Anticancer drugs

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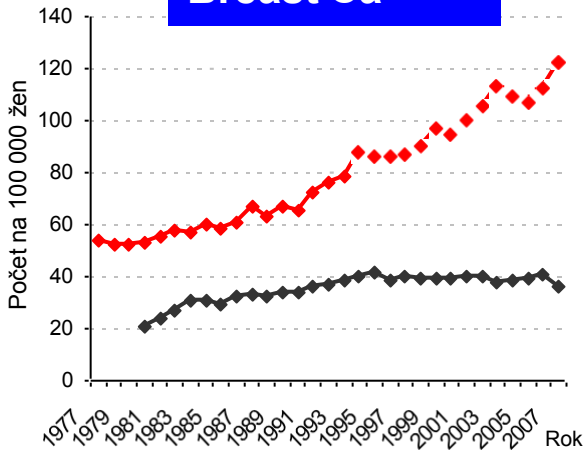
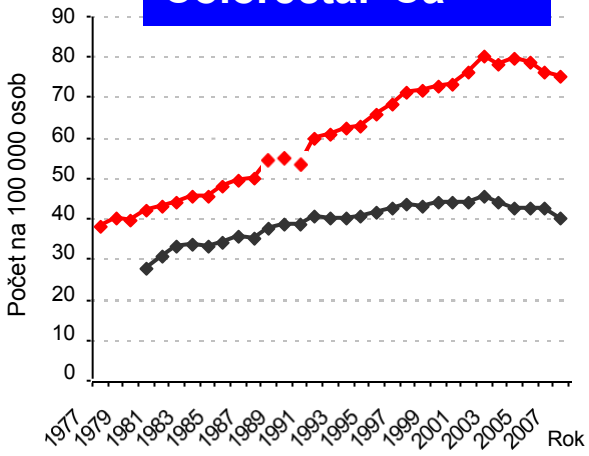
Cancer epidemiology - incidence and mortality in the Czech Republic

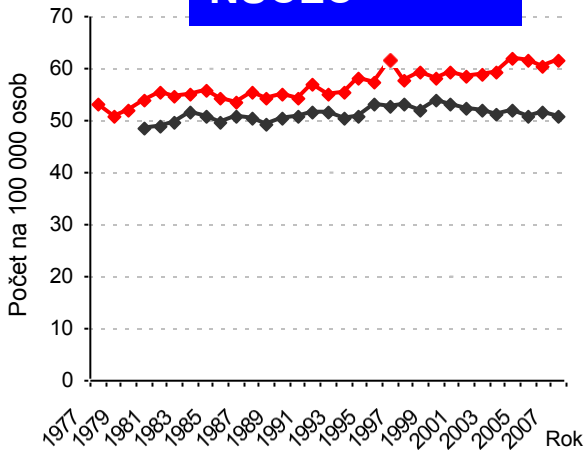
Breast Ca



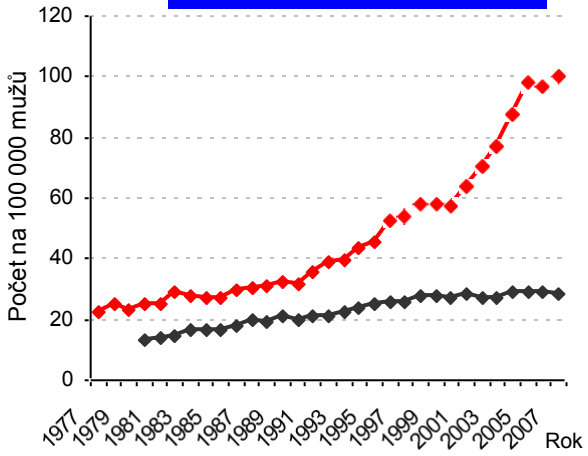
Colorectal Ca



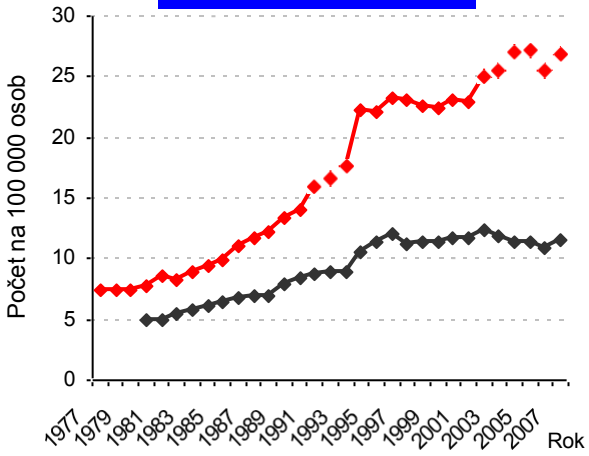
NSCLC



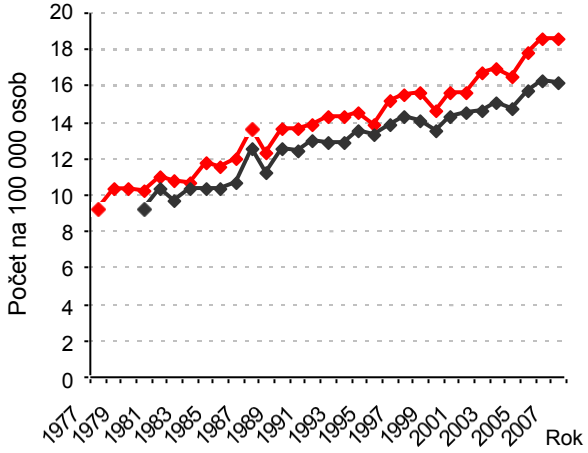
Prostatic Ca



Renal ca



Pancreatic Ca



incidence mortalita

Czech Cancer Care in Numbers 2015

Complex Cancer Treatment

- Surgery
- Radiotherapy
- Pharmacoterapy
- *Psychotherapy, physiotherapy, nutrition care*

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Pharmacotherapy

- **cytostatic agents**
  - classification according to the mechanism of action
- **endocrine (hormonal) therapy**
- **targeted therapy**
  - monoclonal antibodies targeting extracellular part of receptors
  - tyrosine kinase inhibitors / intracellular signaling cascades inhibitors
- **pain management, supportive care**

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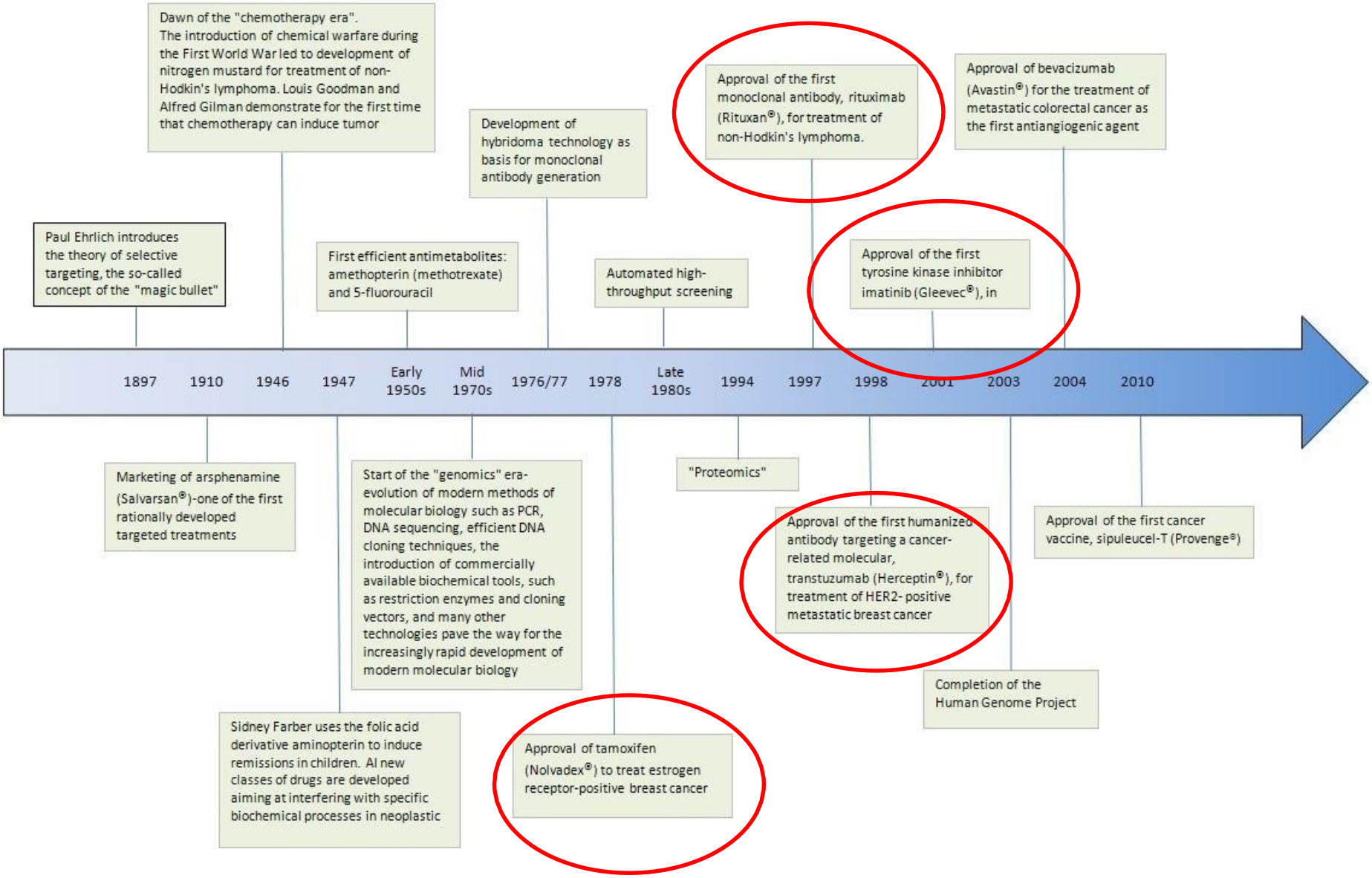
Dawn of the "chemotherapy era". The introduction of chemical warfare during the First World War led to development of nitrogen mustard for treatment of non-Hodkin's lymphoma. Louis Goodman and Alfred Gilman demonstrate for the first time that chemotherapy can induce tumor
Development of hybridoma technology as basis for monoclonal antibody generation
Approval of the first monoclonal antibody, rituximab (Rituxan®), for treatment of non-Hodkin's lymphoma.
Approval of bevacizumab (Avastin®) for the treatment of metastatic colorectal cancer as the first antiangiogenic agent
Paul Ehrlich introduces the theory of selective targeting, the so-called concept of the "magic bullet"
First efficient antimetabolites: amethopterin (methotrexate) and 5-fluorouracil
Automated high-throughput screening
Approval of the first tyrosine kinase inhibitor imatinib (Gleevec®), in
1897
1910
1946
1947
Early 1950s
Mid 1970s
1976/77
1978
Late 1980s
1994
1997
1998
2001
2003
2004
2010
Marketing of arsphenamine (Salvarsan®)-one of the first rationally developed targeted treatments
Start of the "genomics" era-evolution of modern methods of molecular biology such as PCR, DNA sequencing, efficient DNA cloning techniques, the introduction of commercially available biochemical tools, such as restriction enzymes and cloning vectors, and many other technologies pave the way for the increasingly rapid development of modern molecular biology
"Proteomics"
Approval of the first humanized antibody targeting a cancer-related molecular, transtuzumab (Herceptin®), for treatment of HER2- positive metastatic breast cancer
Approval of the first cancer vaccine, sipuleucel-T (Provenge®)
Completion of the Human Genome Project
Sidney Farber uses the folic acid derivative aminopterin to induce remissions in children. Al new classes of drugs are developed aiming at interfering with specific biochemical processes in neoplastic
Approval of tamoxifen (Nolvadex®) to treat estrogen receptor-positive breast cancer

Cytostatic drugs

- route of administration:
  - parenterally (i.v. bolus, infusion, intrathecally, intravesically…)
  - orally
- posology: dose in mg/m^2 or mg/kg
- monotherapy and combination regimens
- repeated administration in cycles

  pause = patient‘s recovery, prevention of severe AE

  + „waking“ dormant cells in G_0 phase

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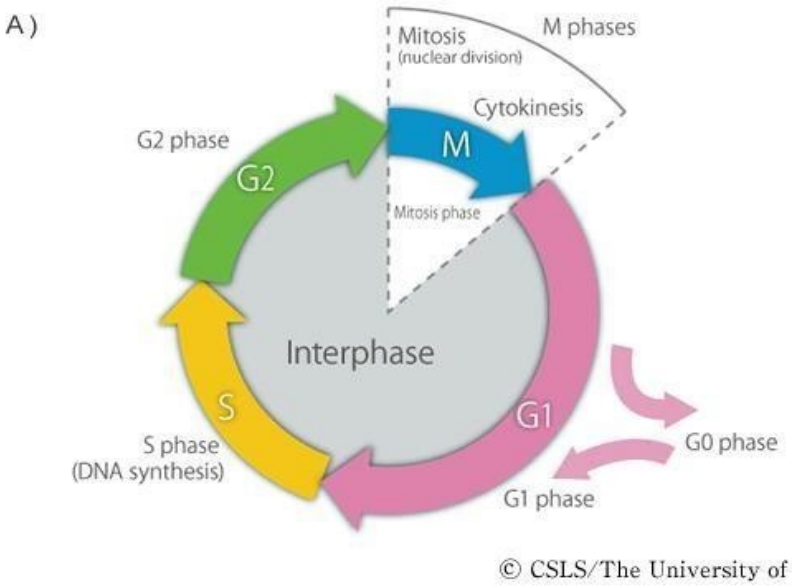
Cytostatic drugs

Different efficacy according to the cell cycle phase:

- *Cell cycle non-specific cytostatics* (e.g., busulfan)
- *Cell cycle specific cytostatics:*
  - Phase-nonspecific (e.g., some of alkylating agents)
  - Phase-specific (e.g., antimetabolites, taxanes)



http://csls-text3.c.u-tokyo.ac.jp/active/13_01.html

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Cytostatics according to their MoA

1. **Drugs that damage the structure of DNA**
   a) Alkylating agents
   b) Platinum derivatives
   c) Intercalating agents
   d) Bleomycin
2. **Drugs that inhibit key enzymes of DNA metabolism**
   a) Antimetabolites:
      i. Purine analogues
      ii. Pyrimidine analogues
      iii. Folic acid analogues
      iv. Hydroxyurea
   b) Topoisomerase inhibitors:
      i. Inhibitors of topoisomerase I – camptothecins
      ii. Inhibitors of topoisomerase II – podophyllotoxins
3. **Drugs that alter microtubules**
   a) Inhibitors of tubulin polymerization – *Vinca* alkaloids
   b) Inhibitors of tubulin depolymerization – taxanes
4. **Others**
   a) Drugs that inhibit protein synthesis – L-asparaginase

Drug groups overview

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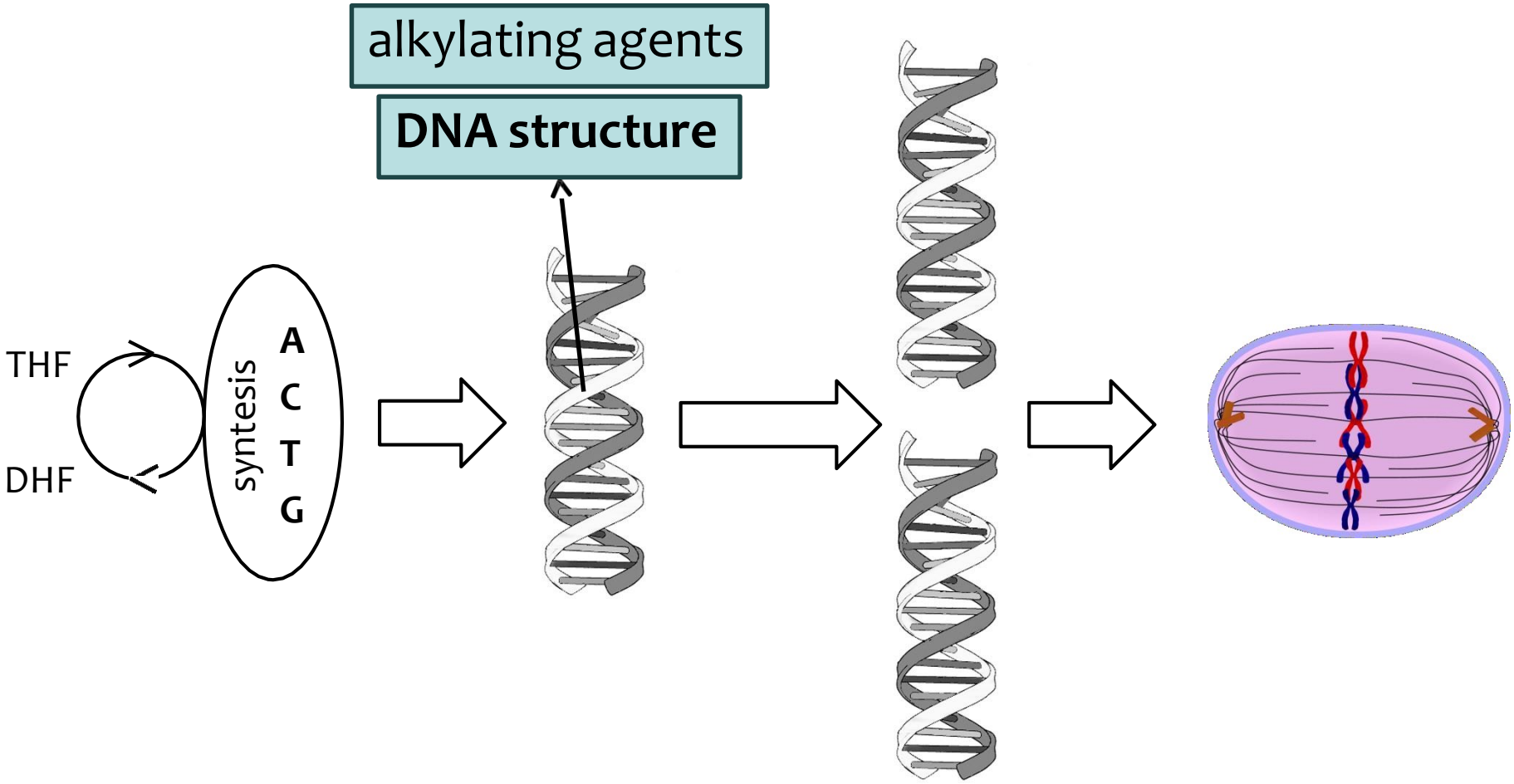
1a) Alkylating agents



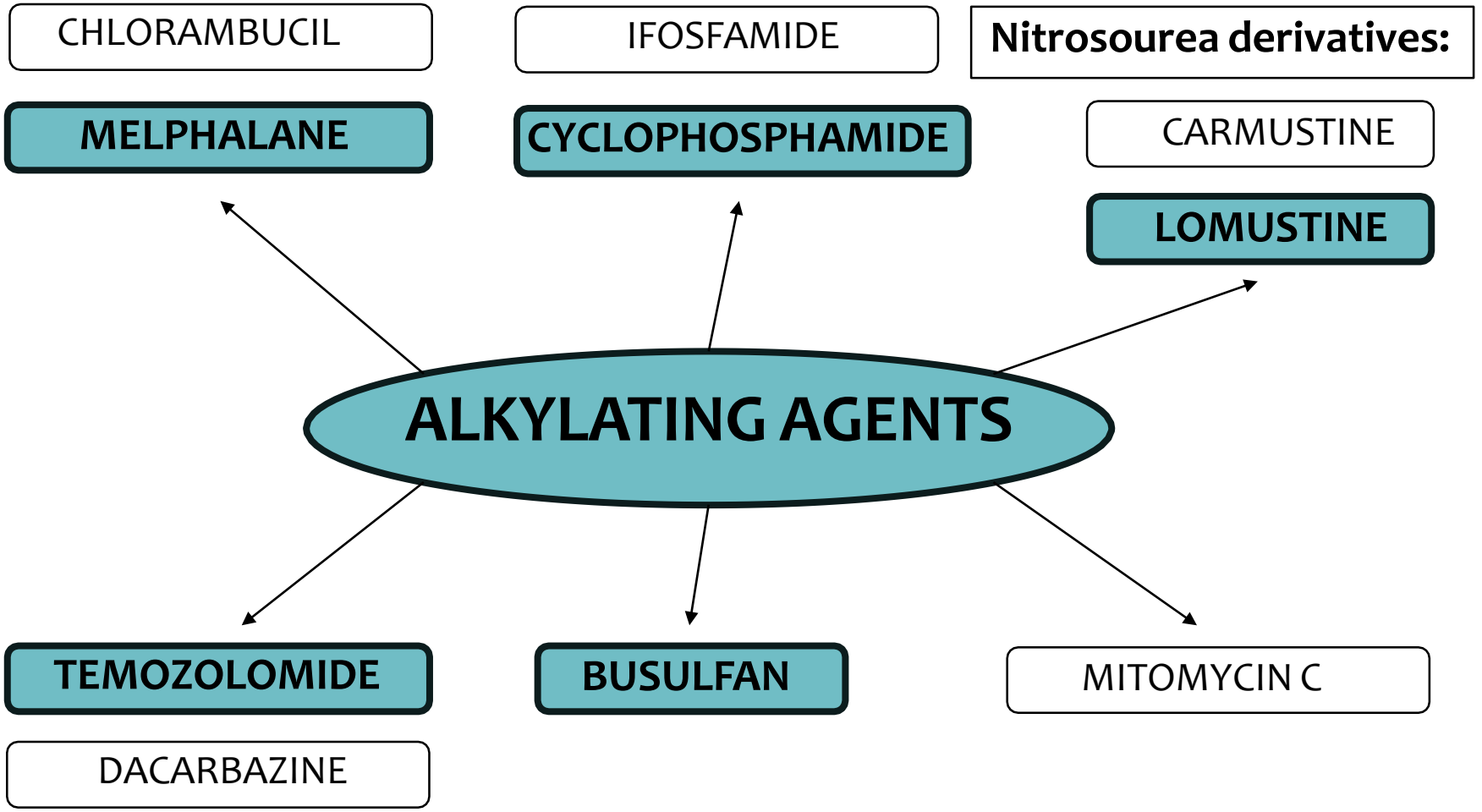
1a) Alkylating agents

- **MoA:** transfer of the alkyl group on nitrogen in nucleobases, covalent bond between two guanines of one or two DNA strands
  - Inhibition of replication, cell cycle arrest

- 50s: first derivatives of sulphur mustard in the clinical practice

- **AE – typical toxicity:** secondary malignancies – hematological

1a) Alkylating agents – main drugs



1a) Alkylating agents

Melphalane

- i.v., p.o. administration
- treatment of hematological malignancies and solid tumors

Cyclophosphamide

- i.v., p.o. administration
- prodrugs → CYP450 → cytotoxic metabolites
- **AE:** urotoxicity, **emetogenity**
- low doses – immunosuppressant
- hematological malignancies and solid tumors

Lomustine

- p.o. administration
- lipophilic, crosses BBB → treatment of brain tumors

1a) Alkylating agents

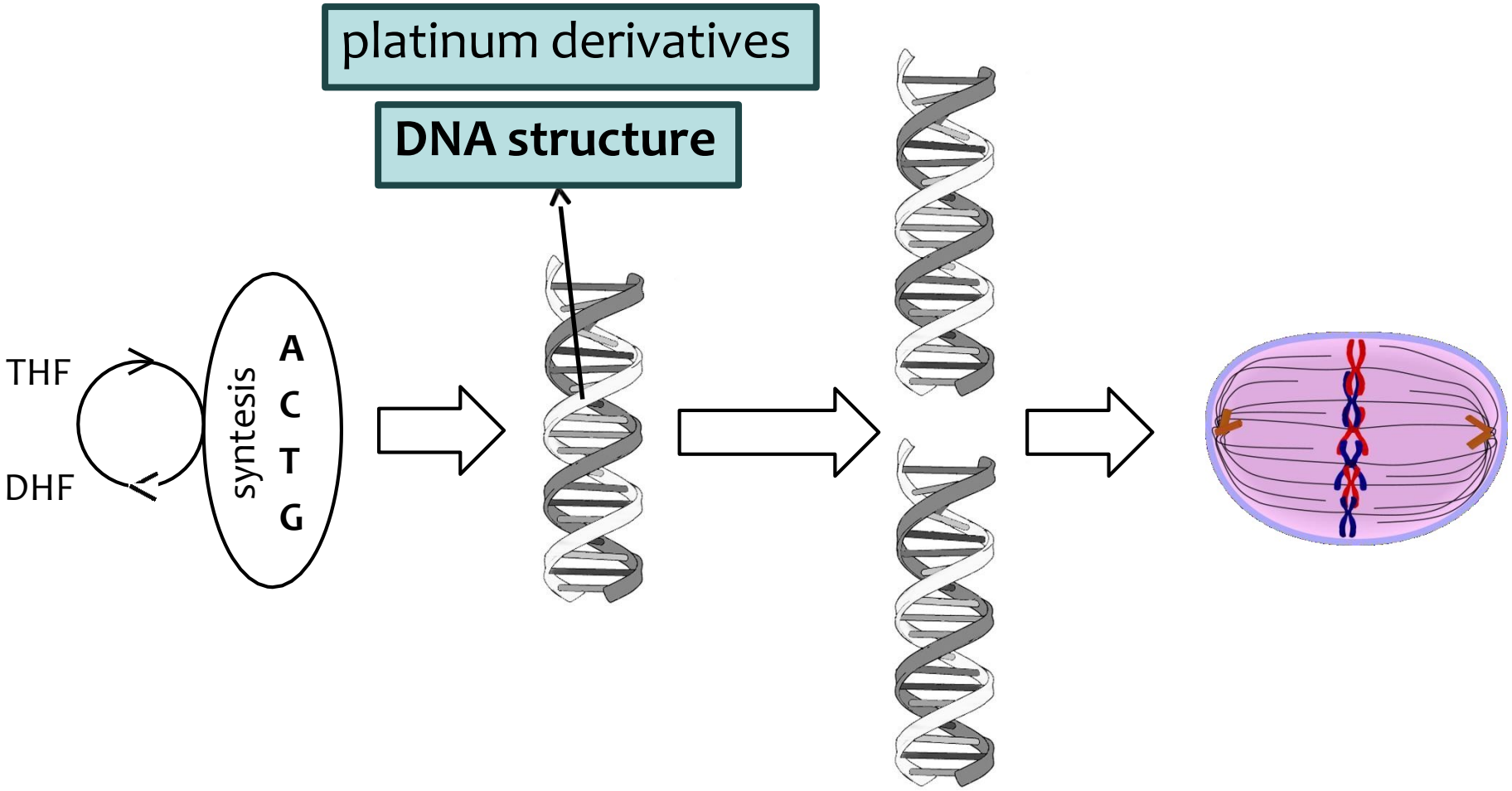
Temozolomide

- 100% bioavailability after oral administration
- crosses BBB → treatment of brain tumors

Busulfan

- i.v., p.o. administration
- bone marrow transplantation
- treatment of hematological malignancies

1b) platinum derivates

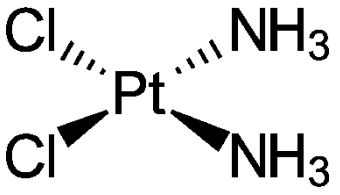


1b) platinum derivates

- **MoA:** binding on DNA, cross-linking of DNA strands, inhibition of topoisomerases

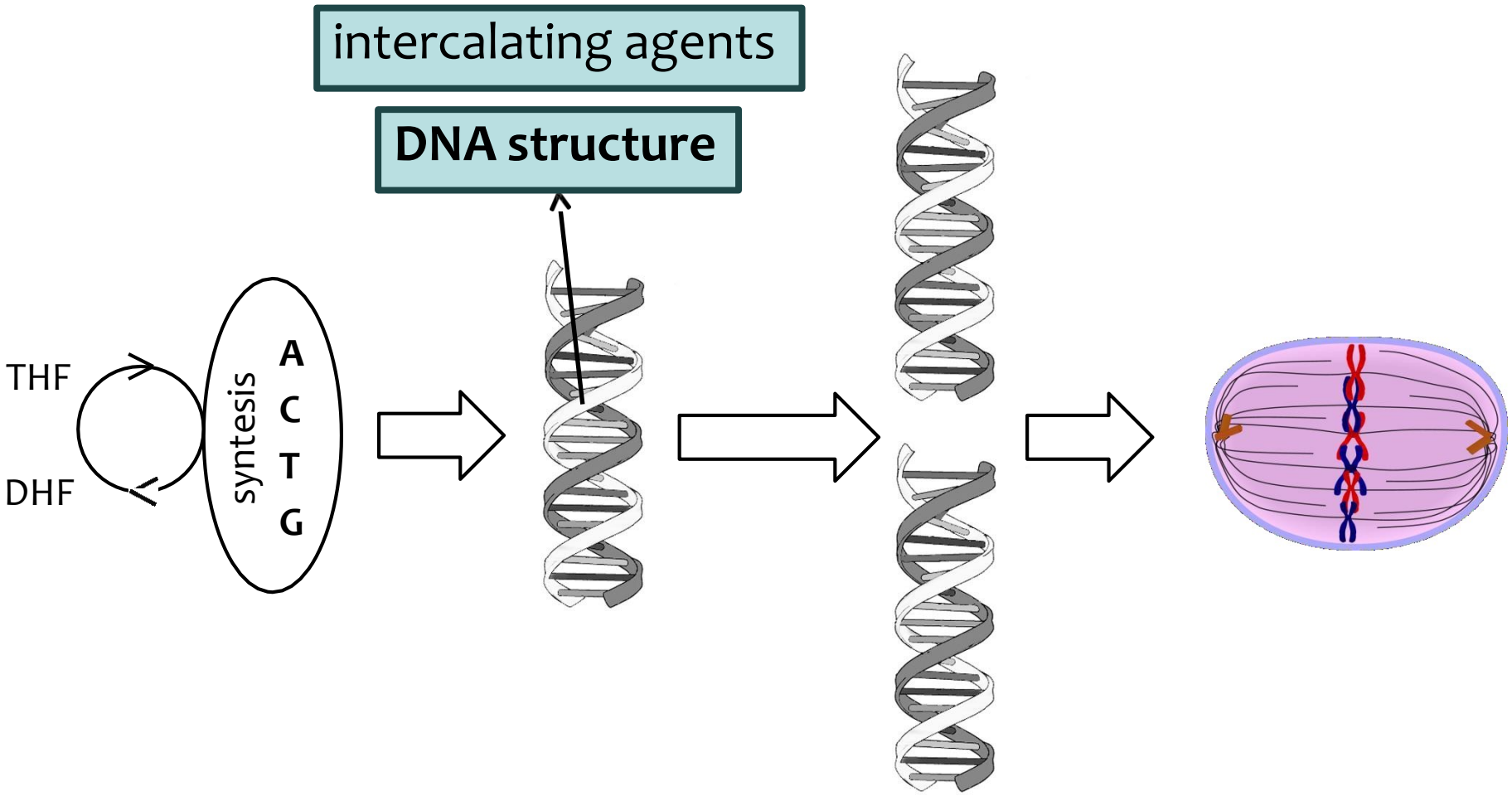
- **AE – most important: emetogenity, nephrotoxicity**
  - AE are dose-dependent
  - prevention of nephrotoxicity: i.v. **hydration**, forced diuresis

- **cisplatin** – high nephrotoxicity
  - treatment of solid tumors



- others:
  - carboplatin
  - oxaliplatin – typical **neurotoxicity**

1c) intercalating agents



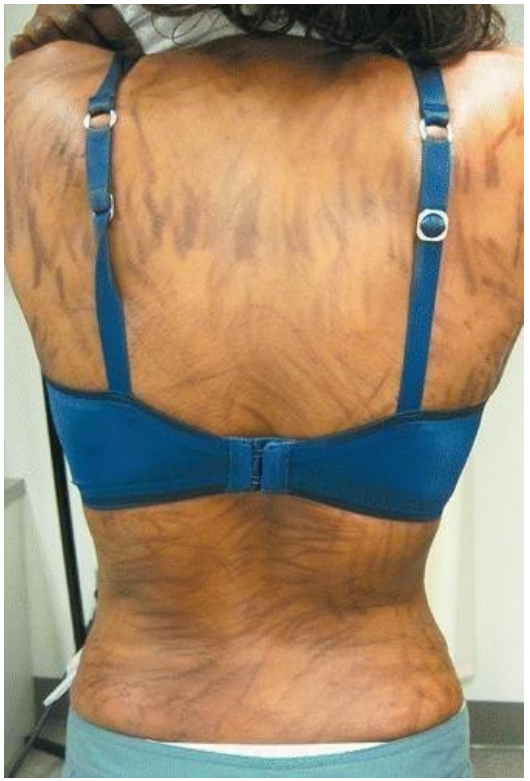
1c) intercalating agents

Anthracyclines

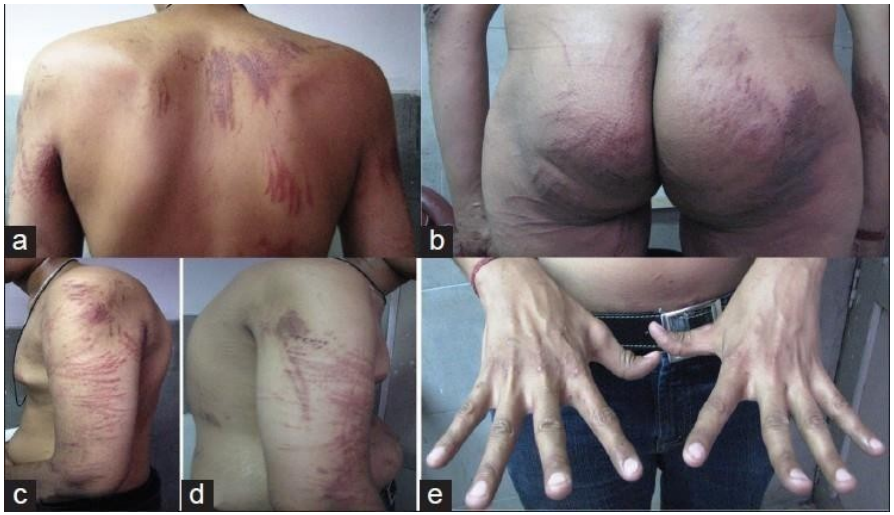
- **MoA: intercalation** = insertion between base pairs, binding of DNA strands
- **AE – typical toxicity:** acute and chronic cardiotoxicity
- cardioprotective cumulative dose = restraint of therapy (e.g., doxorubicin 550 mg/m^2)
- i.v., intravesical administration
- **doxorubicin**
  - treatment of hematological malignancies and solid tumors
  - modern dosage form (PEGylated liposomes) – higher cumulative dose (860 mg/m^2)

- others: epirubicin…

1d) bleomycin



- **MoA:** intercalation between base pairs + inhibition of thymine incorporation → breaks → DNA fragmentation („radiomimetic“ effect)
- i.v. administration
- treatment of solid tumors
- **typical AE:** fever, hyperkeratosis and hyperpigmentation of skin (flagellate = whip-like)



- risk of anaphylactic reaction

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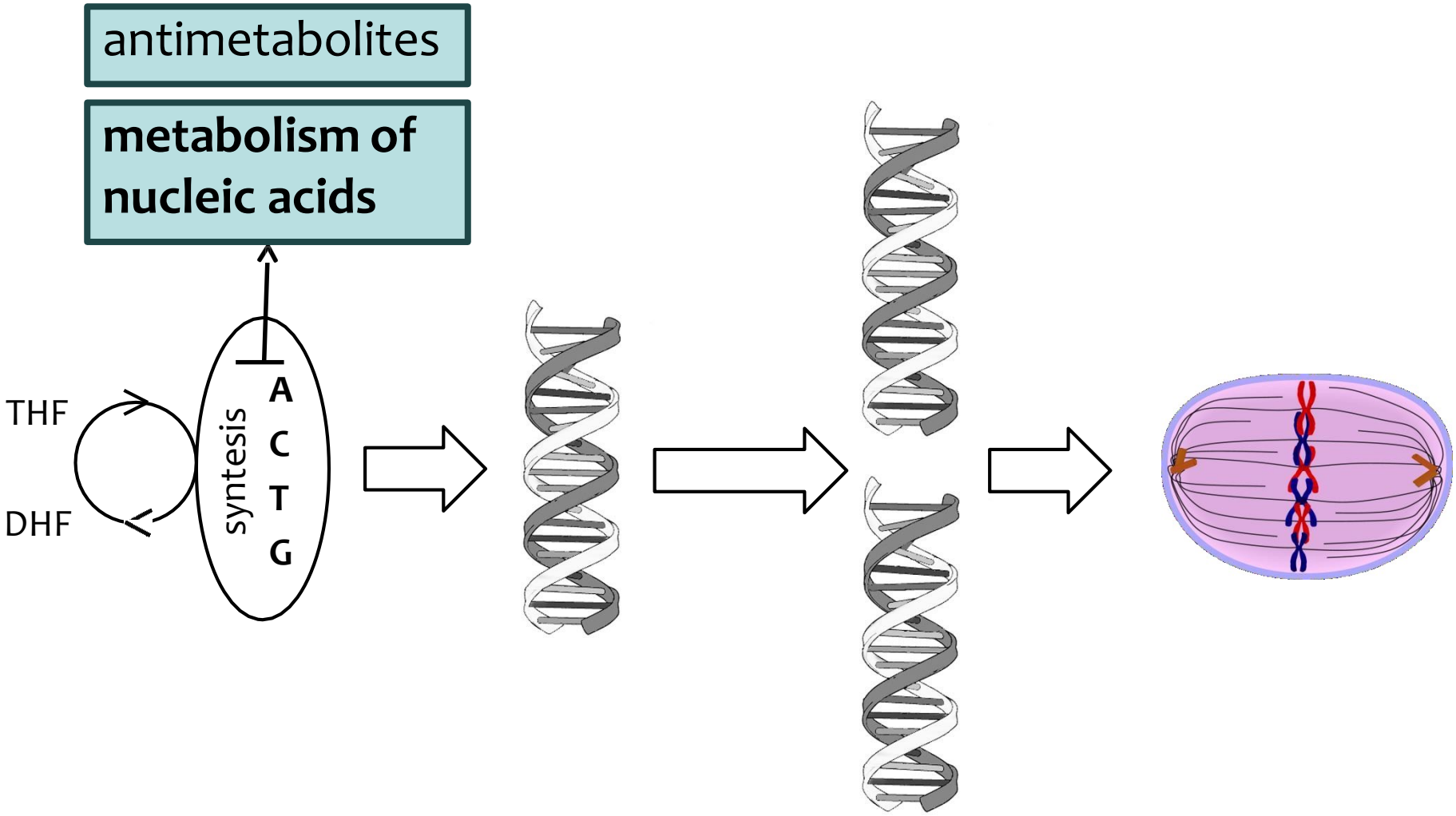
2a. antimetabolites



2a. antimetabolites

- MoA: false substrates = affinity to target structure, loss of endogenous effect → blockade of nucleic acid synthesis, inhibition of nucleotides metabolism enzymes, production of *non-sense* DNA sequences

- prodrugs: intracellular activation mostly by phosphorylation

a) purine analogues – **6-mercaptopurine,** azathioprine, fludarabine…

b) pyrimidine analogues – **fluorouracil**, capecitabine, gemcitabine…

c) folic acid analogues – **methotrexate**, pemetrexed…

2a. Antimetabolites – i/ purine analogs

6-Mercaptopurin

- **MoA:** inhibition of purine nucleobases biosynthesis *de novo*, inhibition of mutual conversion of purine nucleotides
- thiopurin methyltransferase (TPMT): MP → $\overset{\text{inactive}}{\text{MeMP}}$
  - **genetic polymorphism** – ↑toxicity / ↓efficacy
  - available pharmacogenetic testing of *TPMT*
- p.o. administration, treatment of hematologic malignancies
- azathioprine – prodrug of MP, immunosuppressant

2a. Antimetabolites – ii/ pyrimidines analogs

5-Fluorouracil

- **MoA:** incorporation to RNA + inhibition of thymidylate synthetase
- combined chemotherapeutic regimens of solid cancers (i.v.)
- **AE – typical toxicity:** GIT toxicity (mucositis)
- biochemical modulation of effect: **leucovorin** (folinic acid) enhances binding on thymidylate synthetase, i.v. administered before FU
  - „FUFA“ regimen = colorectal carcinoma
- capecitabine – prodrug

2a. Antimetabolites – iii/ folic acid analogs

Methotrexate

- **MoA:** inhibition of dihydrofolate reductase, thymidylate synthetase and other enzymes
- i.v., intrathecal administration, p.o.
- **leucovorin** (folinic acid) – *„rescue therapy“*, antidote
  forces free MTX out of healthy cells ; in cancer cells, polyglutamylation is more intensive → more MTXPG → MTXPG cannot be forced out

TDM – calculation of time interval from MTX administration, frequently in pediatric patients, less frequent in adults

- **AE – typical toxicity:**
  nephrotoxicity – precipitation (acute renal failure)
    prevention: hydration, urine alkalinization (pH 7–7,5)
  pneumotoxicity

- low-dose MTX = immunosuppressant (p.o.)
- high-dose MTX = hematological malignancies

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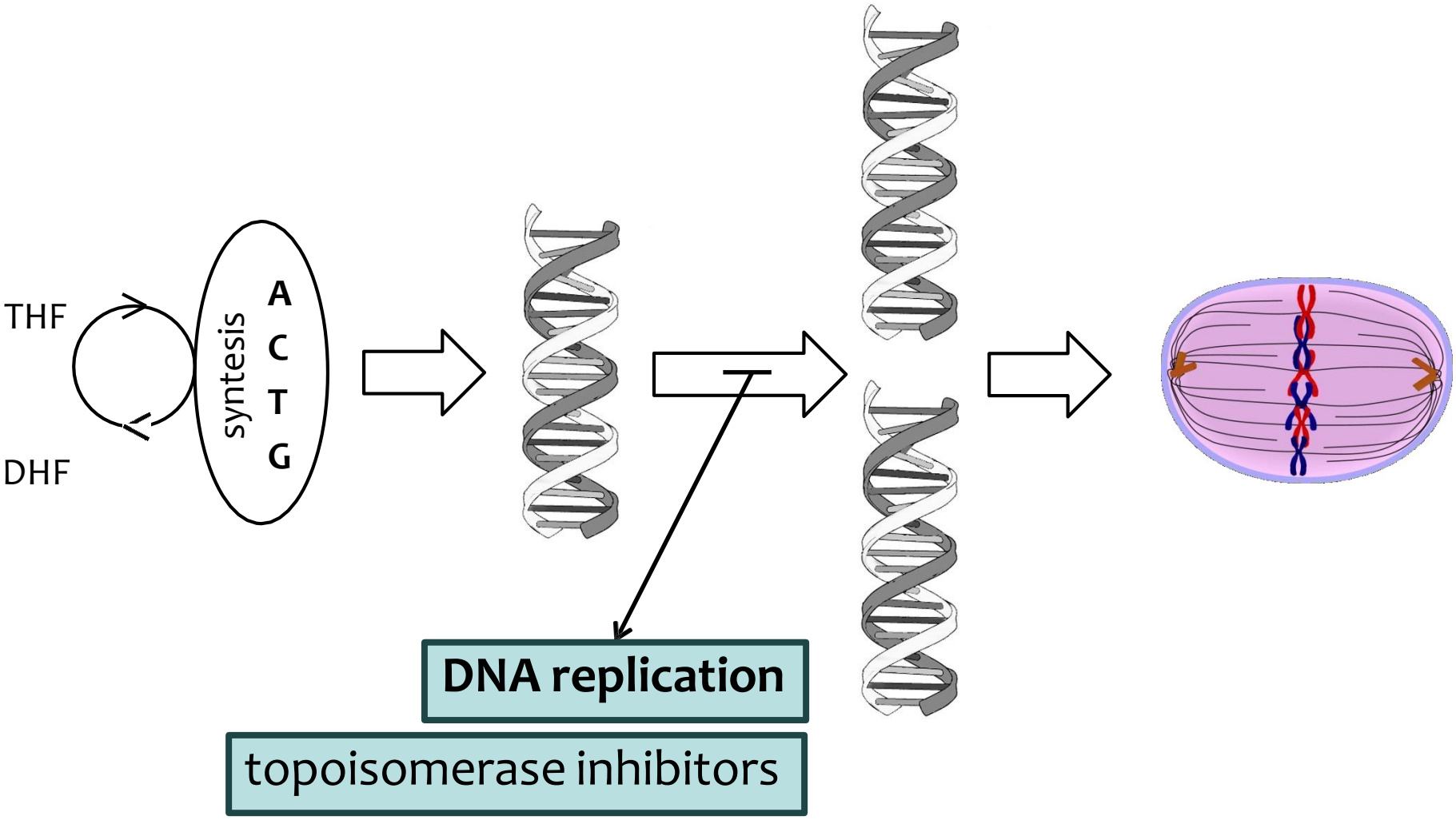
2b. Topoisomerase inhibitors



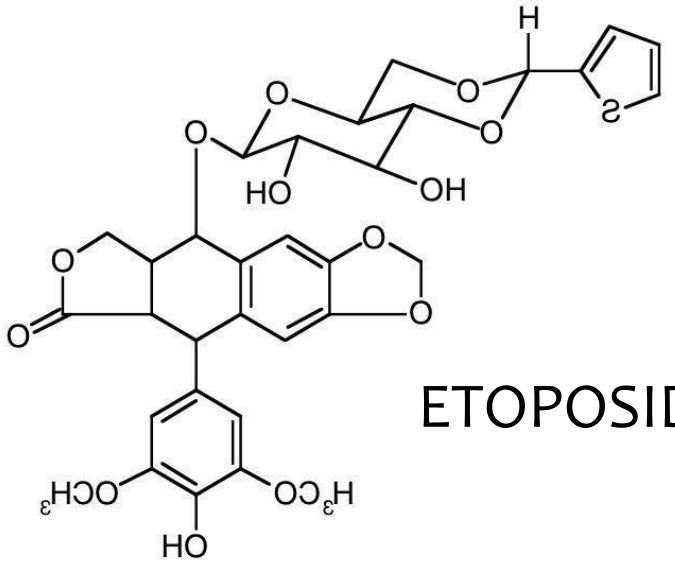
2b. Topoisomerase inhibitors

Topoisomerase I inhibitors – camptothecins

- plant-derived drugs – identification in bark of the tree *Camptotheca acuminata*
- derivatives: **irinotecan**, topotecan
  - treatment of solid tumors

Topoisomerase II inhibitors – podophyllotoxins

- plant-derived drugs – identification in *Podophyllum peltatum*
- derivatives: **etoposide**, teniposide
  - treatment of solid tumors (etoposide) and hematological malignancies (teniposid)



ETOPOSIDE

Podophyllum peltatum L.
Image processed by Thomas Schoepke
www.plant-pictures.de

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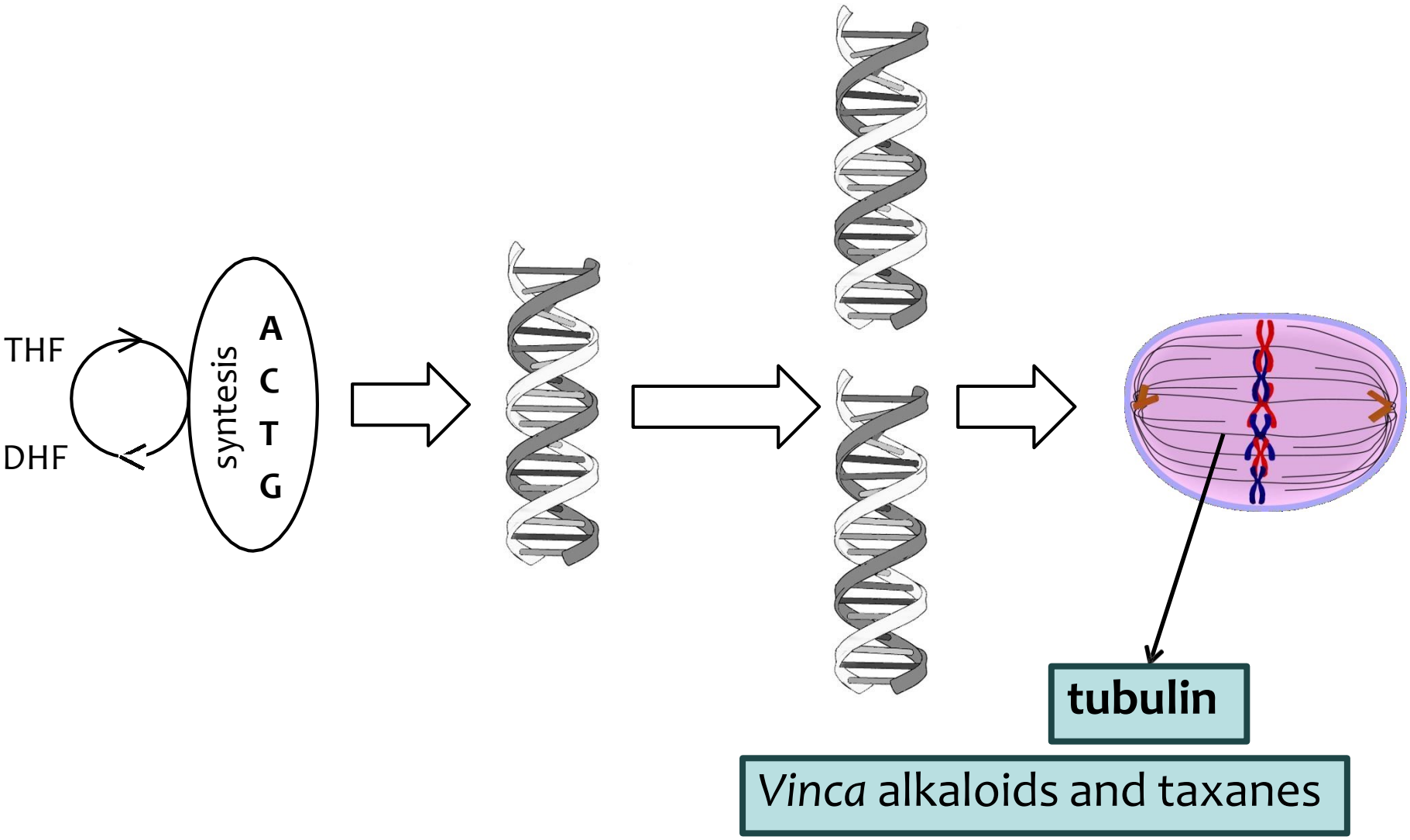
3. Tubulin alterating cytostatics



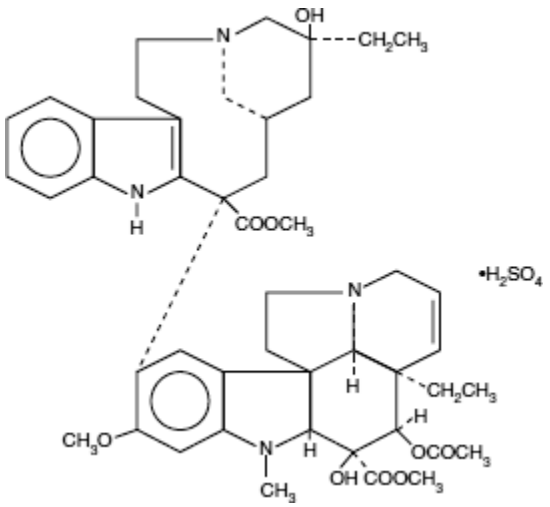
3a. Vinca alkaloids

- ant-derived drugs
- **MoA:** inhibition of tubuline dimers polymerization
  inhibition of mitotic spindle formation, depolymerization prevails
- i.v. administration, some for p.o. (vinorelbine)
- treatment of hematological malignancies and solid tumors
- **AE – typical toxicity:** peripheral neuropathy

- original alkaloids: **vincristine**, vinblastine
- semisynthetic derivatives: vinorelbine, vindesin, vinflunine
  increased affinity to mitotic spindle tubulin, ↓AE

Vinca alkaloids

- identification: lesser periwinkle (*Vinca minor*)
- isolation: *Cataranthus roseus*



VINBLASTINE

3b. taxanes

- plant-based drugs
- **MoA:** inhibition of tubulin depolymerization
- i.v. administration – treatment of solid tumors
- **AE – typical toxicity:** neurotoxicity
- **paclitaxel, docetaxel**, cabazitaxel

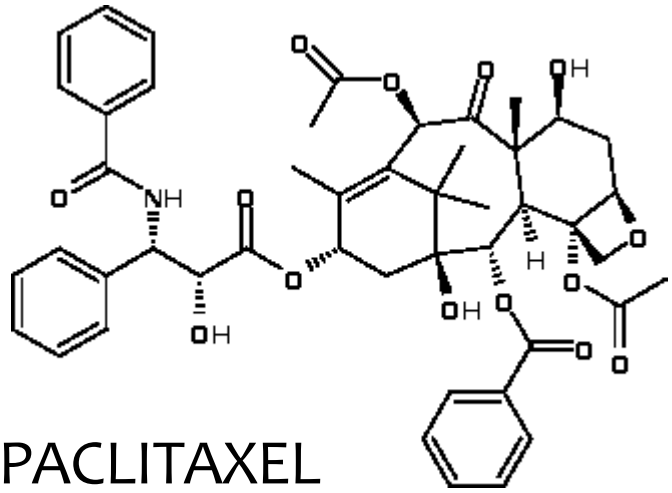
-modern dosage form: paclitaxel conjugated with albumine nanoparticles

- transporter protein for albumine in cancer cells = better distribution from circulation into the tissues

– ↓toxicity, ↑efficacy

Taxanes

- identification and isolation: *Taxus brevifolia* (Pacific yew) a *Taxus baccata* (European yew)



PACLITAXEL

Combination of cytostatics

- monotherapy

- combination regimens – examples:

FUFA	fluorouracil, folinic acid
FOLFOX	folinic acid, fluorouracil, oxaliplatin
ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristin, procarbazine, prednisone

„Targeted therapy“in oncology

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Targeted therapy in oncology (biological therapy)

„target“ should be on

A/ **tumor cells**

- Cell membrane receptor – extracellular part or/ intracellular signalling pathway

B/ **immune system (specific T-cells) –** cancer immunotherapy

- Immune check-point inhibitors (anti-CTLA-4 or anti-PD(L)1)

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