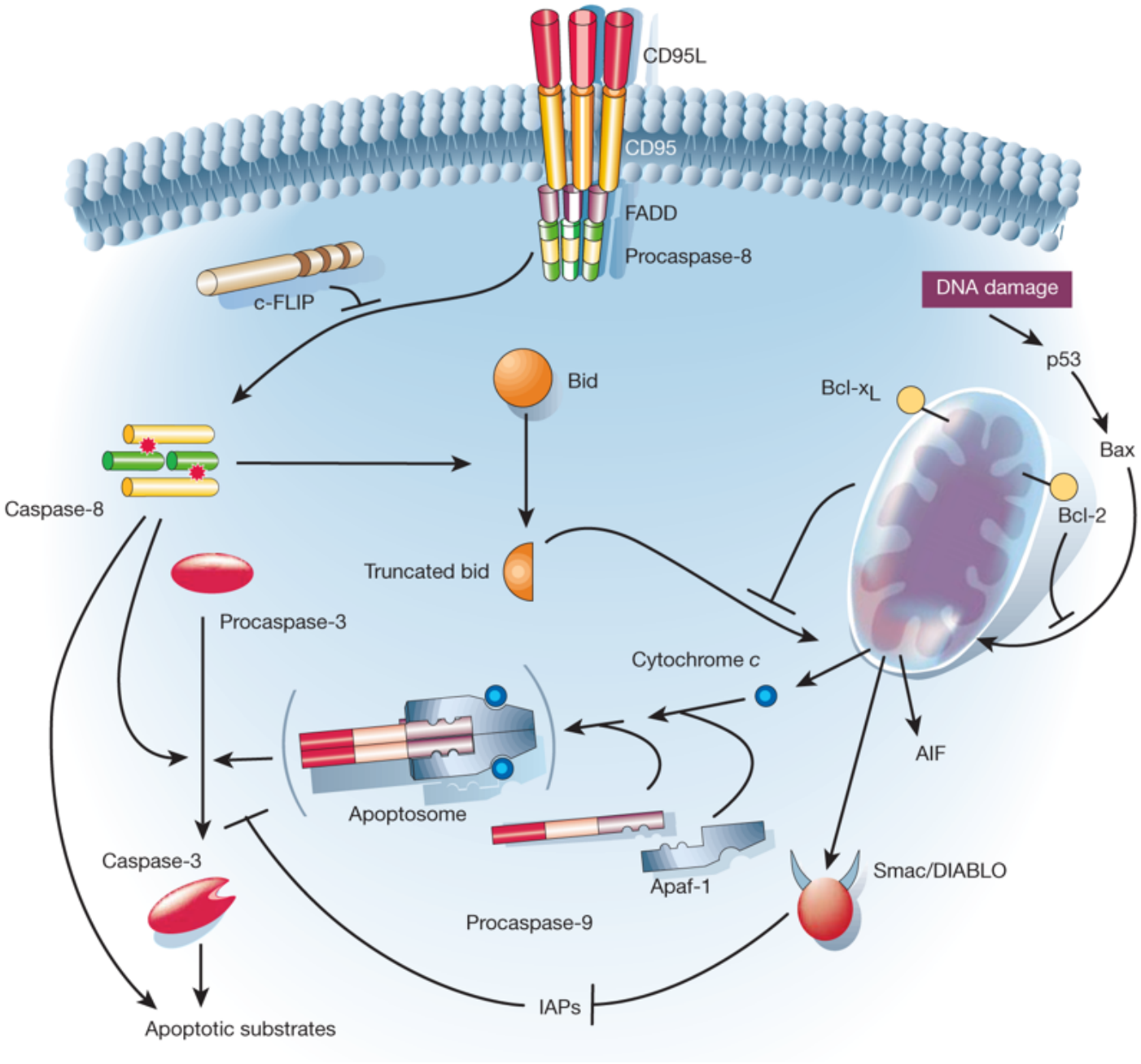
- **Necrosis** is the uncontrolled (pathological) cell death. In contrast with apoptosis, cleanup of cell debris by phagocytes of the immune system is generally more difficult. There are many causes of necrosis including injury, infection, cancer, infarction, toxins and inflammation. Necrosis can arise from lack of proper care to a wound site. Usually cell outlines do not stay intact, and cell debris is released into the environment
- **Apoptosis** is the programmed cell death. It is used by organisms to control the number of cells and tissue size. The cells during apoptosis shrink, but no uncontrolled release of cell debris into the environment occurs. The immune system usually "cleans up" the dying cells, and the content is recycled.

  Apoptosis is triggered by an extracellular signal to the CD95 receptor. In response to that signal a set of cysteine proteases, called **caspases** are activated, that are largely responsible for the morphological changes observed.

# Routes for Apoptosis

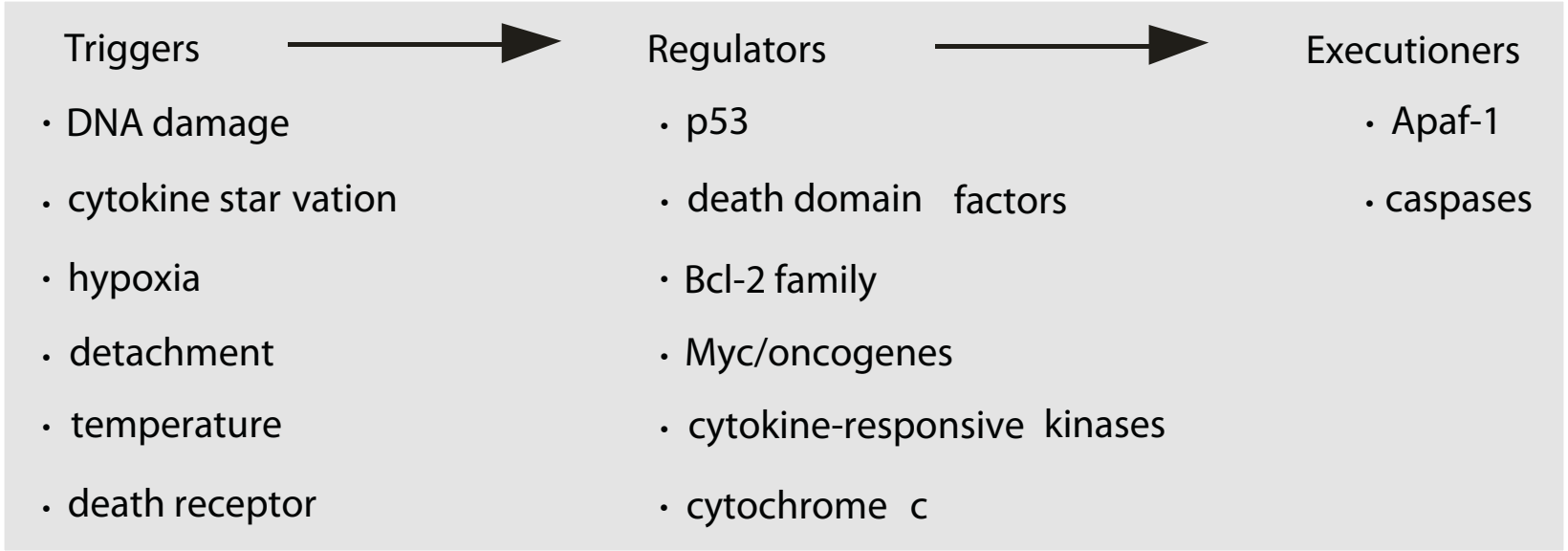
- Two pathways for activation: i) at the plasma membrane via external ligands upon binding to the death receptor or ii) via the mitochondrial pathway
- Binding of external ligands such as **tumor necrosis factor receptor** (TNFa) to Fas receptors of the TNF superfamily induces receptor oligomerization and formation of a death-inducing signaling complex. This complex recruits, via the adaptor molecule FADD (Fas-associated death domain) multiple Pro-caspase-8 molecules, resulting in caspase-8 activation that finally results in caspase-3 activation
- In the mitochondrial pathway release of apoptogenic factors such as cytochrome c, Apaf-1, caspase-9-containing apoptosome complex and inhibitors-of-apoposis proteins trigger caspase-3 activation
- Links between the two pathways exist. For example, caspsase-8 results in cleavage of Bid, a Bcl-2 family protein, which translocates to the mitochondria to release cytochrome c.

# Apoptosis


CD95L
CD95
FADD
Procaspase-8
c-FLIP
DNA damage
p53
Bid
Bcl-xL
Bax
Bcl-2
Caspase-8
Truncated bid
Procaspase-3
Cytochrome c
AIF
Apoptosome
Caspase-3
Apaf-1
Smac/DIABLO
Procaspase-9
IAPs
Apoptotic substrates

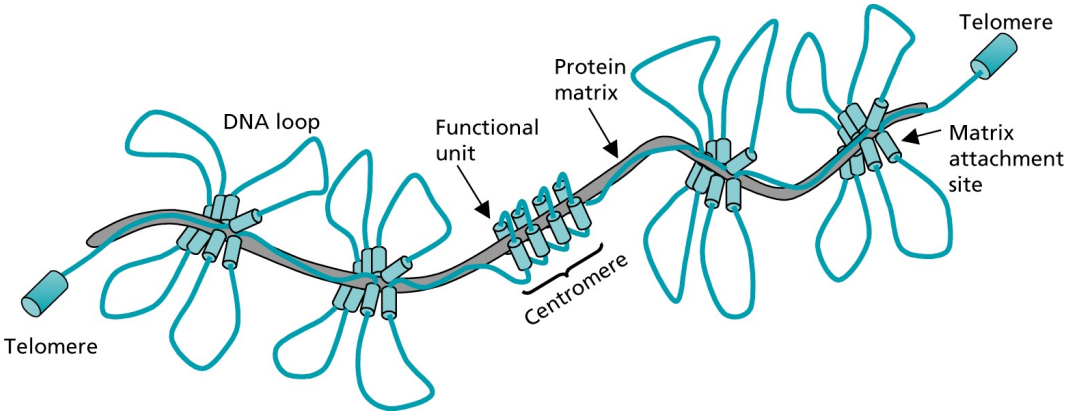
# Regulators of Apoptosis

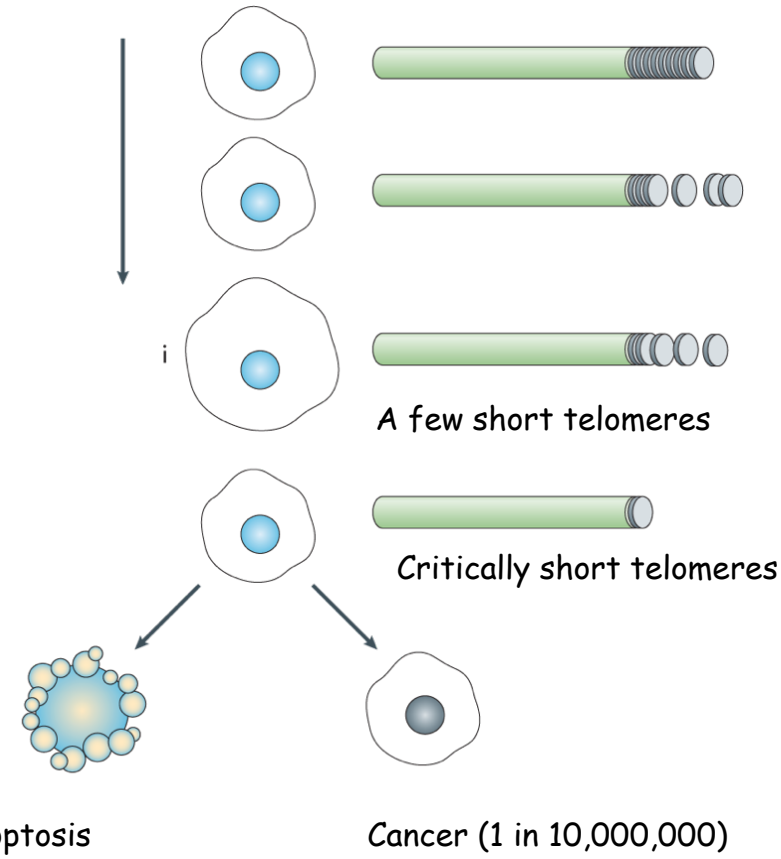
- The Bcl-2 family of factors regulate caspase activation either negatively ( e.g. Bcl-2, Bcl-$X_L$, MCL1) or positively (e.g. Bcl-$X_S$, Bax, BAD, BAK, BID)
- The inhibitors of apoptosis proteins (IAP) retard apoptosis
- Upstream modulators are oncogenes such as c-myc, that activates apoptosis in a manner important in cancer therapy
- the tumor suppressor p53 induces apoptosis under certain circumstances



# Telomeres

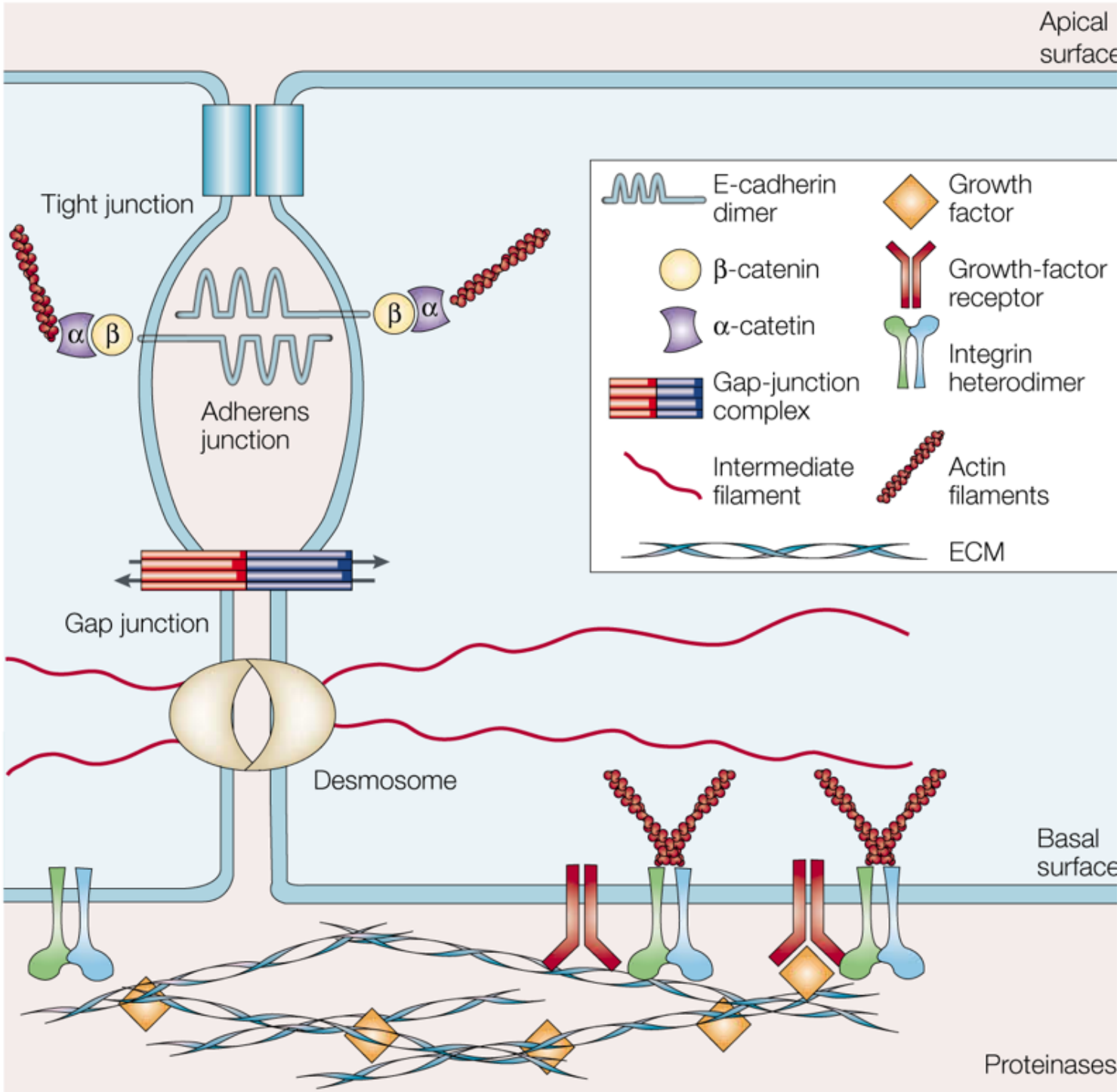
- Cancer cells are often called immortal since there seems to be no limit for how often they can divide
- Life-time of normal cells is limited to 50-60 cell divisions. This is regulated by telomeres. The telomeres are at the 3' end of the chromosomes. After each replication about 50-100 base pairs are lost
- At some point telomeres are too short to be effective and the DNA becomes unstable thereby limiting replication. Cancer cells possess an enzyme called telomerase which maintains the length of the telomeres and thereby allows more DNA replications.



# Tissue Invasion

- In malignant cancers cells cancer cells break away from the primary tumor site, invade a blood or lymphatic vessel, to form metastasis sites
- Usually, cells only stick to similar cells. The signature on the cell-surface is transmitted via **cell-adhesion molecules** (e.g. **cadherins**). Moreover, cells are connected to each other via mounting them on the **extracellular matrix (EM)**.
- Adhesion to the EM involves molecules called **integrins**.
- The protein matrix metalloproteinase degrades the extracellular matrix, and therefore is important for leaving the site of the primary tumor and attaching to the secondary site.
- If a non-cancer cell is detached from the extracellular matrix  it stops growing and apoptosis is triggered.
- In metastized cells cell adhesion molecules are missing, so that they can leave the site of the primary tumor.


Apical surface
Tight junction
α
β
β
α
Adherens junction
Gap junction
Desmosome
Basal surface
Proteinases
E-cadherin dimer
β-catenin
α-catetin
Gap-junction complex
Intermediate filament
ECM
Growth factor
Growth-factor receptor
Integrin heterodimer
Actin filaments

# Angiogenesis

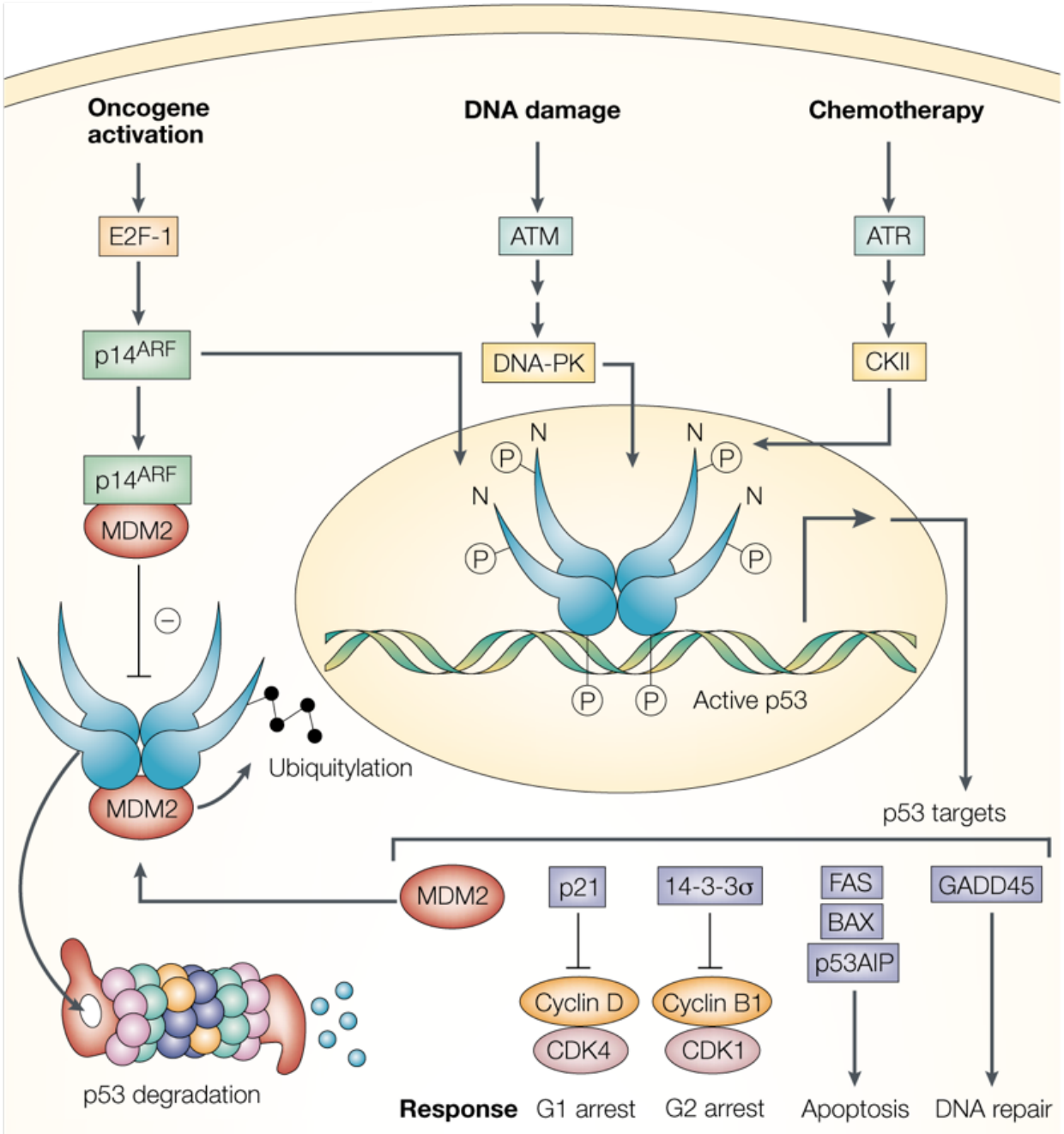
- Tumors are quickly growing tissue that need to have good blood supply.
- Angiogenesis refers to the formation of new blood vessels
- Tumor cells release growth factors such as **vascular endothelial growth factor** (VEGF) or **fibroplast growth factor** (FGF-2) leading to sprouting and extension of existing capillaries
- In healthy tissue repair of injured tissues is controlled by angiogenesis inhibitors such as angiostatin and thrombospondin
- Blood vessels arising from angiogenesis are abnormal in that they are disorganized in structure and leaky.
- These cells display integrins on their surface to protect the newly formed cells from apoptosis
- Before angiogenesis can start the basement membrane around the blood vessel has to be broken down (carried out by matrix metalloproteinases (MMPs))

# Strategies for Anti-Cancer Therapeutics

| Therapeutic target or modality | Targeted process | Mechanism of action of therapeutics | Target example (drug) |
|---|---|---|---|
| Transformation | Apoptosis | Activation of apoptosis pathways | BCL2 |
| | Signalling | Interference with signal transduction, response | ABL (Gleevec; Novartis) |
| | Invasion/metastasis | Inhibition of tumour spread | Cathepsin K |
| Immortalization | Senescence | Induction of senescence | Telomerase |
| Host | Angiogenesis | Interference with blood supply of tumour | VEGF (Avastin; Genentech/Roche) |
| | Tumour-associated membrane proteins | Antibody-directed cytotoxicity | CD20 (Rituxan; Biogen Idec/ Genentech) |
| Traditional cytotoxics | Replication/ cytokinesis | Interference with DNA synthesis, cell division | Microtubules (Taxol) |
| | Metabolism | Reduction of essential metabolite | Thymidylate synthase (5-FU) |
| Neocytotoxics | Protein turnover | Inhibition of acceleration of protein degradation | Proteasome (Velcade; Millennium Pharmaceuticals) |
| | Epigenetics | Remodelling chromatin, DNA methylation | HDAC interactions |
| | Stress response | Interference with cellular stress buffering | ATPase/chaperone superfamily |

ABL, Ableson kinase; BCL2; B-cell lymphoma 2; HDAC, histone deacetylase; VEGF, vascular endothelial growth factor.

# Intrinsic Tumor Suppression: p53




- In response to DNA damage, oncogene activation or other harmful events the tumor suppressor gene **p53** is induced
- various kinases phosporylate p53 which help stabilizing it. Activated p53 results in DNA binding and transcriptional activation
- **MDM2** serves to down-regulate p53, which in turn is regulated by $p14^{ARF}$
- p53 triggers cell-cycle arrest in untransformed cells via cell-cycle regulators such as CDKs
- it also triggers apoptosis in transformed cells via Bax
- in most tumor cells p53 is mutated and inactivated

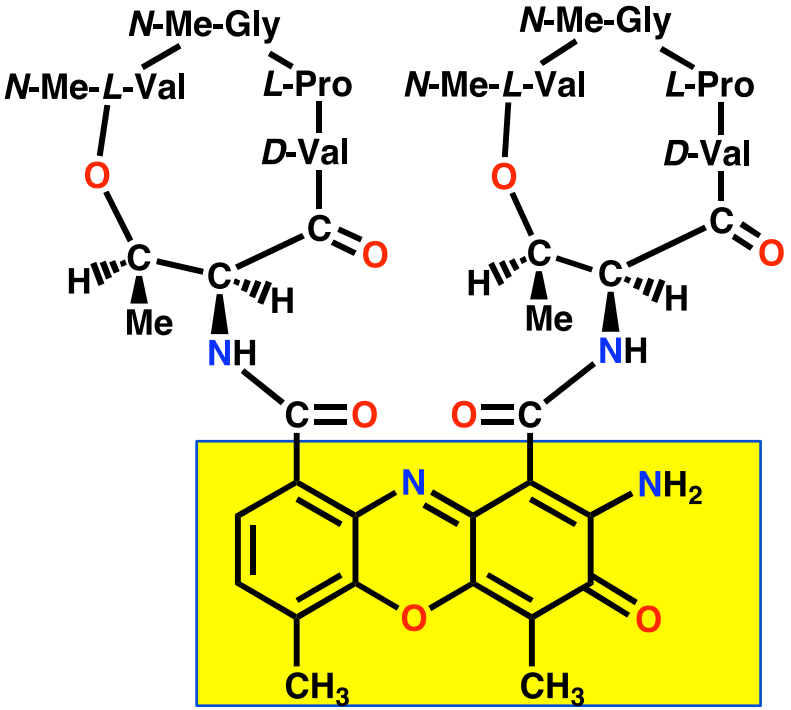
# Drugs directly interacting with DNA

# Intercalating agents

**Mechanism of action**

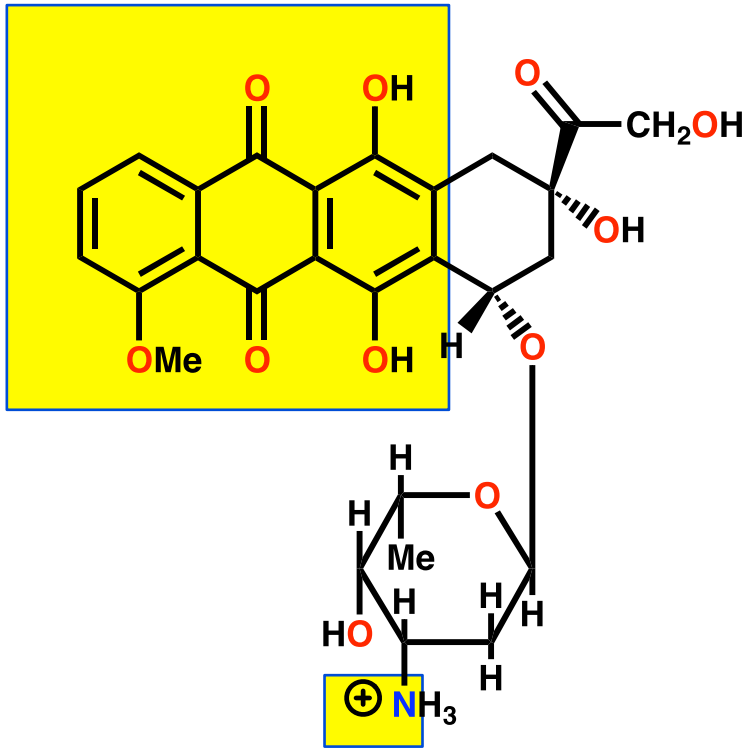
- Contain planar aromatic or heteroaromatic ring systems
- Planar systems slip between the layers of nucleic acid pairs and disrupt the shape of the helix
- Preference is often shown for the minor or major groove
- Intercalation prevents replication and transcription
- Intercalation inhibits topoisomerase II (an enzyme that relieves the strain in the DNA helix by temporarily cleaving the DNA chain and crossing an intact strand through the broken strand.

# Intercalating agents




**Dactinomycin**

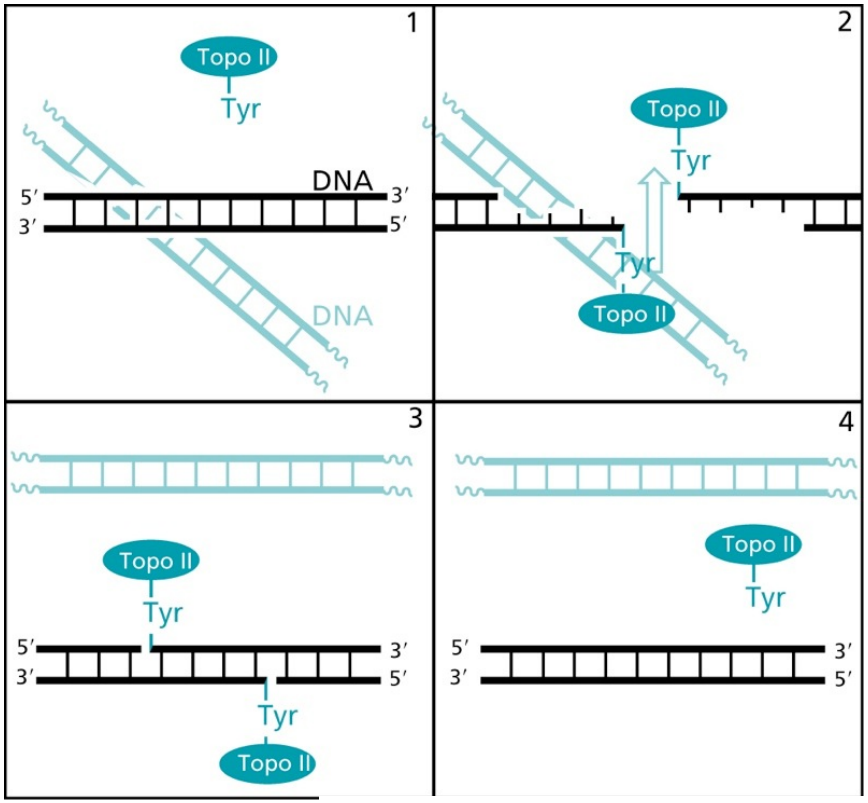
(Extra binding to sugar phosphate backbone by cyclic peptide)



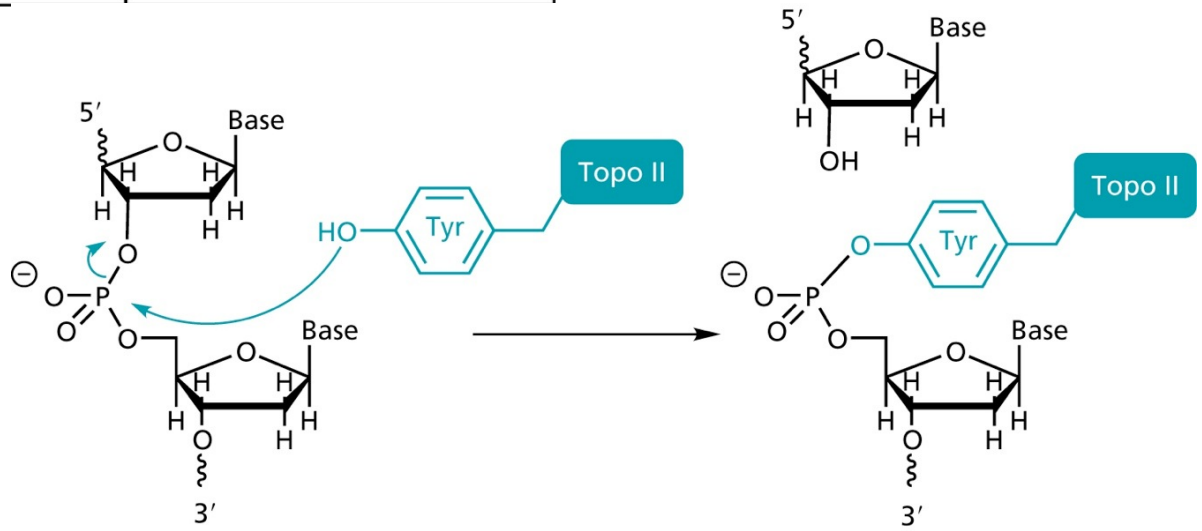

**Doxorubicin (Adriamycin)**

(Extra binding to sugar phosphate backbone by $NH_3$)

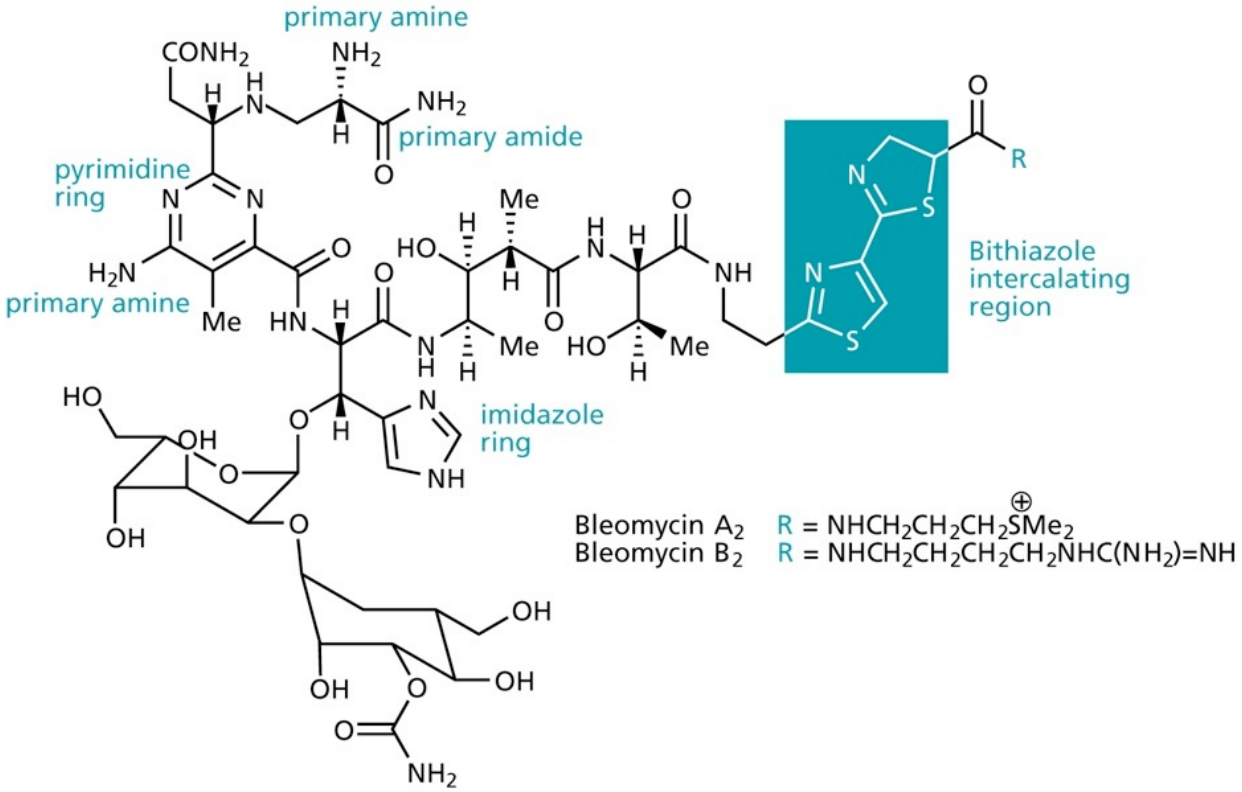
# Intercalating reagents (II)




- During replication, supercoiled DNA is unwound by the helicase. The thereby created tension is removed by the topoisomerase II, that cuts and rejoins the DNA strands.
- When doxorubicin is bound to the DNA it stabilizes the DNA-topoII complex at the point where the enzyme is covalently bound



# Natural Products in Cancer Therapy: Bleomycins

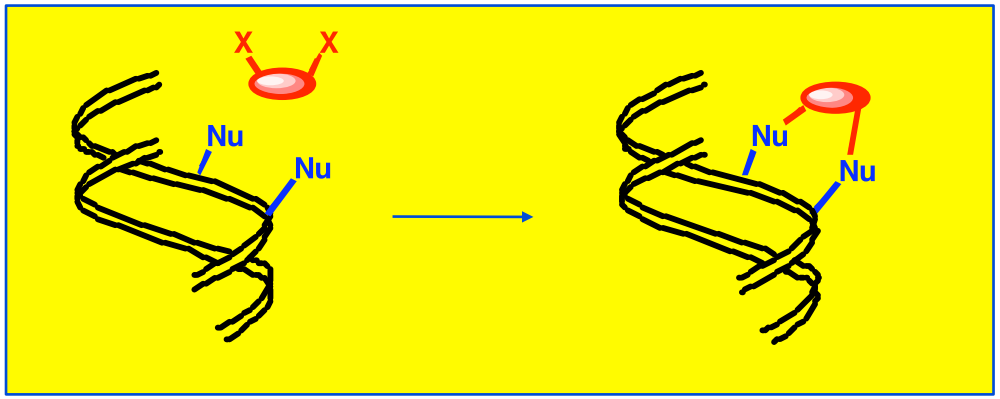



- intercalate via the bithiazole moiety
- the N-atoms of the primary amines, pyrimidine ring and imidazole ring chelate Fe, which is involved in the formation of superoxide radicals, which subsequently act to cut DNA between purine and pyrimidine nucleotides

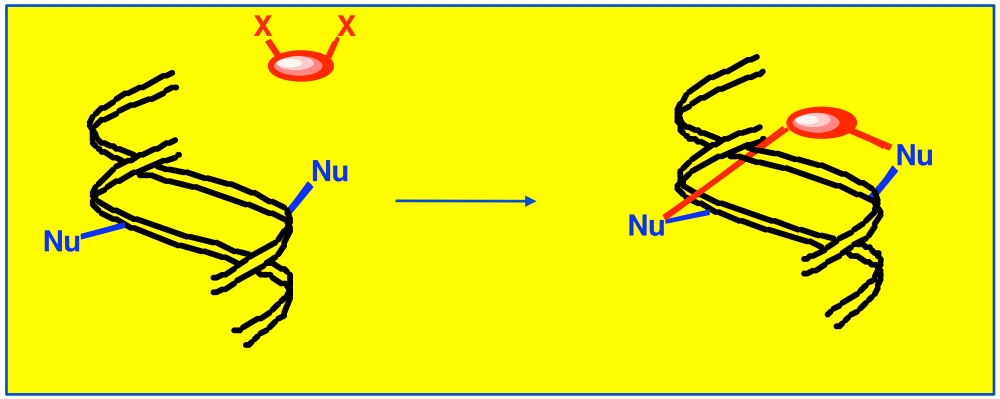
# Drugs directly interacting with DNA

## Alkylating agents

- Contain highly electrophilic groups
- Form covalent bonds to nucleophilic groups in DNA
- Attack N-1 and N-3 of adenine and N-3 of cytosine, and in particular N-7 of guanine bases
- Prevent replication and transcription
- Useful as anti-tumour agents
- Toxic side effects (e.g. alkylation of proteins)

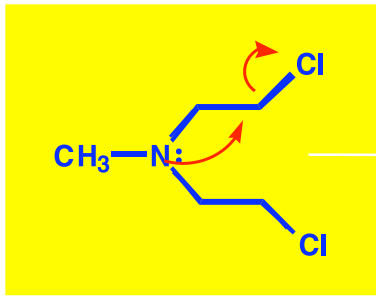



**Intrastrand cross linking**

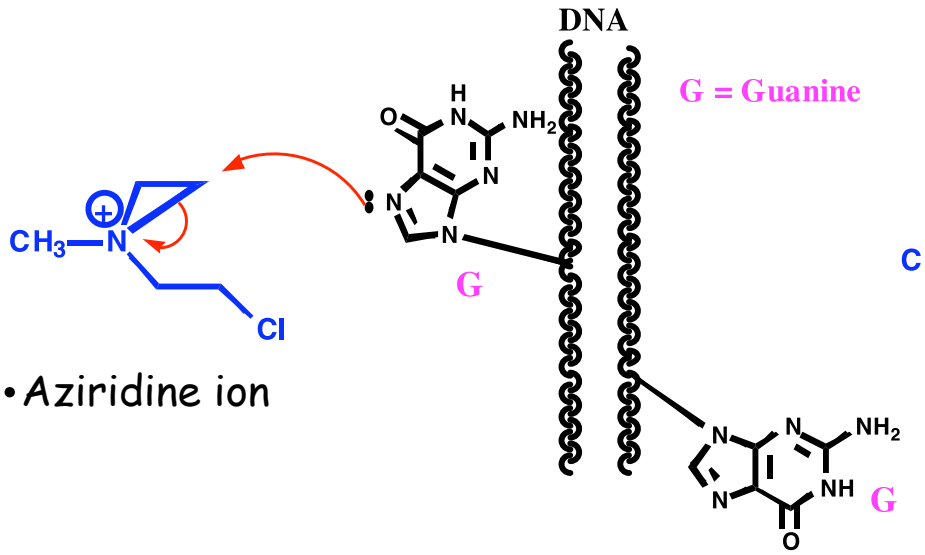



**Interstrand cross linking**

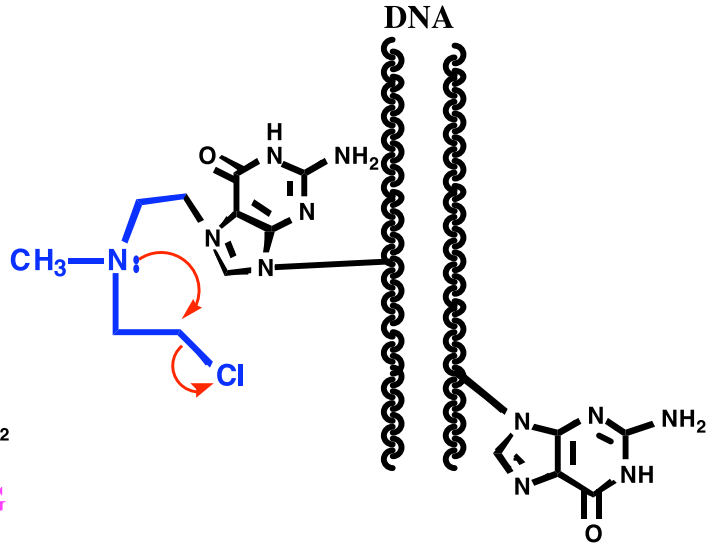
# Mechanism of action of Chlormethine

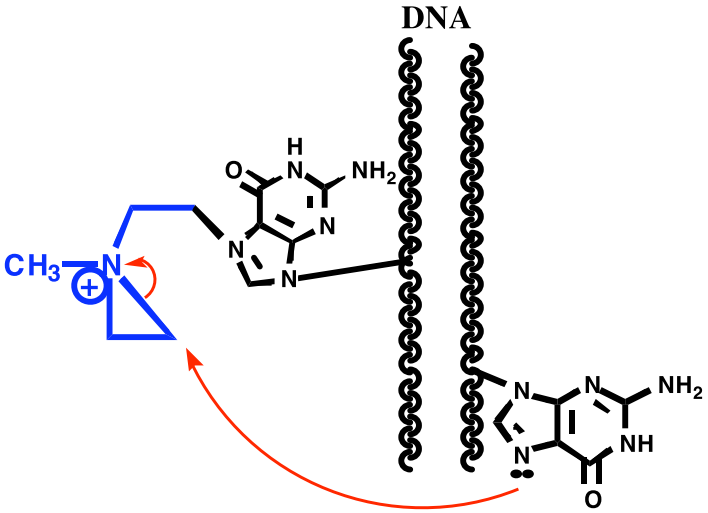


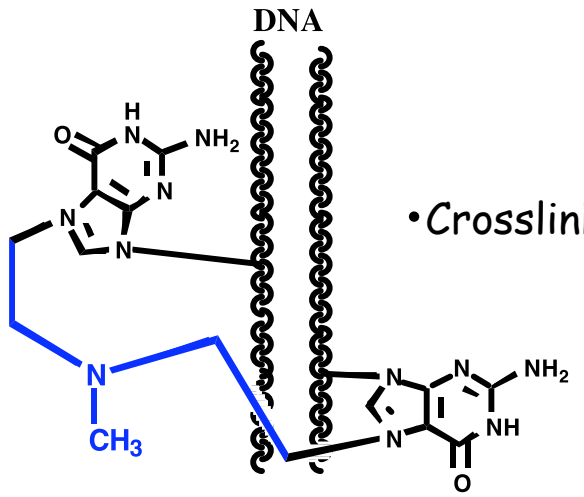

•Chlormethine




•Aziridine ion



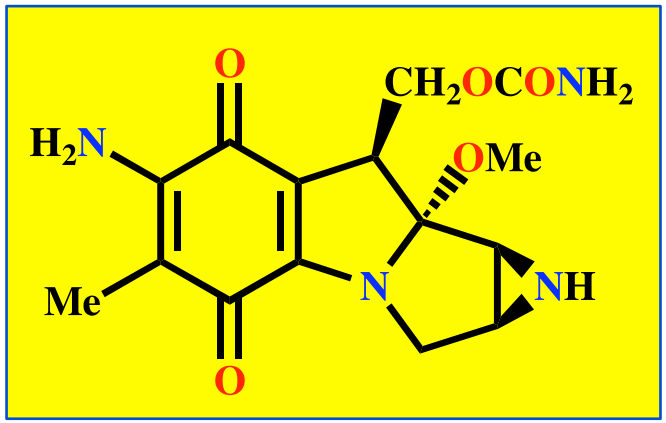




•Crosslinked DNA

• too reactive to survive oral route, putting an aromatic moiety instead of the Me group lowers reactivity (and moreover, mimics the amino acid Phe)

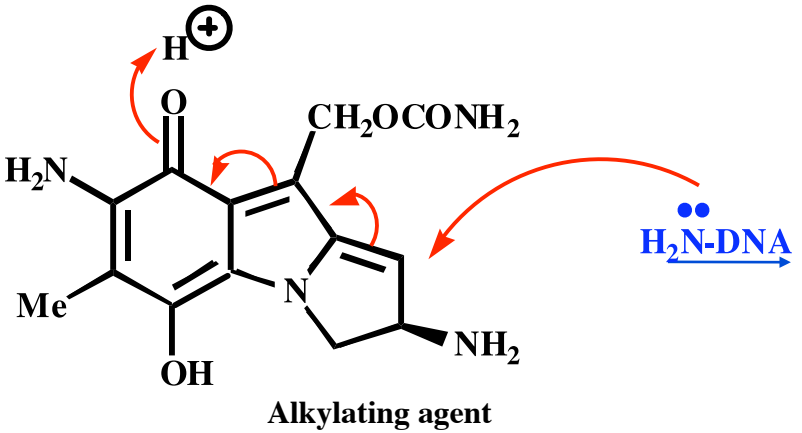
# Alkylating Drugs: Mitomycin C

**Mitomycin C**

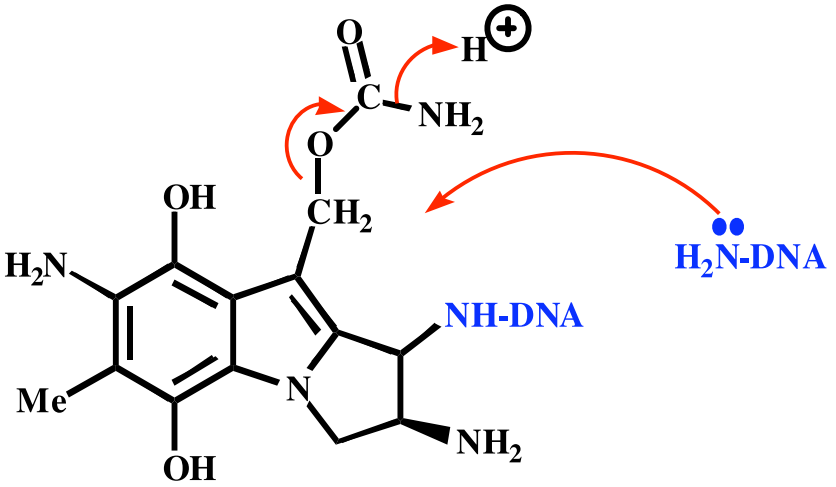


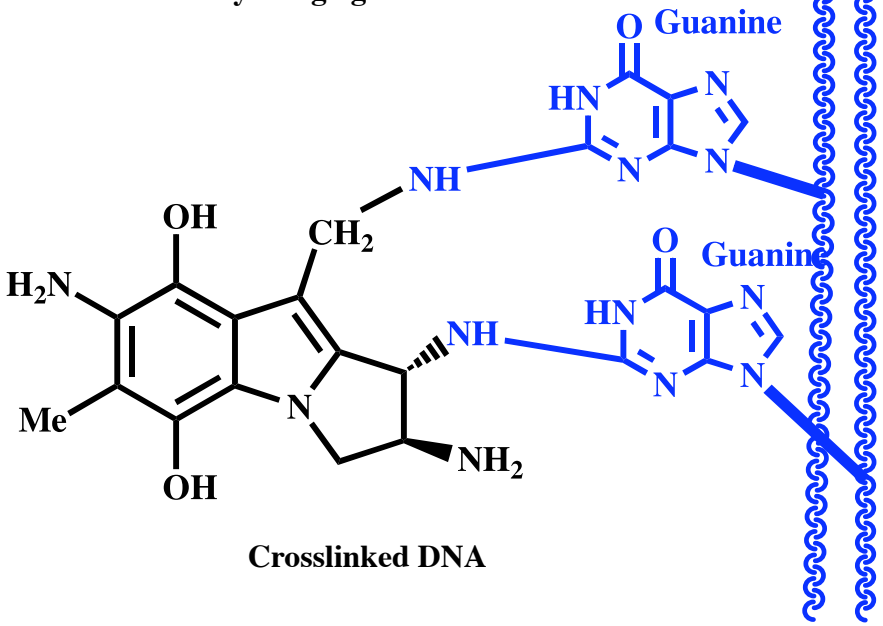

Reduction

**Converted to alkylating agent in the body**




Alkylating agent

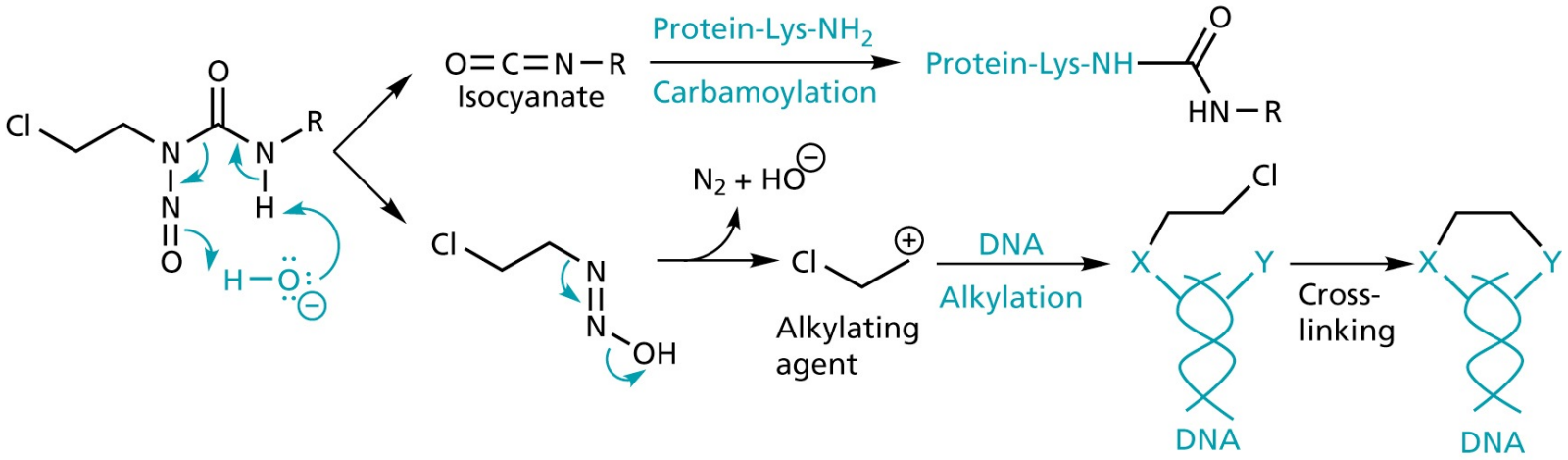


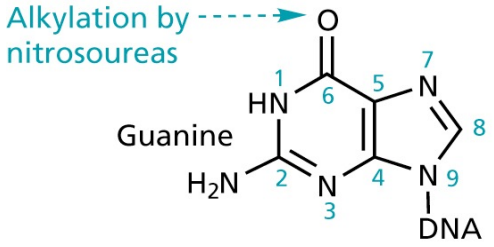



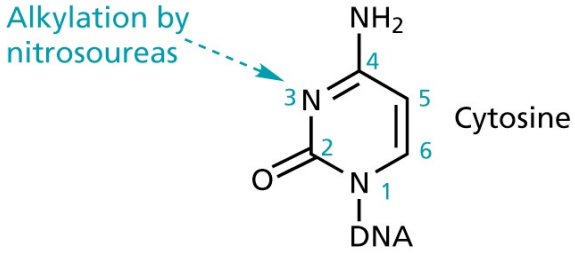

Crosslinked DNA

# Nitrosoureas

- Lomustine and carmustine are lipid-soluble and can cross the blood-brain barrier
- The drugs decompose to form alkylating and carbamoylating

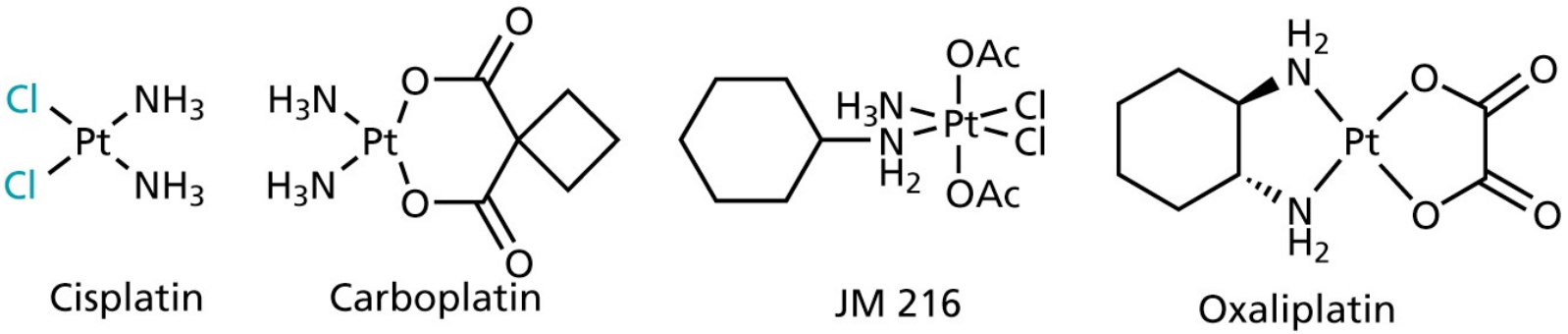


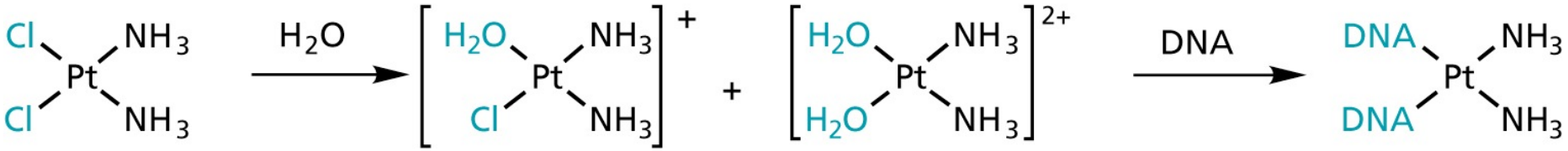



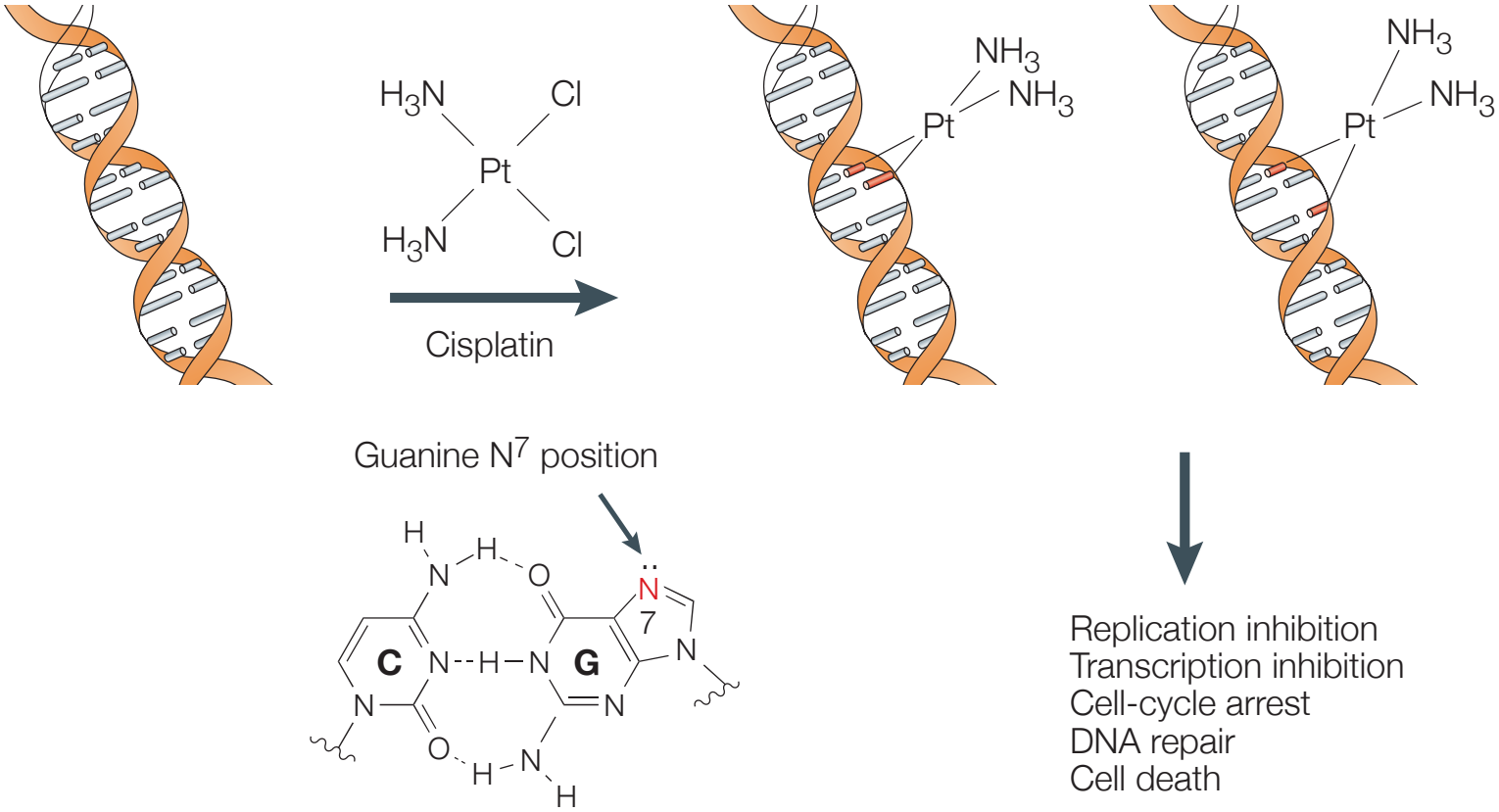

- the formed isocyanate reacts with lysine NH3 groups thereby inactivating DNA repair enzymes
- the alkylating agent reacts first with O-6 of guanine followed with N-3 of cytosine of the other strand

# Pt-Alkylating agents

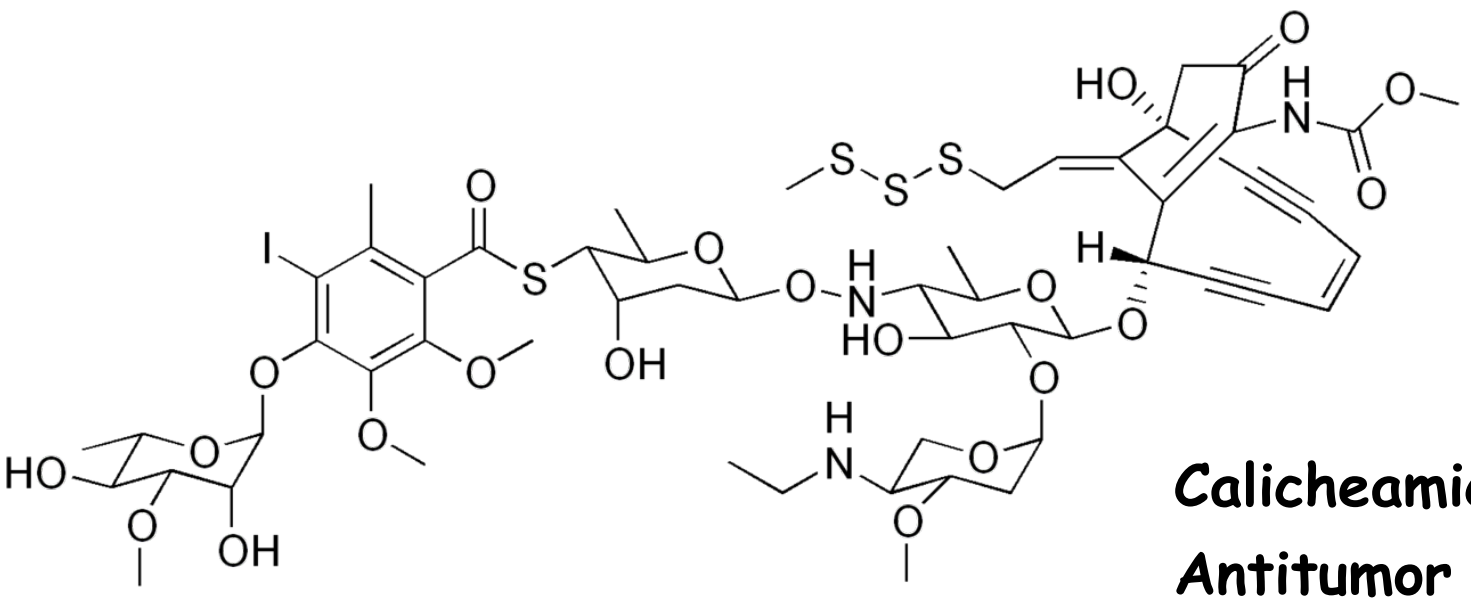



- Binds to DNA in regions rich in guanine units
- Intrastrand links rather than interstrand
- Inhibits transcription
- In solution the Cl- ligands are exchanged against water to result in positively charged ligands that bind to the DNA (to N-7 or O-6 of adjacent guanine groups)
- Results in localized unwinding of the DNA




H3N
Cl
Pt
H3N
Cl
Cisplatin
NH3
NH3
Pt
NH3
NH3
Pt
Guanine N7 position
H
N
H
O
N
7
C
N
H
N
G
N
N
O
H
N
H
Replication inhibition
Transcription inhibition
Cell-cycle arrest
DNA repair
Cell death

# DNA chain cutters



**Calicheamicin $\gamma_1^I$**

**Antitumor agent**

- Generates DNA diradical
- DNA diradical reacts with oxygen
- Results in chain cutting

# siRNA-based anti-cancer approaches

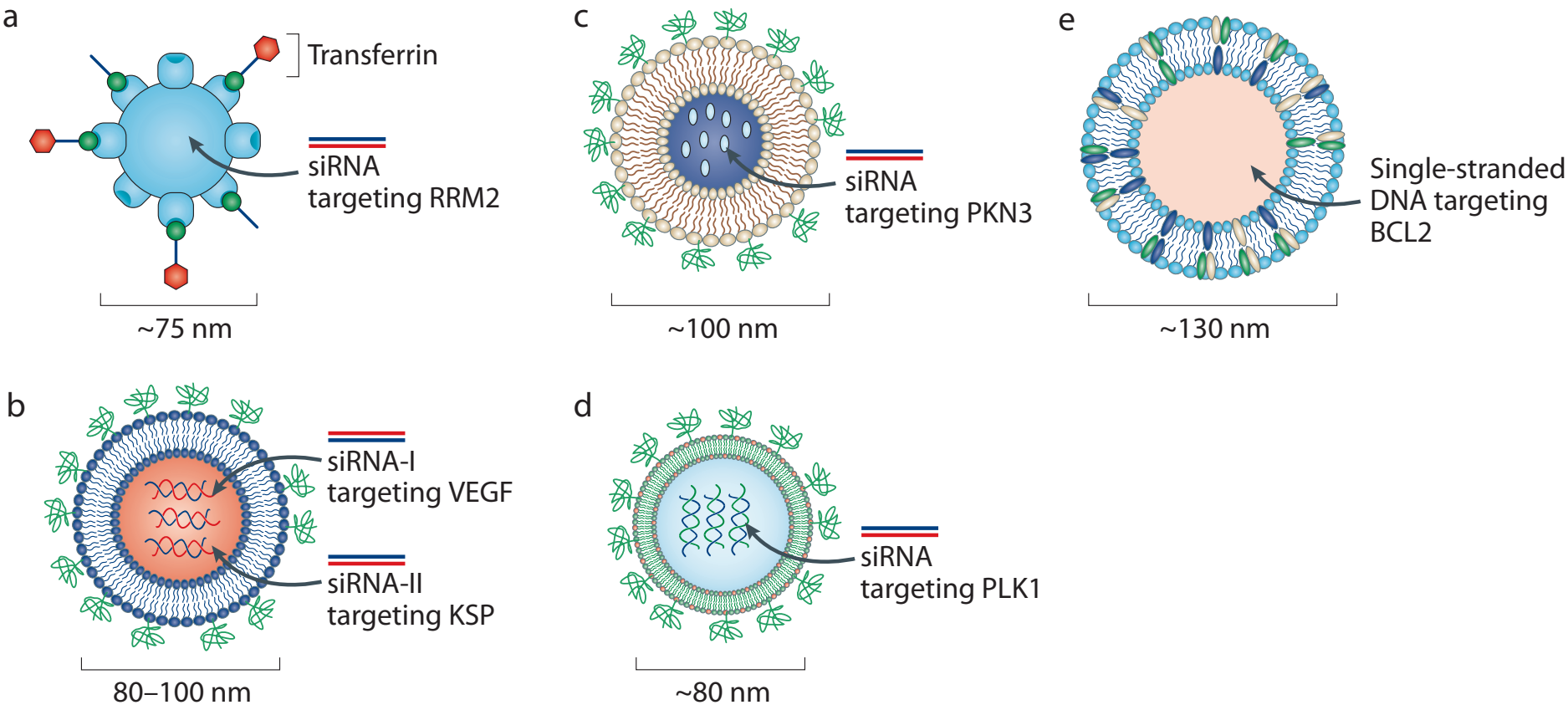
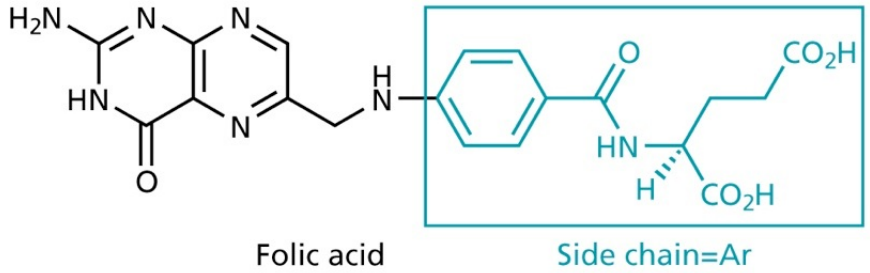
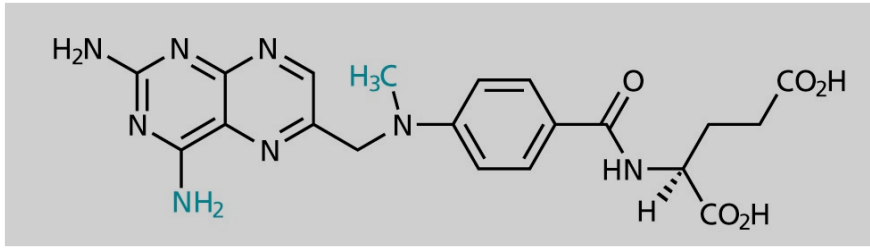



Figure 1 | Schematic illustrations of the siRNA-based therapeutics used in Phase I trials to treat patients with solid cancers. a | CALAA-01 is a polymer-based nanoparticle containing a targeting ligand on its surface (the human protein transferrin) and a small interfering RNA (siRNA) that targets the M2 subunit of ribonucleotide reductase (RRM2). b | ALN-VSP is a lipid-based nanoparticle that contains two different siRNAs that target vascular endothelial growth factor A (VEGFA) and kinesin spindle protein (KSP). c | Atu27 is a lipid-based nanoparticles that contains an siRNA that targets protein kinase N3 (PKN3). d | TKM-PLK1 is a lipid-based nanoparticle that contains an siRNA that targets polo-like kinase 1 (PLK1). e | PNT2258 is a lipid-based nanoparticle that contains single-stranded DNA (rather than siRNA) that targets BCL2.

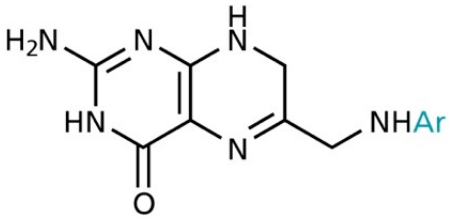
# Antimetabolites

- inhibit the synthesis of DNA or nucleotide building blocks
- Dihydrofolate reductase inhibitors

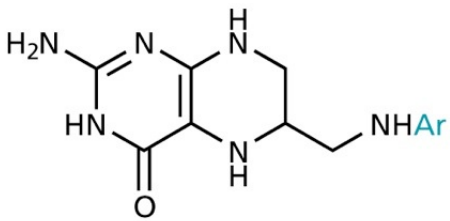



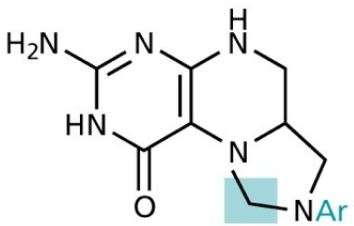
**methotrexate**



Dihydrofolate ($FH_2$)



Tetrahydrofolate ($FH_4$)

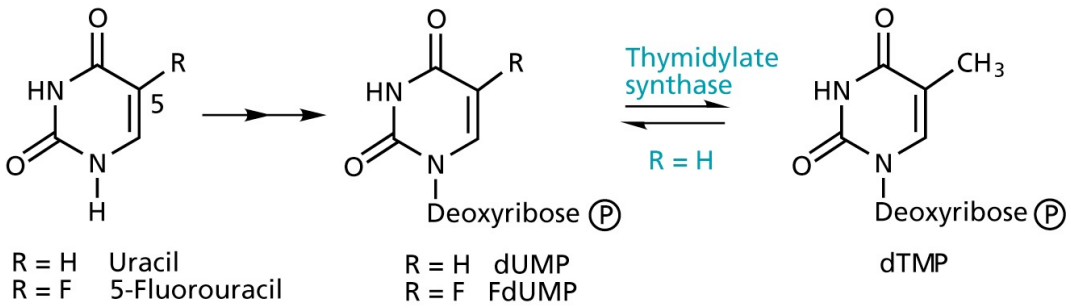


$N^5,N^{10}$-Methylene-$FH_4$

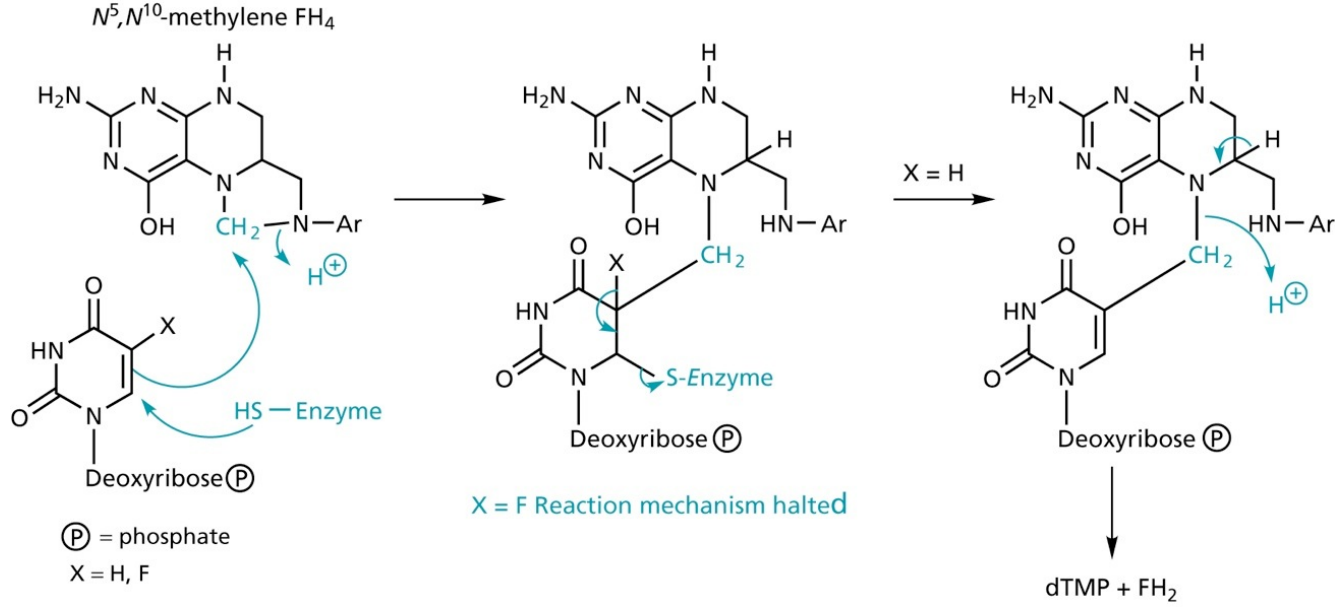
**source of one-C unit for methylations of deoxyuridinemonophosphate (dUMP) to form deoxythymidinemonophosphate (dTMP)**

# Antimetabolites

- Thymidylate synthase inhibitors

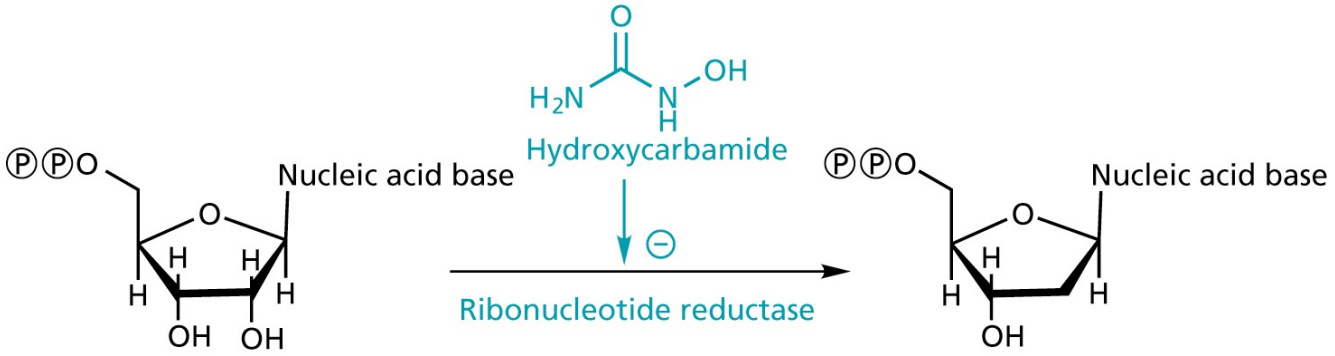



- **5-Fluorouracil** acts as an suicide inhibitor

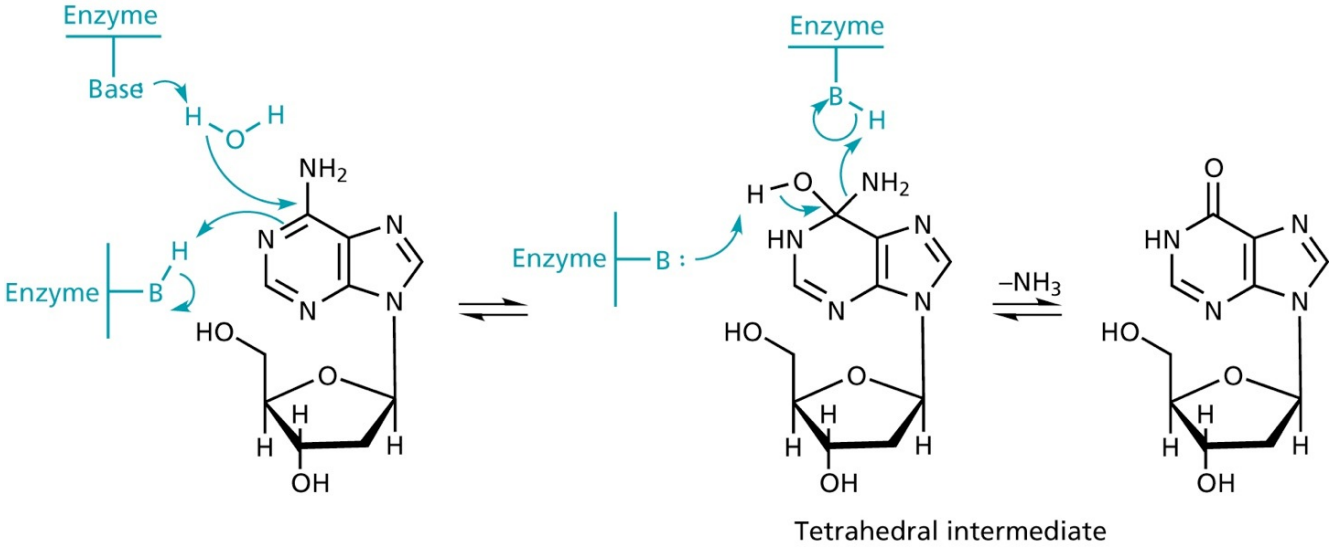


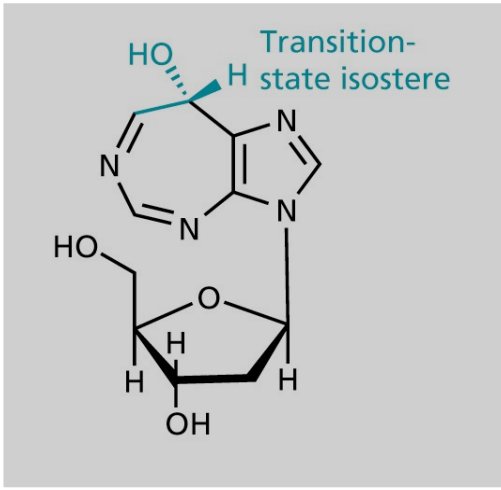
# Antimetabolites

- Inhibitors of **ribonucleotide reductase**
- enzyme converts ribonucleotide diphosphates into desoxyribonucleotide diphosphates, inhibited by **Hydroxycarbamide**




- adenosine deaminase inhibitors, e.g. Pentostatin

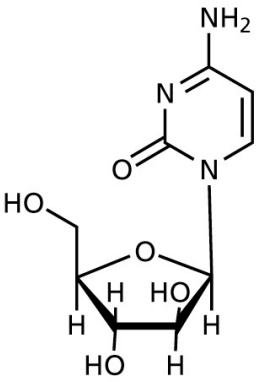


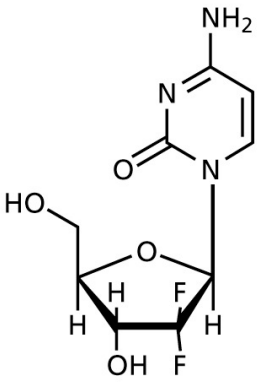

Pentostatin

# Antimetabolites:

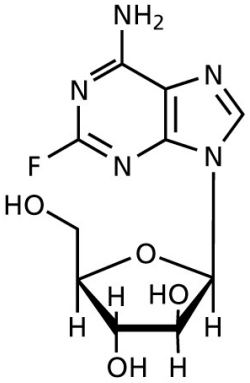
## Purine antagonists



Cytarabine (cytosine arabinoside)

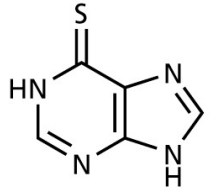


Gemcitabine

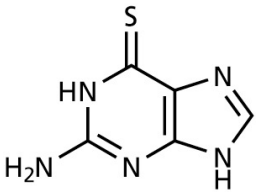


Fludarabine

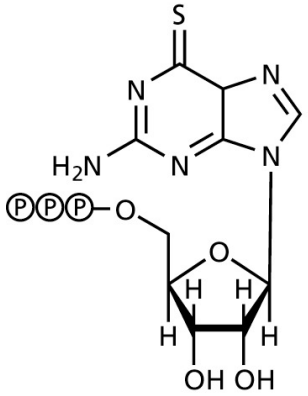
## DNA polymerase inhibitors



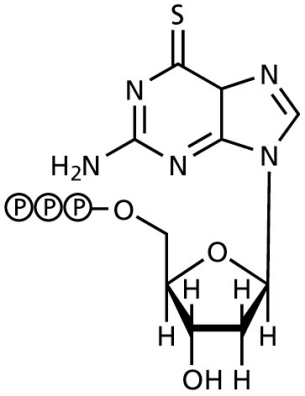
6-Mercaptopurine



6-Tioguanine



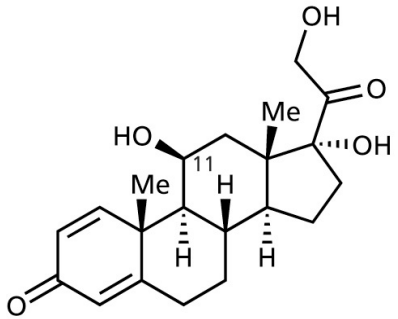
ThioGTP



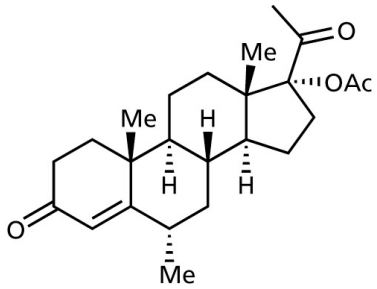
ThiodGTP

# Hormone-based Anti-Cancer Therapies

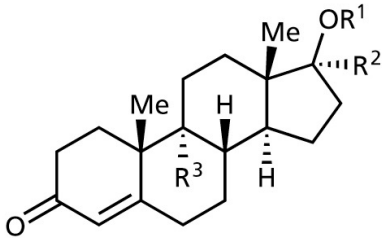
- steroid hormones bind to nuclear receptors and act as transcription factors
- if the cancer requires a specific hormone, a hormone resulting in the opposite effect can be administered
- Used: glucocorticoides (hormones involved in the biosynthesis of glucose, e.g. prednisolone), oestrogens, progestins (e.g. medroxyprogesterone acetate), analogues of the luteinizing hormone-releasing hormones (LHRH)



Prednisolone



Medroxyprogesterone acetate

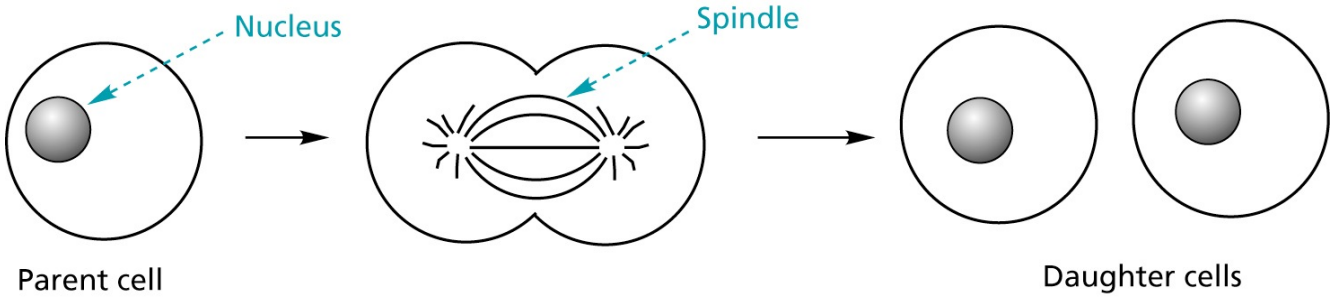


Fluoxymesterone,
$R^1 = H$, $R^2 = Me$, $R^3 = F$
Testosterone propionate,
$R^1 = COEt$, $R^2 = R^3 = H$

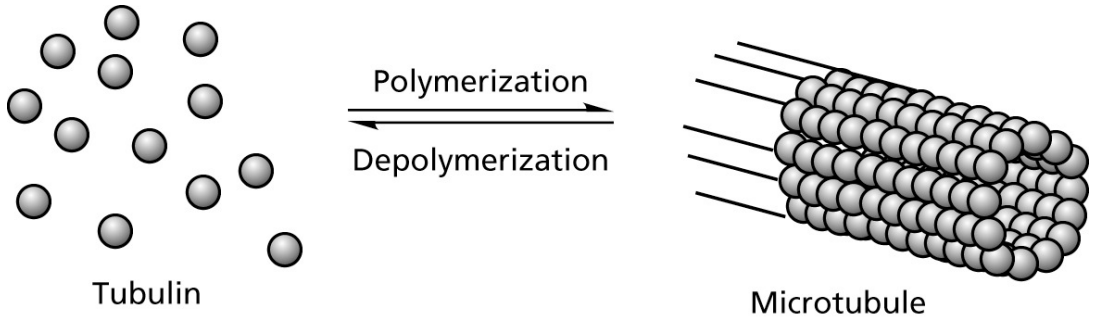
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
|---|---|---|---|---|---|---|---|---|---|---|
| pyroGlu | His | Trp | Ser | Tyr | Gly | Leu | Arg | Pro | Gly-$NH_2$ | LHRH |
| pyroGlu | His | Trp | Ser | Tyr | (D-Leu) | Leu | Arg | Pro | ethylamide | Leuprolide |
| pyroGlu | His | Trp | Ser | Tyr | (D-(t-Bu)Ser) | Leu | Arg | Pro | Azgly-$NH_2$ | Goserelin |

# Drugs acting on structural proteins

- mitosis is a ordered series of events in which identical copies of the genome are moved to discrete locations within the dividing cell
- The mitotic spindle is very important for that event. The filaments in the mitotic spindle are formed from microtubule

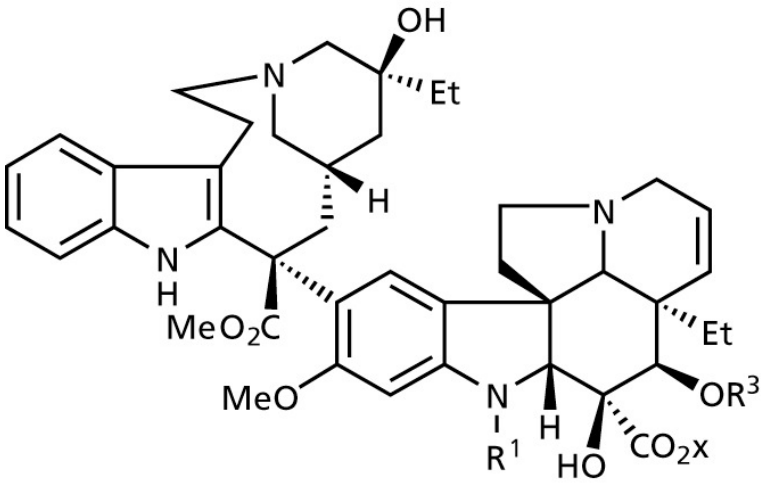



- microtubule are cytoskeletal elements present in all eukaryotic cells.
- they are composed of α- and β-subunits
- both, formation (polymerization) and destruction (depolymerization) of microtubules are important for proper execution of cell division
- drugs interfering with microtubule polymerization/depolymerization interfere with mitosis , cause cell-cycle arrest and trigger apoptosis

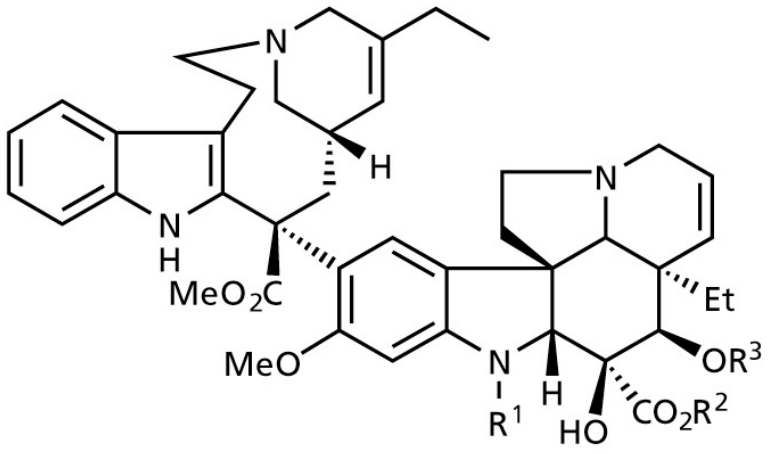


# Drugs acting on structural proteins

## Inhibitors of tubulin polymerization




Vinblastine ($R^1$ = Me; x = OMe; $R^3$ = COMe)
Vincristine ($R^1$ = CHO; x = OMe; $R^3$ = COMe)
Vindesine ($R^1$ = Me; x = $NH_2$; $R^3$ = H)



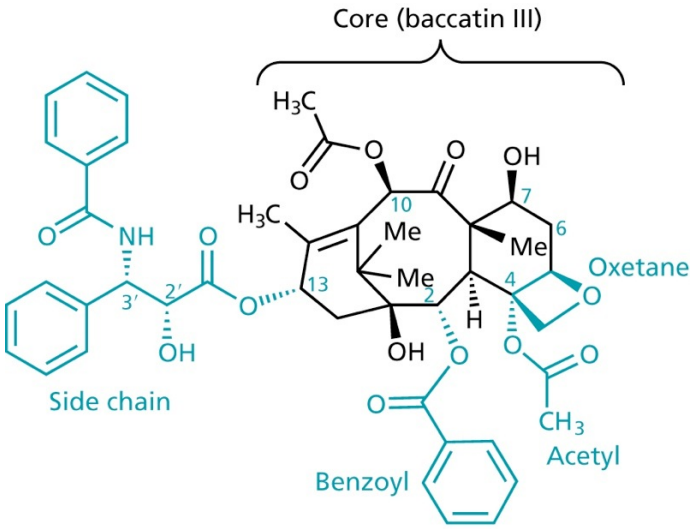

Vinorelbine

- vinca alkaloids from the Madagascar periwinkle plant
- can be substrate for the P-glycoprotein efflux pump

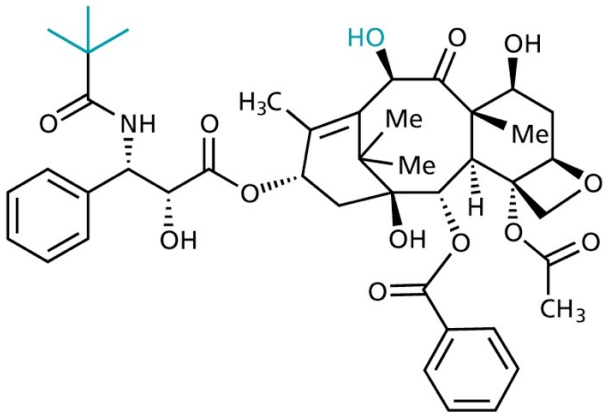
# Drugs acting on structural proteins

## Inhibitors of tubulin depolymerization

### Taxol

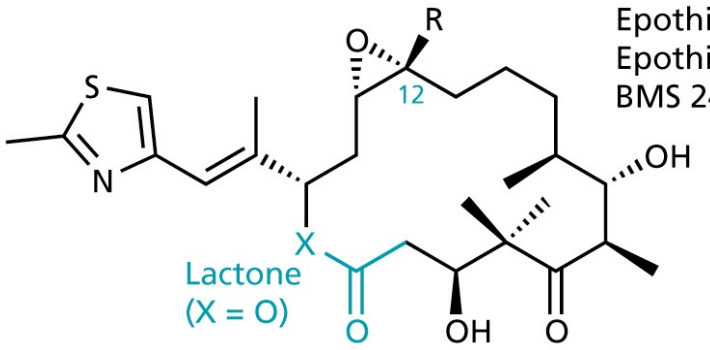



Paclitaxel



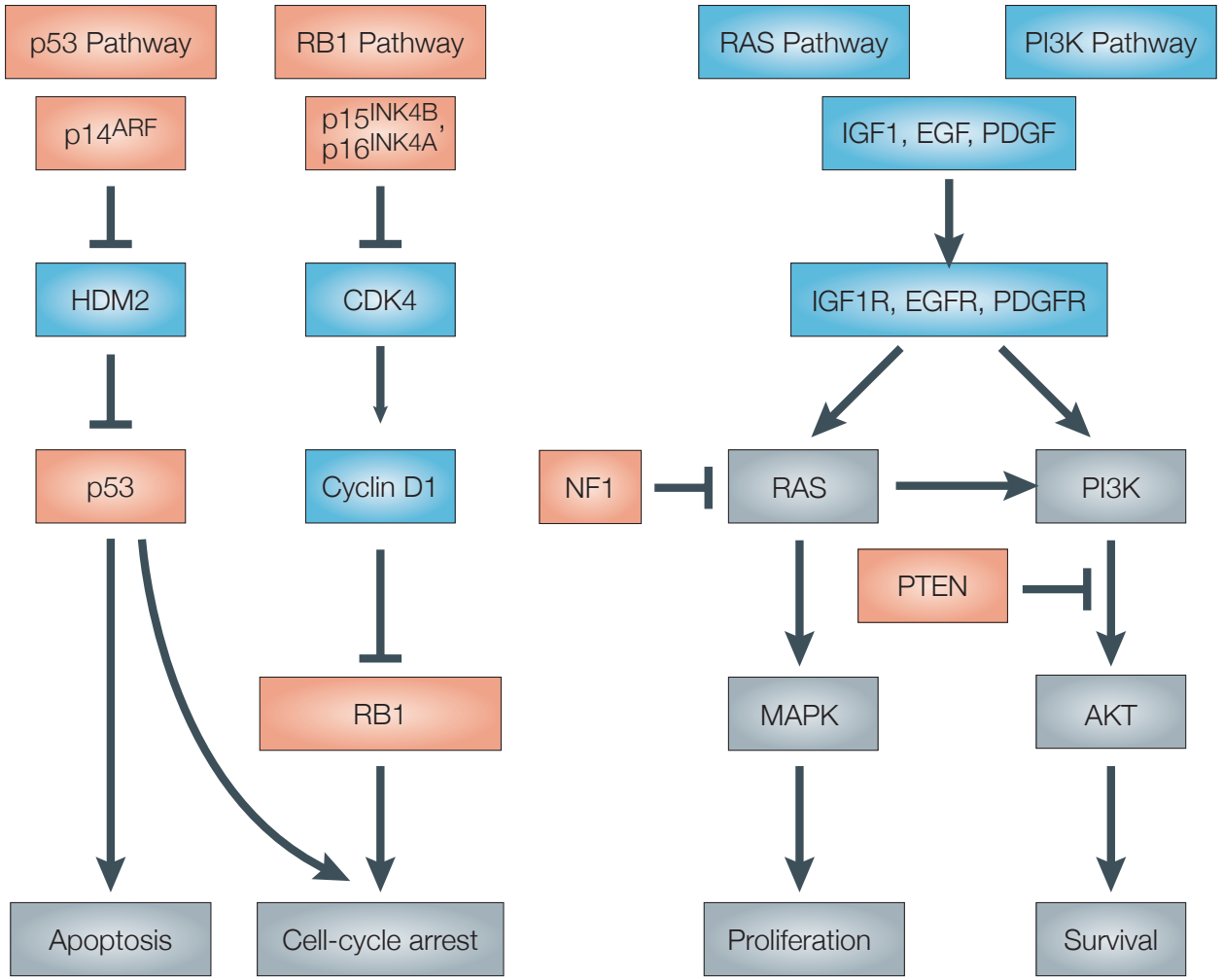
Docetaxel

### Epothilone




- Taxol is harvested from the bark of the yew trees
- binds to the β-subunit of tubulin and accelerates polymerization
- the resultant microtubules are stabilized, inhibiting depolymerization
- cell cycle is halted at the G2/M stage
- prepared semi-synthetically from a compound from yee needles
- cannot be taken orally
- causes multidrug resistance (substrate for p-glycoprotein)
- ephothilones are bacterial metabolites. They are not substrate for P-GP

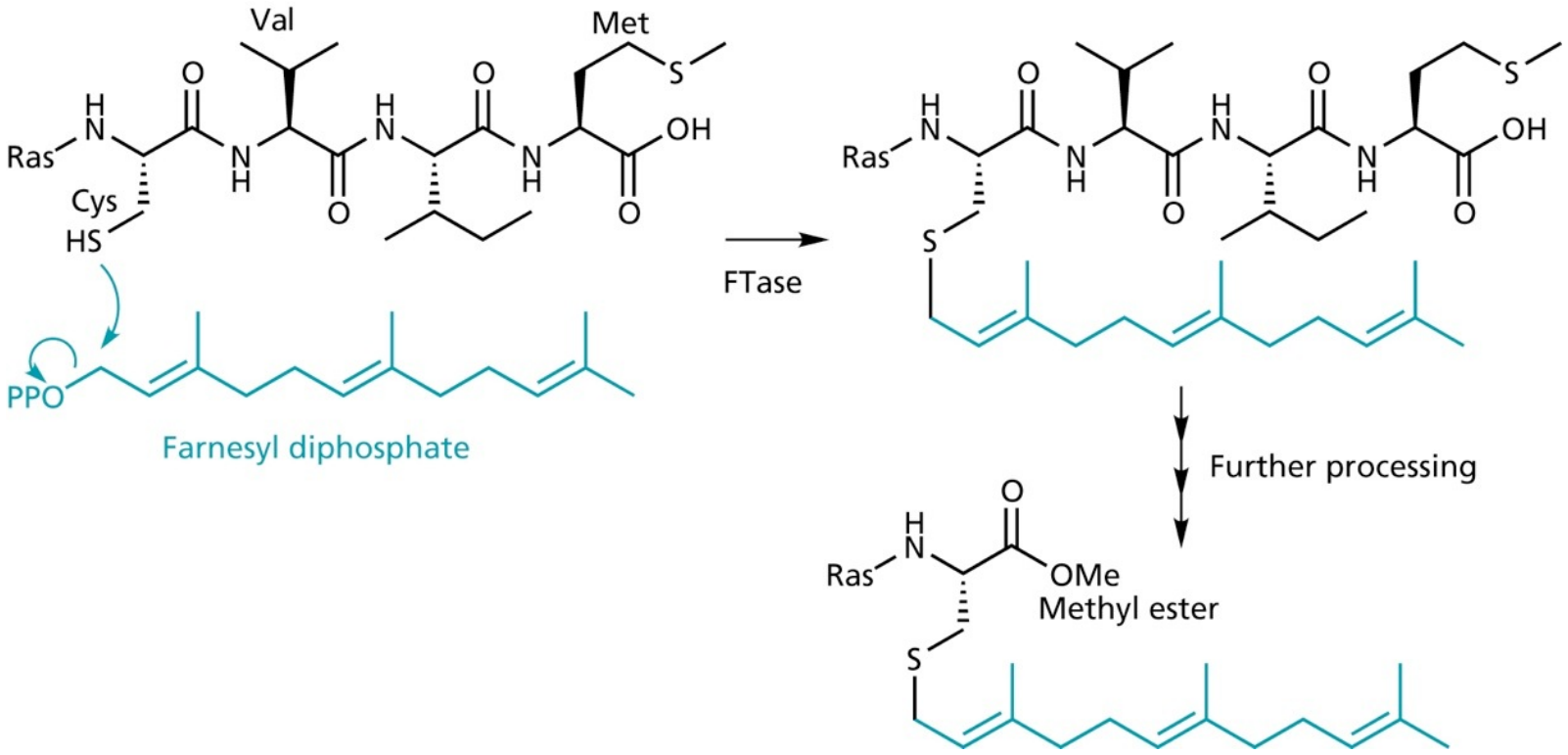
# Signaling pathways important for Cancer



- **Ras**: (**Ra**t **s**arcoma) Ras protein family members belong to the **GTPases**, and are involved in transmitting signals within cells. When Ras is 'switched on' it subsequently switches on other proteins, that turn on genes involved in **cell growth, differentiation and survival**. As a result, mutations in ras genes can lead to the production of permanently activated Ras proteins. Because these signals result in cell growth and division, **overactive Ras signaling can ultimately lead to cancer.**
- **p53/HDM2: Tumor suppressor**. p53 has many mechanisms of anticancer function and plays a role in **apoptosis, genomic stability, and inhibition of angiogenesis**. It is **modulated by MDM2**.
- **PIK3: phosphatidylinositol-3-kinase.** PI3Ks are a family of signal transducer enzymes capable of phosphorylating the 3 hydroxyl of the inositol ring of phosphatidylinositol. PI 3-kinases have been linked to cell growth, proliferation, differentiation, motility, survival and intracellular trafficking.The class IA PI 3-kinase p110a is mutated in many cancers. PI 3-kinase activity contributes significantly to cellular transformation and the development of cancer.
- **AKT**: **Protein kinase B** (PKB, Akt) is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration.
- **MAPK**: **Mitogen-activated protein kinases** (MAPK) are protein kinases that are specific to the amino acids serine, threonine, and tyrosine. They regulate cell functions including proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis

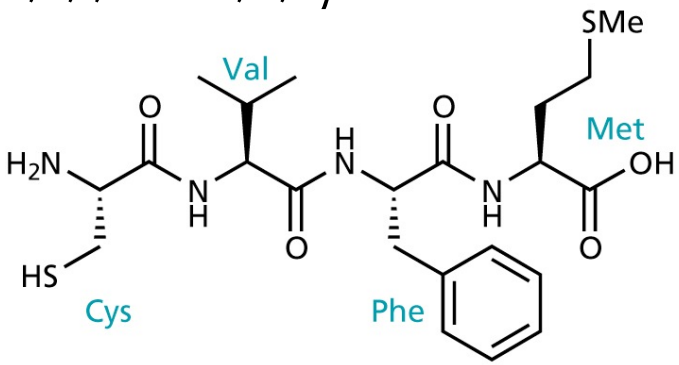
# Farnesyltransferase inhibitors

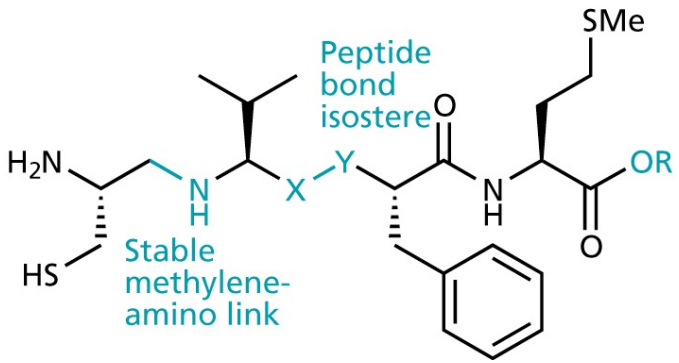
- The RAS signaling protein is involved in cancer. Mutations in RAS are found in 30% of cancer cells. Mutant RAS is constitutively active.
- RAS signaling requires linking RAS to the inner membrane leaflet. This is done by adding a carbon chain by the farnesyl transferase.

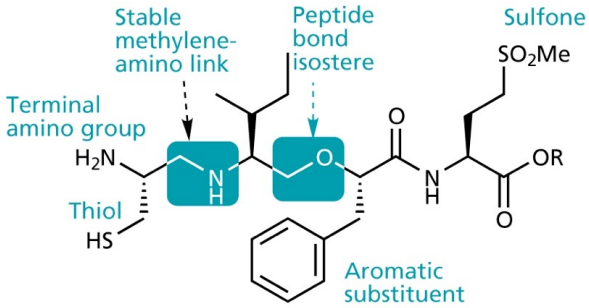


# Design of Farnesyltransferase inhibitors

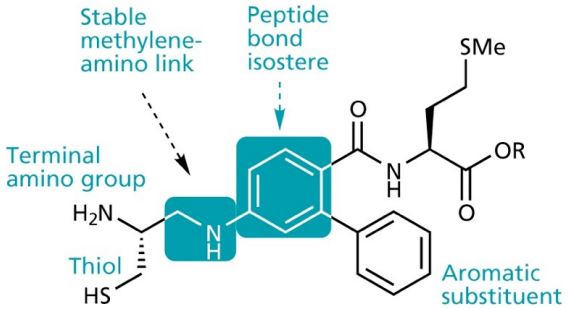
- substrate has Cys-aa-X architecture (a=V,L,I; X=M,E,S)



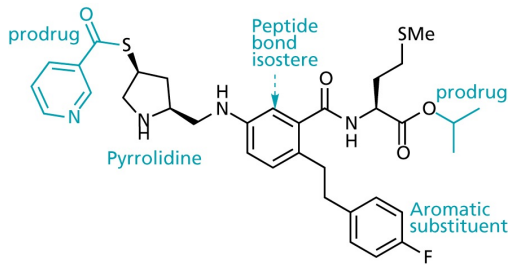




R = H L 739750
R = $^{i}$Pr L 744832




R = H FTI 276
R = Me FTI 277



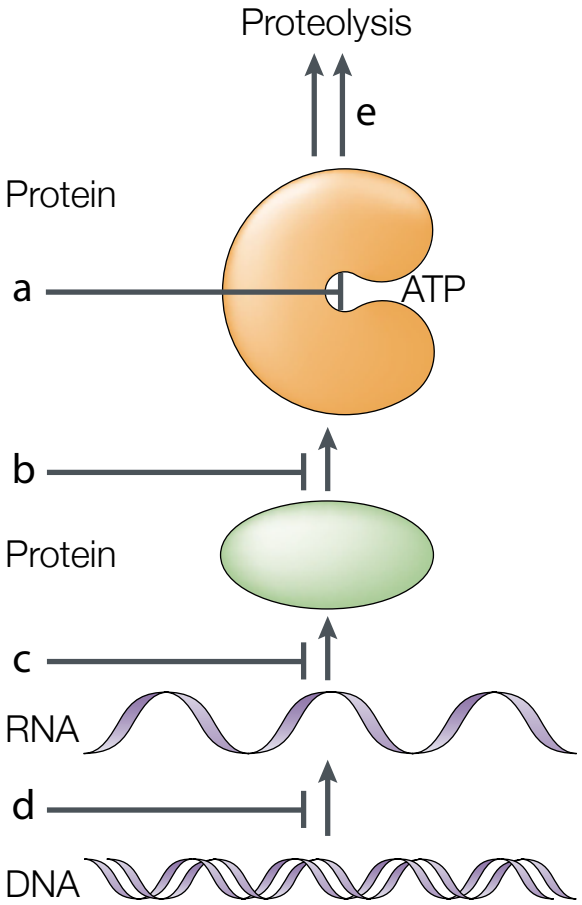

- masking of C-terminal free acid
- removal of susceptibility to peptide bond cleavage by proteases
- both carboxyl acid and thiol masked as prodrugs

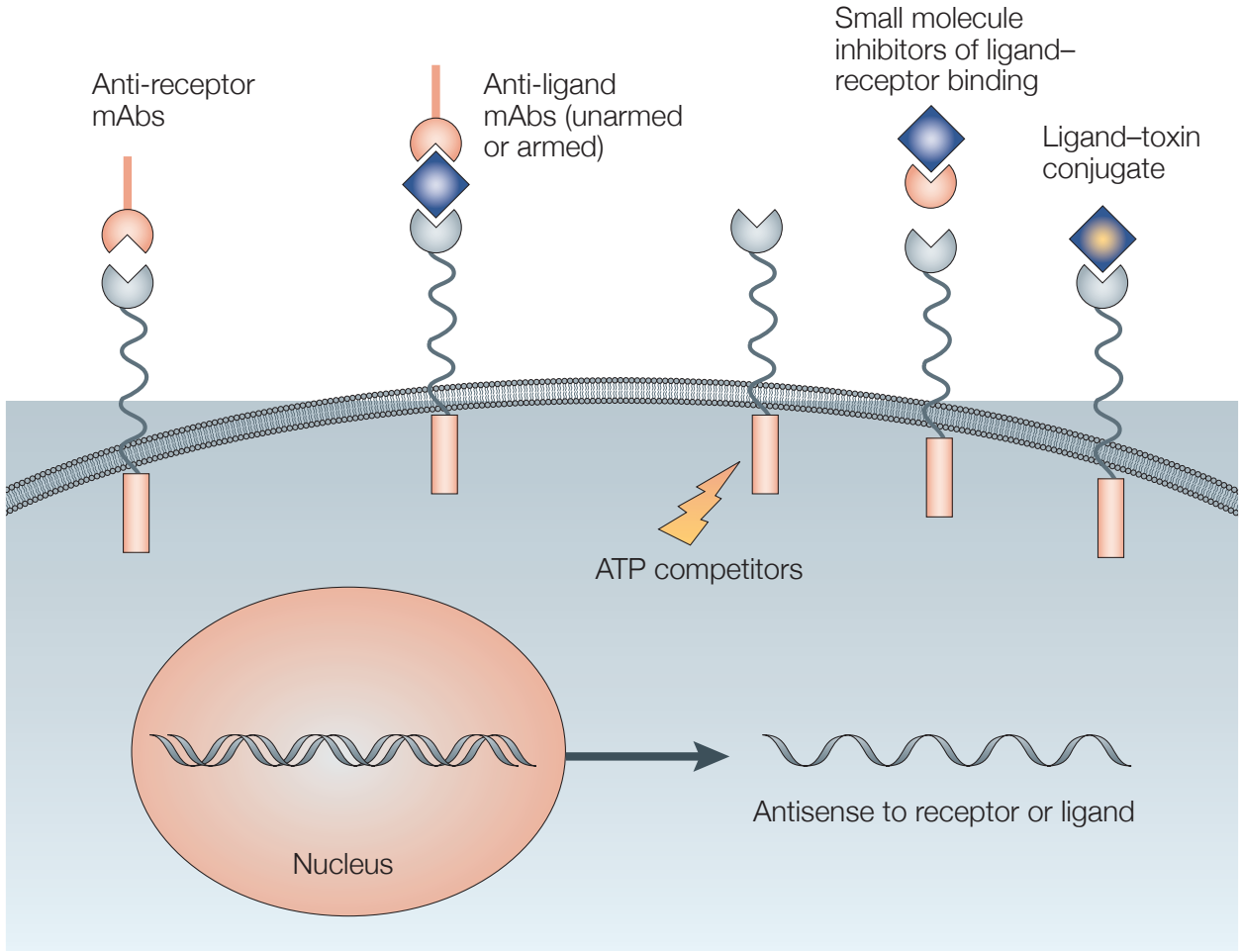
# Tyrosine Kinase Inhibitors

- Small molecule tyrosine kinase inhibitors (or TKIs) – generic names end in "-nib"
- Generally oral
- Side effects vary, depending on which enzymes they inhibit (what their target is)
- Several are effective against cancers resistant to most previous therapies

| **Generic Name** | **Brand Name** | **Cancer** |
|---|---|---|
| Imatinib | Gleevec | CML, GIST, others |
| Dasatinib | Sprycel | CML, ALL |
| Nilotinib | Tasigna | CML |
| Gefitinib | Iressa | Lung |
| Erlotinib | Tarceva | Lung, Pancreas |
| Lapatinib | Tykerb | Breast |
| Sorafenib | Nexavar | Kidney, Liver |
| Sunitinib | Sutent | Kidney |

# Strategies for targeting kinases



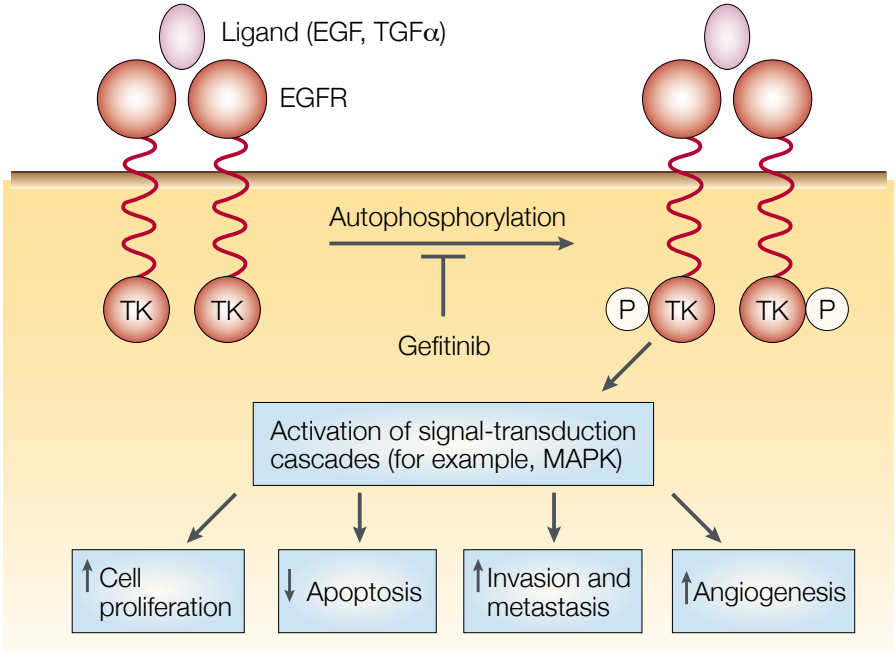

- inhibition of ATP binding (a)
- inhibition of kinase folding (b)
- inhibition of translation (siRNA, c)
- inhibition of transcription (antisense, d)

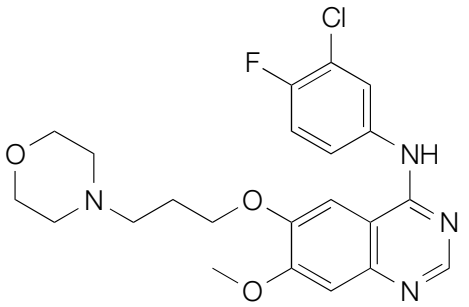
- antibodies against the ligand-binding epitope
- antibodies against the bound ligand
- ATP competitors
- ligand antagonists

Dancey et al. Nature Rev Drug Discov. 2 (2003),296

# Inhibitors of Growth Factors: Targeting the EGF receptors, a TK receptor

- Overexpression of altered Epidermal Growth Factor receptors results (EGFR, ERBB family) in formation of a oncogene.



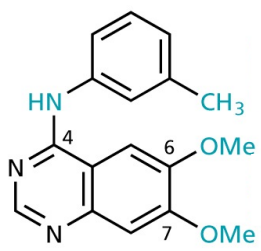




**Gefitinib (ZD1839)**

ATP competitor

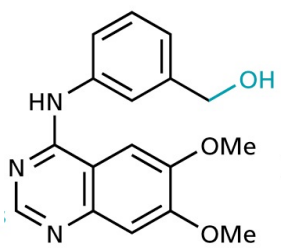
$IC_{50}$ (EGFR) = 0.033 μM
$IC_{50}$ (ERBB2) >3.7 μM
$IC_{50}$ (KDR) >3.7 μM
$IC_{50}$ (FLT-1) >100 μM

morpholine groups improves solubility



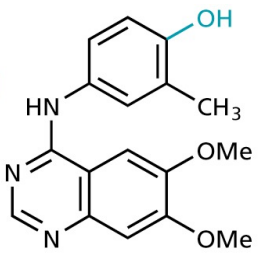

I ($IC_{50}$ 5 nM)

lead



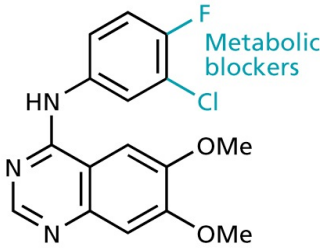

II

metabolite of I




III

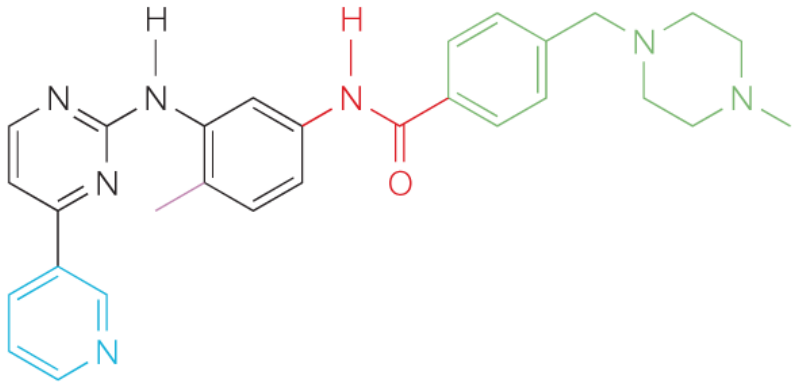
metabolite of I




IV ($IC_{50}$ 9 nM)

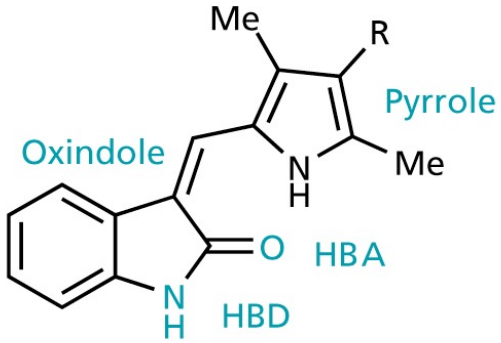
# Inhibitor of the Abelson Tyrosine Kinase (BCR-ABL)

- the BCR-ABL kinase is the sole oncogene responsible in rare blood cancer
- Inhibition of autophosphorylation of BCR-ABL by Gleevec
- treatment of BCR-ABL transformed cell-lines with Gleevec results in dose-dependent reduction of tumor growth
- the anti-tumor effect is specific for BCR-ABL expressing cells
- Gleevec re-activates apoptosis in BCR-ABL cells

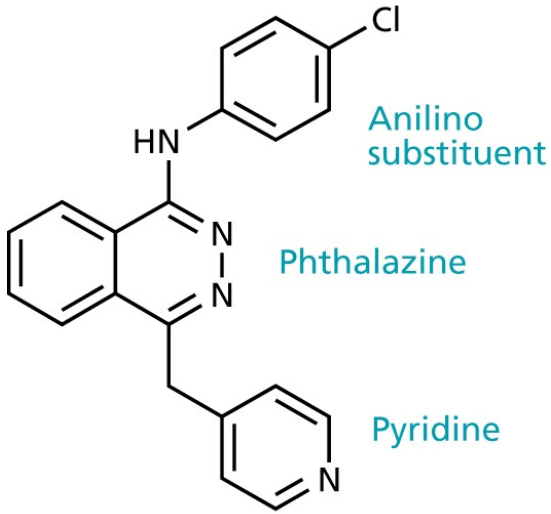


# Angiogenesis Inhibitors

## Targeting the VEGF receptor, a protein tyrosine




SU 5416, R = H
SU 6668, R = $CH_2CH_2CO_2H$

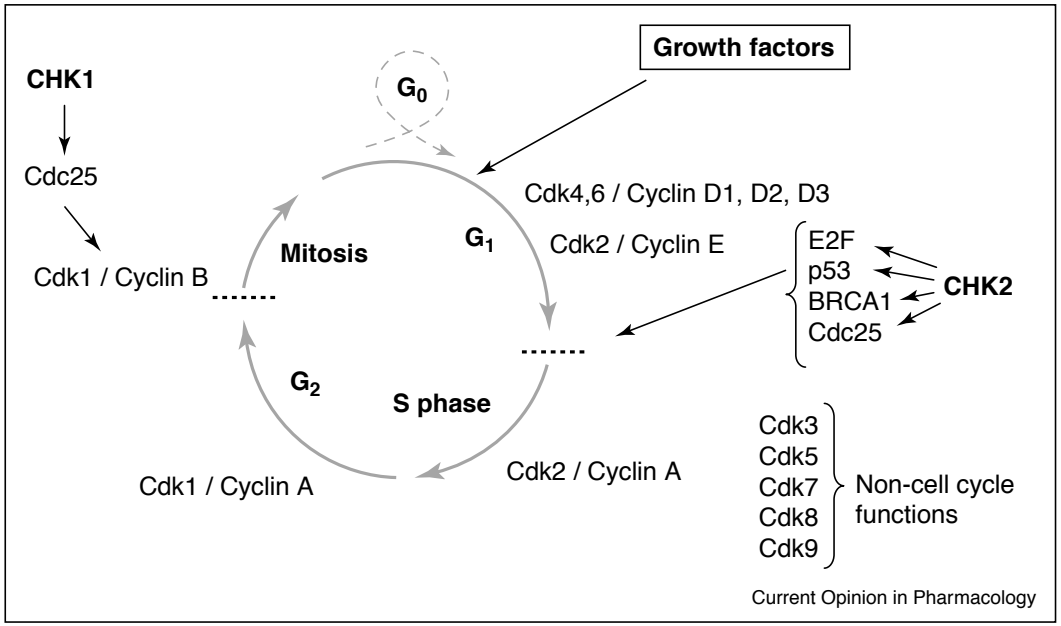


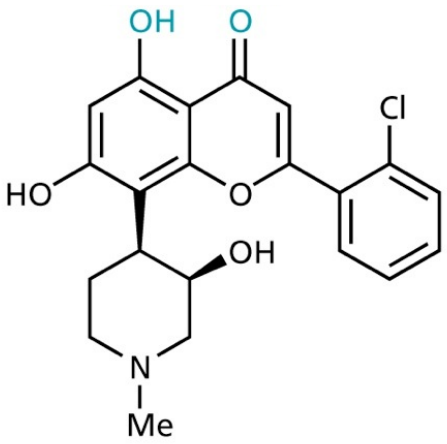

PTK 787 / ZK 222584

- elevated levels of fibroplast growth factors (FGF) and **vascular endothelial growth factor** (**VEGF**) **receptor** are associated with angiogenesis
- VEGF is regulated by multiple cytokines, e.g. the **transforming growth factor (TGF-β)**, the **epidermal growth factor (EGF)** and the **platelet-derived growth factor (PDGF)**
- inhibitors mostly target the ATP binding site other kinase targets: platelet-derived growth factors (PDGF-R), mitogen-activated protein kinases (MAPK), insulin growth factor 1 receptor (IGF-1R), protein kinase B (PKB), c-Src tyrosine kinase, inositol triphosphate kinase (IP3K)

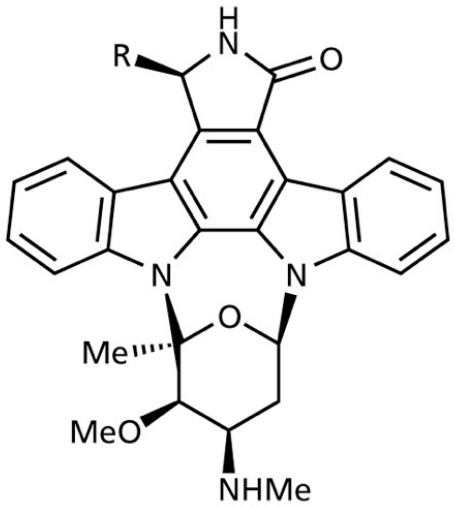
# Inhibitors of cyclin-dependent kinases, S/T kinases

- CDKs are important for the control of the cell-cycle (mainly at G1/G2 depending on DNA damage for example)
- Ser/Thr kinases
- they are activated by cyclins and inhibited by cyclin-dependent kinase inhibitors

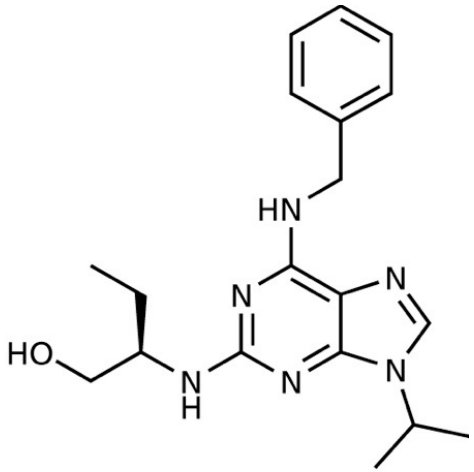



Flavopiridol



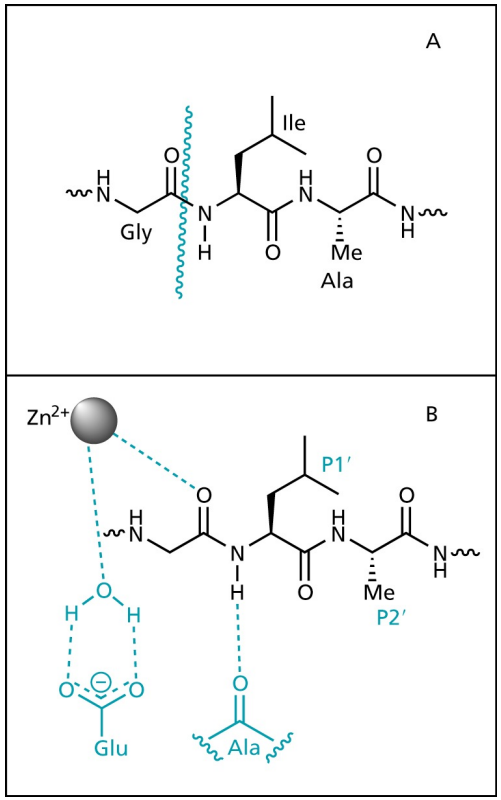

Staurosporine; R = H
7-Hydroxystaurosporin; R = OH

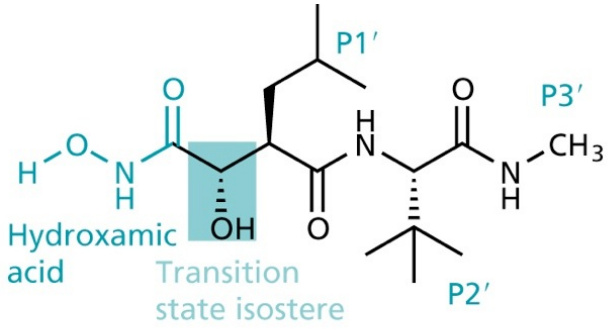



*R*-Roscovitine

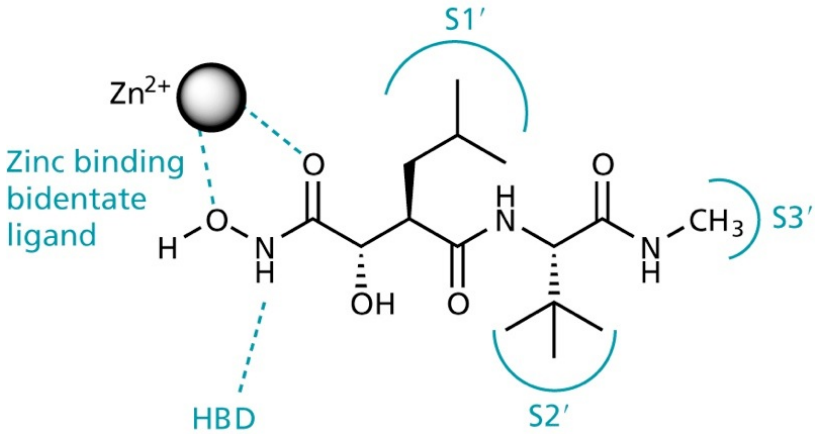
# Matrix Metalloproteinase Inhibitors

- MMP are zinc-dependent enzymes (proteases)
- extremely destructive enzymes involved in the remodelling of the extracellular matrix or the connective tissue
- MMPs comprise callagenases, gelatinases, stromelysins and the membrane type (MT)
- They inhibit angiogenesis
- collagenase cleaves between glycine and isoleucine



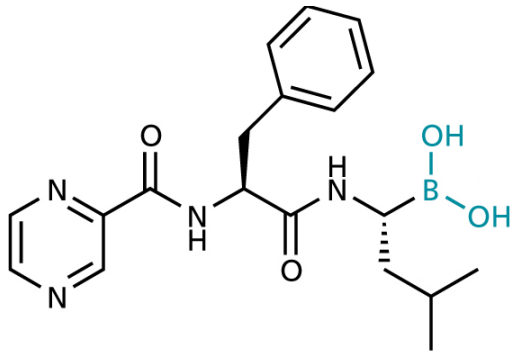




**marimastat**

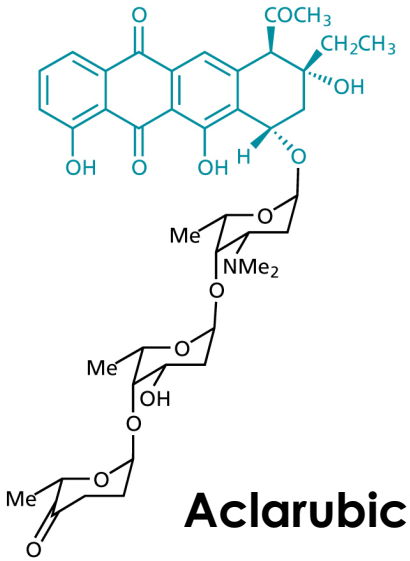


# Proteasome Inhibitors

- is the unit for degradation of damaged or misfolded proteins, but also degrades protein involved in regulation
- protein marked for degradation are labeled with ubiquitin
- inhibiting the proteasome leads to accumulation of regulatory proteins such as the apoptosis promoter Bax
- Accumulation of regulatory proteins leads to cell crisis and triggers apoptosis




**Bortezomib**




**Aclarubicin**

# Antibody Cancer Therapy

• The killing of tumour cells using monoclonal antibodies (mAbs) can result from **direct action** of the antibody (through receptor blockade, for example), **immune-mediated cell killing** mechanisms, **payload delivery**, and specific effects of an antibody on the tumour vasculature and stroma.

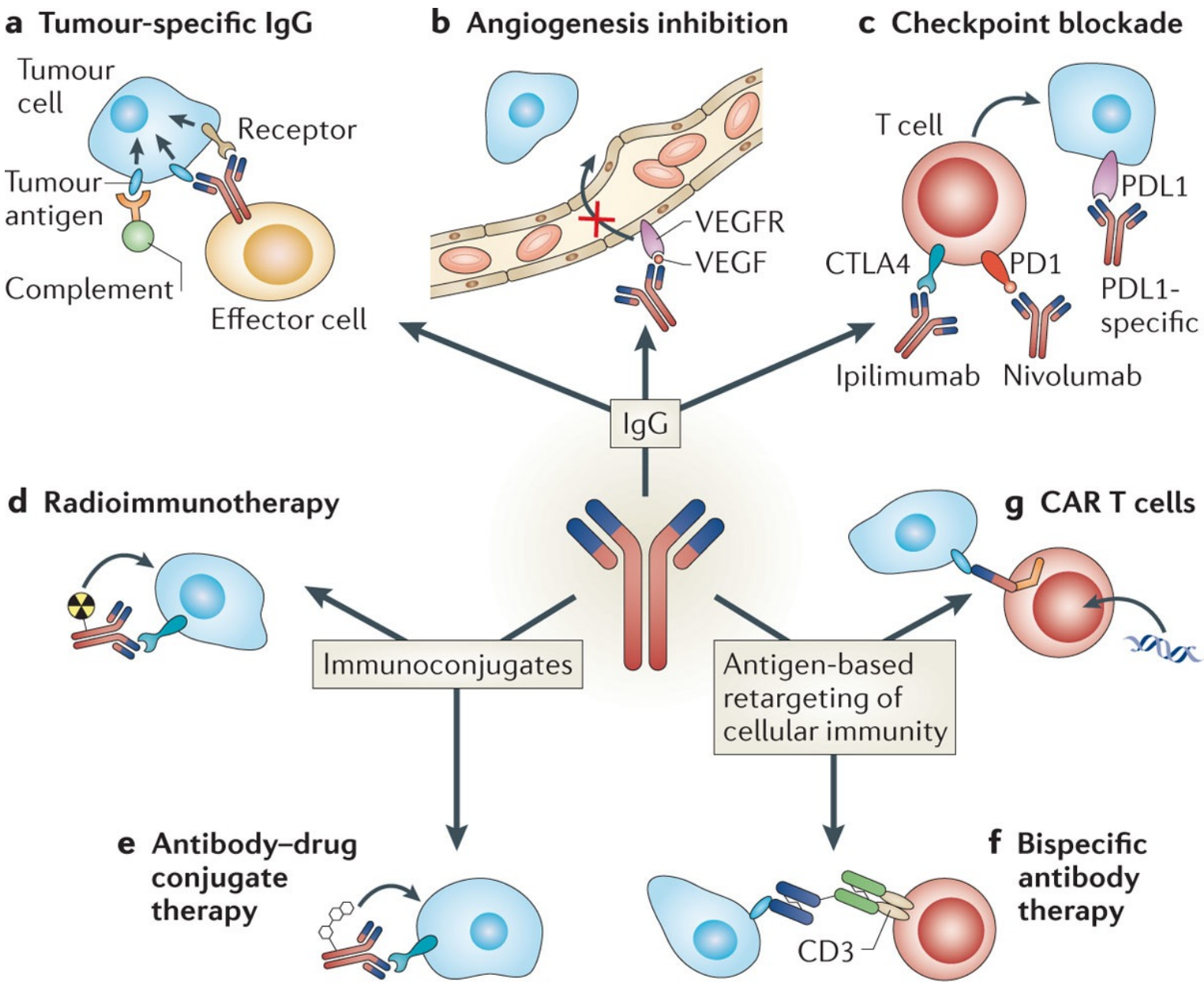
• Tumour antigens that have been successfully targeted include epidermal growth factor receptor (EGFR), ERBB2, vascular endothelial growth factor (VEGF), cytotoxic T lymphocyte-associated antigen 4 (CTLA4), CD20, CD30 and CD52.

• Serological, genomic, proteomic and bioinformatic databases have also been used to identify antigens and receptors that are overexpressed in tumour cell populations or that are linked to gene mutations identified as driving cancer cell proliferation (**tumor markers**).

• A major objective for the clinical evaluation of mAbs has been determining the toxicity and therapeutic efficacy of the antibody alone or as a delivery system for radioisotopes or other toxic agents. It is also crucial to assess its *in vivo* specificity by determining its biodistribution in patients and to assess the ratio of antibody uptake in the tumour versus normal tissues.

• Twelve antibodies (2012) have received approval from the US FDA for the treatment of various solid tumours and haematological malignancies, and a large number of additional therapeutic antibodies are currently being tested in early stage and late-stage clinical trials.

# Antibody Cancer Therapy




Weiner et al., Nature Rev. Cancer **15**, 361–370 (2015)

Nature Reviews | Cancer

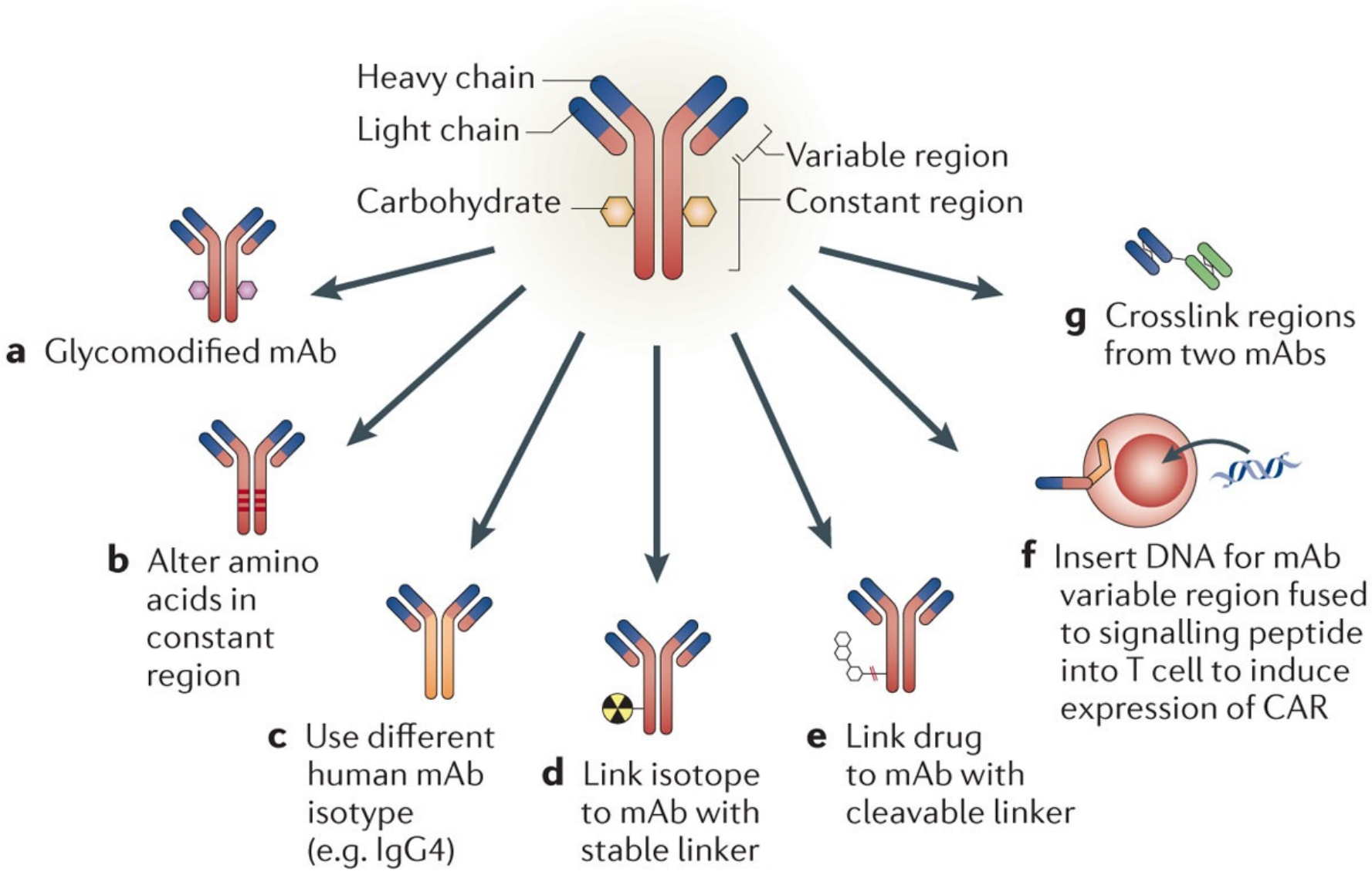
# Antibody Applications

| mAb-based therapeutic | Structure | Characteristics of target antigen | Example of major ongoing research questions |
|---|---|---|---|
| Antitumour mAbs | Unmodified IgG or IgG modified to mediate enhanced ADCC | Tumour-associated surface antigen | Are IgGs with enhanced affinity for Fc receptors more clinically effective than unaltered IgG? |
| Angiogenesis inhibition | Unmodified IgG | Host molecules that control angiogenesis | What is the best way to evaluate clinical response in patients treated with angiogenesis inhibitors? |
| T cell checkpoint blockade | IgG1 (blocks checkpoint and mediates ADCC) or IgG4 (blocks checkpoint without mediating extensive ADCC) | Molecules that limit the anticancer T cell response | How should we combine checkpoint blockade mAbs with each other, with other immunotherapeutics and with other anticancer agents? |
| Radioimmunotherapy | Unmodified IgG or mAb fragment | Tumour-associated antigen that is not shed or present in the circulation | How can the logistics of administering successful radioimmunotherapeutic agents be simplified to enhance their clinical utility? |
| Antibody–drug conjugate | IgG modified with cleavable linker and drug | Highly specific tumour-associated antigen that can internalize when bound by a mAb | What is the best combination of linkers and drugs with each mAb and target antigen? |
| Bispecific antibody | Variable regions from cancer-specific mAbs linked to variable regions specific for activating receptors on T cells | Tumour-associated antigen that is not commonly absent in antigen-loss-resistant cancer variants | Can effective bispecific constructs that have modified kinetics (thereby avoiding the logistic complexities of continuous infusion) be developed? |
| Chimeric antigen receptor T cell | Gene therapy approach to modifying T cells by inserting DNA coding for the mAb variable region fused to DNA coding for signalling peptides | Highly tumour-specific antigen that is not commonly absent in antigen-loss-resistant cancer variants | Can very promising preliminary results be extended to solid tumours, or will toxicity be associated even with low levels of target antigen expression by benign cells? |

ADCC, antibody-dependent cellular cytotoxicity; IgG, immunoglobulin G; mAb, monoclonal antibody.

Scott, Nature Rev. Cancer, **12** (2012), 278

# Antibody Modifications




Weiner et al., Nature Rev. Cancer **15**, 361–370 (2015)

Nature Reviews | Cancer

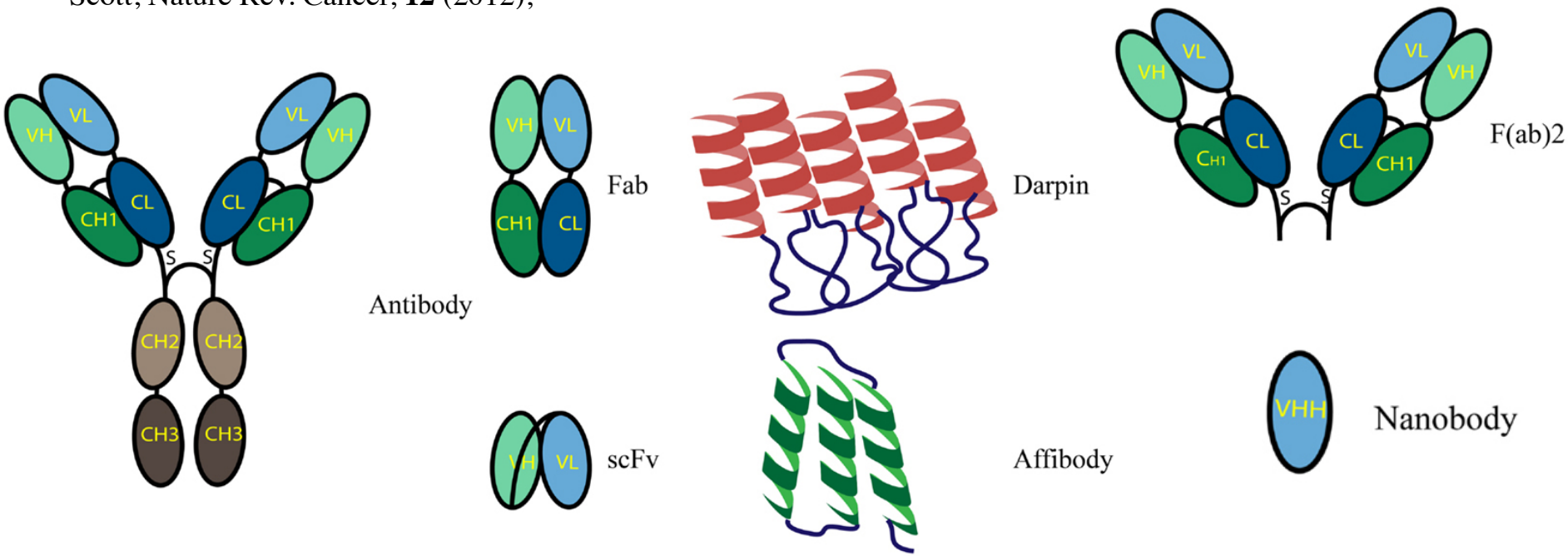
# Nomenclature of Monoclonal Antibodys

- Last syllable is always *–mab*
- Next to last syllable
  - *-u-* human (100%) : Panitum<u>u</u>mab
  - *-zu-* humanized (95%) : Trastu<u>zu</u>mab
  - *-xi-* chimeric (65%) : Ritu<u>xi</u>mab
  - *-o-* mouse, *-a-* rat, *-e-* hamster, *-i-* primate : Tositum<u>o</u>mab
- Previous syllable
  - *-tu(m)-* for tumor in general [*-ma(r)-* breast, *-pr(o)-* prostate, *-co(l)-* colon, etc.]
  - *-ci(r)-* for circulatory : Beva<u>ci</u>zumab

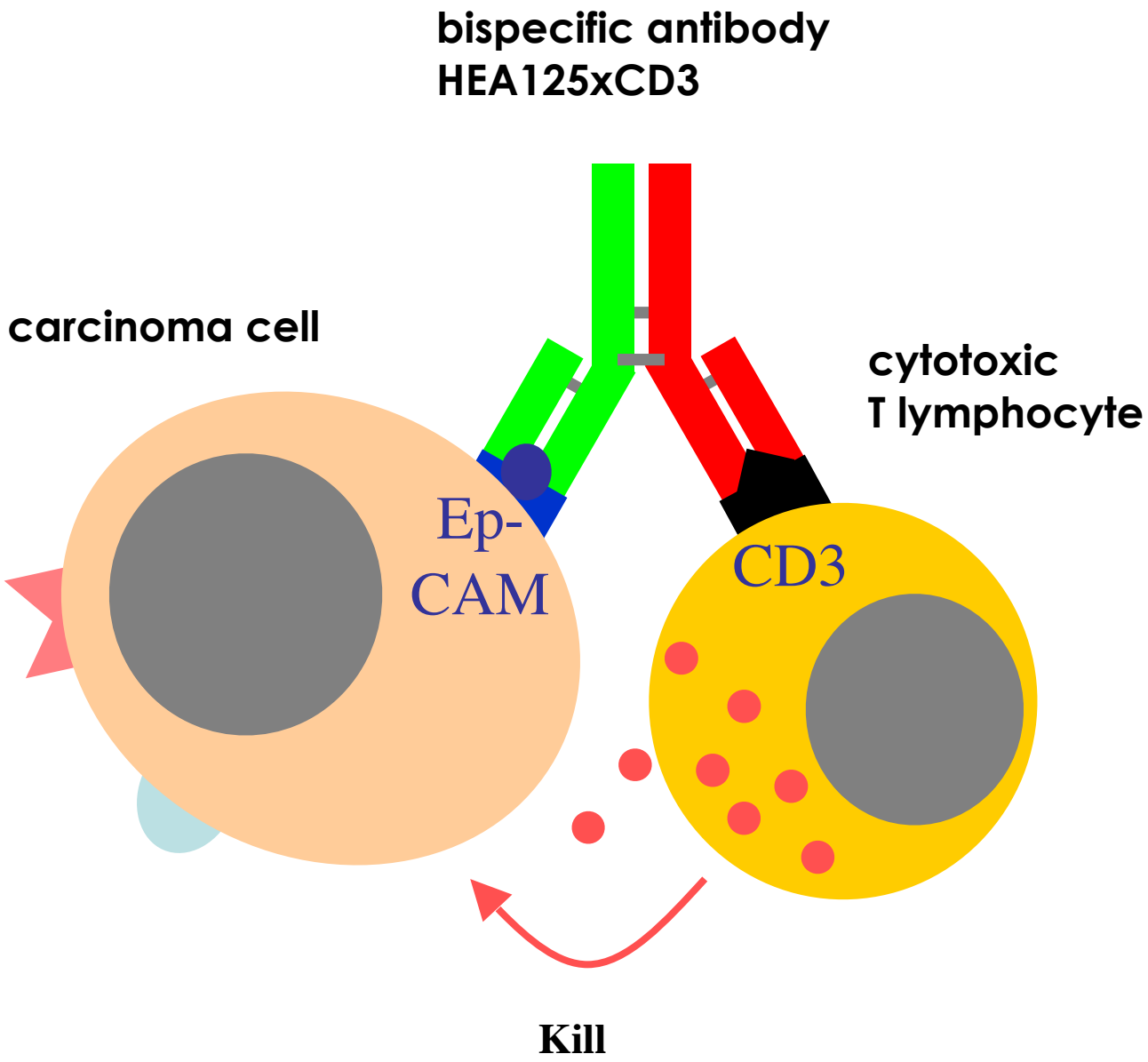
| Antibody constructs | Examples of targets | Potential clinical use |
|---|---|---|
| scFv | CC49, ERBB2 and $Le^y$ | Imaging and cell targeting |
| Diabody | $Le^y$ and TAG-72 | Imaging and drug delivery |
| Affibody | ERBB2 | Imaging and drug delivery |
| Minibody | CEA and ERBB2 | Imaging and drug delivery |
| Protein–Fc | Angiopoietin 1, angiopoietin 2, VEGFR1 and VEGFR2 | Imaging and therapy |
| Intact IgG | CD20, CD33, EGFR, ERBB2 and VEGF | Imaging therapy and drug delivery |
| IgE and IgM | GM2 | Therapy |
| Drug conjugates | CD30, CD33 and ERBB2 | Therapy |
| Loaded nanoparticles | A33, EGFR and transferrin | Drug delivery |
| Bispecifics | CD19–CD3, EPCAM–CD3 and gp100–CD3 | Therapy |

CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; gp100, glycoprotein 100; Ig, immunoglobulin; $Le^y$, Lewis Y antigen; scFv, single-chain variable fragment; TAG-72, tumour-associated glycoprotein 72; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Scott, Nature Rev. Cancer, **12** (2012),



# Cytotoxic T-cell Targeting



# Antibody Targets

| | | | |
|---|---|---|---|
| Targets of anti-angiogenic mAbs | VEGF | Bevacizumab | Tumour vasculature |
| | VEGFR | IM-2C6 and CDP791 | Epithelium-derived solid tumours |
| | Integrin αVβ3 | Etaracizumab | Tumour vasculature |
| | Integrin α5β1 | Volociximab | Tumour vasculature |
| Growth and differentiation signalling | EGFR | Cetuximab, panitumumab, nimotuzumab and 806 | Glioma, lung, breast, colon, and head and neck tumours |
| | ERBB2 | Trastuzumab and pertuzumab | Breast, colon, lung, ovarian and prostate tumours |
| | ERBB3 | MM-121 | Breast, colon, lung, ovarian and prostate, tumours |
| | MET | AMG 102, METMAB and SCH 900105 | Breast, ovary and lung tumours |
| | IGF1R | AVE1642, IMC -A12, MK-0646, R1507 and CP 751871 | Glioma, lung, breast, head and neck, prostate and thyroid cancer |
| | EPHA3 | KB004 and IIIA4 | Lung, kidney and colon tumours, melanoma, glioma and haematological malignancies |
| | TRAILR1 | Mapatumumab (HGS-ETR1) | Colon, lung and pancreas tumours and haematological malignancies |
| | TRAILR2 | HGS-ETR2 and CS -1008 | |
| | RANKL | Denosumab | Prostate cancer and bone metastases |
| Stromal and extracellular matrix antigens | FAP | Sibrotuzumab and F19 | Colon, breast, lung, pancreas, and head and neck tumours |
| | Tenascin | 81C6 | Glioma, breast and prostate tumours |

CAIX, carbonic anhydrase IX; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; EPHA3, ephrin receptor A3; FAP, fibroblast activation protein; gpA33, glycoprotein A33; IGF1R, insulin-like growth factor 1 receptor; Le $^{y}$, Lewis Y antigen; mAbs, monoclonal antibodies; PSMA, prostate-specific membrane antigen; RANKL, receptor activator of nuclear factor -κB ligand; TAG-72, tumour-associated glycoprotein 72; TRAILR, tumour necrosis factor-related apoptosis-inducing ligand receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Scott, Nature Rev. Cancer, **12** (2012), 278

Table 2 | Tumour-associated antigens targeted by therapeutic monoclonal antibodies in oncology

| Antigen category | Examples of antigens | Examples of therapeutic mAbs raised against these targets | Tumour types expressing antigen |
|---|---|---|---|
| Haematopoietic differentiation antigens | CD20 | Rituximab | Non-Hodgkin's lymphoma |
| | | Ibritumomab tiuxetan and tositumomab | Lymphoma |
| | CD30 | Brentuximab vedotin | Hodgkin's lymphoma |
| | CD33 | Gemtuzumab ozogamicin | Acute myelogenous leukaemia |
| | CD52 | Alemtuzumab | Chronic lymphocytic leukaemia |
| Glycoproteins expressed by solid tumours | EpCAM | IGN101 and adecatumumab | Epithelial tumours (breast, colon and lung) |
| | CEA | Labetuzumab | Breast, colon and lung tumours |
| | gpA33 | huA33 | Colorectal carcinoma |
| | Mucins | Pemtumomab and oregovomab | Breast, colon, lung and ovarian tumours |
| | TAG-72 | CC49 (minretumomab) | Breast, colon and lung tumours |
| | CAIX | cG250 | Renal cell carcinoma |
| | PSMA | J591 | Prostate carcinoma |
| | Folate-binding protein | MOv18 and MORAb-003 (farletuzumab) | Ovarian tumours |
| Glycolipids | Gangliosides (such as GD2, GD3 and GM2) | 3F8, ch14.18 and KW-2871 | Neuroectodermal tumours and some epithelial tumours |
| Carbohydrates | $Le^y$ | hu3S193 and IgN311 | Breast, colon, lung and prostate tumours |

Scott, Nature Rev. Cancer, **12** (2012), 278

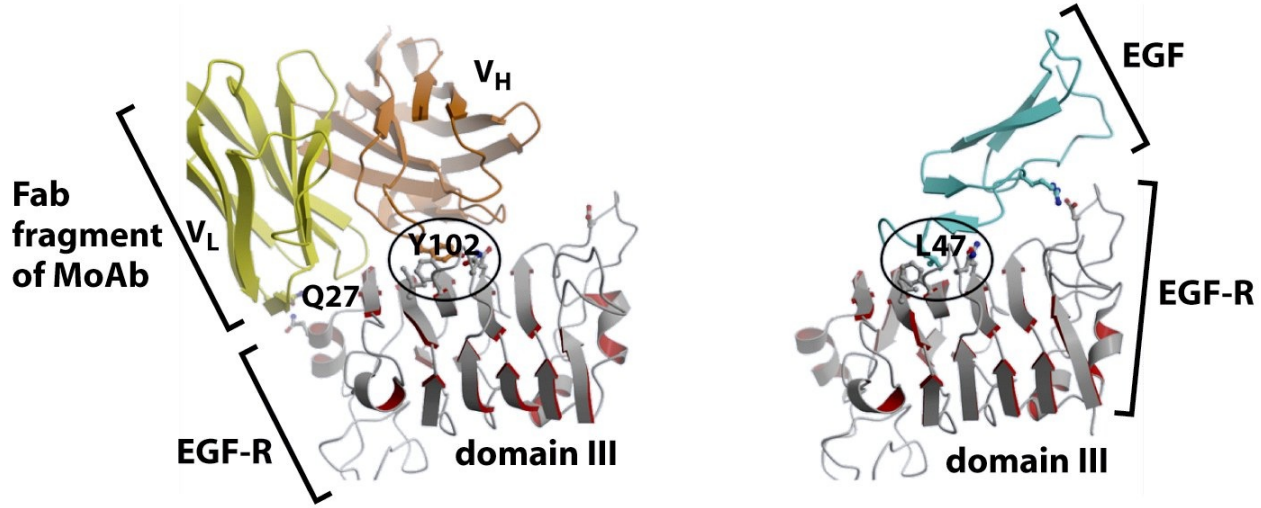



Figure 15-38a The Biology of Cancer (© Garland Science 2007)

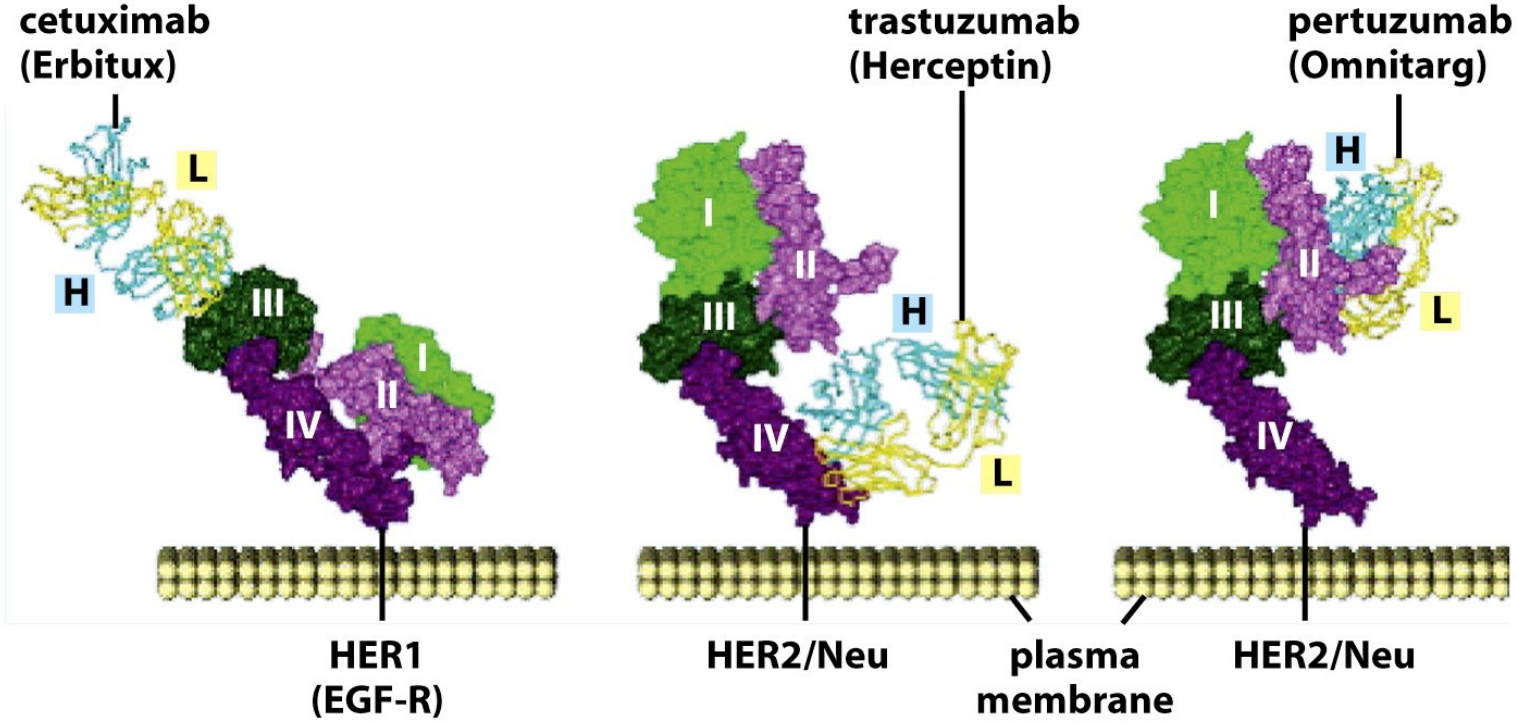



Figure 15-38b The Biology of Cancer (© Garland Science 2007)

blocks binding site of EGF ligand

receptor can still heterodimerize

receptor cannot heterodimerize

# A short primer on the immune system

| **Innate immune system** | **Adaptive immune system** |
|---|---|
| Response is non-specific | Pathogen and antigen specific response |
| Exposure leads to immediate maximal response | Lag time between exposure and maximal response |
| Cell-mediated and humoral components | Cell-mediated and humoral components |
| No immunological memory | Exposure leads to immunological memory |
| Found in nearly all forms of life | Found only in certain vertebrates |

# Cellular and Humoral Immunity

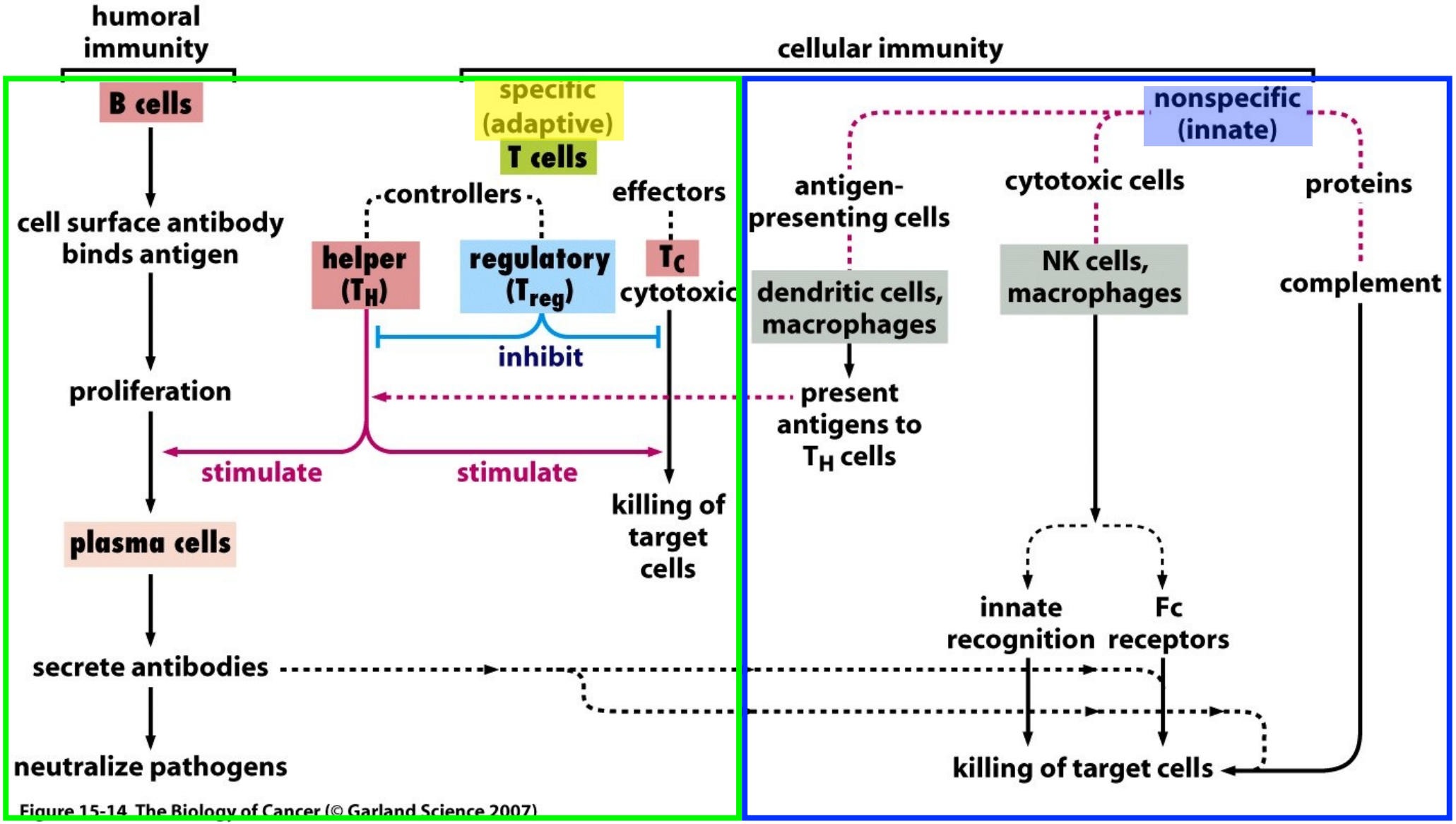
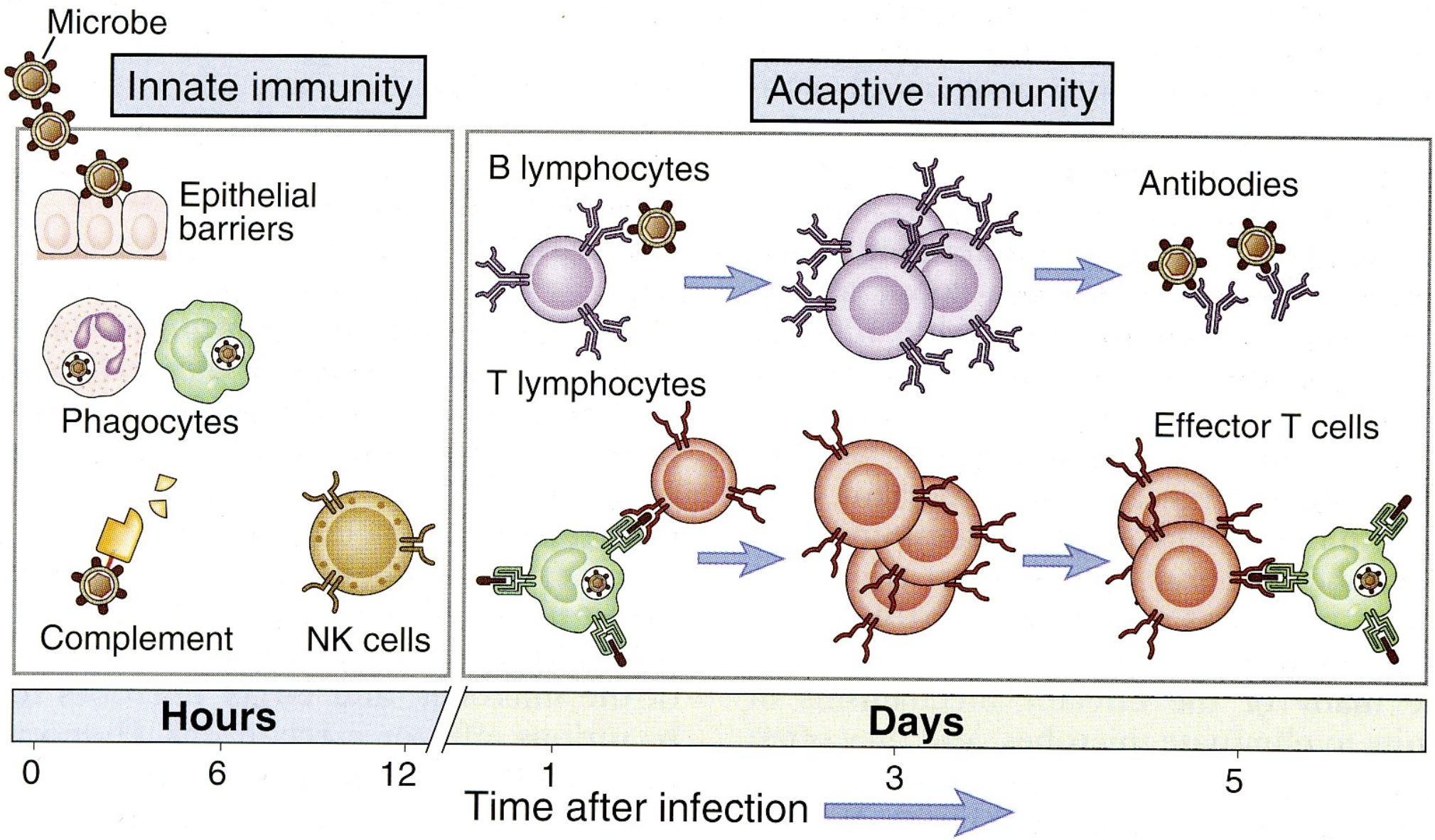


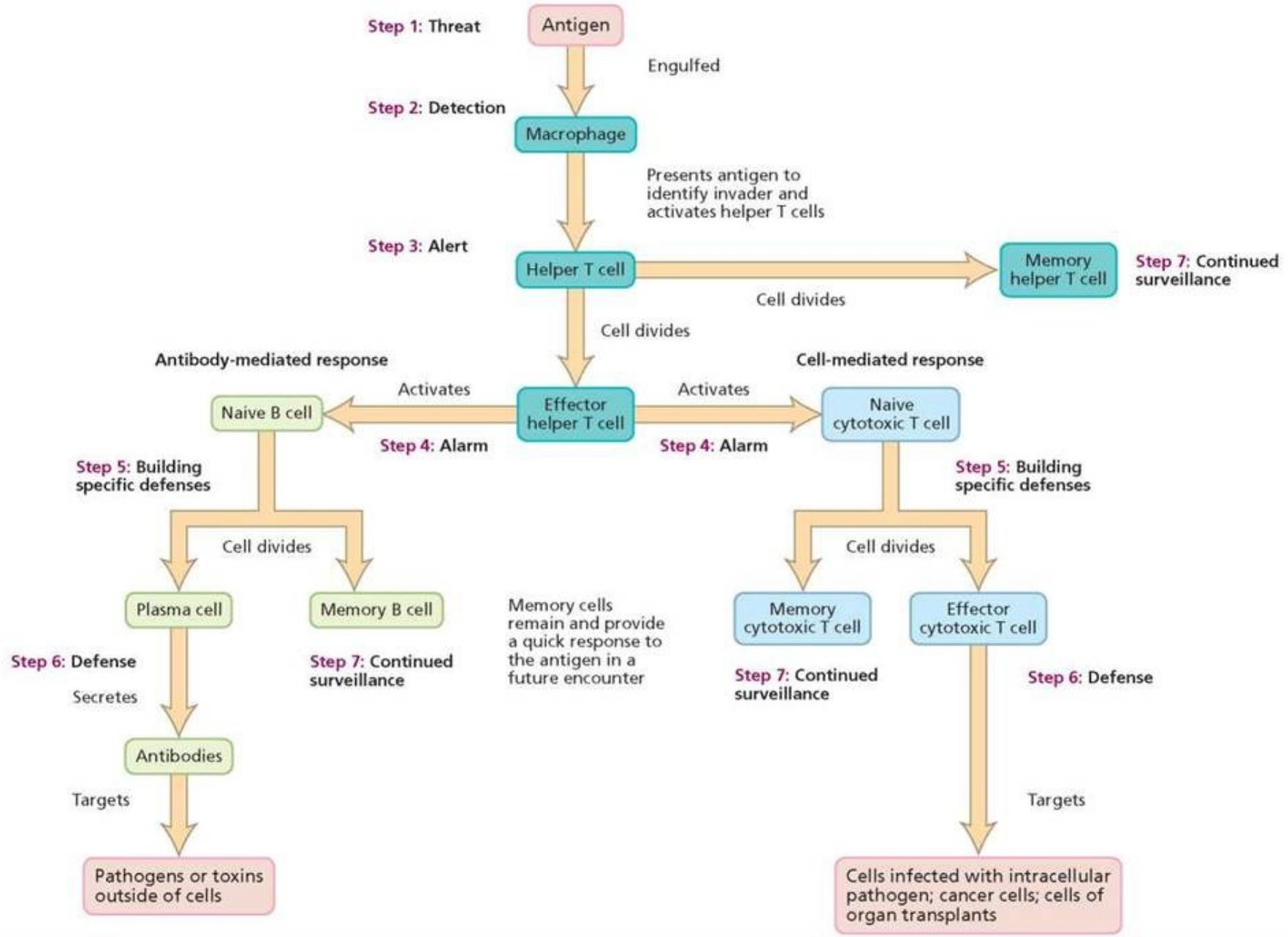

Figure 15-14 The Biology of Cancer (© Garland Science 2007)

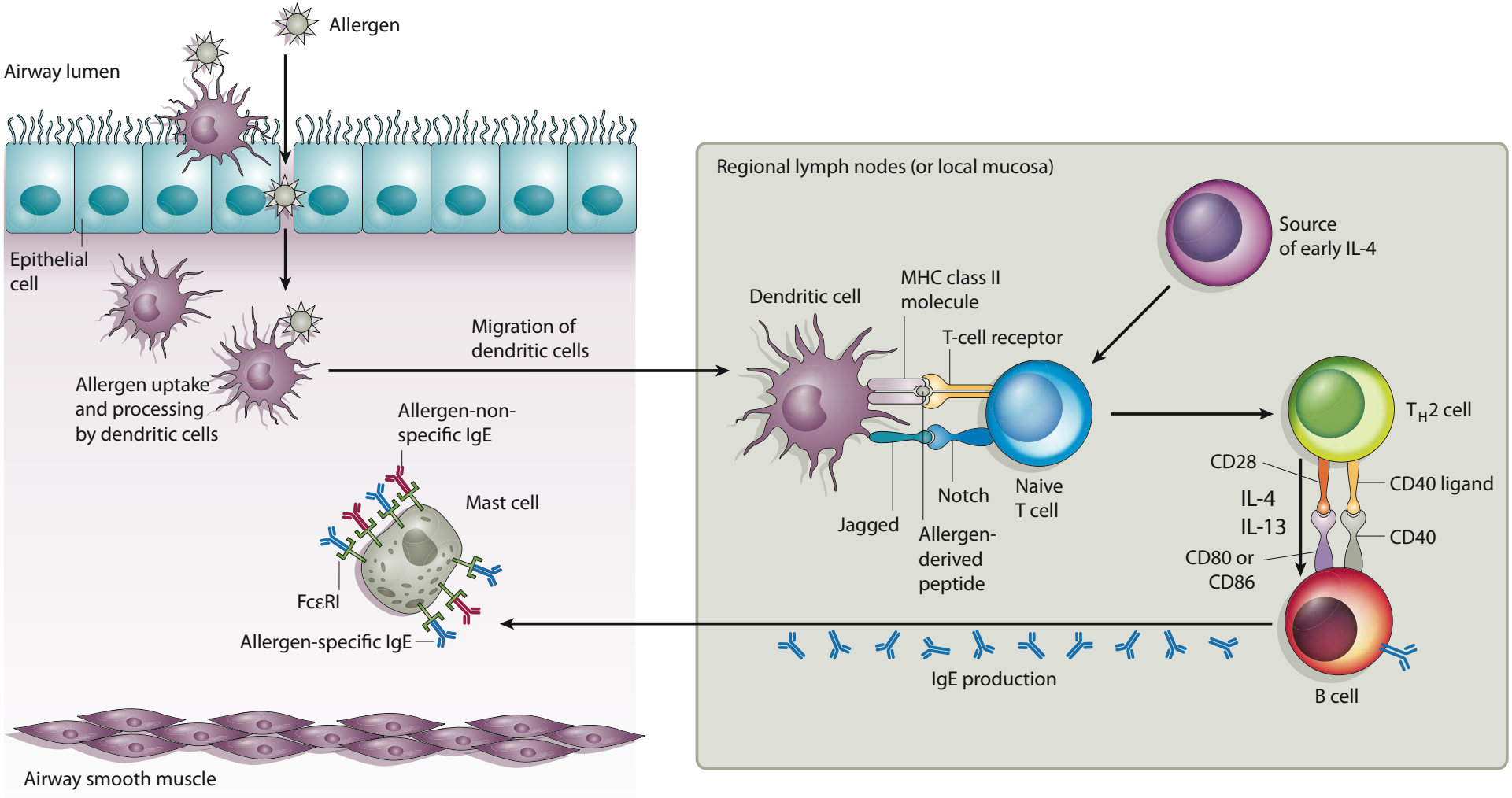
# Innate and Adaptive Immunity




Abbas & Litchman, Basic Immunology

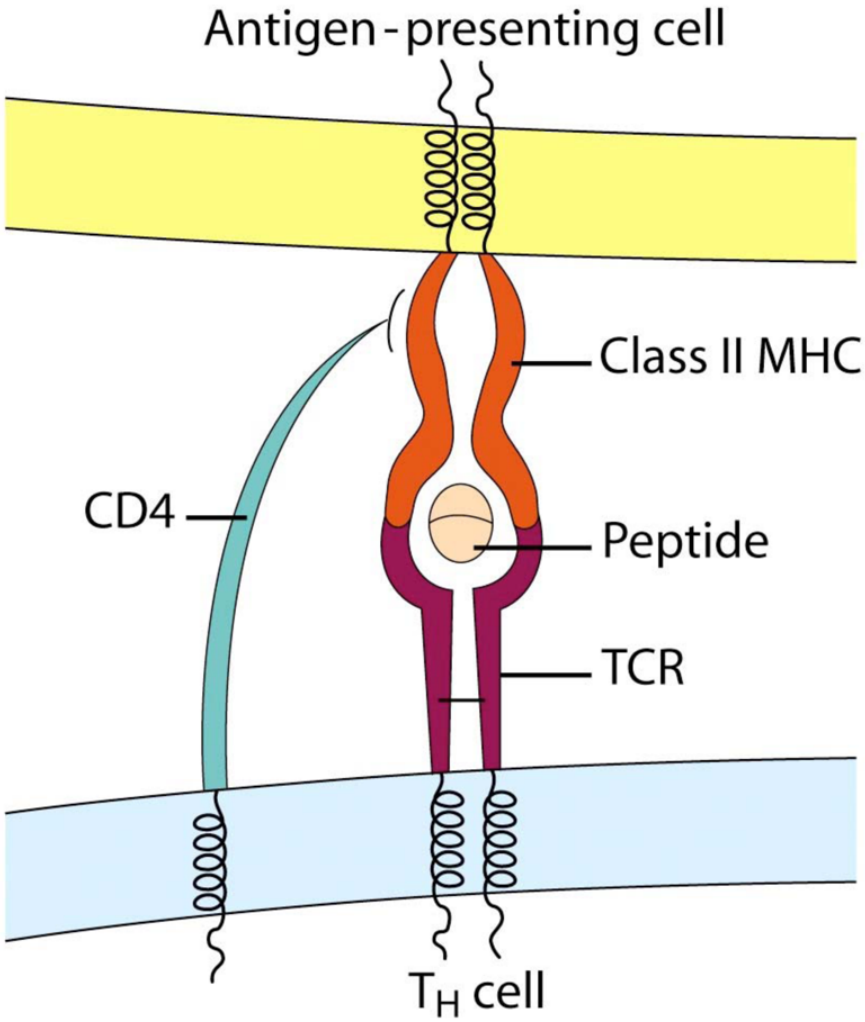
# Phases of Adaptive Immune Response






Galli et al., Nature **454** (2008),445

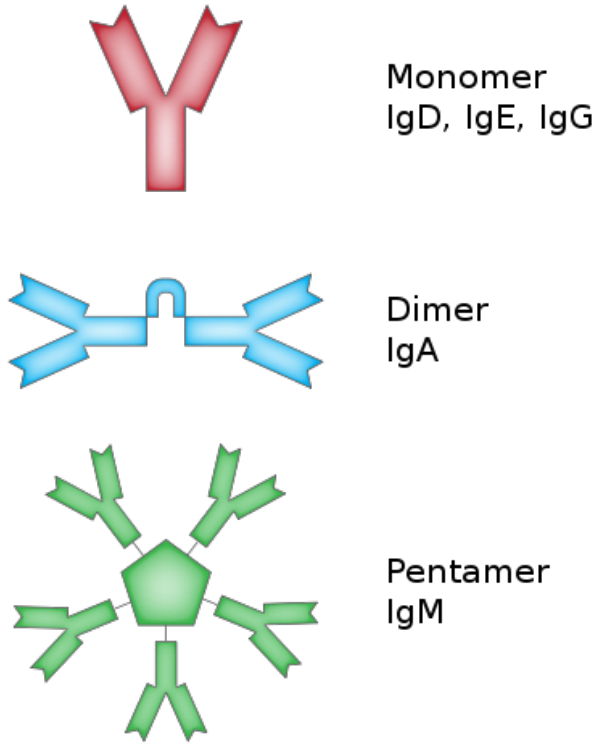
# T-cell mediated immune response




- **T-cell** triggered immune reaction involves formation of antigen, T-cell receptor and MHC (major histocompatibility complex)
- it presents fragments from proteins and peptides processed by the cell (no need to be surface exposed)
- The APC-T-cell complex then triggers the immune response (production of cytokines, cell-lysing factors etc.)

# Types of Antibodies

| Name | Types | Description |
|---|---|---|
| **IgA** | 2 | Found in mucosal areas, such as the gut, respiratory tract and urogenital tract, and prevents colonization by pathogens. Also found in saliva, tears, and breast milk. |
| **IgD** | 1 | Functions mainly as an antigen receptor on B cells that have not been exposed to antigens. It has been shown to activate basophils and mast cells to produce antimicrobial factors. |
| **IgE** | 1 | Binds to allergens and triggers histamine release from mast cells and basophils, and is **involved in allergy**. Also protects against parasitic worms. |
| **IgG** | 4 | In its four forms, provides the **majority of antibody-based immunity** against invading pathogens. The only antibody capable of crossing the placenta to give passive immunity to the fetus. |
| **IgM** | 1 | Expressed on the surface of B cells (monomer) and in a secreted form (pentamer) with very high avidity. Eliminates pathogens in the **early stages** of B cell-mediated (humoral) immunity before there is sufficient IgG. |




source: Wikipedia

Some daughter cells of the activated B cells undergo **isotype switching**, a mechanism that causes the production of antibodies to change from IgM or IgD to the other antibody isotypes, IgE, IgA, or IgG, that have defined roles in the immune system

# Antibody/T-cell Response

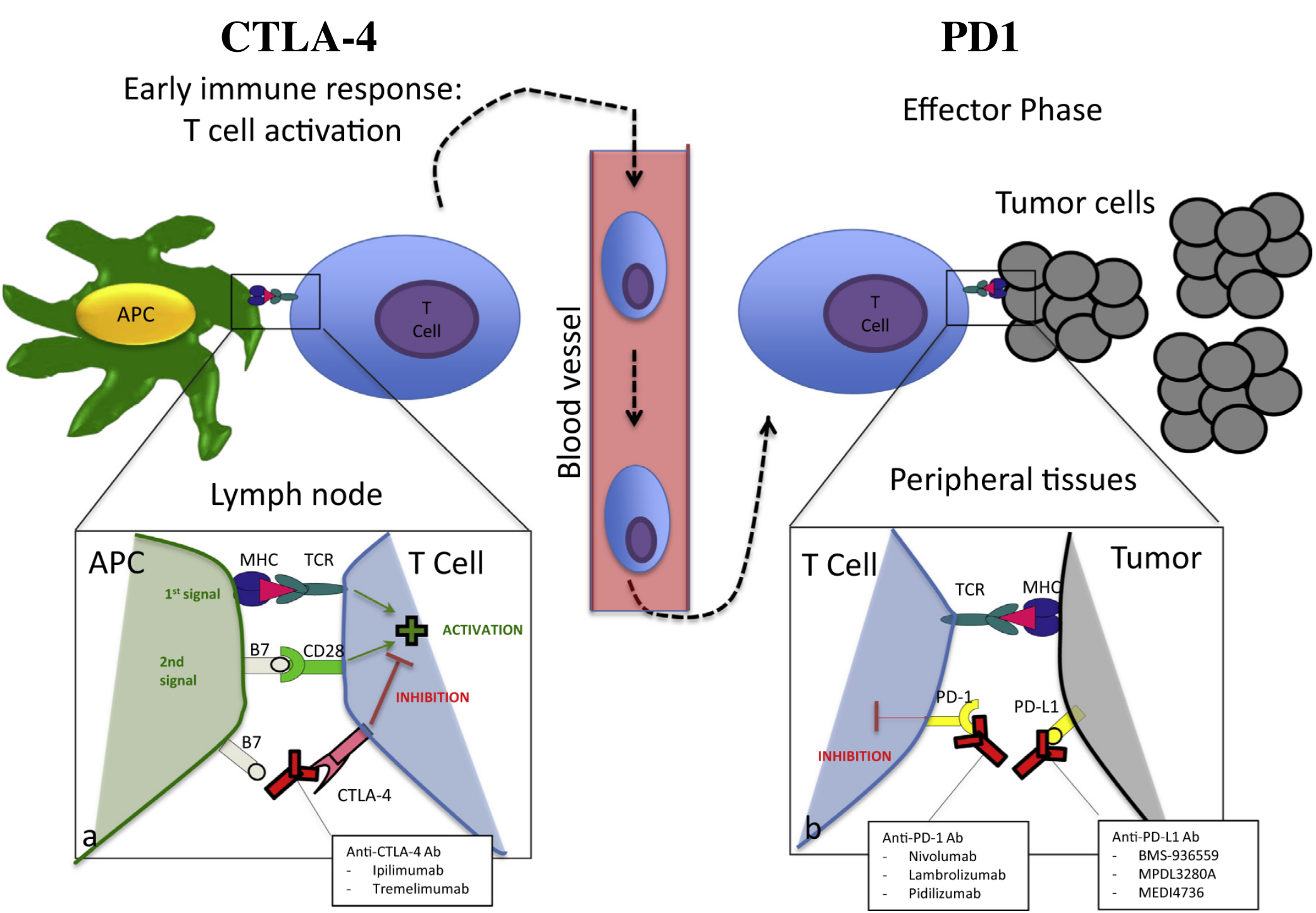
- After entry antigens are engulfed (mostly by **dendritic cells**), and proteins degraded internally. Fragments are presented on the surface in association with the major histocompatibility complex (MHC). Non-self proteins or capsular polysaccharides activate B-cells via the **B-cell receptor** (BCR)
- Initial antibodies are predominantly low-affinity immunoglobulin-M (IgM) abs.
- **Re-exposure triggers a more rapid immune response**. Antibodies are predominantly **IgG or IgA** class. They have in general much higher affinity.
- Likewise there is a **10'000-fold higher number of cytotoxic T-cells**
- The receptor on B-cells is membrane bound immunoglobulin (BCR), that can recognise entire proteins. In contrast the T-cell receptors (TCRs) recognise only small peptides. B- and C-cells recognise **different** epitopes.
- Within the naive (unchallenged) B- and T-cell population cells capable of recognising **all epitopes** are present.
- Upon challenge by an antigen **only** the corresponding B-cells that can recognise the antigen are rapidly multiplied (**clonal expansion**). Likewise T-cells undergo similar activation
- Antibody binding affinity is increased (**affinity maturation**) . During this process many mutations in the hypervariable loops occur (somatic hypermutation). During this process **antibody class switching** may occur.

# Cancer Immunotherapy: Blockade of Immune Checkpoints

- Tumors result in many mutations in gene products, that can be recognised as non-self and trigger a immune response for their clearance
- **Immune checkpoints** refer to **inhibitory pathways** of the immune system that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage.
- Tumors misuse immune-checkpoint to evade the immune system clearance, in particular to avoid tumor-antigen specific T-cell responses
- Immune checkpoints are often initiated by ligand-receptor interactions, and these can be blocked by antibodies, or modulated by recombinant forms of the ligands or receptors.
- These antibodies do not target the tumor cell, but target molecules involved in regulation of T cells, the soldiers of the immune system.
- The goal of the immune checkpoint therapy is not to activate the immune system to attack particular targets on tumor cells, but rather to remove inhibitory pathways that block effective antitumor T cell responses.

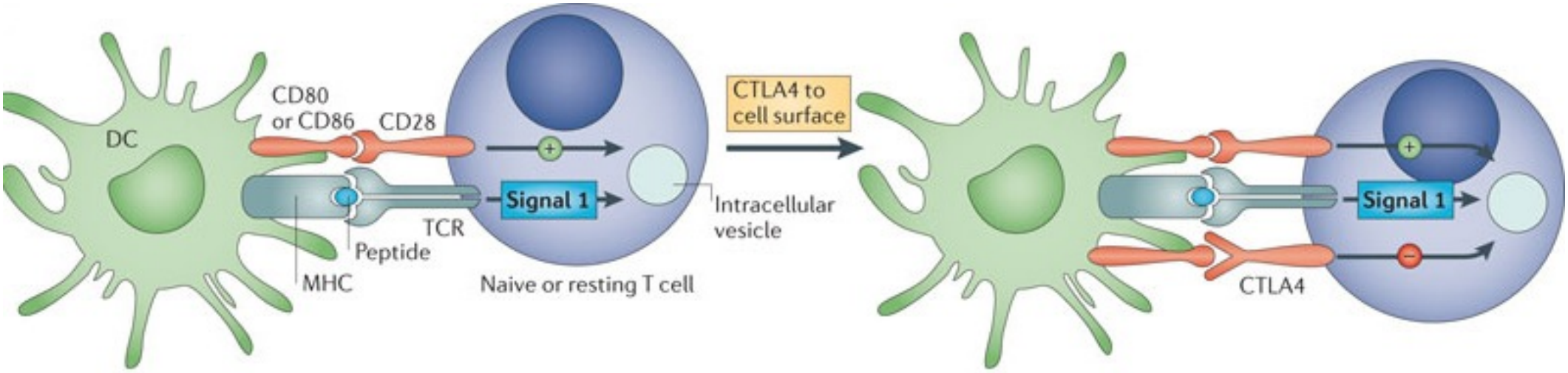
# Blockade of Immune Checkpoints (II)

- An important immune-checkpoint is cytotoxic **T-lymphocyte associated antigen 4(CTLA4)**, that down-regulates T-cell activation.
- The programmed **cell-death protein 1 (PD1)** limits T-cell effector function in tissues. By up regulating ligands for PD1, tumor cells block anti-tumor immune response in the tumor microenvironment.
- Immunotherapy- induced tumour destruction, in contrast, is often delayed or even preceded by a period of apparent tumour growth.
- Only a fraction of patient responds to the blockade of immune checkpoints
- In these cases the tumor microenvironment may be not immunogenic. Combination therapy can then still create an immunogenic microenvironment that responds to immune checkpoint therapy.
- many of these therapies are limited by toxicity…




Kyi, FEBS Lett. **588** (2014) 368–376

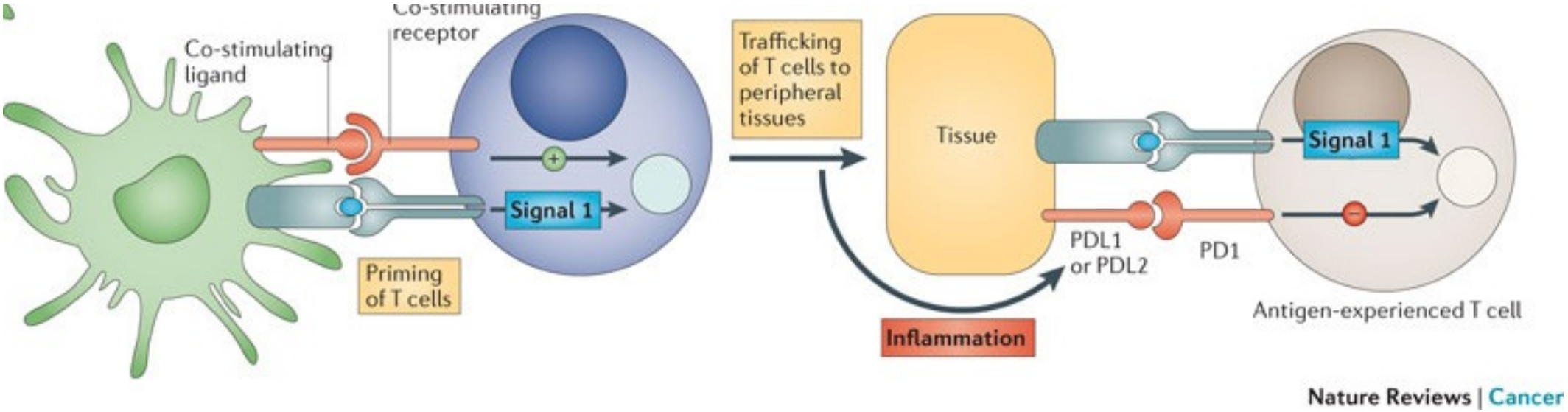
# CTLA4




The cytotoxic T-lymphocyte-associated antigen 4 (CTLA4)-mediated immune checkpoint is induced in T cells at the time of their **initial response** to antigen. The level of CTLA4 induction depends on the amplitude of the initial T cell receptor (TCR)-mediated signalling. High-affinity ligands induce higher levels of CTLA4, which dampens the amplitude of the initial response. Naive and memory T cells express high levels of cell surface CD28 but do not express CTLA4 on their surface. Instead, CTLA4 is sequestered in intracellular vesicles. After the TCR is triggered by antigen encounter, CTLA4 is transported to the cell surface. The stronger the stimulation through the TCR (and CD28), the greater the amount of CTLA4 that is deposited on the T cell surface. Therefore, CTLA4 functions as a **signal dampener** to maintain a consistent level of T cell activation in the face of widely varying concentrations and affinities of ligand for the TCR.

Pardoll, Nature Rev. Cancer **12** (2012), 252

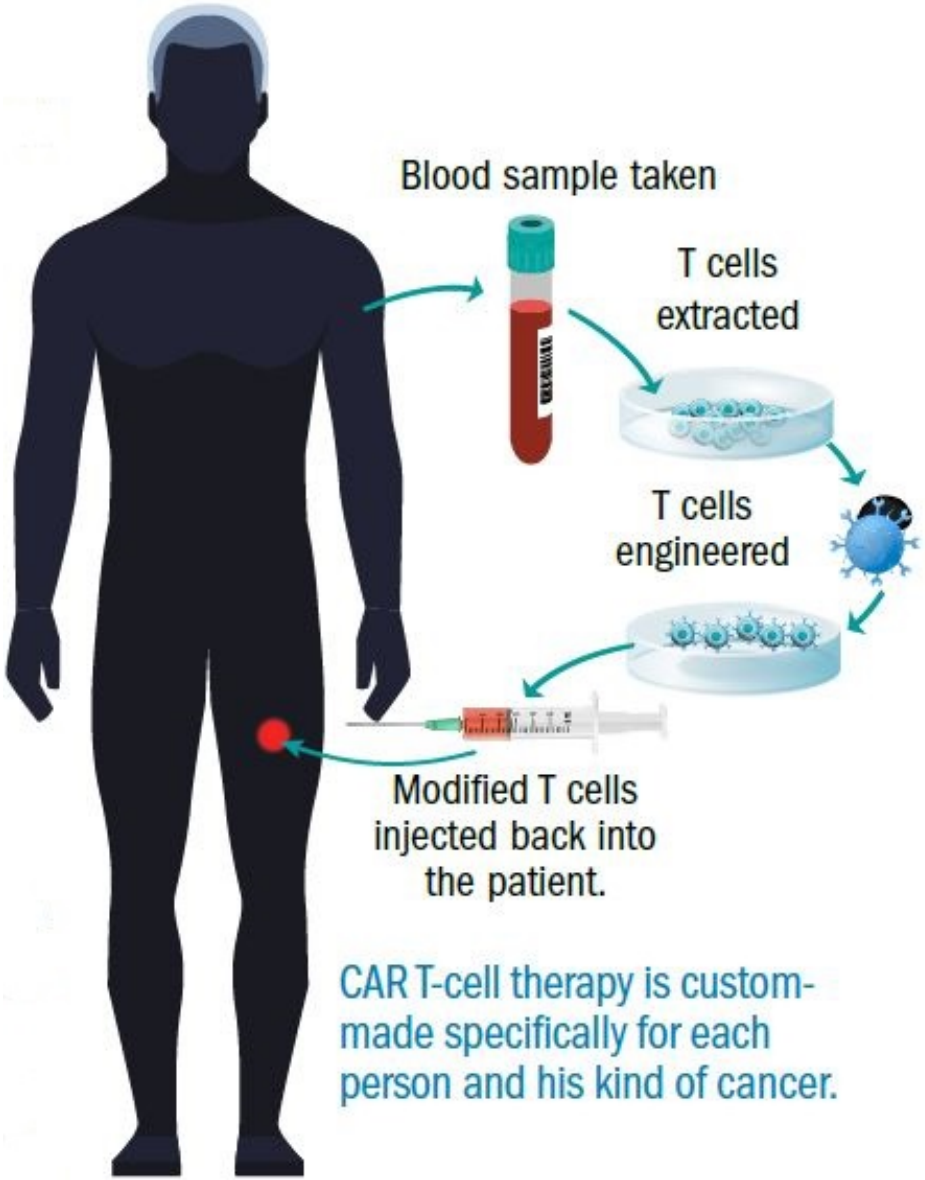
# PD1



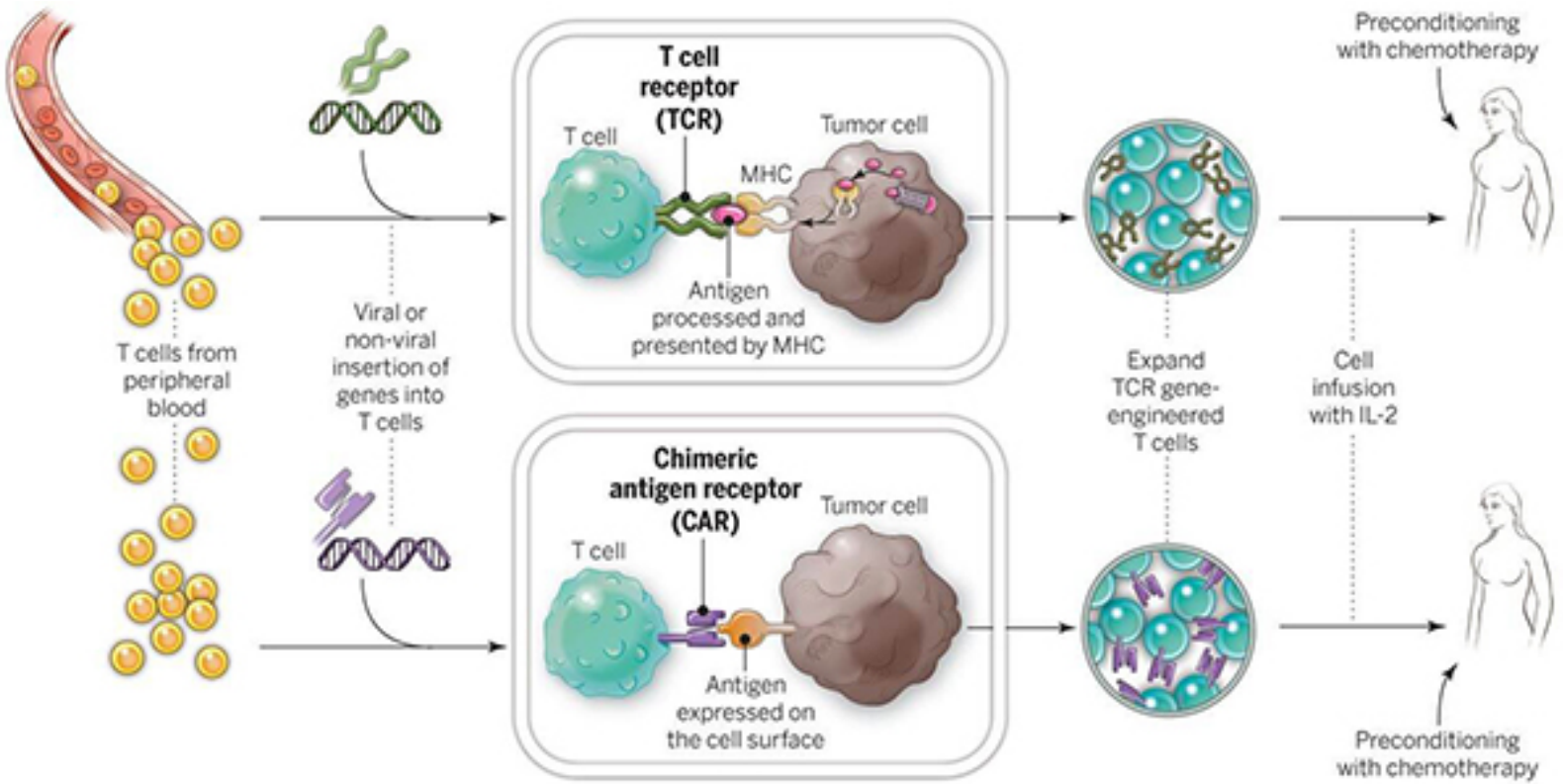

The major role of the **programmed cell death protein 1** (**PD1**) pathway is not at the initial T cell activation stage but rather to regulate inflammatory responses in tissues by effector T cells recognizing antigen in peripheral tissues. **Activated T cells upregulate PD1** and continue to express it in tissues. Inflammatory signals in the tissues induce the expression of PD1 ligands, which **downregulate the activity of T cells** and thus limit collateral tissue damage in response to a microorganism infection in that tissue. The best characterized signal for PD1 ligand 1 (PDL1; also known as B7-H1) induction is **interferon-γ** (IFNγ), which is predominantly produced by T helper 1 (TH1) cells.

Pardoll, Nature Rev. Cancer **12** (2012), 252

# Cancer Immunotherapy II: Reengineering T-cells: CAR T Cells

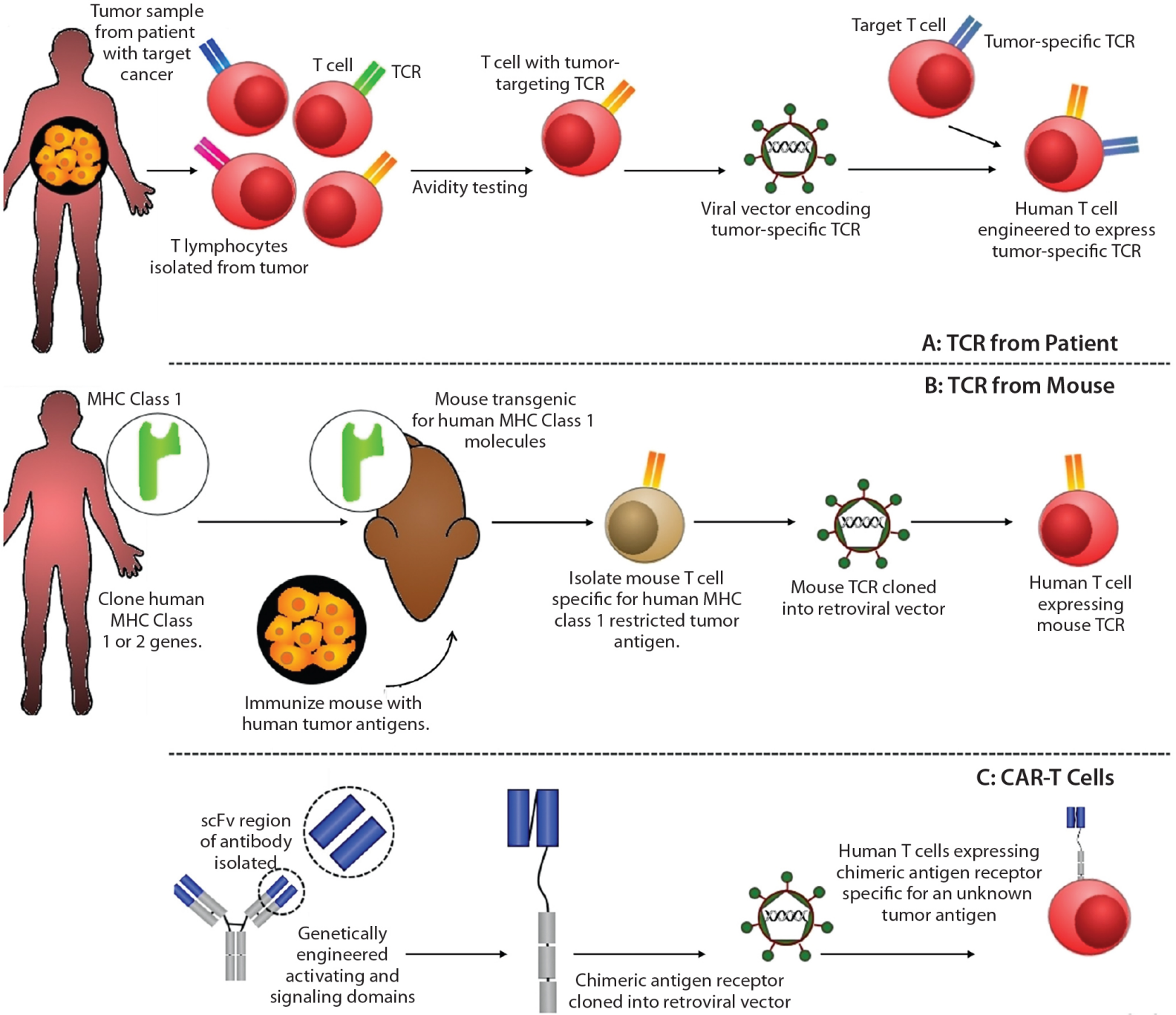


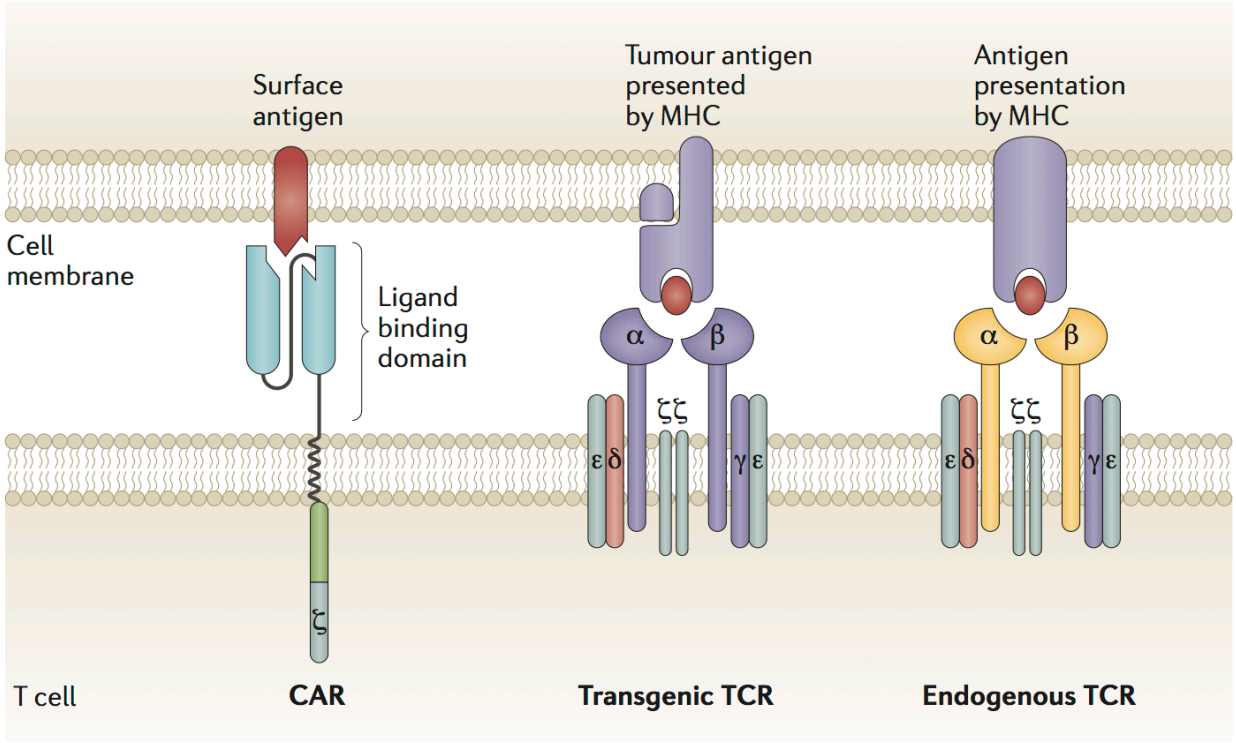

- Doctors collect a patient's T cells
- they place a protein on the outside of the (cytotoxic) cells
- the protein is either a T-cell receptor or a **chimeric antigen receptor** (CAR)
- the engineered T cells are then injected back into the patient.
- the added protein has two roles: it guides the T cell directly to the tumour, and on arrival, it triggers the T cell's fighting power to attack the cancer cells.




NCI information

- T cells interact via their T-cell receptors with major histocompatibility complex (MHC) proteins, that present tumour antigens on the surface of the tumour cells
- T cells can be reengineered to present antibody-like molecules (CAR cells) on their surface. The antibodies are often single-chain ABs directed against the tumour cell antigens.


Tumor sample from patient with target cancer
T cell
TCR
T lymphocytes isolated from tumor
Avidity testing
T cell with tumor-targeting TCR
Viral vector encoding tumor-specific TCR
Target T cell
Tumor-specific TCR
Human T cell engineered to express tumor-specific TCR
A: TCR from Patient
B: TCR from Mouse
MHC Class 1
Clone human MHC Class 1 or 2 genes.
Mouse transgenic for human MHC Class 1 molecules
Immunize mouse with human tumor antigens.
Isolate mouse T cell specific for human MHC class 1 restricted tumor antigen.
Mouse TCR cloned into retroviral vector
Human T cell expressing mouse TCR
C: CAR-T Cells
scFv region of antibody isolated
Genetically engineered activating and signaling domains
Chimeric antigen receptor cloned into retroviral vector
Human T cells expressing chimeric antigen receptor specific for an unknown tumor antigen

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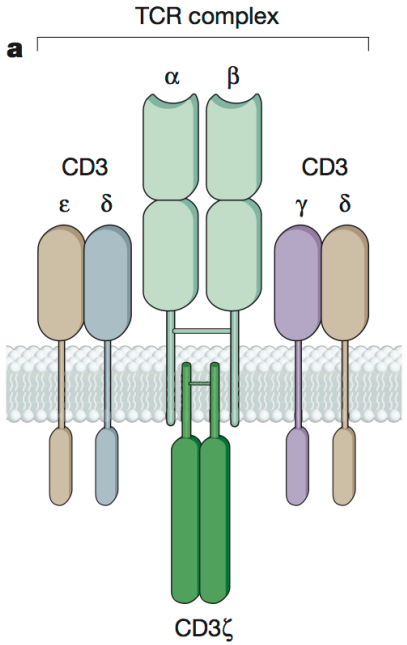
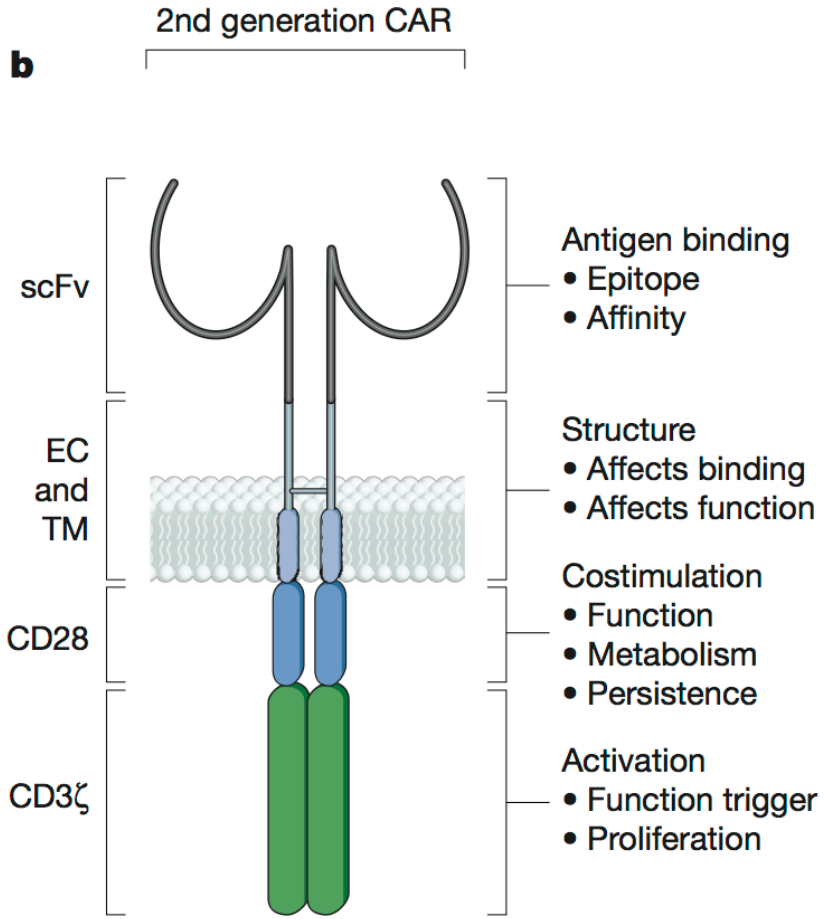



Sadelain, Nature 2017

**Unheilbare Krankheit**

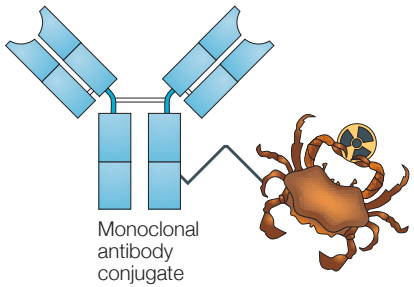
# Forscher schleusen Genschere in Patienten ein

**Brian Madeux ist der erste Mensch, dem kleine Genscheren in den Körper injiziert wurden, um einen Defekt in seinem Erbgut zu beheben. Ob der Versuch glückt, wird sich erst in mehreren Monaten zeigen.**

DPA

Brian Madeux im UCSF Benioff Childrens Hospital in Oakland

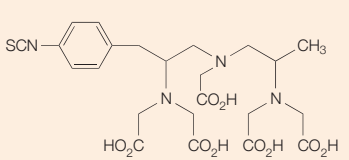
# Antibody-Conjugates: Radionuclei



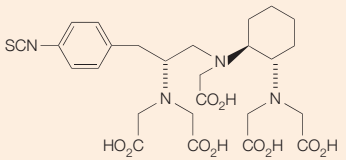

Representative monoclonal antibodies in advanced radioimmunotherapy clinical trials

| Antibody | Antibody form | Radionuclide | Antigen | Disease | Clinical trial status |
|---|---|---|---|---|---|
| Tositumomab (Bexxar) | muIgG2a | $^{131}$I | CD20 | NHL | Approved by FDA |
| Epratuzumab (Lymphocide) | huIgG1 (LL2) | $^{90}$Y | CD22 | NHL | Phase III |
| Labetuzumab (CEA-Cide) | huIgG1 | $^{90}$Y | CEA | Colorectal, breast, lung, pancreatic, stomach carcinoma | Pending Phase III |
| chTNT-1/B (Cotara) | chIgG1 | $^{131}$I | DNA | Glioblastoma multiforme, anaplastic astrocytoma | Phase III |
| $^{131}$I Lym-1 (Oncolym) | huIgG1 | $^{131}$I | HLA-DR10 | NHL, CLL | Phase II/III |
| Pemtumomab (Theragyn) | muIgG1 | $^{90}$Y | PEM | Ovarian, gastric carcinoma | Phase III |
| Ibritumomab tiuxetan (Zevalin) | muIgG1 | $^{90}$Y | CD20 | NHL | Approved by FDA; Phase IV |

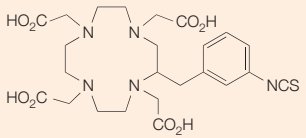
CEA, carcinoembryonic antigen; CLL, chronic lymphocytic leukaemia; huIg, human immunoglobulin; muIg, murine immunoglobulin; NHL, non-Hodgkin's lymphoma; PEM, polymorphic epithelial mucin.



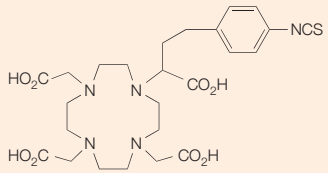
**1B4M-DTPA**
**MX-DTPA**
**Tiuxetan**



**CHX-A" DTPA**



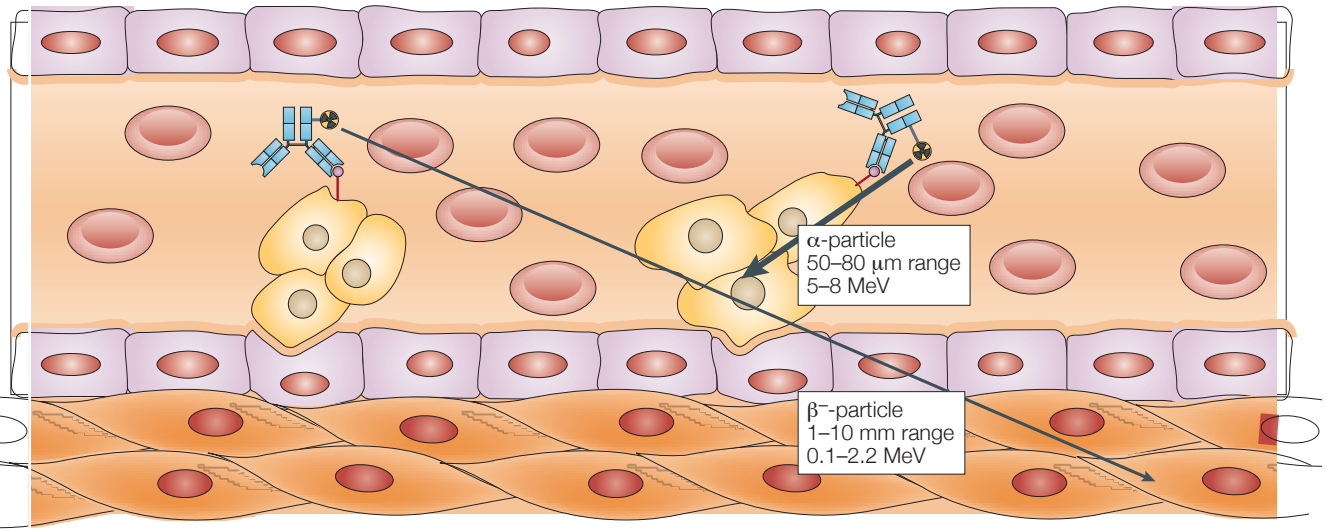
***c*-DOTA**



**PA-DOTA**

Therapeutic radionuclides

| Radionuclide | Type | Half-life | $E_{max}$ (MeV) | Mean range (mm) | Imageable |
|---|---|---|---|---|---|
| $^{90}$Y | β | 2.7 d | 2.3 | 2.76 | No |
| $^{131}$I | β, γ | 8.0 d | 0.81 | 0.40 | Yes |
| $^{177}$Lu | β, γ | 6.7 d | 0.50 | 0.28 | Yes |
| $^{153}$Sm | β, γ | 2.0 d | 0.80 | 0.53 | Yes |
| $^{186}$Re | β, γ | 3.8 d | 1.1 | 0.92 | Yes |
| $^{188}$Re | β, γ | 17.0 h | 2.1 | 2.43 | Yes |
| $^{67}$Cu | β, γ | 2.6 d | 0.57 | 0.6 | Yes |
| $^{225}$Ac | α, β | 10 d | 5.83 | 0.04–0.1 | Yes |
| $^{213}$Bi | α | 45.7 min | 5.87 | 0.04–0.1 | Yes |
| $^{212}$Bi | α | 1.0 h | 6.09 | 0.04–0.1 | Yes |
| $^{211}$At | α | 7.2 h | 5.87 | 0.04–0.1 | Yes |
| $^{212}$Pb | β | 10.6 h | 0.57 | 0.6 | Yes |
| $^{125}$I | Auger | 60.1 d | 0.35 | 0.001–0.02 | Yes |
| $^{123}$I | Auger | 13.2 h | 0.16 | 0.001–0.02 | No |
| $^{67}$Ga | Auger, β, γ | 3.3 d | 0.18 | 0.001–0.02 | Yes |
| $^{195m}$Pt | Auger | 4.0 d | 0.13 | 0.001–0.02 | No |




Milenic et al. Nature Rev Drug Discov. **3** (2004),488

Figure 3 | **Comparison of path lengths and emission tracks of α- and β⁻-particle emissions used in antibody-targeted**

**Table.** Estimated Drug Costs for Eight Weeks of Treatment for Metastatic Colorectal Cancer.

| Regimen | Drugs and Schedule of Administration | Drug Costs* |
|---|---|---|
| | | $ |
| **Regimens containing fluorouracil** | | |
| Mayo Clinic | Monthly bolus of fluorouracil plus leucovorin | 63 |
| Roswell Park | Weekly bolus of fluorouracil plus leucovorin | 304 |
| LV5FU2 | Biweekly fluorouracil plus leucovorin in a 48-hr infusion | 263 |
| **Regimens containing irinotecan or oxaliplatin** | | |
| Irinotecan alone | Weekly bolus | 9,497 |
| IFL | Weekly bolus of fluorouracil plus irinotecan | 9,539 |
| FOLFIRI | LV5FU2 with biweekly irinotecan | 9,381 |
| FOLFOX | LV5FU2 with biweekly oxaliplatin | 11,889 |
| **Regimens containing bevacizumab or cetuximab** | | |
| FOLFIRI with bevacizumab | FOLFIRI with fortnightly bevacizumab | 21,399 |
| FOLFOX with bevacizumab | FOLFOX with biweekly bevacizumab | 21,033 |
| Irinotecan with cetuximab | Weekly irinotecan plus cetuximab | 30,790 |
| FOLFIRI with cetuximab | FOLFIRI and weekly cetuximab | 30,675 |

* Costs represent 95 percent of the average wholesale price in May 2004.