Paclitaxel and Docetaxel

- Semisynthetic

the backbone is natural but with some modifications that are synthetic.

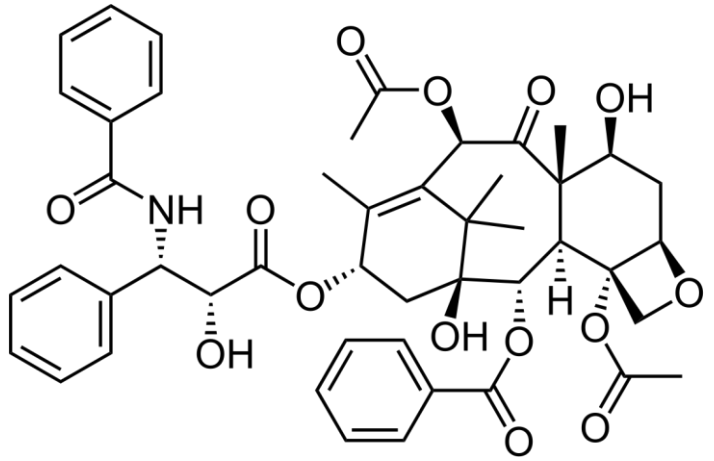
Therapeutic Uses:

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

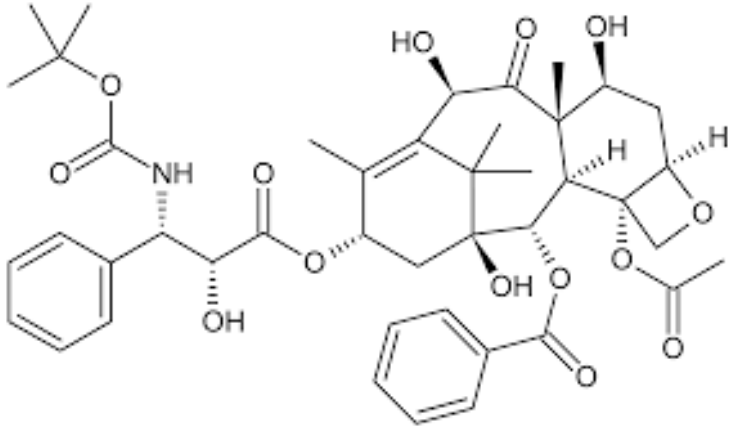
Docetaxel with the breast cancer is a fundmental treatment.

5. GI cancers

all of those tumors are solid tumors and both drugs "paclitaxel and docetaxel" aren't commonly used to treat liquid or soft tissue cancer such as leukemia.



Paclitaxel



Docetaxel

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The cytoskeleton is made of multiple components such as microtubules, actin microfilaments and so on.

*The main function of the cytoskeleton is to maintain the structure of the cellular signal travelling to the inside of the cell.

also,
one of its functions is the ability of microtubules to facilitate cellular division by forming the mitotic spindles.

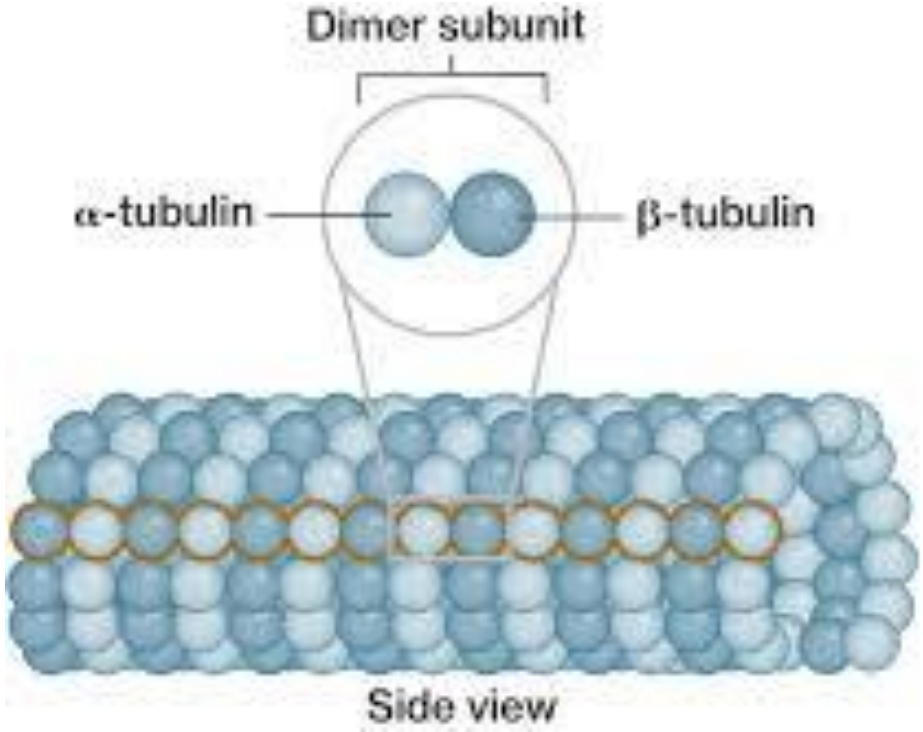
either α or β tubulin and both types together form the dimer subunits.

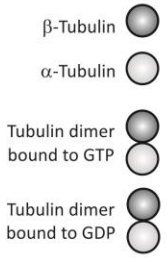
a dimer, two molecules of tubulin, which is the building unit of the microtubules.

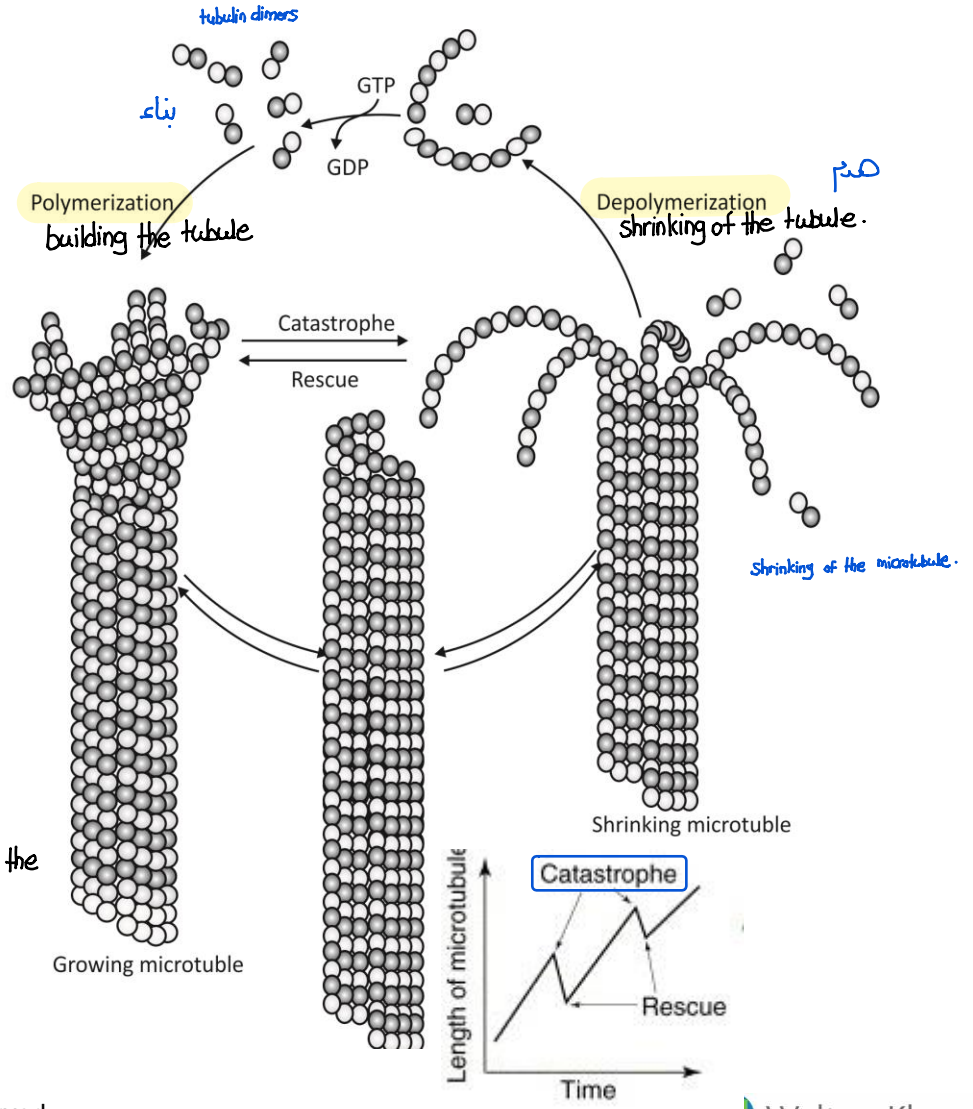
microtubules are polymers consisting of multiple repeated units "monomers" in the shape of repeated dimers to form a clyindrical shape of the microtubule.

microtubules are dynamic structures meaning that they won't be fixed/rigid all the time, but they will go under constant remodeling "بناء وهدم" and they're completely active.

Microtubules







we can interfere with the polymerization and depolymerization to destroy the DNA seperation process and thus the cell division process.

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is very important for the seperation of the sister chromosomes thus being very important for the mammalian cells undergoing the division.

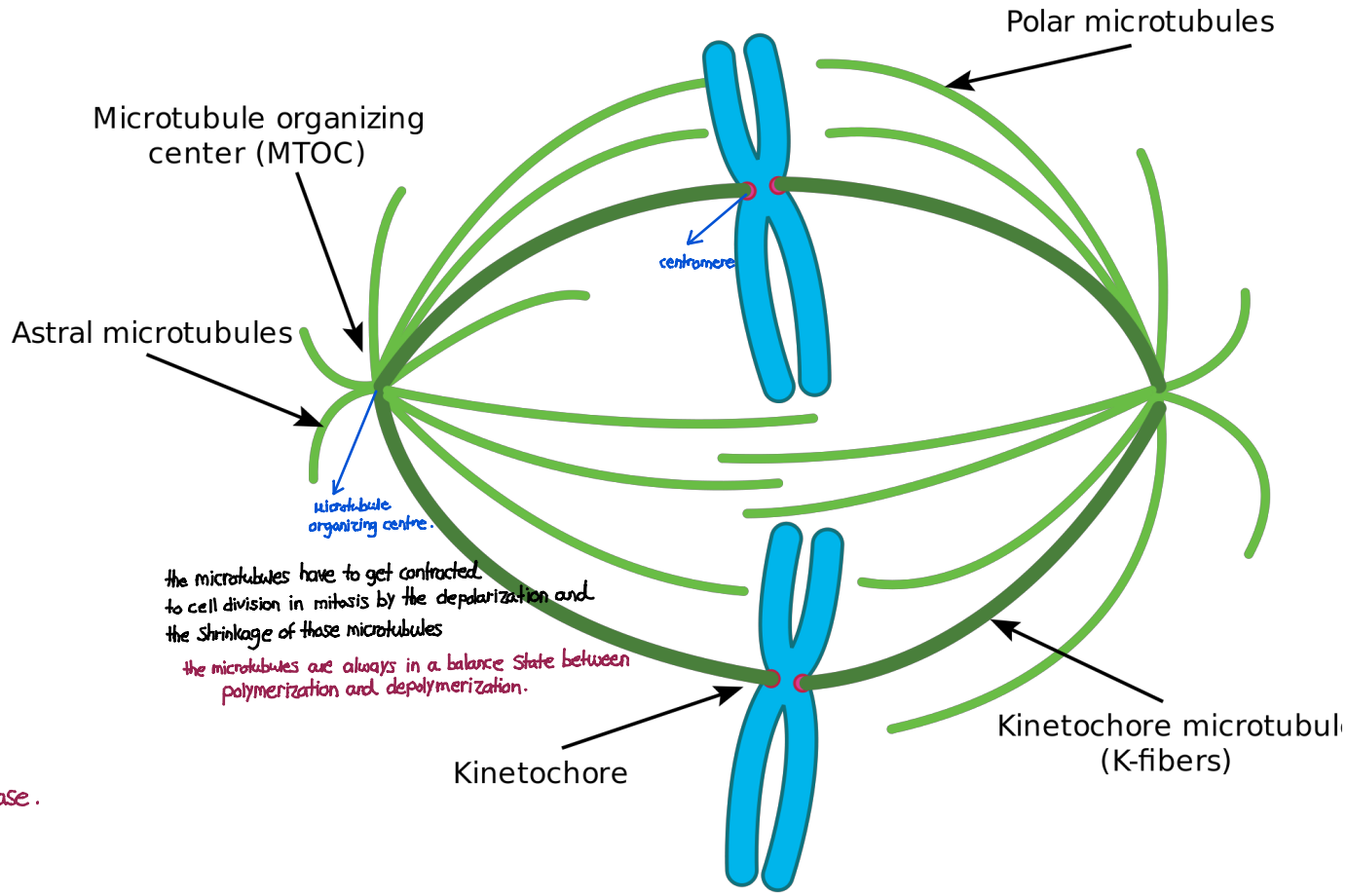
The Mitotic Spindle

" Chromatin or DNA "

Microtubules are responsible for the formation of the mitotic spindels.

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

Drugs that interfere with the mitotic spindles are cell-cycle specific drugs especially for the M phase.



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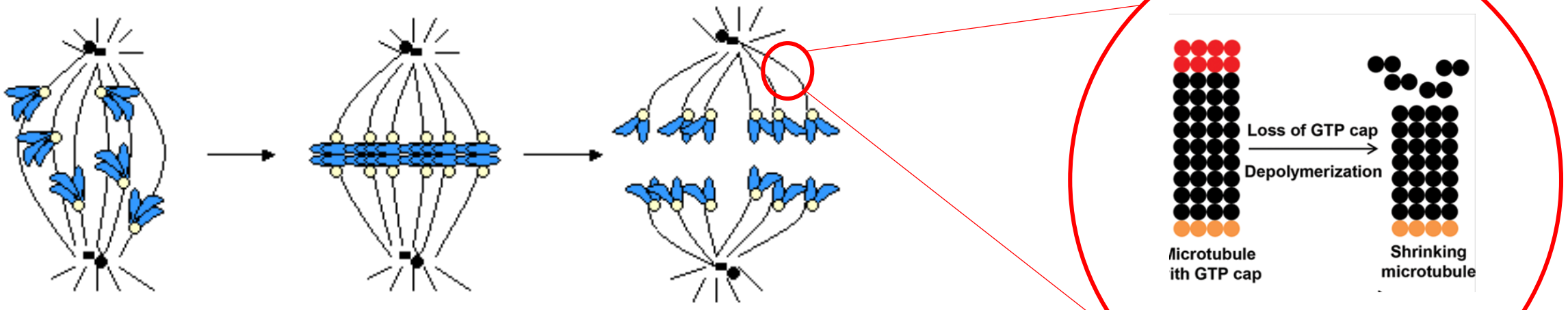
The Mitotic Spindle



Prometaphase

Chromosomes associated to mitotic spindle

Metaphase

Chromosomes congressed in the metaphase plate

Anaphase

Sister chromatid separation

complete cell division.

as we said that the shrinkage of those microtubules leads to the seperation of the sister chromatins, depending on the depolymerization of the mitotic spindles.

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

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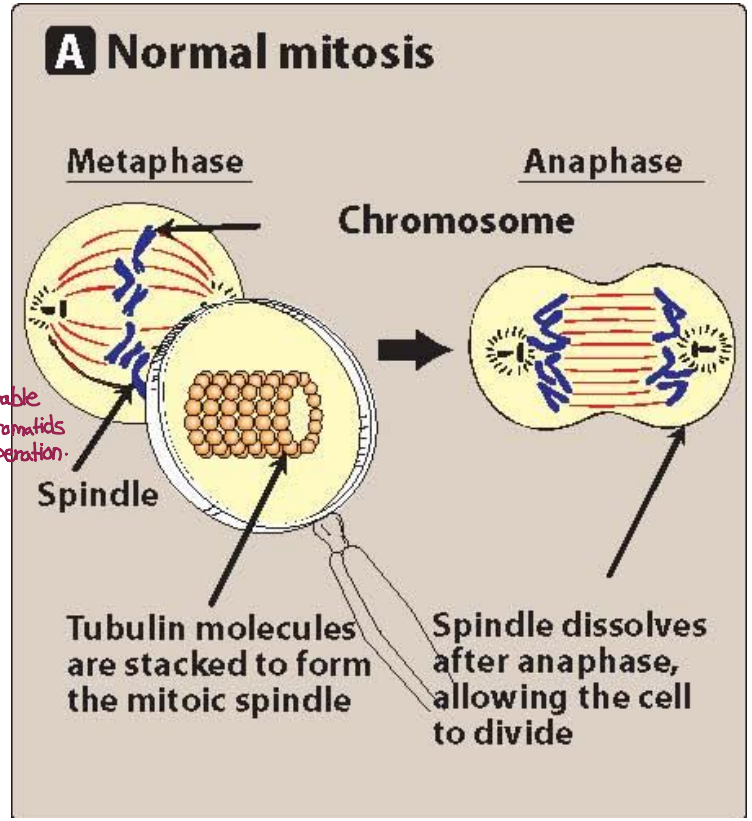
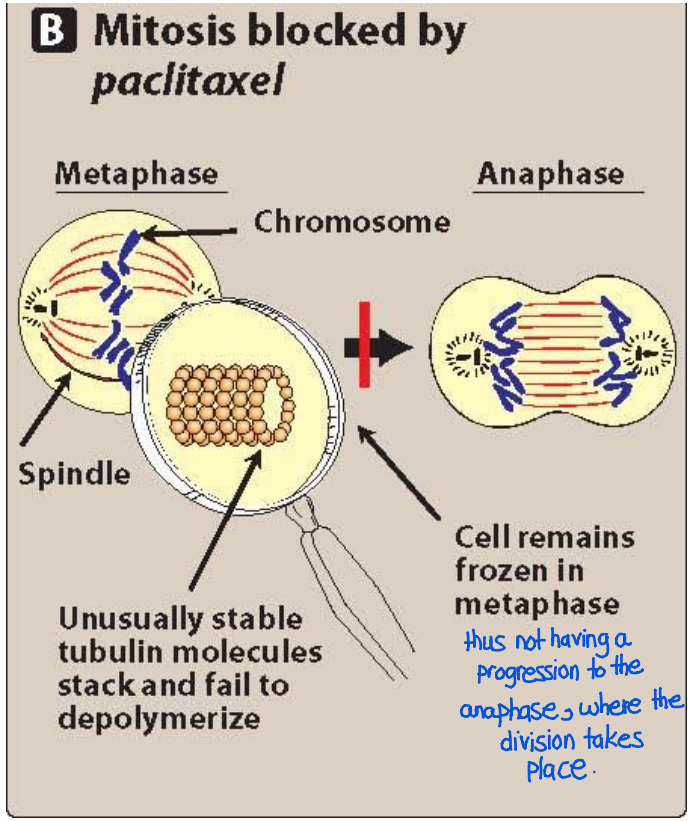
Paclitaxel and Docetaxel

they're very toxic and deadly drugs and promote cell death of tumor cells.

Mechanism of Action

- Cell-cycle specific
- Promote the polymerization and stabilization of the polymer rather than disassembly
  preventing the depolymerization. the microtubules/mitotic spindles will stay rigid and stable without any contraction, thus interfering with the sister chromatids separation.
- Forming microtubules are overly stable and nonfunctional
- Failure of chromosomal separation
  the cell will be in a frozen metaphase. this is considered to be catastrophic to the mammalian cells.
- Cell death
  either by apoptosis or by another mode of death called the mitotic catastrophe.





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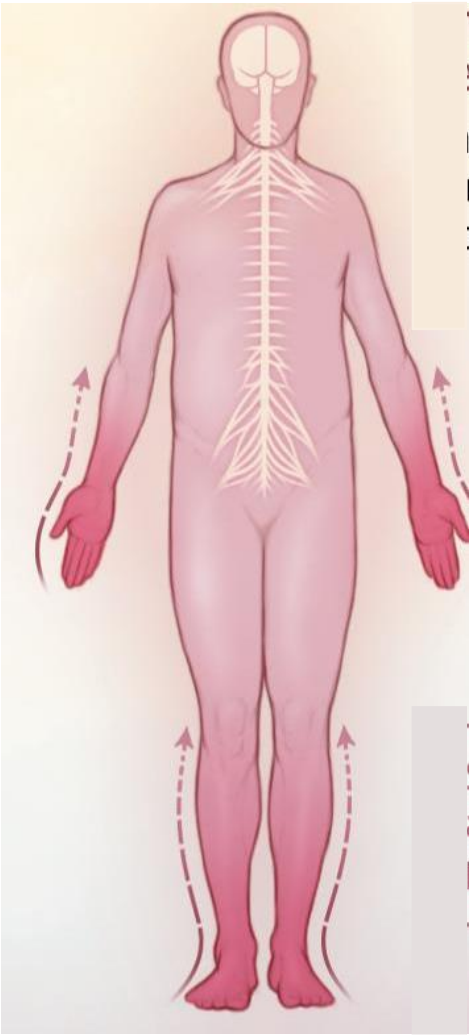
Paclitaxel and Docetaxel

they also harm normal human tissues that are rapidly proliferating and dividing not only the cancer cells.

Adverse effects

- Neutropenia, leukopenia (the decrease in the number of the WBCs; "Bone Marrow suppression".)
- Chemotherapy-Induced Peripheral Neuropathy (important to know because it's special to this drug. damage in the peripheral nerves, so after the patients ended to take their medication, they will have signs of peripheral neuropathy like tingling, paraesthesia, abnormal sensation, pain in the lower and upper extremities and so on.)
- Hypersensitivity
- Alopecia
- Arthralgia/myalgia
- Renal impairment



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Platinum Coordination Complexes

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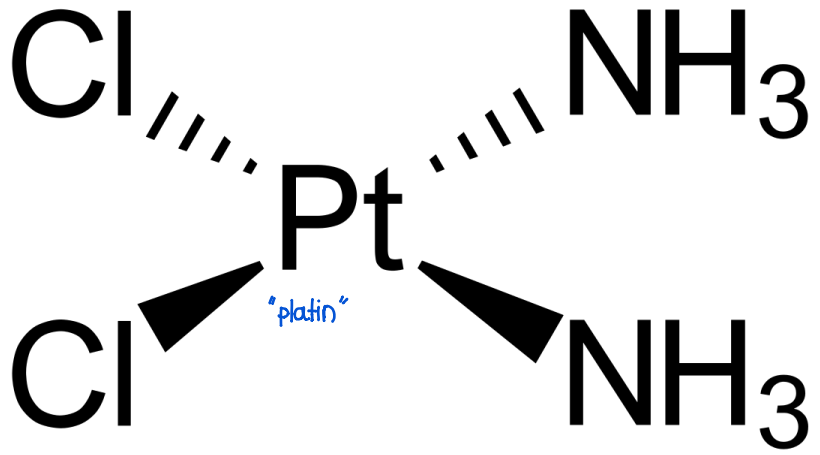
Cisplatin, Carboplatin and Oxaliplatin

those two drugs are promoted to be less toxic than cisplatin.

- 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

a famous antidrug.

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Cisplatin, Carboplatin and Oxaliplatin

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Cisplatin it was a main drug in treating lung cancer with combination with paclitaxel	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 only causes the normal and common side effects.	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.

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will also cause DNA damage and breaking down the DNA chromosomes.

Cisplatin, Carboplatin and Oxaliplatin

they are DNA damaging agents causing direct damage to the DNA of cancer cells.

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

the drug molecules will

through a covalent bond.

زي كأني بحط صمغ على الـ DNA وبخليه يلزق بأماكن معيّنة لحتى يلزق فيها

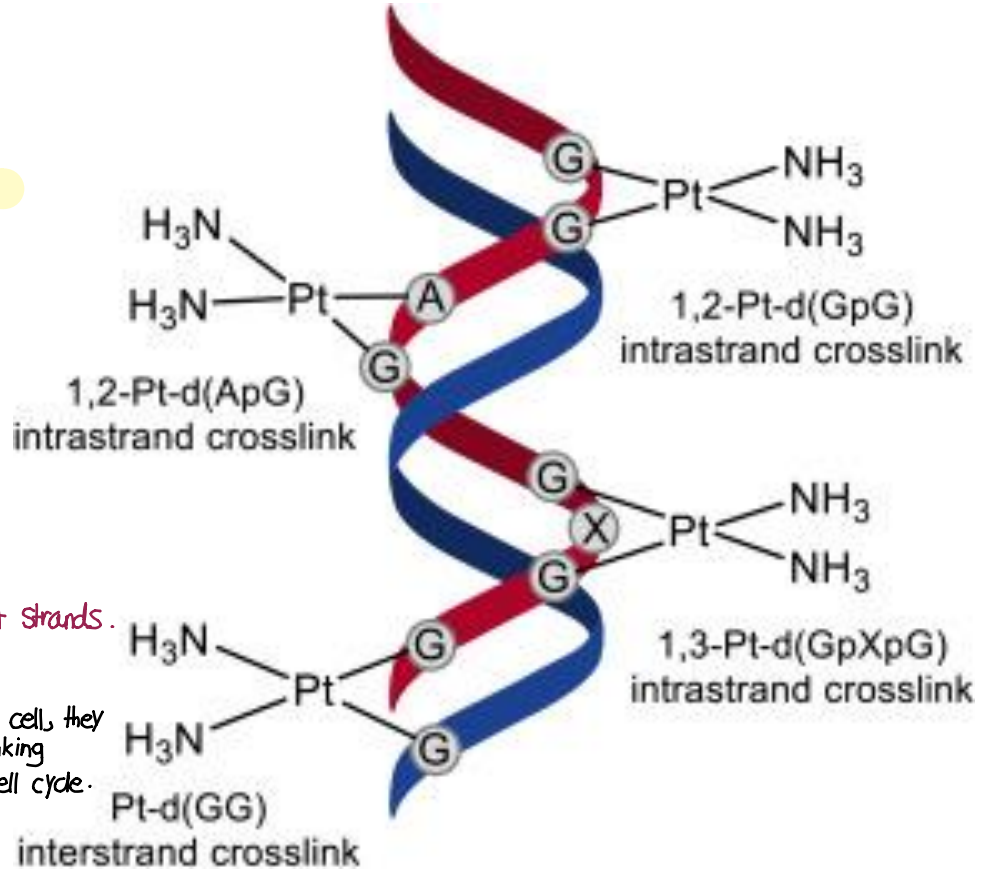
cross-linking in the same strand.

combining two chromosomes together.

inhibiting the unwinding of the DNA strands.

this means that whenever they reach the cell, they will bind to the DNA and cause cross-linking regardless of the phase of the cell cycle.

this will lead the cancer cells to go under cell death like apoptosis.



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Cisplatin, Carboplatin and Oxaliplatin

Adverse effects

- Severe nausea and vomiting (Chemotherapy-Induced Nausea and Vomiting) a common side effect for all anticancer drugs.
- Nephrotoxicity (cisplatin), prevented by excessive hydration
- Ototoxicity injury to the inner ear.
- Myelosuppression damage to the bone marrow and the other rapidly proliferating cells and tissue.
- Cold-induced peripheral neuropathy (oxaliplatin)
- Hepatotoxicity
- Hypersensitivity

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Topoisomerase Poisons

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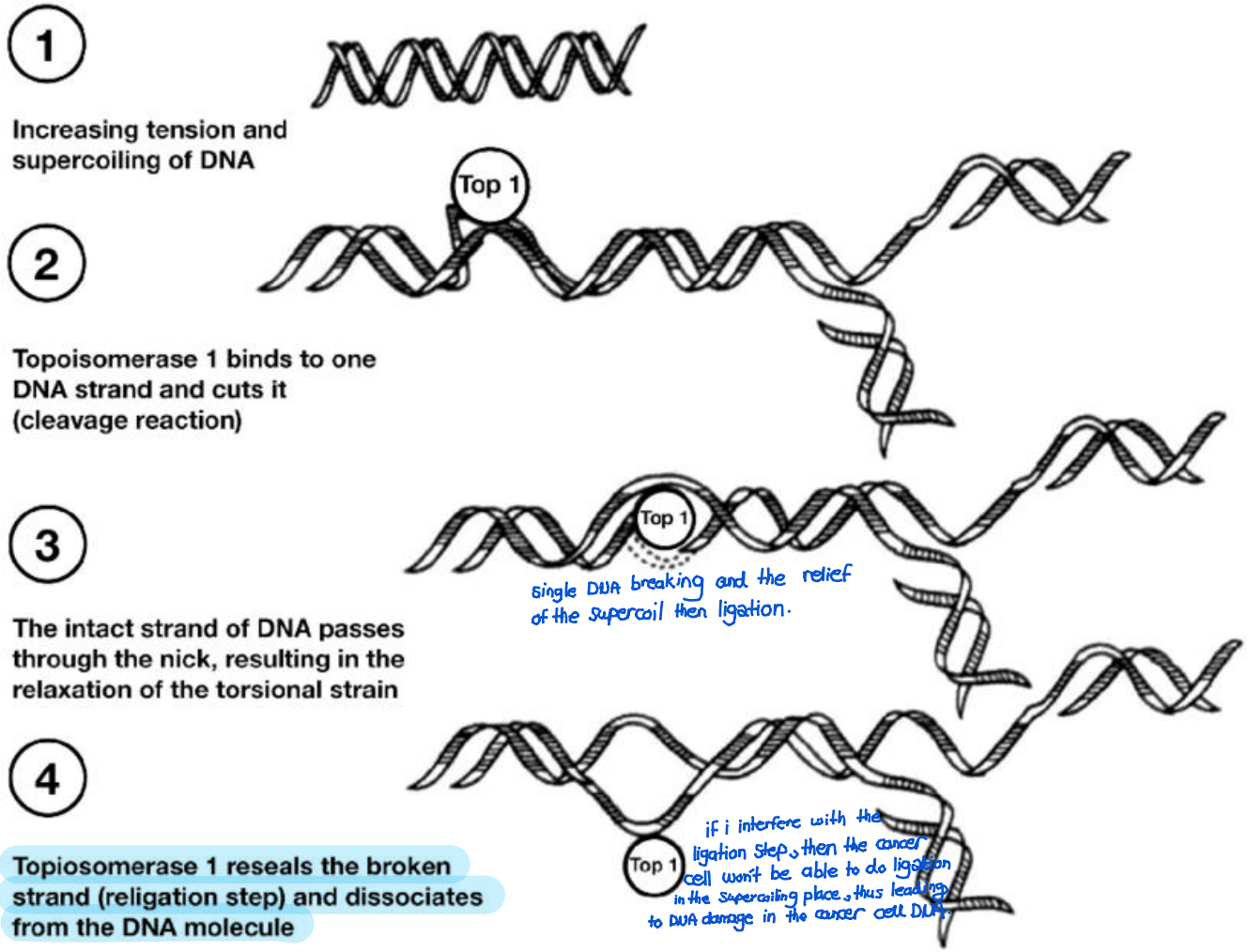
Remember that the fluoroquinolones interfere with topoisomerase II and IV of the bacterial cell and thus causing DNA breaks in the bacterial DNA.

Topoisomerase I

responsible for releasing tension and supercoilings that could happen in the DNA.

the mammalian topoisomeroses in the human are more in number than the bacterial because DNA related processes are more complex.



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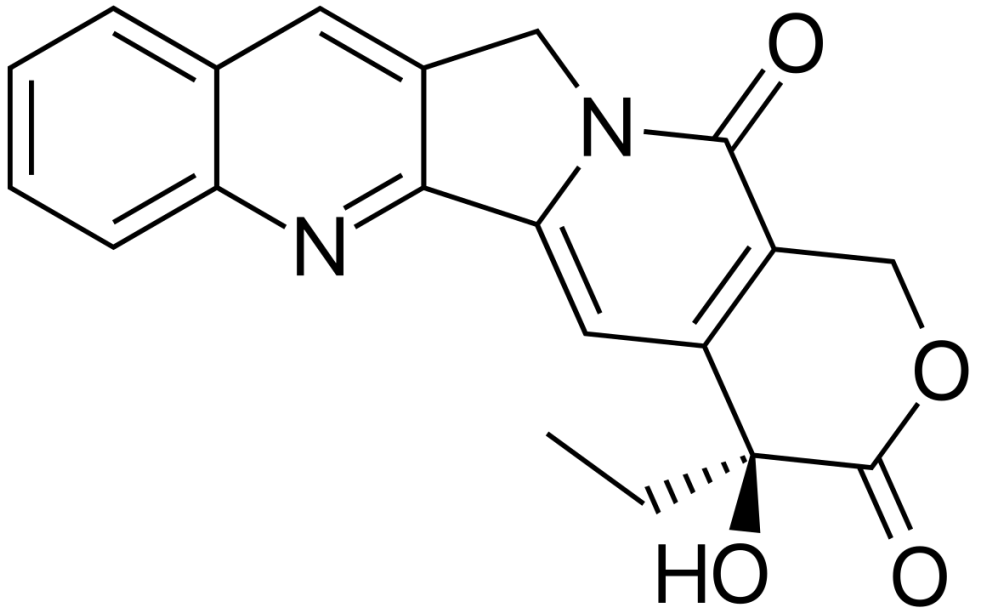
Camptothecins

they're inhibitors of the topoisomerase I

- Camptothecin, irinotecan, topotecan
- Semisynthetic

Therapeutic uses

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



Camptothecin

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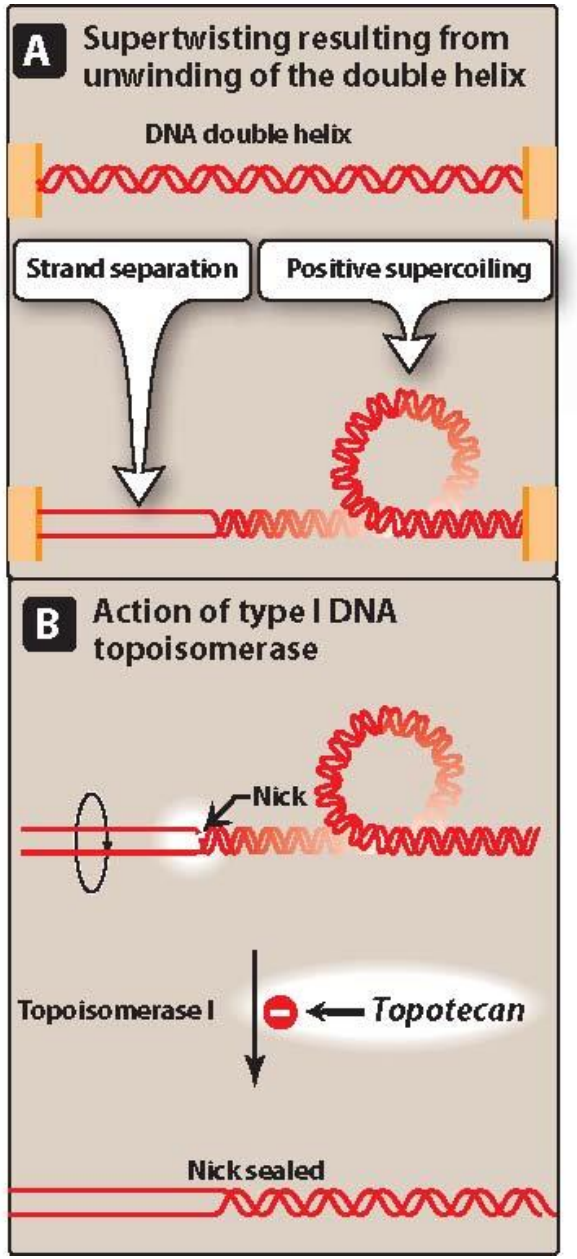
Camptothecins

Mechanism of action

- Topoisomerase I inhibitors
- Cause single-stranded breaks (breaks in a single DNA strand.) (induction of cell death.)
- S-phase specific
- Irinotecan metabolite is 1000-folds more potent



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Etoposide

the whole DNA will turn to double stranded breaks.

حاج يقدير جع يلحم الـ Breaks مع بعض.

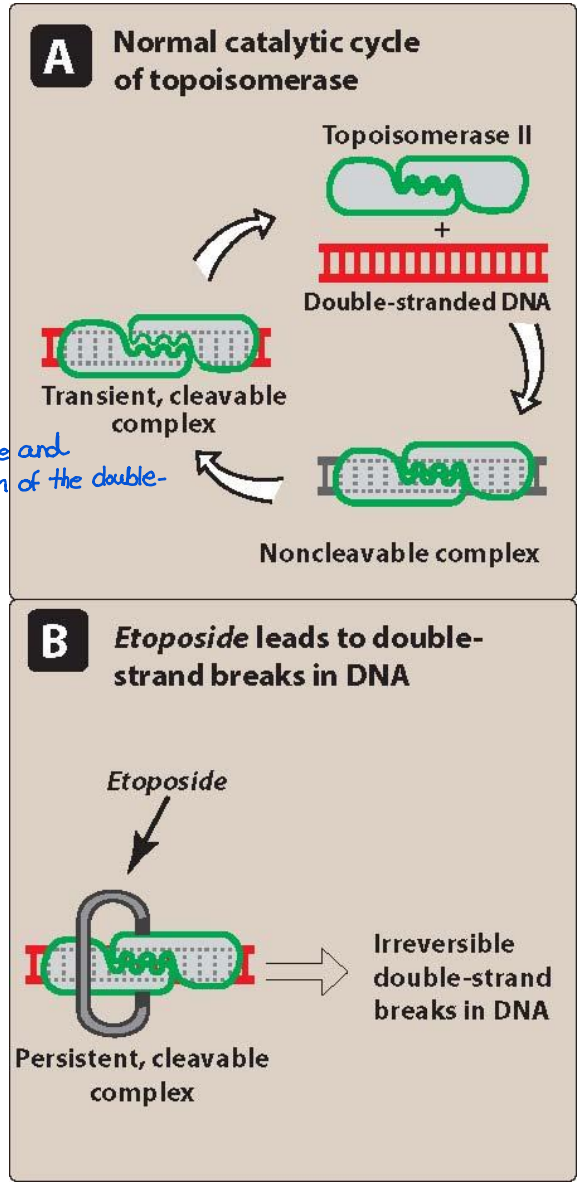
- Semisynthetic derivative of podophyllotoxin
- Topoisomerase II inhibitor

they cause a cut in the DNA as a whole and relief to the supercoils, then the ligation of the double-stranded DNA.

- Causes irreversible double-stranded breaks
- Used for lung cancer, testicular cancer

usually for the treatment of solid tumors.

- Causes myelosuppression



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"targeting only the cancer cells with lower effectivness to the normal cells".

Targeted Therapy

↑ effectiveness
↓ Toxcity.

Remember that:
those anticancer drugs lack of selective toxcity and will also damage the normal rapidly proliferating cells like bone marrow and gastrointestinal cells.

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the ability to synthesize antibodies by the immune system to fight infections.

*those antibodies are specific and target certain antigen on a specific type of cells like the bacterial cells.

How Antibodies Are Produced?

- Immunization of horses/rabbits with human lymphoid cells

  → mixture of polyclonal and monoclonal antibodies

  produced from more than one immune cells.

  produced from one immune cell.

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

  → monoclonal antibodies

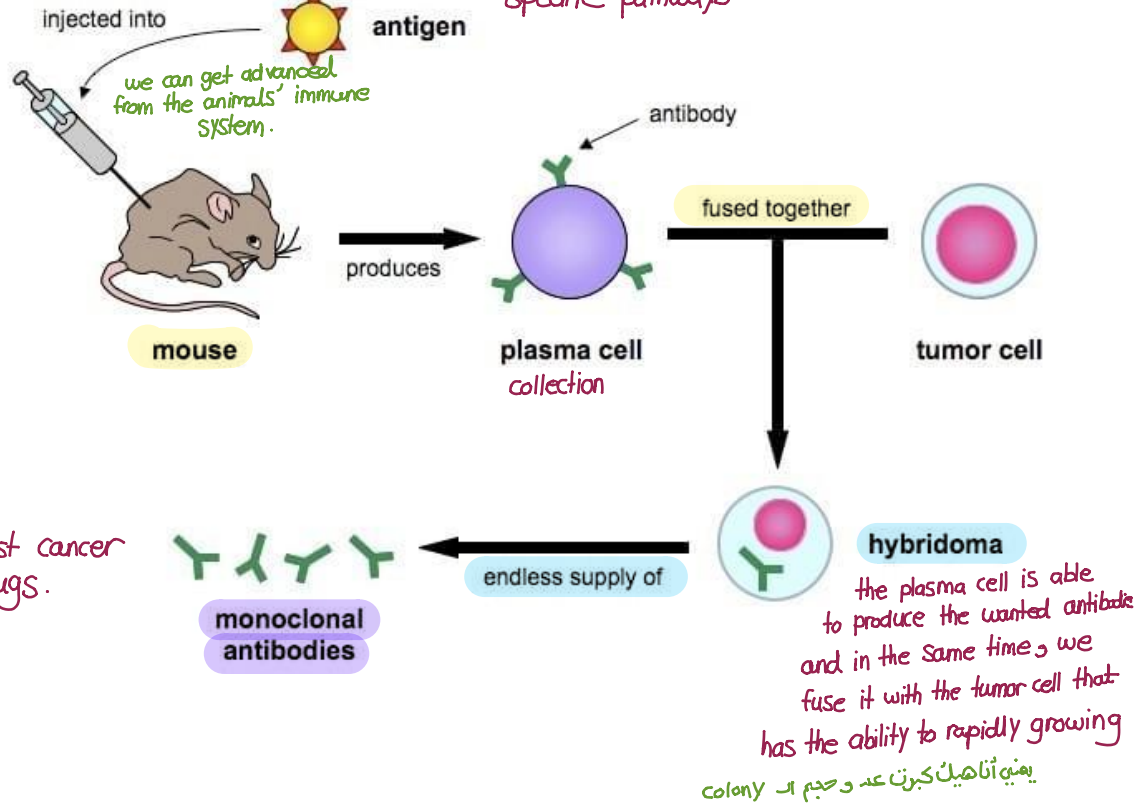
  most of the newly effective drugs against cancer and other diseases are monoclonal drugs.

- Using recombinant DNA →humanize antibodies

← by the mature B cells.

will produce antibodies against the injected material.

most of the targeted drugs are now like antibodies that go to a specific protein or an active site inside a protein, they have very specific pathways.



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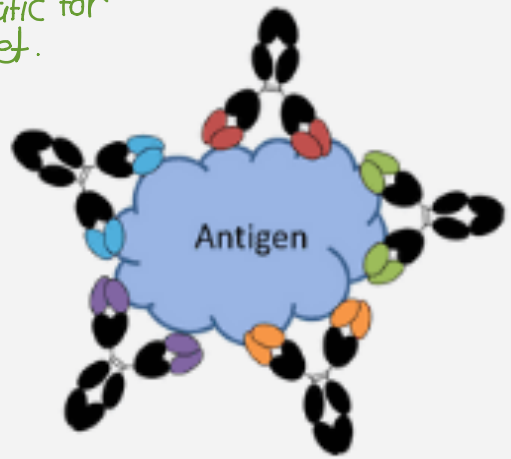
multiple immune cells

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

less specific for the target.



one immune cell

Monoclonal Antibody

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

Monoclonal antibody

labclinics

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Terminology

examples: basiliximab, idarucizumab

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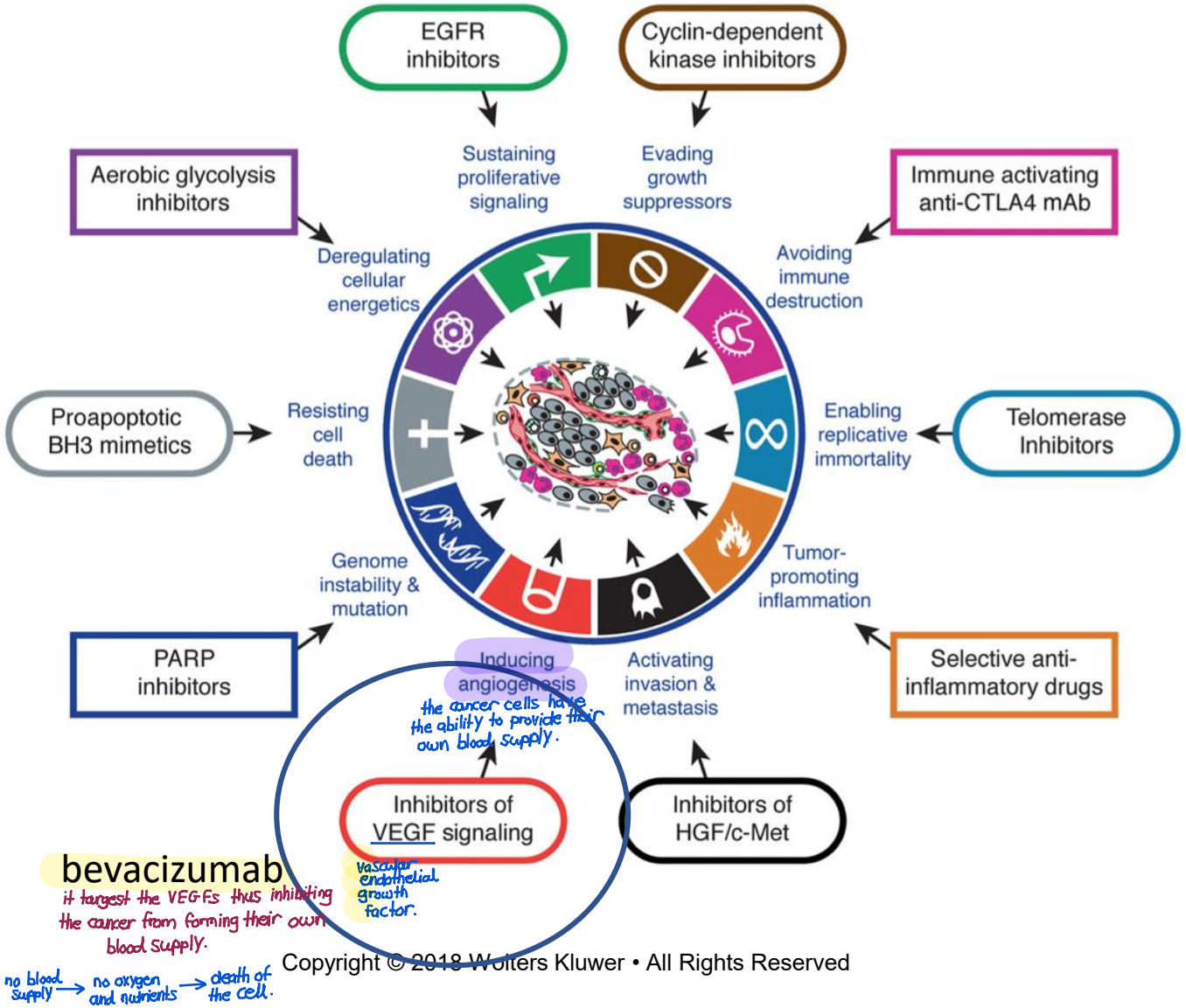
Targeted Therapy



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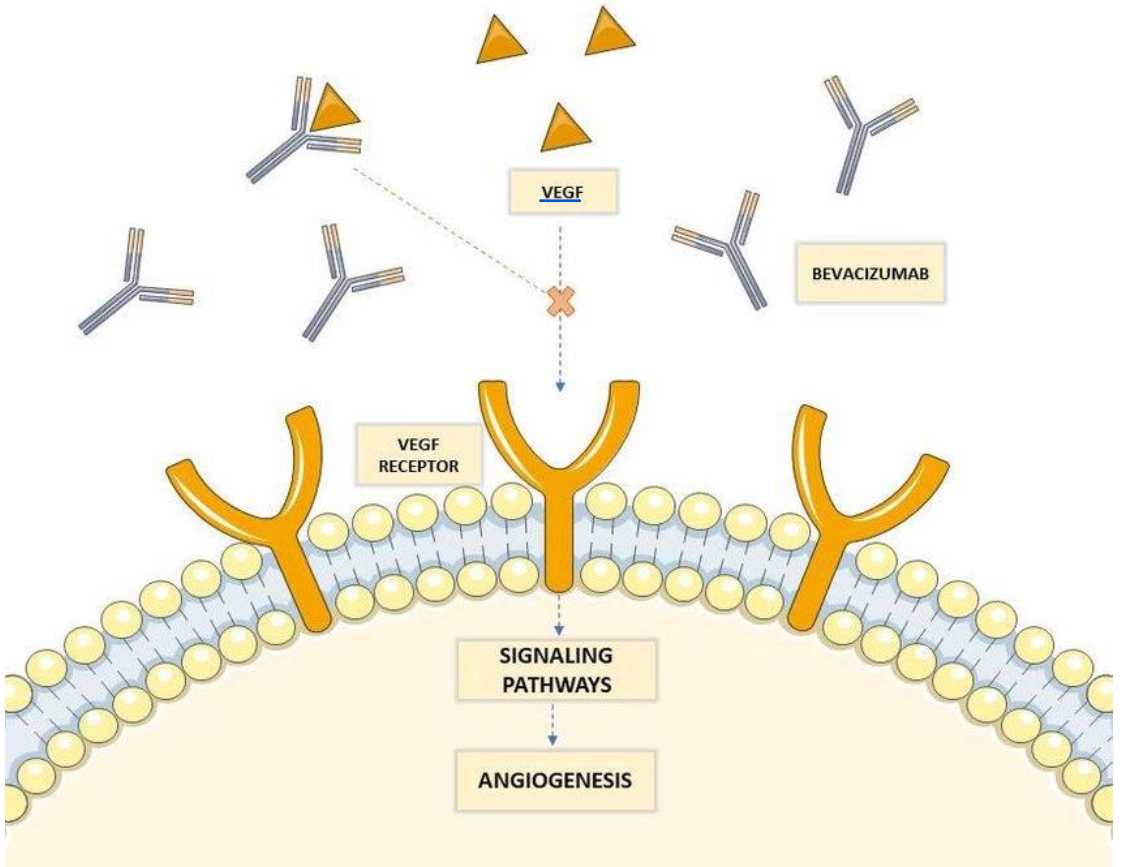
Antiangiogenesis bevacizumab



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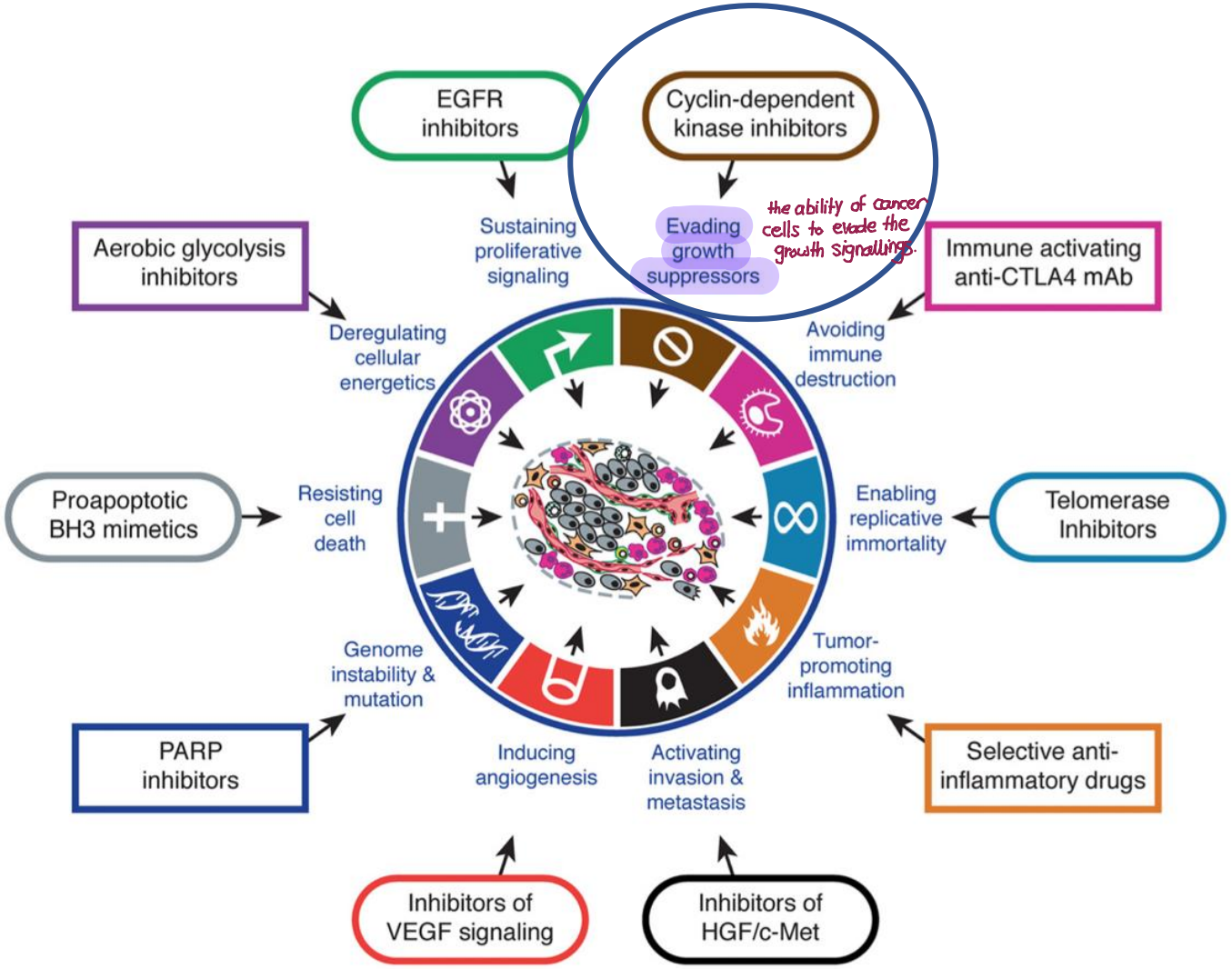
Targeted Therapy



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Palbociclib

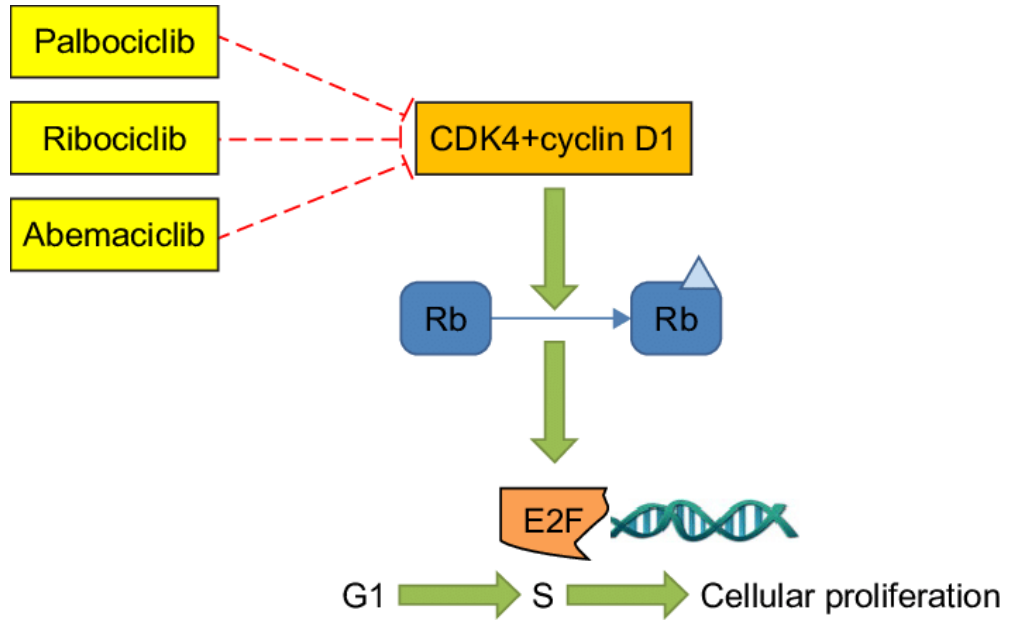
in order for the cell to go through the cell cycles there must be an activation to some proteins called the cyclins and they attach to other proteins named cyclin-dependent proteins and the phosphorylation of many targets.

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

thus preventing the cell from moving from one phase to the other.

we now start targeting new processes related to the growth of the cancer.

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



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Immunotherapy

كيف نخلي الجهاز المناعي
يتعرف على الخلايا السرطانية ويحسس انه يقضي عليها زي ما
الـantibiotics .

the mission of the facilitating of the immune system to eleminate the pathogen.

* cancer cells are either:
  - unrecognized from the immune system.
  - having mechanisms to escape the immune system.

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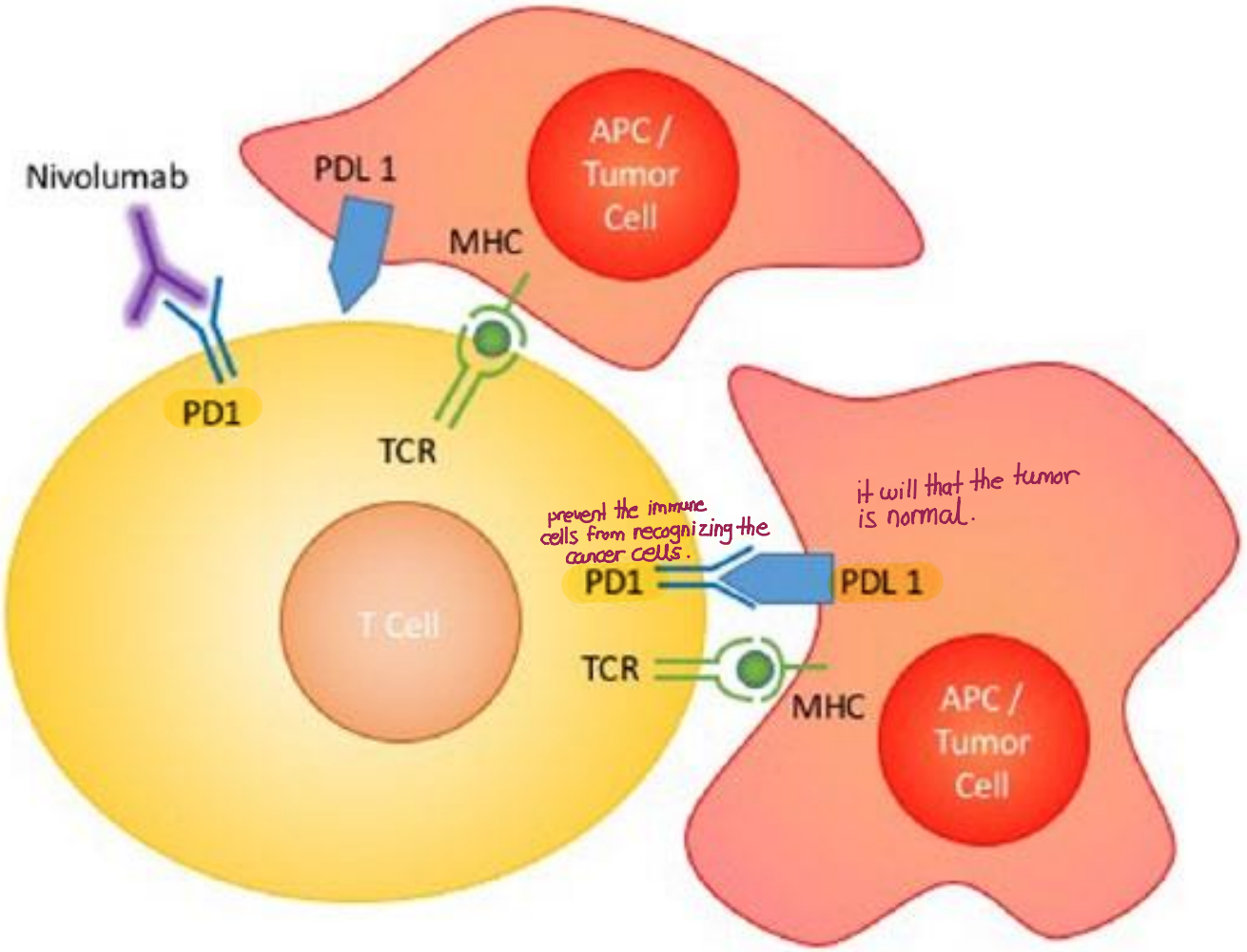
Nivolumab



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

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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

مش مطلوب منّا حفظه ت

targeted therapy for cancer cells.

more selective & effective than traditional cancer chemotherapy.

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2018 Nobel Prize in Medicine for Cancer Immunotherapy

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