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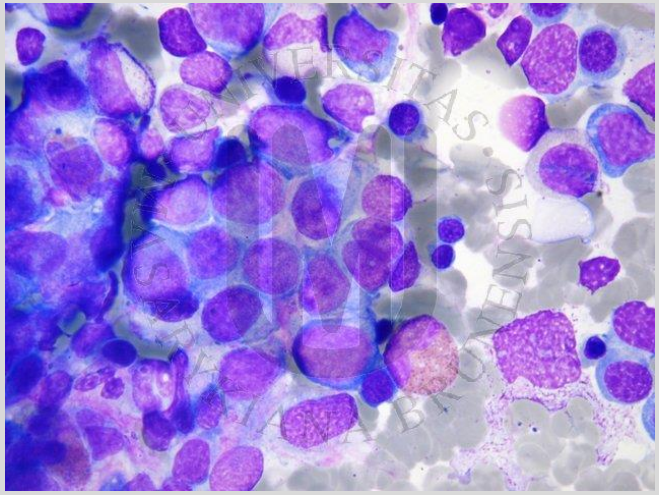
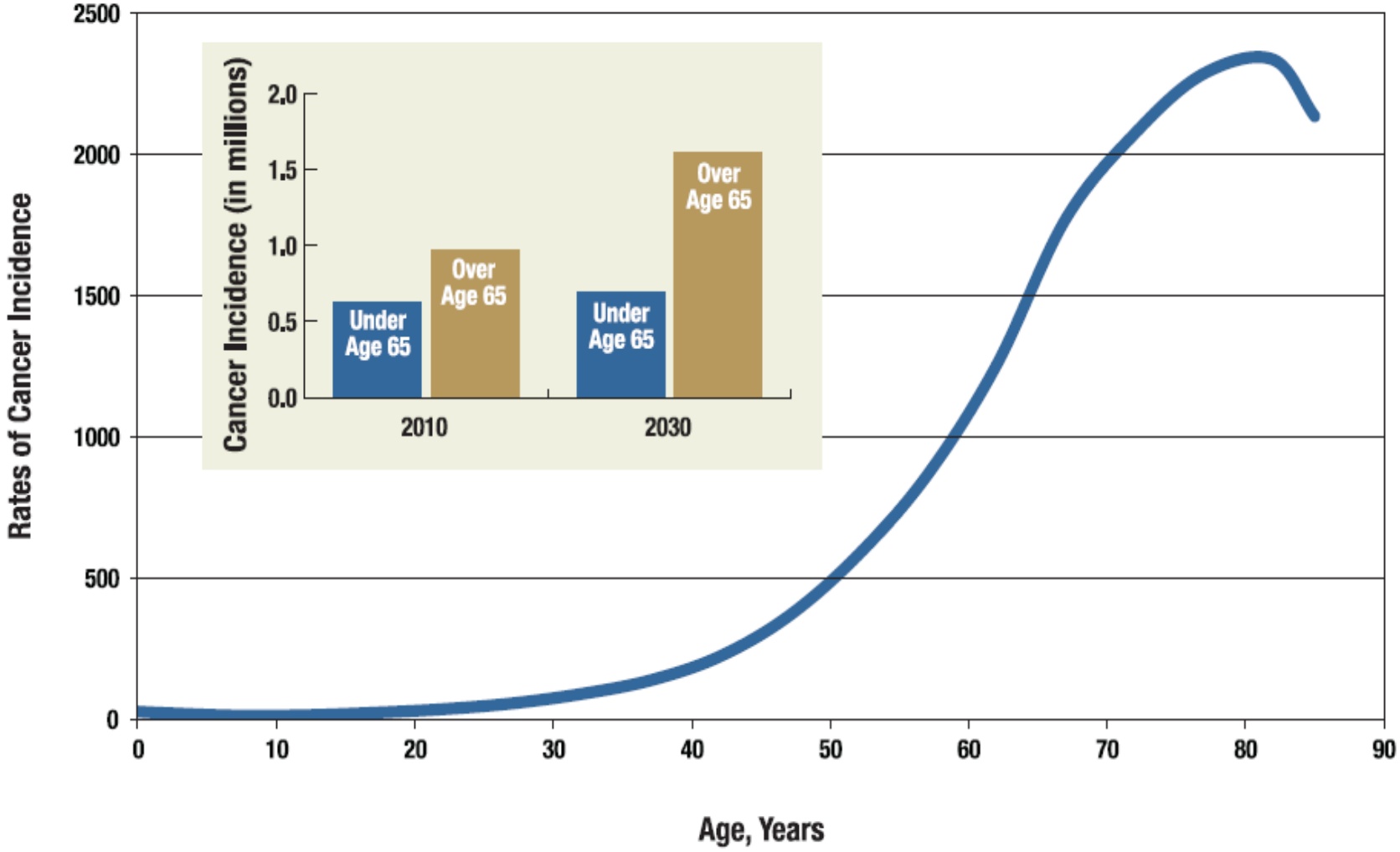
Cytostatic drugs and targeted therapy in oncology



Regina Demlova, 2019

AACR Cancer Progress Report 2012



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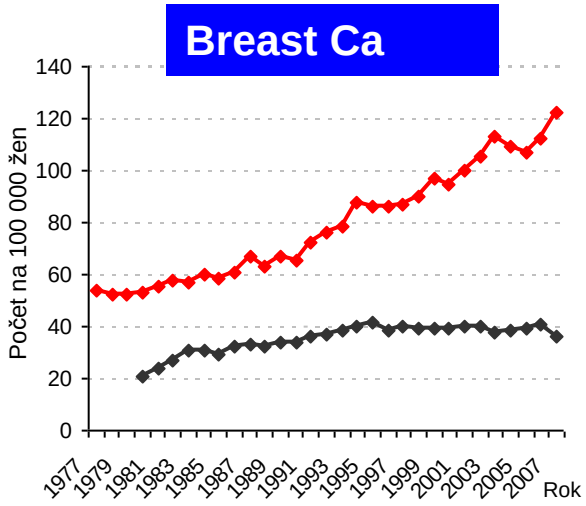
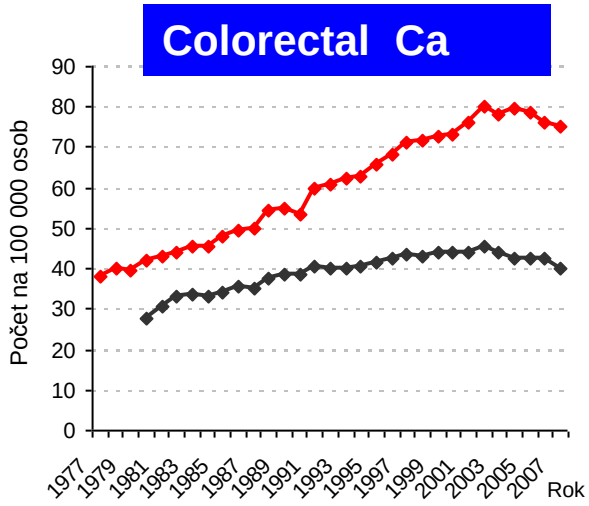
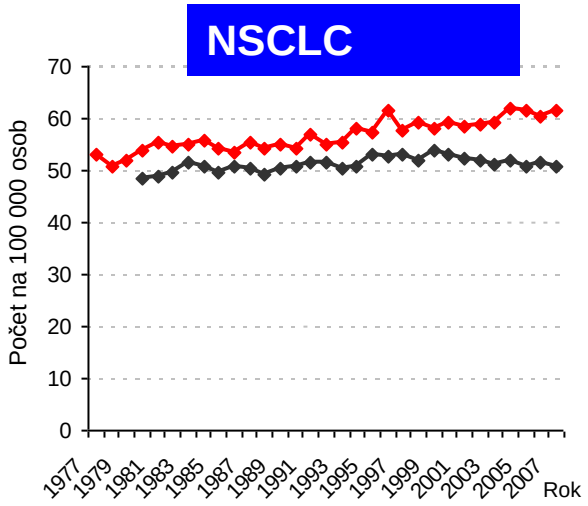
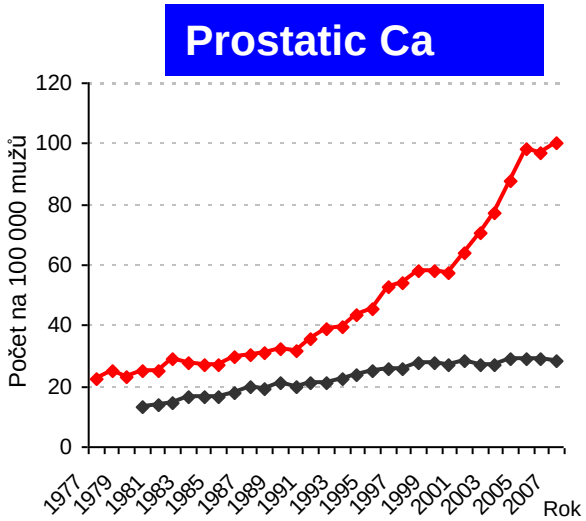
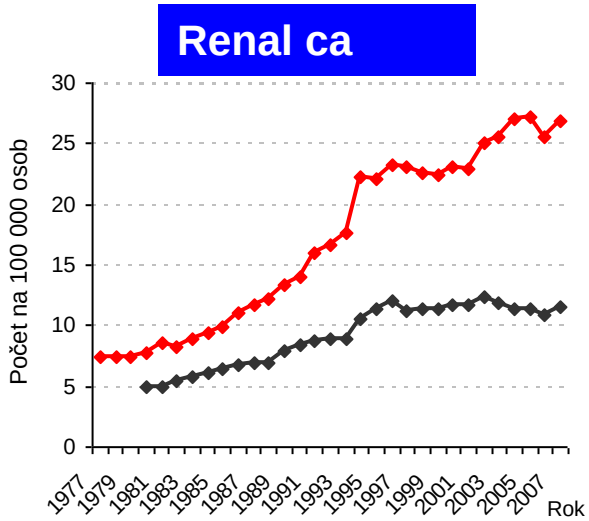
Cancer epidemiology - incidence and mortality in the Czech Republic

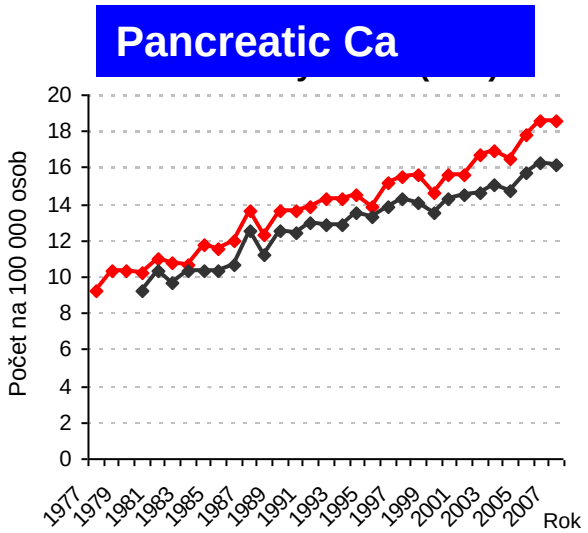












incidence mortalita

Czech Cancer Care in Numbers 2009

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
  - tyrosine kinase inhibitors
  - intracellular signaling cascades inhibitors
  - others
- targeted immunotherapy
- pain management, supportive care

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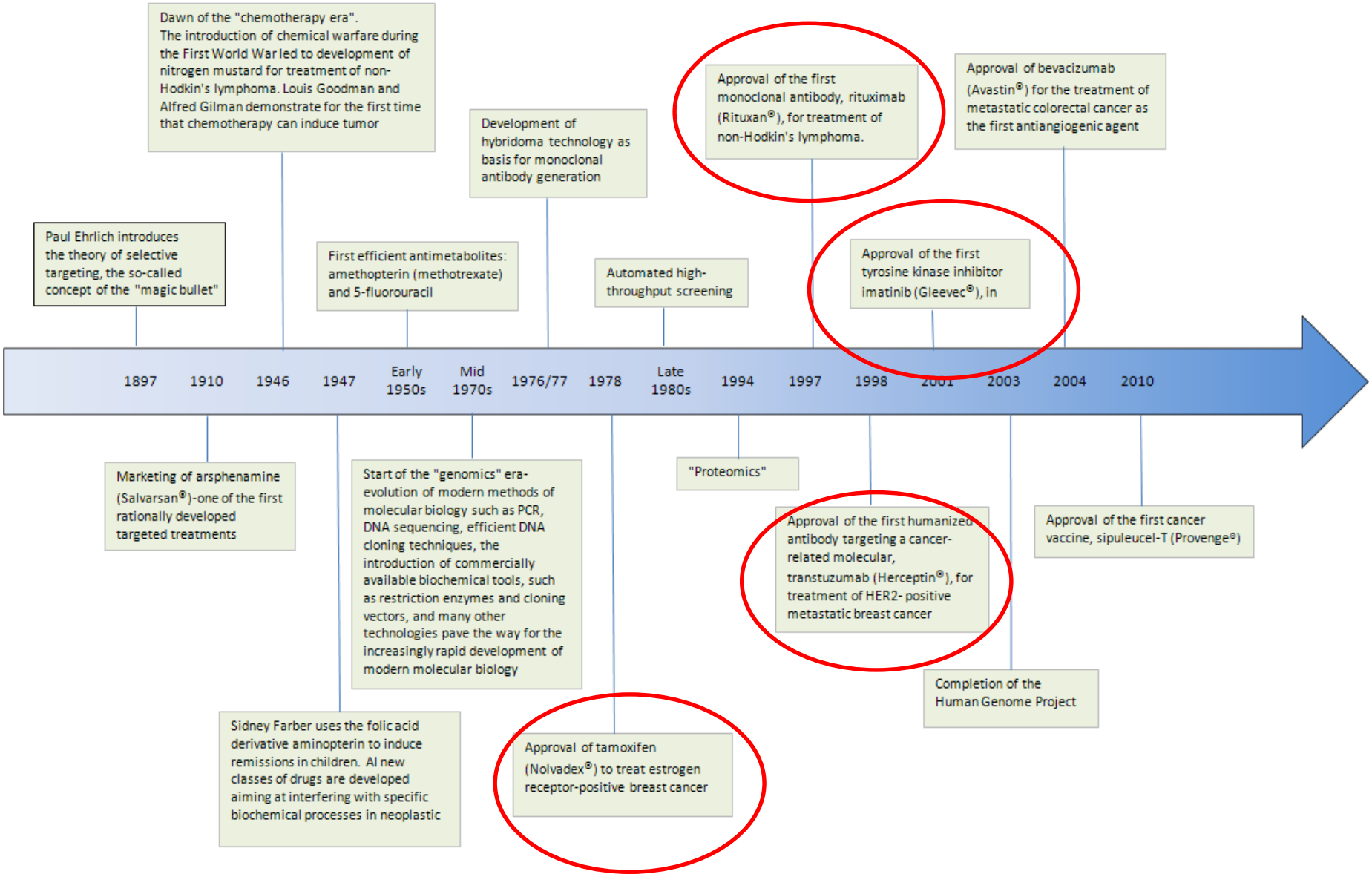
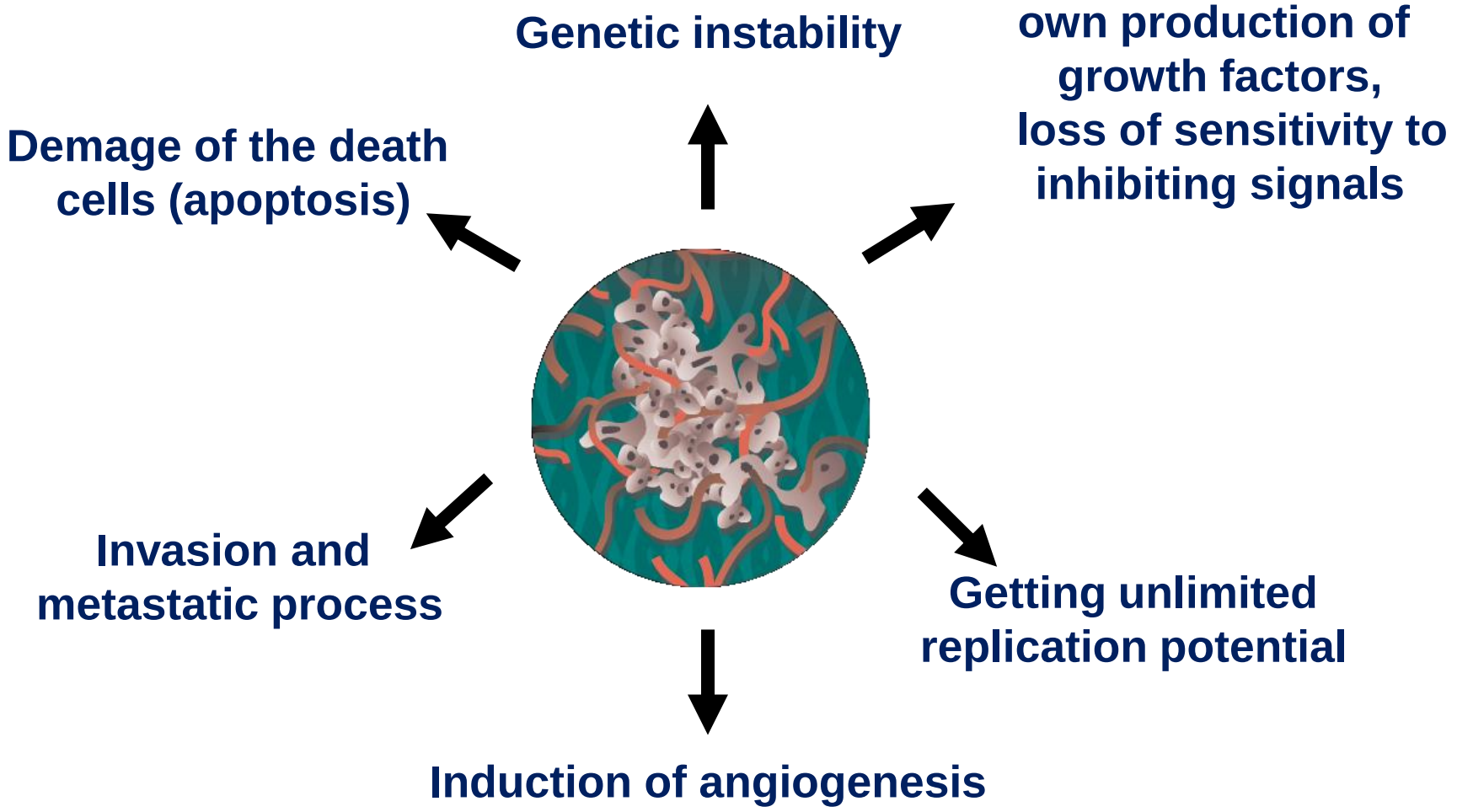
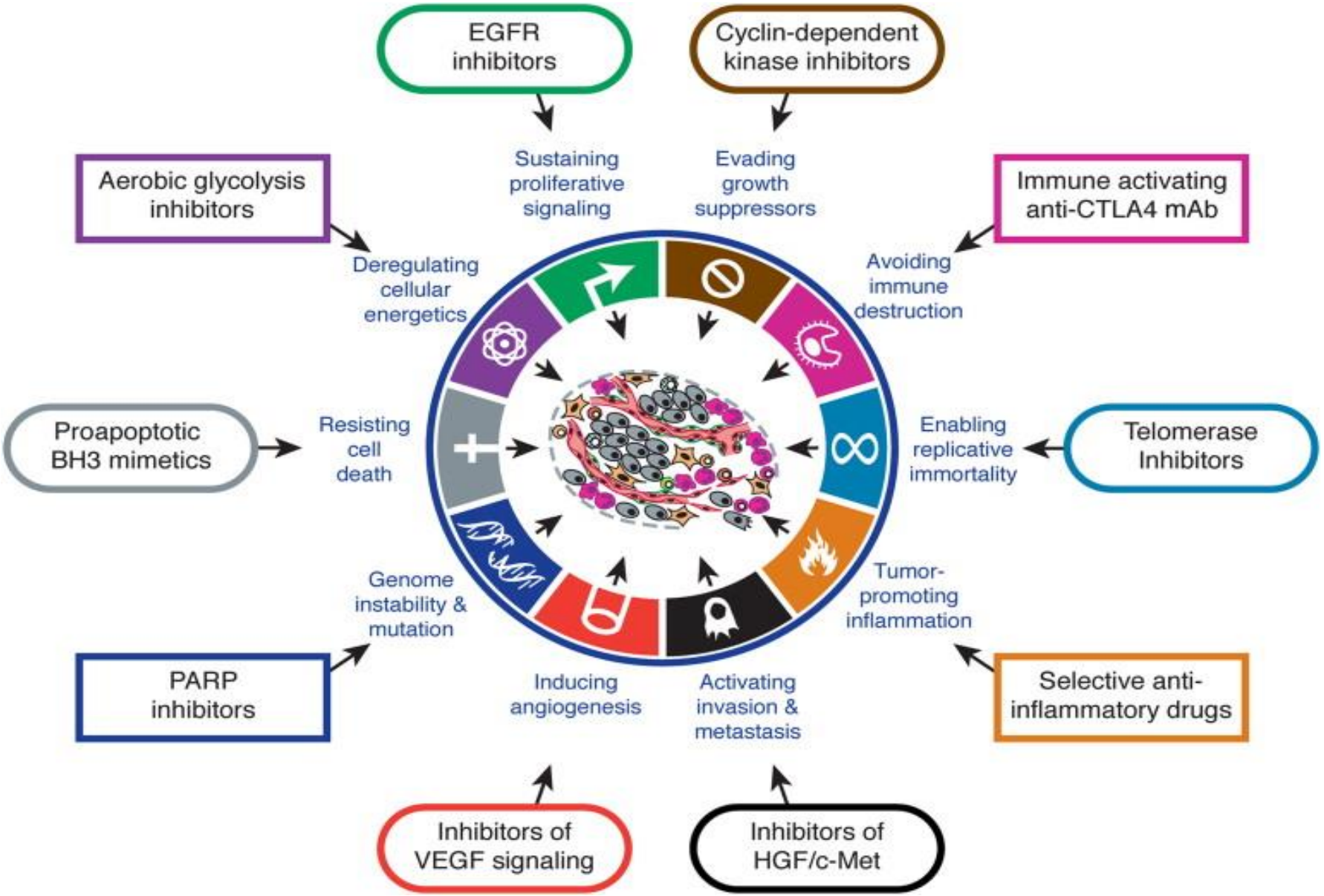

Paul Ehrlich introduces the theory of selective targeting, the so-called concept of the "magic bullet"
Dawn of the "chemotherapy era". The introduction of chemical warfare during the First World War led to development of nitrogen mustard for treatment of non-Hodkin's lymphoma. Louis Goodman and Alfred Gilman demonstrate for the first time that chemotherapy can induce tumor
First efficient antimetabolites: amethopterin (methotrexate) and 5-fluorouracil
Development of hybridoma technology as basis for monoclonal antibody generation
Automated high-throughput screening
Approval of the first monoclonal antibody, rituximab (Rituxan®), for treatment of non-Hodkin's lymphoma.
Approval of the first tyrosine kinase inhibitor imatinib (Gleevec®), in
Approval of bevacizumab (Avastin®) for the treatment of metastatic colorectal cancer as the first antiangiogenic agent
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
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
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
Approval of tamoxifen (Nolvadex®) to treat estrogen receptor-positive breast cancer
"Proteomics"
Approval of the first humanized antibody targeting a cancer-related molecular, transtuzumab (Herceptin®), for treatment of HER2- positive metastatic breast cancer
Completion of the Human Genome Project
Approval of the first cancer vaccine, sipuleucel-T (Provenge®)

Cancer cell


Genetic instability
own production of growth factors, loss of sensitivity to inhibiting signals
Demage of the death cells (apoptosis)
Invasion and metastatic process
Getting unlimited replication potential
Induction of angiogenesis

„Cancer hallmarks“ (Hannahan D., Weinberg RA.) Cell; 2011 – terapeutic targets



1. Cytostatic drugs

- therapeutic intention: curative, palliative
- 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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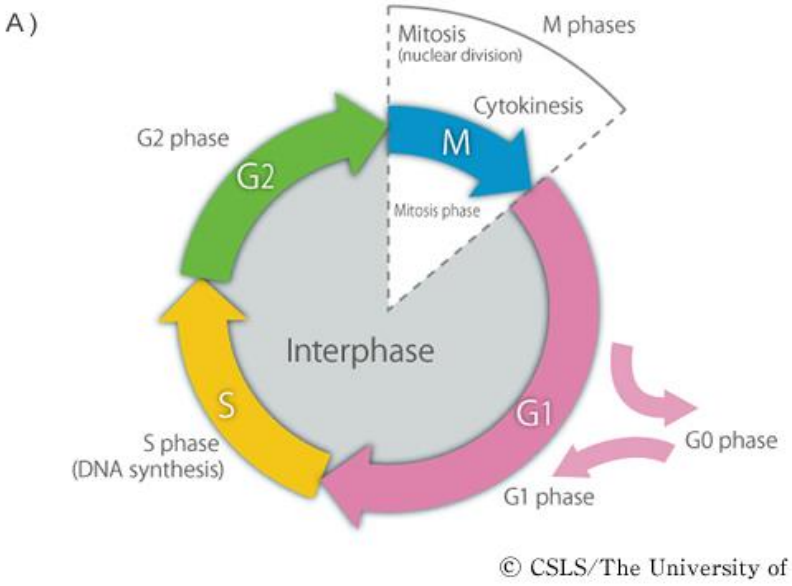
Cytostatic drugs

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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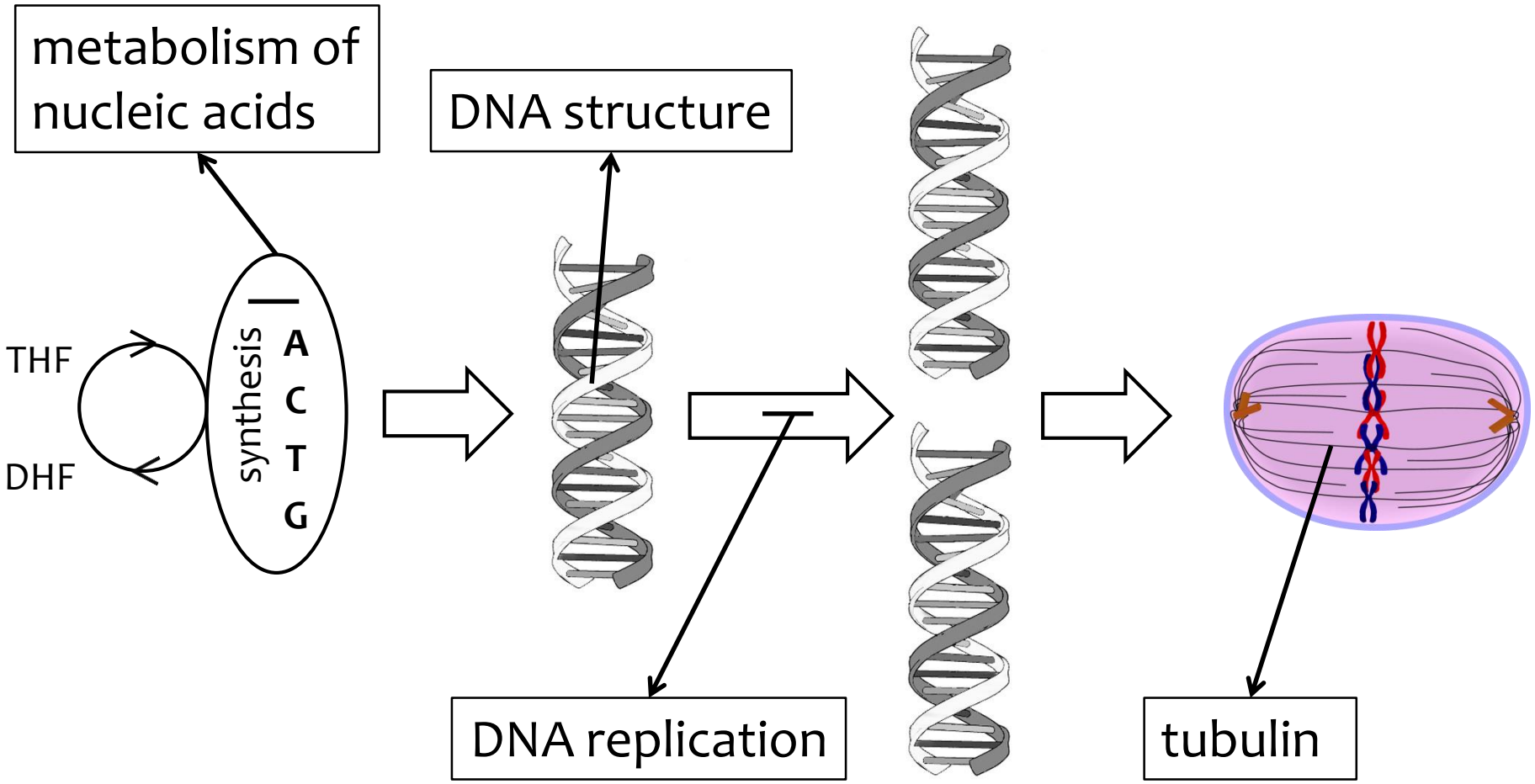
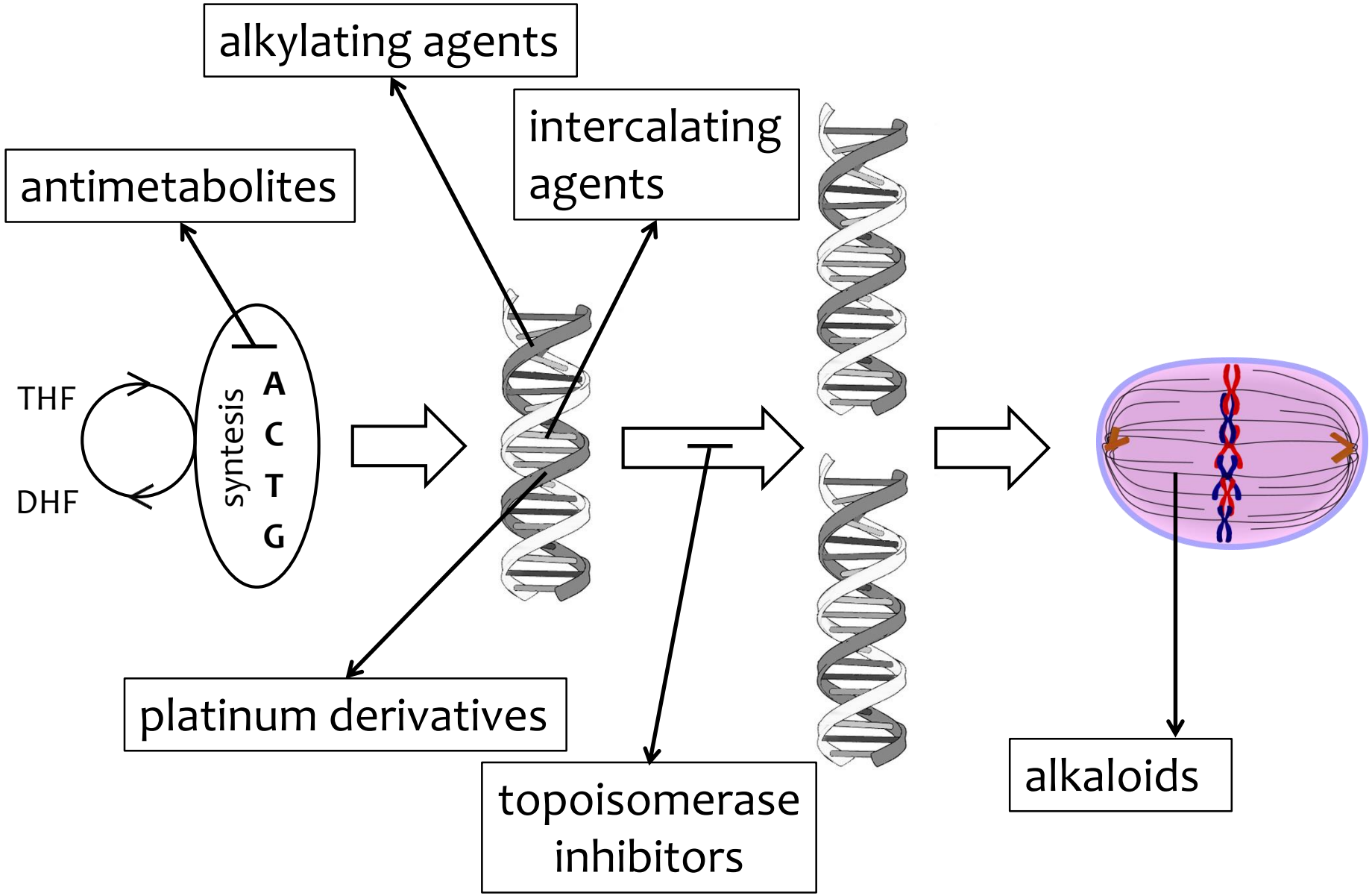
Intracelullar targets of cytostatics



Mechanisms of action

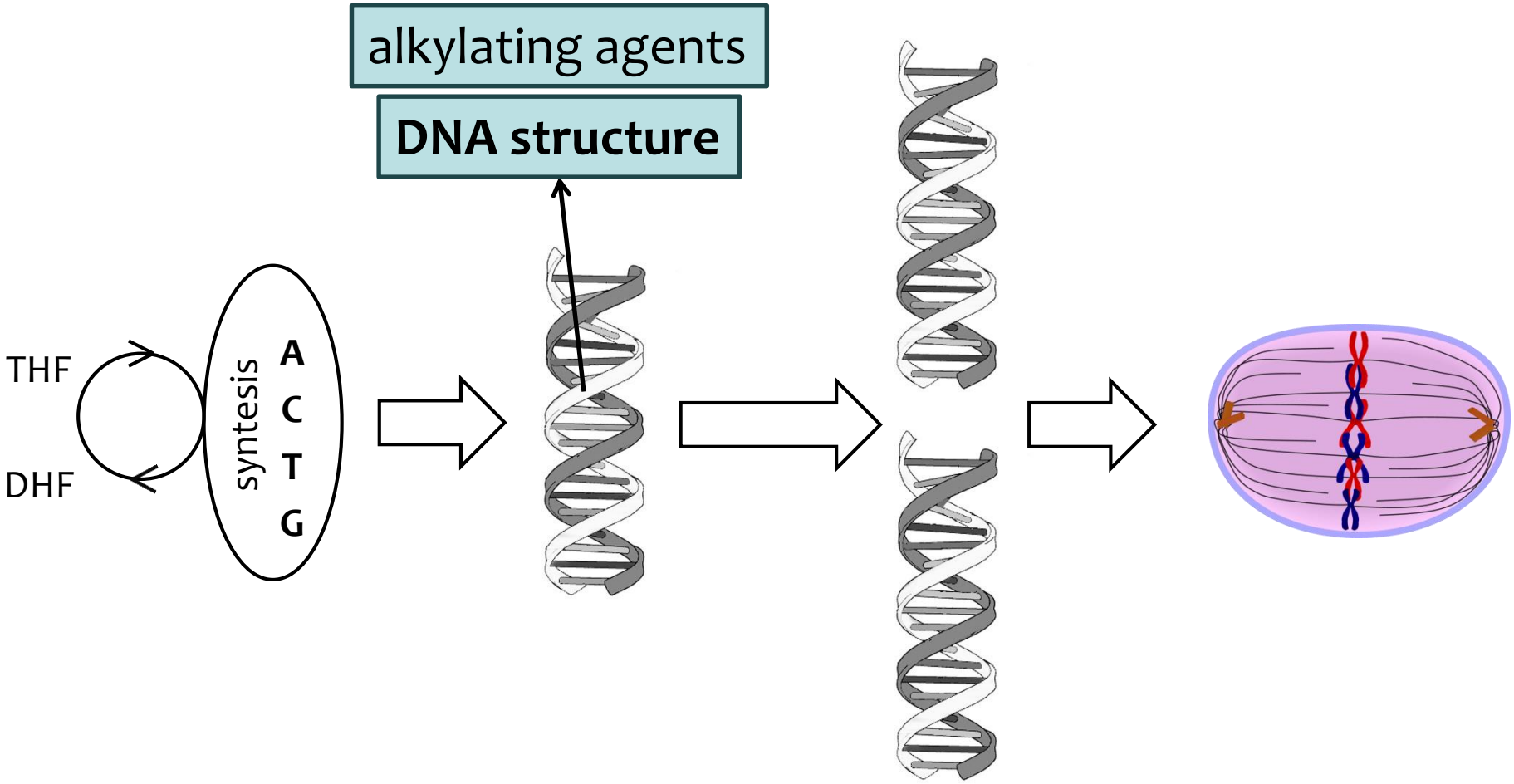


Cytostatics according to their MoA

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

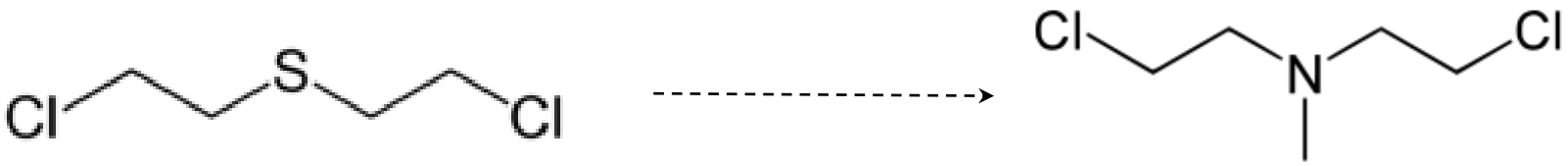
Intracelullar targets of cytostatics



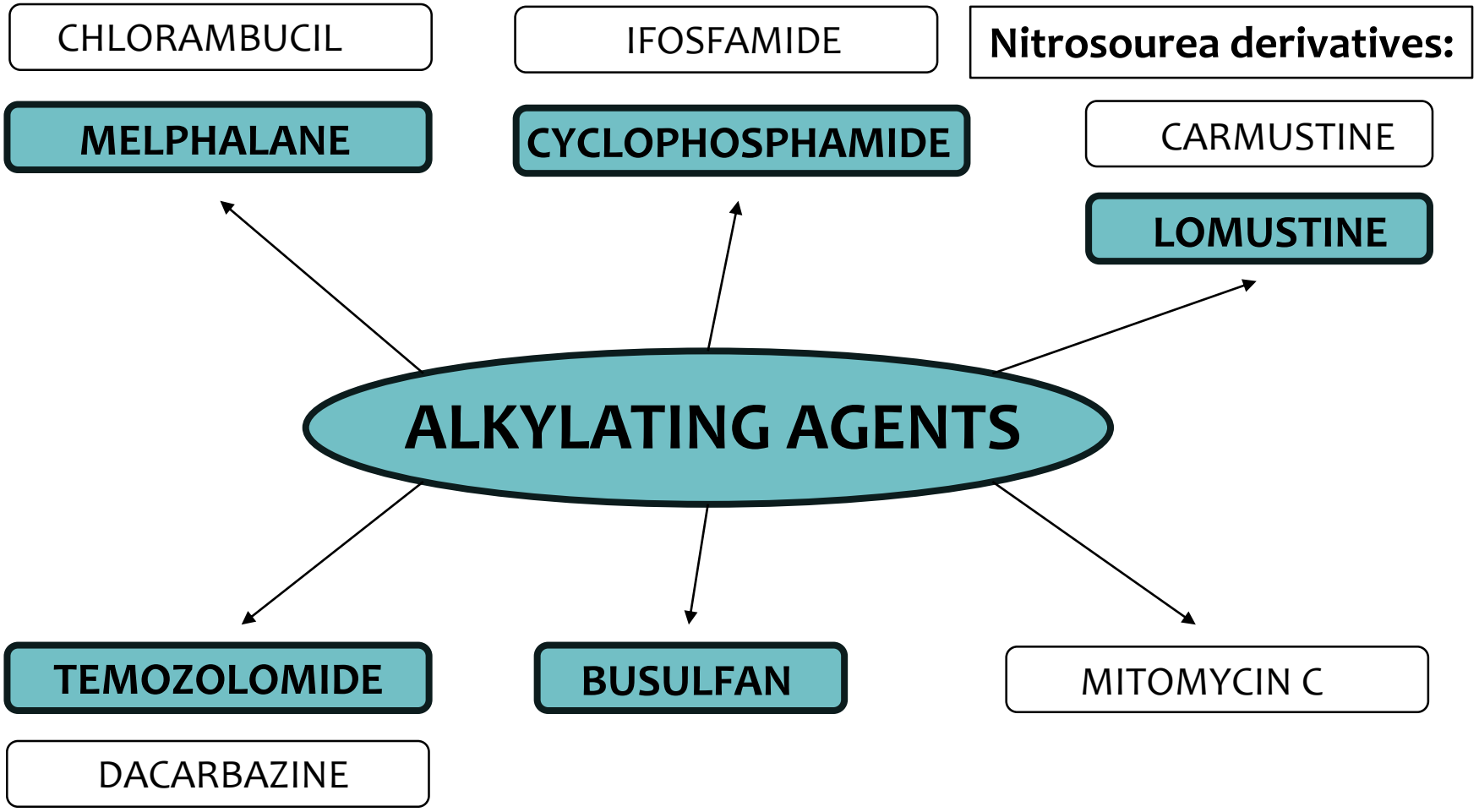
Alkylating agents

- **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


CHLORAMBUCIL
IFOSFAMIDE
Nitrosourea derivatives:
MELPHALANE
CYCLOPHOSPHAMIDE
CARMUSTINE
LOMUSTINE
ALKYLATING AGENTS
TEMOZOLOMIDE
BUSULFAN
MITOMYCIN C
DACARBAZINE

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

Alkylating agents

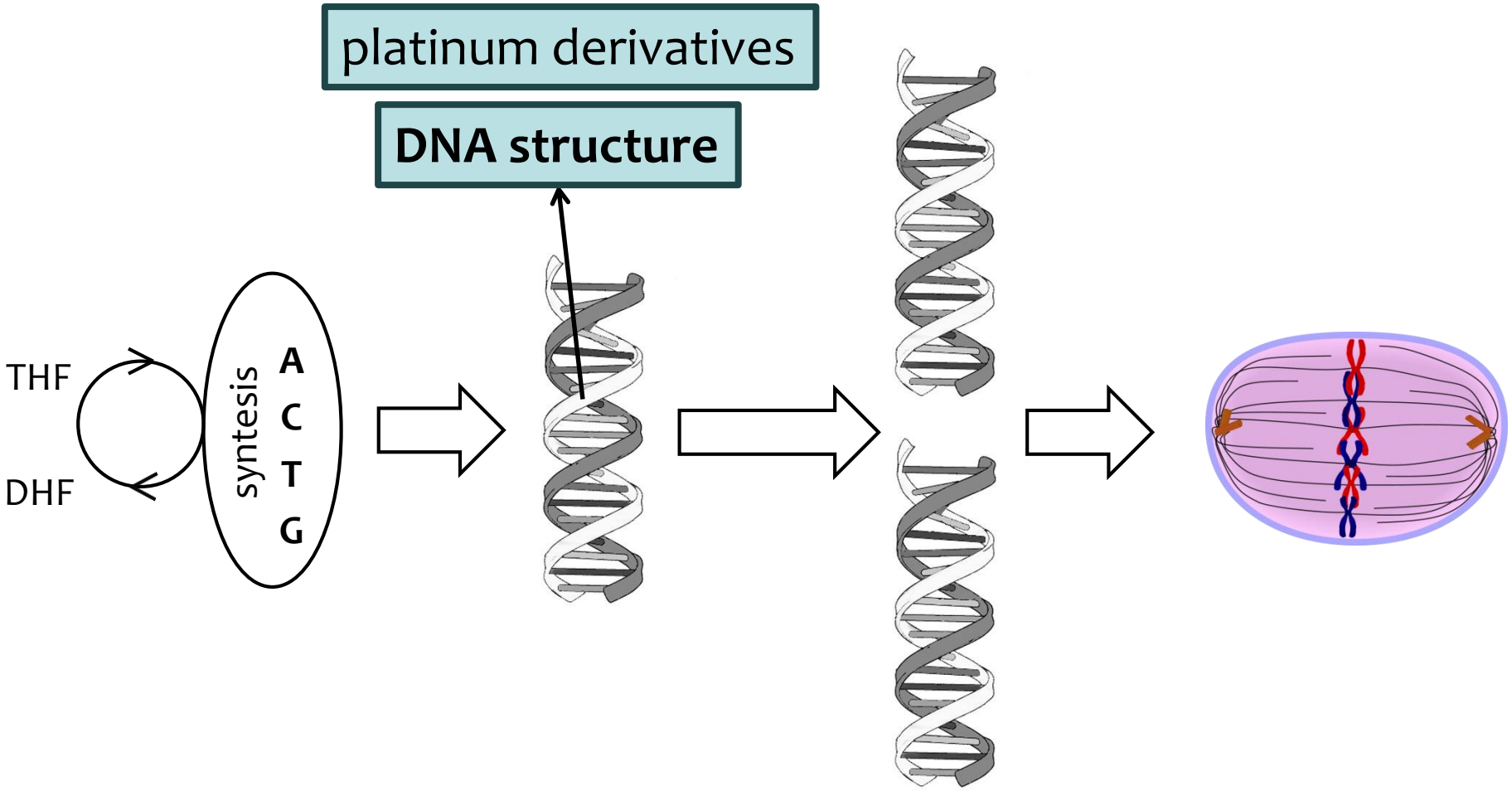
Temozolomide

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

Busulfan

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

Intracelullar targets of cytostatics

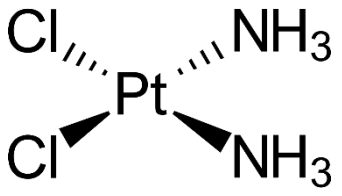


Platinum derivatives

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

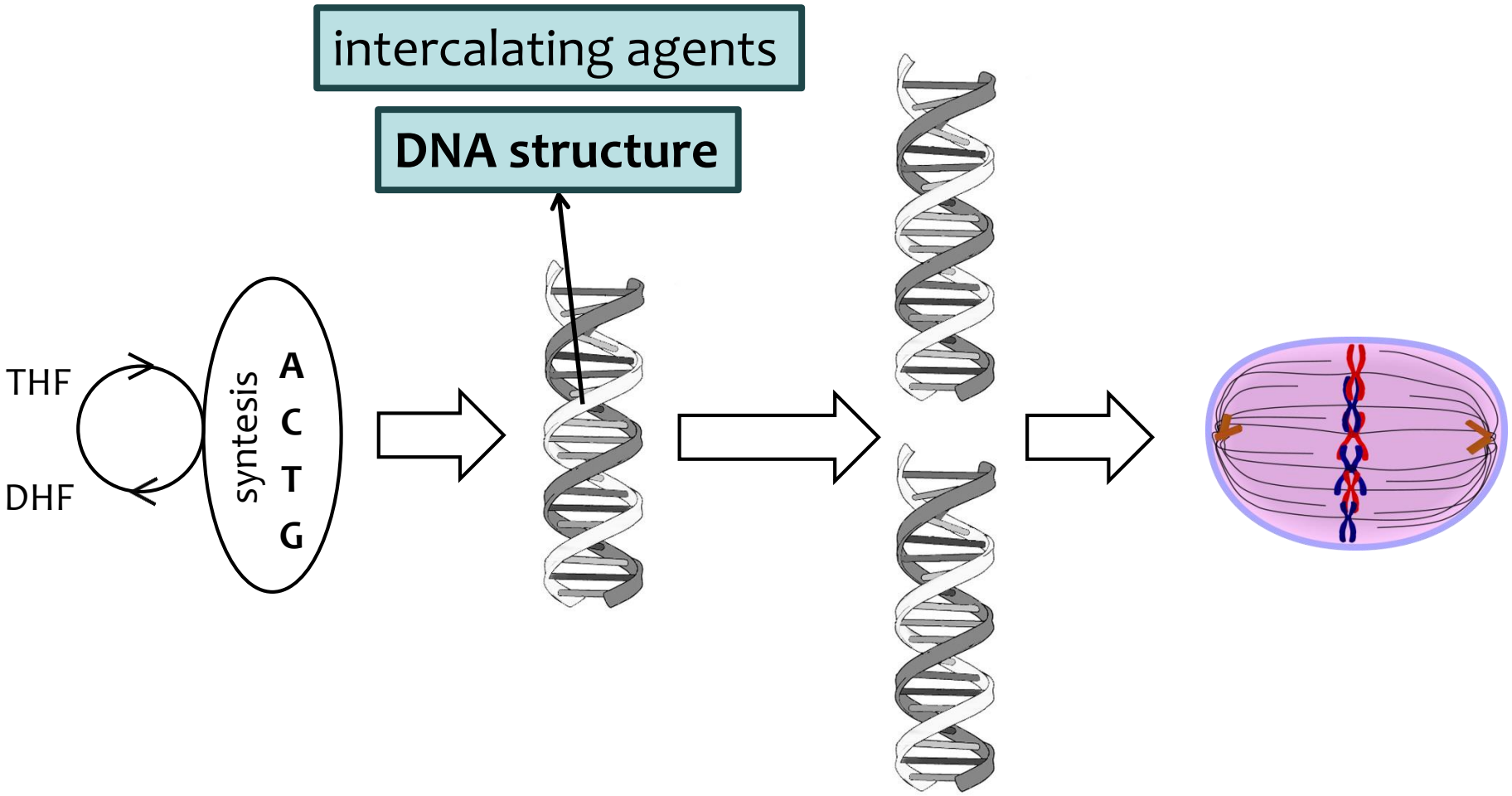
- **AE – most important: emetogenity, nephrotoxicity**
  - AE are dose-dependent
  - prevention of nephrotoxicity: i.v. **hydration**, forced diuresis

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



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

Intracelullar targets of cytostatics



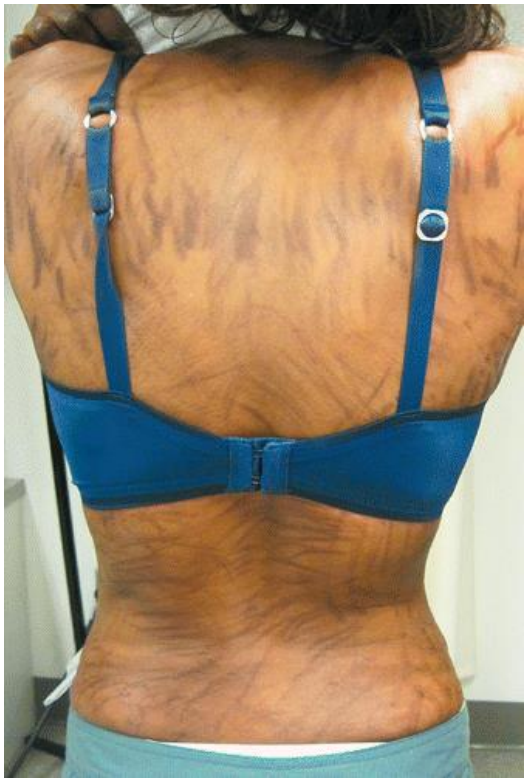
Intercalating agents

Anthracyclines

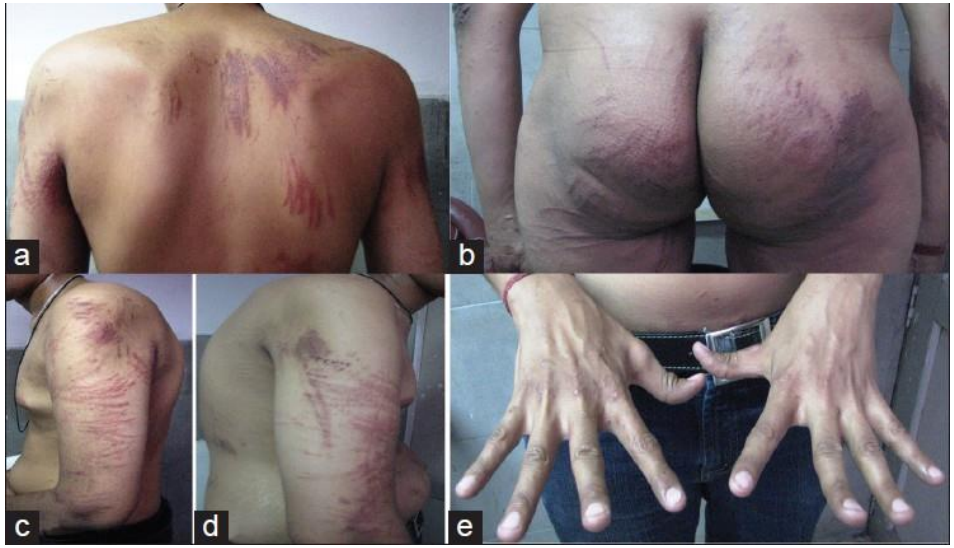
- **MoA: intercalation** = insertion between base pairs, binding of DNA strands
- **AE – typical toxicity:** acute and chronic cardiotoxicity
- cardioprotective cumulative dose = restraint of therapy (e.g., doxorubicin 550 mg/m^2)
- i.v., intravesical administration
- **doxorubicin**
  - treatment of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

- others: epirubicin…

Bleomycin

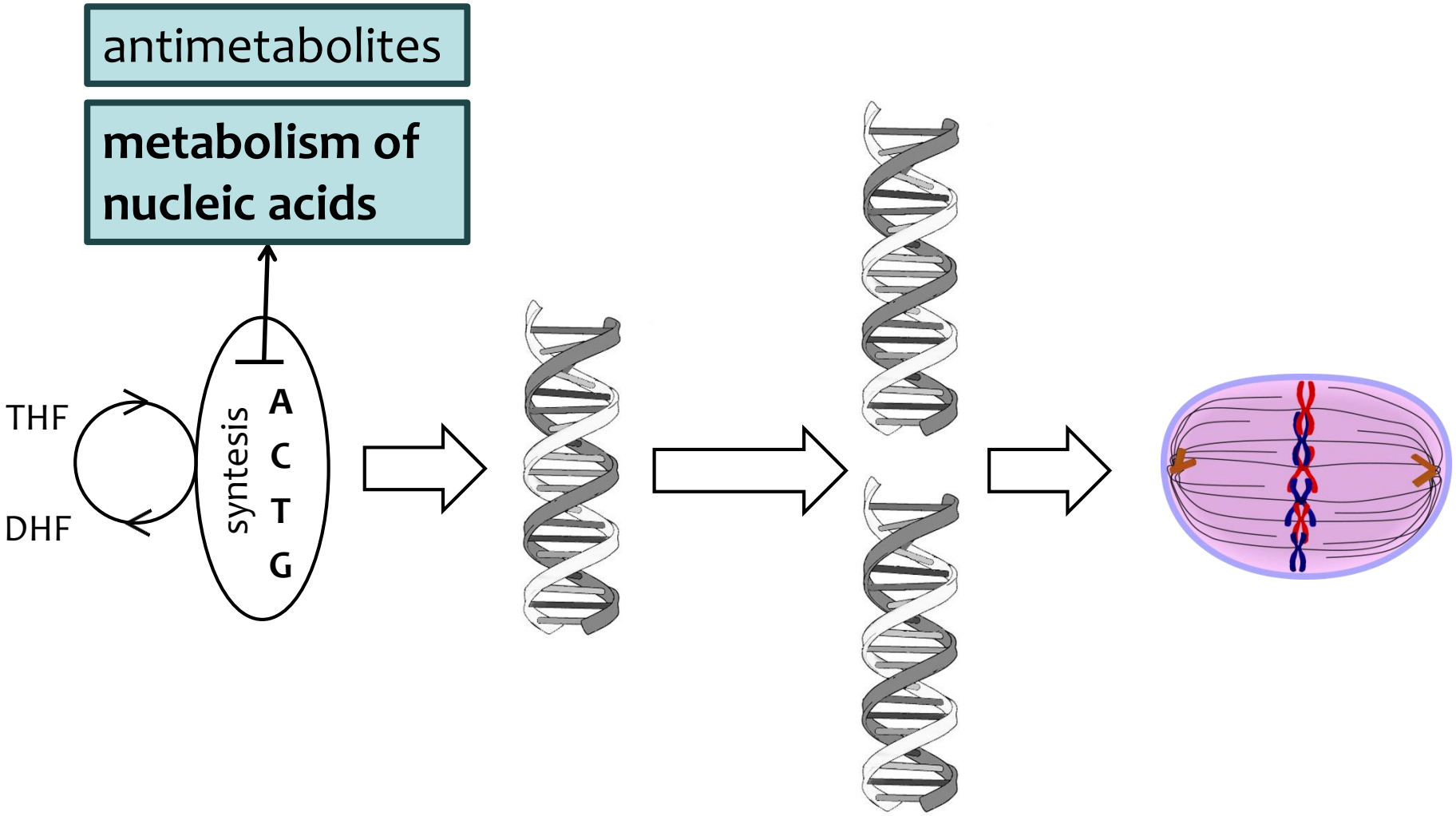


- mixture of glycopeptides
- **MoA:** intercalation between base pairs + inhibition of thymine incorporation → breaks → DNA fragmentation („radiomimetic“ effect)
- i.v. administration
- treatment of solid tumors
- **typical AE:** fever, hyperkeratosis and hyperpigmentation of skin (flagellate = whip-like)



- risk of anaphylactic reaction

Intracelullar targets of cytostatics



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*** – mercaptopurine, azathioprine, fludarabine…

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

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

Antimetabolites – purines

Mercaptopurin

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

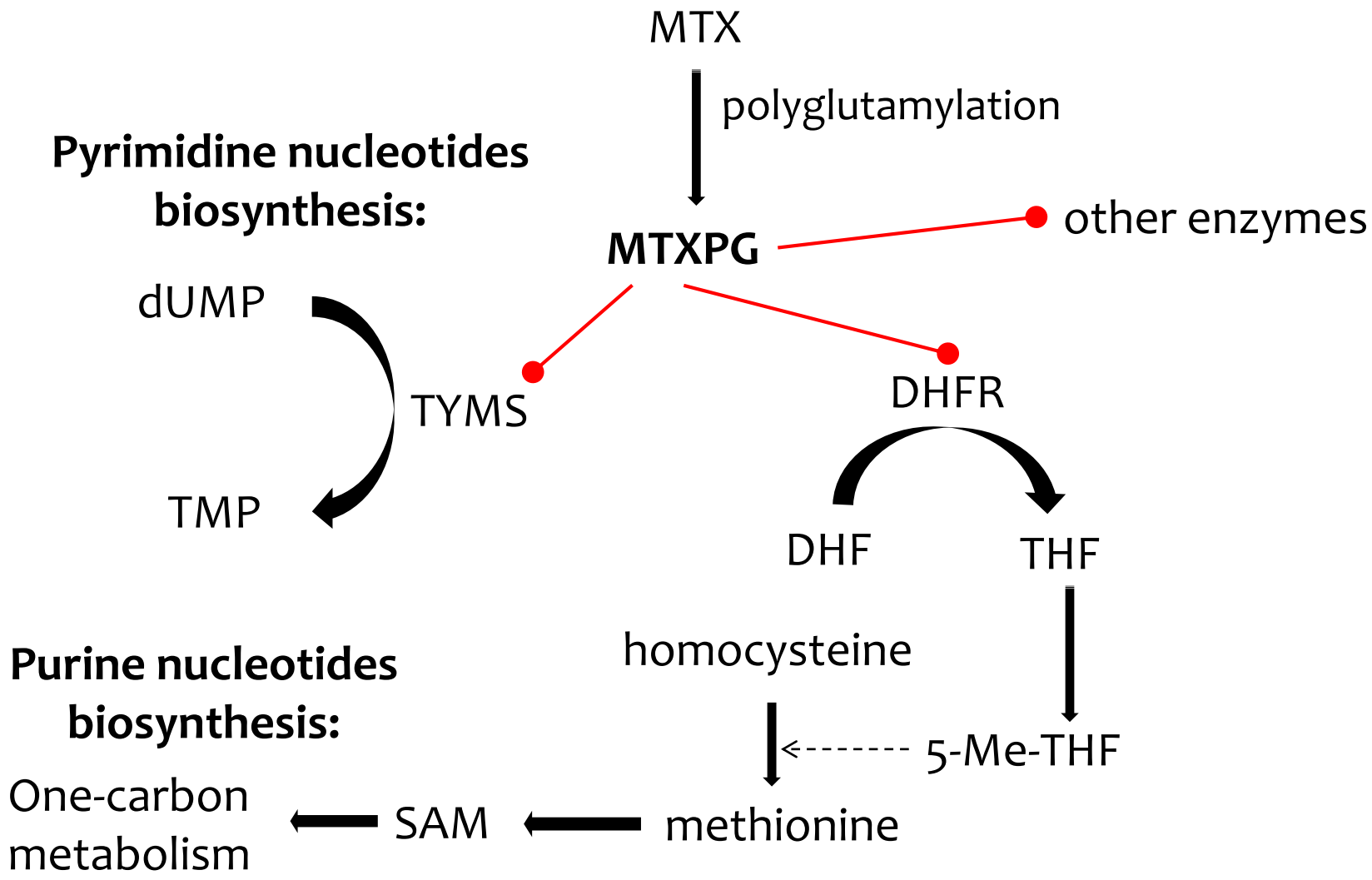
Antimetabolites – pyrimidines

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

Antimetabolites – folic acid

Methotrexate – intracellular mechanism of action:

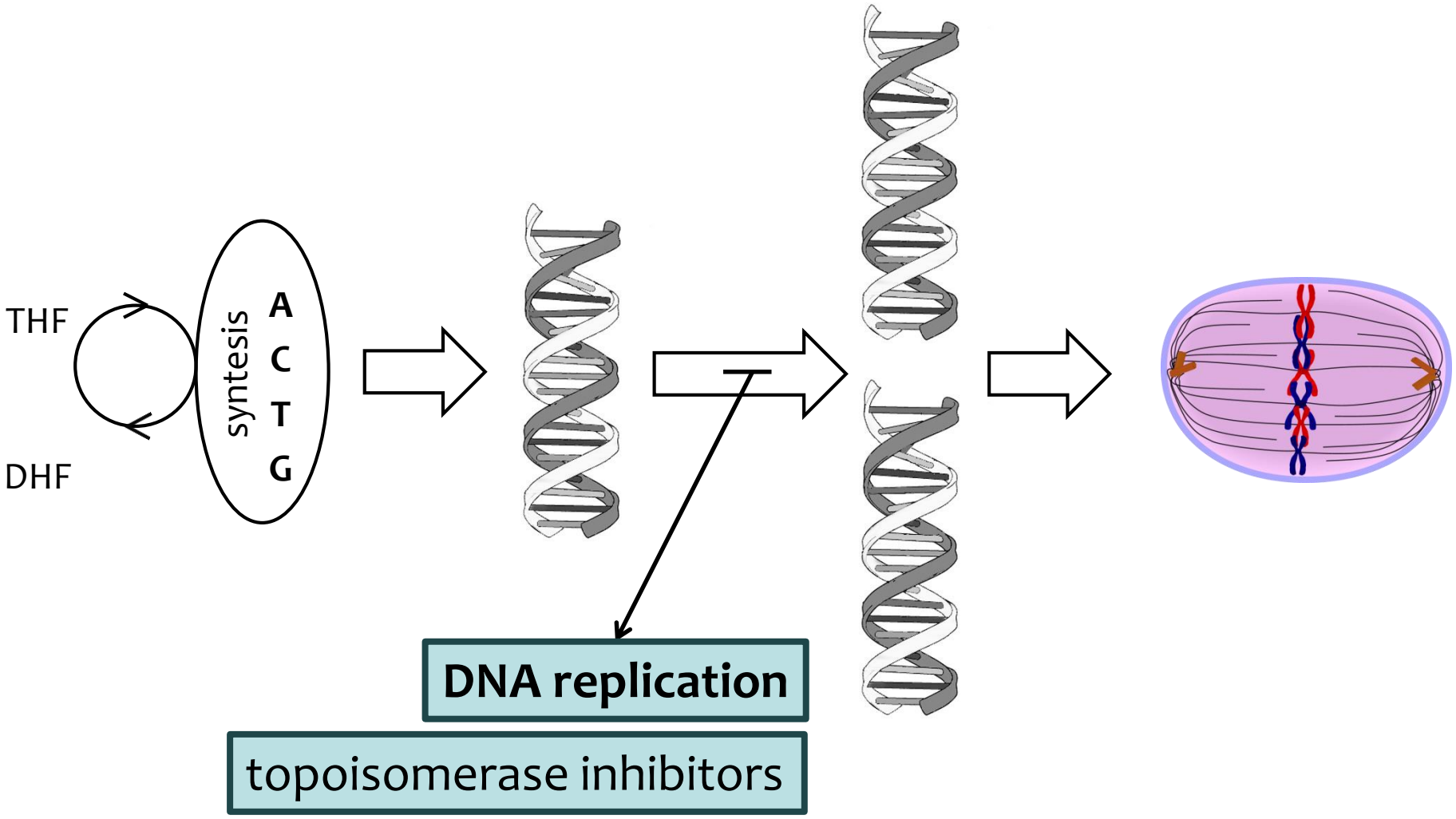


Antimetabolites – folic acid

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 and aggresive solid tumors

Intracelullar targets of cytostatics



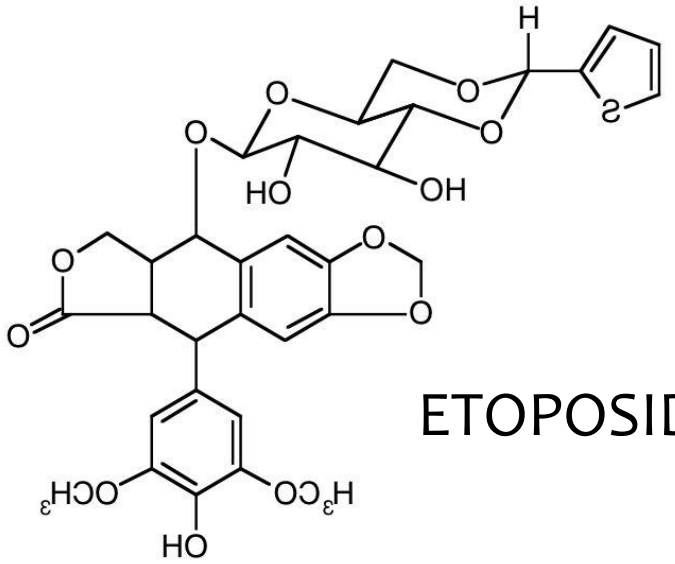
Topoisomerase inhibitors

Topoisomerase I inhibitors – camptothecins

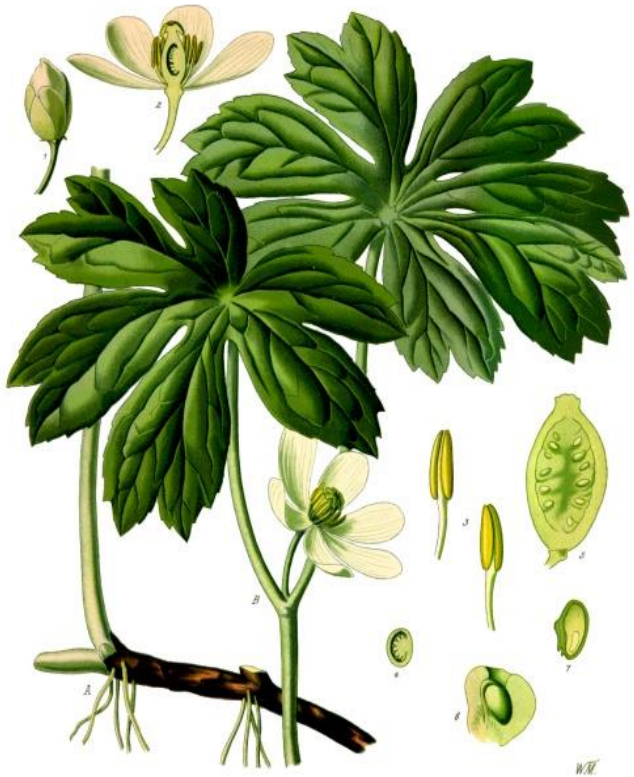
- plant-derived drugs – identification in bark of the tree *Camptotheca acuminata*
- derivatives: **irinotecan,** topotecan
  - treatment of solid tumors

Topoisomerase II inhibitors – podophyllotoxins

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

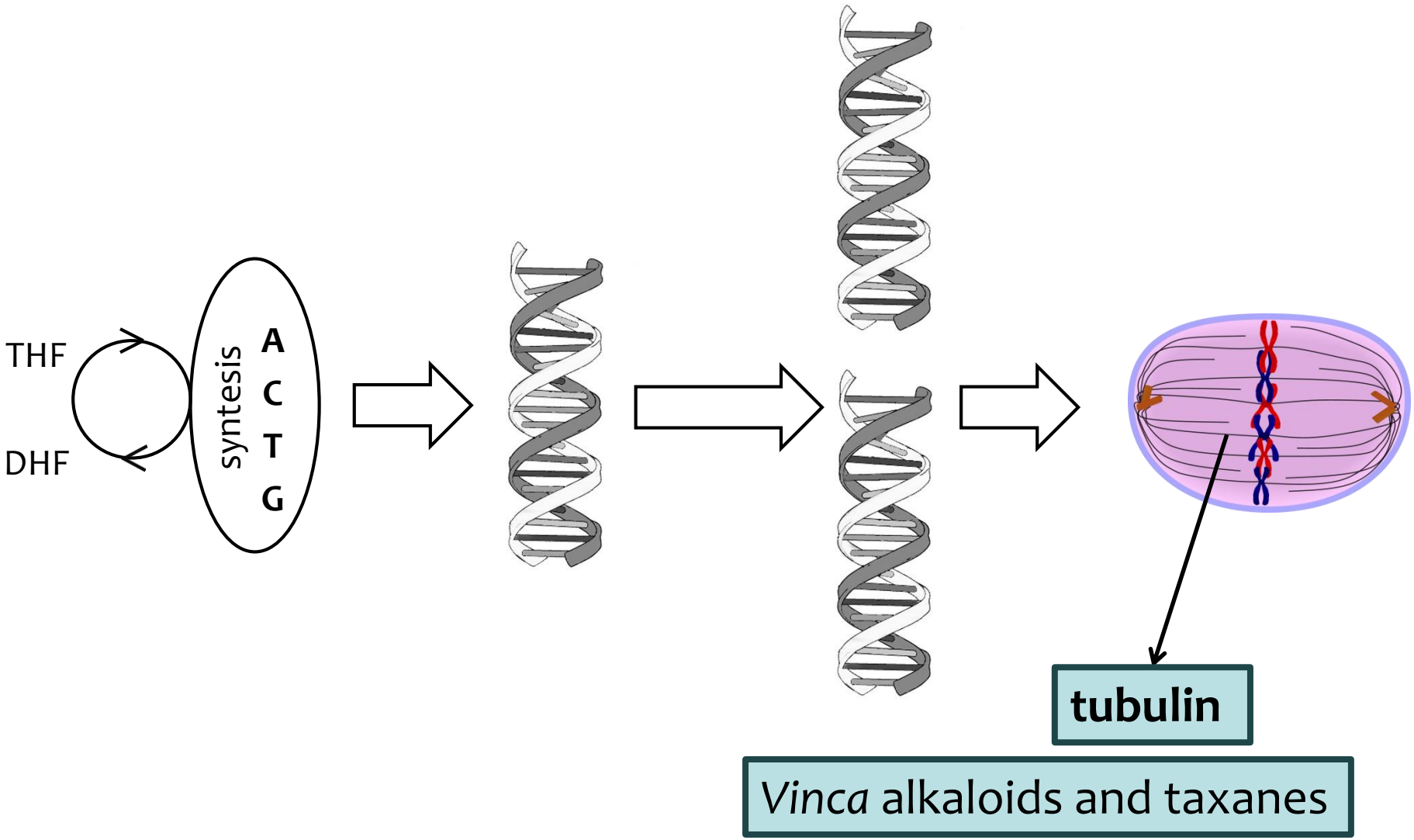


ETOPOSIDE

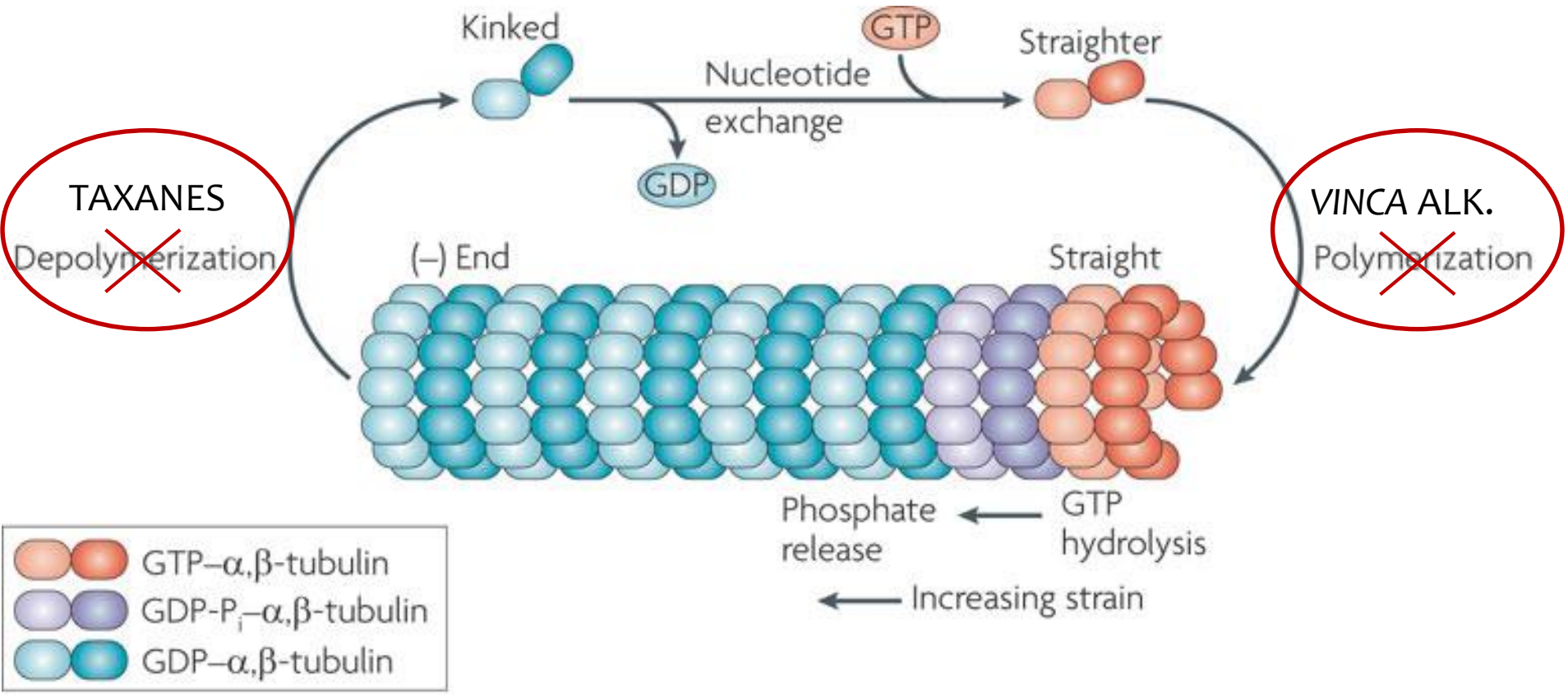


Podophyllum peltatum L.
Image processed by Thomas Schoepke
www.plant-pictures.de

Intracelullar targets of cytostatics



Cytostatics that alter microtubules



Nature Reviews | Molecular Cell Biology

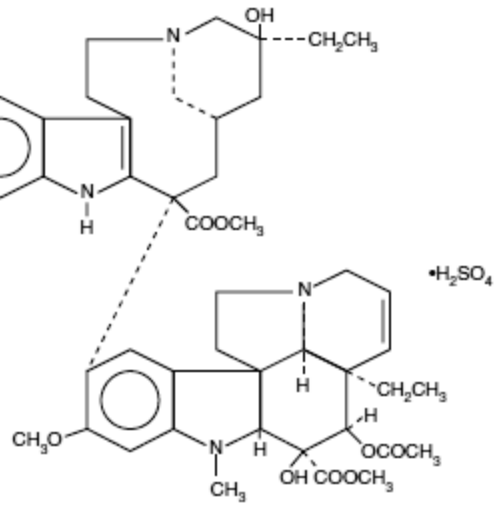
Vinca alkaloids

- plant-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

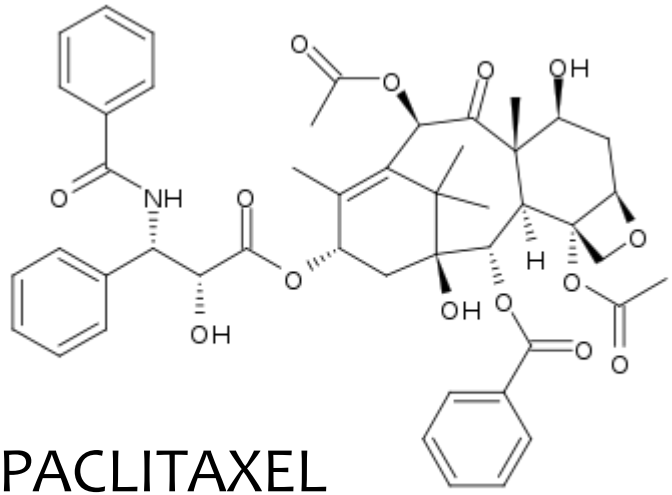
Taxanes

- 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

2. Targeted therapy in oncology

- „target“ in cancer cell
  - Extracellular part of receptors
  - Intracellular part of receptors
  - Intracellular signaling pathway

- „target“ in immune system (T-cell)
  - Immune check-point inhibitors (CTLA-4)

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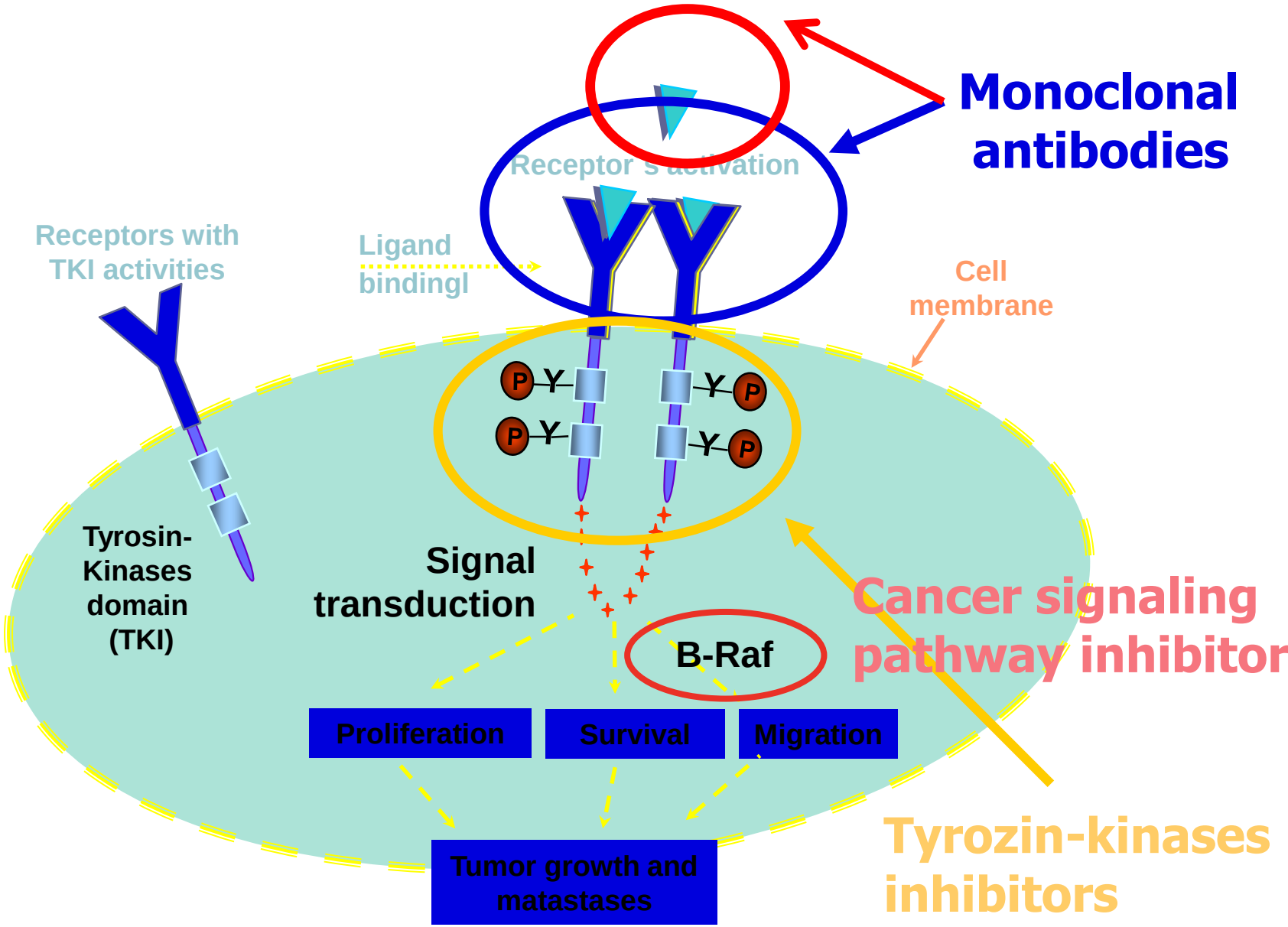
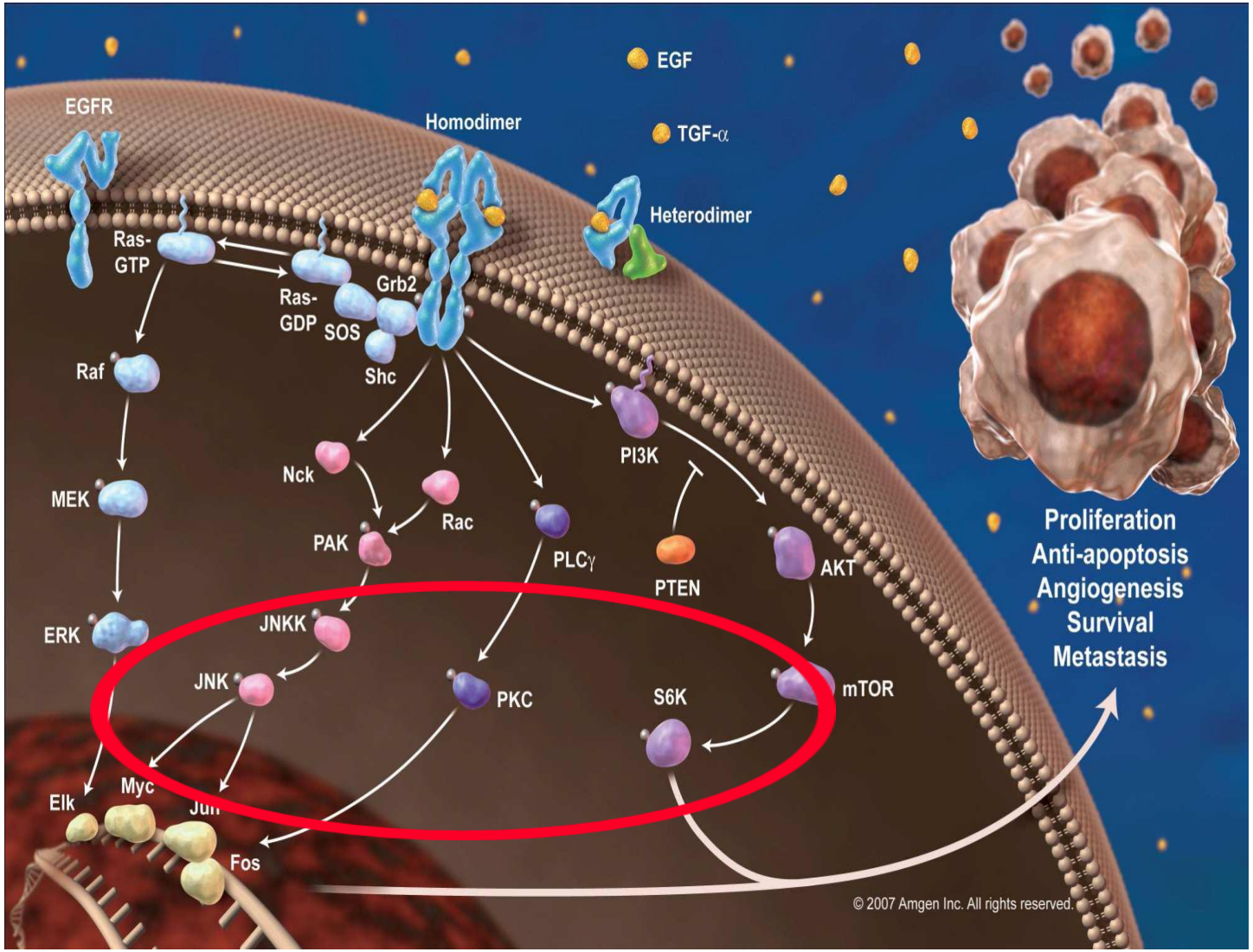
Targeted therapy – „mAbs and –nibs“




EGF
EGFR
Homodimer
TGF-α
Heterodimer
Ras-GTP
Ras-GDP
Grb2
SOS
Shc
Raf
MEK
ERK
Nck
Rac
PAK
JNKK
JNK
PLCγ
PKC
PI3K
PTEN
AKT
mTOR
S6K
Elk
Myc
Jun
Fos
Proliferation
Anti-apoptosis
Angiogenesis
Survival
Metastasis
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Current „targets“

….on example of breast cancer

Receptors

- **EGFR** *(epidermal growth factor receptor)*
- VEGF*(vascular endothelial growth factor receptor)*
- PDGF (*platelet derived growth factor receptor)*
- FGF (*fibroblast growth factor receptor)*

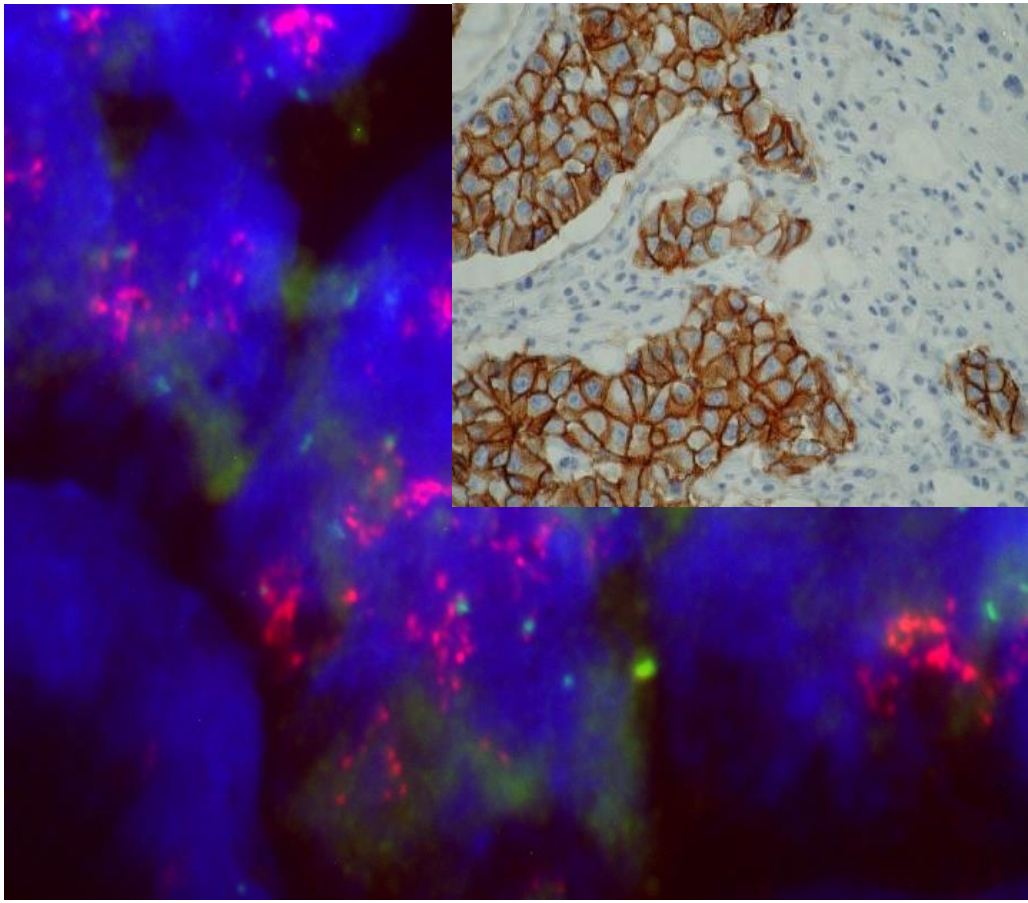
HER-2 positive breast cancer

1985 – identification of
the human Her-2/neu gene
as a negative prognostic
marker

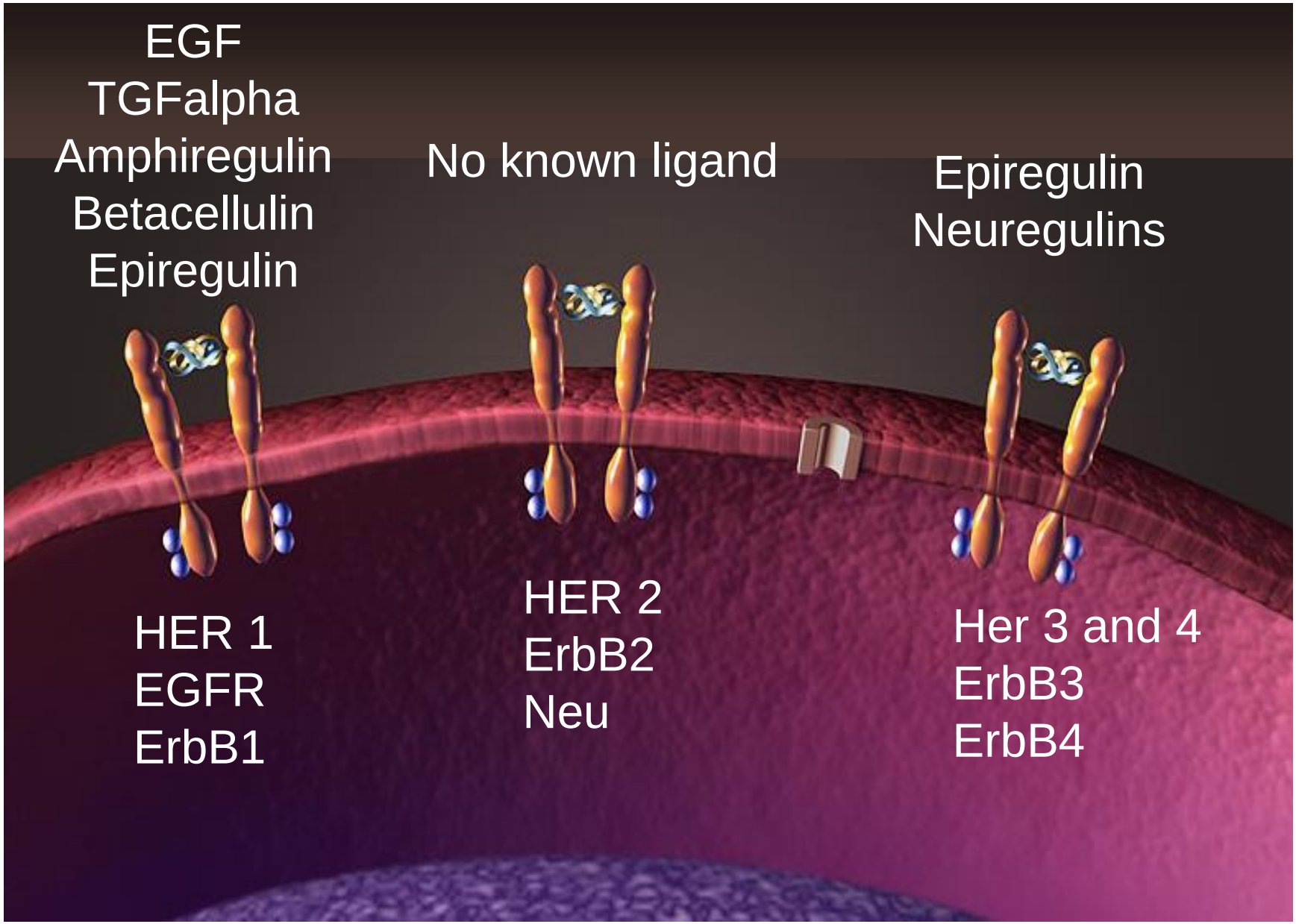
Methods : IHC, FISH

Incidence:

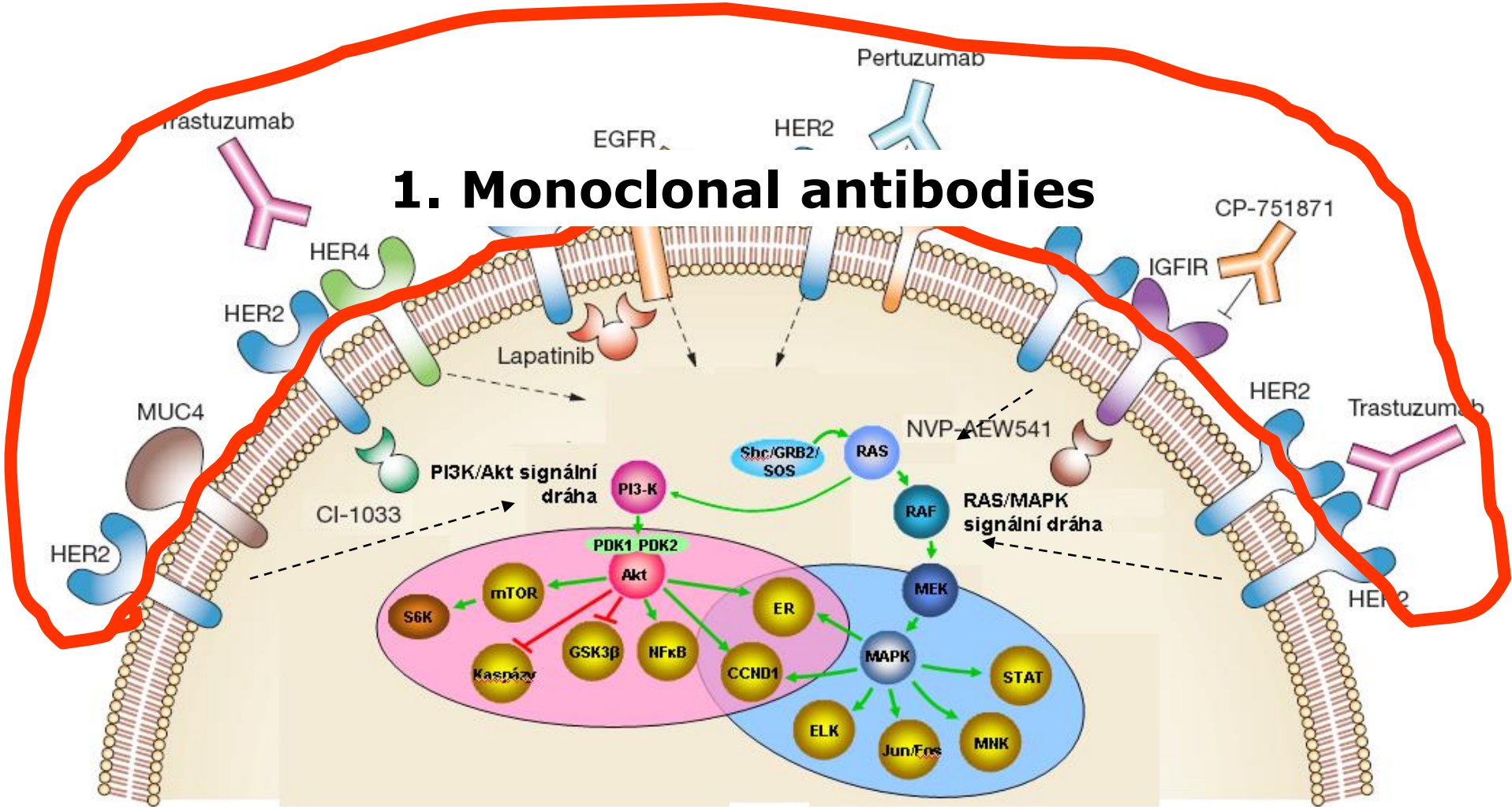
- **worldwide: 10-25%**
- **european: 17%**
- **czech:**



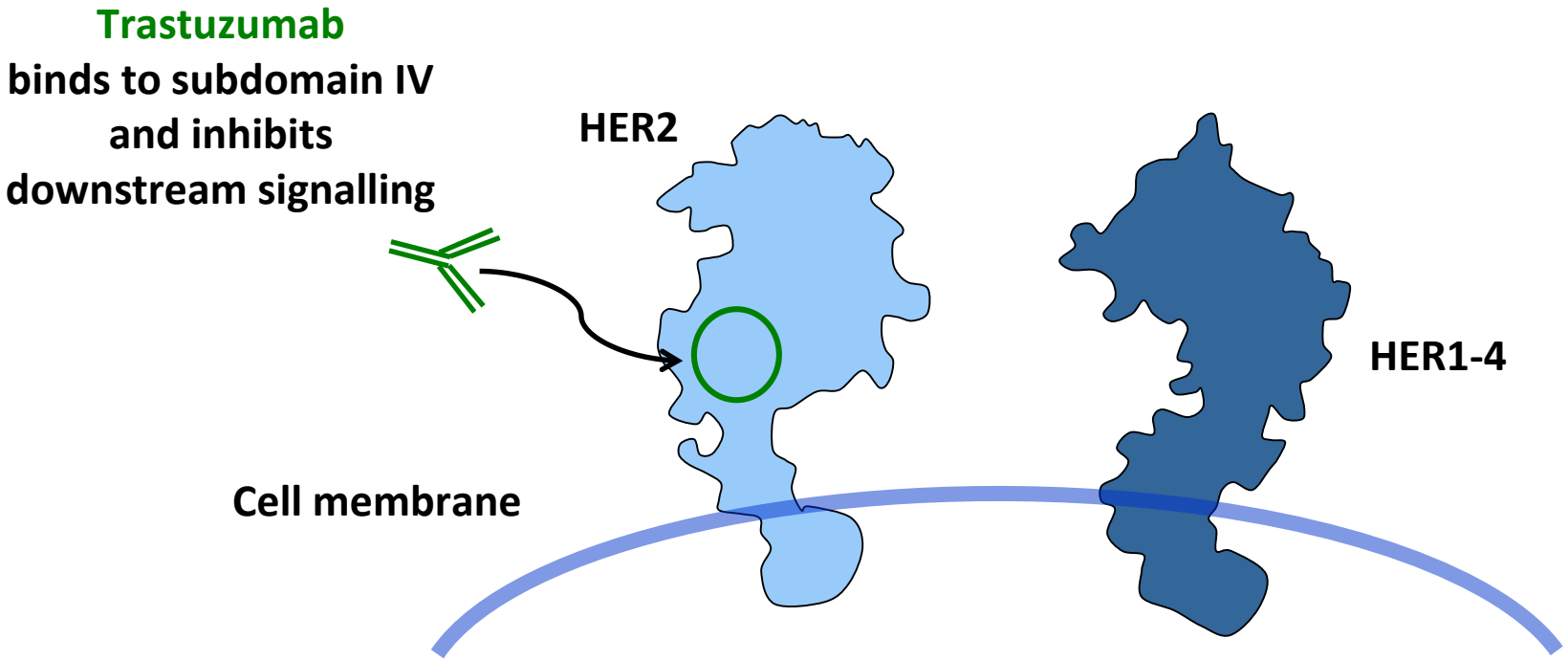
Yang-Feng et al. Cytogenet. Cell Genet. 1985; Slamon et al, Science 1987; Pegram et al, JCO 1998; Owens et al. Clin Breast Can 2004; Al-Kuraya K et al. Mod Pathol 2000; Fabian et al, Sborník BOD 2006,


EGF
TGFalpha
Amphiregulin
Betacellulin
Epiregulin
No known ligand
Epiregulin
Neuregulins
HER 1
EGFR
ErbB1
HER 2
ErbB2
Neu
Her 3 and 4
ErbB3
ErbB4

HER-2 TARGETING



Trastuzumab (HERCEPTIN): Mechanisms of Action



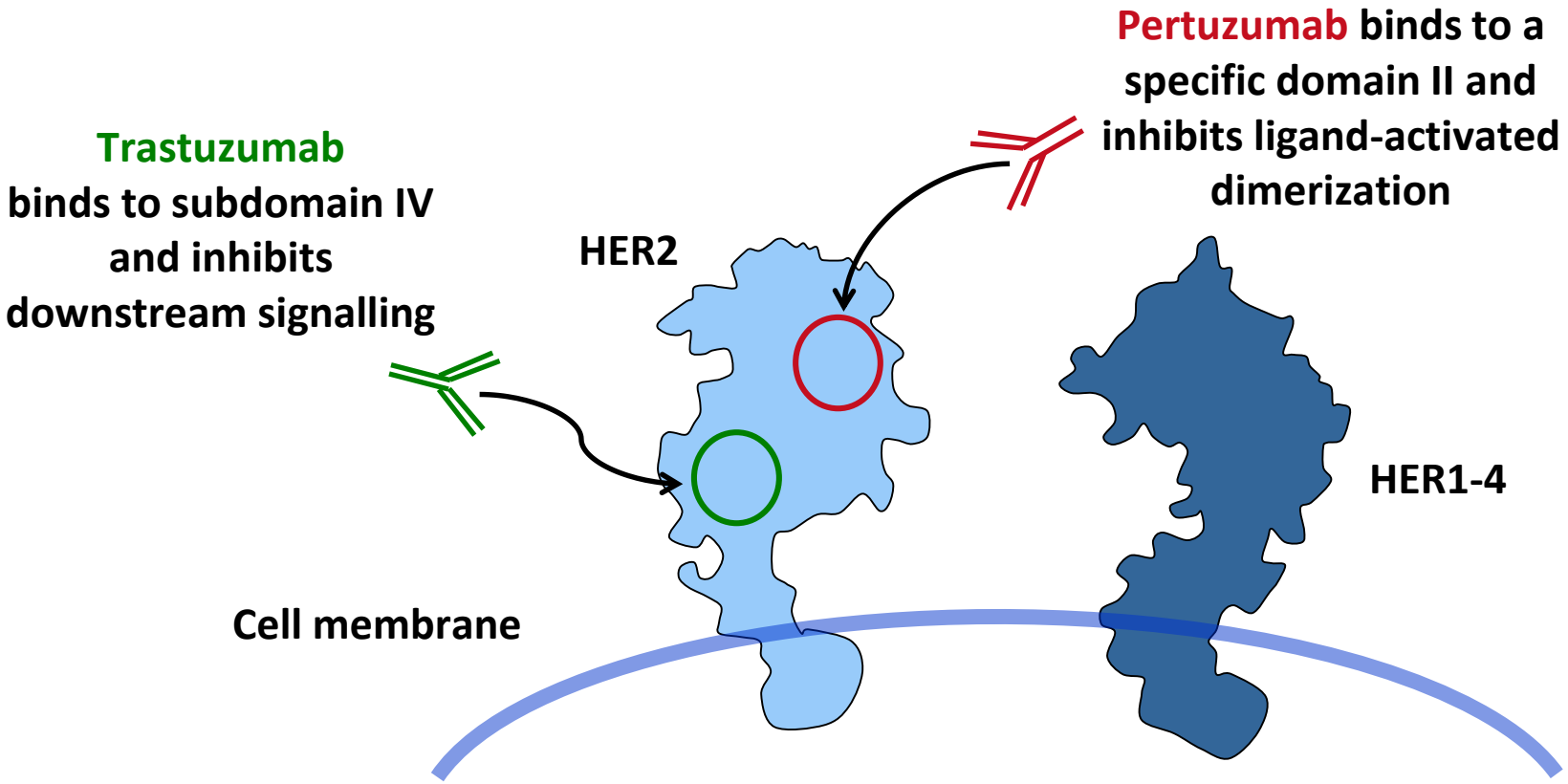
Franklin MC, et al. *Cancer Cell*. 2004;5(4):317-328.

TRASTUZUMAB (Herceptin®)

- INDICATIONS:
  treatment of locally advanced and metastatic HER-2 positive breast cancer
-

  ADVERSE EVENTS:
  allergic reaction, fever, chills, hypotension
  cardiotoxicity
  diarrhea, nausea, vomiting, rash
  muscle and joint pain
  pulmonary infiltrates, penumonitis

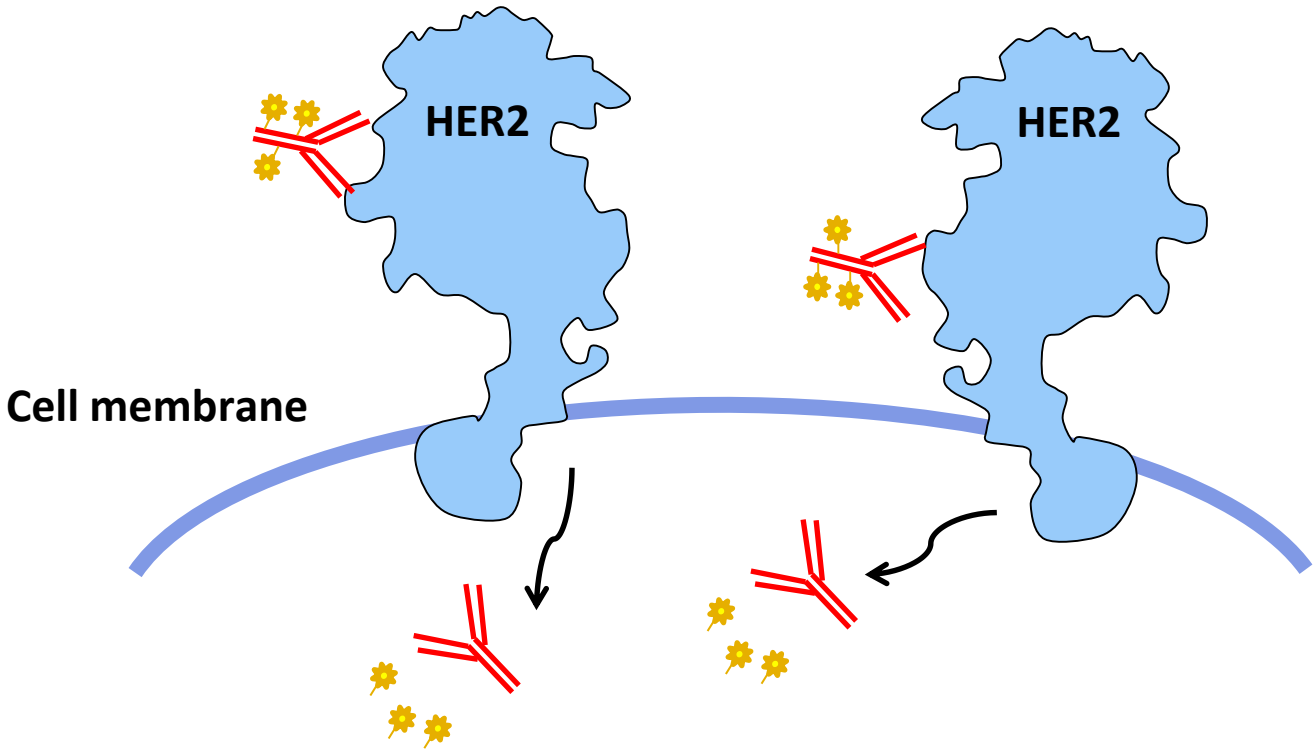
Pertuzumab (PERJETA): Mechanisms of Action



The combined regimen of pertuzumab and trastuzumab offers the potential for a more comprehensive HER blockade

Franklin MC, et al. *Cancer Cell*. 2004;5(4):317-328.

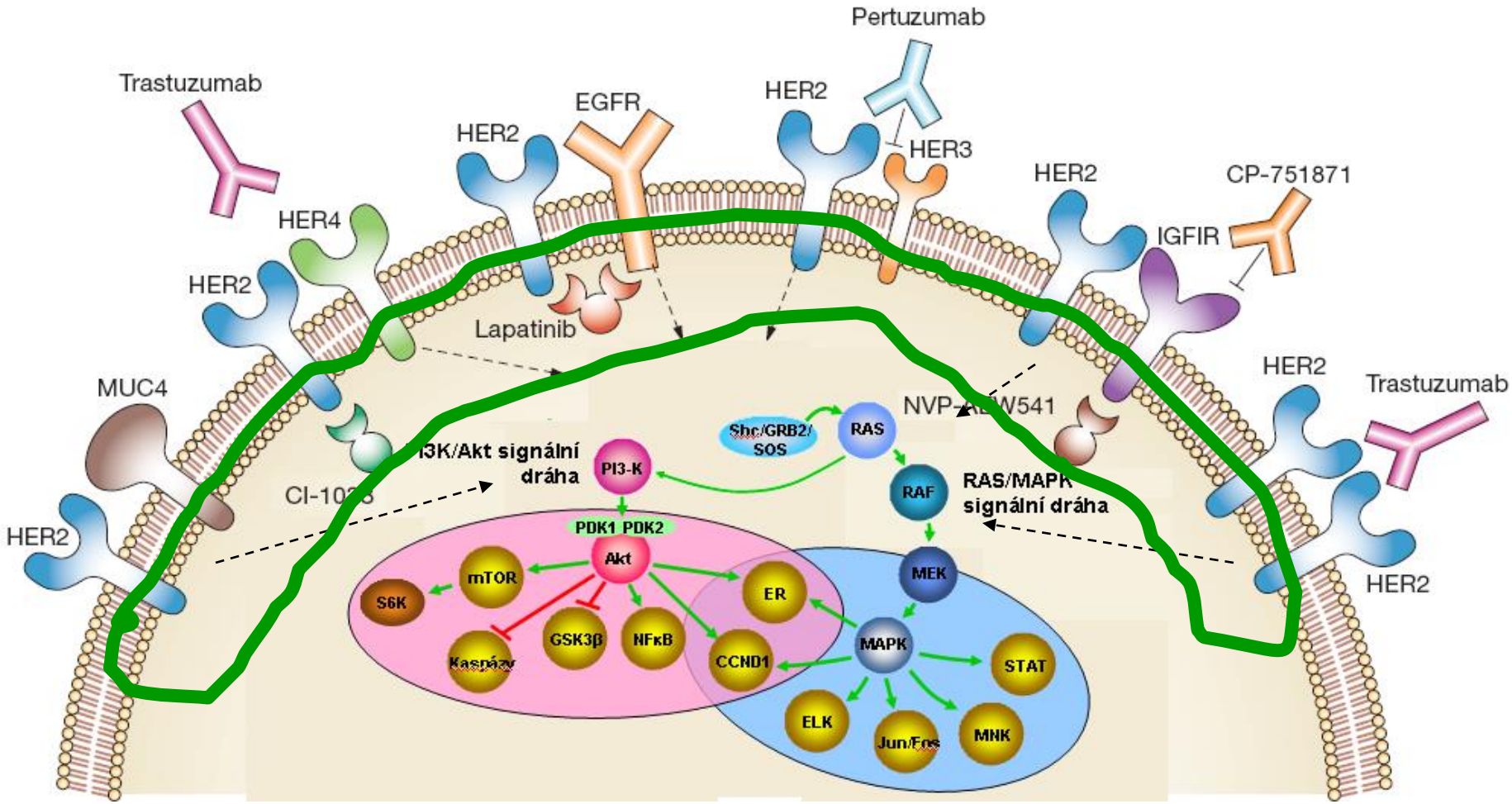
T-DM1: Antibody Drug Conjugate
trastuzumab + emtansin conjugate



Intracellular emtansine release →
inhibition of microtubule polymerization

LoRusso PM, et al. *Clin Cancer Res*. 2011;17(20):6437-6447.

HER-2 TARGETING – tyrosinkinase inhibitors

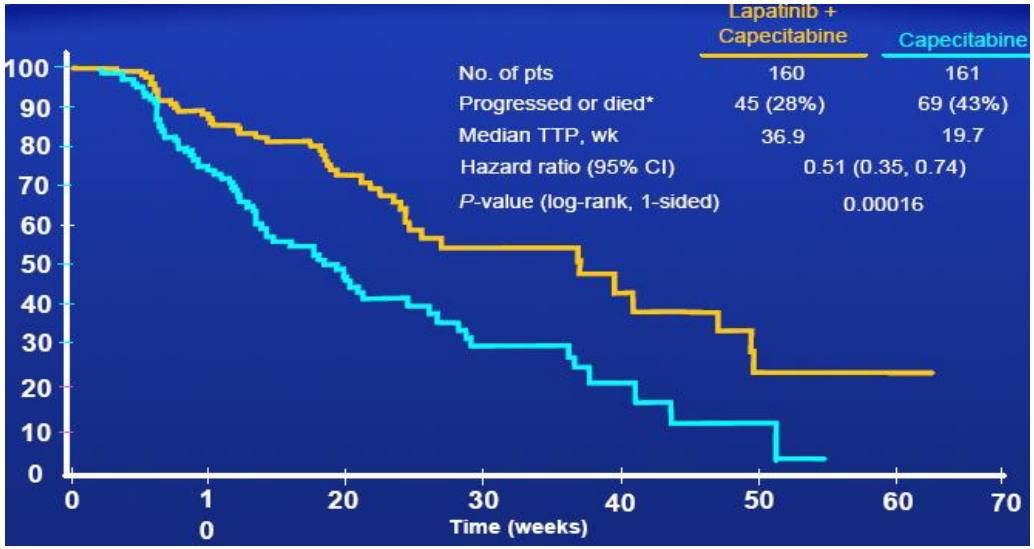


LAPATINIB (Tyverb®) – tyrosinkinase inhibitor

- **Reversible inhibitor EGFR (HER-1), HER-2**
- **Activity in trastuzumab-rezistent tumors**
- **Oral administration, well tolerated**

INDICATION:

Metastatic breast carcinoma after trastuzumab failure



Konecny et al, 2006, Allen et al, 2002

LAPATINIB (Tyverb®)

MAIN ADVERSE EVENTS:

- gastrointestinal toxicity (diarrhea, dehydration, abdominal pain, nausea, vomiting)
- dermal toxicity - rash, pruritus, dry skin

RARE ADVERSE EVENTS:

- cardiotoxicity (2,5% pts.)
- neutropenia
- lung toxicity
- hepatotoxicity
-

Current „targets“

….on example of colorectal cancer

Receptors

- EGFR *(epidermal growth factor receptor)*
- **VEGF *(vascular endothelial growth factor receptor)***
- PDGF (*platelet derived growth factor receptor)*
- FGF (*fibroblast growth factor receptor)*

Example : colorectal carcinoma and VEGF targeting

- The growth of malignant tumor needs the continuous supply of oxygen and nutrients
- Simple diffusion and not enough nutrition to the cells under the influence of hypoxia
- Tumor produced a series mediators, particularly VEGF (vascular endothelial factor).

VEGF - bevacizumab

- Antibody against VEGF, Avastin (bevacizumab), binds to VEGF and prevents it from binding to receptors.

- This induced inhibition of angiogenesis and its long-term use leads to regression of tumor vasculature, the normalization of surviving tumor vessels and inhibition of recovery and growth of new blood vessels

Bevacizumab (AVASTIN®)

INDICATION:

- Metastatic colorectal carcinoma
- Metastatic breast Ca, renal Ca, NSCLC

ADVERSE EVENTS:

- Akceleration of hypertenzion
- proteinurie
- Trombembolic complication

Current „targets“

….on example of colorectal cancer

(overexpressed up to 90% of metastatic colorectal Ca)

Receptors

- **EGFR *(epidermal growth factor receptor)***
- VEGF*(vascular endothelial growth factor receptor)*
- PDGF (*platelet derived growth factor receptor)*
- FGF (*fibroblast growth factor receptor)*

EGFR inhibition in mCRC

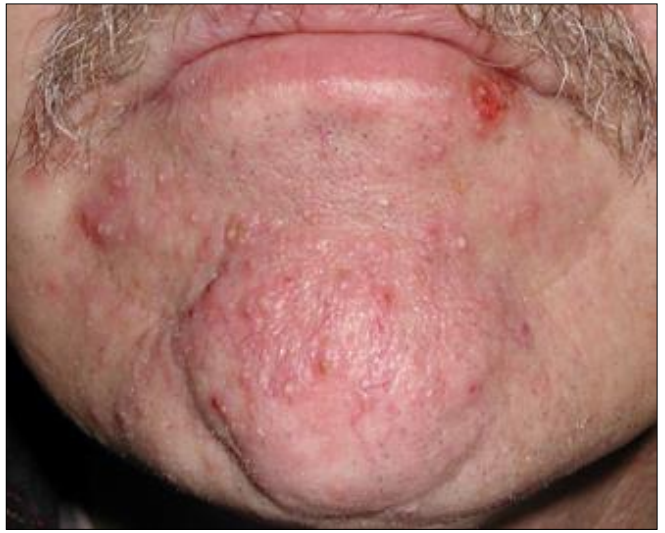
- Monoclonal antibodies antiEGFR
  - **Cetuximab, panitumumab**

- Tyrosine kinase inhibitors (TKIs)
  - **regorafenib**

Venook A. Oncologist. 2005;10:250-261
Mayer A, et al. Cancer. 1993;71:2454-2560.

Cetuximab (ERBITUX®)

EGFR overexpression up to 90%
of metatatic colorectal Ca



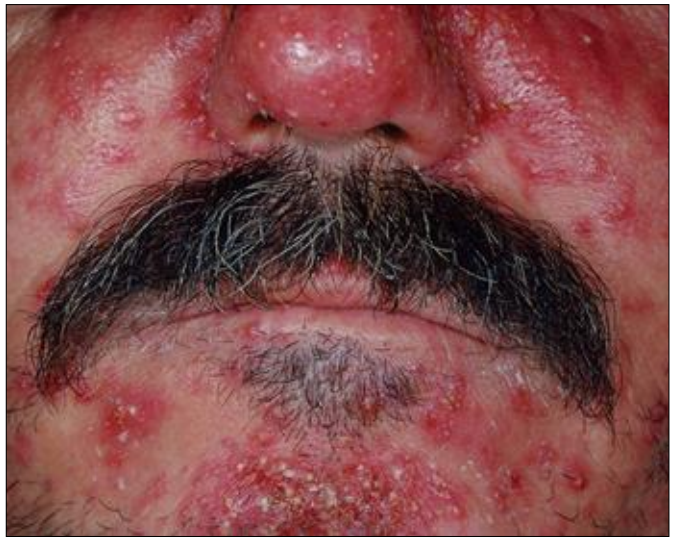
INDICATION:

- Anti - EGFR Mab
- **metastatic colorectal cancer**

AE:

- Akneiform rash 76 – 90%

  Prognostic marker ??? !!!
- Alergic reaction
- Diarrhoea
- Fatigue



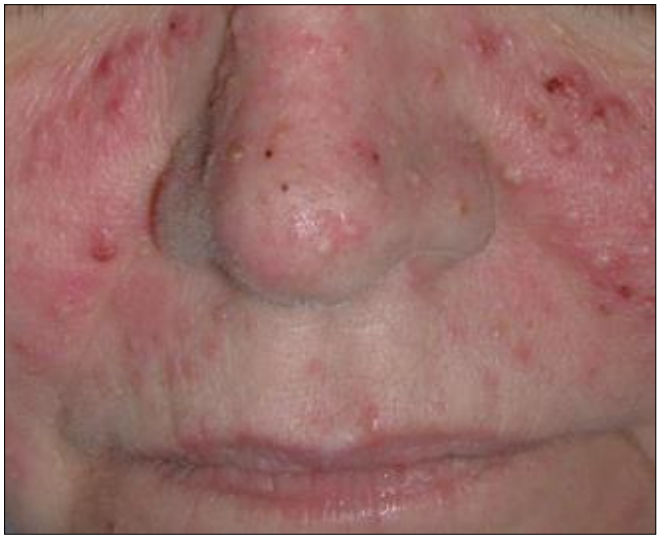
Panitumumab (VECTIBIX®)

INDICATION:

- Anti - EGFR Mab
- **metastatic colorectal cancer**

AE:

- Akneiform rash
- Diarrhoea
- Fatigue



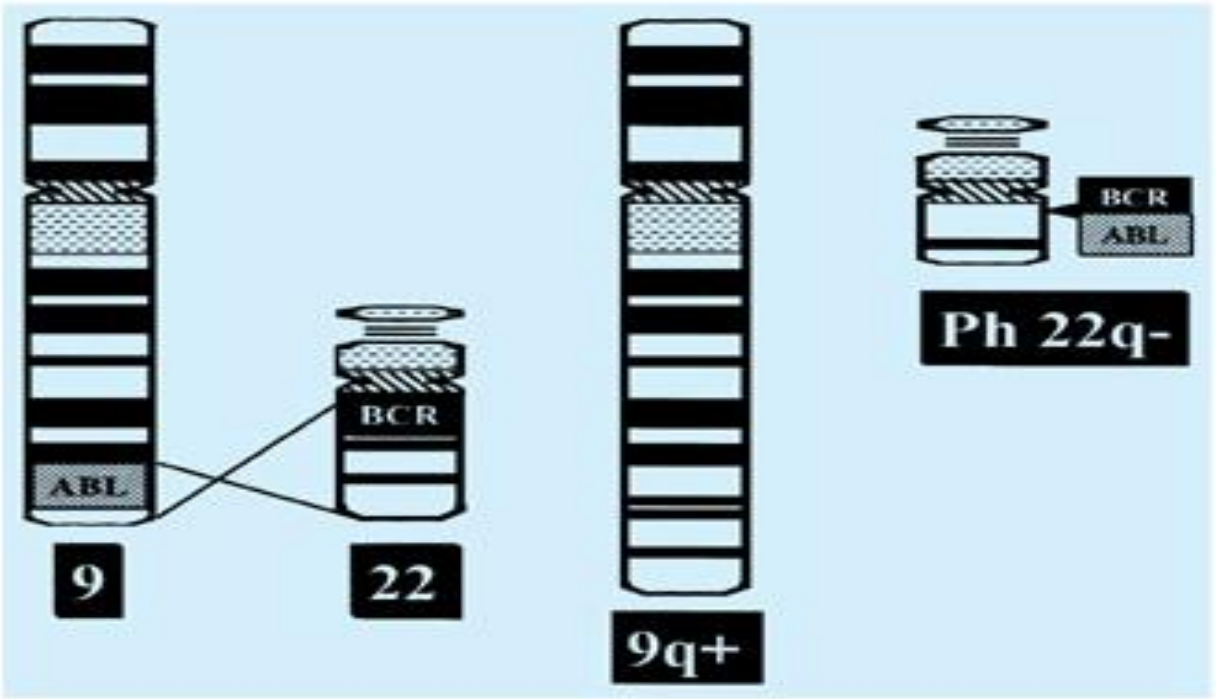
PDGFR a c-KIT inhibitory

- PDGFR – endothelial growth
- C-KIT – formation of blood cells, melanocytes, intestinal cells

- Mutation of c-KIT – leukemia (CML), GIST….

Philadelphia Chromosome

(BCR-ABL Translocation)



Imatinib mesylát (GLIVEC®)

- Bcr-abl inhibitor – chronic myeloid leukémia
- c-KIT inhibitor – 1st line treatment of GIST (mutation c-KIT in 85% pts.) – 70% of the pts. Are responders!!!

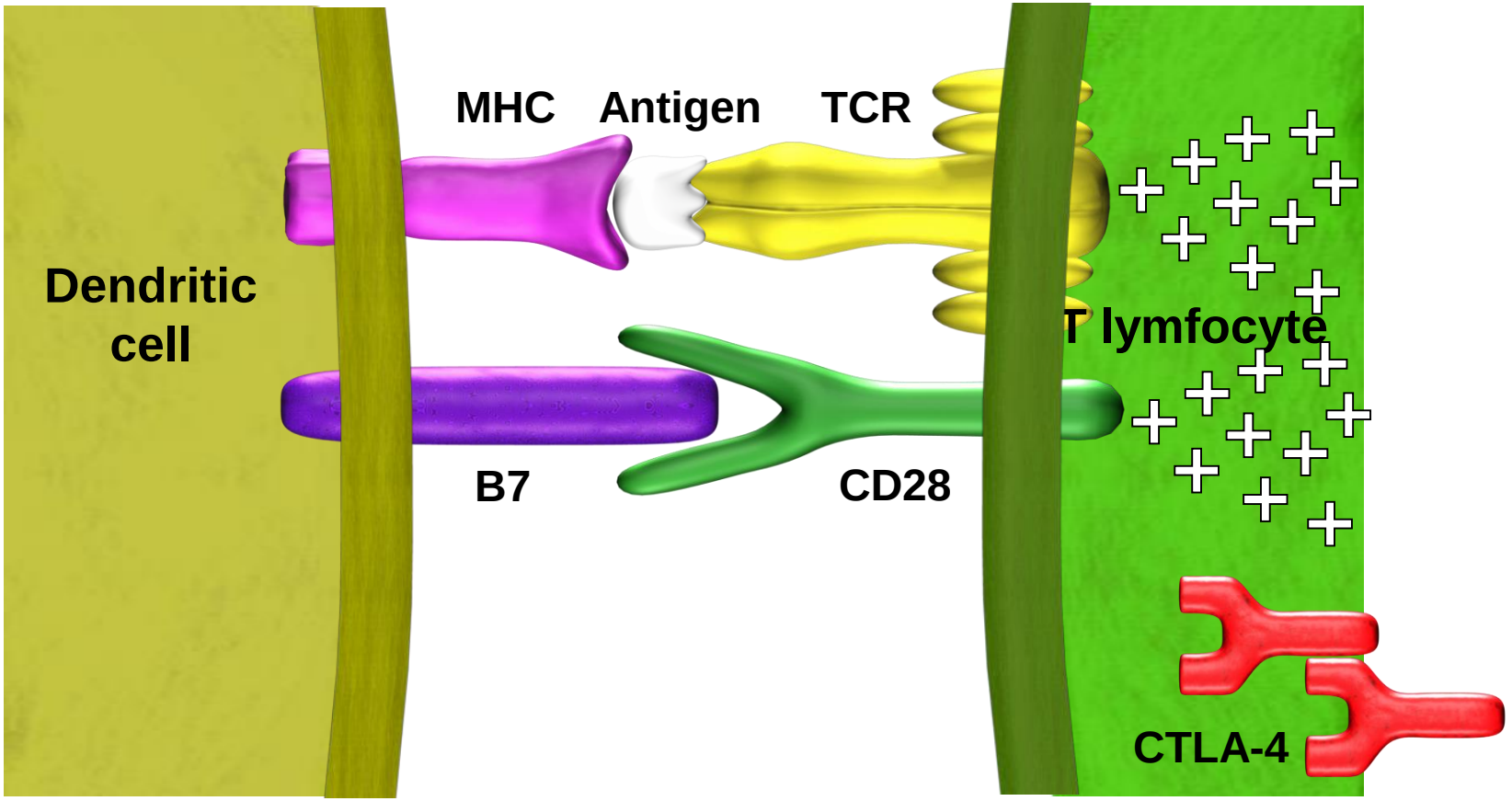
AE:

- neutropenia, trombocytopenia
- diarrhoea, vomiting
- joint pain

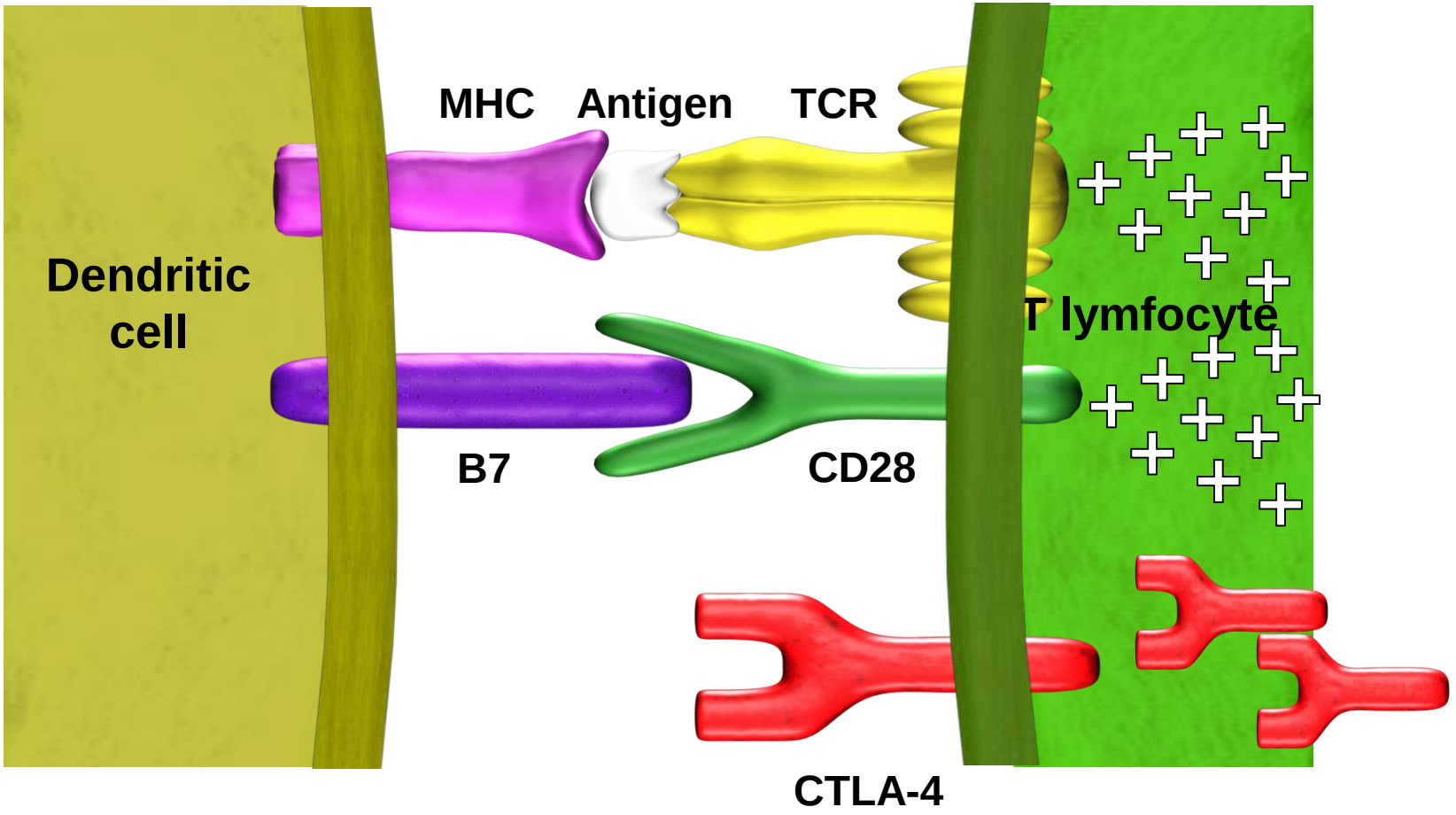
Immunotherapy in oncology „Checkpoint“ inhibitors – CTLA-4 a PD-1/PD-L1 antagonists

- **anti-CTLA-4 (cytotoxic T-lymphocyte antigen 4) – ipilimumab,** tremelimumab
- **anti-PD-1** (programmed death-1 receptor) - **nivolumab,** pembrolizumab
- **anti-PD-L1** – BMS-936559, MPDL3280A

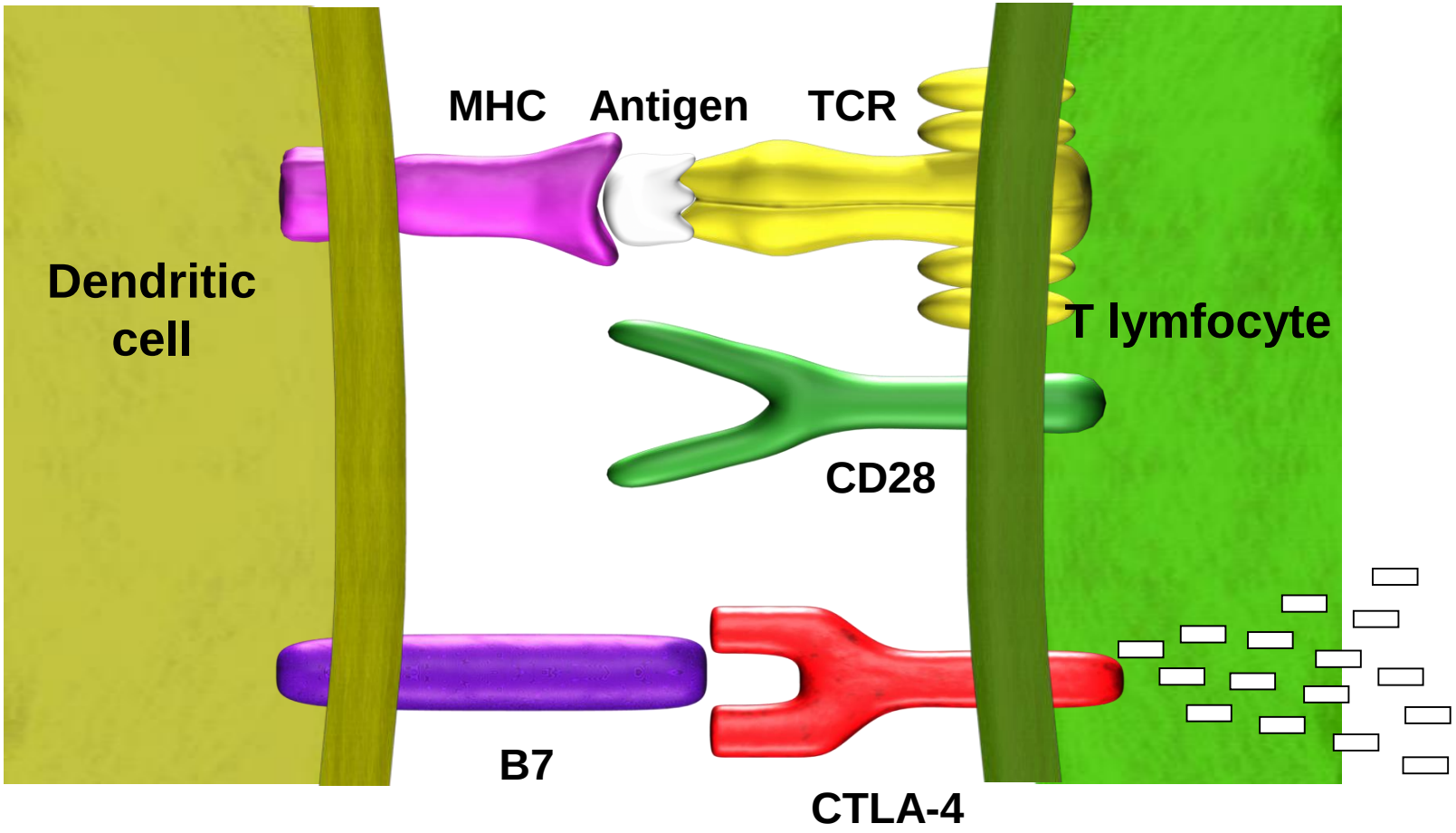
Activation of T lymfocytes through TCR and co-stimulating molecule CD28



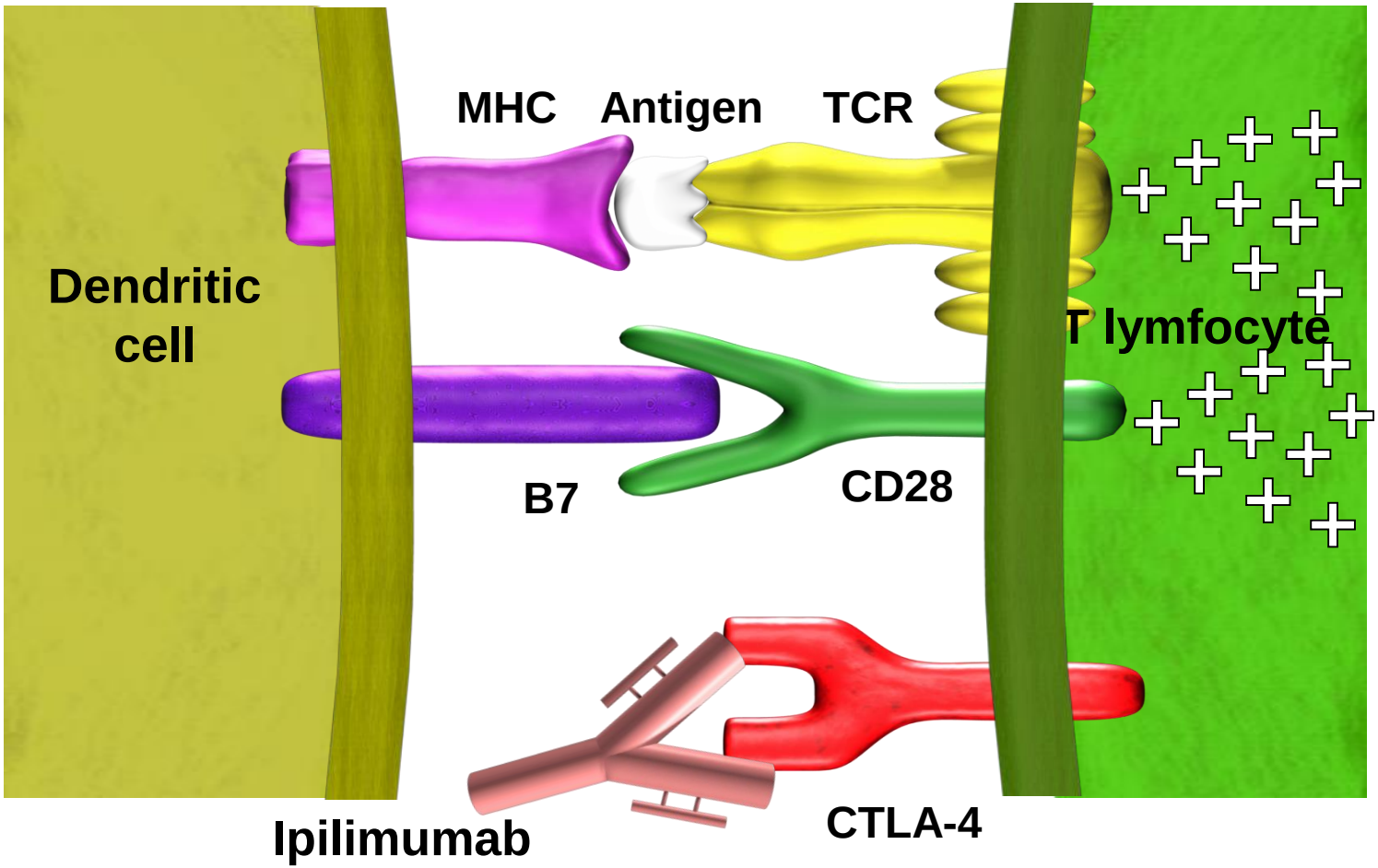
Up-regulation of CTLA-4 receptors after T- cell activation



CTLA-4 receptor inhibition



Antagonisation of CTLA-4 receptors Ipilimumab

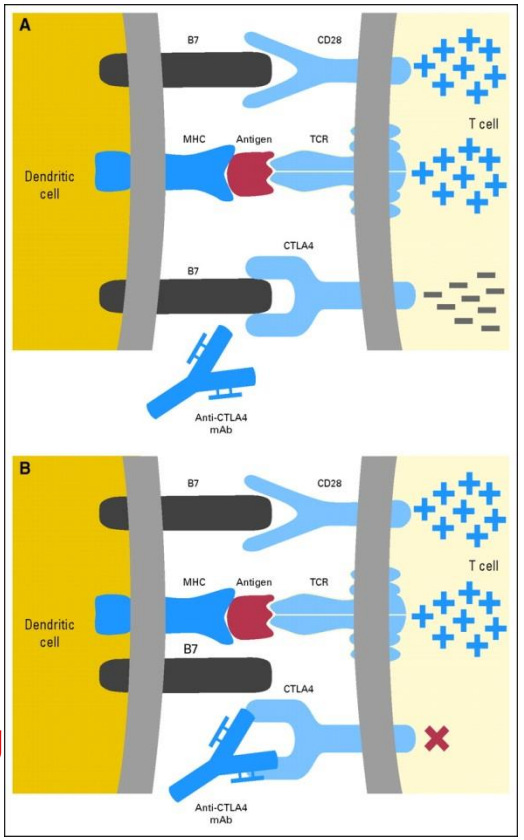


Leach DR, Science 1996;271:1734-1736.

anti-CTLA-4 mAbs

- **Tremelimumab (IgG2, Pfizer)**
  - Phase III ongoing
  - Tremelimumab 15 mg/kg vs DTIC/Temozolomid

- **Ipilimumab (IgG1, Bristol-Myers Squibb)**
  - **EMA registration**
  - I. line treatment of melanoma
    - Ipilimumumab (10 mg/kg)
  - **II. line**
    - **Ipilimumab (3 mg/kg) vs Ipilimumab/gp100 vs g**



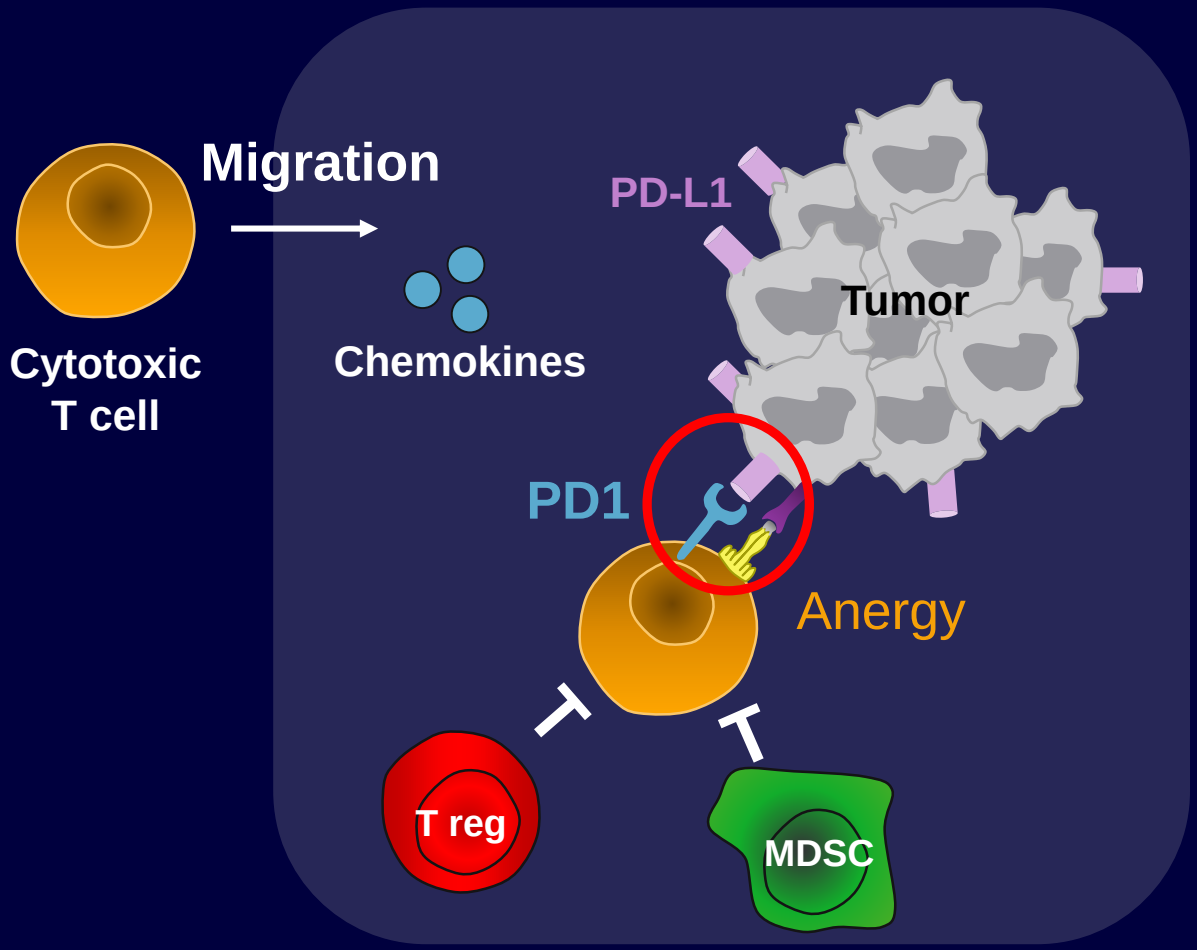
Kirkwood JM et al., JCO 2008;26:3445-3455
Ribas A et al., JCO 2008;26:,abstr.9011
Robert C et al., NEJM 2011;364:2517-2526
Hodi FS et al., NEJM 2010;363:711-723

Ipilimumab: Managing Immune-Related Adverse Events

System	Symptoms	Management
GI tract	Diarrhea Abdominal pain Dark, bloody stools	Moderate enterocolitis: hold ipilimumab, administer antidiarrheal. Persistent diarrhea (> 1 wk): systemic corticosteroids. 7+ stools/day: start methylprednisone, permanently discontinue ipilimumab. Consider infliximab for corticosteroid-refractory patients
Skin	Rash (± itching) Blistering/peeling Oral sores	Moderate/nonlocalized rash: hold ipilimumab, start topical or systemic corticosteroids. Severe dermatitis: permanently discontinue ipilimumab, start corticosteroids
Liver	Jaundice Nausea/vomiting	Assess ALT/AST, bilirubin, and thyroid function before each dose and as necessary. Hold ipilimumab if ALT/AST > 2.5 x but ≤ 5 x ULN; permanently discontinue if AST/ALT > 5 x ULN or bilirubin > 3 x ULN. The immunosuppressant mycophenolate can be used for hepatotoxicity in corticosteroid-refractory patients
CNS	Weakness in extremities Numbness/tingling Sensory changes	Moderate neuropathy: hold ipilimumab. New or worsening neuropathy: permanently discontinue ipilimumab. Consider corticosteroids
Endocrine	Headaches Fatigue Behavior/mood changes Menstruation changes Dizziness/light-headedness	Moderate endocrinopathy: hold ipilimumab, start corticosteroids. Endocrine abnormalities can be difficult to detect, due to nonspecific symptoms. Consider having an endocrinologist follow the patient
Eyes	Vision problems Irritation	Monitor for redness suggesting uveitis, treat with topical steroidal eye drops

Ipilimumab adverse reaction management guide.

Checkpoint inhibitors – PD-(L)-1



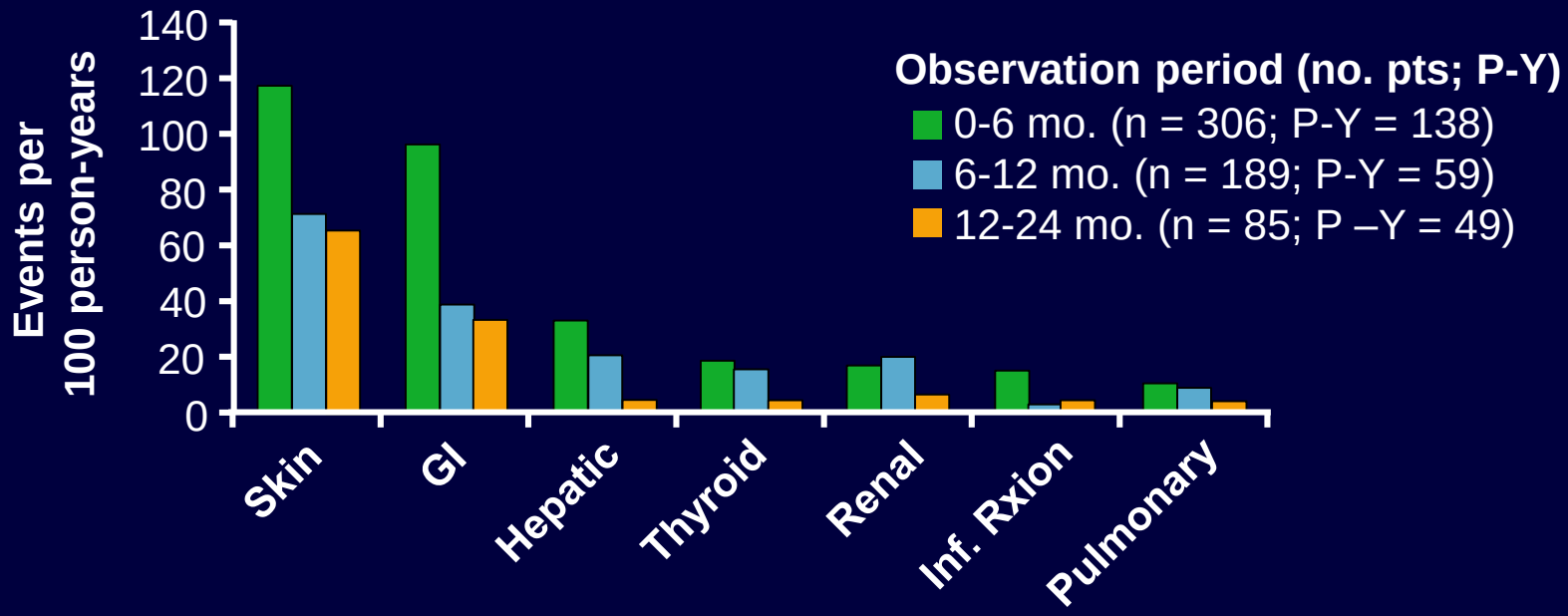
- T cell recruitment
  - High levels of innate immune signals
  - Chemokine expression
- Nevertheless, negative immune regulators dominate
- Blocking PD1:PD-L1 binding might activate immunity within the tumor microenvironment

Gajewski TF, et al. Curr Opin Immunol. 2011;23:286-292. Spranger S, Gajewski T. J Immunother cancer. 2013;1:16.

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Development stage
PD-1	Nivolumab (BMS-936558)	Fully human IgG4	Phase III multiple tumors (melanoma, RCC, NSCLCa, HNSCC)
	Pembrolizumab (MK-3475)	Humanized IgG4	Phase I-II multiple tumors Phase III NSCLC/melanoma
	Pidilizumab (CT-011)	Humanized IgG1	Phase II multiple tumors
PD-L1	MEDI-4736	Engineered human IgG1	Phase I-II multiple tumors
	MPDL-3280A	Engineered human IgG1	Phase I-II multiple tumors Phase III NSCLC
	MSB0010718C	Fully human IgG1	Phase I solid tumors

Nivolumab Exposure-adjusted irAEs: Toxicity Is Not Cumulative



- Multiple occurrences of all-cause select AEs in individual pts are included in this exposure-adjusted analysis.
- Treatment-related Gr 3-4 AEs occurred in 17% of pts, including select AEs in 6%.

Topalian SL, et al. J Clin Oncol. 2014;32:1020-1030.

Thank you for your attention

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