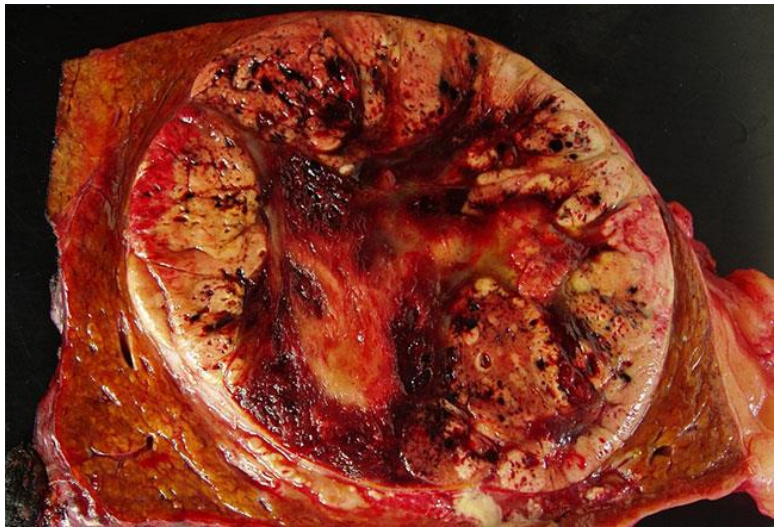
Chemotherapy for Neoplastic Diseases

Pharmacology and Toxicology
General Pharmacology
Second Year Medical Students
Tareq Saleh, MD, PhD
Faculty of Medicine
The Hashemite University

History of Cancer

- The earliest reference to cancer goes back to ancient Egypt (3000 BC). Those cases of cancer were treated by cauterization.
- The word “cancer” (which means crab) was described by Hippocrates (460-370 BC) because of the invasive projections of cancer in the adjacent tissue.
- Later, the Greek root “oncos” (which means swelling) was used to describe tumors.
- Giovanni Morgagni identified and described cancers by performing autopsies (1761); John Hunter (1728-1793) proposed surgical removal of tumors.

American Cancer Association



Liver Cancer, Image courtesy of Arief Suriawinata, MD, Department of Pathology, Dartmouth Medical School

Cancer Statistics

Estimated New Cases

Males				Females		
Prostate	248,530	26%		Breast	281,550	30%
Lung & bronchus	119,100	12%		Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%		Colon & rectum	69,980	8%
Urinary bladder	64,280	7%		Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%		Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%		Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%		Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%		Pancreas	28,480	3%
Leukemia	35,530	4%		Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%		Leukemia	25,560	3%
All Sites	**970,250**	**100%**		**All Sites**	**927,910**	**100%**

Estimated Deaths

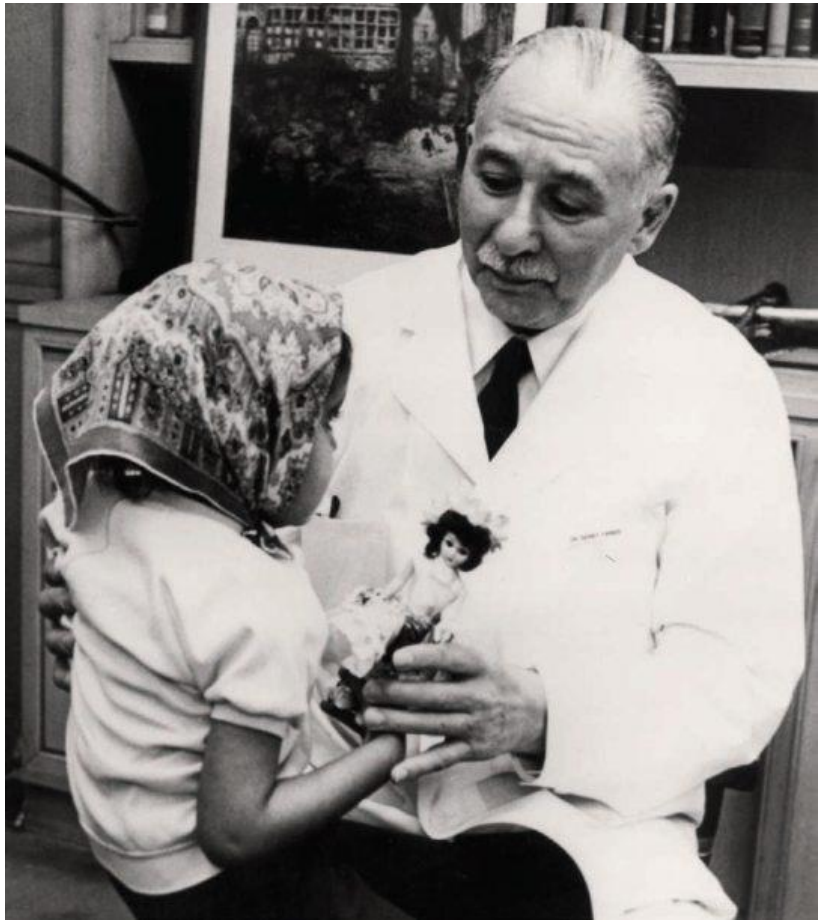
Males				Females		
Lung & bronchus	69,410	22%		Lung & bronchus	62,470	22%
Prostate	34,130	11%		Breast	43,600	15%
Colon & rectum	28,520	9%		Colon & rectum	24,460	8%
Pancreas	25,270	8%		Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%		Ovary	22,950	5%
Leukemia	13,900	4%		Uterine corpus	12,940	4%
Esophagus	12,410	4%		Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%		Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%		Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%		Brain & other nervous system	8,100	3%
All Sites	**319,420**	**100%**		**All Sites**	**289,150**	**100%**

- Cancer is the second leading cause of death in the US.
- >25% of the US population will be diagnosed with a type of cancer during their lifetime.
- In 2021, 1,898,160 new cancer cases and 608,570 cancer deaths are projected to occur in the United States

Siegel et al, 2021

History of Chemotherapy

- During WWII, *nitrogen mustard* was developed, and found to work against *lymphoma* (studies by Goodman and Gilman).
- Sidney Farber studied *aminopterin*, which interferes with folic acid metabolism necessary for DNA replication.
- After Farber, the era of chemotherapy has begun.
- About a quarter of cancer patients will be cured solely by *surgery*.
- Most cancer patients will receive systemic *chemotherapy* and only 10% will be cured or have a prolonged remission.



Sidney Farber, Boston, MA

History of Chemotherapy

SOME OBSERVATIONS ON THE EFFECT OF FOLIC ACID ANTAGONISTS ON ACUTE LEUKEMIA AND OTHER FORMS OF INCURABLE CANCER

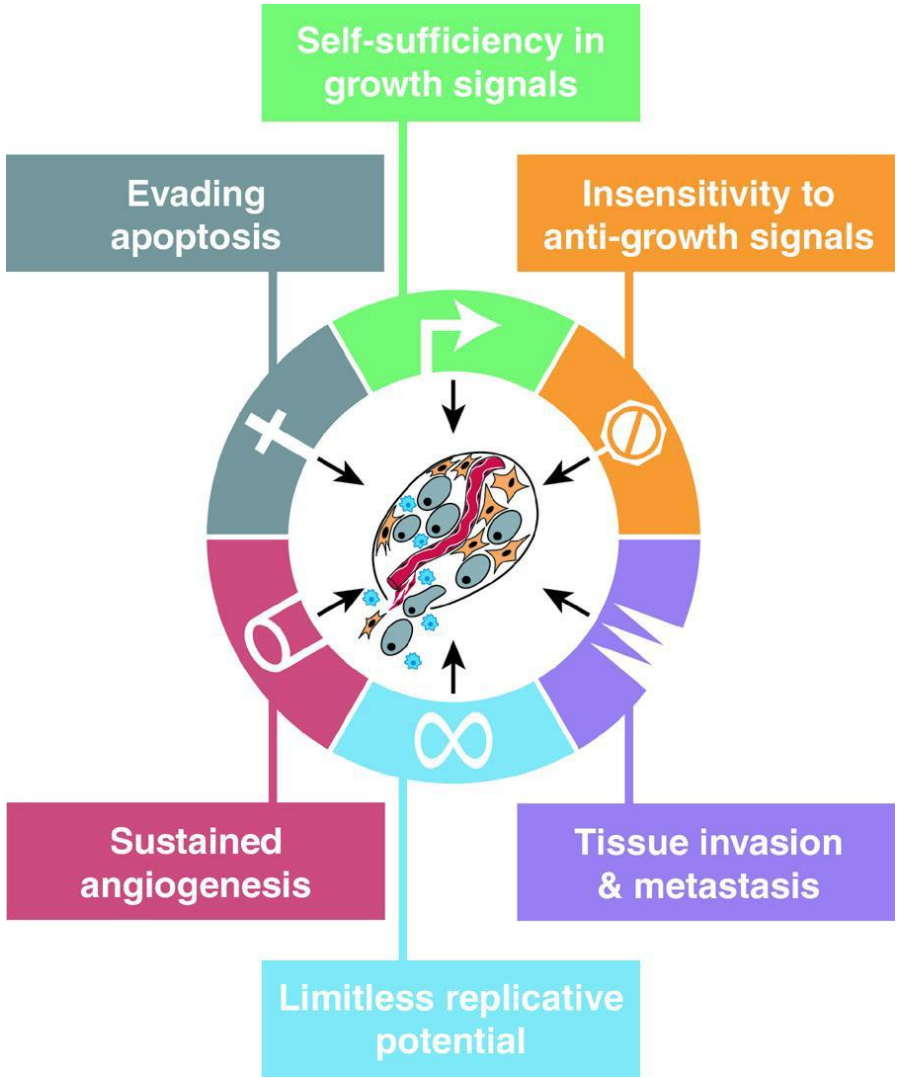
By Sidney Farber, M.D.

THE PRODUCTION of temporary remissions in the course of acute leukemia in children by the administration of the compound, 4-aminopteroylglutamic acid (aminopterin)[1,2]—a biologic antagonist to folic acid*—has raised a number of theoretic and practical questions. Confirmation of this finding has been reported from several sources[3]; temporary remissions equally impressive have been obtained in adults with acute leukemia by Dameshek.[4]

It is the purpose of this paper to summarize briefly the status of our observations† on the action of folic acid antagonists on acute leukemia and other incurable forms of cancer for the interest of those now working with these agents, to state the nature of some of the problems which have arisen, and to indicate some directions of further research.

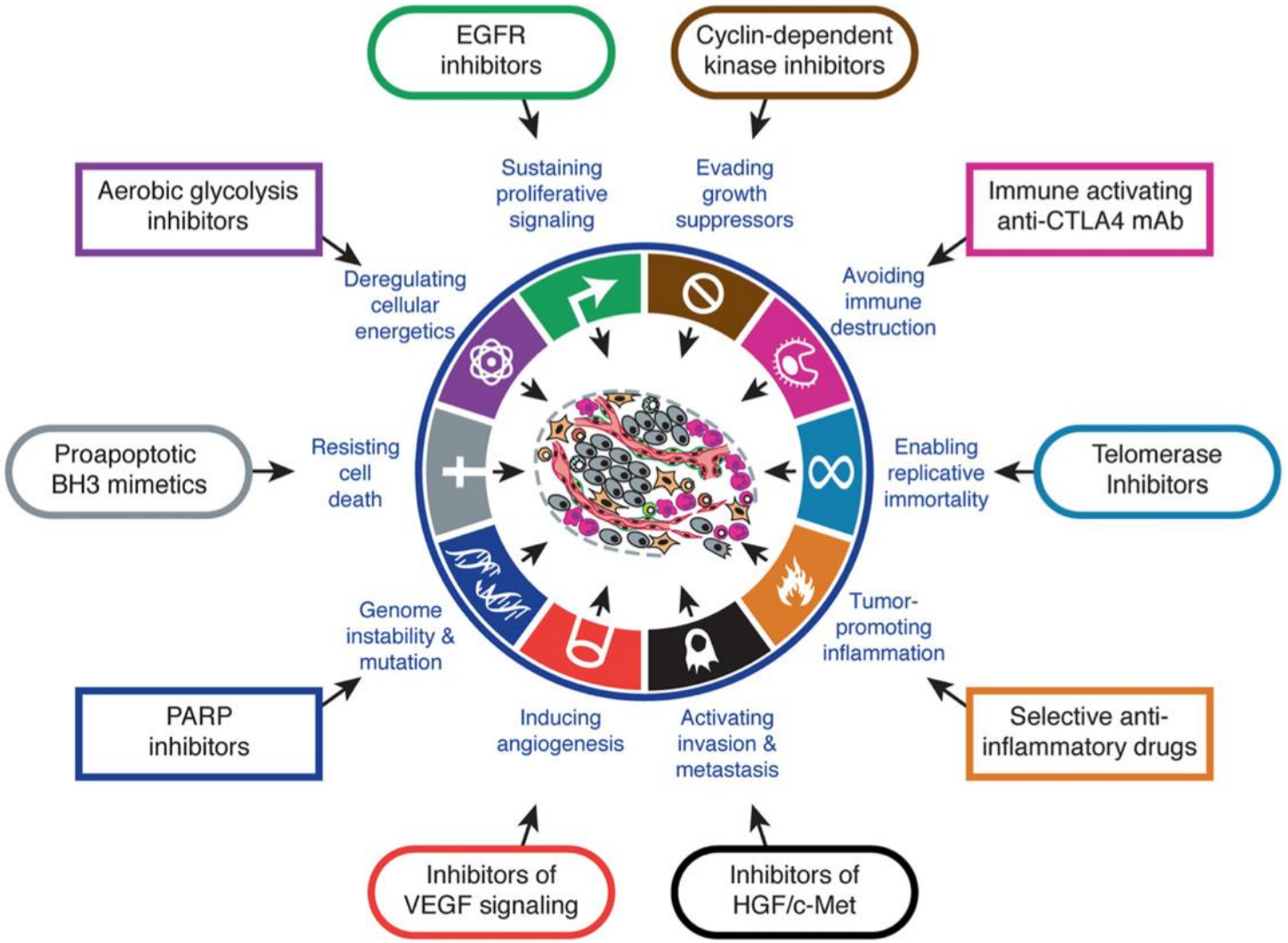
The demonstration by Lewisohn and his colleagues[5] of the occurrence of complete regression in about one-third of single spontaneous breast cancers in three different strains of mice treated with fermentation L. casei factor, later shown to be pteroyltriglutamic acid (Hutchings et al.[6]) and the subsequent synthesis of this compound by SubbaRow and his co-workers[7] led to our study of the effect of pteroyltriglutamic acid on incurable cancer in man. Among the patients so treated were 11 children with acute leukemia. The occurrence of what we called an "acceleration phenomenon" in the viscera and bone marrow of these patients and an experience with folic acid deficiency experimentally produced in the rat suggested that it would be worth while to ascertain if this acceleration phenomenon might be employed to advantage in the treatment of acute leukemia in children, either by the use of radiation or nitrogen mustard therapy after pretreatment with folic acid or conjugates of folic acid, or by the immediate use of folic acid inhibitors or

Hallmarks of Cancer



Hanahan and Weinberg, 2000

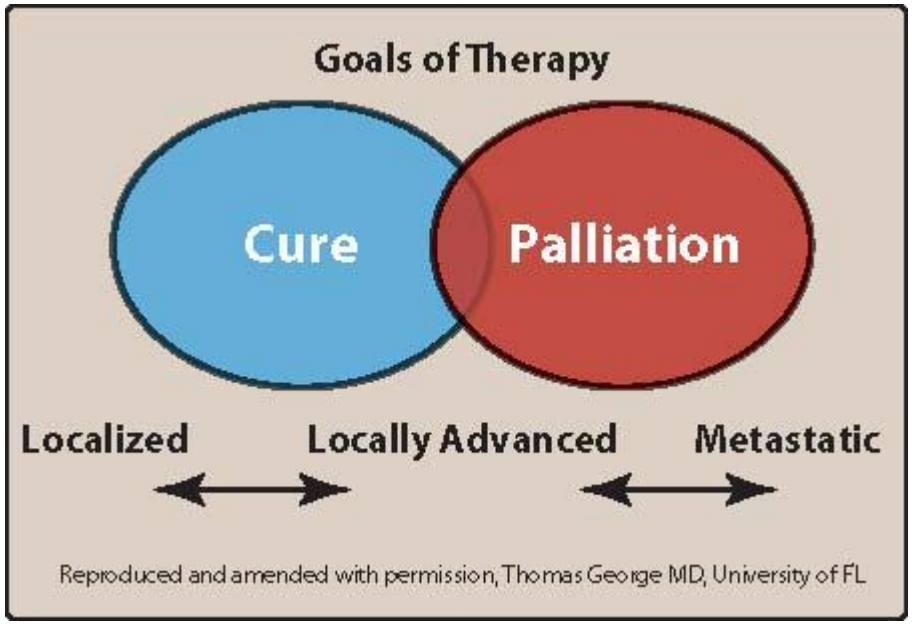
Hallmarks of Cancer



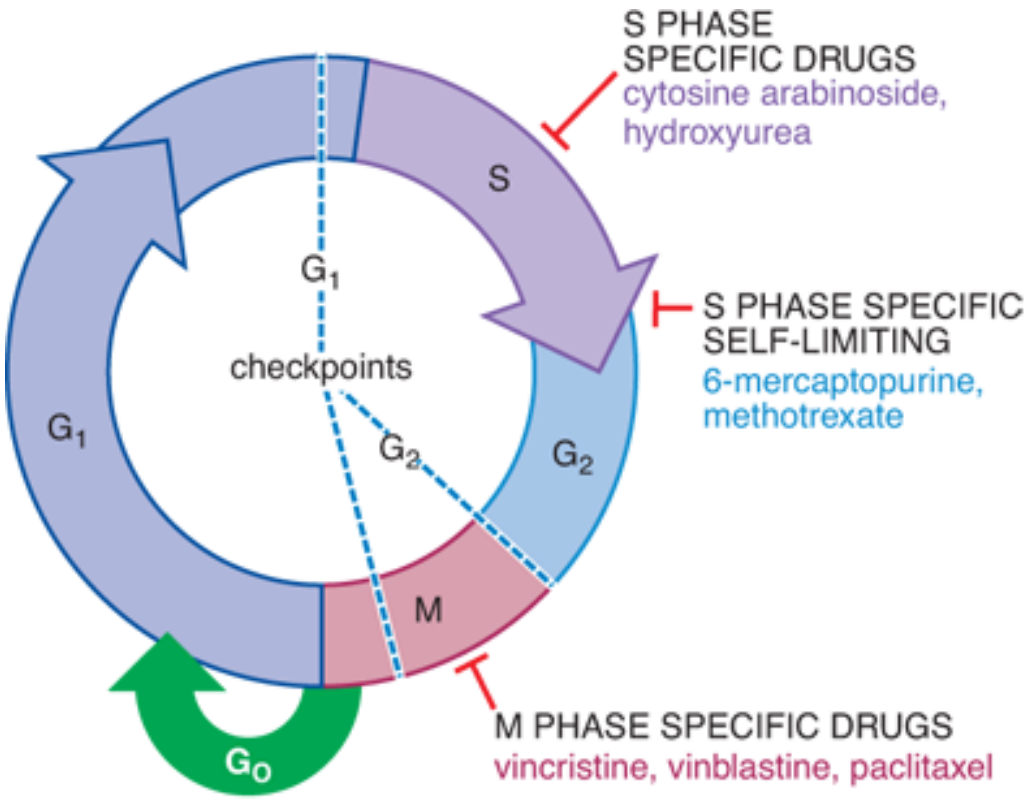
Hanahan and Weinberg, 2011

Principles of Antineoplastic Chemotherapy

- **Main goal**: to induce cell death/growth arrest (apoptosis, necroptosis, senescence, cytotoxic autophagy, mitotic catastrophe….) in tumor cells.
  - Cure, long-term, disease-free survival
  - Debulking, treating cancer as a chronic disease
  - Palliative treatment
- Selective toxicity?
- Recent therapies aim at utilizing the immune system in eliminating tumor cells.

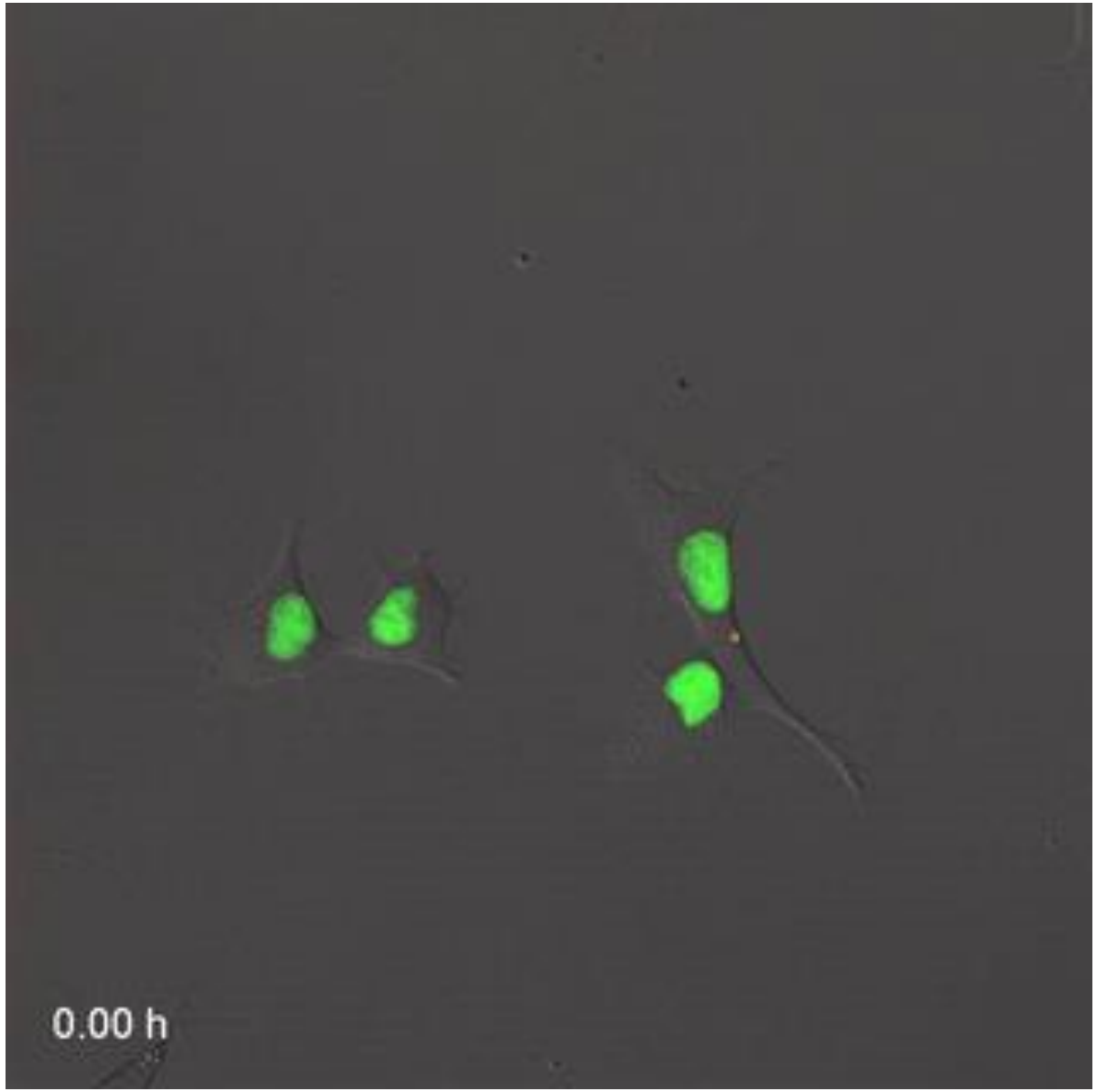


Understanding the cell cycle



- Neoplasms with high percentage of proliferation are, most susceptible to cycle-specific therapy
- Slow growing tumors e.g., CRC, NSCLC are less responsive to cycle-specific drugs

Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

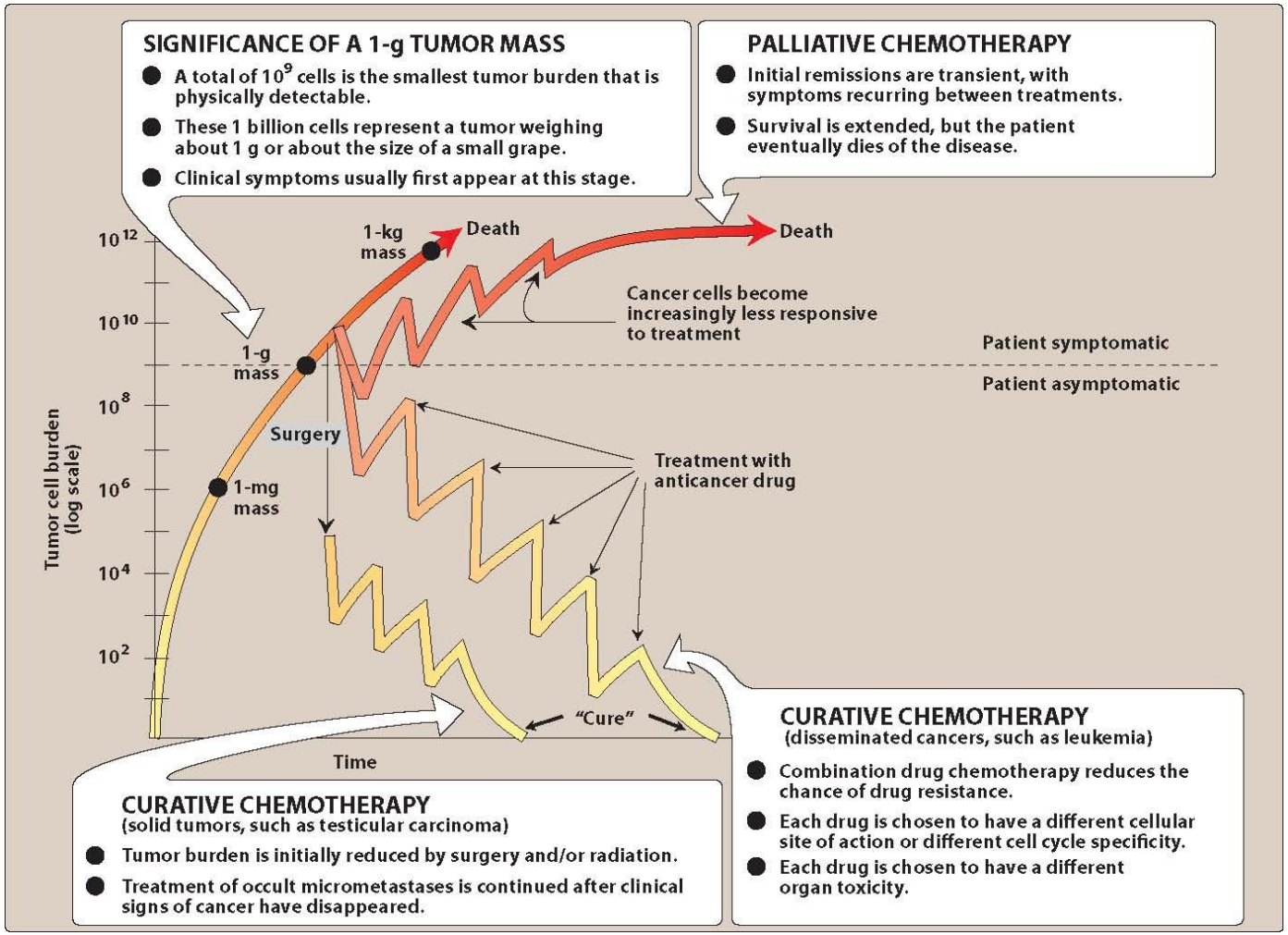


By Erin Rod - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=50866822

Log-kill phenomenon

- Destruction of cancer cells by chemotherapeutic agents follows **first-order kinetics** *OR* **log kill phenomenon.**

A given dose of drug destroys a constant fraction of cells



Log-kill phenomenon

- Example: Diagnosis of leukemia is made at 10^9 leukemic cells
- If treatment results in 99.999% killing → 0.001% remain
- This is equal to log kill 5
- State of remission (asymptomatic)
- Comparison with antibiotics?

Cell Fraction Killed	Surviving Cell Fraction	Log Surviving Cell Fraction	Log Kill
.9	.1	-1	1
.99	.01	-2	2
.999	.001	-3	3
.999999999	.000000001	-9	9

Chemotherapy: anticancer vs. antimicrobial

- **Selective Toxicity**

-Biological processes (DNA synthesis, protein synthesis, metabolism, etc) in bacteria, fungi, parasites, etc are essentially different from host cells.

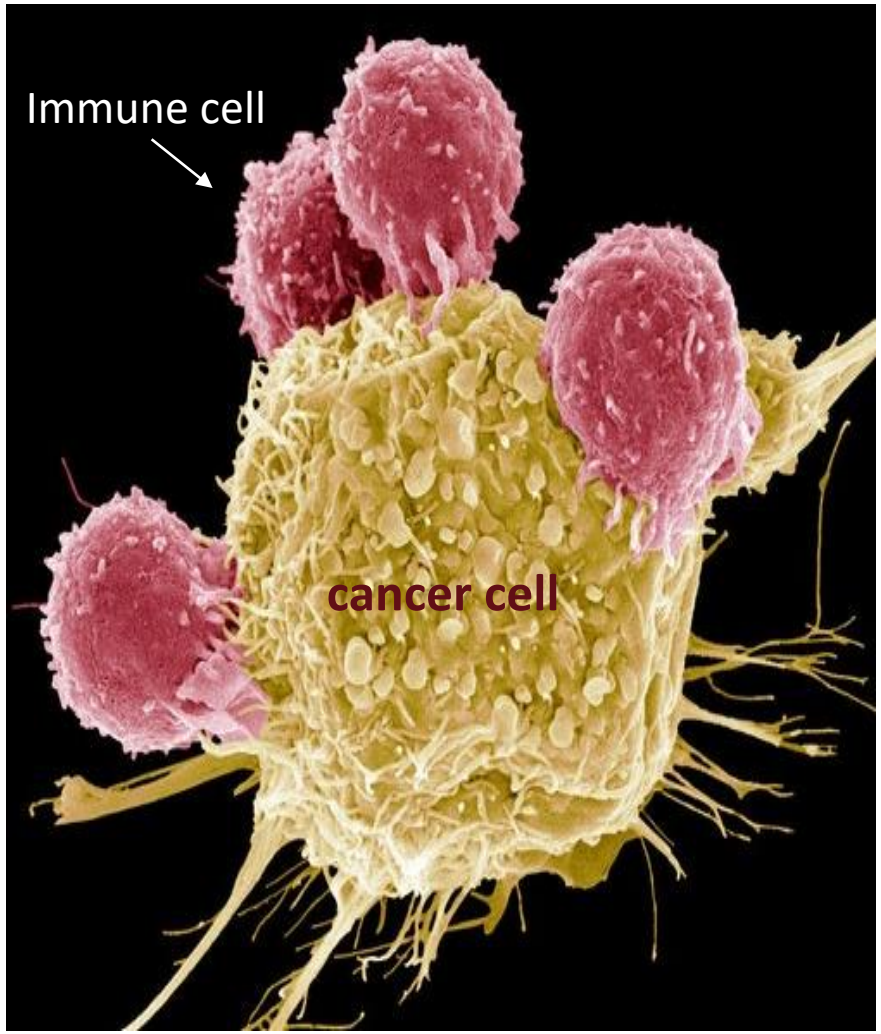
-Cancer cells are transformed host cells and their metabolic processes are similar (only altered).

- **Immune system**

-The host immune system targets and eliminates invading, foreign microorganisms.

- **Diagnostic Complexity**

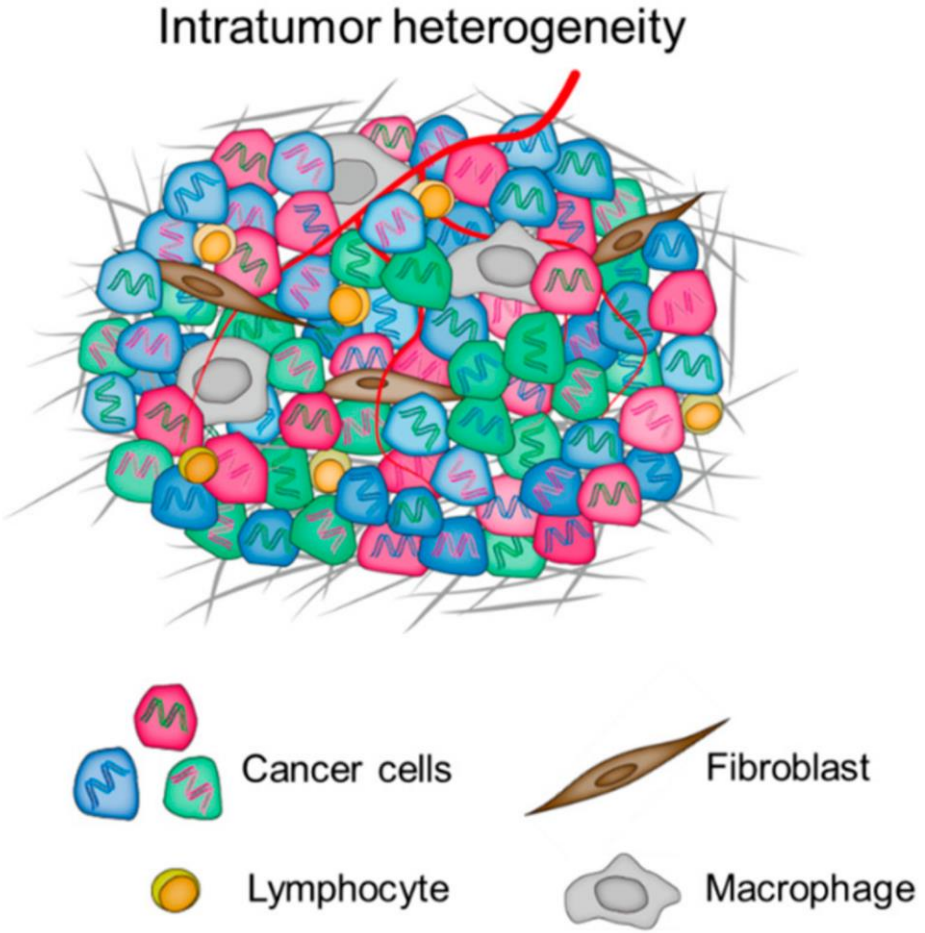
- Cancer early detection and diagnosis is challenging.



Treatment Protocols

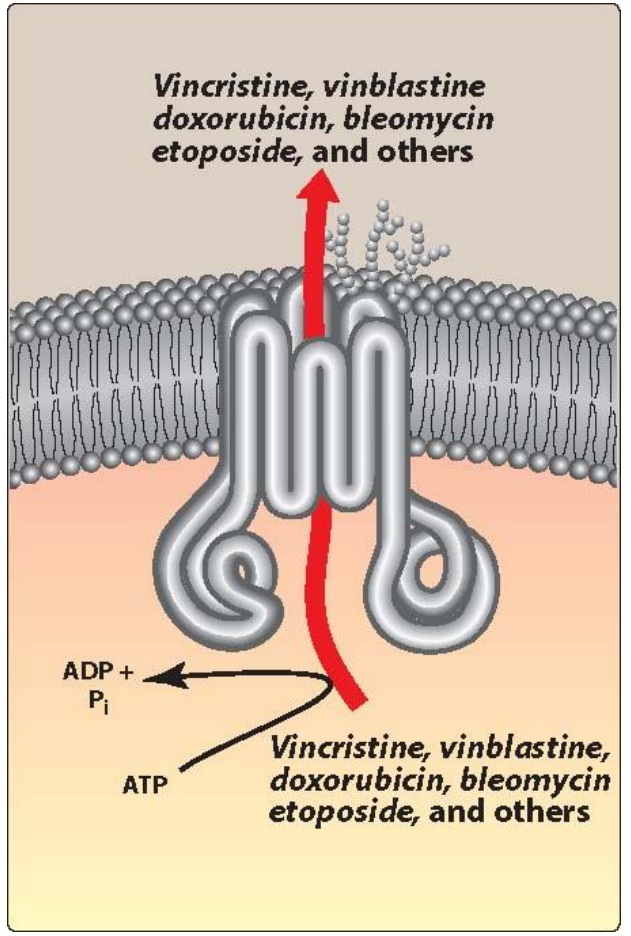
Combination Chemotherapy

- Chemotherapies with different mechanisms of action are usually combined
- More successful than monotherapy
  - ❖ Additive/synergistic effects – maximal cell killing
  - ❖ Covers broader range of cell lines (heterogeneous tumor population)
  - ❖ Delay resistance
  - ❖ Non-overlapping host toxicities (different adverse effects)



Resistance Against Antineoplastic Chemotherapy

- **Inherent resistance**
  - ❑e.g., melanoma cells
- **Acquired resistance**
  - ❑Several mechanisms:
    1. P-glycoprotein efflux pump (multi-drug)
    2. Specific to antineoplastic agent
  - ❑After prolonged administration of suboptimal doses

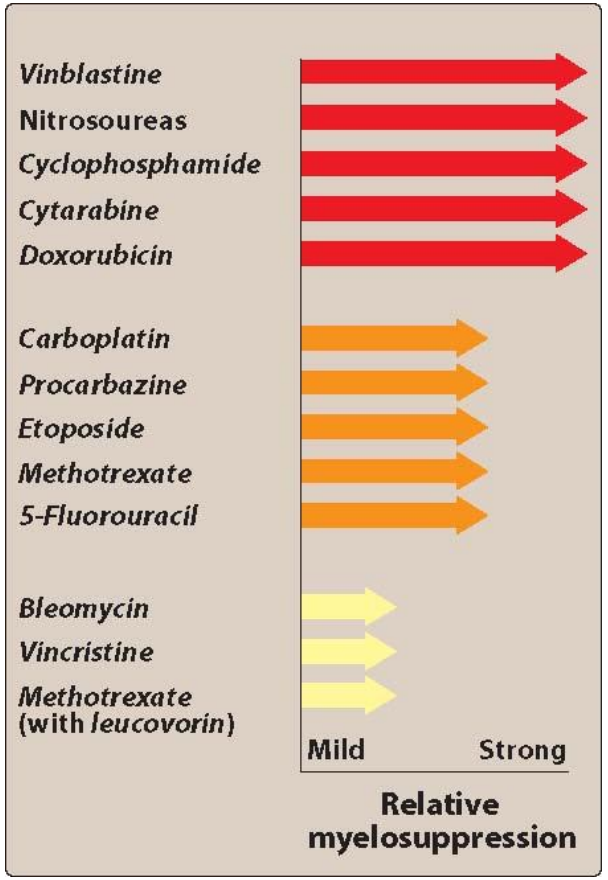


How is Antineoplastic Given?

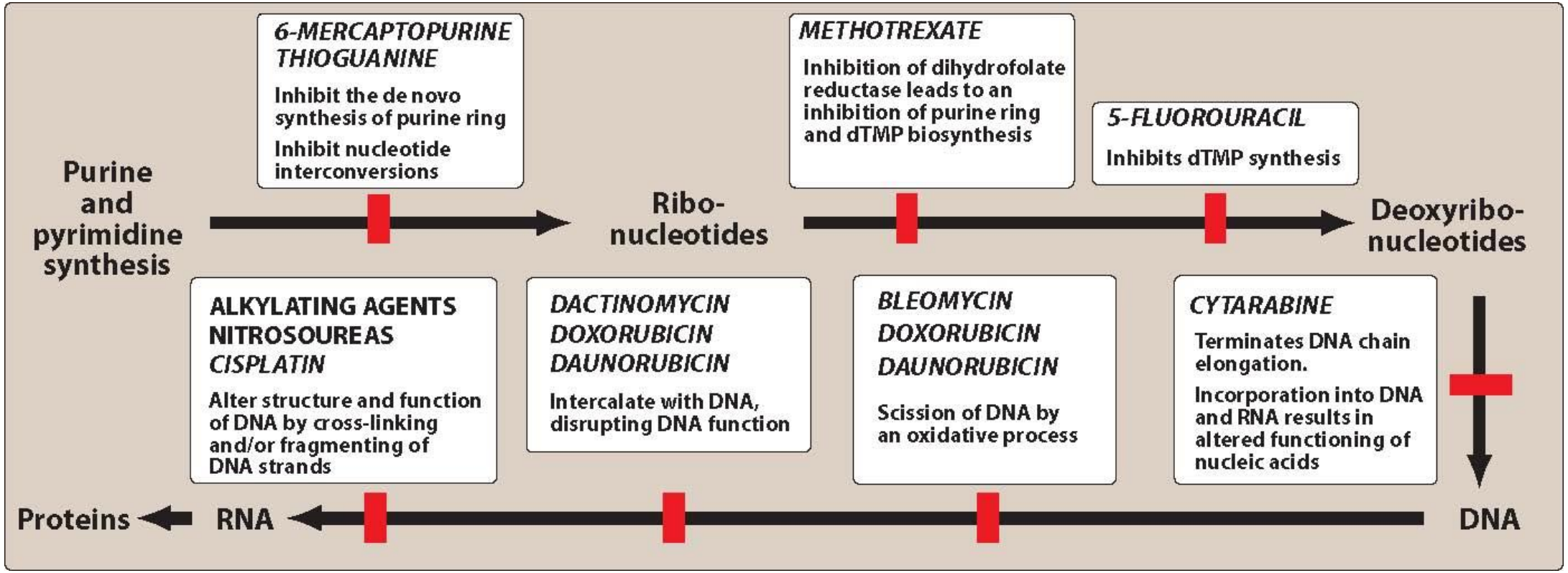
- Adjuvant chemotherapy:
  - Chemotherapy given after surgery or irradiation to destroy micrometastasis & prevent development of secondary neoplasm.
- Neo-adjuvant chemotherapy:
  - Chemotherapy given before surgery or radiotherapy in order to diminish the volume of large primary neoplasm

Adverse Effects of Antineoplastic Chemotherapy

- Rapidly proliferating non-tumor cells are most susceptible:
  - ❑Buccal mucosal cells, bone marrow, gastrointestinal mucosa, hair follicles…)
- **Examples:**
  - ➢Chemotherapy-Induced Nausea/Vomiting
  - ➢Alopecia
  - ➢Bone Marrow Suppression
  - ➢Chemotherapy-Induced Peripheral Neuropathy
  - ➢Carcinogenesis
  - ➢Hypogonadism
  - ➢Teratogenicity
  - ➢Organ-specific Adverse Effects



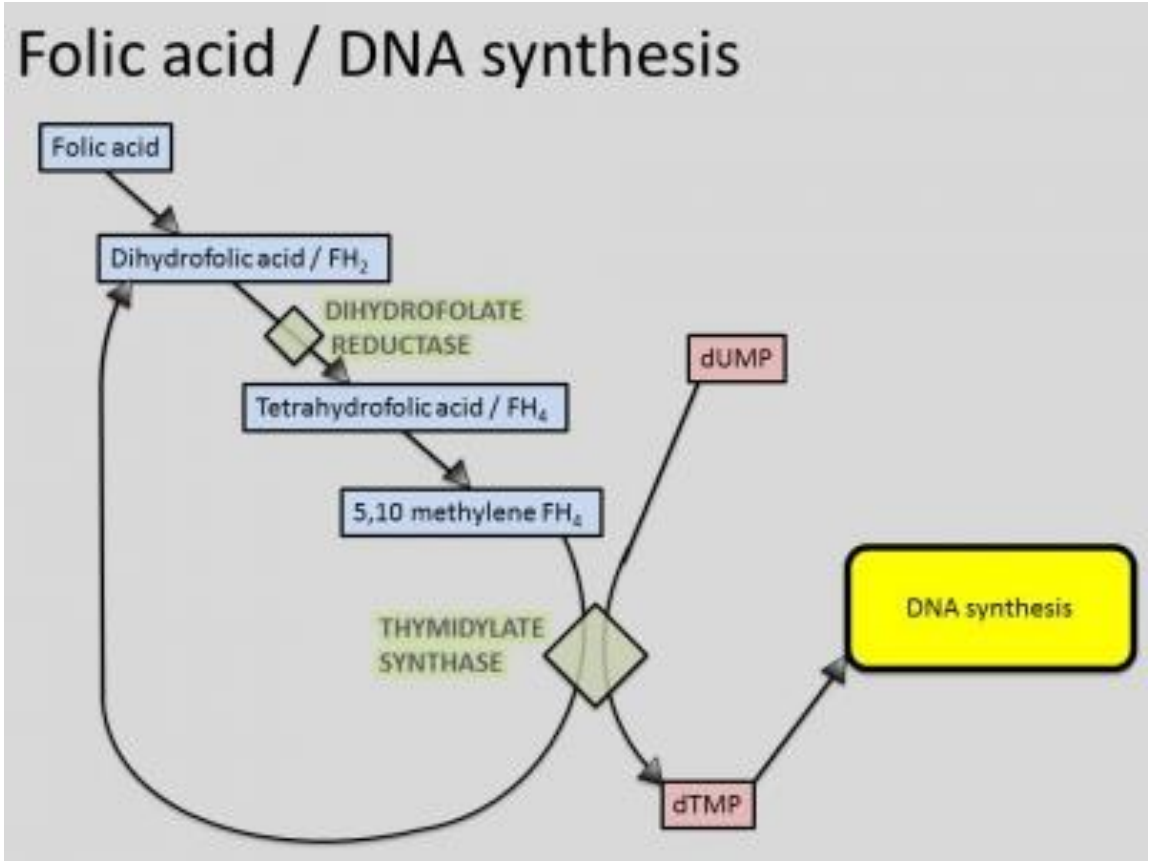
Most Common Conventional Chemotherapy



Antimetabolites

Antimetabolites

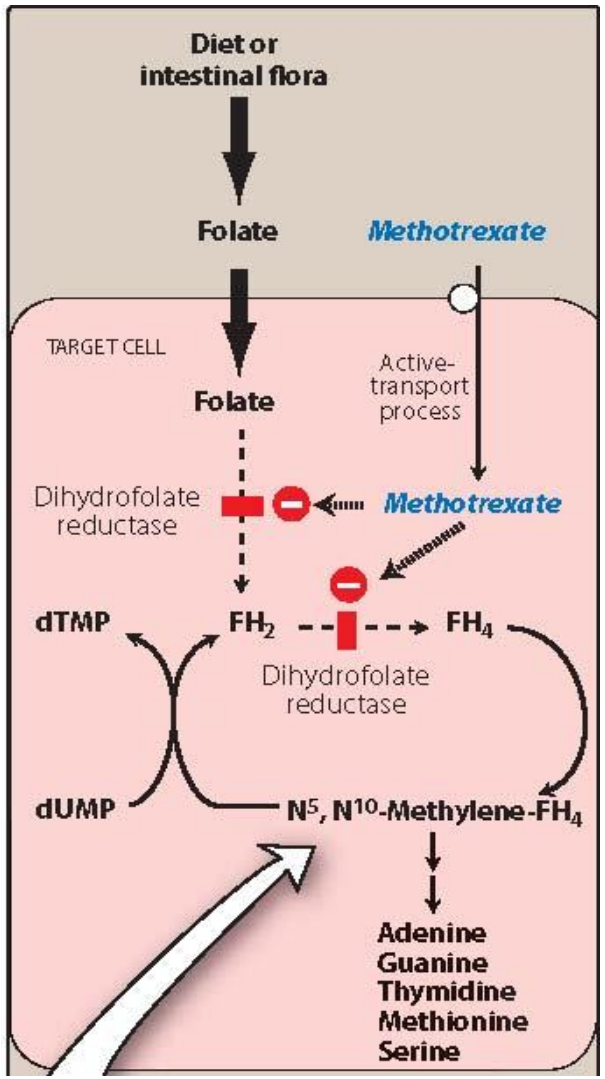
Folic acid plays a pivotal role in purine and thymidylate synthesis involving the transfer of one-carbon units, thus, is essential for cell replication



Methotrexate and pemetrexed

- *Methotrexate* is structurally related to folic acid
- **Mechanism of action:** INHIBITS MAMMALIAN DIHYDROFOLATE REDUCTASE (DHFR)
- **Cell cycle specific:** S phase

Pemetrexed inhibits DHFR and thymidylate



Methotrexate

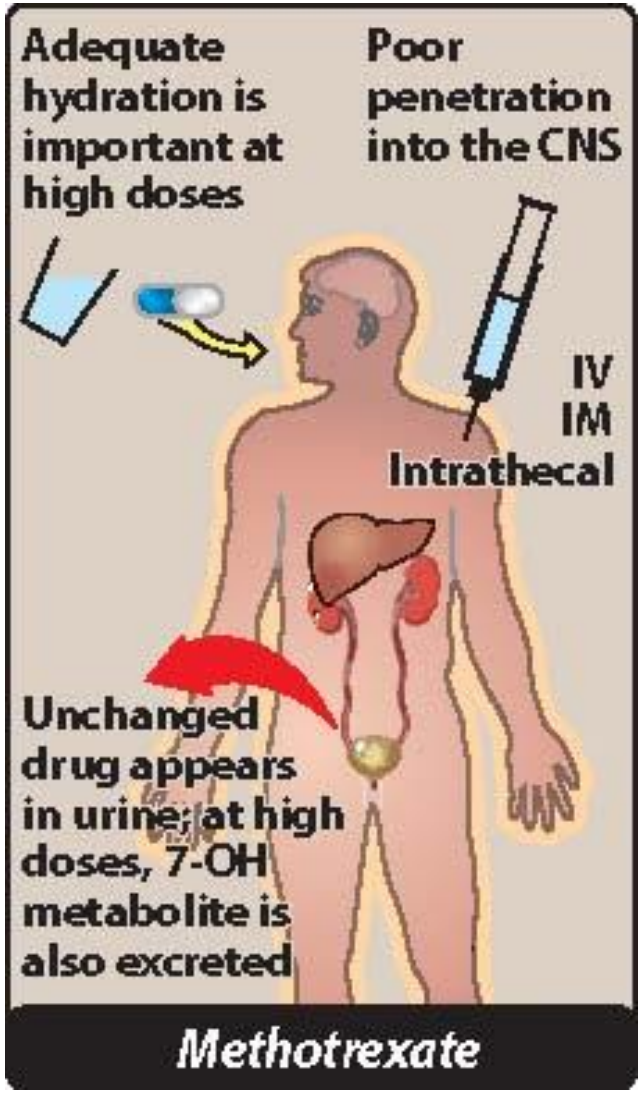
- **Therapeutic uses (methotrexate):**

(in combination with other chemotherapies)

1. Acute lymphocytic leukemia
2. Burkitt lymphoma
3. Other cancers (breast, bladder and head and neck cancers ….)
4. Autoimmune diseases e.g., rheumatoid arthritis, Crohn's disease

Methotrexate

- Oral, IM, IV, intrathecal
- Poor penetrance across the BBB
- Metabolism: MTX undergo hydroxylation at 7th position to form 7-hydroxymethotrexate (less water soluble)
- Excretion of metabolites in urine



Methotrexate

- **Adverse effects:**

❑N/V/D

❑Cutaneous reactions/rash

❑Alopecia

❑Myelosuppression

❑Renal damage

❑Neurologic toxicities (if given intrathecally)

Reason for discontinuation	Discontinued methotrexate permanently (n)	Per cent of discontinuations (n = 46)	Per cent of all patients (n = 248)
Adverse effects	26	56.5%	10.4%
Gastrointestinal	6	13.0%	2.4%
Oral ulcers	3	6.5%	1.2%
Skin rash	3	6.5%	1.2%
Malaise	3	6.5%	1.2%
Pulmonary symptoms	3	6.5%	1.2%
Pneumonia	2	4.3%	0.8%
Nodules	2	4.3%	0.8%
Laboratory abnormalities	2	4.3%	0.8%
Other side effects	2	4.3%	0.8%
Inefficacy	15	32.6%	6.0%
Other reasons	5	10.9%	2.0%
Disease improved	3	6.5%	1.2%
Other diseases	1	2.2%	0.4%
Pregnancy	1	2.2%	0.4%

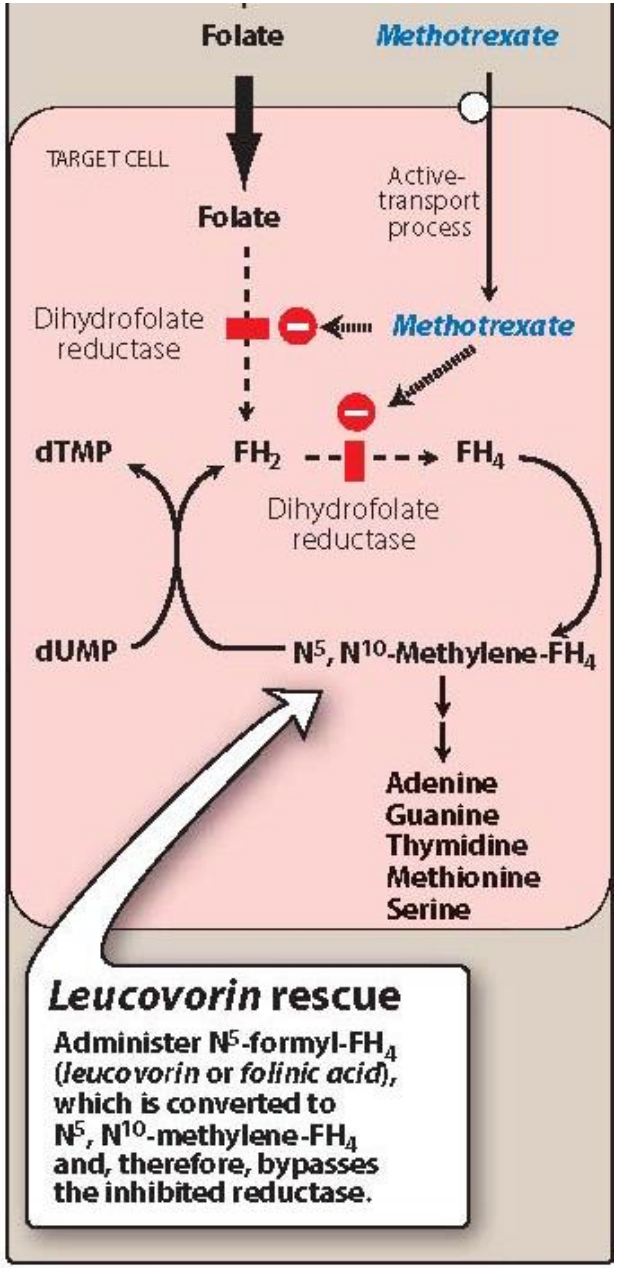
How to overcome the adverse effects of methotrexate?

A. Always administer with folic acid and vitamin B_{12} (to reduce GI/hematologic side effects)
B. Pretreatment with corticosteroids (to reduce cutaneous reactions)
C. Leucovorin

Leucovorin

- Leucovorin (folinic acid) is *tetrahydro* derivative of folic acid used to rescue normal, proliferating cells from the effects of methotrexate.

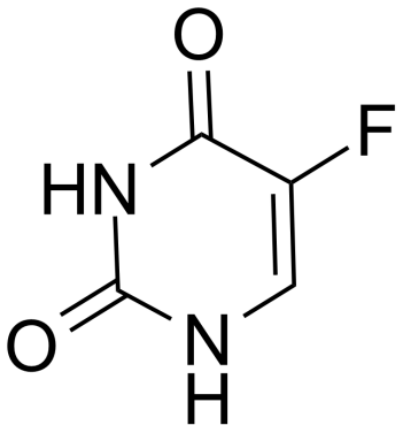
- Leucovorin is usually administered 24 hours after methotrexate so that it does not interfere with the therapeutic effect of methotrexate.



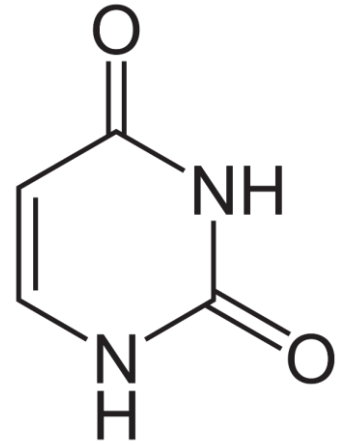
5-Fluorouracil

- Pyrimidine analog
- **Therapeutic Uses**

1. Slow-growing solid tumors. e.g. colorectal, breast, gastric cancers….
2. Topically for superficial basal cell carcinoma



5-Fluorouracil

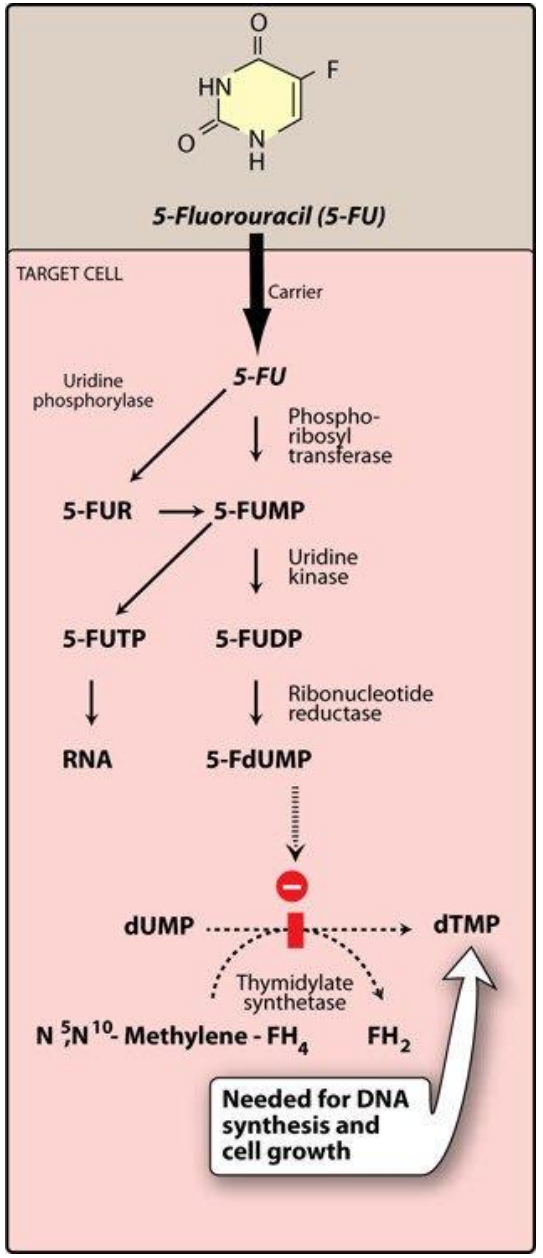


Uracil

5-Fluorouracil

Mechanism of action

- 5-FU itself has no antitumor effect
- Enters tumor cells through carrier-mediated transport system
- Converted to 5-FdUMP
- Inhibits thymidylate synthase



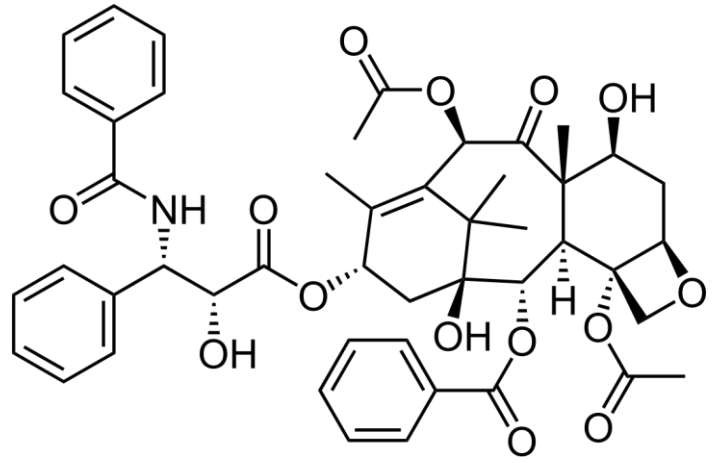
Microtubule Inhibitors

Paclitaxel and Docetaxel

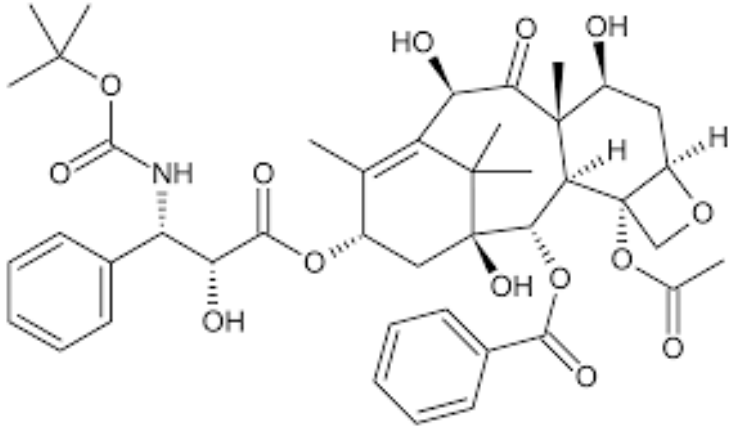
- Semisynthetic

Therapeutic Uses:

1. Non-Small Cell Lung Cancer (NSCLC)
2. Ovarian Cancer
3. Prostate Cancer
4. Breast Cancer
5. GI cancers

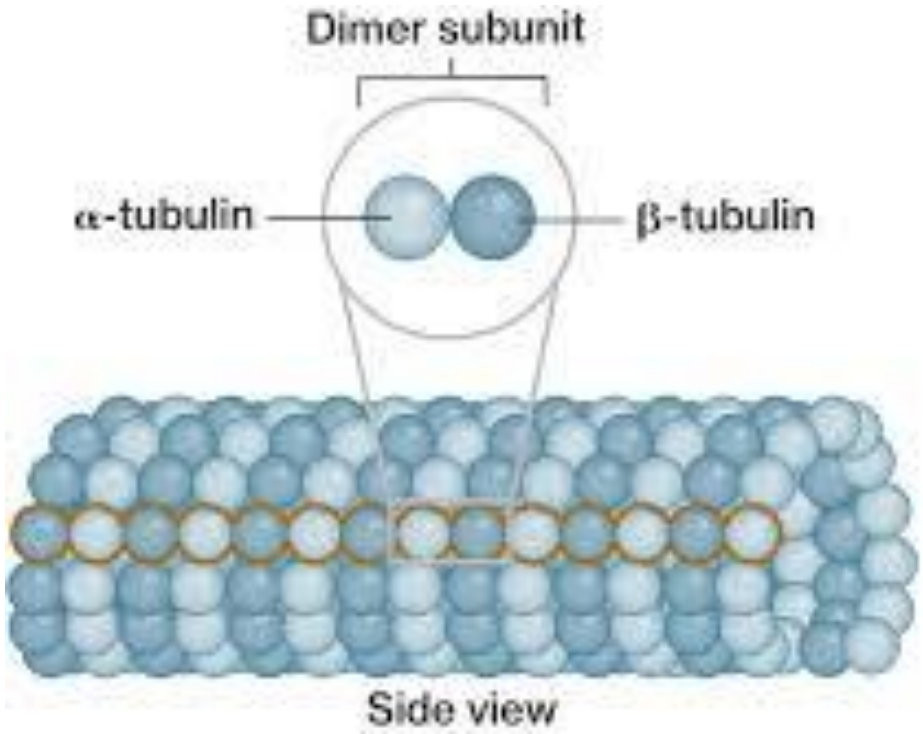


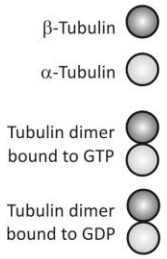
Paclitaxel

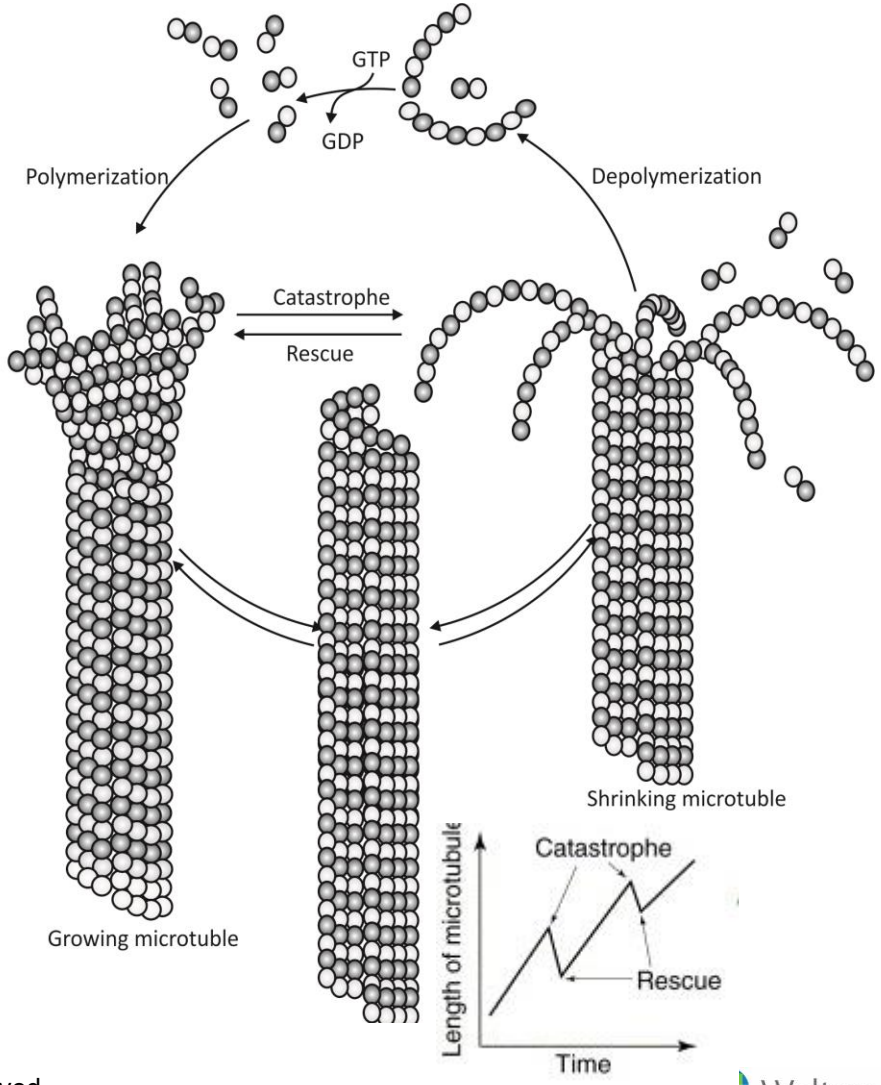


Docetaxel

Microtubules

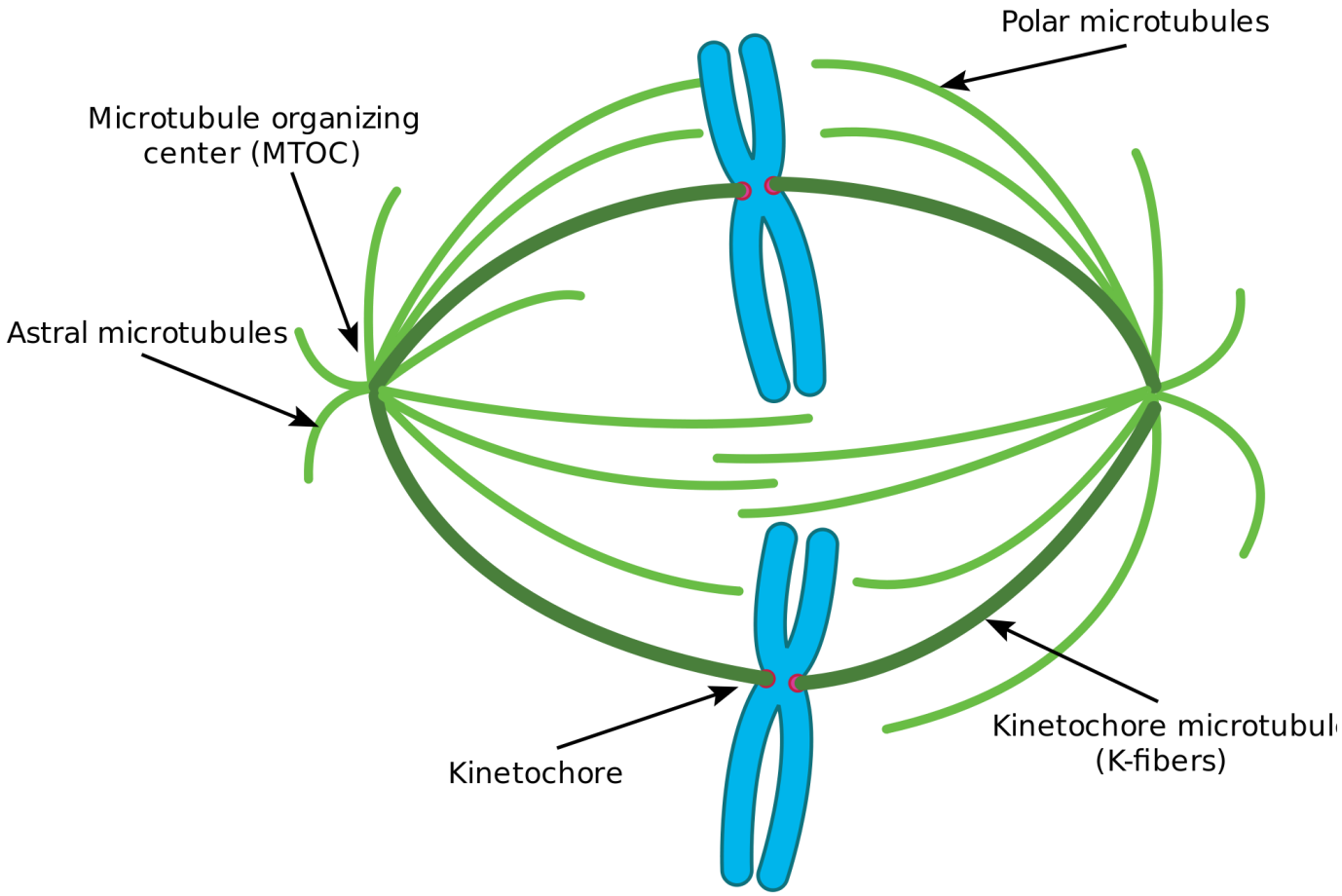




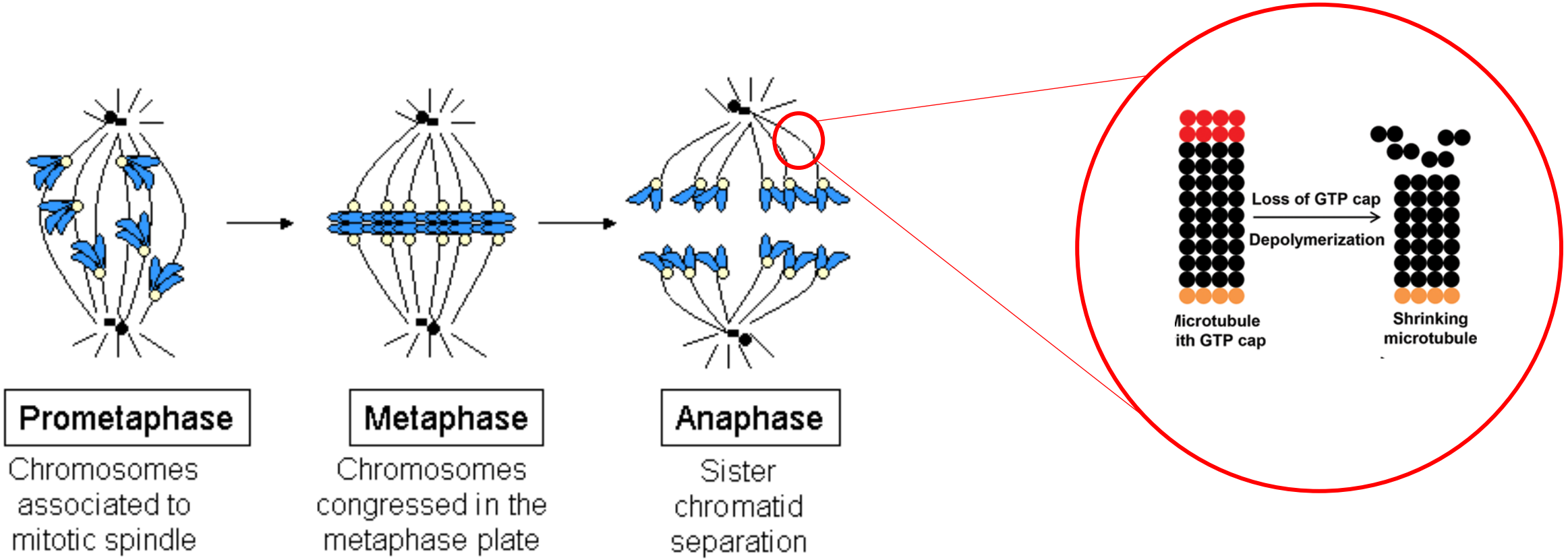


The Mitotic Spindle

- Consists of chromatin + microtubule system
- Essential for equal partitioning of DNA into two daughter cells
- Which phase of the cell cycle?



The Mitotic Spindle

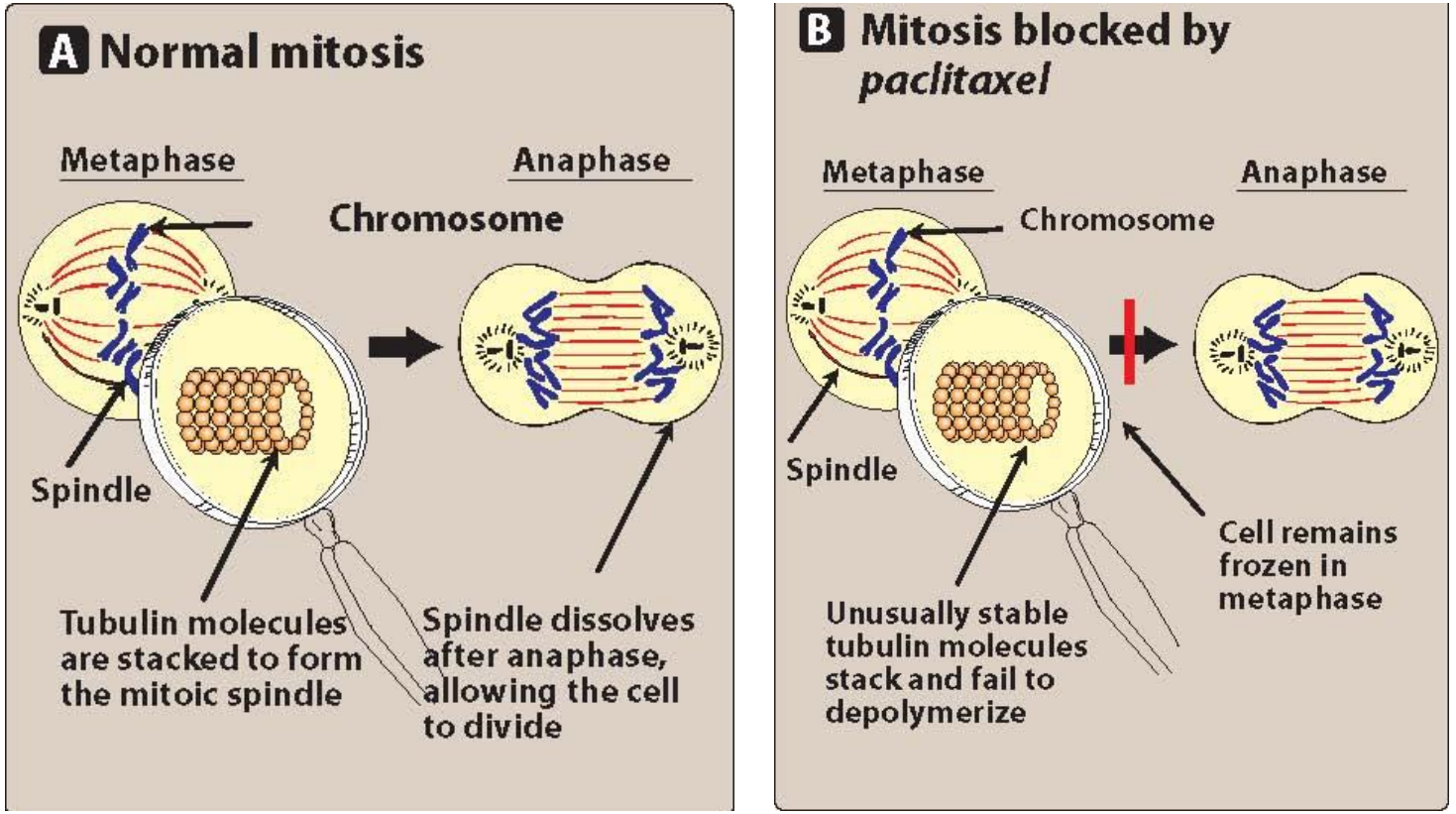


https://www.youtube.com/watch?v=Xw1Dac39QQY

Paclitaxel and Docetaxel

Mechanism of Action

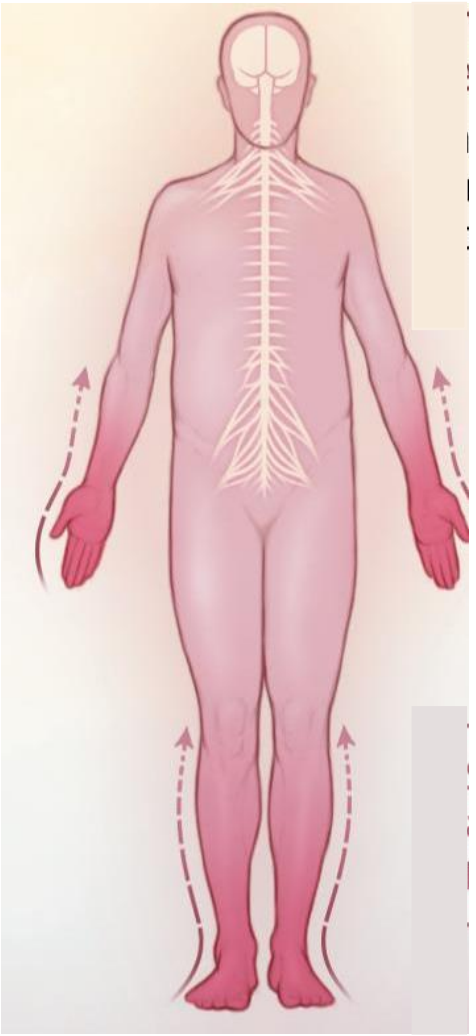
- Cell-cycle specific
- Promote the polymerization and stabilization of the polymer rather than disassembly
- Forming microtubules are overly stable and nonfunctional
- Failure of chromosomal separation
- Cell death



Paclitaxel and Docetaxel

Adverse effects

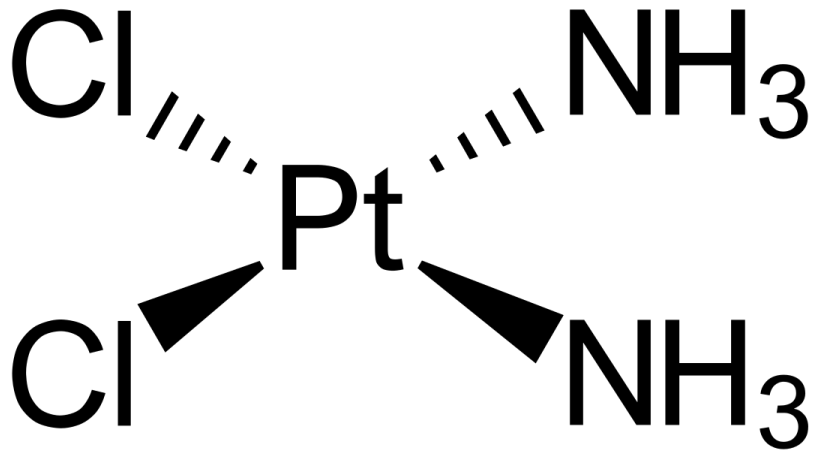
- Neutropenia, leukopenia
- Chemotherapy-Induced Peripheral Neuropathy
- Hypersensitivity
- Alopecia
- Arthralgia/myalgia
- Renal impairment



Platinum Coordination Complexes

Cisplatin, Carboplatin and Oxaliplatin

- Cisplatin is the prototype of this drug family
- Cisplatin has synergistic effect with radiation/other chemotherapy
- Effective against solid tumors: testicular, lung, ovarian, bladder
- Carboplatin is used in patients with kidney dysfunction, or prone to neurotoxicity
- Oxaliplatin used for ovarian and colorectal cancers



Cisplatin

Cisplatin, Carboplatin and Oxaliplatin

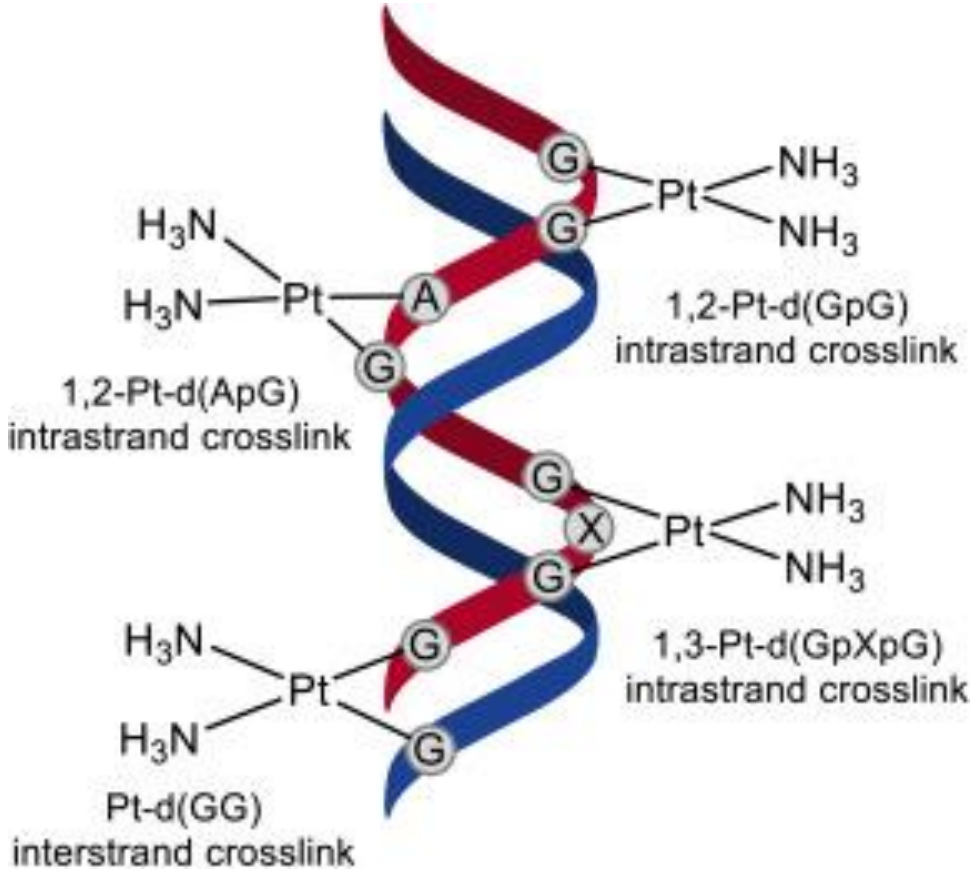
DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Cisplatin	IV, IP, IA	Neurotoxicity, myelosuppression, ototoxicity, N, V, electrolyte wasting, infusion reaction, nephrotoxicity	Anticonvulsants	CBC, CMP, electrolytes, hearing	Aggressive pre- and posthydration required, high incidence of nausea and vomiting
Carboplatin	IV, IP, IA	Myelosuppression, N, V, infusion reaction	Aminoglycosides	CBC	Dose calculated using AUC
Oxaliplatin	IV	Neurotoxicity, N, V, infusion reaction, hepatotoxicity, myelosuppression	*Warfarin*	CBC, neurologic function, hepatic function	Cold-related and cumulative peripheral neuropathy

IV=intravenous; IP=intraperitoneally; IA=intraarterially; AUC=area under the curve; N=nausea; V=vomiting; CBC=complete blood count; CMP=complete metabolic panel.

Cisplatin, Carboplatin and Oxaliplatin

Mechanism of action

- These drugs work as alkylating agents
- Bind to guanine in DNA, forming inter- and intrastrand cross-links
- The resulting lesion inhibits DNA/RNA polymerases
- Non-cell cycle-specific



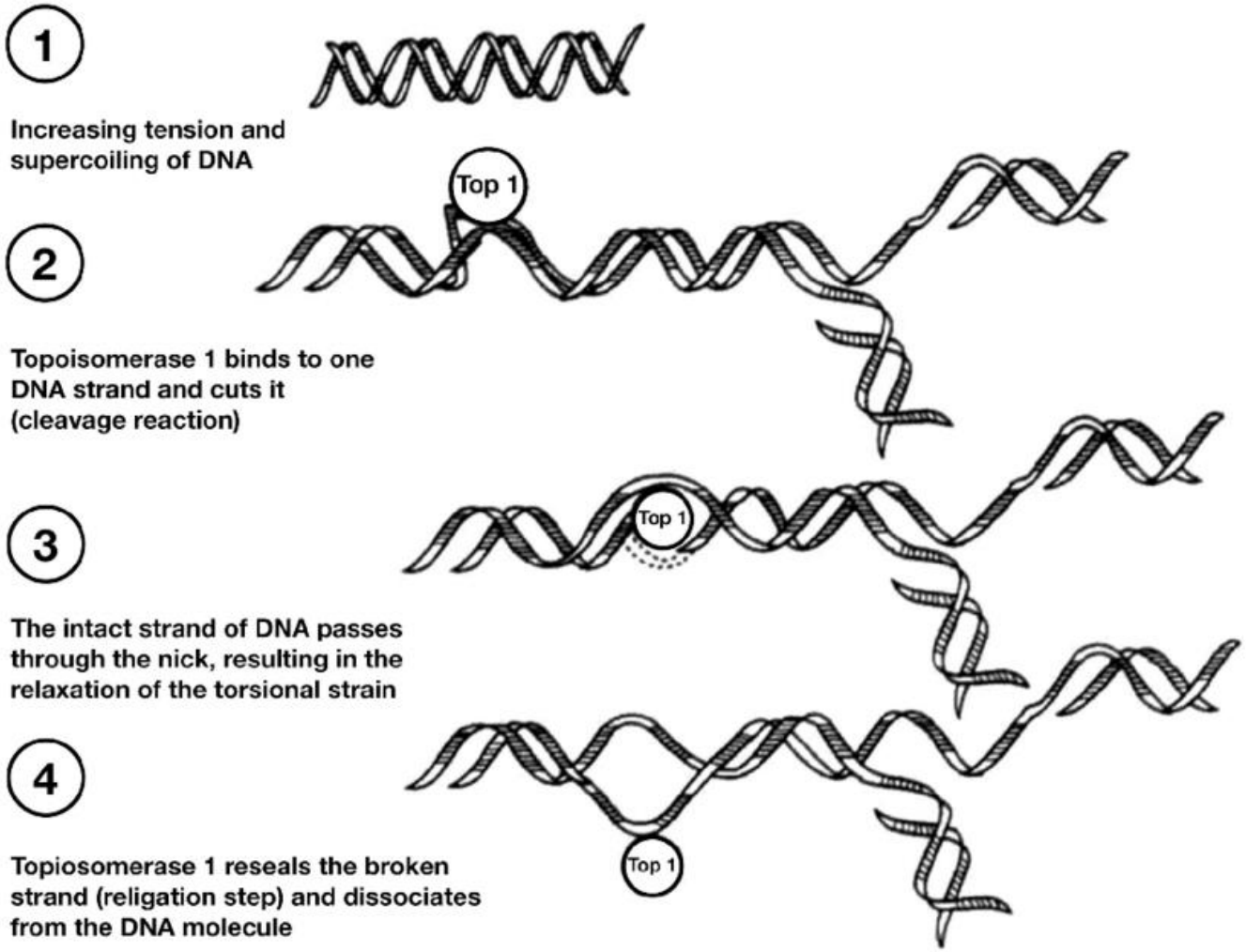
Cisplatin, Carboplatin and Oxaliplatin

Adverse effects

- Severe nausea and vomiting (Chemotherapy-Induced Nausea and Vomiting)
- Nephrotoxicity (cisplatin), prevented by excessive hydration
- Ototoxicity
- Myelosuppression
- Cold-induced peripheral neuropathy (oxaliplatin)
- Hepatotoxicity
- Hypersensitivity

Topoisomerase Poisons

Topoisomerase I

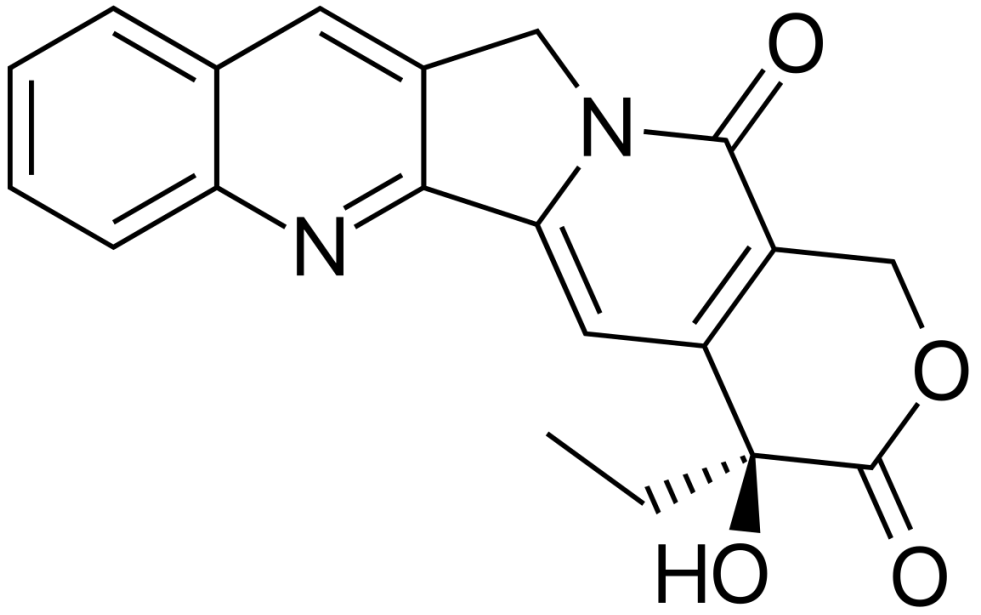


Camptothecins

- Camptothecin, irinotecan, topotecan
- Semisynthetic

Therapeutic uses

1. Metastatic ovarian cancer (topotecan)
2. Irinotecan + 5-FU for colorectal carcinoma

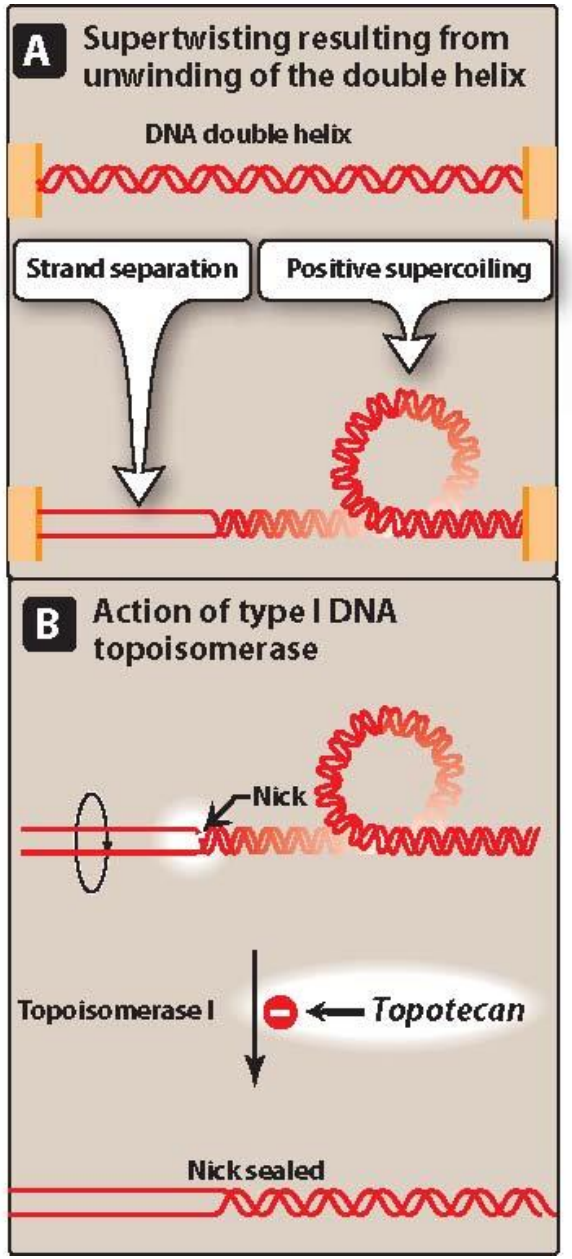


Camptothecin

Camptothecins

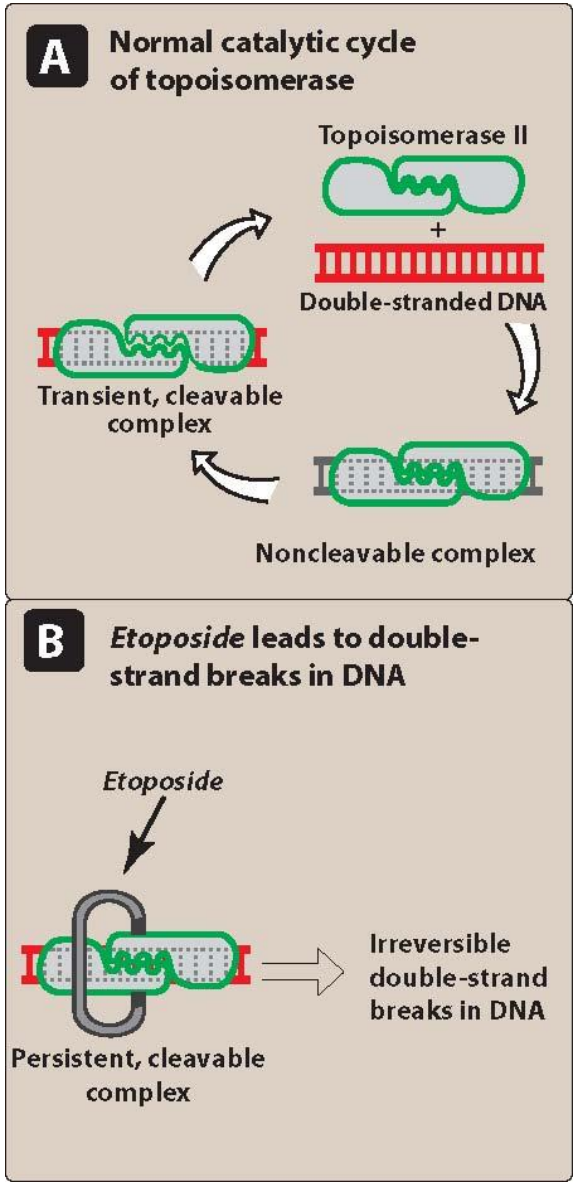
Mechanism of action

- Topoisomerase I inhibitors
- Cause single-stranded breaks
- S-phase specific
- Irinotecan metabolite is 1000-folds more potent



Etoposide

- Semisynthetic derivative of podophyllotoxin
- Topoisomerase II inhibitor
- Causes irreversible double-stranded breaks
- Used for lung cancer, testicular cancer
- Causes myelosuppression



Targeted Therapy

How Antibodies Are Produced?

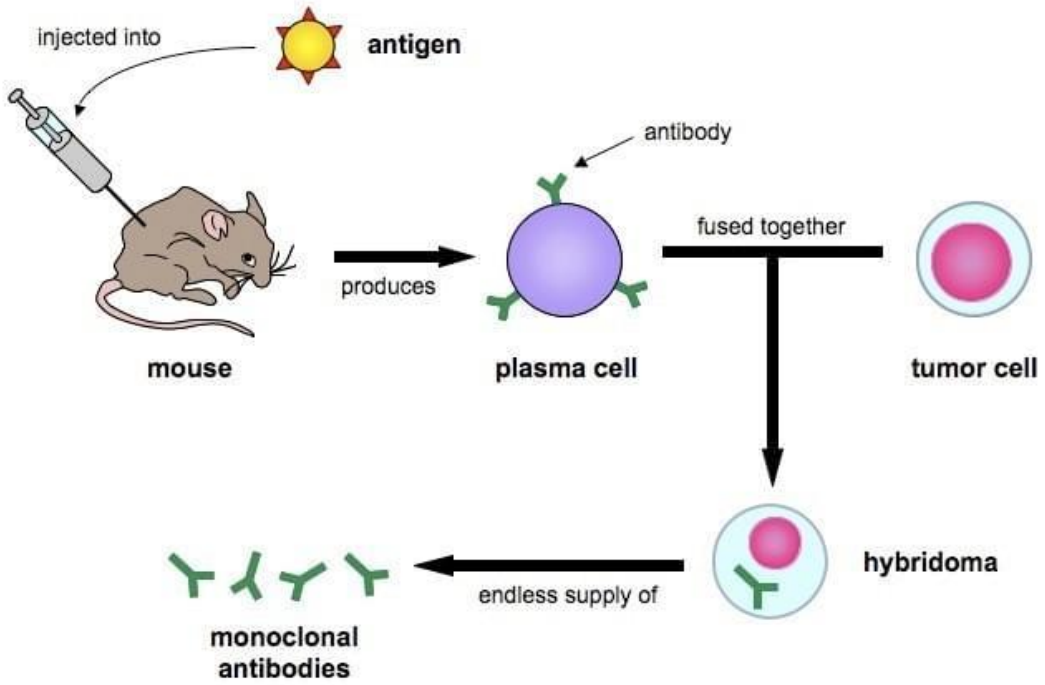
- Immunization of horses/rabbits with human lymphoid cells

  → mixture of polyclonal and monoclonal antibodies

- *Hybridoma*: injecting an antigen in a mouse then fusing mouse antibody-producing cells with tumor cells

  → monoclonal antibodies

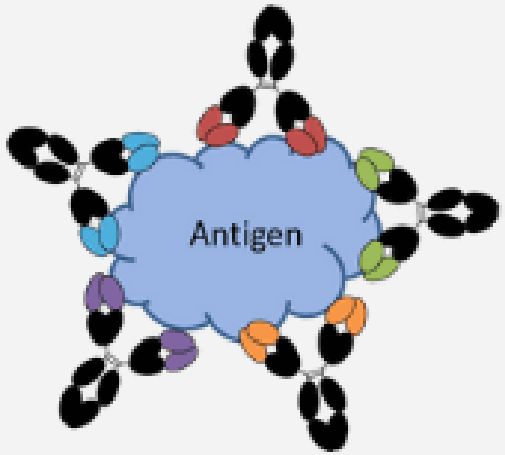
- Using recombinant DNA →humanize antibodies



Polyclonal Antibody

- Cheap to produce
- Mixed population of antibodies
- May bind to different areas of the target molecule
- Tolerant of small changes in protein structure

Polyclonal antibody



Monoclonal Antibody

- Expensive to produce
- Single antibody species
- Will only bind single specific site
- May recognise a particular protein form

Monoclonal antibody

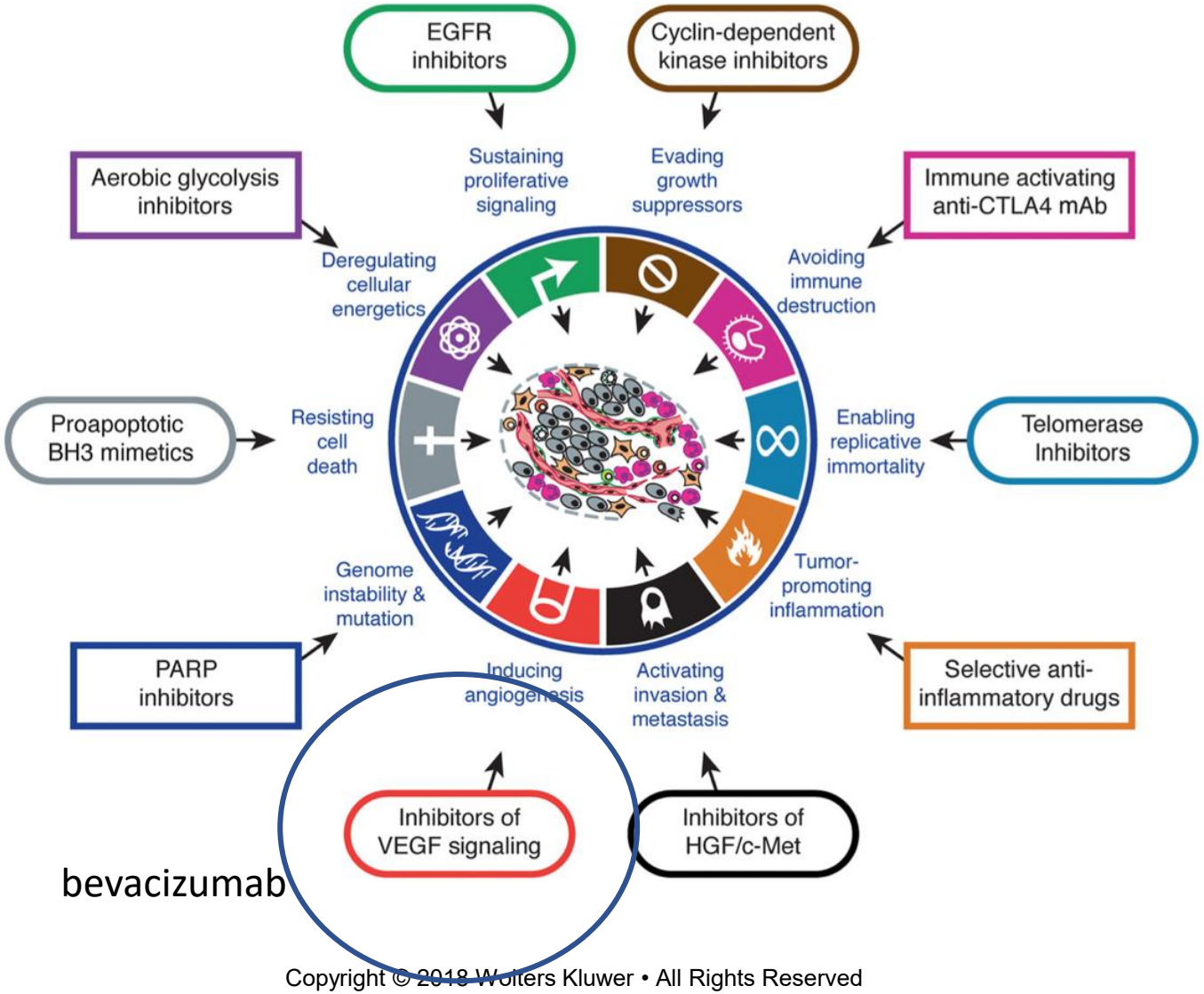
labclinics

Terminology

Monoclonal antibodies: “xi” “zu” “-mab”

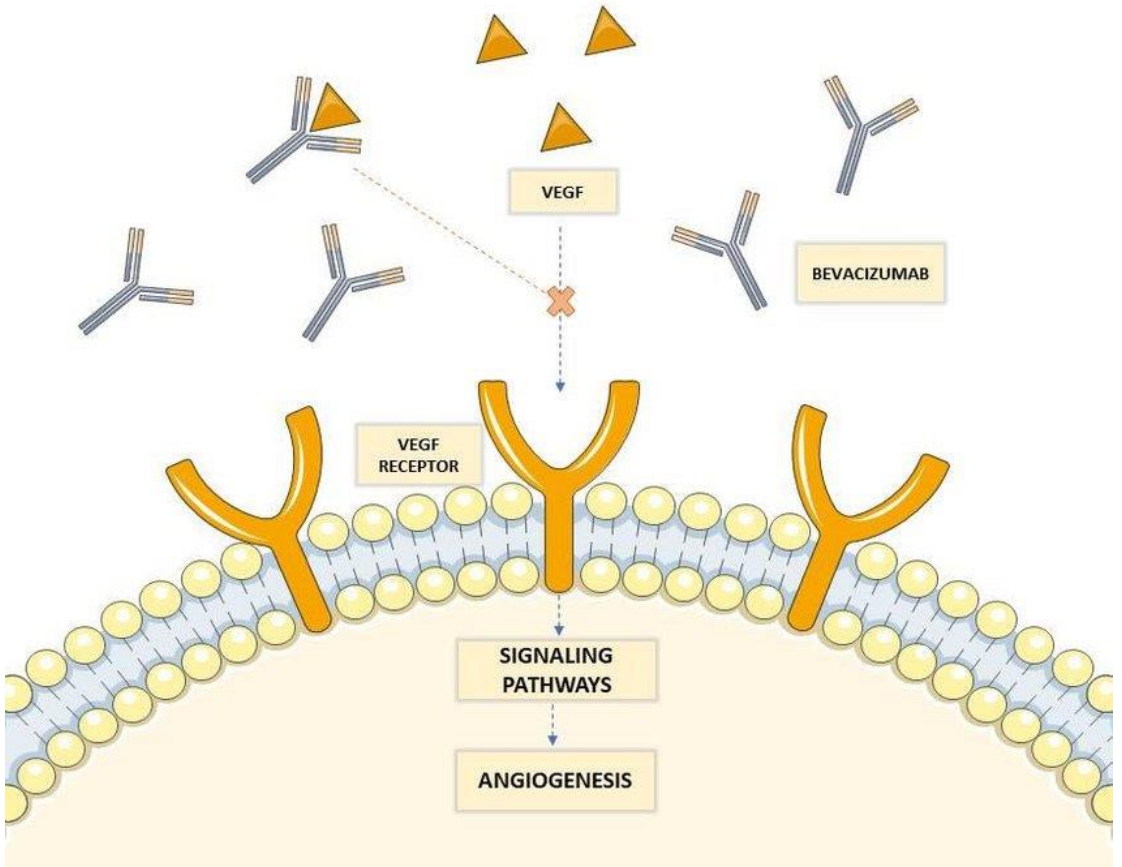
examples: basiliximab, idarucizumab

Targeted Therapy

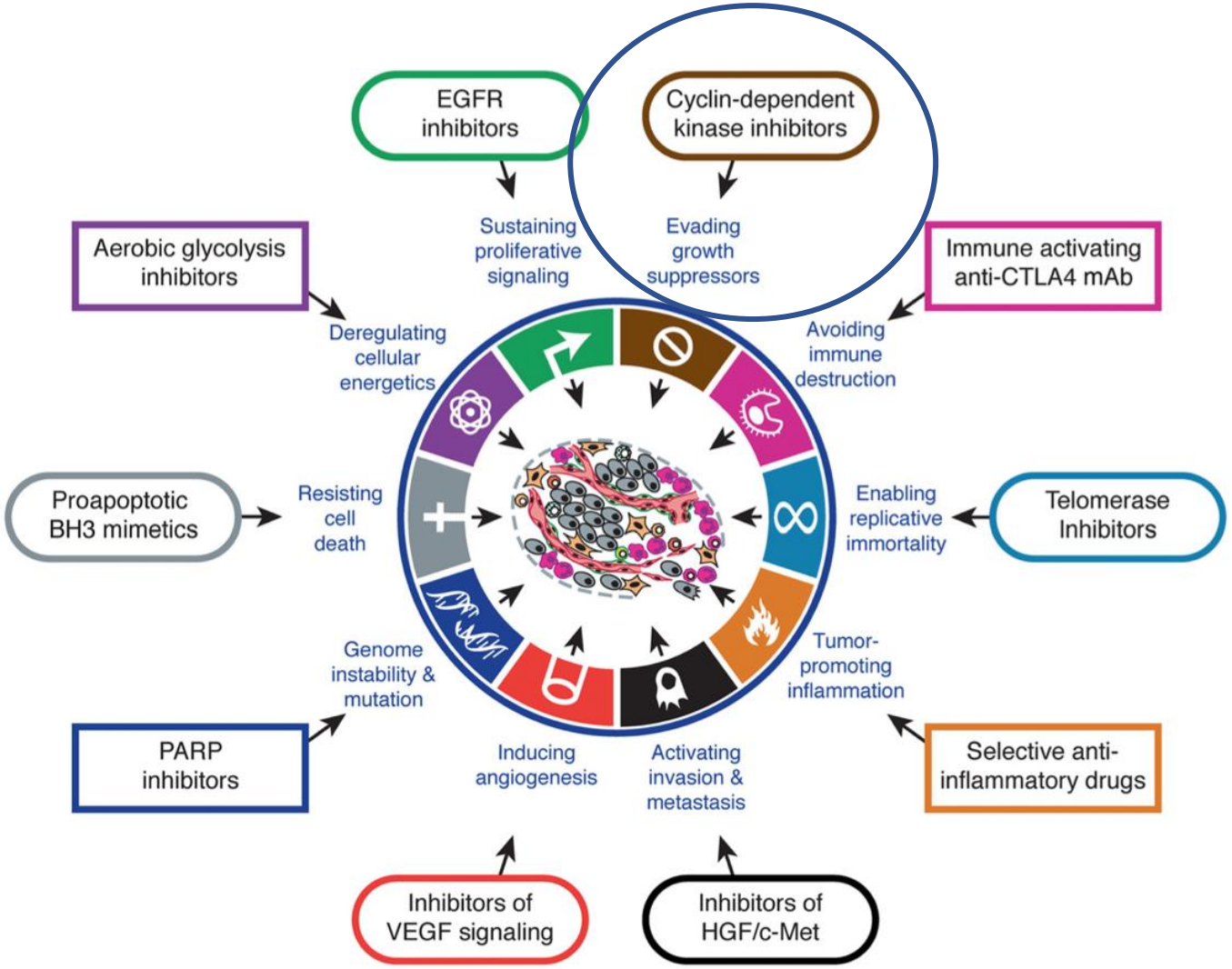


bevacizumab

Antiangiogenesis bevacizumab



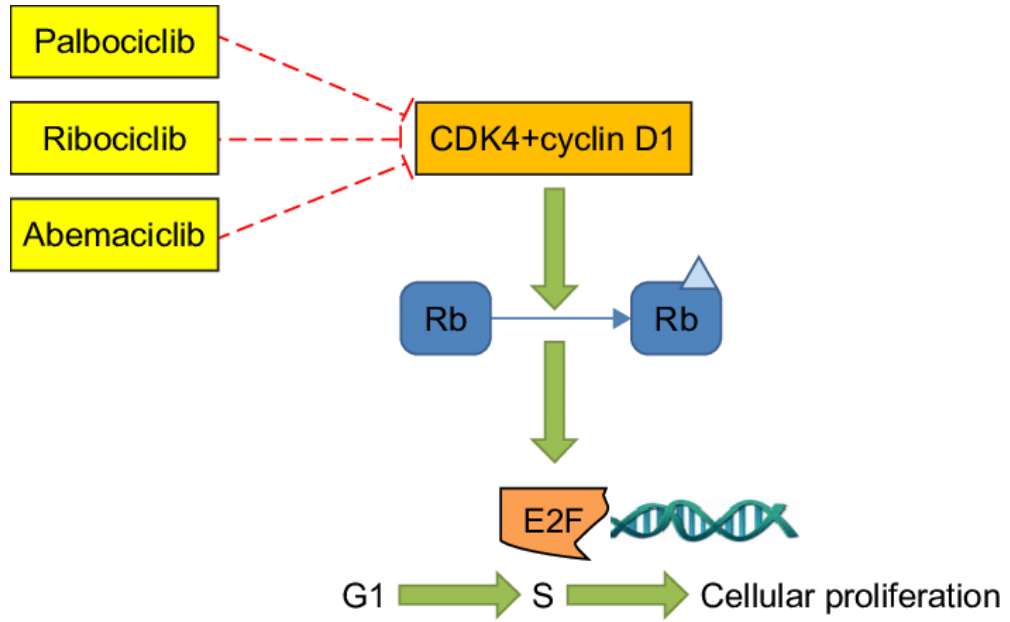
Targeted Therapy



Palbociclib

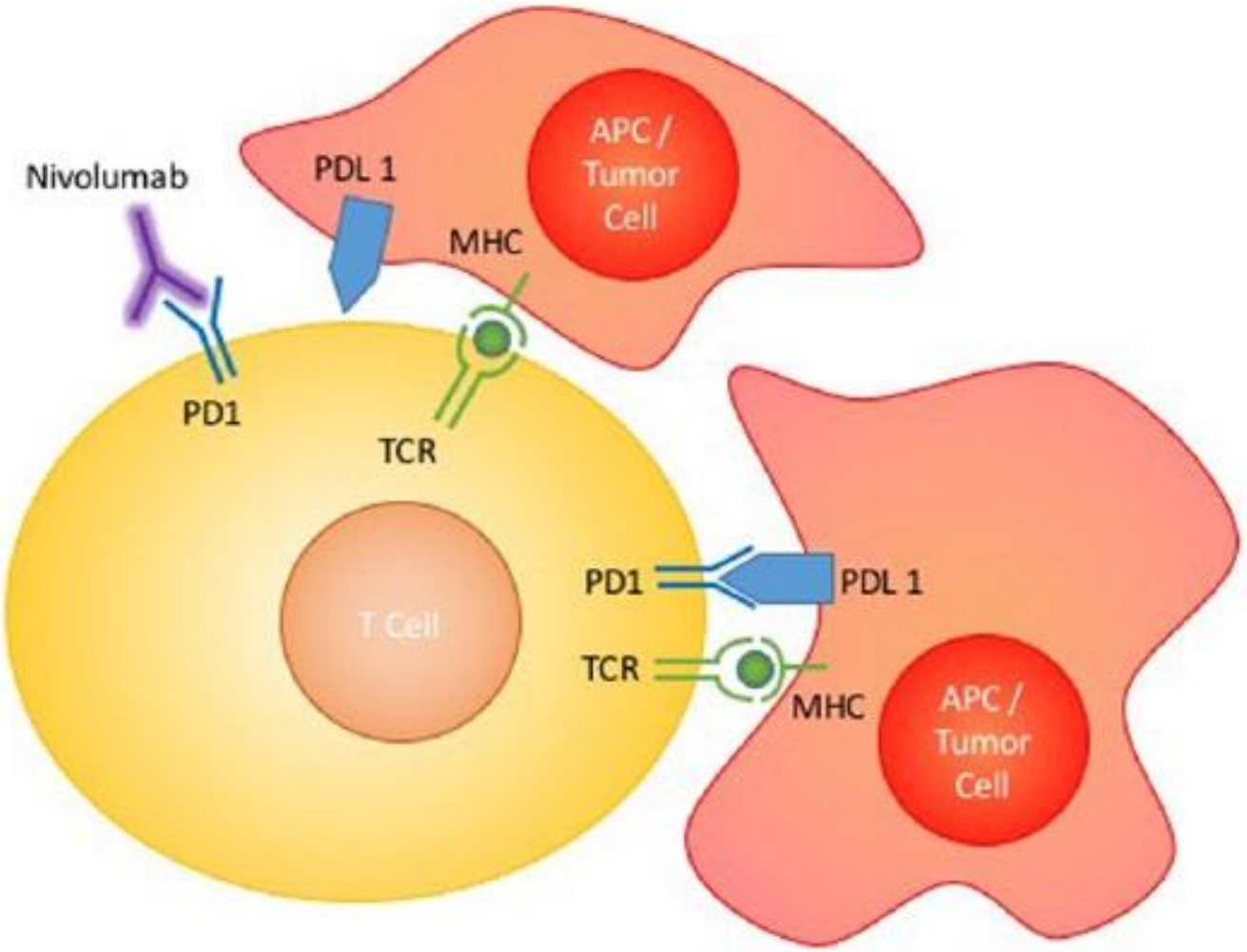
- selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6

- **Uses**: treatment of HR-positive and HER2-negative breast cancer



Immunotherapy

Nivolumab



binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response

2014 FDA approved anticancer drugs

Generic Drug Name	Mechanism of Action
Belinostat	HDAC inhibitor
Ceritinib	ALK inhibitor
Olaparib	PARP inhibitor
Ramucirumab	VEGFR2 inhibitor
Pembrolizumab	PD-1 inhibitor
Idelalisib	PI3K d inhibitor

2018 Nobel Prize in Medicine for Cancer Immunotherapy

Jonathan Nackstrand/Agence France-Presse — Getty Images