Uterotonics, tocolytics, smooth muscle relaxants Cancer chemotherapy

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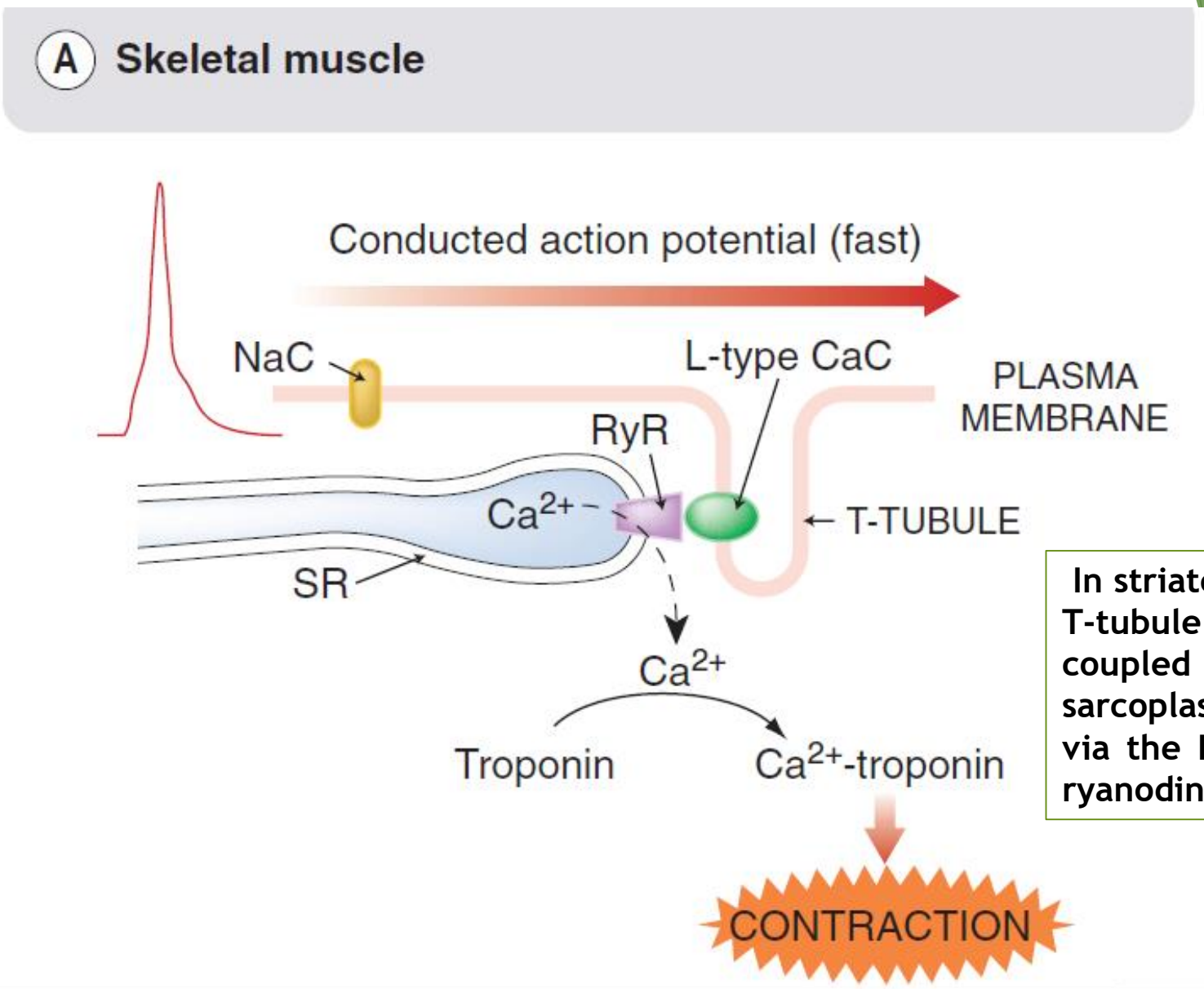
Comparison of excitation-contraction coupling in [A] striated muscle, [B] cardiac muscle and [C] smooth muscle

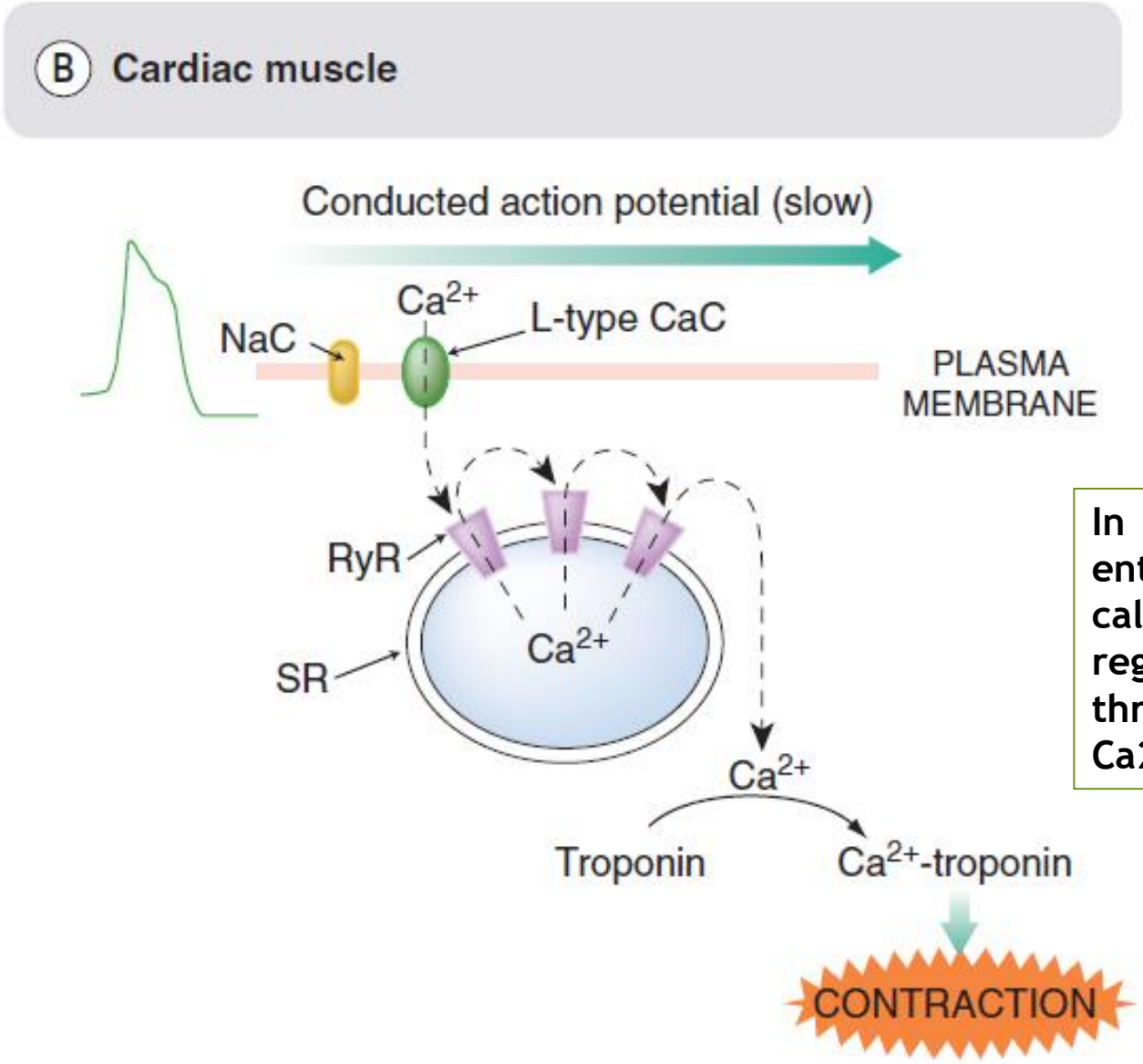


In striated muscle, the T-tubule membrane is coupled closely to the sarcoplasmic reticulum (SR) via the L-type CaC and the ryanodine receptor (RyR).

A&P Flix

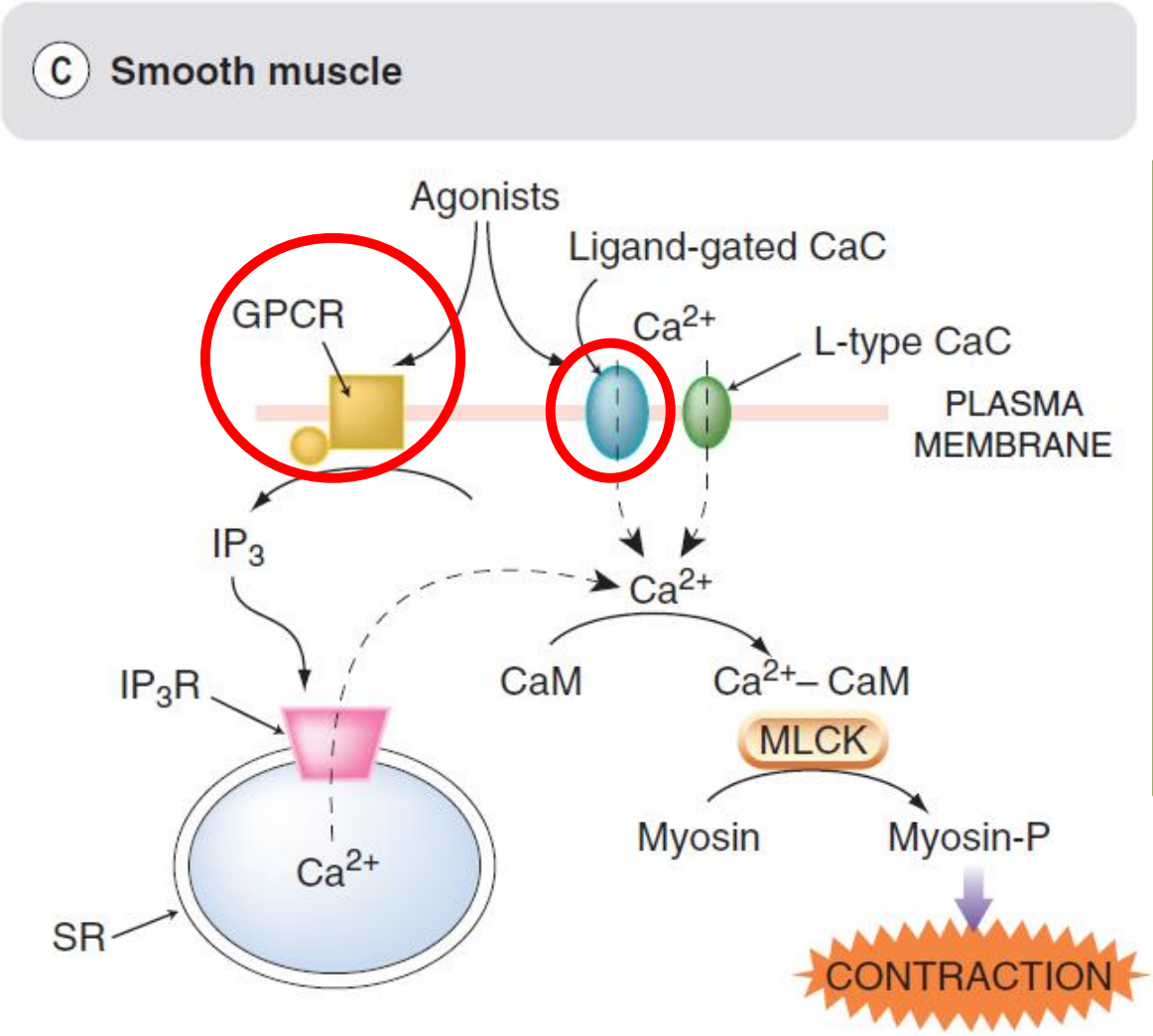
Muscle Contraction

Part 3: The Cross Bridge Cycle



In cardiac muscle, Ca2+ entry via voltage-gated calcium channels initiates a regenerative release through activation of the Ca2+-sensitive RyRs.

Important: Troponin is a complex of three regulatory proteins (troponin C, troponin I, and troponin T) that is essential to muscle contraction in skeletal muscle and cardiac muscle, but not in smooth muscle.



In smooth muscle, Ca2+ entry can be initiated through many different mechanisms:

- via voltage-gated calcium channels initiates (green)
- Ligand gated calcium-channels (blue)
- Ligand gated G-protein coupled mechanisms (from SR) (yellow+pink)

In skeletal muscle, myosin is always active, just waiting for binding sites of actin to reveal.

In smooth muscle Myosin Light Chain has to be activated = phosphorylated first to be active.

Thus in smooth muscle no other regulating proteins are needed (= no troponin in smooth muscle)

Mechanisms controlling smooth muscle contraction and relaxation

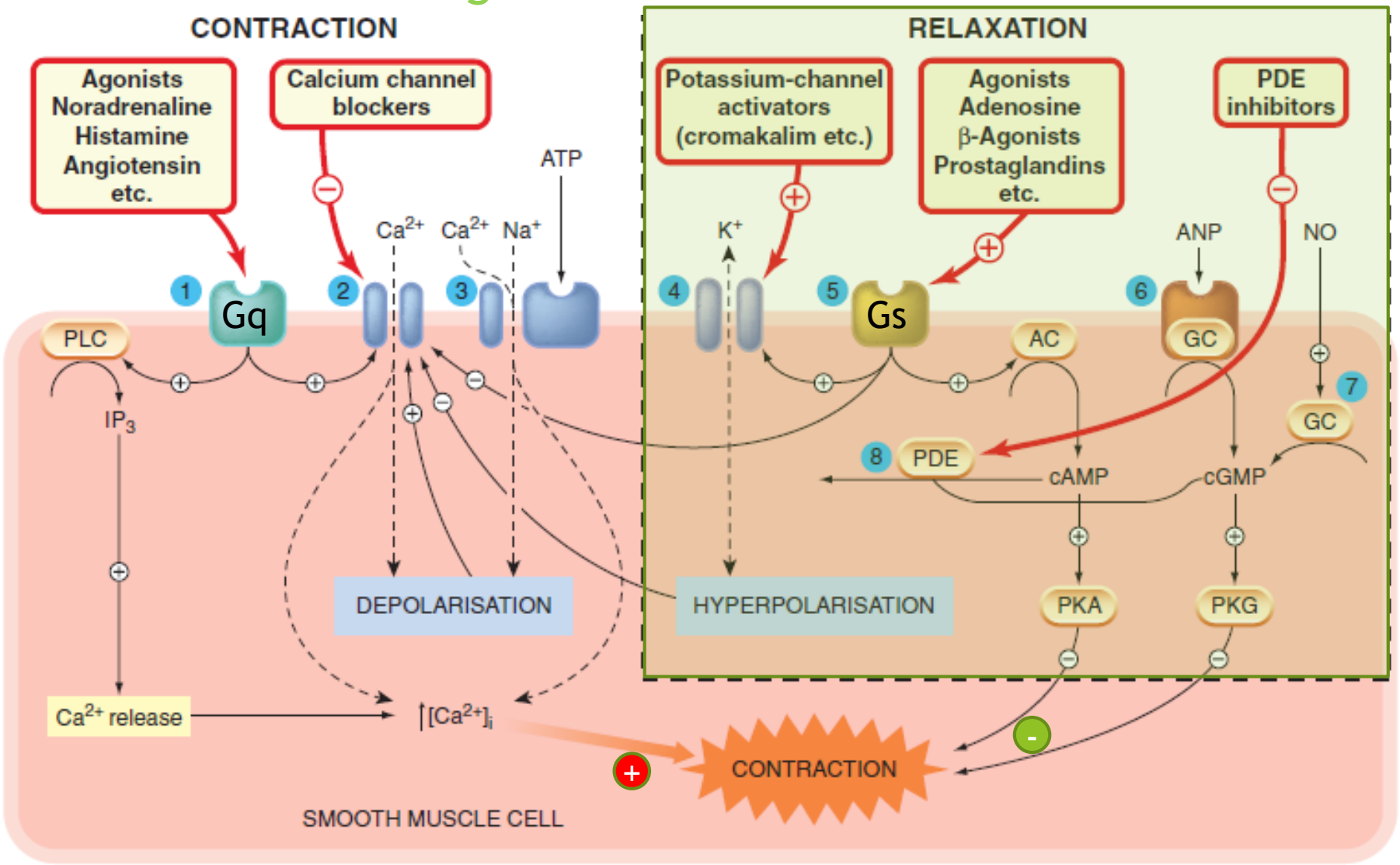


Fig. 4.10 Mechanisms controlling smooth muscle contraction and relaxation. 1. G-protein-coupled receptors for excitatory agonists, mainly regulating inositol trisphosphate formation and calcium channel function. 2. Voltage-gated calcium channels. 3. P2x receptor for ATP (ligand-gated cation channel). 4. Potassium channels. 5. G-protein-coupled receptors for inhibitory agonists, mainly regulating cAMP formation and potassium and calcium channel function. 6. Receptor for atrial natriuretic peptide (ANP), coupled directly to guanylyl cyclase (GC). 7. Soluble guanylyl cyclase, activated by nitric oxide (NO). 8. Phosphodiesterase (PDE), the main route of inactivation of cAMP and cGMP. AC, adenylate cyclase; PKA, protein kinase A; PKG, protein kinase G; PLC, phospholipase C.

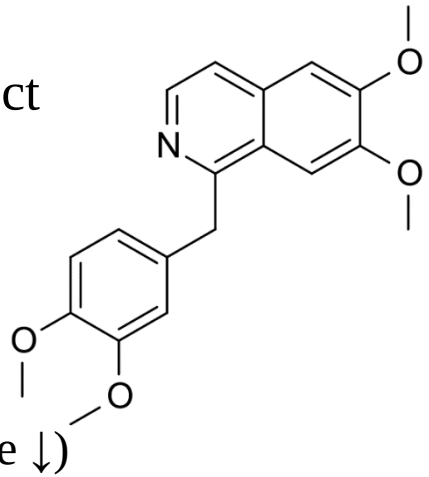
Drugs acting on smooth muscle

- Spastics
  - cholinomimetics
    - pilocarpin, muscarin
    - neostigmin, organo-phosphates
  - ergot-alkaloids, 5HTR agonists
    - ergometrin
  - oxytocine
  - prostaglandines
- Spasmolytics
  - cholinolytics
    - atropin, homatropin, ipratropium-bromid
  - sympathomimetics
    - selective βR agonists
      - fenoterol, salbutamol
  - smooth muscle relaxants
    - papaverin, drotaverin
    - methylxanthines (PDE inhibitors) (caffeine, theobromine, theophylline, aminophylline)

Spasmolytics

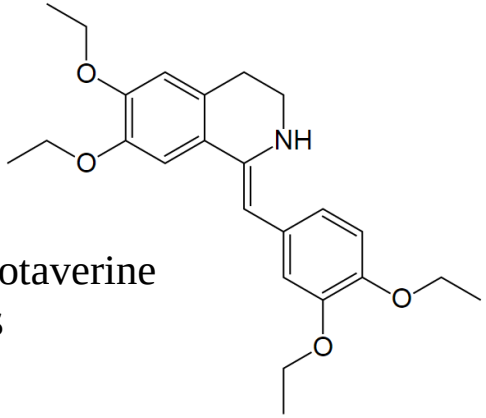
Papaver somniferum – garden poppy

- papaverine
  - Papaverinium chloratum
  - opium (morfine, codein, narcotin, papaverine)
  - Mechanism of effects:
    - blocking VG Ca^{2+} channels
    - inhibiting PDE 2, 3, 4
  - Smooth muscle relaxing effect
    - GIT, biliary tract
    - Urogenital tract
    - Respiratory system
  - Cardiovascular effects
    - (-) chronotrop effect
    - vasodilation (blood pressure ↓)
    - a. pulmonalis, cerebral art. dilation (pulm. emb., migrain th.)
  - analgetic, sedative effect (high doses)
  - Highly protein bound
  - 50-100 mg i.v, i.m.
  - contraindications: bradycardia, AV-block, ES, VF
  - p.o.: slow absorption → for this purpose use: drotaverine, ethaverin, moxaverin



Spasmolytics

- drotaverine (No-Spa®)
  - izoquinoline-derivative
  - drotaverine > papaverine (potency)
  - oral bioavailability is also higher
  - p.o., i.m., i.v.
  - th.: 40-120 mg
  - co-application
    - ibuprofen/diclofenac + drotaverine
  - More safety, less side-effects
  - Uses:
    - Gallstone, cholecystitis
    - Kidney stone, bladder inflammation, bladder spasm

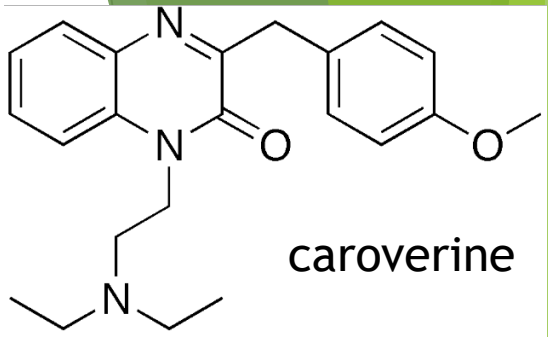


Add-on therapy:

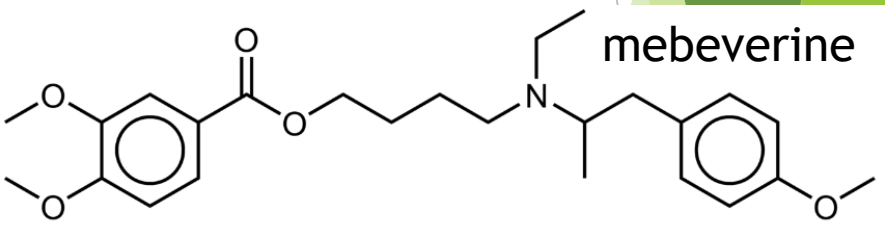
- GI smooth muscles spasm, stomach spasm, gastric ulcer, distension
- Tension-type headache
- Gynecological disease or painful menstruation

Spasmolytics

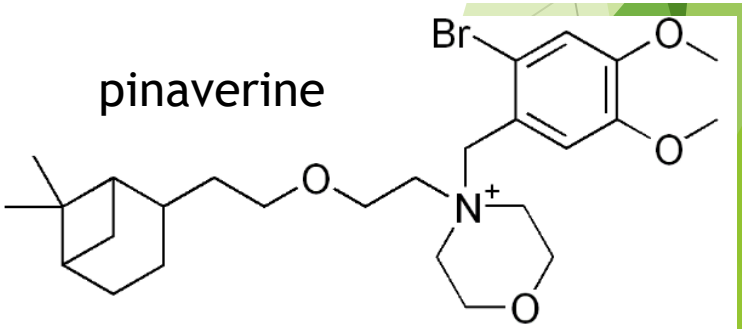
- caroverine, mebeverine
  - effect:
    - VG Ca^{2+} channel blockade
    - 10x (papaverine)
  - p.o. absorption↑
  - th.:
    - Spasms of GIT, biliary tract
    - caroverine: 20-40mg
      (also used in tinnitus)
      (also AMPA/NDMA antagonist effect; antioxidant)
    - mebeverine: 150-200 mg
      (also in IBS for colicky abdominal pain)
      (also has antimuscarinic action)
- pinaverine
  - pinaverium bromide
  - smooth relaxing effect
    - blocking of VG Ca2+ channels
    - cholinolytic effect
  - ↓CV side effect profile
  - th.:
    - spasms of GIT, biliary tract
    - urogenital tract
    - Premenstrual syndrome, dysmenorrhea



caroverine

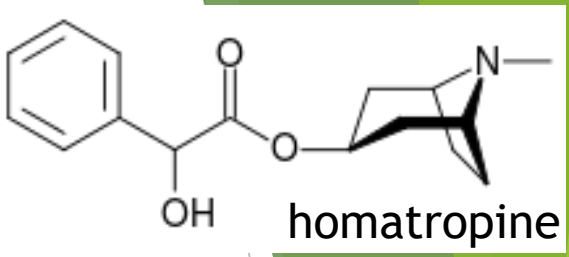


mebeverine



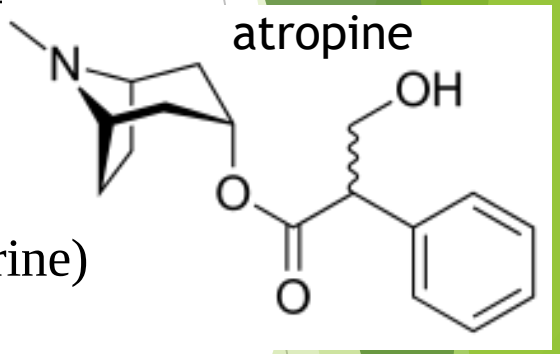
pinaverine

Spasmolytics



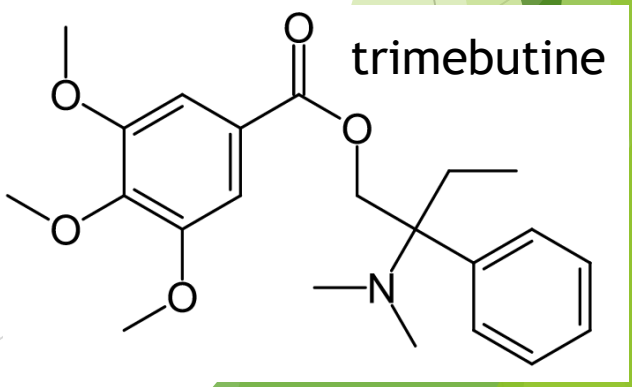
homatropine

- AchR blocking drugs
  - no primer/solitaer application
    - broad side effect profile! – like atropin intoxication!
    - Coapplication with other synergistic agents (+NSAID)
      - Troparinum combinatum® (homatropine + papaverine)
      - Meristin® (atropine + papaverine + aminophenazone + phenobarbital)
      - Steralgin® (methylhomatropine + drotaverine)
      - Reasec® (atropine + diphenoxylate)



atropine

- trimebutine
  - effect
    - Antimuscarinic agent
    - peripheral agonist of μ κ δ R
    - th.: IBS

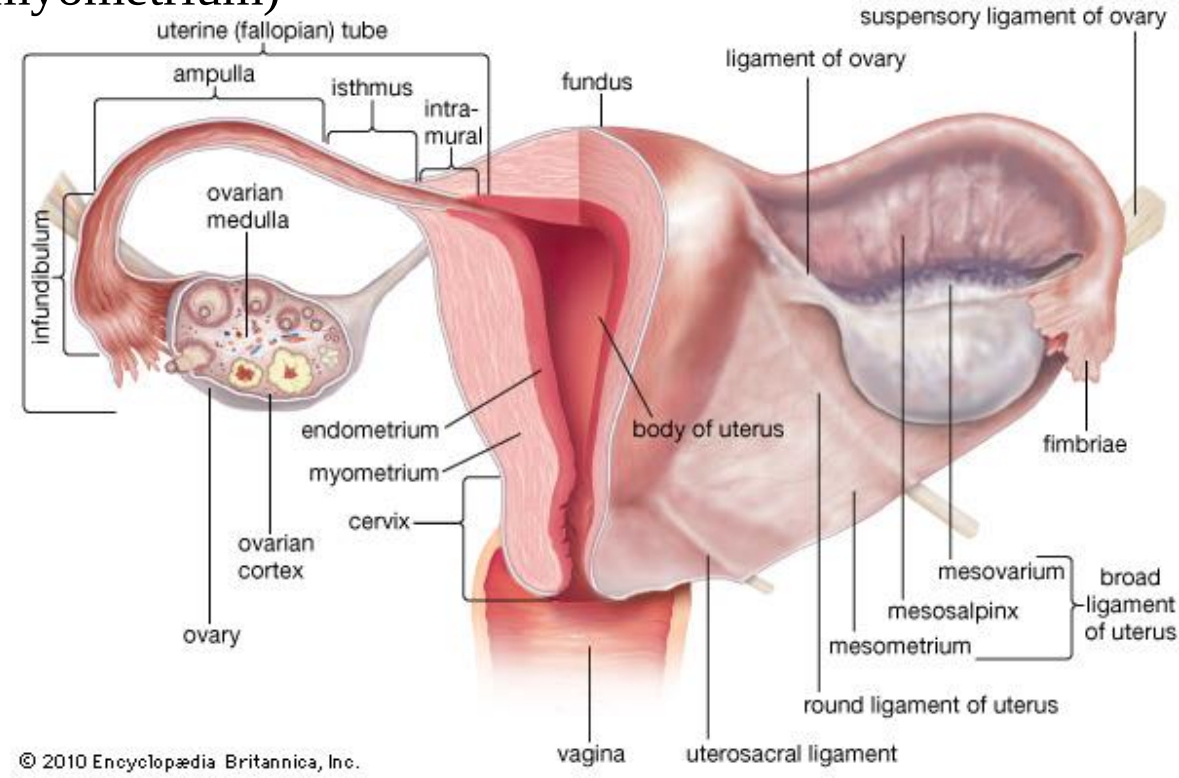


trimebutine

Uterotonics, tocolytics

Physiologic, neuroendocrine regulation of the uterinal tone

- pacemaker cells - fundus (myometrium)
- regular, rhythmic, coordinated, spontaneous myometrium contractions (fundus→cervix)
- regulated by:
  (during pregnancy this is suppressed)
  - oestrogen
  - progesterone
  - oxytocin
  - prostaglandines
  - uterinal adrenerg system
- labour
  - (fetal) cortisol↑ → oestrogen/progesterone ratio↑ (placenta)



Endocrine regulation of the uterinal tone (motility)

Oestrogen

- membrane depolarisation (myometrium)
- oxytocin R ↑
- αR sensitivity ↑
- endogenous PG synthesis ↑ in decidual cells
- gap junction ↑

Progesteron

- membrane-stabilising effect (myometrium)
- oxytocin R ↓
- βR ↑ sensitivity ↑
- endogenous PG synthesis↓

Endocrine regulation of the uterinal tone

- Prostaglandines - $PGF_{2\alpha}$, PGE_2, PGI_2-(prostacyclin)
  - endogenous prostaglandin are synthesized by endometrium-myometrium
  - Particularly in 2. phase of menstrual cycle (luteal phase)

- uterinal tone (motility) frequency↑, amplitude↑, cervix dilation
  - in every period of gestation!
  - before terminus: placenta

- Prostaglandins also play a part in: dysmenorrhoea (painful menstruation) and menorrhagia (excessive blood loss)
  these are caused by increased PGE2 and PGF2α; ➔ NSAIDs are good in menstrual pain
- PG synthesis can be…..:

stimulated:

- Ca2+
- platelet activating factor (PAF)
- β-agonists
- oestrogene
- TGF-α
- cortisol
- EGF
- IL-1 (α és β)
- lipopolisacharides
- TNF
- CRH, ACTH

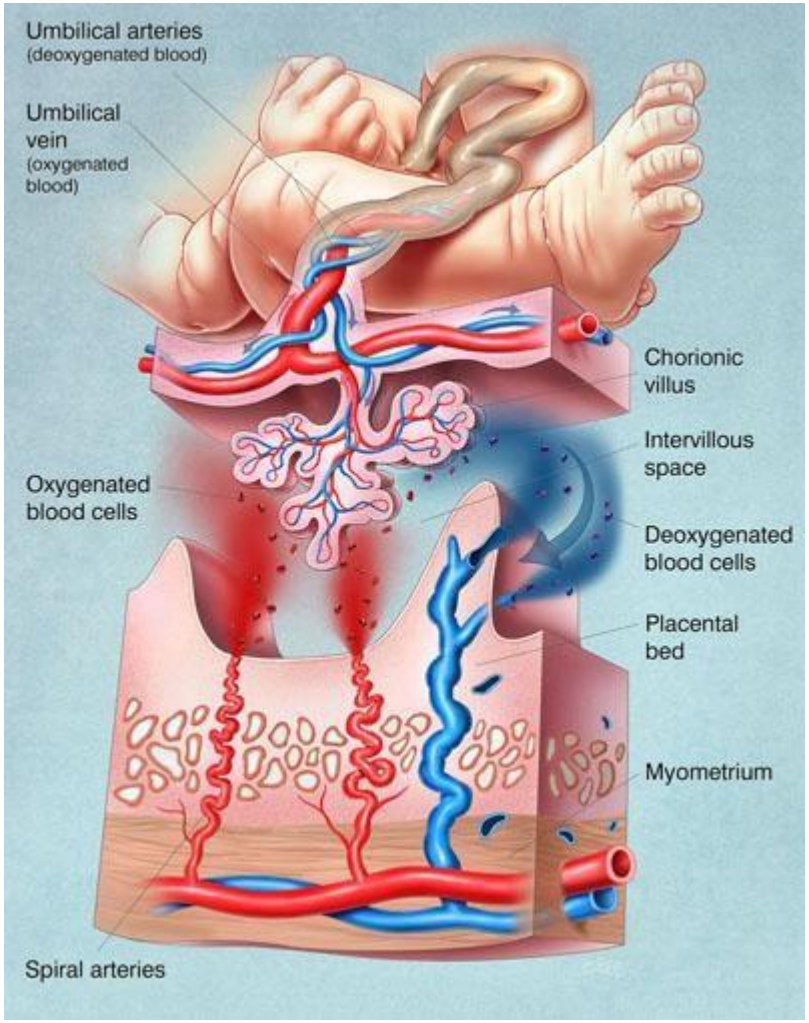
inhibited:

- lipocortin
- progesterone
- interferon α
- chorial phospholipase A2 inhibitor (lipocortin VII)

Uterotonics

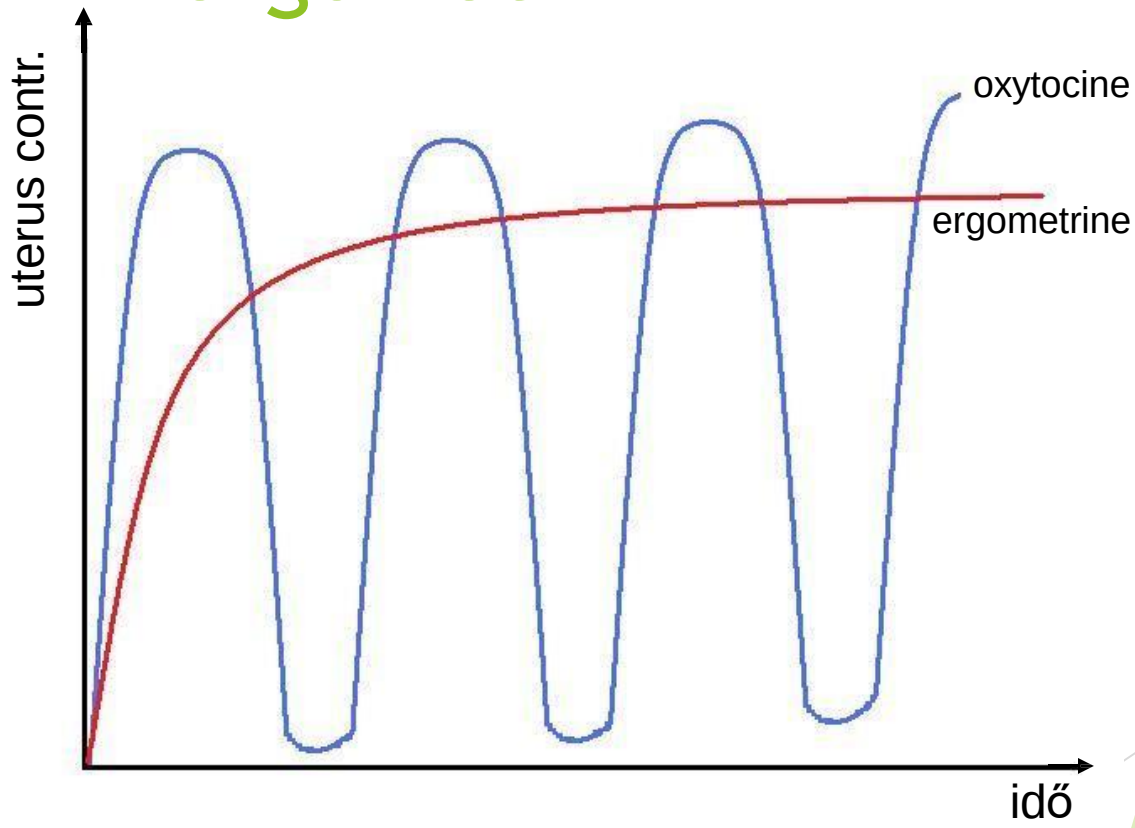
- Uses:
  - Labour induction (delivery, abortus)
  - Labour stimulation, enhancement (inertia uteri)
  - 3rd (placentar) stage induction
  - Prevention and therapy of postpartum haemorrhage (tonic cc.)
    - i.v. application
    - monitoring! (CTG)
  - Contraindications:
    - rupture of uterus
    - placenta praevia
    - abruption of placenta

Uteroplacentar unit



- phases of labor:
  - 1st stage (cervix<10 cm)
    - early labor phase
    - active widening phase
    - transient phase
  - 2nd stage (pushing phase)
  - 3rd stage (placentar phase)

oxytocin vs. ergometrin



tonic or rhythmic uterus contraction?

DRUGS PRODUCING UTERINE CONTRACTIONS (Uterotonic Drugs)

1. **OXYTOCIN**

2. **ERGOT ALKALOIDS**

   Ergometrine (Ergonovine)

3. **PROSTAGLANDINS**

   a) **PGE2**

   b) **PGF2α**

Uterotonics

- oxytocin
  - synthesis, storage:
    - hypothalamus (nucleus supraopticus/paraventricularis)
    - neurohypophysis
    - structural resemblence to ADH
    - $t_{1/2}$: 5 min
  - effect:
    - Oxytocin R (ic. Ca2+↑)
    - uterus contraction↑
    - myoepthelial cell contraction↑ („milk let down")
    - clinical use: 500ml dextrose – 5IU oxytocin (10IU/l) intra venously
    - in high doses – tonic uterus contraction
  - th.: 2-3 IU (1IU=0,5 mg)
    - stimulating/augmenting labor
    - 1st, 2nd stage
  - th.: 5-10 NE
    - 3rd stage
    - prevent postpartum haemorrhage
  - a.e.:
    - hypotension, tachycardia
    - rupture of uterus
    - electrolyte disturbances (ADH-resembl.!)

Oxytocin secretion occurs by sensory stimulation from cervix ,vagina , and from suckling at breast.

Immature uterus is resistant to oxytocin. Contracts uterine smooth muscle only at term. Sensitivity increases to 8 fold in last 9 weeks and 30 times in early labor.

Used as intra nasal spray in impaired milk ejection: One puff in each nostril 2-3 min before nursing

Uterotonics

- ergot-alkaloids
  - Claviceps purpurea – alkaloids – 5HTR, αR, DR
  - ergotism
    - gangraena
    - abortus
    - psychotic dysfunctions (hallucination)
  - effect:
    - KIR:
      - hallucinogene ($5HT_2R$ agonism)
      - extrapyramidal effect (D_2R agonism)
      - migraine th. (5HTR agonism/antagonism)
    - CV
      - Blood pressure↑ (αR, DR)
    - uterus
      - in low doses – rhytmic, regular, phasic uteruscontr..↑
        easily overdosed ➔ contraindicated in 1st and 2nd stage of labor
      - in large doses – TONIC, CONSTANT uteruscontr..↑
  - adverse effects:
    - tachycardia, angina pectoris
    - necrosis in extremities
  - clinical application: postpartum hemorrhage
    - ergotamine- (Ergam) - 0,15-0,6 mg i.m. v. 3x20 drops p.o.
    - methylergometrine (Methergin)– 0,2 mg i.m./.i.v.

Uterotonics

- Prostaglandines (PGE_1, PGE_2, $PGF_{2\alpha}$)
  - uterinal tone frequency↑, amplitude↑, cervix dilation↑
    - in every phase of gestation ➔ for abortion
  - th.: stimulating /induction of labor, induction of abortus
  - clinical use
    - local– gel/vaginal suppository (dinoprostone = PGE_2)
    - sulproston injection - postpartum haemorrhage
    - Dinoprost = $PGF_{2\alpha}$ and analogues (e.g. carboprost) intra muscularly – also anti-glaucoma agent
    - gemeprost or misoprostol (PGE_1 analogues) intra vaginally – also for therapy of gasric ulcer
  - a.e..:
    - headache
    - GIT (nausea, vomitus)
    - bronchospasm, chest pain
  - CI.:
    - asthma bronchiale
    - epilepsy

Abortion tablets

- Mifepristone + misoprostol/gemeprost
- Not to be confused with „morning after pill" (=emergency contraception; 72hours after act)
- This may be used by the end of 49th day from last menstruation or 35th day after conception.
- **Mifepristone** is a competitive progesterone receptor partial agonist that **sensitises the uterus to prostaglandins**,

Tocolytics

- Tocolysis = inhibition of uterinal motility (tone)
  - delaying premature birth (25%)
  - in emergency
    - acute fetal distress
    - placenta praevia
    - rupture of uterus
  - Main purpose: maturing fetal lungs - distress↓(app.48-72 hours)
  - CI:
    - haemorrhage
    - maternal disease: DM, arrhythmia
    - fetal disease (infection, abortus, dead fetus)

DRUGS PRODUCING UTERINE RELAXATION(Tocolytic Drugs)

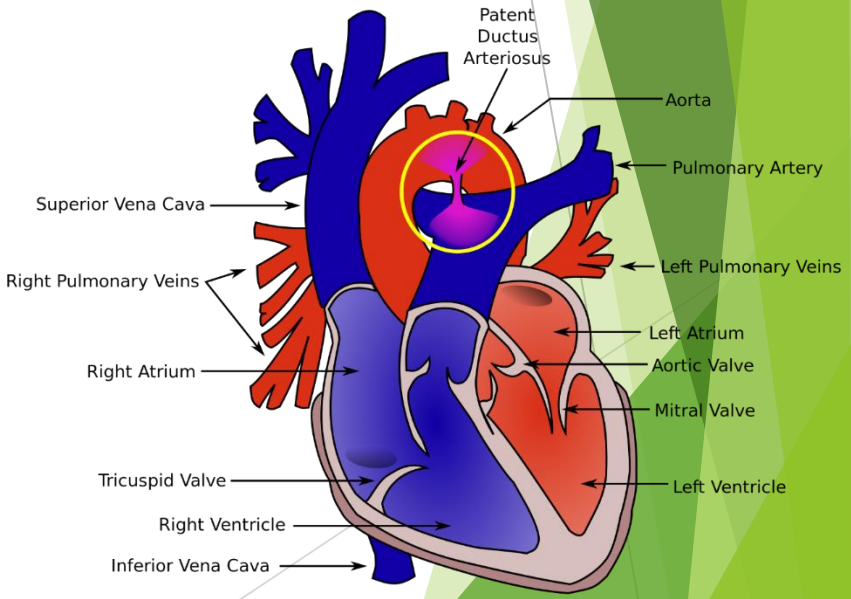
1. B-ADRENOCEPTOR AGONISTS
2. OXYTOCIN RECEPTOR ANTAGONIST
3. Mg^{2+}
4. PROSTAGLANDIN SYNTHESIS INHIBITORS i.e. NSAIDS
5. CALCIUM CHANNEL BLOCKERS
6. XANTHINE DERIVATIVES
7. Others

Tocolytic drugs

- β sympathomimetics
  - th.: asthma bronchiale.! – selective β_2 agonists (Gs signal transduction cAMP ↑)
  - Short-acting: ritodrine, salbutamol, fenoterol
    salbutamol (Brycanil) -10 μgramm/min i.v. (8-12h)
  - (Long-acting for asthma therapy: salmeterol, bambuterol, formoterol)
  - a.e:
    - tachycardia – ECG monitor!
    - Hypotension
    - hyperglycaemia – Blood Glucose controll!
- atosiban
  - oxytocine receptor antagonist
  - given as i.v. bolus followed by i.v. infusion for max 48 h.
  - Adverse effects:
    - vasodilatation,
    - nausea, vomiting and
    - hyperglycaemia.

Tocolytic drugs

- $MgSO_4$
  - mechanism of action:
    - bivalent cation
    - β sensitivity↑
  - th.:
    - 4-6 g/15-20 min i.v. bolus , 2-4g/h i.v.
    - clinical use: VT (torsade de pointes)
    - ANTIDOTE: Ca^{2+} gluconate
    - a.e.:.:
      - AV-block, bradycardia
      - dizziness
- NSAIDs
  - mechanism of action:
    - COX inhibition ($PGF_{2\alpha}$, PGE_2, PGI_2↓)
  - significant tocolytic effect
  - reversible vs. irreversible
  - irreversible: aspirin (postpartum haemorrhage)
  - indometacin: 50-75mg/day p.o.
  - th.: only before 28. gestation week: premature closure of arterious duct (Botalli)



Tocolytic drugs

- Ca2+ channel blockers
  - mechanism of action:
    - blocking L type Ca2+ channels - DHP (nifedipin)
  - efficacy↑
  - a.e.:
    - „flushing”, headache
  - Contraindications: fetal distress, pulmonary edema
- metilxanthines
  - aminophylline
  - PDE-inhibition (= cAMP↑)
  - th.: temporary effect
  - side effect profile↑
- ethanol
  - hypophyseal oxytocin release↓
  - direct relaxing effect
- anxiolytic drugs
  - sedative, anxiolytic effect
  - diazepame, promethazine

What/When should I administer….?

- Uterotonic agent
  - Labor induction
  - Labor „augmentation”
  - Postplacentar phase
  - Postpartum haemorrhage
- Tocolytic agent
  - Premature birth
    - prevention
    - prolongation
  - Emergency
    - acut fetal distress
    - placenta praevia
    - prolapse of umbilical cord
    - threatening rupture of uterus

Anticancer chemotherapy

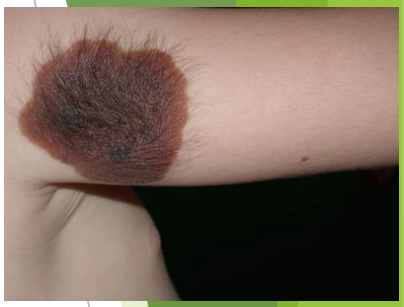
Introduction

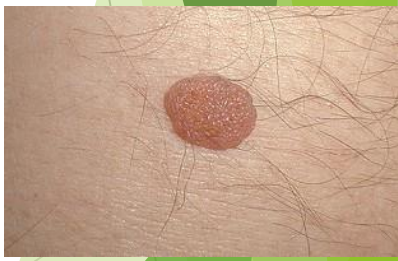
- In 2016, cancer was the second leading cause of mortality in the USA, causing almost 600,000 deaths.

- It is characterized by a loss in the normal control mechanisms that govern cell survival, proliferation, and differentiation.
- The anticancer drugs are more toxic than any other pharmaceutic agents, and thus their benefit must be carefully weighed against their risks.
- Many of the available drugs are cytotoxic agents that act on all dividing cells, cancerous or normal.

Definitions

- **Neoplasm** (from ancient Greek νεο- *neo-*, "new" + πλάσμα *plasma*, "formation", "creation") is an abnormal mass of tissue as a result of **neoplasia.**
- **Neoplasia** = abnormal growth/proliferation of cells
- **tumor** or **tumour**
  - Originally tumor (Latin) was used for *swelling*, currently it is used as a synonym of *neoplasm*
- **Types:** benign and malignant (cancer)
- **Benign**
  - e.g.: uterine fibroids and melanocytic nevus (plural: nevi) (=”skin moles”)
  - They are circumscribed and localized
  - They optimally do not transform into cancer.
  - lacks the ability to invade neighboring tissue (non-invasive)
  - They do not metastasize.
  - They have a slower growth rate
  - the tumor cells are usually more differentiated (cells have normal features)
- **Malignant** (=cancer)
  - The opposite of benign
  - Unregulated cell growth and division



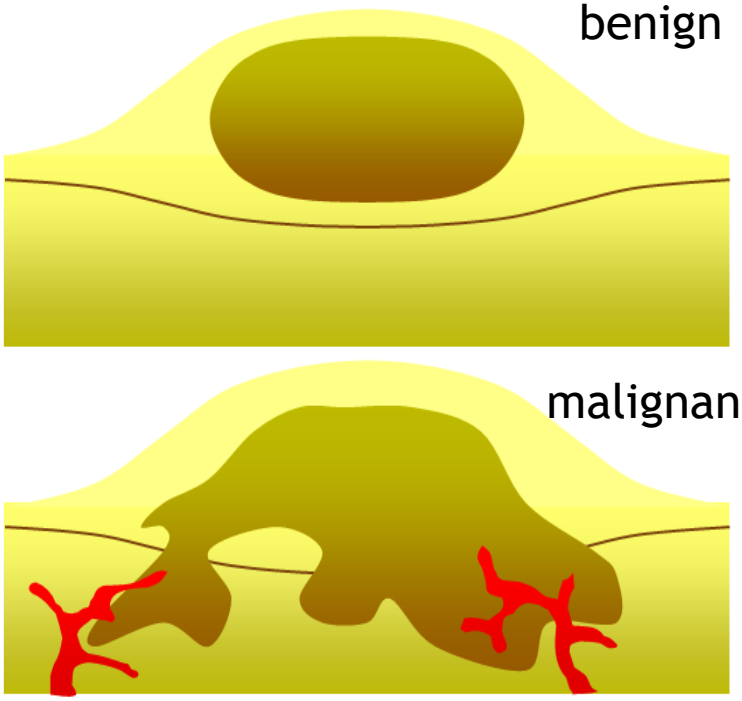


Metastasis

- Greek word meaning "displacement", from μετά, *meta*, "next", and στάσις, *stasis*, "placement".
- **Metastasis** (plural: metastases) or **metastatic disease**, is the spread of a cancer from one organ/part to another non-adjacent organ/part.

- a malignant neoplasma may invade nearby parts of the body then
- may also spread through the lymphatic system or bloodstream ➔ distant metastasis

Two epithelial tumours

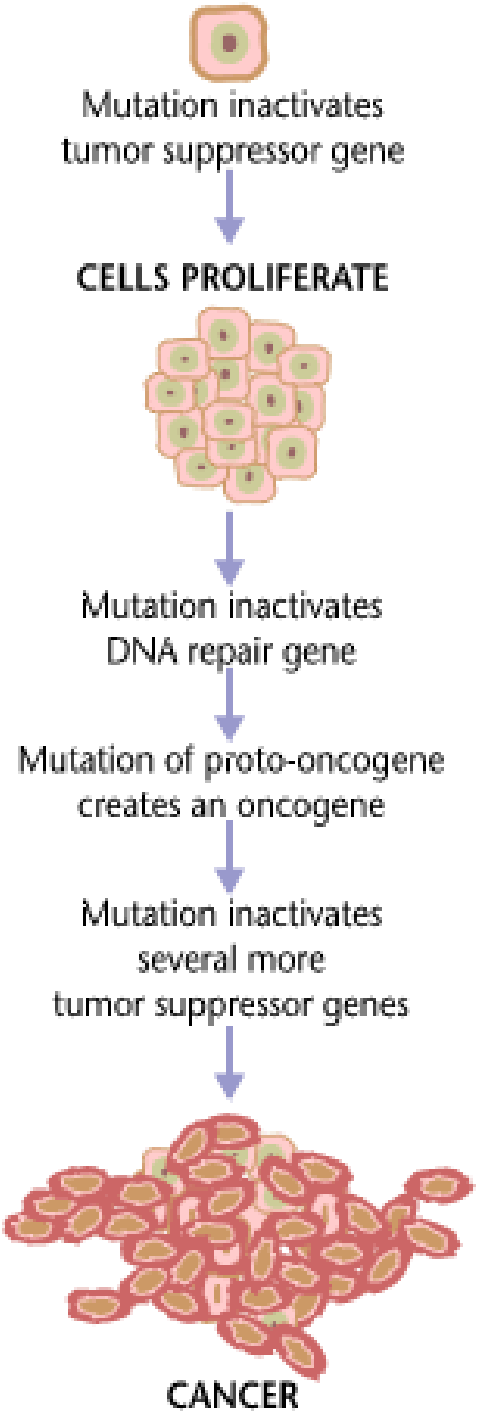


- Benign tumours are usually round in shape and encapsulated by fibrous connective tissue.
- Malignant tumours are irregularly shaped, vascular, and are invasive, crossing the basement membrane.

Pathophysiology

- failure of regulation of tissue growth
- regulatory genes are altered
- The affected genes can be:
  1. Oncogenes are genes which promote cell growth and reproduction
  2. Tumor suppressor genes are genes which inhibit cell division and survival

a **mutation** is the permanent alteration of the genetic material



Classification

- Carcinoma: Cancers derived from epithelial cells.
  - E.g.: most common cancers, particularly in the aged
  - most of breast, prostate, lung, pancreas, and colon cancers
- Sarcoma: Cancers arising from connective tissue
  - E.g.: bone, cartilage, fat, nerve,
  - develop from cells originating from mesenchymal cells outside the bone marrow.
- Lymphoma and leukemia: arise from bone marrow-derived hematopoietic (blood-forming) cells
  - Leukemia is the most common type of cancer in children (30%)
- Germ cell tumor: Cancers derived from pluripotent cells of the testicle or the ovary (seminoma and dysgerminoma, respectively).
- Blastoma: Cancers derived from immature, embryonic "precursor" cells.
  - Blastomas are more common in children than in older adults.

Treatment

- Cancer is usually treated with:
  - chemotherapy
  - radiation therapy
  - surgery

Chemotherapy

- The word "chemotherapy" alone refers to cancer treatment, but: *antibacterial chemotherapy*

- often abbreviated to ***chemo***
- is the treatment of cancer with one or more cytotoxic/antineoplastic drugs ("chemotherapeutic agents") as part of a standardized regimen
- Chemotherapy may be given:
  - with a curative intent or it may aim
  - to prolong life or
  - to palliate/alleviate symptoms
- Traditional agents act by killing rapidly dividing cells, one of the main properties of most cancer cells
- They also harm cells that divide rapidly under normal circumstances:
  - cells in the bone marrow,
  - digestive tract,
  - hair follicles

- side-effects of chemotherapy:
  - myelosuppression = decreased production of blood cells, hence also
  - immunosuppression
  - mucositis = inflammation of the lining of the digestive tract
  - alopecia = hair loss

Targeted therapy

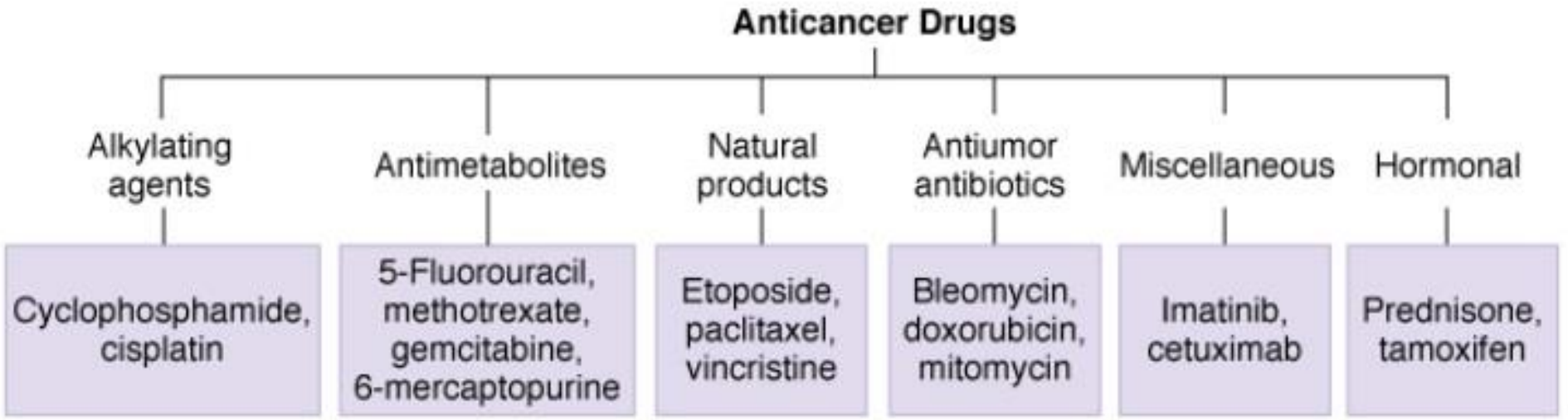
- Some newer anticancer drugs (e.g.: various monoclonal antibodies) are not indiscriminately cytotoxic, but rather target proteins
- Monoclonal antibody+ citotoxin

Drug resistance

It is a major problem in cancer chemotherapy

- Increased rate of DNA repair
- Formation of free radical scavenging/trapping agents (e.g.: glutathione)
- Changes in target enzymes
- Decreased activation of prodrug
- Decreased drug accumulation: e.g. expression of P-glycoprotein on the cell surface increases ➔ drugs efflux transport increases

Classes of antitumor agents



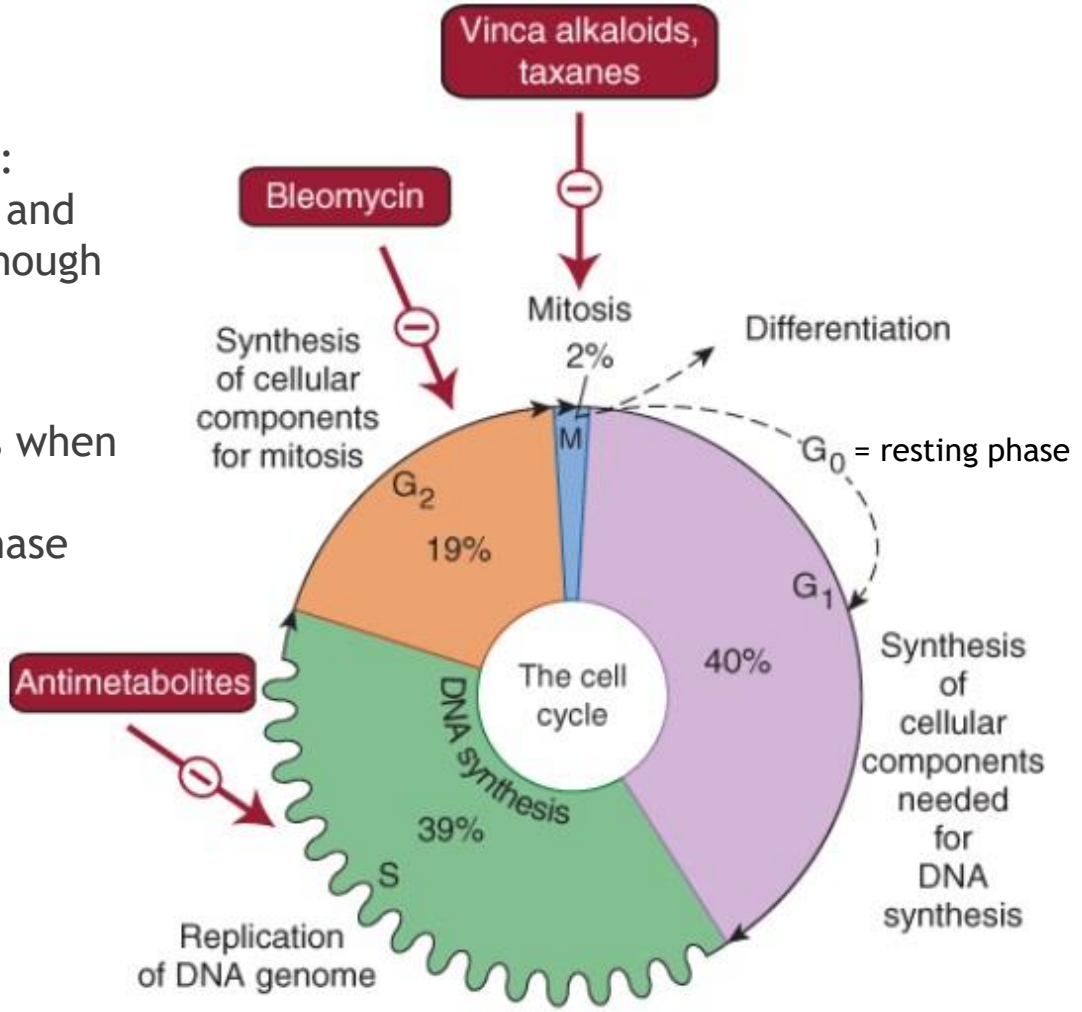
Produced by plants

Produced by microbes

Antibodies and small molecule enzyme- inhibitors

Cancer Cell Cycle Kinetics

- **Cell cycle-nonspecific (CCNS) drug:** they kill tumor cells in both cycling and resting phases of the cell cycle (although cycling cell are more sensitive).
- **Cell cycle-specific (CCS) drug:** acts selectively on tumor stem cells when they are traversing the cell cycle (and not when they are in the G_0 phase (resting phase))



Source: Trevor AJ, Katzung BG, Masters SB: *Pharmacology Examination & Board Review, 9th Edition:* www.accesspharmacy.com

Classes of antitumor agents

Cell Cycle-Specific (CCS) Agents

- Antimetabolites (S phase)
- Podophyllotoxins (topoisomerase II inhibitor) (G_1–S phase)
- Antimicrotubule inhibitors (M phase)
  - Taxanes (M phase)
  - Vinca alkaloids (M phase)
- Antitumor antibiotics (G_2–M phase) (are also CCNS)

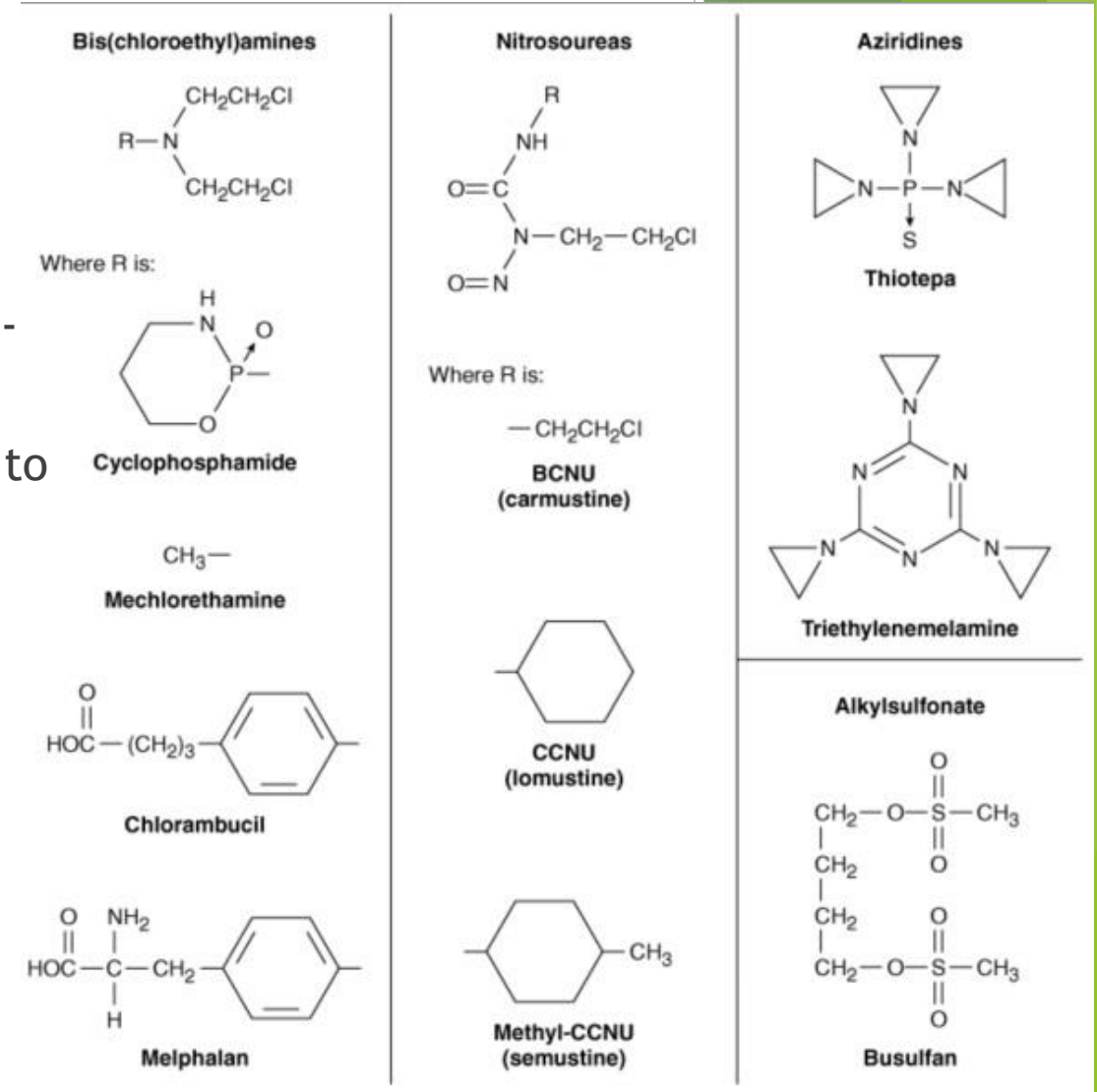
Classes of antitumor agents

Cell Cycle-Nonspecific (CCNS) Agents

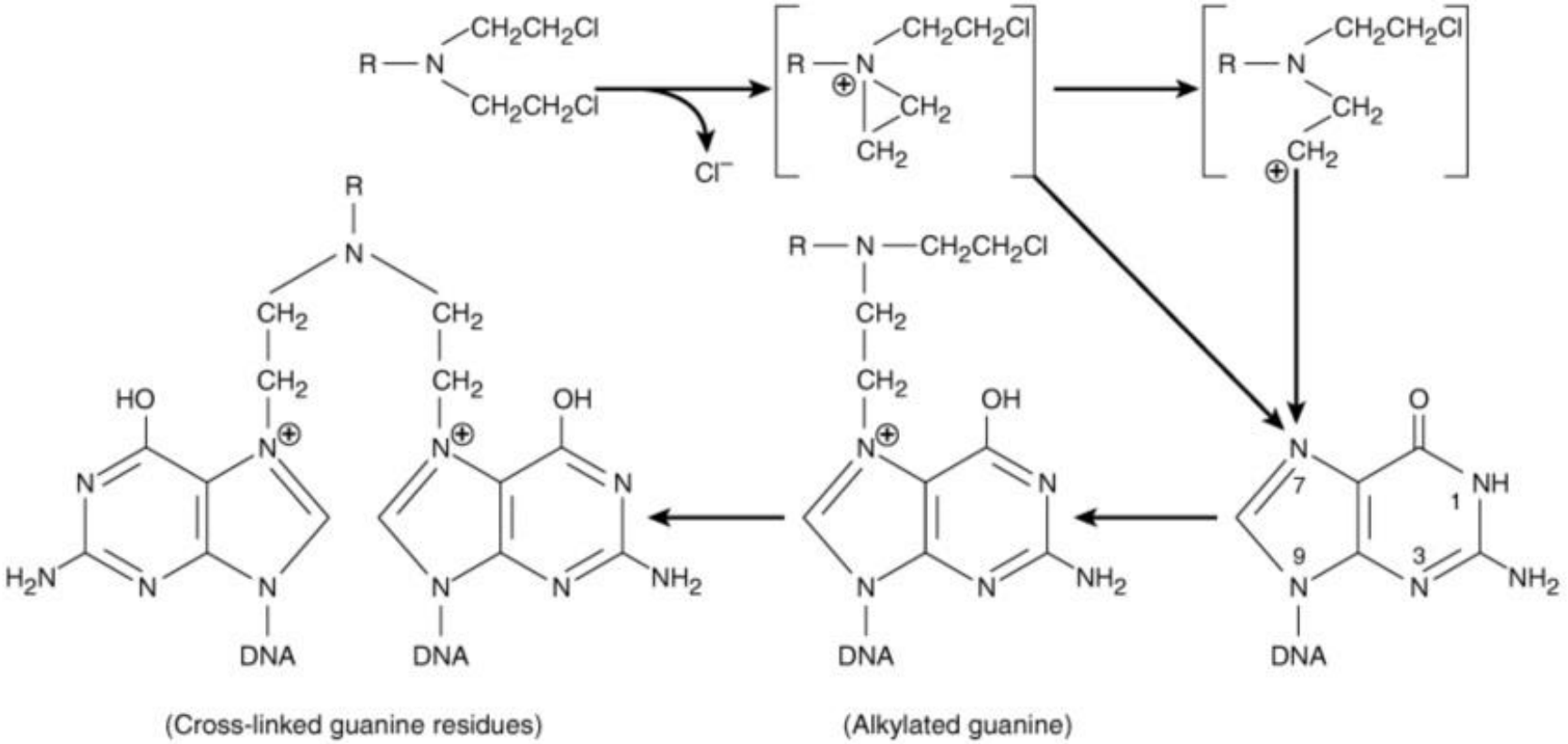
- Alkylating agents
- Antitumor antibiotics (are also CCS)
- Camptothecins (topoisomerase I inhibitors)
- Platinum analogs

Alkylating Agents

- are CCNS drugs
- Their structure containes: bis(chloroethyl)amine, ethylene-imine, or nitroso-urea moiety
- They transfer their alkyl groups to various cellular constituents
- Alkylations of DNA leads to cell death
- They form DNA cross-links, resulting in inhibition of DNA synthesis and function



Mechanism of alkylation of DNA guanine



Alkylating Agents - Classification

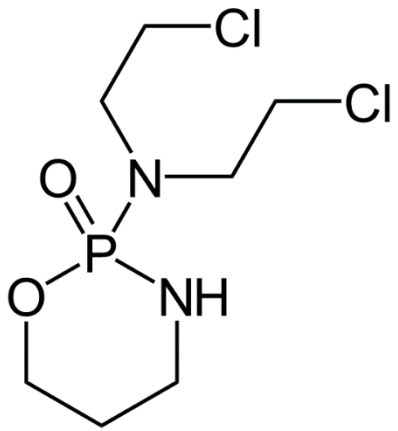
- nitrogen mustards **(chlorambucil, cyclophosphamide, mechlorethamine)**
- nitrosoureas **(carmustine, lomustine)**
- alkyl sulfonates **(busulfan)**

- Other drugs that act in part as alkylating agents include **cisplatin (and other platinum-analogs), dacarbazine,** and **procarbazine**

Other DNA-crosslinking agents

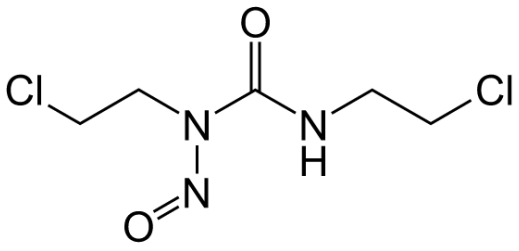
Alkylating agents- Cyclophosphamide

- breast cancer, ovarian cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, neuroblastoma
- Also in RA
- Acute Toxicities: nausea and vomiting
- Chronic Toxicities: myelosuppression, alopecia, hemorrhagic cystitis

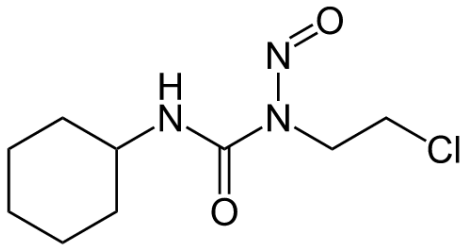


Alkylating agents - Nitrosoureas

- **carmustine, lomustine**
- non-cross-resistant with other alkylating agents
- all require biotransformation
- are highly lipid-soluble and are able to cross the blood-brain barrier → brain tumor



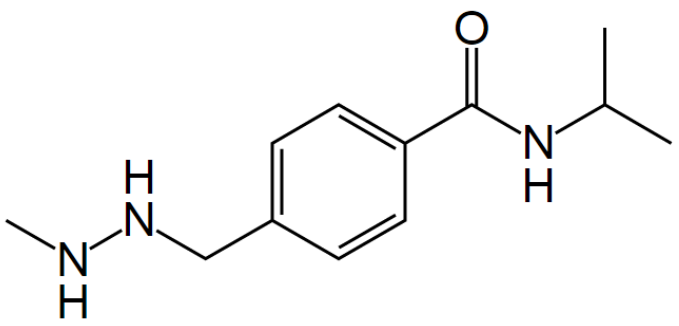
carmustine



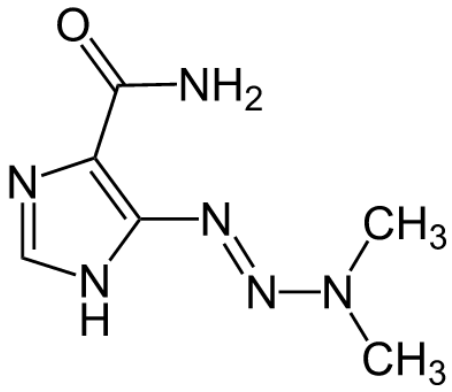
lomustine

Other DNA crosslinking agents – Procarbazine and dacarbazine

- Procarbazine is a reactive agent that forms hydrogen peroxide, which generates free radicals that cause DNA strand scission
- Also they methylate DNA
- penetrate into most tissues, including the cerebrospinal fluid
- It is used in Hodgkin's and non-Hodgkin's lymphoma, and brain tumors

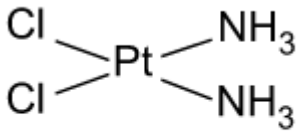


Procarbazine

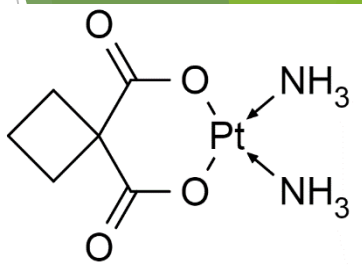


Dacarbazine

Other DNA crosslinking agents - Platinum Analogs

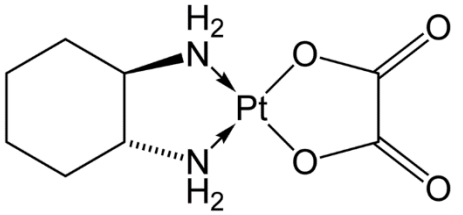


cisplatin



carboplatin

- Cisplatin, Carboplatin, Oxaliplatin
- inorganic metal complexes
- Mechanism of action:
  - precise mechanism of action unknown, probably alkylating,
  - inhibition of DNA synthesis and function
- Administration and pharmacokinetics:
  - intravenously
  - distribute to most tissues and are cleared in unchanged form by the kidney
- Therapeutical uses:
  - Cisplatin, Carboplatin: testicular carcinoma, bladder-, lung-, and ovary-cancer
  - Oxaliplatin: in advanced colon cancer



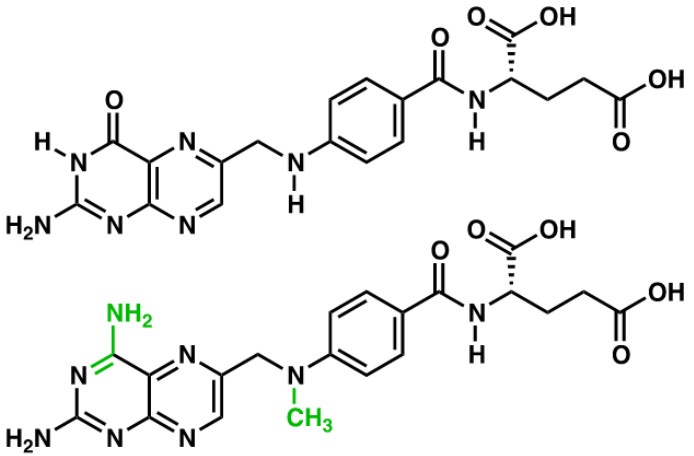
oxaliplatin

Antimetabolites

- They are CCS drugs acting primarily in the S phase of the cell cycle
- Many of these agents have been rationally designed and synthesized based on knowledge of critical cellular processes involved in DNA biosynthesis:
- They are structurally similar to endogenous compounds and are antagonists of
  - folic acid (**methotrexate**),
  - purines (**mercaptopurine, thioguanine**), or
  - pyrimidines (**fluorouracil, cytarabine, gemcitabine**)
- the antimetabolites also have immunosuppressant actions

Antimetabolite – Methotrexate (MTX)

- inhibitor of dihydrofolate reductase (DHFR) ➔ leads to a decrease in the synthesis of thymidylate (TS ↓), purine nucleotides, and amino acids and thus interferes with nucleic acid and protein metabolism ➔ ↓DNA
- Tumor cell resistance mechanisms include
  - decreased drug accumulation,
  - changes in the drug sensitivity or
  - activity of dihydrofolate reductase, and
- effective in:
  - choriocarcinoma, acute leukemias, non-Hodgkin's and primary central nervous system lymphomas, and a number of solid tumors, including breast cancer, head and neck cancer, and bladder cancer
- Methotrexate is also a DMARD = used in rheumatoid arthritis



Antimetabolites- 6-Mercaptopurine (6-MP) and 6-Thioguanine (6-TG)

- are purine antimetabolites
- Both drugs are activated by hypoxanthine-guanine phospho-ribosyl-transferases (HGPRTases) ➔ toxic nucleotides ➔ inhibit several enzymes involved in purine metabolism
- Resistant tumor cells have a decreased activity of HGPRTase
- used mainly in:
  - acute leukemias and chronic myelocytic leukemia
- Azathioprine (AZT, see RA seminar) is a prodrug of 6-MP, and is a DMARD

Antimetabolites- 5-Fluorouracil (5-FU)

- is converted in cells to 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP) ➔ inhibits thymidylate synthase ➔ "thymineless death" of cells
- Also converted to 5-fluorouridine-5'-triphosphate (5-FUTP)
- Incorporation of FdUMP into DNA inhibits DNA synthesis and function
- incorporation of FUTP into RNA interferes with RNA processing and function
- Tumor cell resistance mechanisms include
  - decreased activation of 5-FU,
  - increased thymidylate synthase activity, and
  - reduced drug sensitivity of this enzyme
- Fluorouracil is used in:
  - bladder, breast, colon, anal, head and neck, liver, and ovarian cancers

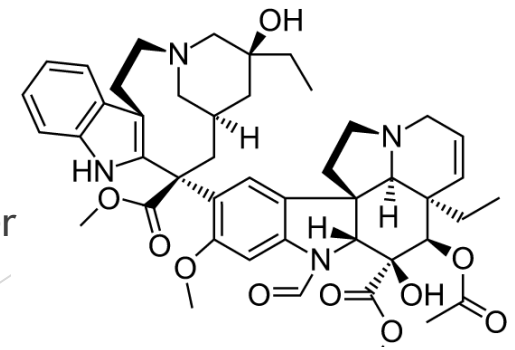
Natural Product Anticancer Drugs

- These can be CCS or CCNS drugs
- vinca alkaloids **(vinblastine, vincristine, vinorelbine)**
- podophyllotoxins **(etoposide, teniposide)**
- camptothecins **(topotecan, irinotecan)**
- taxanes **(paclitaxel, docetaxel)**

Natural Product Anticancer Drugs Vinblastine, Vincristine, and Vinorelbine

Catharantus roseus (formerly known as Vinca roseus)

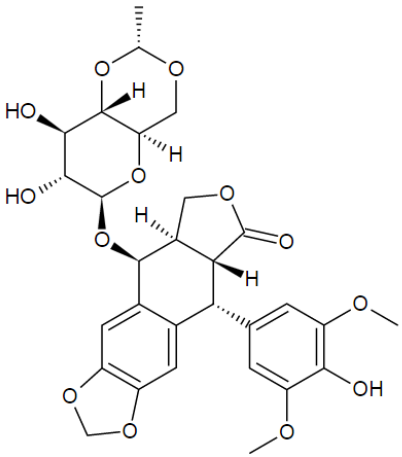
- These are called **vinca alkaloids**
- inhibit assembly of tubulin dimers into microtubules ➔ block the formation of the mitotic spindle
- act primarily in the M phase of the cancer cell cycle
- drugs must be given parenterally
- penetrate most tissues except the cerebrospinal fluid
- **Vincristine** is used in acute leukemias, lymphomas, Wilms' tumor, and neuroblastoma
- **Vinblastine** is used for lymphomas, neuroblastoma, testicular carcinoma, and Kaposi's sarcoma
- **Vinorelbine** is used in non-small cell lung cancer and breast cancer



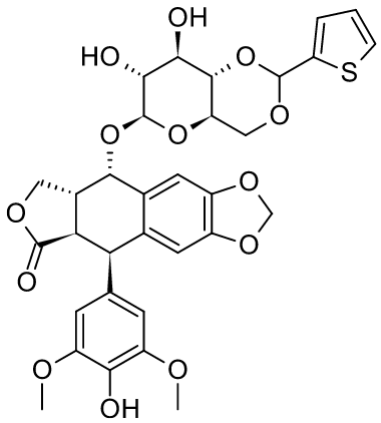
vincristine

Natural Product Anticancer Drugs Etoposide and Teniposide

- **Etoposide** , a semisynthetic derivative of **podophyllotoxin**,
- inhibits topoisomerase II ➔induces DNA breakage
- **Etoposide** is most active in the late S and early G_2 phases of the cell cycle
- **Teniposide** is an analog with very similar pharmacologic characteristics
- These agents are used in combination drug regimens for therapy of lymphoma, and lung, germ cell, and gastric cancers



Etoposide



Teniposide

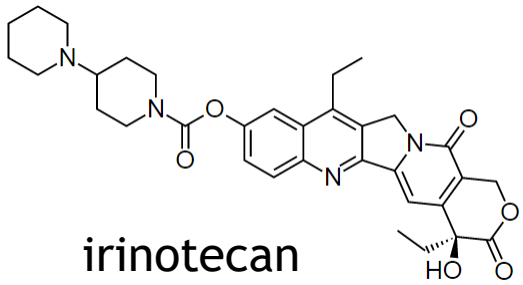
Podophyllum peltatum

Topoisomerases

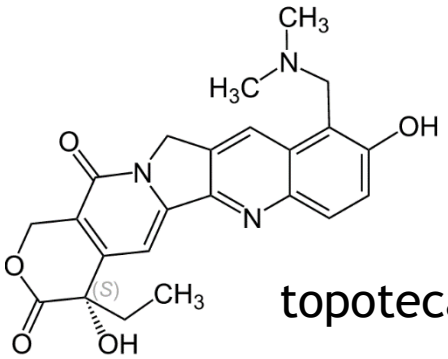
- Difference between Topoisomerase I and II:
  - I cuts single strand of a DNA,
  - II cuts both strands of DNA
- Topoisomerase I aids in transcription, replication, recombination, mitosis;
- topoisomerase II aids in DNA unwinding

Natural Product Anticancer Drugs Topotecan and Irinotecan

- These are camptothecin analogs. camptotechin was isolated from the bark and stem of Camptotheca acuminata (Camptotheca, Happy tree), a tree native to China
- produce DNA damage by inhibiting topoisomerase I.
- This enzyme cuts and removes single DNA strands during normal DNA repair processes
- **Irinotecan** is a prodrug
- **Topotecan** is used as second-line therapy for advanced ovarian cancer and for small cell lung cancer
- **Irinotecan** is used for metastatic colorectal cancer

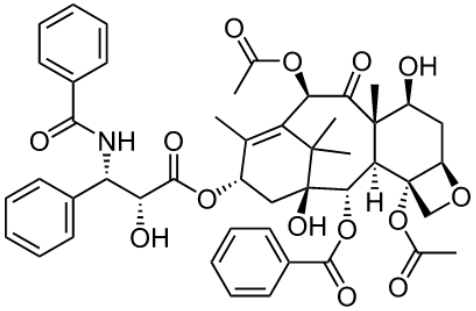


irinotecan

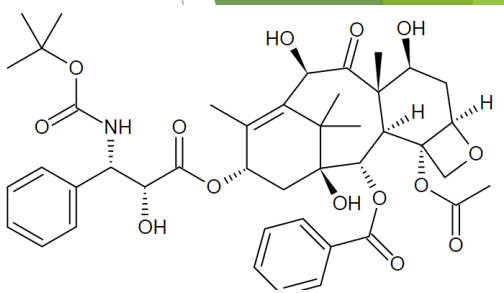


topotecan

Natural Product Anticancer Drugs Paclitaxel and Docetaxel



paclitaxel



docetaxel

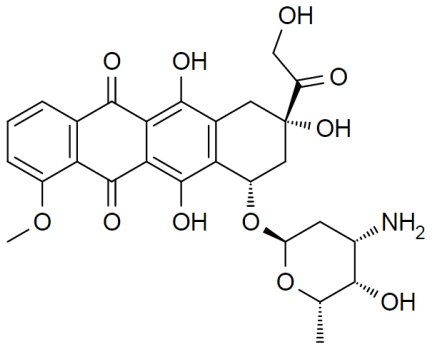
- These are called taxanes
- **Paclitaxel** and **docetaxel** interfere with the mitotic spindle
- They act differently from vinca alkaloids, since they prevent microtubule *disassembly* into tubulin monomers
- They are are given intravenously

Taxus baccata

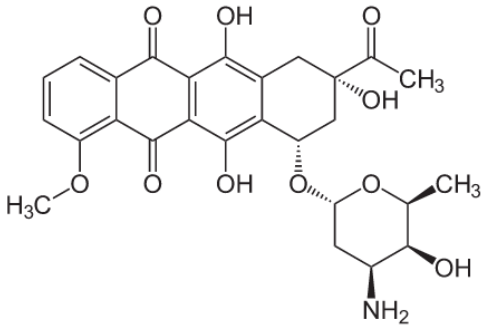
Antitumor Antibiotics

- includes the:
- **anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone)**
- **Bleomycin**
- **mitomycin**

Antitumor Antibiotics
Anthracyclines



doxorubicin

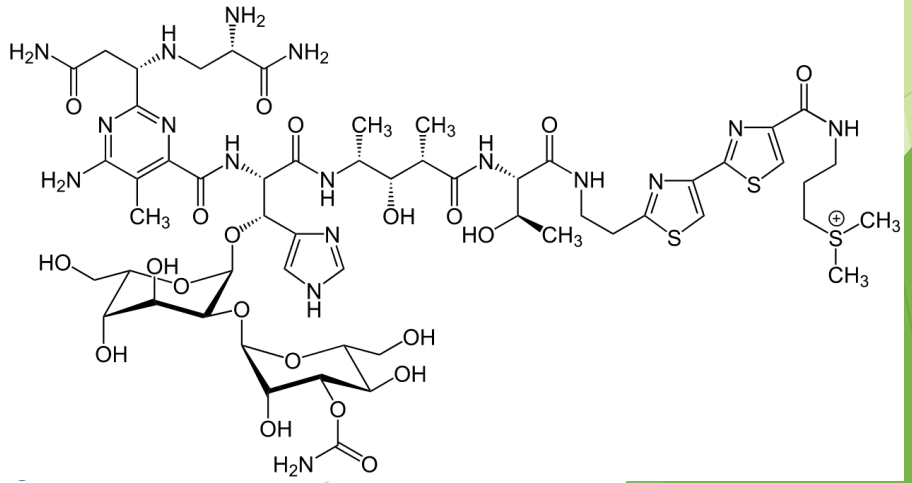


daunorubicin

- **doxorubicin**, **daunorubicin**, **idarubicin**, **epirubicin**, **mitoxantrone**
- They are both CCS and CCNS drugs (depending on mechanism of actions)
- intercalate between base pairs (CCNS action), inhibit topoisomerase II (CCS action), and generate free radicals
- They block the synthesis of RNA and DNA and cause DNA strand scission
- Membrane disruption also occurs
- Doxorubicin and daunorubicin must be given intravenously
- **Doxorubicin** is used in Hodgkin's and non-Hodgkin's lymphoma, myelomas, sarcomas, and breast, lung, ovarian, and thyroid cancers
- The main use of **daunorubicin** is in the treatment of acute leukemias

Antitumor Antibiotics Bleomycin

- Bleomycin is a mixture of glycopeptides that generates free radicals, which bind to DNA, cause strand breaks, and inhibit DNA synthesis
- It also intercalates into DNA inhibiting its use
- It is made by the bacterium Streptomyces verticillus
- Bleomycin is a CCNS drug
- must be given parenterally
- Bleomycin is a component of drug regimens for Hodgkin's lymphoma and testicular cancer

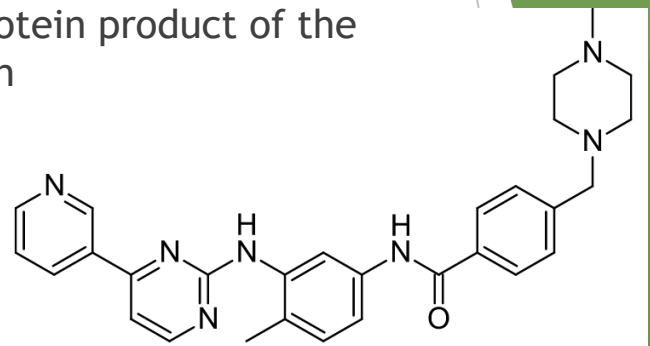


Miscellaneous Anticancer Agents

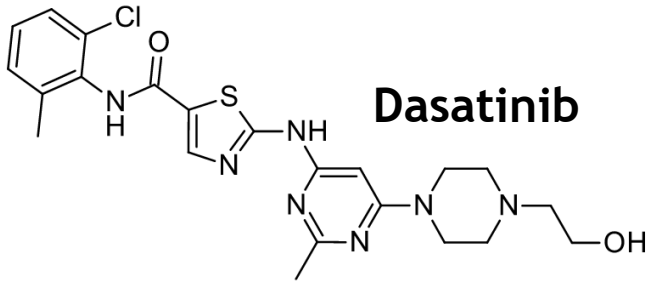
- Two main types:
  - Tyrosine-kinase inhibitors ("-nib")
    - Non-receptor tyrosin-kinase inhibitors (inhibitors of enzymes with tyrosine kinase activity)
    - Receptor tyrosin-kinase inhibitors
  - Cancer immunotherapy monoclonal antibodies („-mab”) (=proteins (immunoglobulins))

Miscellaneous Anticancer Agents - non-receptor Tyrosine Kinase Inhibitors

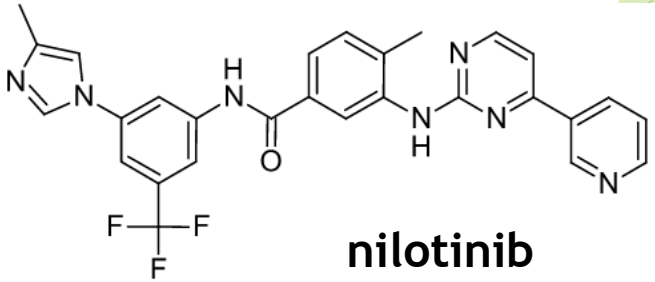
- **Imatinib** is an example of a selective anticancer drug whose development was guided by knowledge of a specific oncogene.
- It inhibits the tyrosine kinase activity of the protein product of the ***bcr-abl*** oncogene that is commonly expressed in chronic myeloid leukemia (CML).
- effective for treatment of:
  - CML
  - gastrointestinal stromal tumors
- Resistance may occur from mutation of the *bcr-abl* gene.
- Toxicity of imatinib includes
  - diarrhea, myalgia, fluid retention, and congestive heart failure.
- **Dasatinib** and **nilotinib** are newer anticancer kinase inhibitors.



Imatinib



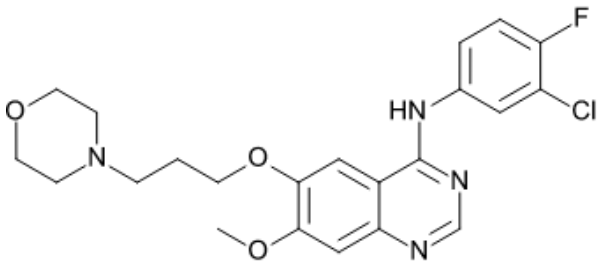
Dasatinib



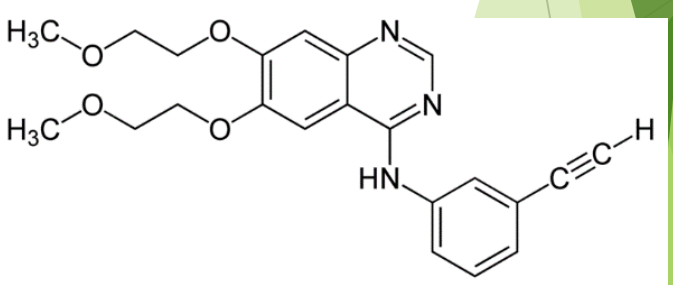
nilotinib

Miscellaneous Anticancer Agents - receptor Tyrosine Kinase Inhibitors

- **Gefitinib** and **erlotinib**
- are small molecule inhibitors of the EGFR's tyrosine kinase domain (EGFR is a „receptor tyrosine kinase”)
- gefitinib: used for certain breast, lung and other cancers
- erlotinib: non-small cell lung cancer (NSCLC), pancreatic cancer and several other types of cancer

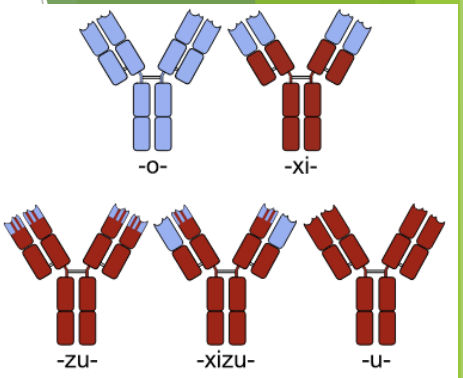


gefitinib



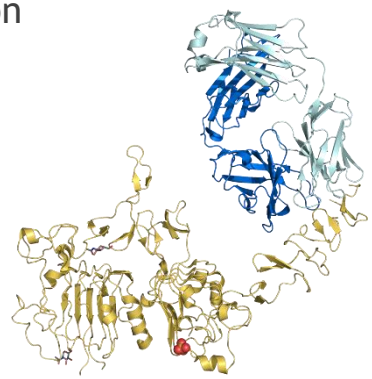
erlotinib

Miscellaneous Anticancer Agents - Growth Factor Receptor Inhibitors



- **Trastuzumab (Herceptin®)** , a monoclonal antibody targeting HER-2/*neu* receptor for epidermal growth factor (**EGFR**).
  Used in HER-2-positive breat cancer
- **Cetuximab** is a chimeric monoclonal antibody directed to the extracellular domain of the **EGFR**.
  used for the treatment of metastatic colorectal cancer, metastatic non-small cell lung cancer and head and neck cancer
- **Panitumumab** is a fully human monoclonal antibody directed against the **EGFR**; indication: metastatic colorectal cancer
- **Bevacizumab** is a monoclonal antibody that binds to **vascular endothelial growth factor** (**VEGF**) and prevents it from interacting with VEGF receptors indication: used i.v. for colon cancer, lung cancer, glioblastoma, and renal-cell carcinoma; as injection into the eye for age-related macula degeneration

Sketches of chimeric (top right), humanized (bottom left) and chimeric/humanized (bottom middle) monoclonal antibodies. Human parts are shown in brown, non-human parts in blue.



Trastuzumab
Fab region (cyan)
binding HER2/neu (gold)

Miscellaneous Anticancer Agents - Rituximab

- **Rituximab** is a monoclonal antibody that binds to a surface protein in non-Hodgkin's lymphoma cells and induces complement-mediated lysis, direct cytotoxicity, and induction of apoptosis.
- Use: together with conventional anticancer drugs (eg, cyclophosphamide plus vincristine plus prednisone) in low-grade lymphomas.
- Adverse effects:
  - hypersensitivity reactions and myelosuppression.

Miscellaneous Anticancer Agents - Interferons

- Interferons (IFNs) are cytokines: endogenous glycoproteins
- Effect: antineoplastic, immunosuppressive, and antiviral actions
- **Alpha-interferons** are effective against a number of neoplasms, including:
  - hairy cell leukemia,
  - the early stage of chronic myelogenous leukemia, and
  - T-cell lymphomas
- Toxic effects:
  - myelosuppression and
  - neurologic dysfunction

Miscellaneous Anticancer Agents - Asparaginase

- Asparaginase is an enzyme that depletes serum asparagine; it is used in the treatment of T-cell auxotrophic cancers (leukemia and lymphomas) that require exogenous asparagine for growth.
- Asparaginase is given intravenously and may cause severe hypersensitivity reactions, acute pancreatitis, and bleeding.

Hormonal Anticancer Agents - Glucocorticoids

- **Prednisone** is the most commonly used glucocorticoid in cancer chemotherapy and is widely used in combination therapy for leukemias and lymphomas.

Hormonal Anticancer Agents - Gonadal Hormone Antagonists (SERM agents)

- **Tamoxifen, raloxifene, clomifene** are selective estrogen receptor modulators (SERM),
- Mechanism of action:
  - They block the binding of estrogen to its receptor AND
  - their action is different in various tissues (=selective), thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues.
- Uses:
  - They are used as estrogen agonists on bone (estrogenic/agonist effect)
    ➔ used against osteoporosis (**raloxifene, clomifene**)
  - **Tamoxifen** inhibit estrogen-receptor of estrogen-sensitive cancer cells in breast tissue. ➔ used in receptor-positive breast carcinoma and for prevention in women at high risk for breast cancer.

Hormonal Anticancer Agents - Gonadotropin-Releasing Hormone (GnRH) Analogs

- **Leuprolide, goserelin,** and **nafarelin** are GnRH agonists, effective in prostatic carcinoma
- they *inhibit* release of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH)