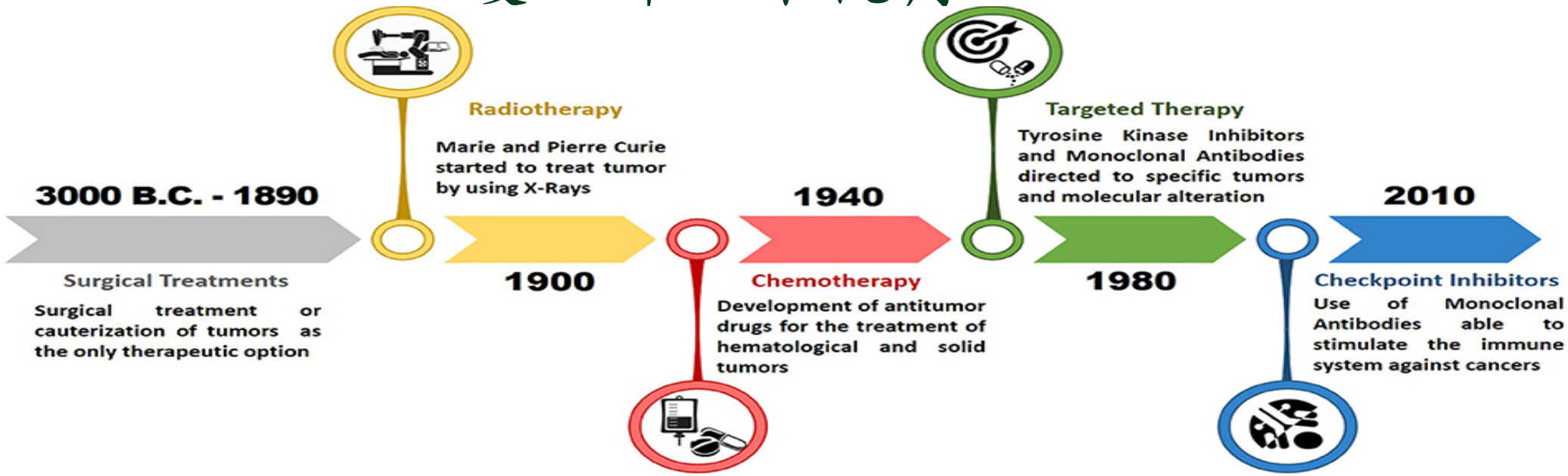
Cancer Pharmacology and Treatment
A Clinical Perspective for Nurse Practitioners

癌症藥理學與治療
護理師臨床視角



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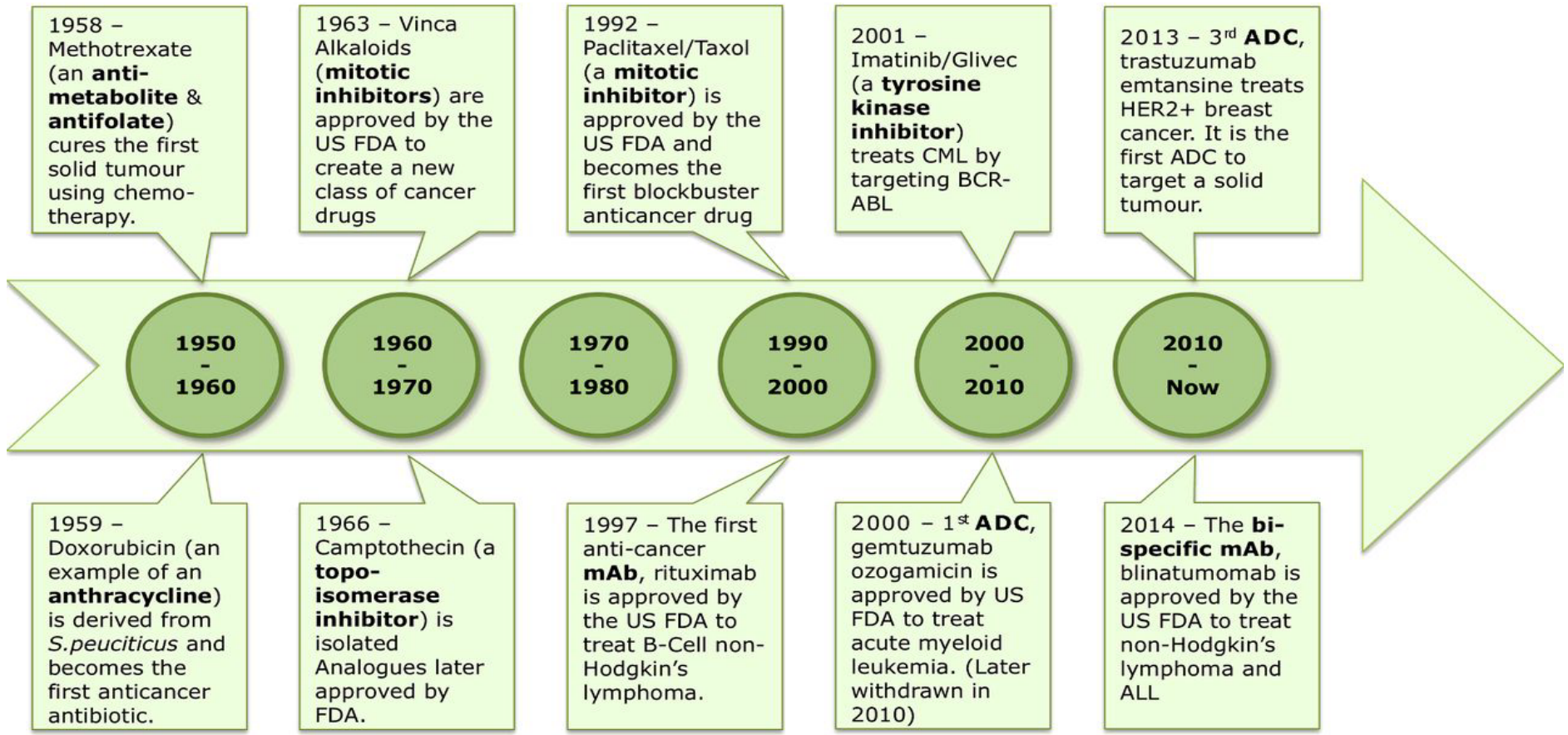
Foundations of Cancer and Pharmacology
(癌症與藥理學的基礎)

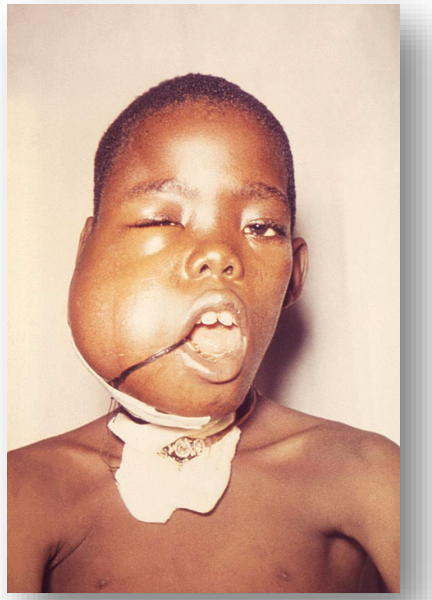
- **Overview of Cancer Biology**
  - Hallmarks of cancer癌症的標誌
  - Tumor classification: benign vs. malignant腫瘤分類：良性與惡性
  - Common cancer types and staging (TNM system)常見癌症類型及分期（TNM 系統）
- **Principles of Cancer Pharmacology 癌症藥理學原則**
  - Pharmacokinetics vs. pharmacodynamics in cancer therapy癌症治療中的藥物動力學與藥物效應學
  - Therapeutic index and cytotoxicity治療指數和細胞毒性
  - Drug resistance (intrinsic vs. acquired)藥物抗性（內在抗性與獲得抗性）
- **Classes of Anticancer Drugs – Introduction 抗癌藥物類別**
  - Hormone therapy
  - Cytotoxic chemotherapy overview 細胞毒性化療概述
  - Targeted therapy introduction 標靶療法介紹
  - Immunotherapy overview (checkpoint inhibitors, CAR-T) 免疫療法概述（檢查點抑制劑，CAR-T）

History of cancer treatment modalities

	Surgery	Radiation	Chemotherapy	Targeted drug	Immunotherapy
Approach	Cut out accessible tumor cells to stop growth and prevent their spread	Use highly concentrated X-ray or radioactive isotopes to kill cancer cell	Use cytotoxic drugs to kill or inhibit cancer cells	Interfere with a mechanism required for or that supports tumor growth	Support the immune system's innate ability to recognize and eliminate cells
Since	1800s	Early 1900s	Late 1940s	2000s	2010s
Limitation	Many inaccessible tumors ineligible; limited effectiveness if the tumor has already begun to spread	Limited effectiveness if the tumor has already begun to spread; potentially dangerous for tumors near vital organs	High toxicity and often does not destroy the whole tumor, leading to high rates of recurrence	Limited tumor types eligible; high efficiency, but short durability, driving high rates of recurrence	Applicable to all tumors at all stages of disease, including metastatic tumors; responses are highly durable; synergistic with other treatments

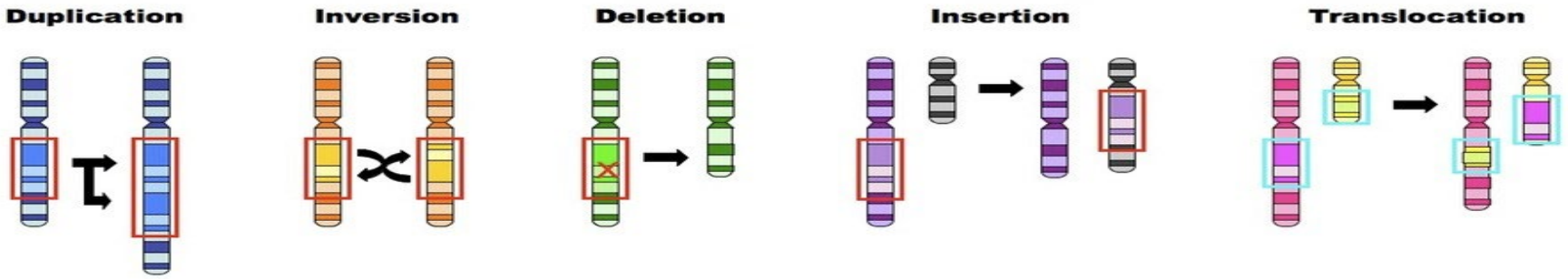

1958 – Methotrexate (an **anti-metabolite** & **antifolate**) cures the first solid tumour using chemo-therapy.
1963 – Vinca Alkaloids (**mitotic inhibitors**) are approved by the US FDA to create a new class of cancer drugs
1992 – Paclitaxel/Taxol (a **mitotic inhibitor**) is approved by the US FDA and becomes the first blockbuster anticancer drug
2001 – Imatinib/Glivec (a **tyrosine kinase inhibitor**) treats CML by targeting BCR-ABL
2013 – 3rd **ADC**, trastuzumab emtansine treats HER2+ breast cancer. It is the first ADC to target a solid tumour.
1950 - 1960
1960 - 1970
1970 - 1980
1990 - 2000
2000 - 2010
2010 - Now
1959 – Doxorubicin (an example of an **anthracycline**) is derived from *S.peuciticus* and becomes the first anticancer antibiotic.
1966 – Camptothecin (a **topo-isomerase inhibitor**) is isolated Analogues later approved by FDA.
1997 – The first anti-cancer **mAb**, rituximab is approved by the US FDA to treat B-Cell non-Hodgkin's lymphoma.
2000 – 1st **ADC**, gemtuzumab ozogamicin is approved by US FDA to treat acute myeloid leukemia. (Later withdrawn in 2010)
2014 – The **bi-specific mAb**, blinatumomab is approved by the US FDA to treat non-Hodgkin's lymphoma and ALL

Cancer :

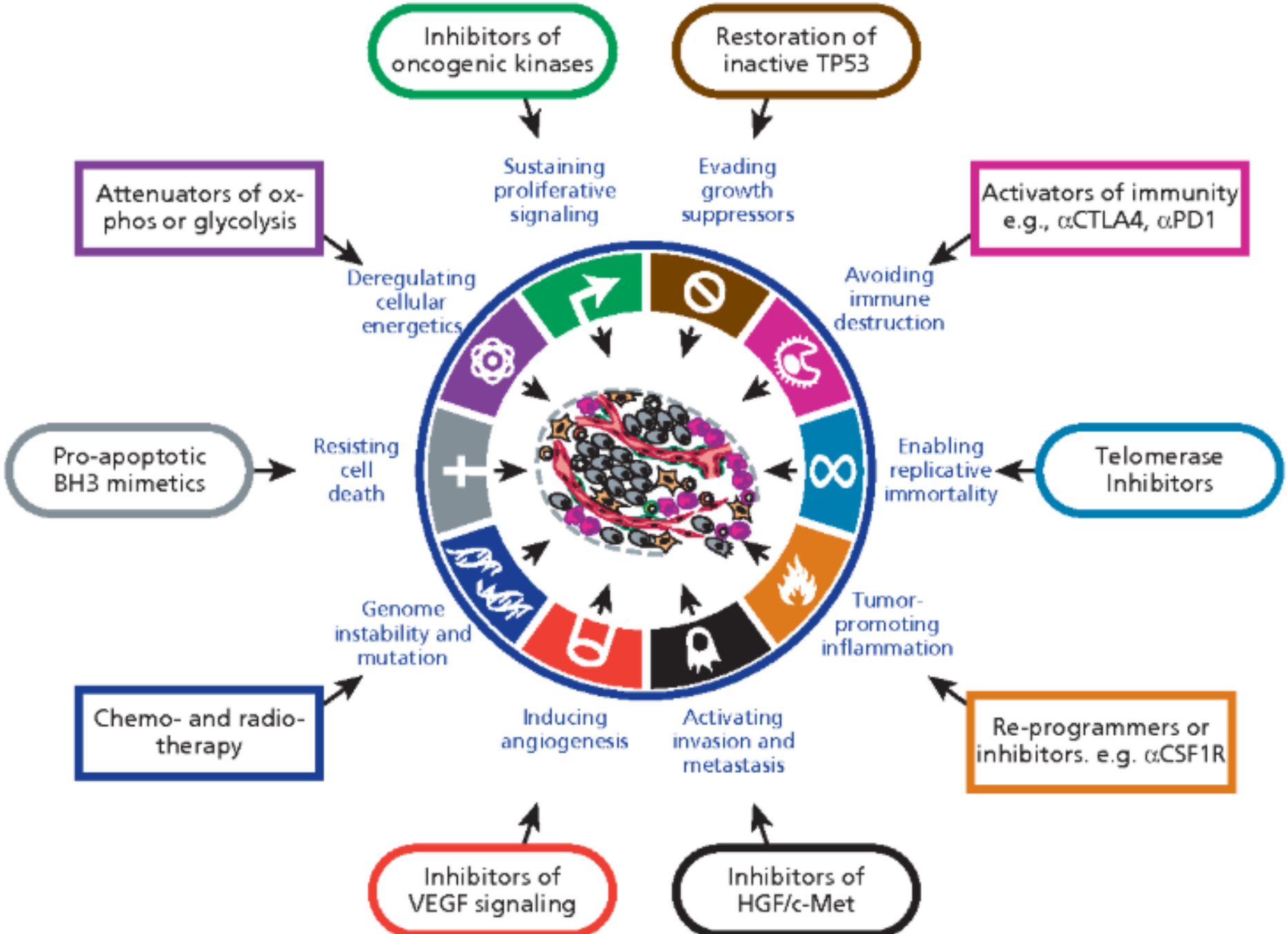


- Diseases of cells that shows uncontrolled **proliferation , anaplasia, invasivness** and ability to **metastasis .**

- Due to **Chromosomal abnormality** and expression of **oncogens** .



- **Second** most common cause of death after cardiovascular disorders in world.


Inhibitors of oncogenic kinases
Restoration of inactive TP53
Sustaining proliferative signaling
Evading growth suppressors
Attenuators of ox-phos or glycolysis
Activators of immunity e.g., αCTLA4, αPD1
Deregulating cellular energetics
Avoiding immune destruction
Pro-apoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability and mutation
Tumor-promoting inflammation
Chemo- and radio-therapy
Inducing angiogenesis
Activating invasion and metastasis
Re-programmers or inhibitors. e.g. αCSF1R
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Tumor classification: benign vs. malignant

Feature特徵	Benign Tumor良性腫瘤	Malignant Tumor (Cancer)惡性腫瘤（癌症）
Growth rate	Slow	Rapid
Invasion入侵	No invasion — remains localized	Invades surrounding tissues
Metastasis	Never	Yes (spread to other organs)
Differentiation	Well-differentiated (resembles normal tissue)良好分化（類似正常組織）	Poorly differentiated or anaplastic差異不明或未分化
Capsule膠囊	Often encapsulated經常被封裝	Rarely encapsulated罕見地被包裹
Recurrence after removal	Rare	Common
Examples	Lipoma, adenoma, fibroma脂肪瘤、腺瘤、纖維瘤	Carcinoma, sarcoma, lymphoma, melanoma癌症、肉瘤、淋巴瘤、黑色素瘤

命名

Benign良性	Malignant惡性
Nevus (mole)痣	Melanoma黑色素瘤

Benign良性	Malignant惡性
Adenoma腺瘤	Adenocarcinoma腺癌
Papilloma乳頭狀瘤	Squamous cell carcinoma鱗狀細胞癌

Benign良性	Malignant惡性
Schwannoma施旺細胞瘤	Glioblastoma, neuroblastoma膠質母細胞瘤，神經母細胞瘤

Benign良性	Malignant惡性
Lipoma (fat)脂肪瘤	Liposarcoma脂肪肉瘤
Fibroma (fibrous tissue)纖維瘤（纖維組織）	Fibrosarcoma纖維肉瘤
Chondroma (cartilage)軟骨瘤(軟骨)	Chondrosarcoma軟骨肉瘤
Osteoma (bone)骨瘤	Osteosarcoma骨肉瘤

Mostly Malignant大多數惡性

Leukemia白血病

Lymphoma淋巴瘤

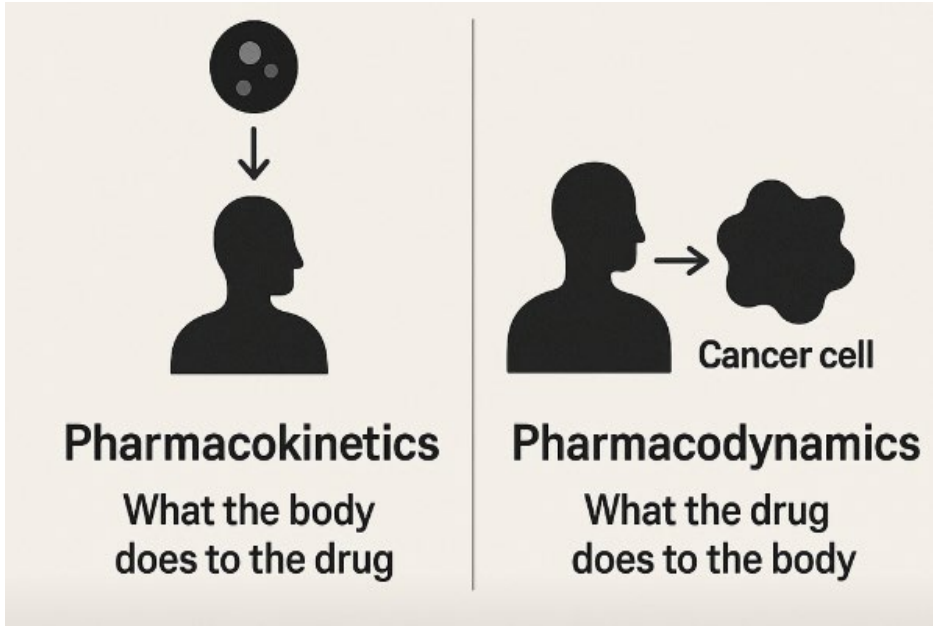
Multiple Myeloma多發性骨髓瘤

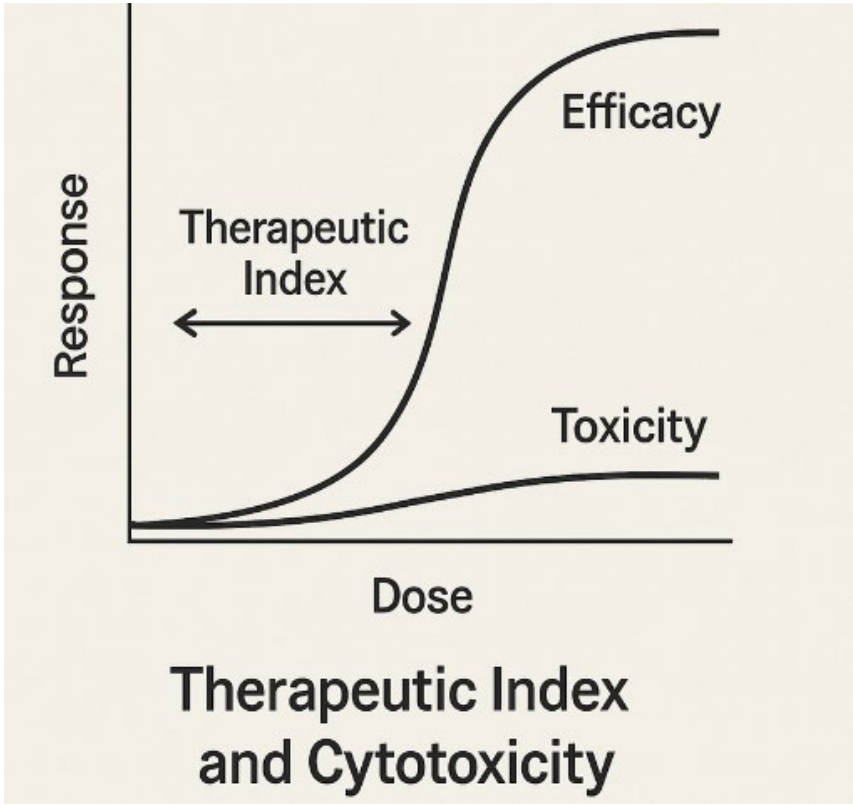
典範轉移

- 癌症藥物發展史
  - 植物: taxane (paclitaxel), vinca Alkaloid (vincristine), podophylotoxins : etoposide, Camptothecins : topotecan, irinotecan)
  - 動物 : Eribulin、Brentuximab vedotin (monomethyl auristatin E, 海洋無殼軟體動物 Dolabella aurillaryia，稱 dolastatin)
  - 細菌 : anthracyclines, bleomycin
  - 化學工業發展 : 戰爭武器 (alkylating agents), DNA 發現(antimetabolites)
- 西元2000年，在各國的通力合作下，完成了人類基因的定序草圖，而接續人類基因圖譜的解碼，也將疾病的治療由化學進入分子時代，分子的時代也等同信息、動能(Tyrosine kinase)時代的來臨，也終於等到標靶藥物的上市。
  - 機轉已超過30種，近200個藥物。
  - 第一個標靶藥物出現於2000年的Glivec，它終結了慢性骨髓白血病的骨髓移植。
- 用活細胞當藥已經來臨了。(以前的藥是沒生命的，現在是有生命的。)

Principles of Cancer Pharmacology 癌症藥理學原則

- Pharmacokinetics vs. pharmacodynamics in cancer therapy癌症治療中的藥物動力學與藥物效應學
- Therapeutic index and cytotoxicity治療指數和細胞毒性
- Drug resistance (intrinsic vs. acquired)藥物抗性（內在抗性與獲得抗性）





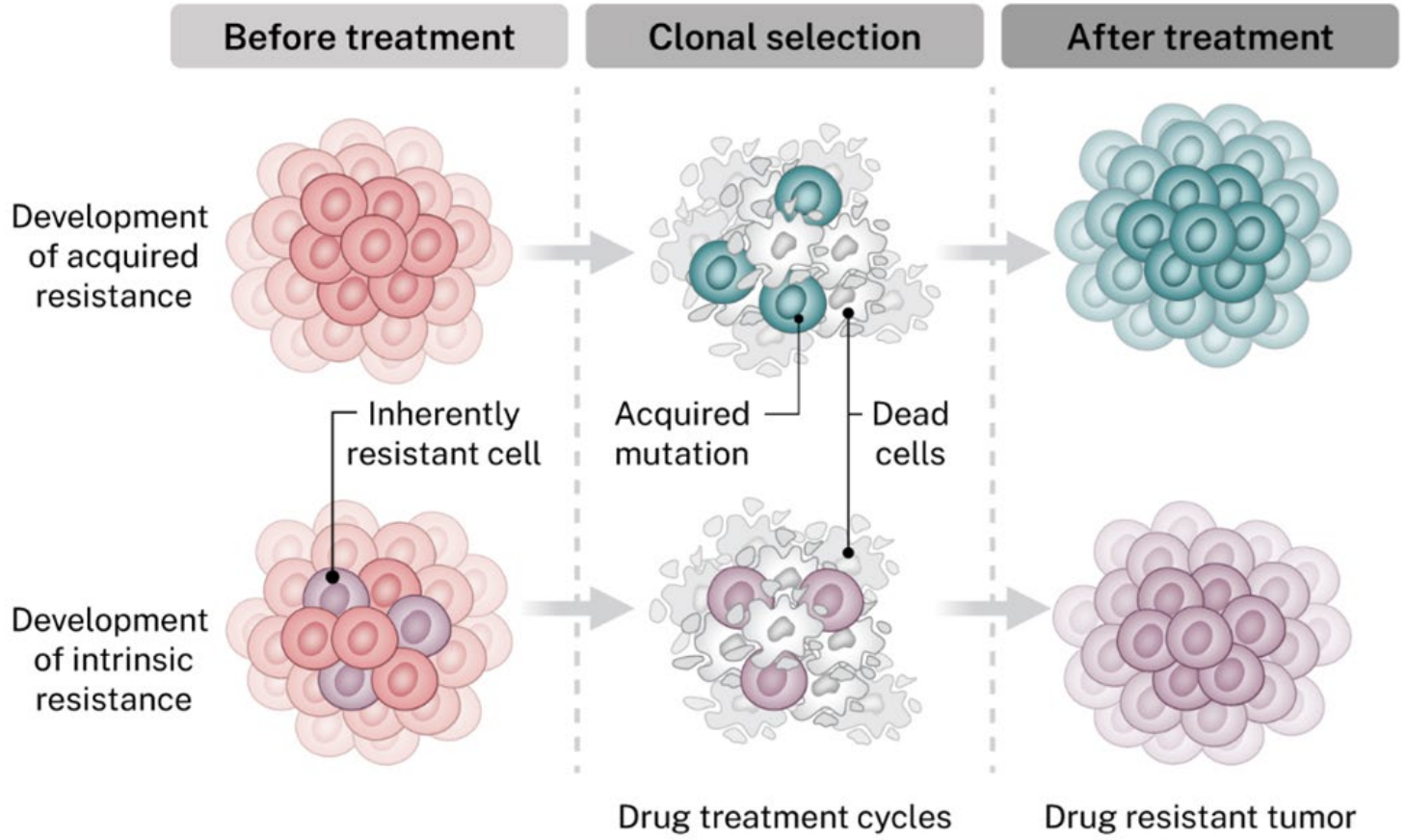
Principles of Cancer Pharmacology 癌症藥理學原則

– Drug resistance (intrinsic vs. acquired)藥物抗性（內在抗性與獲得抗性）

Primary resistance: (一開始就無效)
malignant melanoma, renal tumours.

Acquired resistance : (治療中開始無效) Due to adaption of tumour cells or due to mutation in one or more gene.

- Use of **combination drug therapy** using different classes of drugs with different mechanism of action.（合併治療）
- With **narrowest cycle intervals**, necessary for bone marrow recovery.（縮短給藥間隔）



The 1960s—The Concept of Cure

- 腫瘤專科還未存在 - as underachievers
- Vince DeVita開始其職業生涯的醫療機構中，這位「化療醫生」原本是一位內分泌科醫師
  - 病人接受化療，無醫護人員照顧
- 第一個在對人類進行化療測試的機構在耶魯醫學院
  - Paul Calabresi,一位傑出的教授，因為參與了過多的新抗癌藥物早期測試而被迫離開。
- 在國家癌症研究所的臨床中心
  - 著名的血液學家 George Brecher,閱讀了所有白血病患者的骨髓切片，白血病服務的查房稱為“屠宰場”。

Tumor burden : Gompertzian Growth

- The tumor burden is the size of the tumor as determined by the **number of cells present**.
- **Small tumor burden** → more responsive
- **Higher the tumor burden** → probability of drug resistance.
- Cancer cells usually follows **Gompertzian growth** pattern.

It is model of cancer cell growth.

"Cell rapidly divide early in life, then plateaus."

Significance :

Most anticancer drugs are ineffective in advanced cancers which have very low growth fraction.

Debulking procedures makes tumour again responsive to drugs by inducing remaining cells to divide.

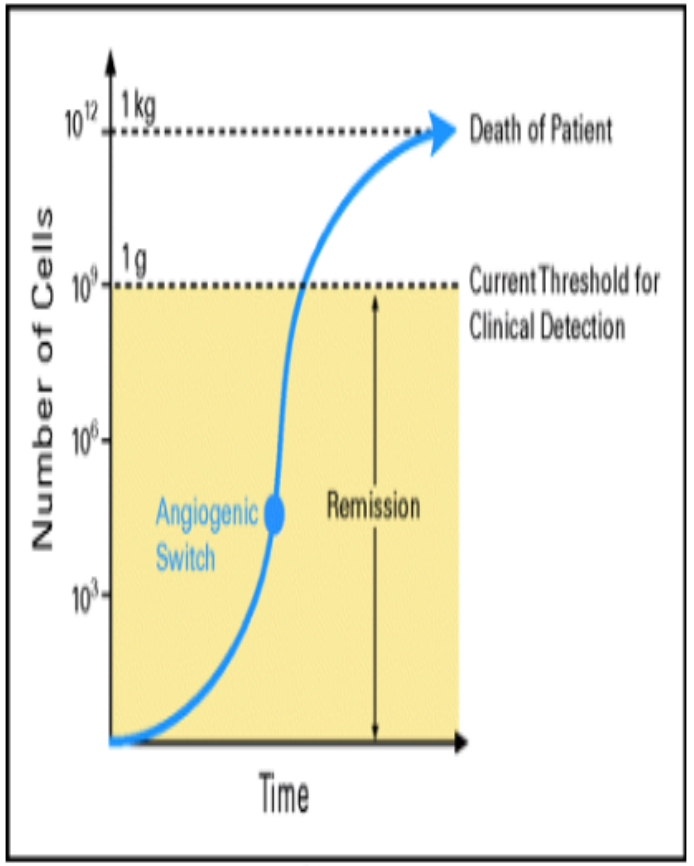
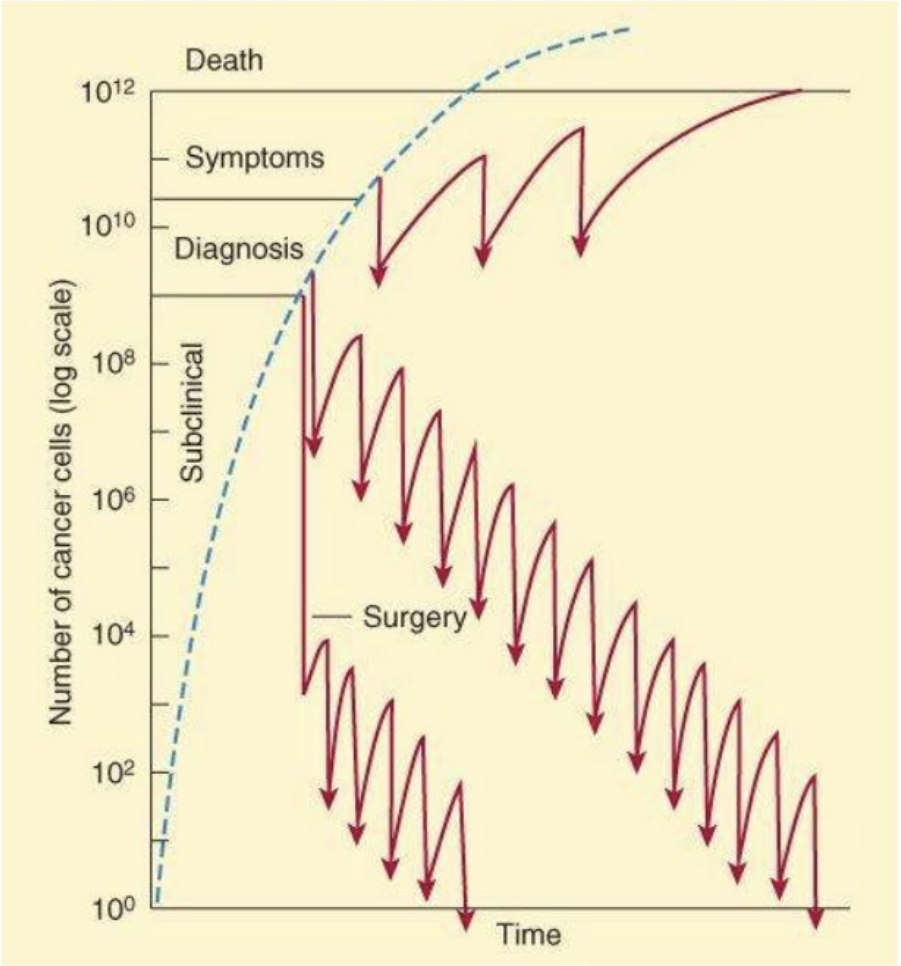


Figure 2: *Gompertzian Growth*. At 10^9, cancer is diagnosed; however at this stage cells are not in the cell cycle anymore, so they are not as responsive to treatment. 10^{12} levels are not compatible with life (death).

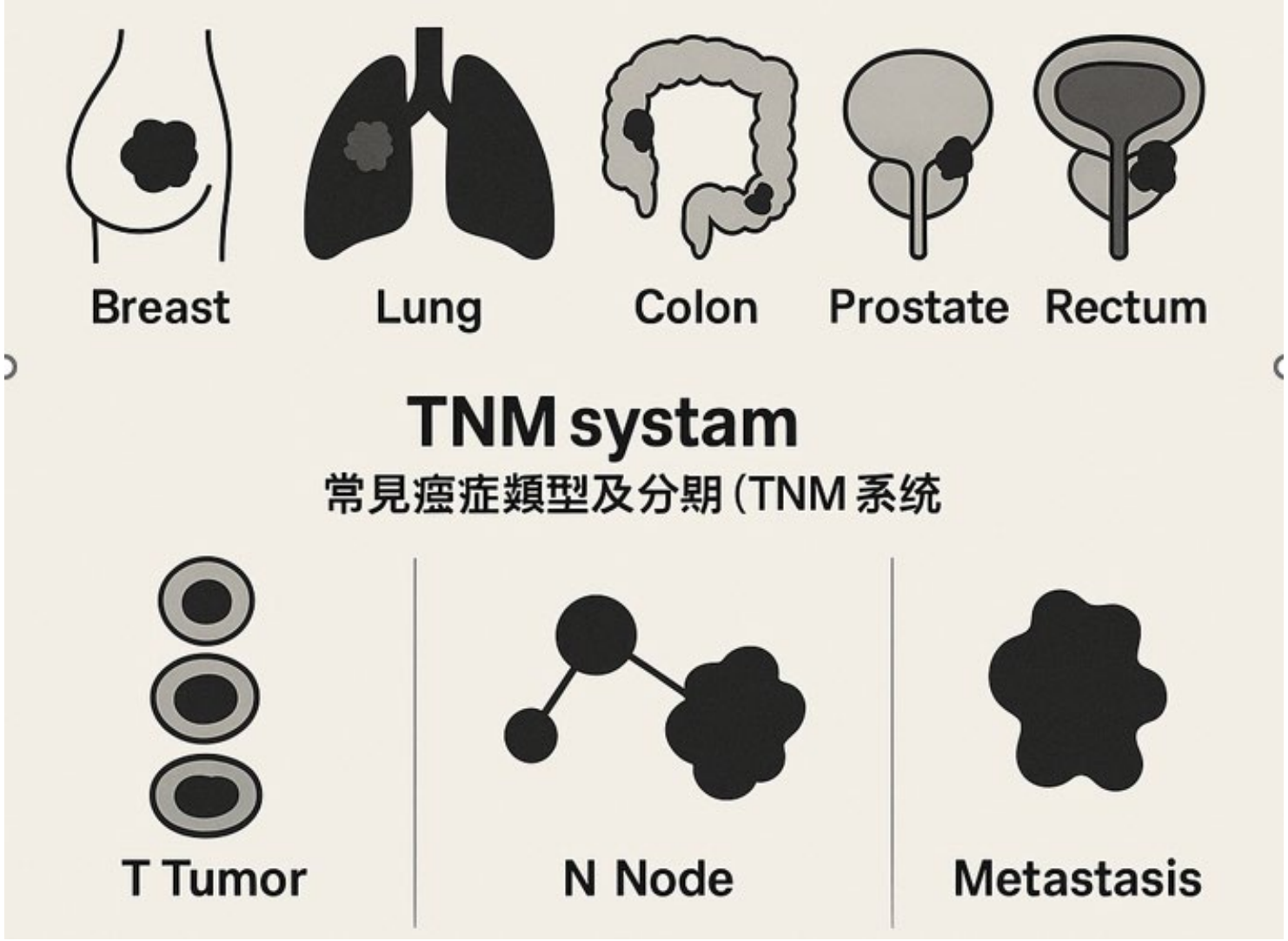
The 1960s—The Concept of Cure :A major breakthrough occurred for both leukemia and Hodgkin's disease

- Plant alkaloids at the Eli Lilly Company and of procarbazine in Hodgkin's disease
- the L1210 leukemia system had been established as both the primary screen and the model for treating acute leukemia
- Furth and Kahn : a single implanted leukemic cell was sufficient to cause the death of an animal.
- Dr. Howard Skipper, a mathematical biologist.Skipper : ''Cell Kill'' hypothesis
  - dosing in favor of more aggressive use of chemotherapy
  - the schedule s of drugs



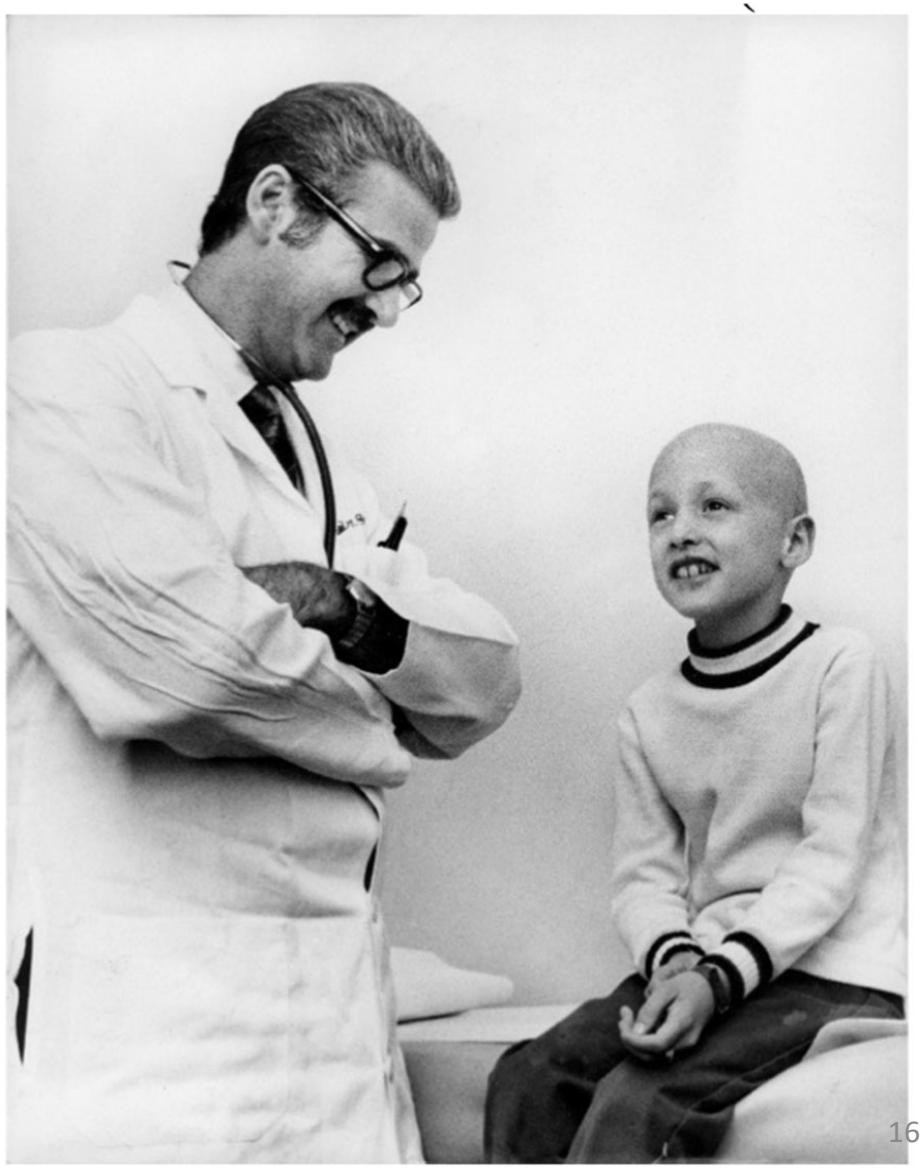
Basic & Clinical Pharmacology, 11th ed. McGraw-Hill, 2009: Fig. 54-1

Common cancer types and staging (TNM system)常見癌症類型及分期（TNM 系統）



The 1960s—The Concept of Cure

- Children : leukemia
  - "VAMP" (vincristine, amethopterin, 6-mercaptopurine, and prednisone). remission rate : In 2012 : childhood ALL is 90%. (Photo: Archive St. Jude's Hospital). 1970 : 17% cure rate
- Platelet transfusions to prevent bleeding
- Aggressive use of combinations of new and old antibiotics
- Advanced Hodgkin's disease treated with single alkylating agents. Remissions : 25%
  - DeVita, Moxley, and Frei Vinca alkaloids/ NCI procarbazine in Hodgkin's disease
  - MOPP (vincristine, procarbazine and prednisone)



Chemotherapy : Historical perspective

- 1970's - **"Golden Age"** of medical oncology.
  Development of effective **combination chemotherapy** regimens.
- New classes of drug developed - **anthracyclines, platinum** compounds .
- **Cures achieved** in some forms of cancer (lymphomas, leukemias, testis cancer).
- Significant responses in some common types of cancer (breast, stomach, small cell lung cancer)
- Effective use of chemotherapy to prevent recurrence in high risk breast cancer patients.

Dosage of chemotherapeutic agents

Dosage of chemotherapy are difficult: If the dose is too low, it will be ineffective , whereas excessive causes toxicity .

In most cases, the dose is adjusted for the **patient's body surface area (BSA),** a measure that correlates with blood volume.

The BSA is usually calculated with a mathematical formula using a patient's weight and height, rather than by direct measurement.

$$BSA = \sqrt{\frac{W \times H}{3600}}$$

W is weight in kg, and
H is height in cm.

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

化療合併治療
Principles of combination therapy

合併兩種以上，對腫瘤有效的化療。
20多年最重要的癌症治療進展

- Prevention of resistant clones. (預防抗藥株)
- Cytotoxicity to resting and dividing cells.(對停止或分裂細胞有毒殺作用)
- Biochemical enhancement or effect – Synergistic effect (協同作用)
  - Higher tumor response rates (高腫瘤反應率)
  - Increased duration of remissions. (增加緩解的時間)
  - Minimal chances of resistance. (較低的抗藥性)

Principles for selecting drugs for combination regimens (合併藥物選擇)

- Active as **single** agents (單一有效藥物)
- Different **mechanism** of action (不同機轉)
- Different dose limiting **toxicity (不同自限毒性)**
- Used at **optimal dose and schedule (合理劑量與間隔)**
- Given at **consistent interval (給藥時間固定)**
- Different **resistance** mechanism (不同拮抗機轉)
- Drugs with known synergistic biochemical interaction (生物協同作用)
- **Cell kinetics scheduling**: on basis of cell cycle specificity / non specificity of drugs and phase of cycle at which drug exert toxicity. (細胞動力間隔)

Examples of combination therapy

MOPP – Hodgkin's Disease

Drug(s)	Toxicity	% Full Dose	% Remission
Nitrog. Mustard	Marrow	100	10
Vincristine (VCR)	Neuropathy	100	5
PRED	Steroid	100	5
Procarbazine	Marrow	100	15
MOPP		60/100/100/60	70 (50% cure)

VBP – Testis

Drug(s)	Toxicity	% Full Dose	% Remission
vinblastine	Marrow	100	20
Bleo	Lung	100	0
Cis-Platinum	Kidney	100	20
VBP		100/100/100	90 (70% cure)

Important drug combinations

REGIMEN	CANCER	DRUGS
ABVD	Hodgkin's	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
CHOP-R	NHL	Cyclophosphamide, Hydroxydaunorubicine, Vincristine, Prednisolone, Rituximab
VAMP	ALL	Vincristine, Amethopterine, 6 MP, Prednisolone
FOLIFIRI	COLON CANCER	5 FU, Leucovorin, Irinotecan,

The 1970s:輔助治療的時代

- In 1973, 腫瘤科才成為內科中的次專科。
- 90% 的乳腺癌呈現局部區域性疾病。\
  - Skipper’s cell kill hypothesis 與可治癒性之間的恆定反比關係在只有微轉移的輔助情況下效果更佳
- 1960 年代末期在晚期乳腺癌中使用的聯合化療取得了一些令人鼓舞的結果
- CMF ((cyclophosphamide, methotrexate, and 5-flurouracil）作為輔助化療
- Bernard Fisher，國家外科輔助乳腺計劃（NSABP），已經進行了一項早期輔助研究輔助化療
  - 在 2008 年，已見證大大降低乳癌與大腸直腸的死亡率。

Current Treatment Modalities of Cancer

癌症的現行治療策略

- **Surgery (手術)**
- **Radiotherapy** (放療)

- For solid cancers
- 1/3 of patients can be cured,
- Effective when tumor has not metastasized

- **Chemotherapy, Immunotherapy, Gene therapy**

Choice of therapy depends upon the

- Location of tumour (位置)
- Stage of tumour (期別)
- General state of the patient. (病人狀況)

Goals of chemotherapy (化療目的)

To Cure

- Wilm's tumor, ALL, Testicular cancer, Burkitt's lymphoma, NHL

To Control

- Prolong remission
- Decreases rate of relapse

Palliation

- Relive symptoms and improved quality of life

Types of chemotherapy

1. Primary Chemotherapy

- Chemotherapy is main modality of treatment
- Can be single drug or combination chemotherapy
- e.g. Hematological malignancy-
- ABVD regimen for hodgkins lymphoma.

2. Adjuvant Chemotherapy

- Combined with radiation or surgery.
- For advanced cancer
- e.g. Ca breast After surgery to remove microscopic foci.

Types of chemotherapy

3. Neoadjuvant chemotherapy

- Chemotherapy is given before surgery.
- Shrink a large cancerous tumour to make surgery easy.
- e.g. laryngeal carcinoma before surgery.

4. Concurrent chemotherapy

- Simultaneously with Rad iation.
- mainly act as radiation sensitizer, enco urages the cancer cells to take radiotherapy.
- e.g.Head and neck CA, rectal CA, lung CA

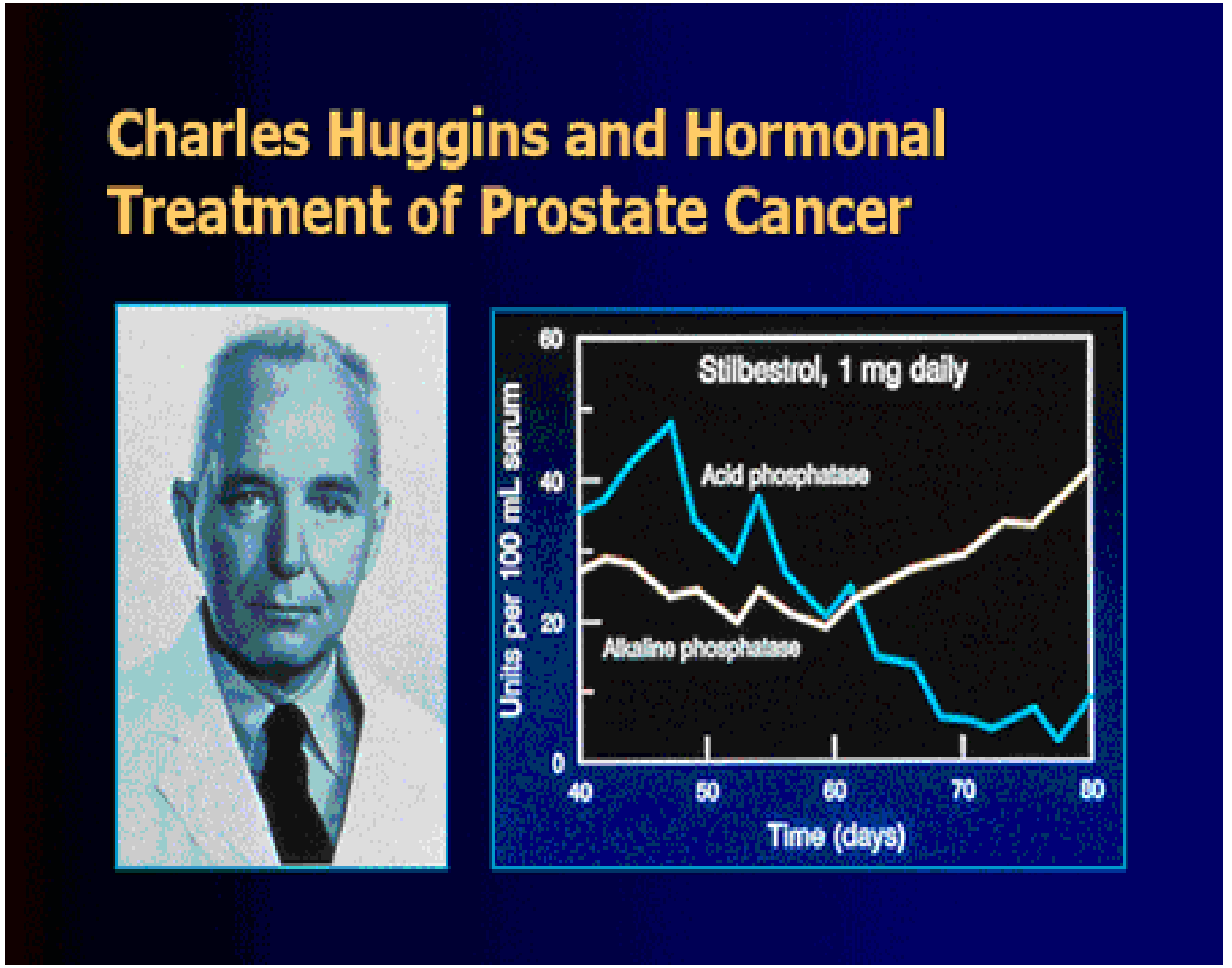
Sensitivity of various tissues to chemotherapy
（各種組織對化療敏感度）

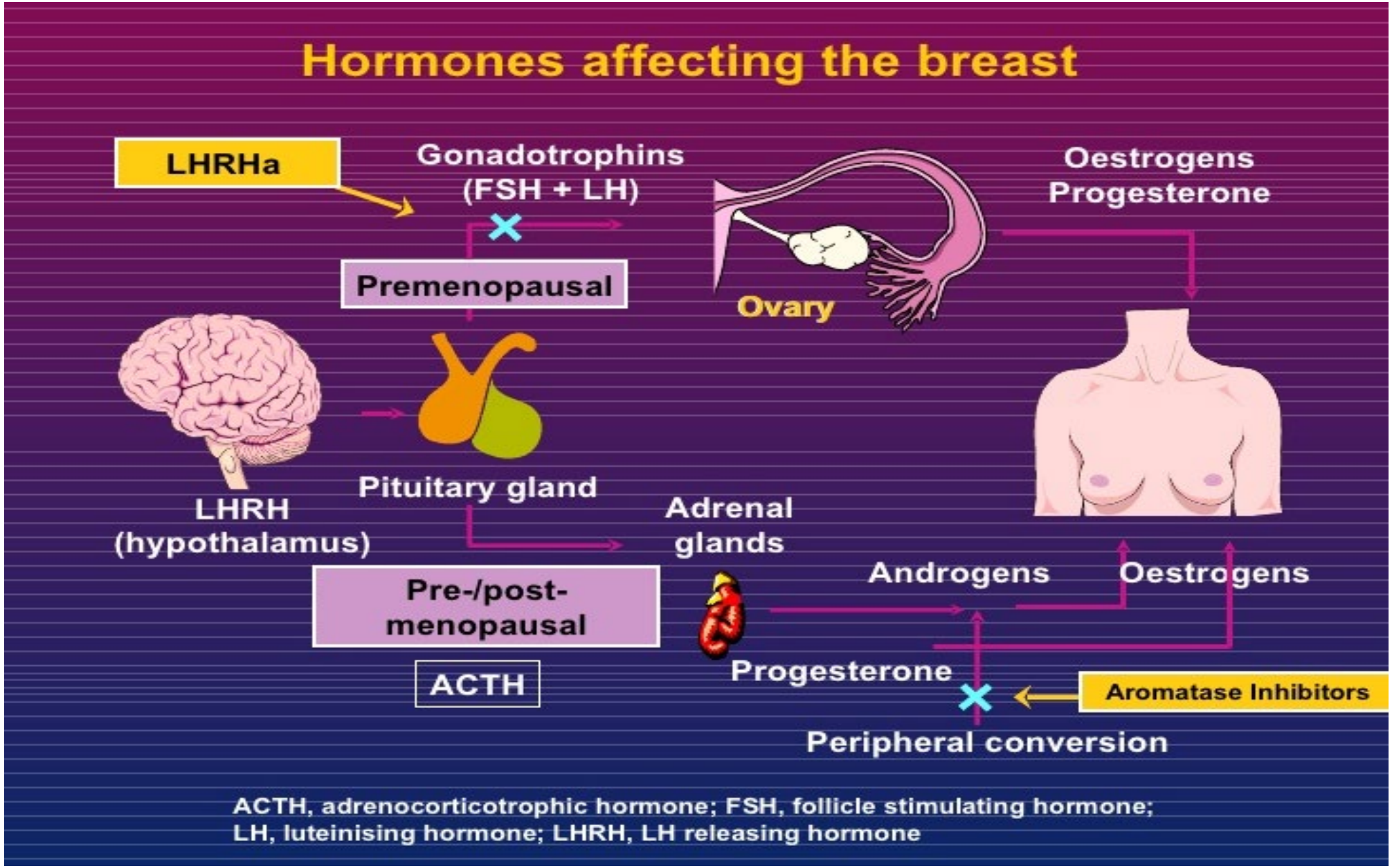
High	Intermediate	Low
Lymphoma	Breast	Head and neck
Leukemia	Colon	Prostate
Small Cell Lung cancer	Non-small cell lung cancer	Gastric
Testicular cancer		Pancreatic

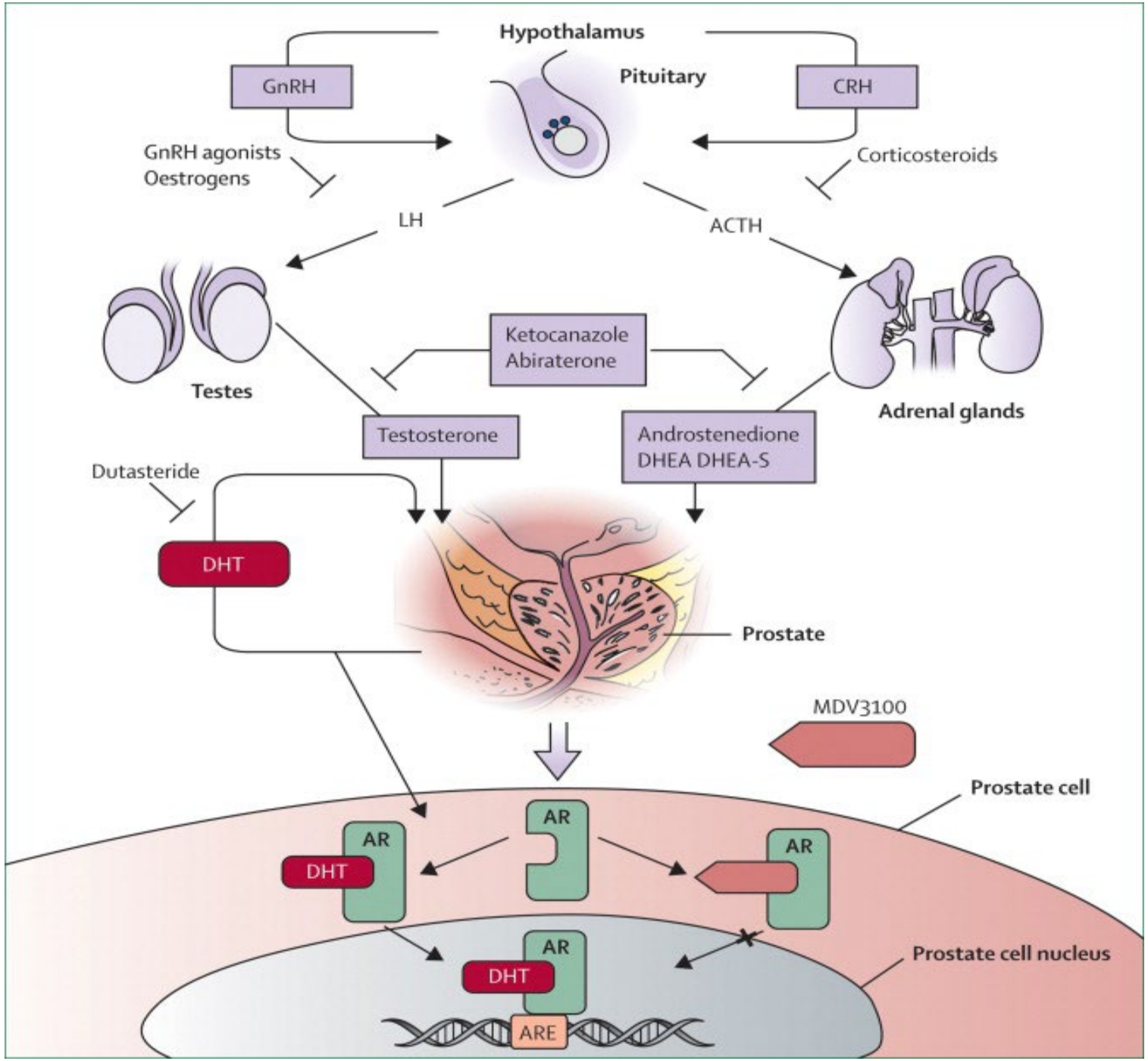
Hormones and antagonists
(Breast cancer and Prostate cancer)

The early period of cancer drug development

- Introduction of hormonal therapy in 1939 by Charles Huggins : early observation on the effect of estrogens on breast cancer
  - **Nobel prize Physiology or Medicine 1966**




Hormones affecting the breast
LHRHa
Gonadotrophins
(FSH + LH)
Premenopausal
Ovary
Oestrogens
Progesterone
LHRH
(hypothalamus)
Pituitary gland
Adrenal
glands
Pre-/post-
menopausal
ACTH
Androgens
Oestrogens
Progesterone
Aromatase Inhibitors
Peripheral conversion
ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone;
LH, luteinising hormone; LHRH, LH releasing hormone


Hypothalamus
Pituitary
GnRH
CRH
GnRH agonists
Oestrogens
Corticosteroids
LH
ACTH
Testes
Ketocanazole
Abiraterone
Adrenal glands
Testosterone
Androstenedione
DHEA DHEA-S
Dutasteride
DHT
Prostate
MDV3100
Prostate cell
AR
DHT
AR
AR
DHT
Prostate cell nucleus
ARE

Hormones and antagonists

CLASS	DRUGS	MAJOR USES
Glucocorticoides	Prednisone	ALL, CLL, HL, multiple myeloma
Progestins	Hydroxyprogesterone caproate, Medoxyprogesterone acetate, Megestrol acetate	Endometrial, breast cancer
Estrogens	Diethylstilbestrol, Ethinyl estradiol	Breast, prostate cancer
Anti-estrogens	Tamoxifen, Toremifene,	Breast cancer
Aromatase inhibitors	Anastrozole, Letrozole,	Breast cancer
Androgens	Testosterone propionate	Breast cancer
Antiandrogen	Flutamide , casodex	Prostate cancer
GnRH analogue	Leuprolide	Prostate cancer

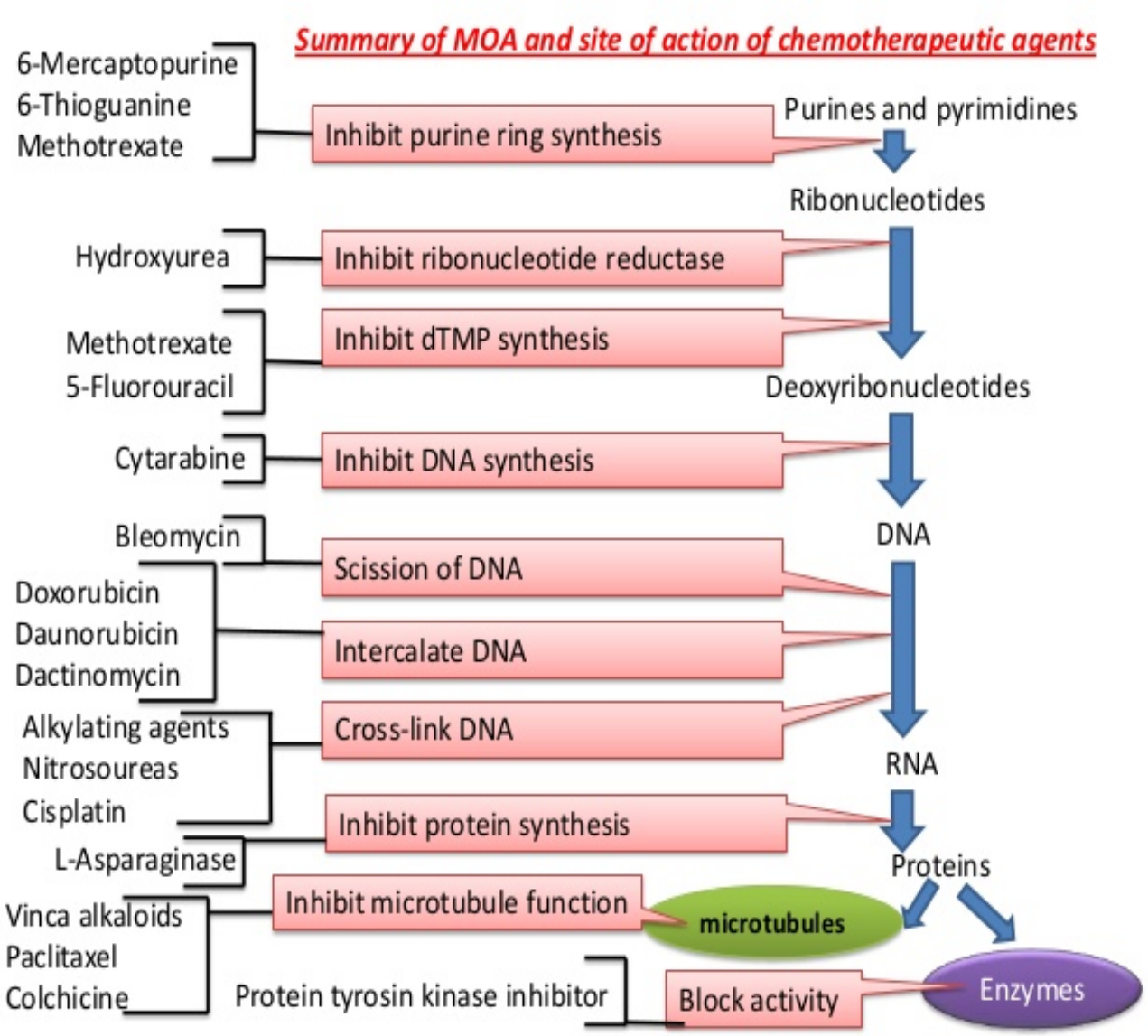
The early period of cancer drug development

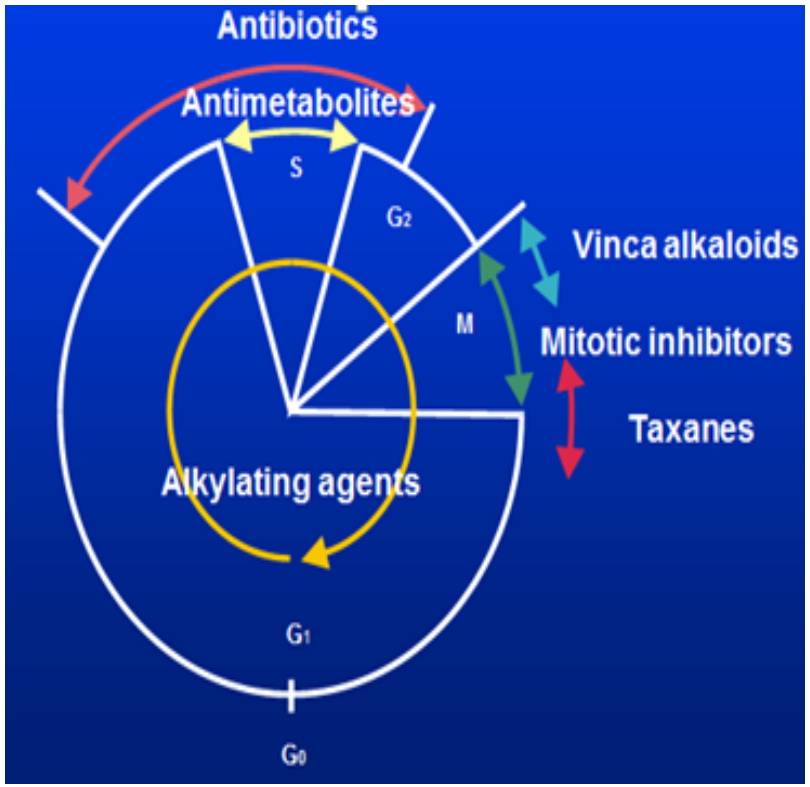
- Nutritional research before and during WWII had identified a factor present in green leafy vegetables that was important for bone marrow function
  - Folic acid, first synthesized in 1937
  - Folic acid deficiency : nitrogen mustard
- Farber, Heinle, and Welch tested folic acid in leukemia
  - Accelerated leukemia

Drug Classes and Mechanisms
Cytotoxic Chemotherapy

- Alkylating agents (烷基化劑)
- Antimetabolites (抗代謝劑)
- Topoisomerase inhibitors (拓撲異構酶抑制劑)
- Microtubule inhibitors (微管抑制劑)
- Side effect profiles and nursing considerations (副作用特徵和護理考量)

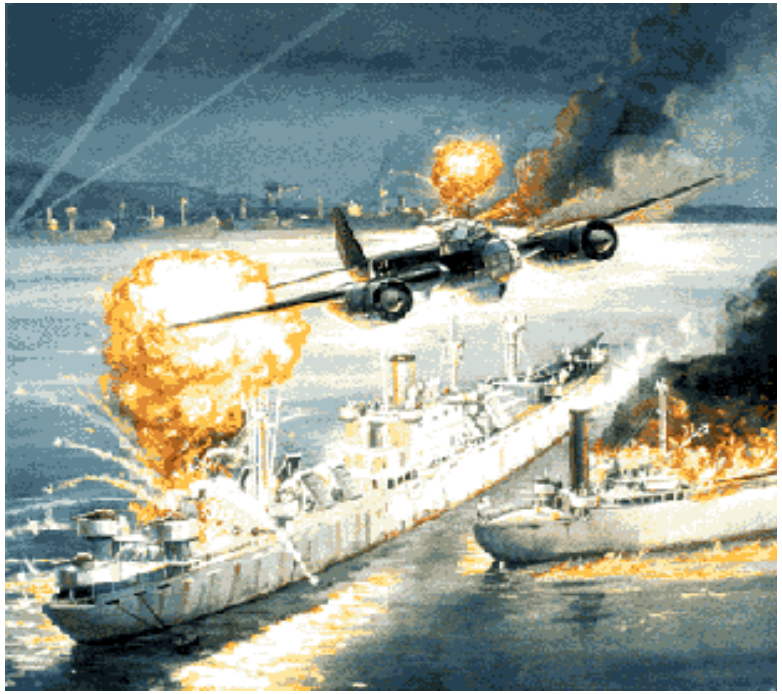
Anticancer drugs : classification

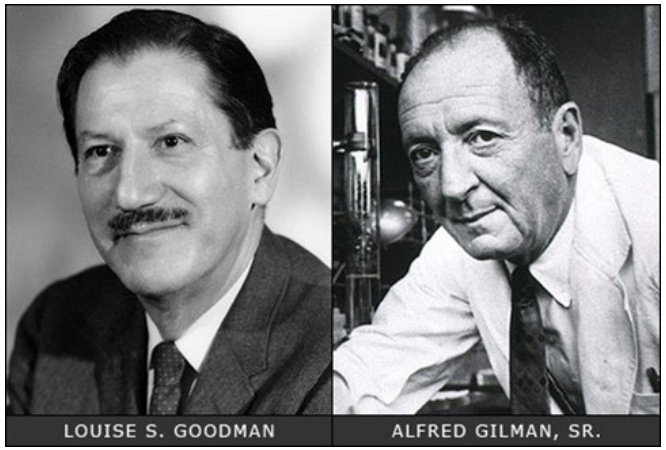




The early period of cancer drug development

- 1943 ： spill of sulfur mustards on troops from a bombed ship in Bari Harbor, Italy, in WWII
  - bone marrow and lymph nodes were markedly depleted
- The U.S. Office of Scientific Research and Development and asked Yale pharmacologists, Alfred Gilman and Louis Goodman
  - to examine the potential therapeutic effects of these chemicals.





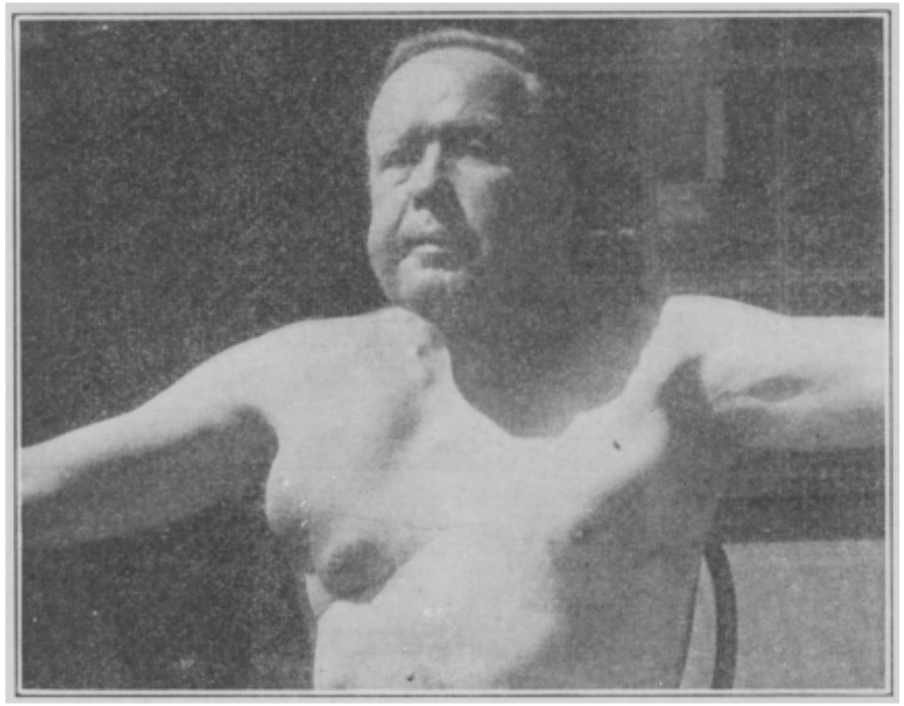


Fig. 1 (case 2).—Appearance in terminal lymphosarcoma in the radiation resistant stage four days after initiation of *tris*(β-chloroethyl)amine hydrochloride therapy. Improvement in well-being, strength, appetite and temperature but no visible change in size of tumor masses.

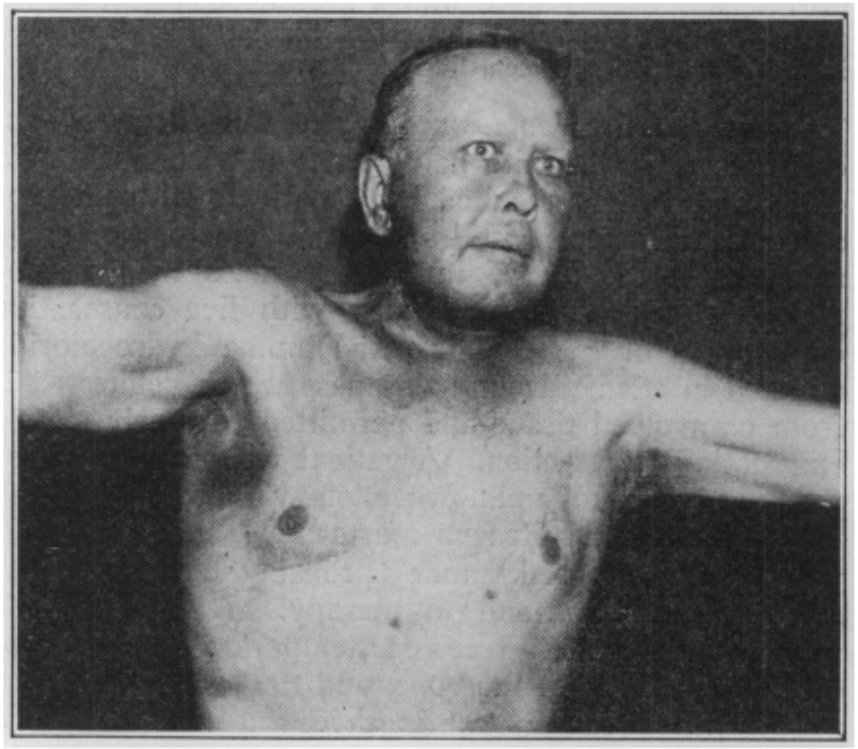
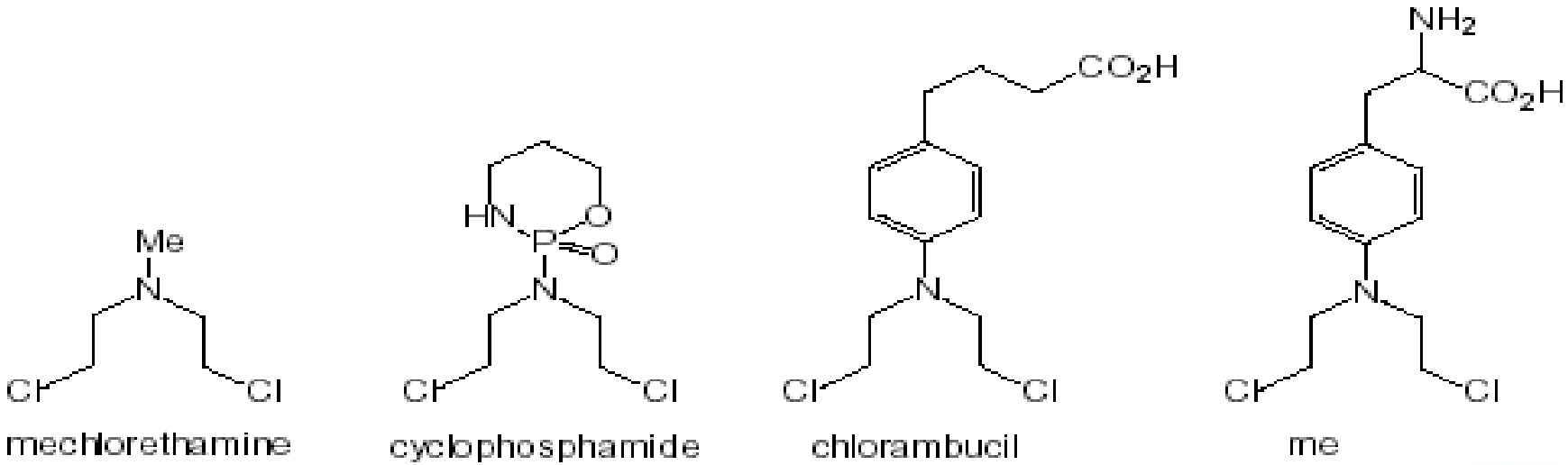
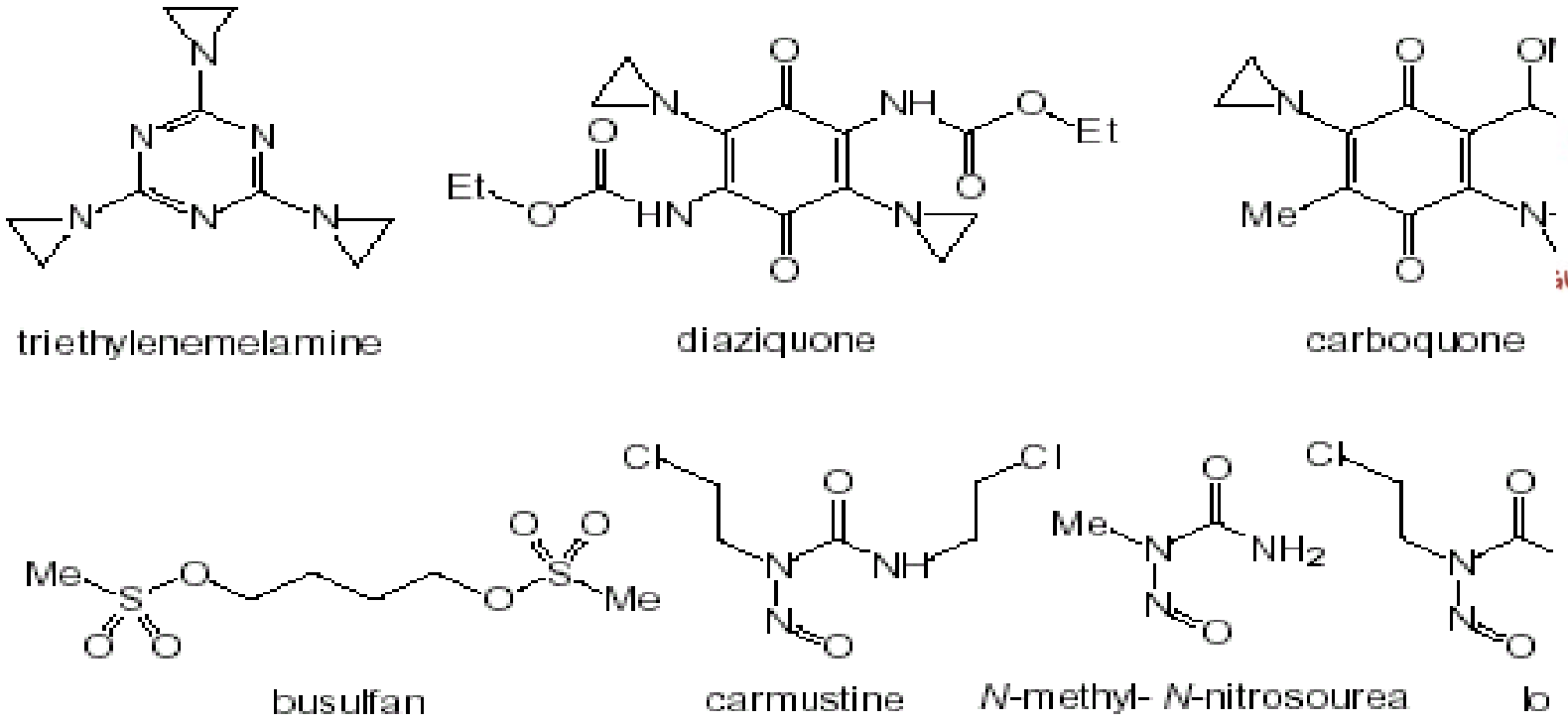


Fig. 2 (case 2).—Eight days later and two days after the last dose. Complete disappearance of tumor masses in axillas, neck, jaw and thorax, with decided improvement in the patient's condition.

GOODMAN, LOUIS S.. (1946). NITROGEN MUSTARD THERAPY. Journal of the American Medical Association, 132(3), 126–129.

ALKYLATING AGENTS





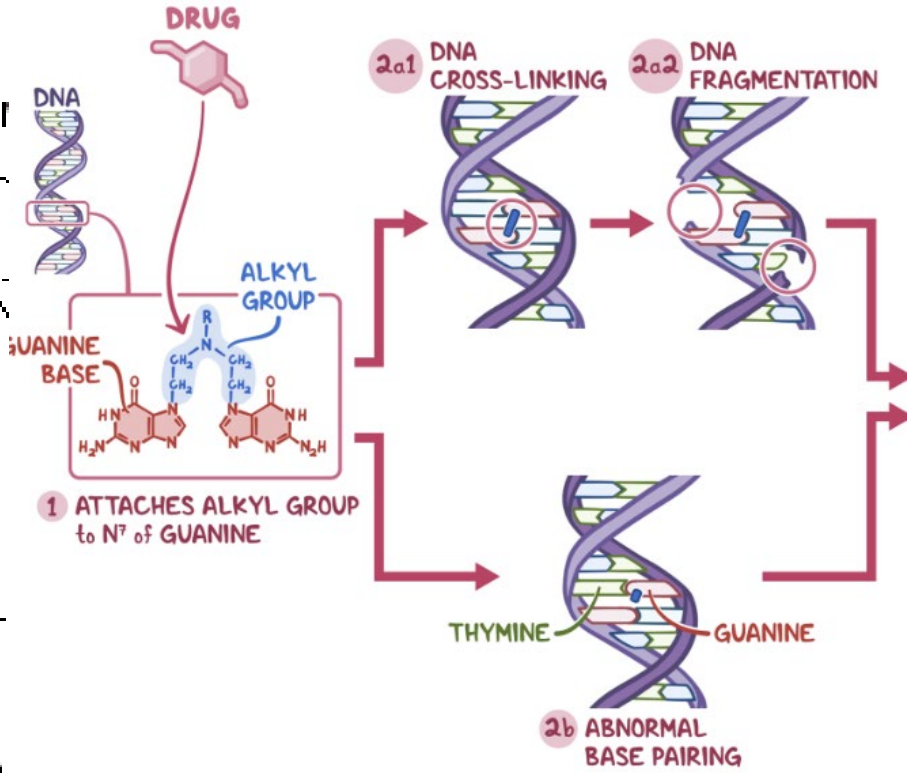


Figure 6. DNA alkylating drugs used in cancer treatment

ALKYLATING AGENTS

- **Nitrogen mustards**
  - Chlorambucil (Leukaran)
  - Bendamustine (Treanda®)
  - Cyclophosphamide (Cytoxan)
  - Ifosfamide
  - Melphalan (Alkeran)
  - Mechlorethamine (Mustargen®)
- **Ethylenimines**
  - Thiotepa (Thioplex®)
- **Nitrosoureas**
  - Carmustine (BCNU, BiCNU)
  - Lomustine (CCNU, CeeNU)
  - Semustine (methyl-CCNU)
  - Streptozocin (Zanosar)
- **Alkyl sulfonates**
  - Busulfan
- **Triazenes (methylating agents)**
  - Dacarbazine (DTIC-DOME)
  - Procarbazine
  - Streptozotocin,
  - Temozolomide
- **Platinum analogues**
  - Cisplatin (Platinol)
  - Carboplatin (Paraplatin)
  - Oxaliplatin (Eloxatin®)

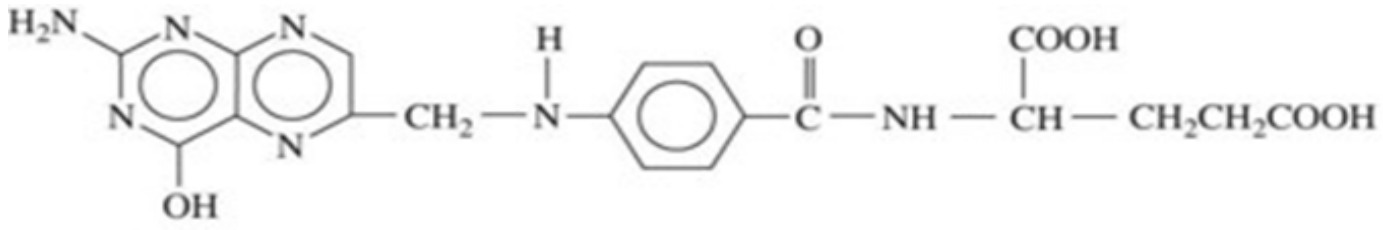
Platinum(cisplatin, carboplatin, Oxaliplatin) induced anaphylaxis

- A 63-year-old woman with hypertension/asthma/COPD was diagnosed with cancer in the descending colon.
  - left hemicolectomy and T-loop colostomy in February 2022 (classify stage pT3N1)
  - six cycles of mFOLFOX6 chemotherapy (adjuvant therapy)
- Liver metastases in June 2022 via CT scan
  - UFUR/leucovorin at MMH
  - Avastin/FOLFIRI, In March 2023, laparoscopic surgery for liver metastases (hepatectomy, cholecystectomy, and radiofrequency ablation (RFA).
  - Pathology : metastatic adenocarcinoma, KRAS gene mutation. Resumed Avastin/FOLFIRI therapy.
- In July 2023
  - CT and PET-CT scans : recurrent tumors, including a hypermetabolic lesion in the liver and another in the left para-iliac region
  - underwent CT-guided RFA for the liver lesion, followed by the surgical removal of the left external iliac tumor.
  - A follow-up CT scan : a 4.6 cm recurrent liver lesion
- two cycles of Avastin and mFOLFOX6 with good tolerance in January 2024
- On February 13, 2024, for her third cycle. After receiving 60 ml of Oxaliplatin, she developed acute dyspnea and desaturation (SpO2: 88%), necessitating non-rebreather (NRB) oxygen therapy. BP rose sharply to 206 mmHg. Treatment : hydrocortisone, diphenhydramine, famotidine, intramuscular epinephrine, and a nebulizer with a dual bronchodilator partially improved her respiratory distress. She required NRB oxygen support.
- Oxaliplatin allergy/ how to management

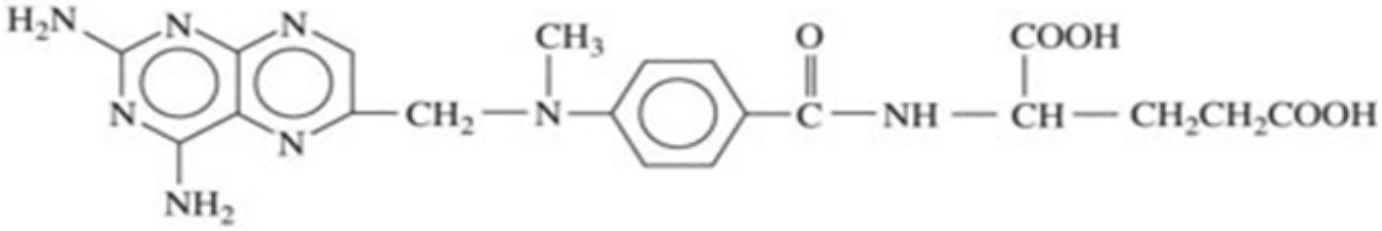
Alkylating agents

CLASS	DRUGS	MAJOR USES
Nitrogen Mustards	Meclorethamine	HL, NHL
	Melphalan	Multiple myeloma; breast, ovarian cancer
	Chlorambucil	ALL, CLL , HL, NHL, Multiple myeloma; Neuroblastoma; Breast, Ovary, Lung cancer; Wilms' tumor; cervix, testis cancer;
	Cyclophosphamide	
	Ifosfamide	
Etylenimine	ThioTEPA	Bladder, breast, ovarian cancer
Alkyl sulfonte-	Busulfan	CML
Nitrosoureas	Carmustine	Primary brain tumor; Melanoma, HL,NHL,
	Streptozocin	Pancreatic insulinoma; Malignant carcinoid
Triazine	Dacarbazine	Malignant melanoma;

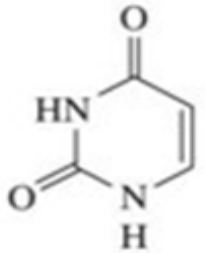
Antimetabolites



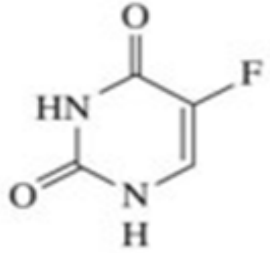
Folic acid



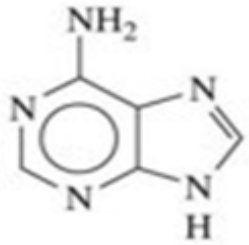
Methotrexate



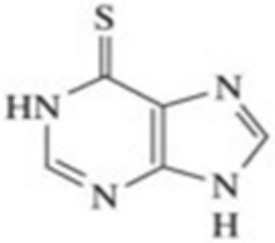
Uracil



Fluorouracil

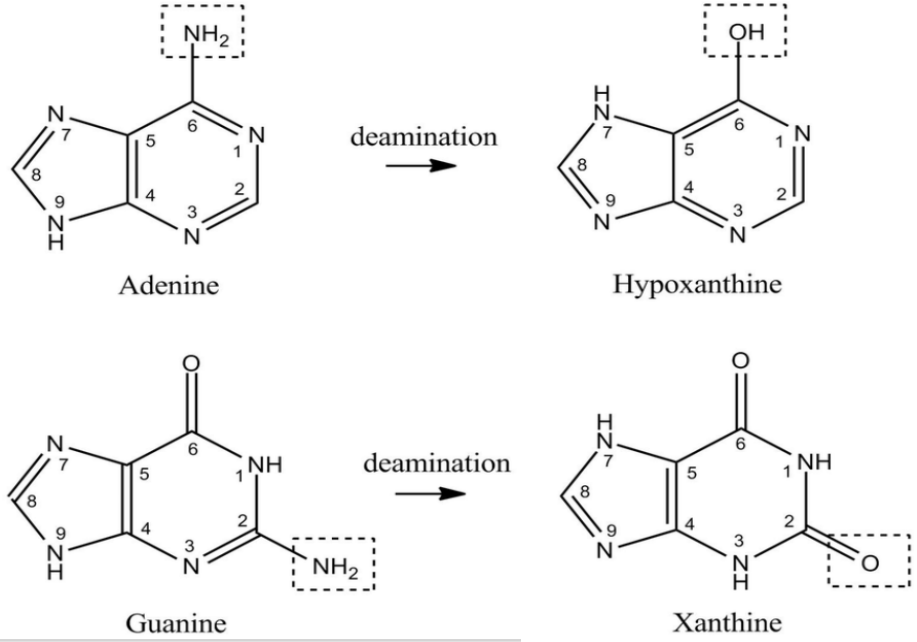


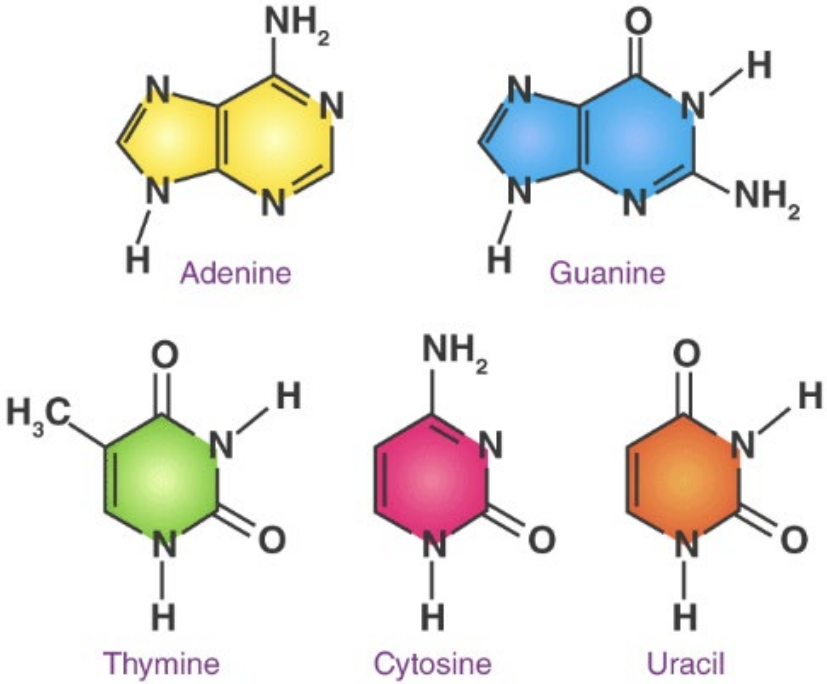
Adenine

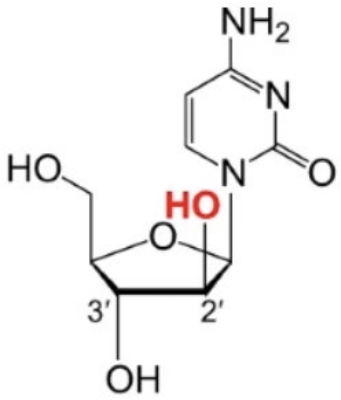


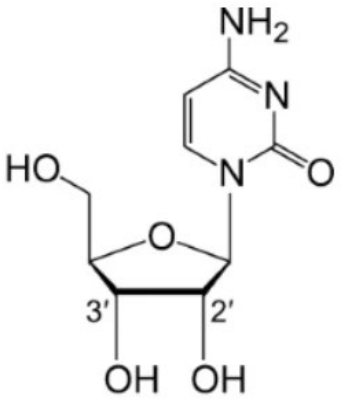
Mercaptopurine

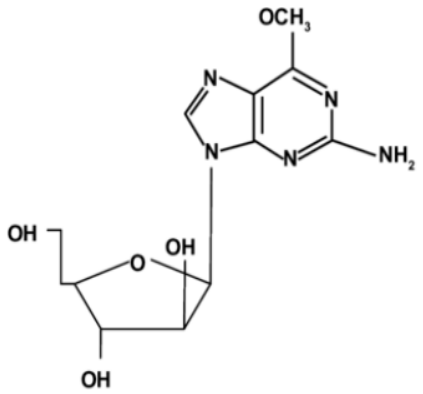
Tricks


deamination
Adenine
Hypoxanthine
deamination
Guanine
Xanthine


Adenine
Guanine
Thymine
Cytosine
Uracil


Cytarabine, AraC


Cytidine, C

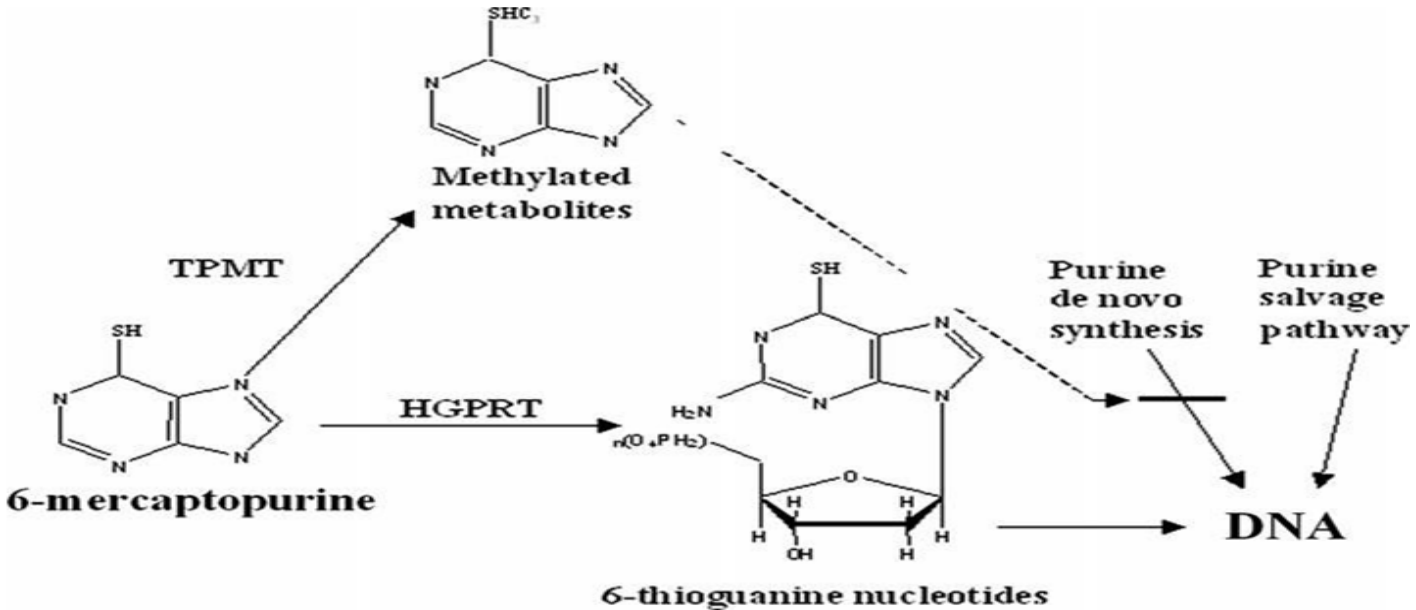

Nelarabine

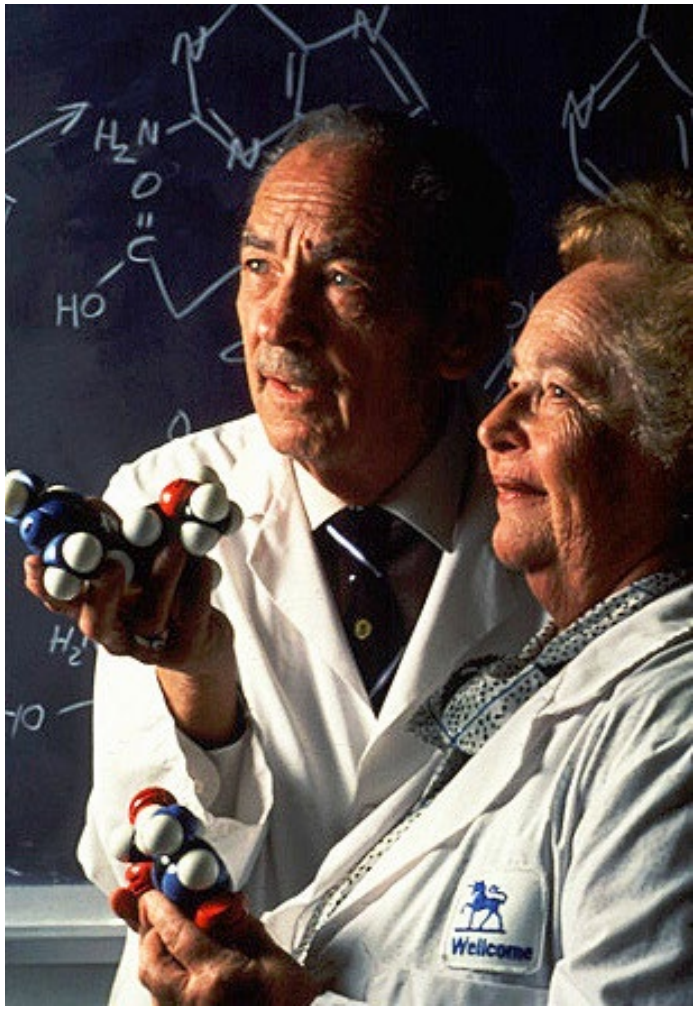
Chemotherapy : Historical perspective

1950- **Actinomycin D** was developed as antibiotics, but found to be very toxic but have significant antitumour activity

1951 - Hitchings and Elion isolated **6-thioquanine and 6-mercaptopurine** that inhibited purine metabolism, which are widely used for various cancer and as immunosuppressant.

- The Nobel Prize in Medicine in 1988.



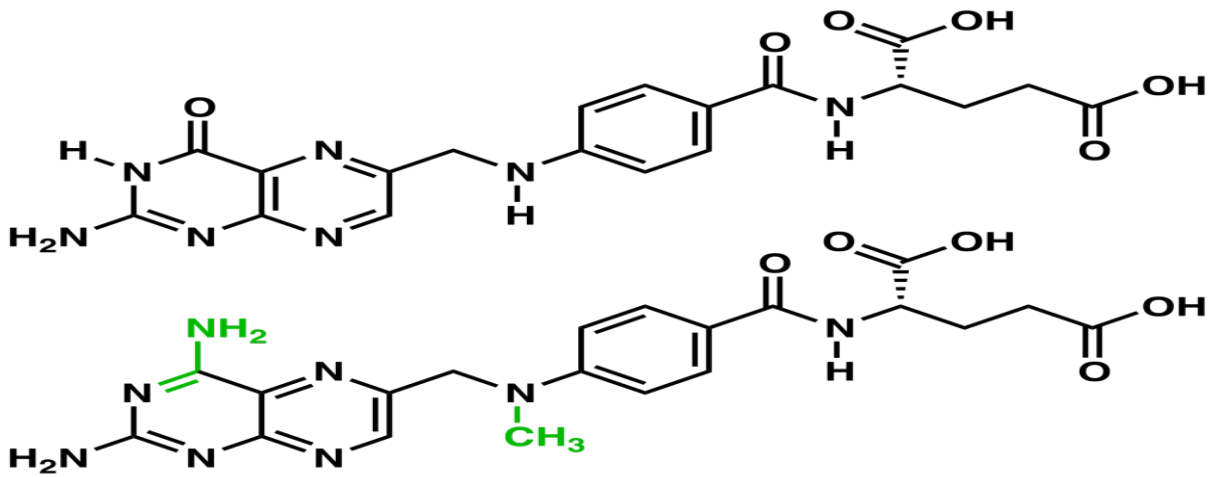


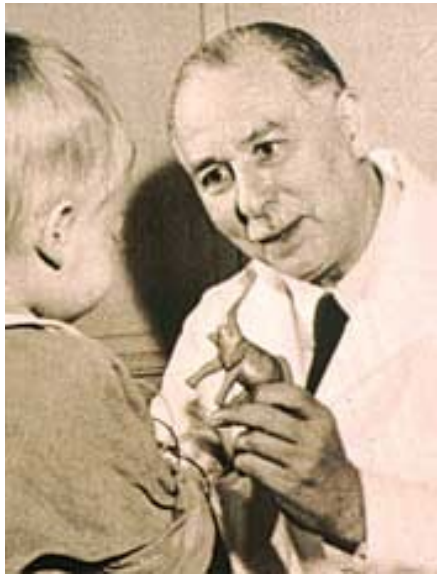
Chemotherapy : Historical perspective

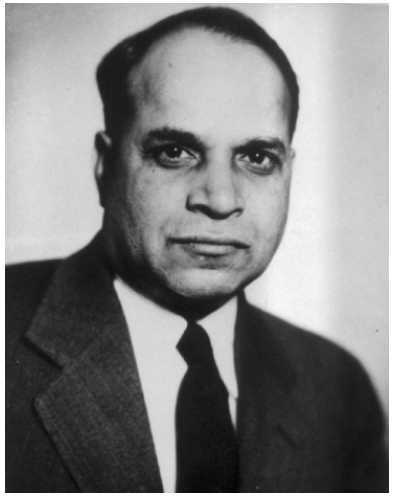
1948 - **Sidney Farber** showed that **aminopterin**, a folic acid analogue, developed by **Y. Subbarao** can induced remission in acute lymphoblastic leukemia.

Latter more safer amethopterin
(Methotrexate) was developed.

Folic acid vs Methotrexate







Y. Subbarao

Folate antagonist

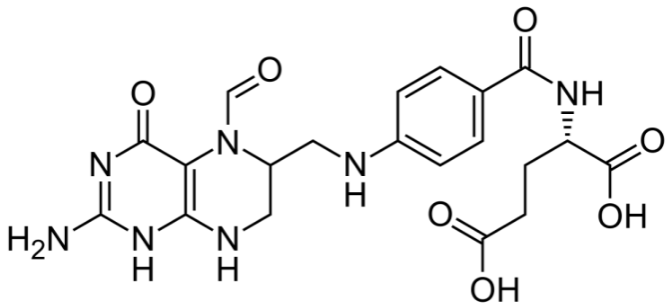
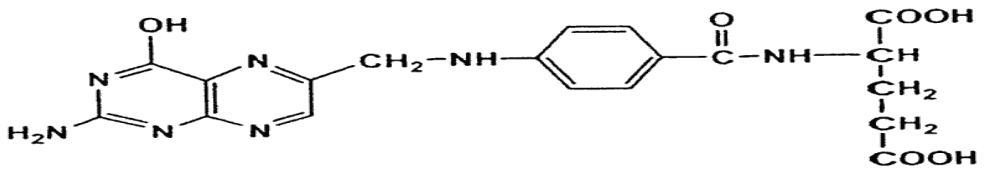
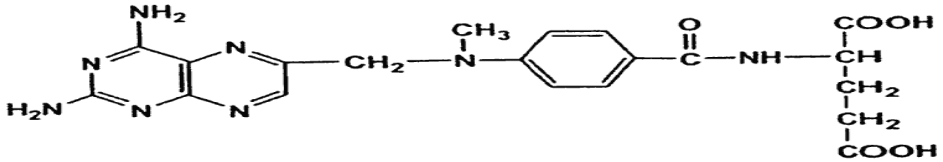


Figure 01: Chemical Structure of Folinic Acid



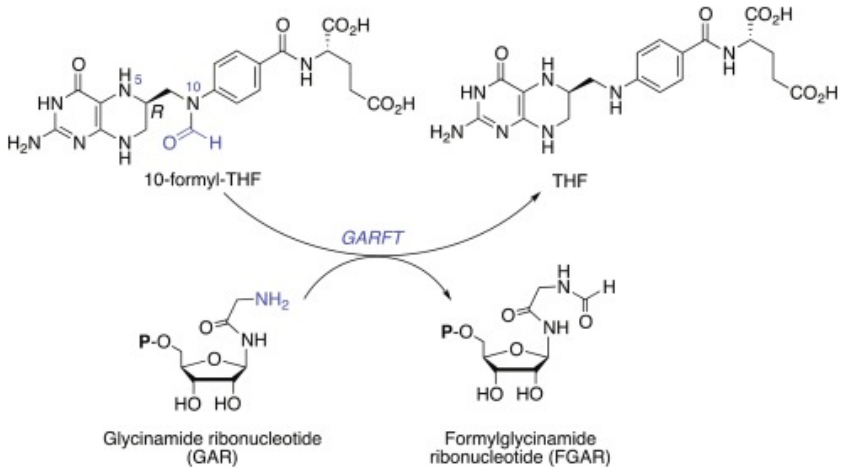
Folic acid



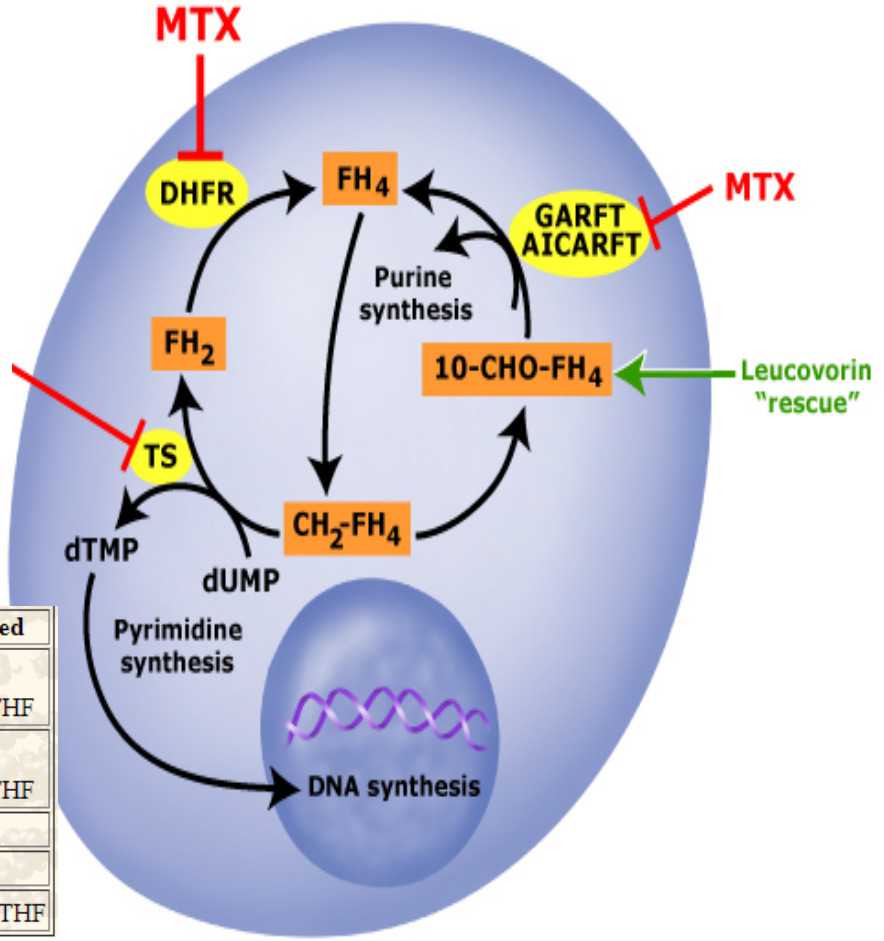
Methotrexate

- Methotrexate
  - Breast cancer, Head and neck cancer, Leptomeningeal cancer, ALL, Lymphoma, Mycosis fungoides, osteogenic Sarcoma
- Pemetrexed
  - NSCLC, Mesothelioma

- folic acid analog
- dihydrofolate reductase (DHFR) inhibitor
- DHFR , catalyzes formation of tetrahydrofolate which is needed for synthesis of purines and pyrimidine synthesis.
- accumulates in cells as a polyglutamate



Nucleotide	Type of base	Present in	Folate form required
Adenylate (AMP or dAMP)	Purine	RNA or DNA	N^{10}-formyl THF N^5, N^{10}-methenyl THF
Guanylate (GMP or dGMP)	Purine	RNA and DNA	N^{10}-formyl THF N^5, N^{10}-methenyl THF
Cytidylate (CMP or dCMP)	Pyrimidine	RNA and DNA	[none]
Uridylate (UMP only)	Pyrimidate	RNA only	[none]
Thymidylate (dTMP only)	Pyrimidine	DNA only	N^5, N^{10}-methylene THF



MTX	Methotrexate	FH_2	Dihydrofolate
DHFR	Dihydrofolate reductase	FH_4	Tetrahydrofolate
GARFT	Glycinamide ribonucleotide transformylase	**10-CHO-FH_4**	10-Formyl tetrahydrofolate
		CH_2-FH_4	Methylenetetrahydrofolate
AICARFT	Aminoimidazole carboxamide ribonucleotide transformylase	**dUMP**	Deoxyuridine monophosphate
		dTMP	Deoxythymidine monophosphate
TS	Thymidylate synthetase		

Leucovorine : 5-formyltetrahydrofolate

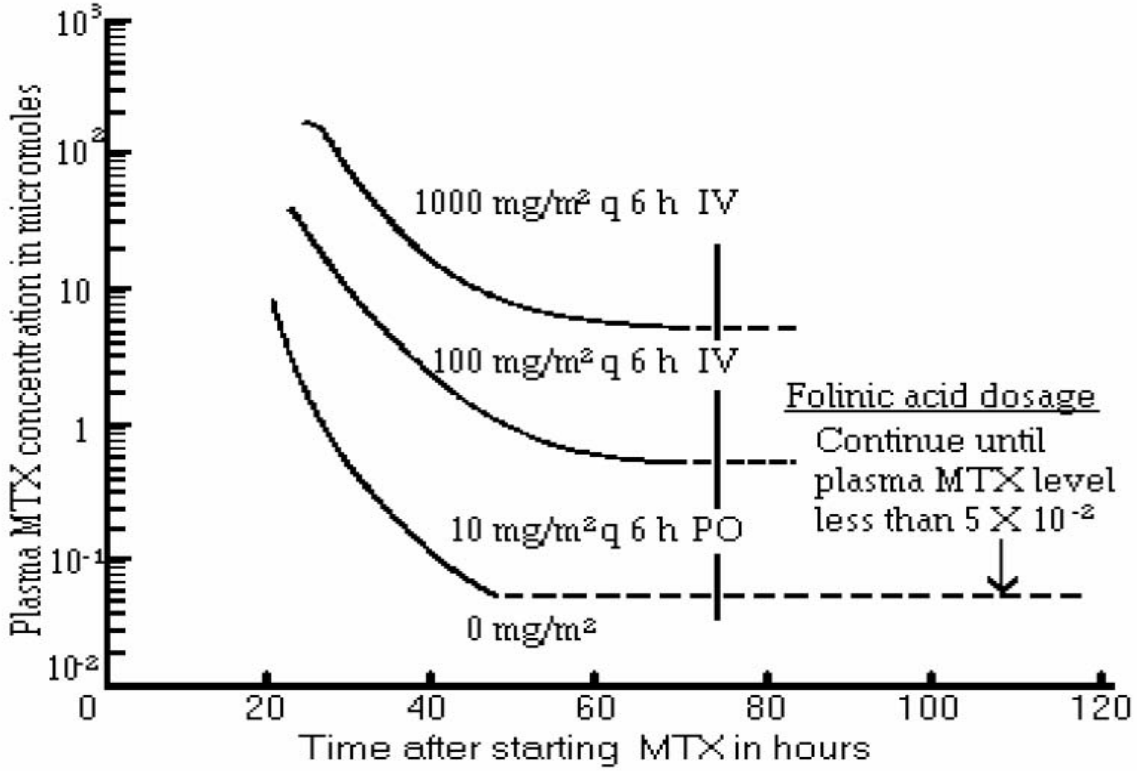
2012 UpToDate

MTX rescue

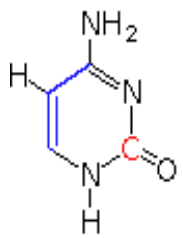
Methotrexate rescue dose:

- >500 mg/m^2 requires leucovorin rescue.
- 100-500 mg/m^2 may require leucovorin rescue

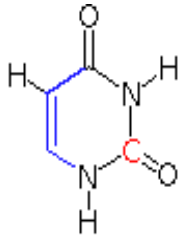
Note: 0.05 µmol/L = 5 x 10-2 micromoles/L
Leucovorin dose PO/IV/IM (see Bleyer nomogram):
J 10-25 mg/m2 q6h 8 to 10 doses, 給藥時間的第24小時 (starting 24 hours after the start of methotrexate infusion)，如果劑量 >25 mg，需要 IV投與。
J Leucovorin dose 根據 methotrexate早上的濃度來調整。 (如., 開始給藥的第 36-48 小時。) Methotrexate 濃度可每天早上抽血，在依濃度線條來調整 leucovorin 劑量。
J 續給 leucovorin 直到 methotrexate 低於濃度 0.05 µmol/L.建議給於 leucovorin rescue 直到 methotrexate 濃度直到 0.01-0.1 µmol/L.



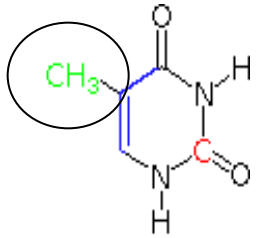
Classification



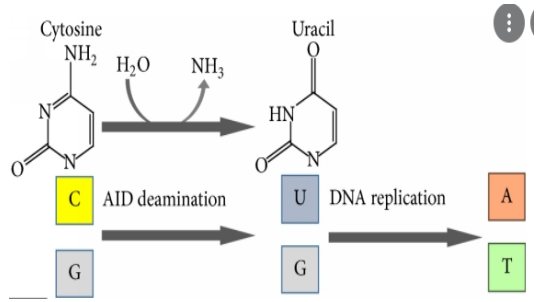
cytosine



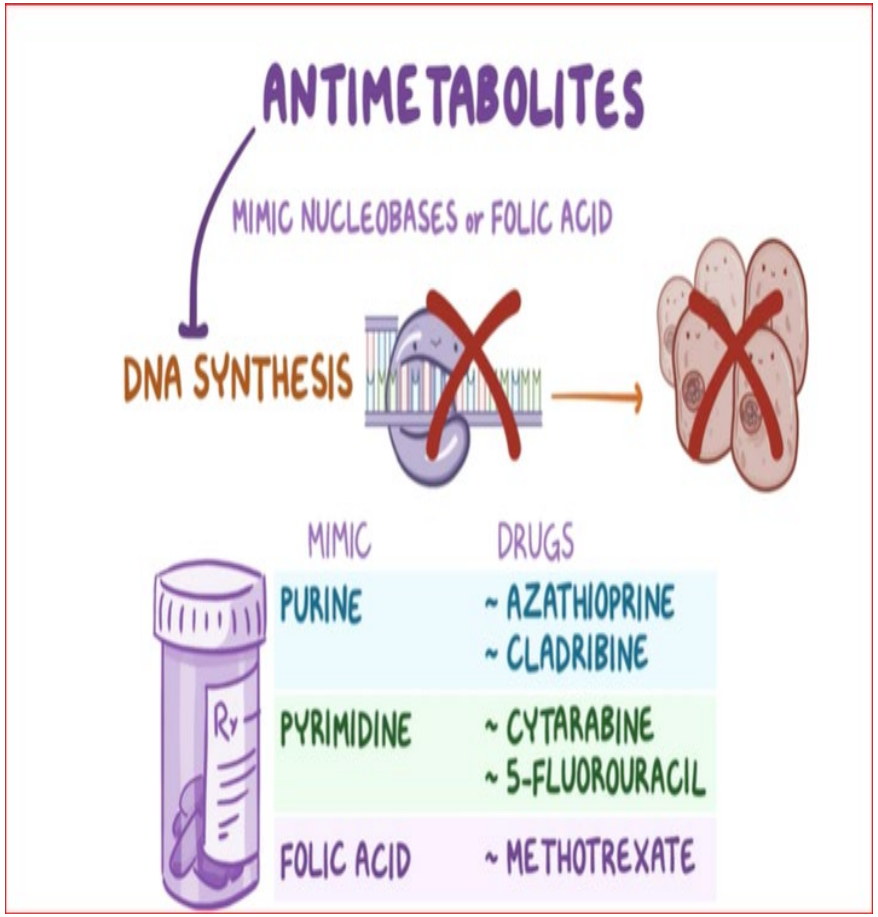
uracil



thymine



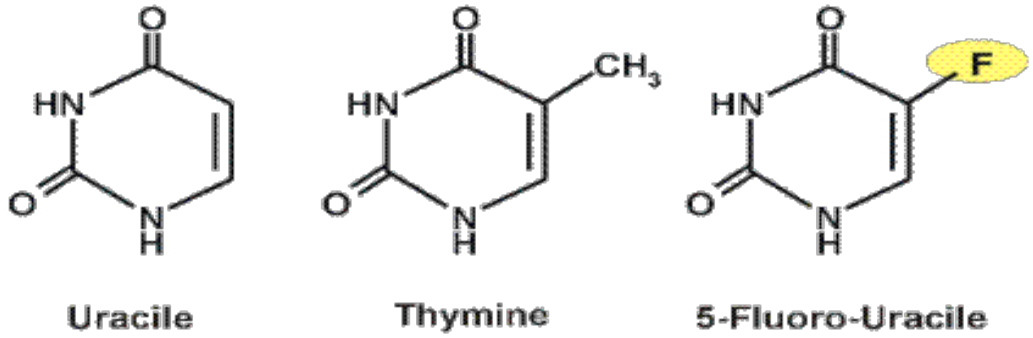
- Pyrimidine (cytosine, Uracil)
  - Cytarabine (Ara-C, Gemcitabine , **5-Azacytidine (cytosine)**
  - Fluorouracil, Capecitabine, UFT (uracil, thymine)
- *Folate antagonist*
  - Methotrexate, pemetrexed
- Purine antagonists (guanine, adenine)
  - Cladribine, Fludarabine, Clofarabine (adenine)
  - Mercaptopurine, Thioguanine, Nelarabine(Ara-G) ->(guanine)
- Ribonucleotide reductase inhibitor
  - Hydroxyurea



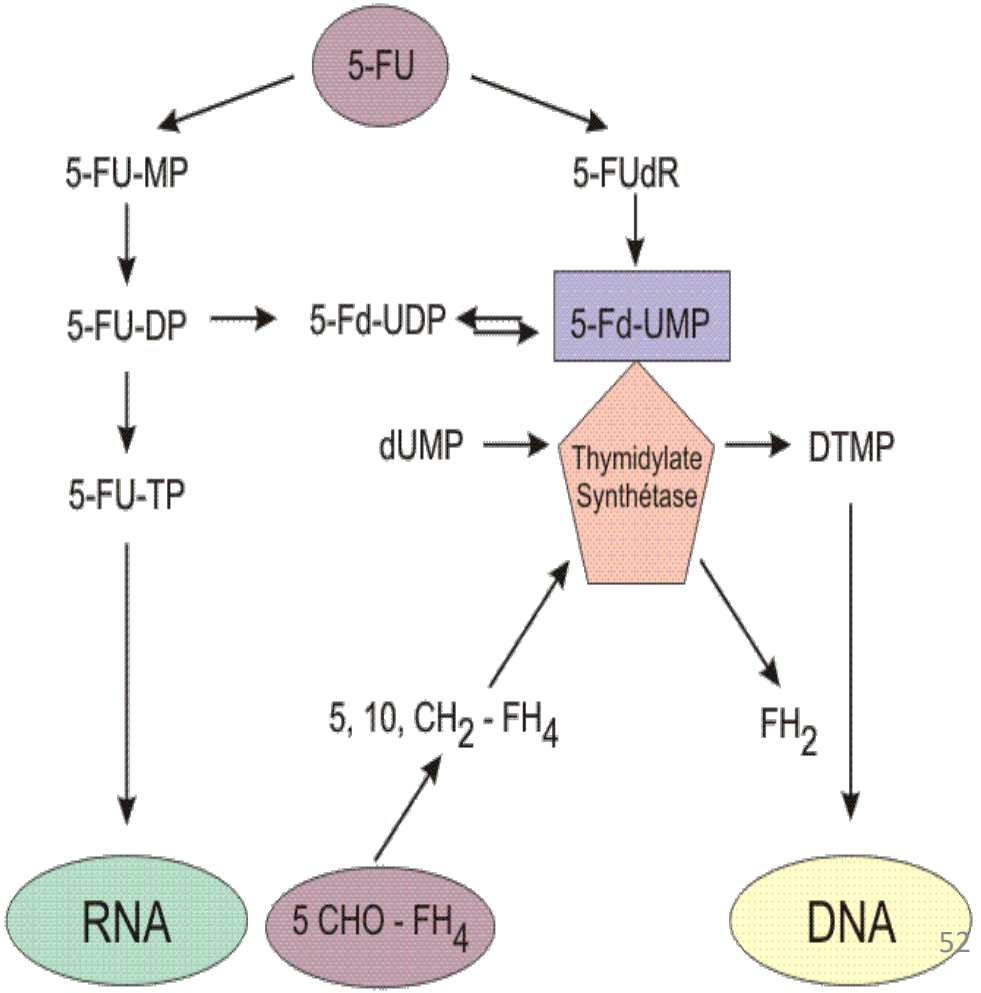
Antimetabolites

CLASS	DRUGS	MAJOR USES
Folic acid analogue	Methotrexate	ALL; choriocarcinoma breast, head, Lung cancer; osteogenic sarcoma; bladder ca
	Pemetrexed	Mesothelioma, lung cancer
Pyrimidine analogue	Fluorouracil Capecitabine	Breast, colon, esophageal, stomach cancer.
	Cytarabine	AML, ALL, NHL
	Gemcitabine	Pancreatic, ovarian, lung ca.
Purine analogue and related inhibitors	Mercaptopurine	AML, ALL
	Pentostatin	Hairy cell leukaemia; CLL, small cell NHL.
	Fludarabine	CLL

5- FU



- Developed for nonhematologic cancers in 1950s
- Heidelberger : aimed at nonhematologic cancers
- A unique biochemical feature of rat hepatoma by attaching a fluorine atom to the 5-position of the uracil pyrimidine base
  - fluoropyrimidine 5-fluorouracil (5-FU)
  - broad-spectrum activity : colorectal cancer



Fluorouracil

- It is a fluorinated pyrimidine that is metabolized intracellulary to its active form, fluorodeoxyuridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting the normal production of thymidine.

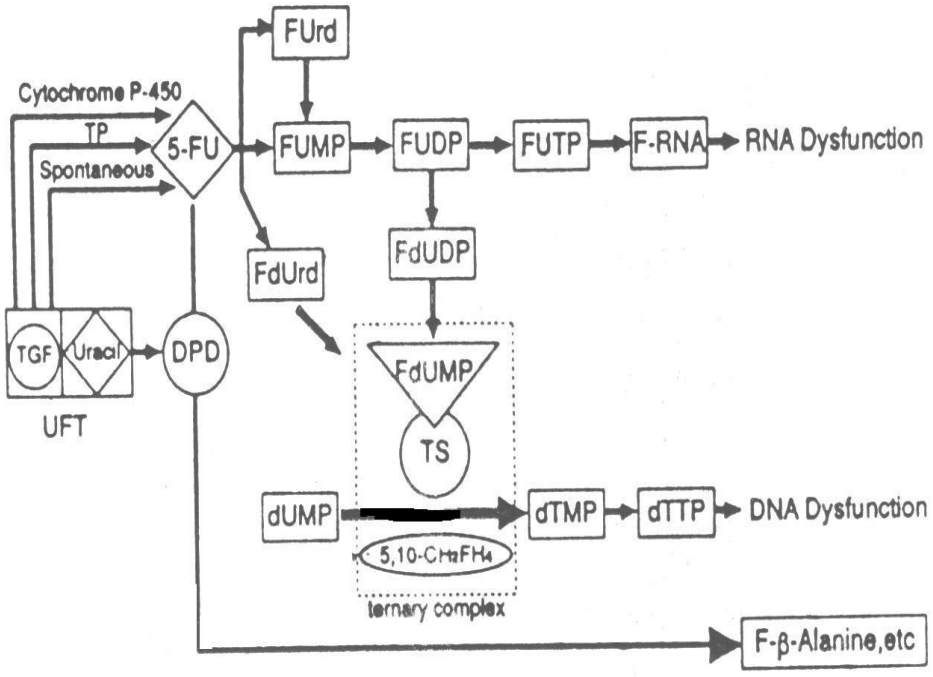
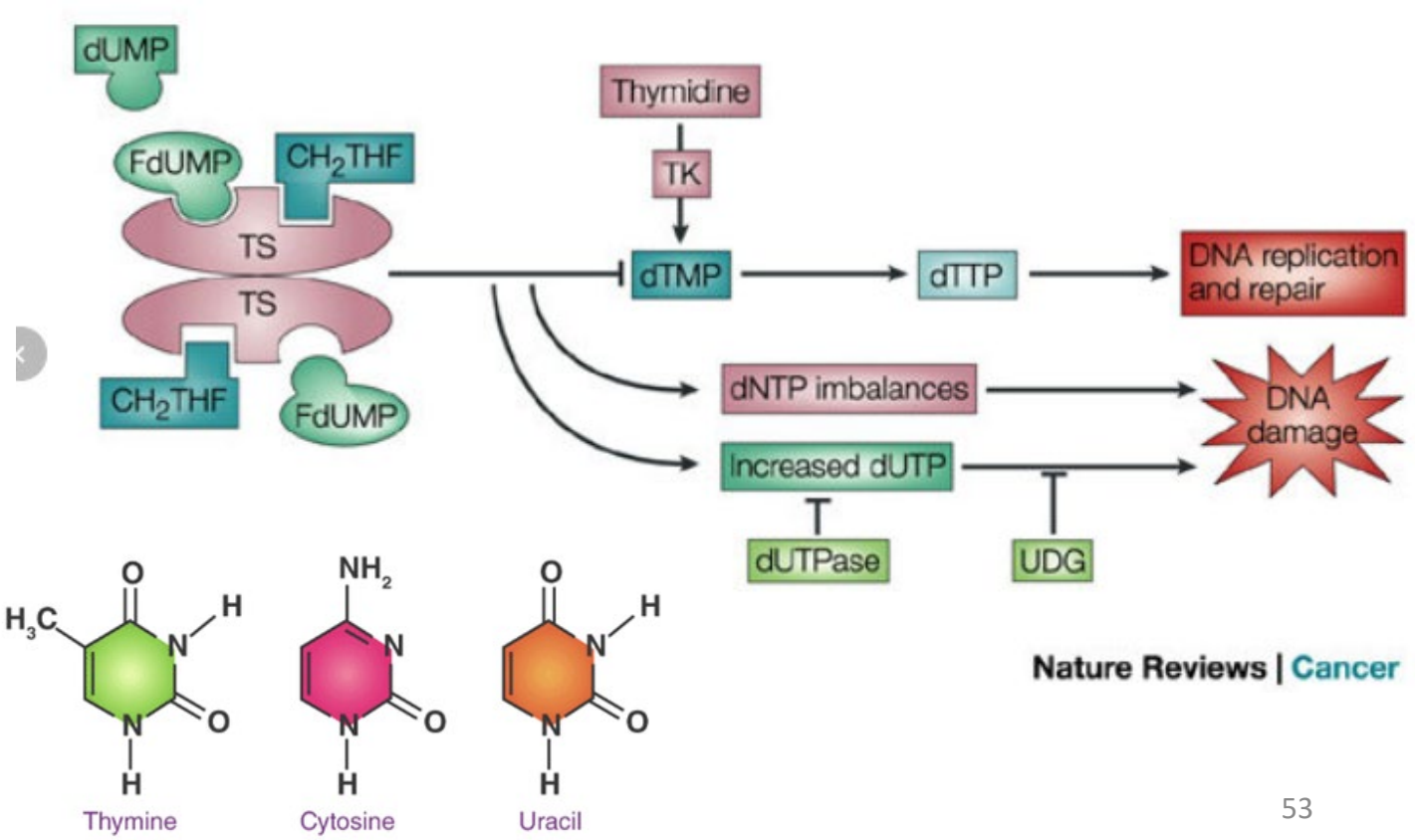
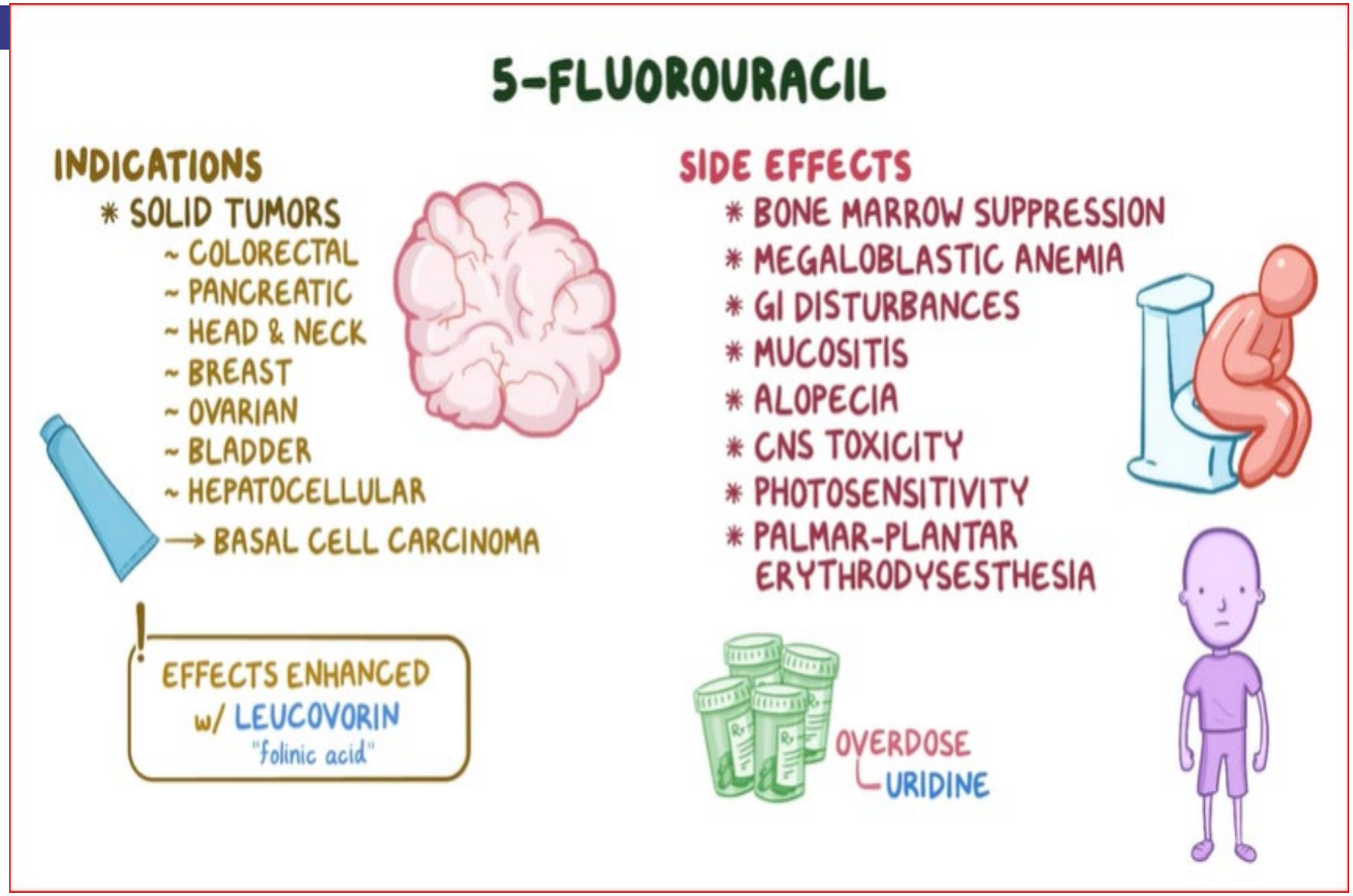


Fig. 6 Modulation of 5-FU by uracil and folinic acid. dUMP, deoxyuridine monophosphate.





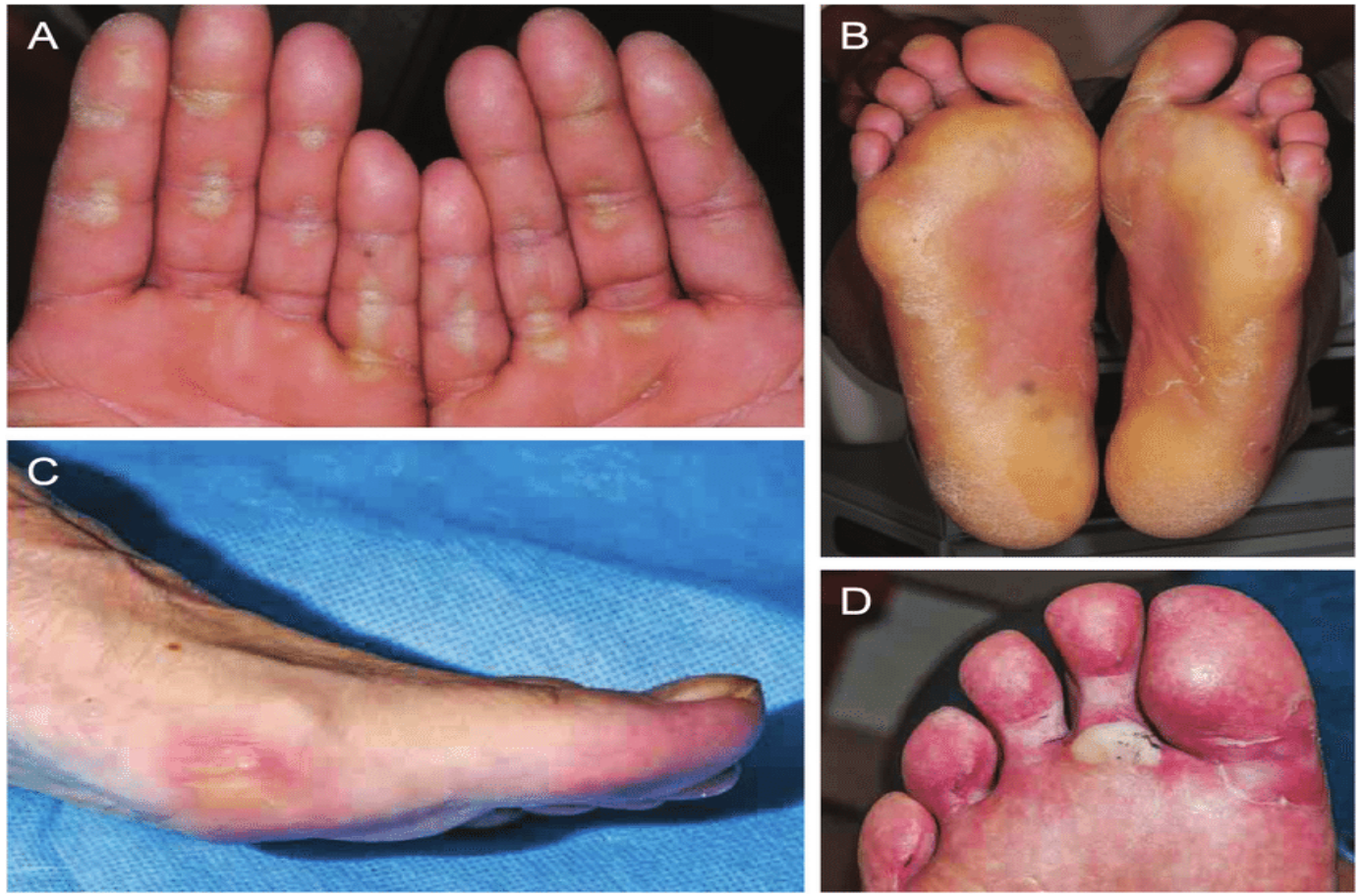
Metabolism via DPD (dihydropyrimidine dehydronase)

T1/2: 8-13 minutes,

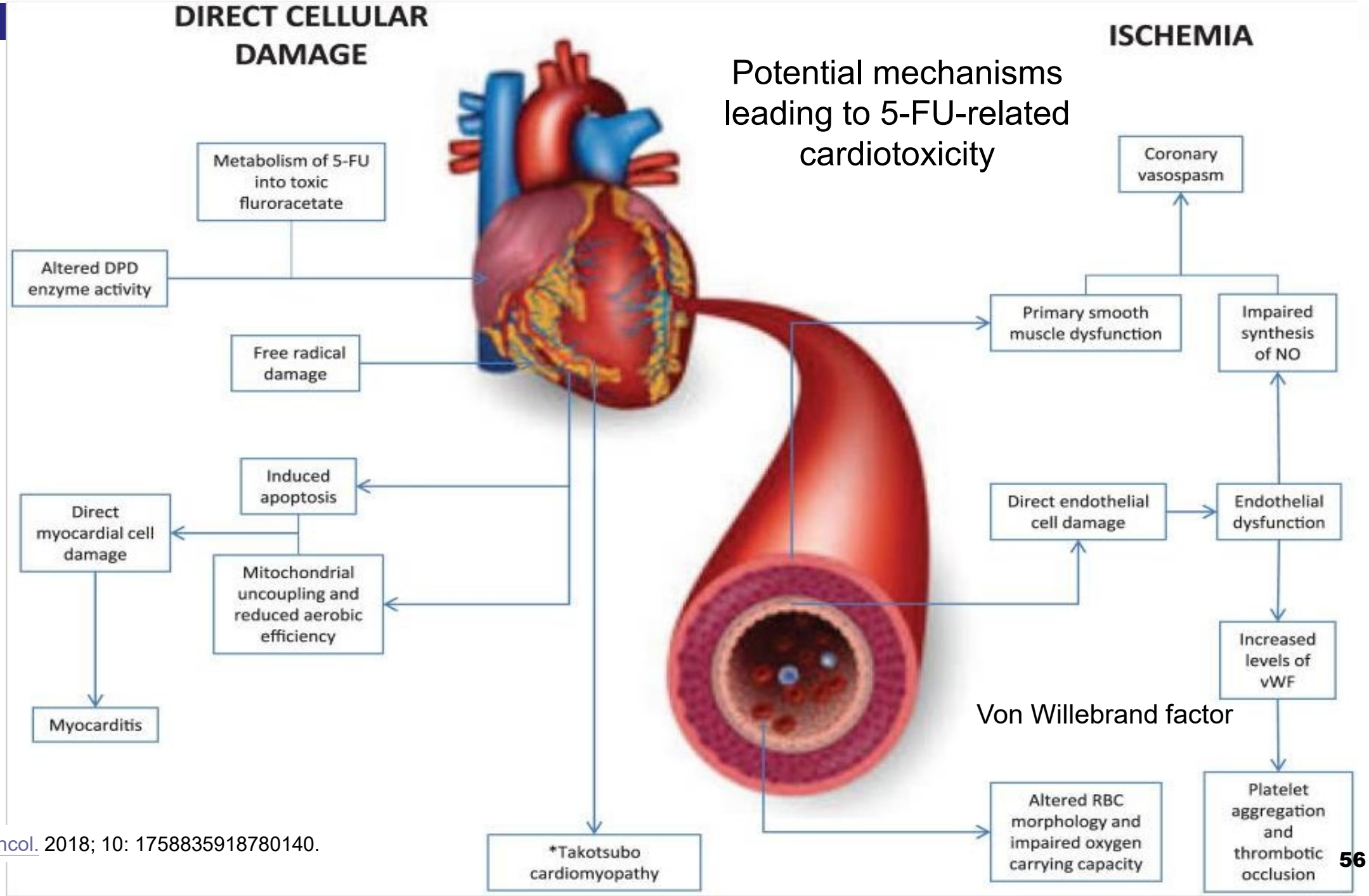
Elimination: respiratory as CO_2 60-80% , 2-3% by biliary system, <5% in urine (unchange)

Adverse effect

- ***Palmar-plantar erythrodysthesia or hand-foot syndrome (*** high dose continuous infusion 23-82%)
  - topical anti-inflammatory medications(clobetasol)
  - Ice packs under the hands and feet while chemotherapy
  - avoid tight-fitting shoes.
- GI : stomatitis, diarrhea, esophago-laryngitis (continuous > bolus)
- Hematologic : myelosuppression (continuous < bolus)



Potential mechanisms leading to 5-FU-related cardiotoxicity



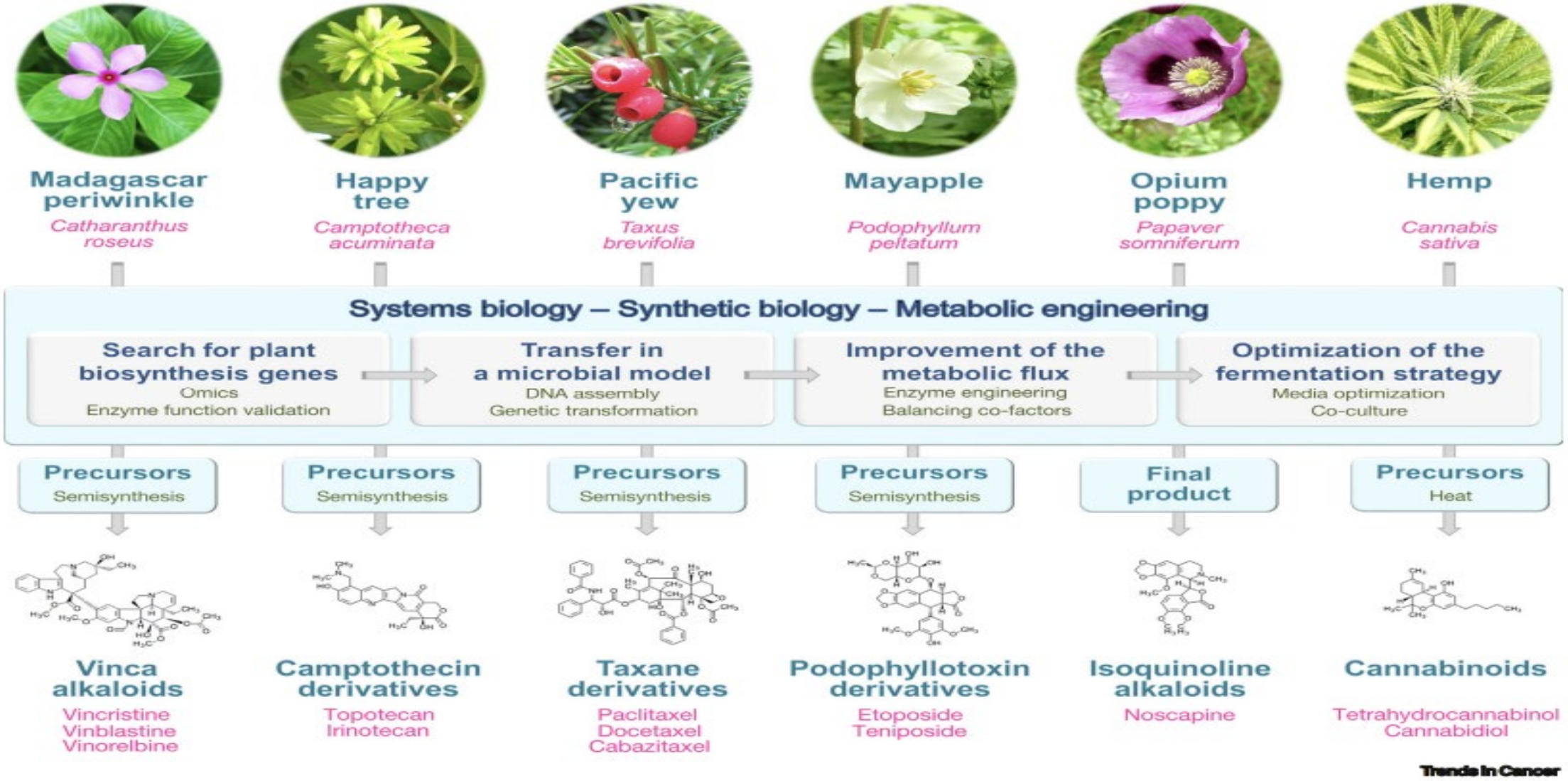
Ther Adv Med Oncol. 2018; 10: 1758835918780140.

Aspect	Capecitabine (Xeloda) (4)	UFT (Tegafur/uracil) (2)	Trifluridine/tipiracil (Lonsurf) (3)	S-1 (1)
Mechanism	Prodrug of 5-FU; metabolized to 5-FU in the tumor, where it inhibits DNA synthesis	Combination of tegafur (a prodrug of 5-FU) and uracil (inhibits degradation of 5-FU)	tipiracil increases bioavailability of trifluridine by inhibiting its degradation	tegafur (prodrug of 5-FU), gimeracil (DPD inhibitor), and oteracil (reduces GI toxicity)
Adverse Reactions	- Handfoot syndrome - Diarrhea - Nausea, Vomiting - Myelosuppression	- Bone marrow suppression - Diarrhea - Nausea, Vomiting - Less hand-foot	- Neutropenia, Anemia, Thrombocytopenia - Fatigue - Nausea, Decreased appetite	- Myelosuppression - Diarrhea, Nausea, Stomatitis - Less hand-foot syndrome compared to capecitabine
Clinical Indication	- Colorectal cancer - Breast cancer	- Colorectal cancer - Gastric cancer	- refractory metastatic colorectal cancer and gastric cancer.	- Gastric cancer - Colorectal cancer -Head and neck cancer
Comparative Benefit	- Activated specifically in tumor tissue, reducing systemic toxicity	- Potentially improved therapeutic index due to uracil component	- Efficacious in heavily pretreated colorectal cancer	- Multitargeted approach to enhancing 5-FU efficacy - less GI toxicity due to oteracil component

S-1 treatment showed superior relapse-free survival (RFS) over UFT. The five-year RFS for S-1 66.4% vs 61.7% for UFT in rectal cancer. ADR grade 3, 4 were increased alanine aminotransferase and diarrhea (each 2.3%) in the UFT arm and anorexia, diarrhea (each 2.6%), and fatigue (2.1%) in the S-1 arm. (Ann Oncol . 2016 Jul;27(7):1266-72.)

Drug	Mechanism of Action	Clinical Indication	ADR
MTX	inhibit dihydrofolate reductase (DHFR), Thymidylate Synthase (TS) GARFT: Glycinamide Ribonucleotide Formyltransferase leading to a decrease in DNA synthesis and cell reproduction. An immune system suppressant.	-breast cancer, -leukemia, -lymphoma, -osteosarcoma, - autoimmune diseases .	ADR : nausea, fatigue, low white blood cell counts, and breakdown of the skin inside the mouth. Liver and lung disease, lymphoma, and severe skin rashes are other serious side effects. -high dose (leucovorin rescue)
Alimta (Pemetrexed)	Pemetrexed is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication.	- Pleural mesothelioma - Non-squamous non-small cell lung cancer.	ADR : fatigue, rash, nausea, loss of appetite, and blood count abnormalities.(Vitamin B12, folic acid)
Pralatrexate	A folate analog metabolic inhibitor similar to methotrexate but with higher affinity for the reduced folate carrier-1, allowing it to enter cells more effectively.	- Relapsed or refractory peripheral T-cell lymphoma.	ADR : mucositis, thrombocytopenia, nausea, fatigue, and increased liver enzymes.(Vitamin B12, folic acid)

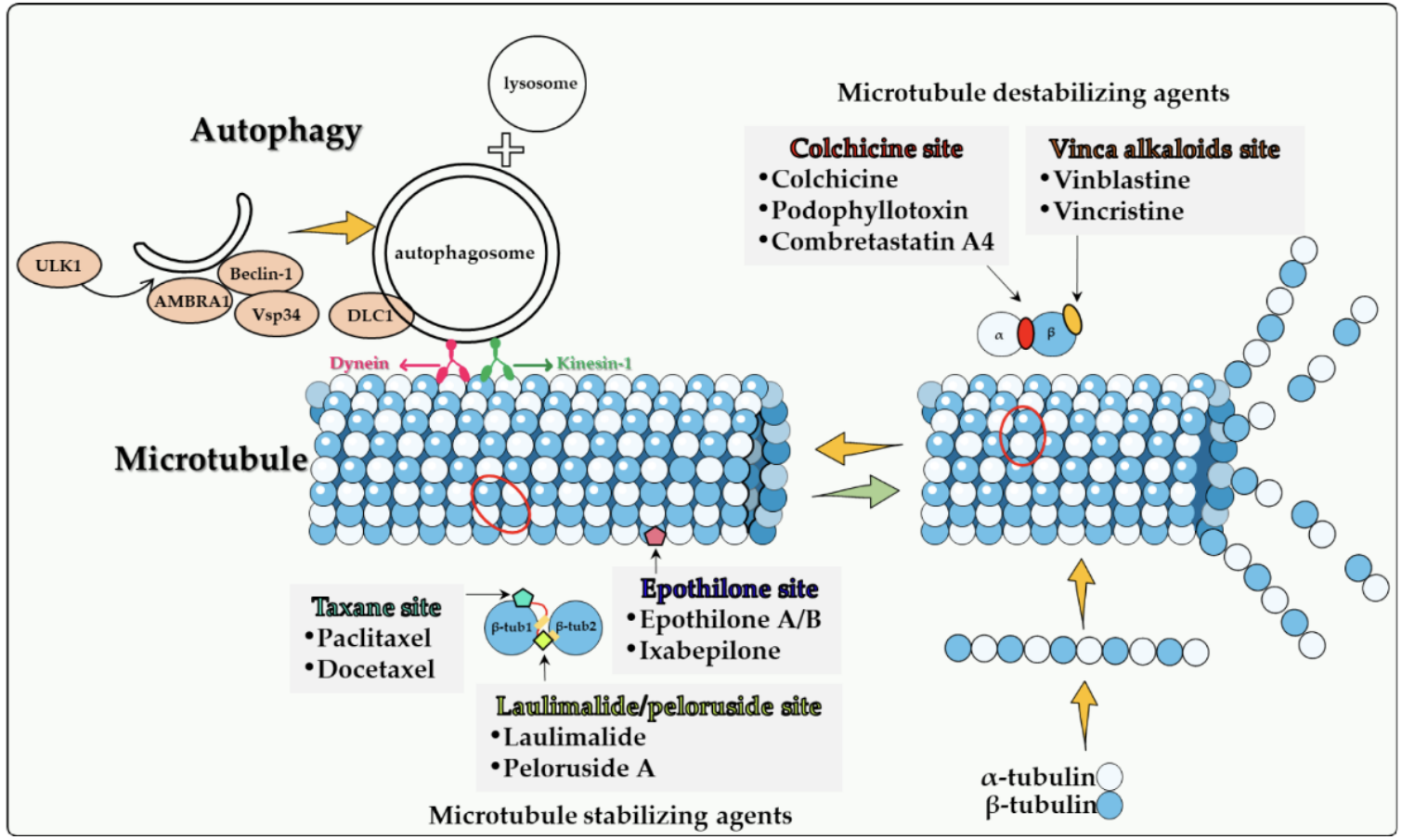
Plant Alkaloids 生物鹼



- Vinca alkaloids: Vincristine, Vinblastine and Vinorelbine. Taxanes: Paclitaxel and Docetaxel. Podophyllotoxins（鬼臼毒素）: Etoposide and Tenisopide. Camptothecin（喜樹鹼）analogs: Irinotecan and Topotecan

Antimitotic Drugs

- Antimotitic agents block (arrest) cells in mitosis by interfering with microtubule dynamics
- Two of the most clinically useful classes of antimitotic drugs are the *vinca* alkaloids and the taxanes
- *Vinca* alkaloids block cells at the metaphase/anaphase junction of mitosis by destabilizing microtubules
- Taxanes arrest cells in mitosis, but promote the polymerization of purified tubulin, causing stabilization and bundling of microtubules



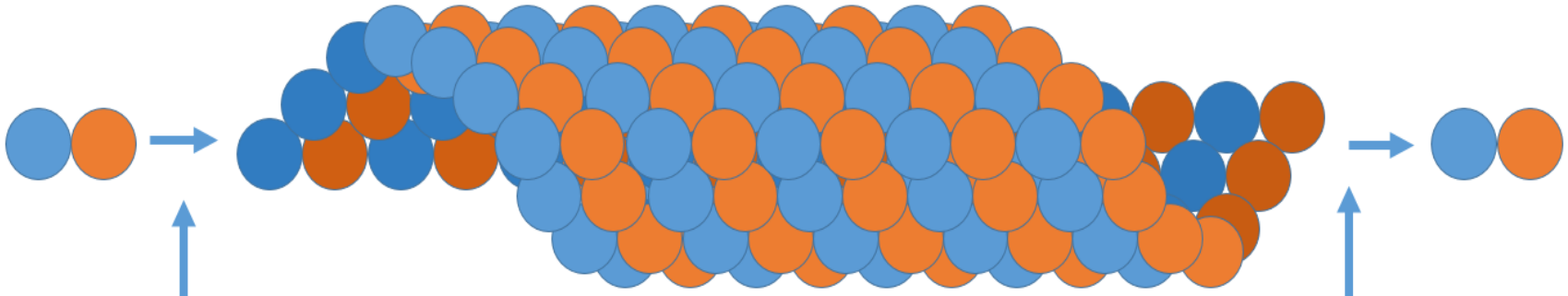
Biomedicines 2022, 10(7), 1632;

Natural Agents

CLASS	DRUGS	MAJOR USES
Vinca alkaloids	Vinblastine	HL, NHL, Testis cancer
	Vinorelbine	Non small cell lung cancer
	Vincristine	ALL, Neuroblastoma; Wilms' tumor;
Taxanes	Paclitaxel, Docetaxel	Metastatic ovarian, breast ca.
Epipodo-phyllotoxins	Etoposide	Testicular tumour, lung cancer ,HL, NHL
Camptothecins	Topotecan, Irinotecan	Ovarian cancer; small-cell lung cancer; colon ca.

	Vinblastine	Vincristine	Vinorelbine
Class/Mechanism	Binding to the tubulin of the mitotic microtubules. (Depolymerization) is nearly fatal if administered by the intrathecal (IT) route. Neurotoxicity is qualitatively similar but quantitatively different (vincristine>vinblastine> Vinorelbine) Vincristine is more neurotoxic (peripheral neuropathy), vinblastine is more bone marrow suppression)		
Metabolism/ adjustment	Dose : 3-6 mg/m2 Metabolized in the liver Scr >3 mg/dL: 50% Serum bilirubin 1.2 to 3 mg/dL: 75% Serum bilirubin >3 mg/dL: 50% serum bilirubin >5 mg/dL: avoid	Dose: 0.4-1.4mg/m2 (max : 2mg) (Extensive liver metabolism Serum bilirubin 1.5 to 3 mg/dL: 50% of dose. Serum bilirubin >3 mg/dL: Avoid use. adjust by liver bilirubin and neurotoxicity	Dose : 25mg/m2 or oral 60-80mg/m2 Primarily metabolized in the liver Adjust by liver bilirubin and neurotoxicity
ADR	Peripheral neuropathy : Numbness, paresthesia,, loss of deep tendon reflex, Central neuropathy : mental depression headache, malaise, dizziness, seizures or psychosis. Cranial nerve neuropathy : vocal cord paresis or paralysis, oculomotor nerve dysfunction and bilateral facial nerve palsies. Severe jaw pain or parotid gland : within a few hours of the first dose of vinblastine. No need to stop or modify the dose; treat with analgesics. Autonomic neuropathy : constipation, abdominal pain, urinary retention and paralytic ileus. (Dose > 20 mg)	Peripheral neuropathy is the most common Cranial nerve toxicities : vocal cord paresis or paralysis (hoarseness, weak voice), ocular motor nerve dysfunction (ptosis, strabismus), bilateral facial nerve palsies, or jaw pain. Autonomic neuropathy constipation (which can be severe, impaction of stool in the upper colon), abdominal pain, urinary retention and paralytic ileus. Central neuropathy : headache, malaise, dizziness, seizures, mental depression, psychosis and SIADH Contraindicated Neurological disorders : hereditary motor and sensory neuropathy disease and childhood poliomyelitis, - Vincristine has produced severe hepatic toxicity when given in conjunction with abdominal radiation therapy.	• *Injection site reactions (Picc line or central line)* • *Acute dyspnea and severe bronchospasm* • Neu*ropathy* -Mild to moderate peripheral neuropathy (paresthesia ,hypesthesia) -Pain in tumour-containing tissue
Indication	Breast cancer, Hodgkin's disease, Kaposi's sarcoma,Testicular cancer	Solid tumors, lymphoma,Leukemia, Multiple myeloma, Retinoblastoma, Kaposi's sarcoma, Waldenstrom's macroglobulinemia, small cell lung cancer	Non–small cell lung cancer Breast cancer, relapse Hodgkin lymphoma

Natural Agents



Vinca alkaloids prevent microtubule assembly.

Alpha tubulin

Beta tubulin

Taxanes prevent microtubule disassembly.

	Paclitaxel	Docetaxel
Class/Mechanism	It promotes the assembly of tubulin into stable microtubules and inhibits their disassembly. (polymerization)	
Metabolism/adjustment	By liver and adjust liver function -weekly dose is less toxicity and response rate	• ***By liver and adjust by liver function*** • ***not recommend weekly dose*** • ***Liver impairment*** – ***> d***ocetaxel 100 mg/m2 are at a higher risk of developing severe adverse reactions if ALT and/or AST > 1.5 times the ULN and ALP (> 2.5 times ULN). – Liver impairment reduces clearance and increases ADR : life-threatening sepsis and GI hemorrhage, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia.
ADR	**Arthralgia, myalgia, neutropenia, neuropathy** • ***Hypersensitivity reactions (HSR):*** – Cremophor EL or paclitaxel itself. – often occur in the first hour of an infusion (75% occur within the first 10 mins) – The frequency and severity HSR are not affected by the dose or schedule – Incidence of HSR are significantly reduced by premedication. Corticosteroids (e.g., dexamethasone), histamine H1-antagonists (e.g., diphenhydramine) and H2-antagonists. • 45 minutes before paclitaxel, dexamethasone 20 mg IV , 30 minutes before paclitaxel, diphenhydramine 50 mg and ranitidine 50 mg IV. • More effective : 12 hours and 6 hours before paclitaxel, dexamethasone 20 mg po and then following the above premedication regime. • Premedicated patients, symptoms of HSR 41%, severe HSR < 2%	**Neutropenia, neuropathy, Fluid retension** **Dexamethasone for Hypersensitivity and fluid retention** – *3-weekly regimen:* dexamethasone 8 mg PO twice a day for 3 days starting one day prior to each docetaxel infusion. (minimum of 3 doses of dexamethasone prior to docetaxel treatment. • If treatment delay is not possible, diphenhydramine 50 mg IV and dexamethasone 10 mg IV may be given 30 minutes before starting docetaxel. Note that this premedication regimen has not been shown to reduce the incidence and severity of fluid retention, but is only an attempt to ameliorate hypersensitivity reactions. • The patient should then be instructed to take dexamethasone 8 mg PO twice a day for two days.

	Paclitaxel	Docetaxel
Class/Mechanism	It promotes the assembly of tubulin into stable microtubules and inhibits their disassembly. (polymerization)	
ADR	• ***Arthralgia/myalgia*** is dose and schedule dependent; worse with higher doses and shorter infusions. – transient, occur within 2-3 days, and resolve after a few days. – If arthralgia/myalgia is not relieved by adequate doses of NSAIDS or ACTwith tramadol, includes • Pregabalin 75 mg po on day prior to paclitaxel, tid x 7-10 days • prednisone 10 mg po bid x 5 days starting 24 hours post-paclitaxel • Dose reduction may be considered • ***Peripheral neuropathy*** – mild paresthesia characterized by numbness and tingling in a stocking-and-glove distribution. – Onset: rapid, within a few days of an infusion. – Frequency and severity : cumulative doses – usually improve or resolve several months after discontinuing paclitaxel. • ***Bradycardia and hypotension :*** asymptomatic and generally does not require treatment. • ***Ethanol :*** at a concentration of 6 mg/mL.	• ***Preexisting effusions:*** – possible exacerbation of the effusions. • Fluid retention (82%: 52% with dexamethasone premedication) • ***Neuropathy:*** moderate to severe neuropathy (600 mg/m2) • ***Rash/pruritus:*** rash, including localized eruptions mainly on feet and hands, but also on arms, face or thorax. (48%) resolve before the next infusion, and are not disabling. • ***Severe nail changes :*** 2% are characterized by discoloration of fingernails or toenails. • ***Hand-foot skin reaction*** • ***Tearing/watery eyes:*** An unexpected toxicity with the weekly schedule is excessive tearing. Dose related median of 400 mg/m² (range, 120-960 mg/m²). Treatment with artifical tears or other ocular moisturizers ameliorated symptoms in some patients. • ***Ethanol: 0.3 to 0.74 mg/mL.***
Indication	Anal cancer, Bladder cancer, Breast cancer, Cervical cancer, Endometrial cancer, Esophageal cancer, Gastric cancer, Head and neck cancers, Non–small cell lung cancer, Ovarian cancer, advanced Penile cancer, unresectable Testicular germ cell tumors, Thymoma/thymic carcinoma, Unknown primary adenocarcinoma	

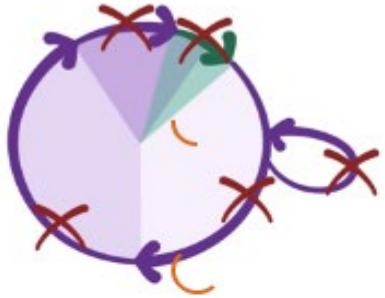
Antibiotics and enzymes

CLASS	DRUGS	MAJOR USES
Antibiotics	Dactinomycin (actinomycin D)	Choriocarcinoma; Wilms' tumor; Rhabdomyosarcoma
	Daunorubicin	AML, ALL.
	Doxorubicin	Soft-tissue, osteogenic, and other sarcoma; HL, NHL , AML, ALL. Breast, Genitourinary, Thyroid, lung, stomach cancer; Neuroblastoma
	Mitoxantrone	AML, breast and prostate cancer
	Bleomycin	Testis, cervical cancer; HL, NHL
	Mitomycin	Stomach, anal, and lung cancer
Enzymes	L-Asparaginase	ALL

ANTHRACYCLINES

DOXORUBICIN
IDARUBICIN
DAUNORUBICIN
EPIRUBICIN

CELL CYCLE NON-SPECIFIC



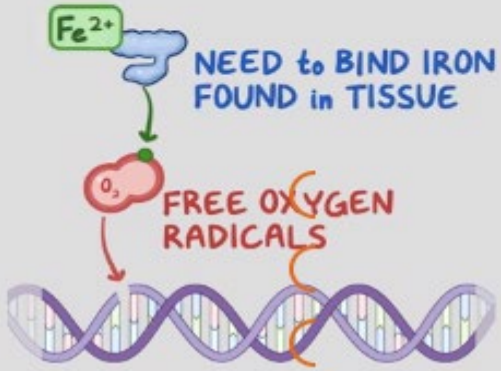
INTERCALATES

INHIBITS RNA & DNA SYNTHESIS

INHIBITS

OVERWINDS

TEARS itself APART



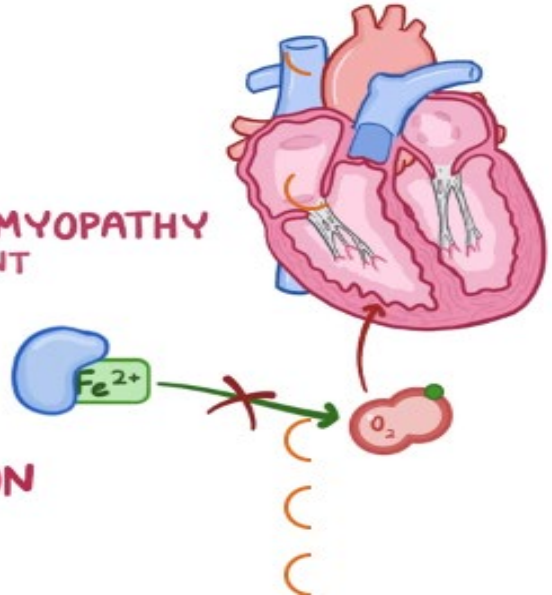
INDICATIONS

- ~ SOLID TUMORS
  - BREAST
  - THYROID
  - LUNG
  - OVARIAN
- ~ LEUKEMIAS & LYMPHOMAS

Sarcoma

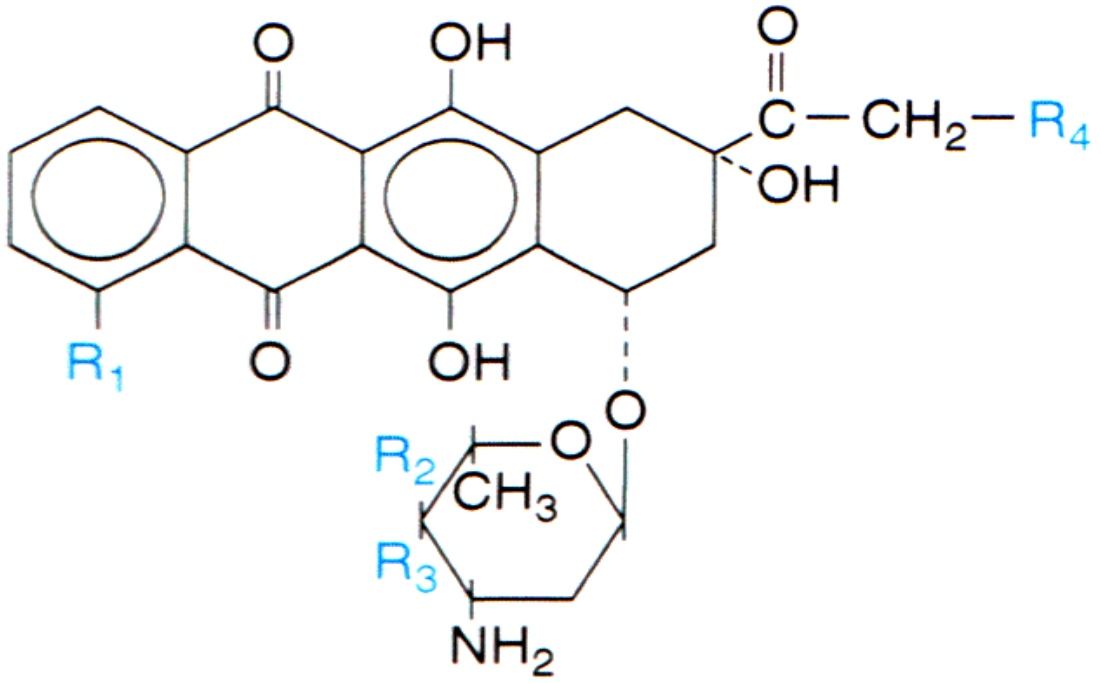
SIDE EFFECTS

- ~ CARDIOTOXICITY
  - DILATED CARDIOMYOPATHY
    - * DOSE DEPENDENT
    - * IRREVERSIBLE
  - PREVENTED by DEXRAZOXANE



- ~ MYELOSUPPRESSION
- ~ ALOPECIA

ANTHRACYCLINE



	DOXORUBICIN	DAUNORUBICIN	EPIRUBICIN	IDARUBICIN
R_1 =	OCH_3	OCH_3	OCH_3	H
R_2 =	H	H	OH	H
R_3 =	OH	OH	H	OH
R_4 =	OH	H	OH	H

ANTHRACYCLINE

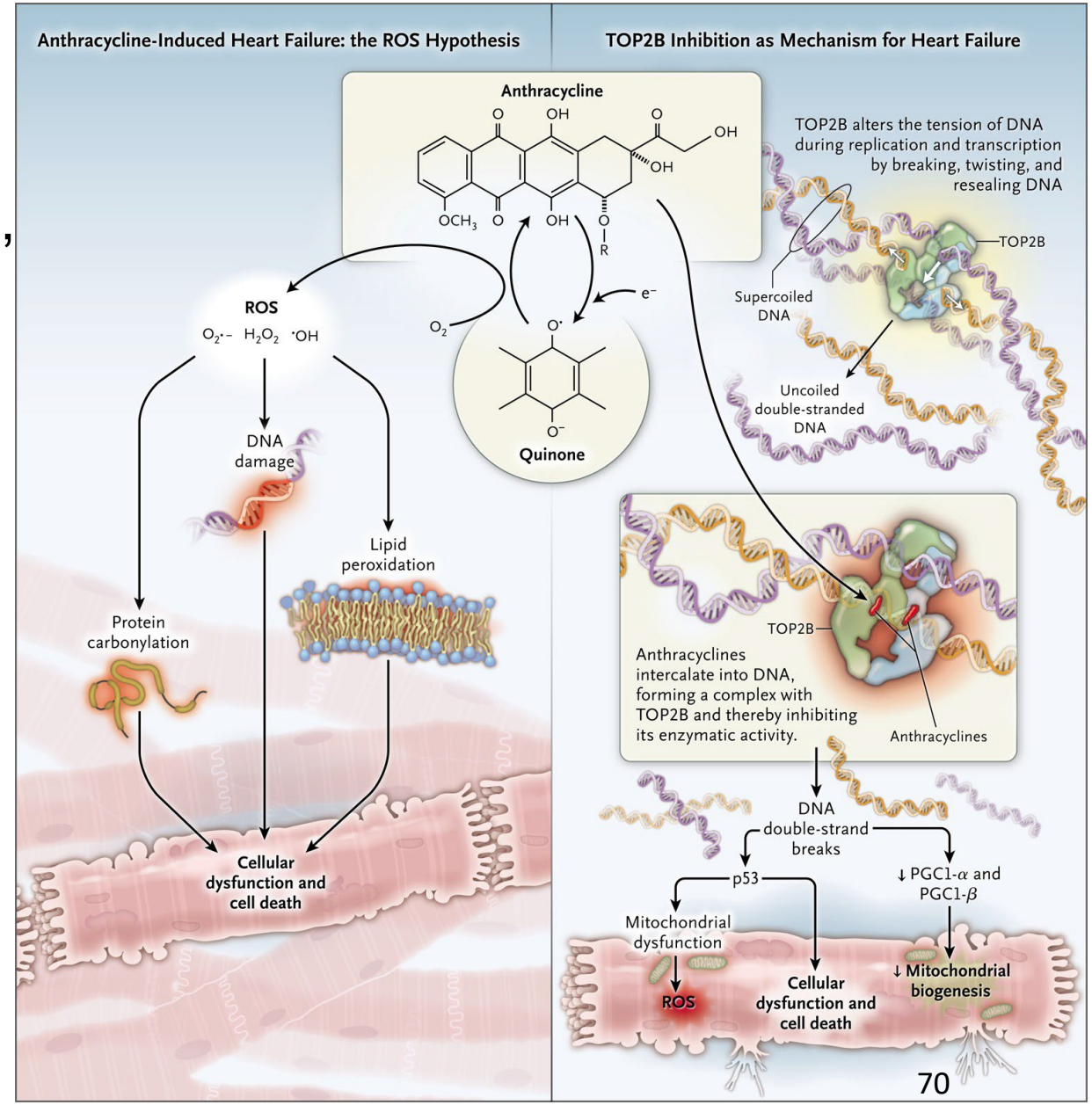
- Cardiotoxicity : is cumulative across members of the anthracycline (daunorubicin, doxorubicin, epirubicin, idarubicin) and anthracenedione (mitoxantrone) class of drugs.
  - Acute (within 24 hrs, nonspecific ST-T wave change, sinus tachycardia, dysrhythmias, 40%), Transient reduction in the ejection fraction can also occur acutely with pericarditis-myocarditis syndrome.
  - Subacute (weeks to months after last dose, CHF with low cardiac output)
  - Late effects (>5 yrs, incidence high 65% 4-10 yrs after receiving anthracyclines)

Anthracyclines

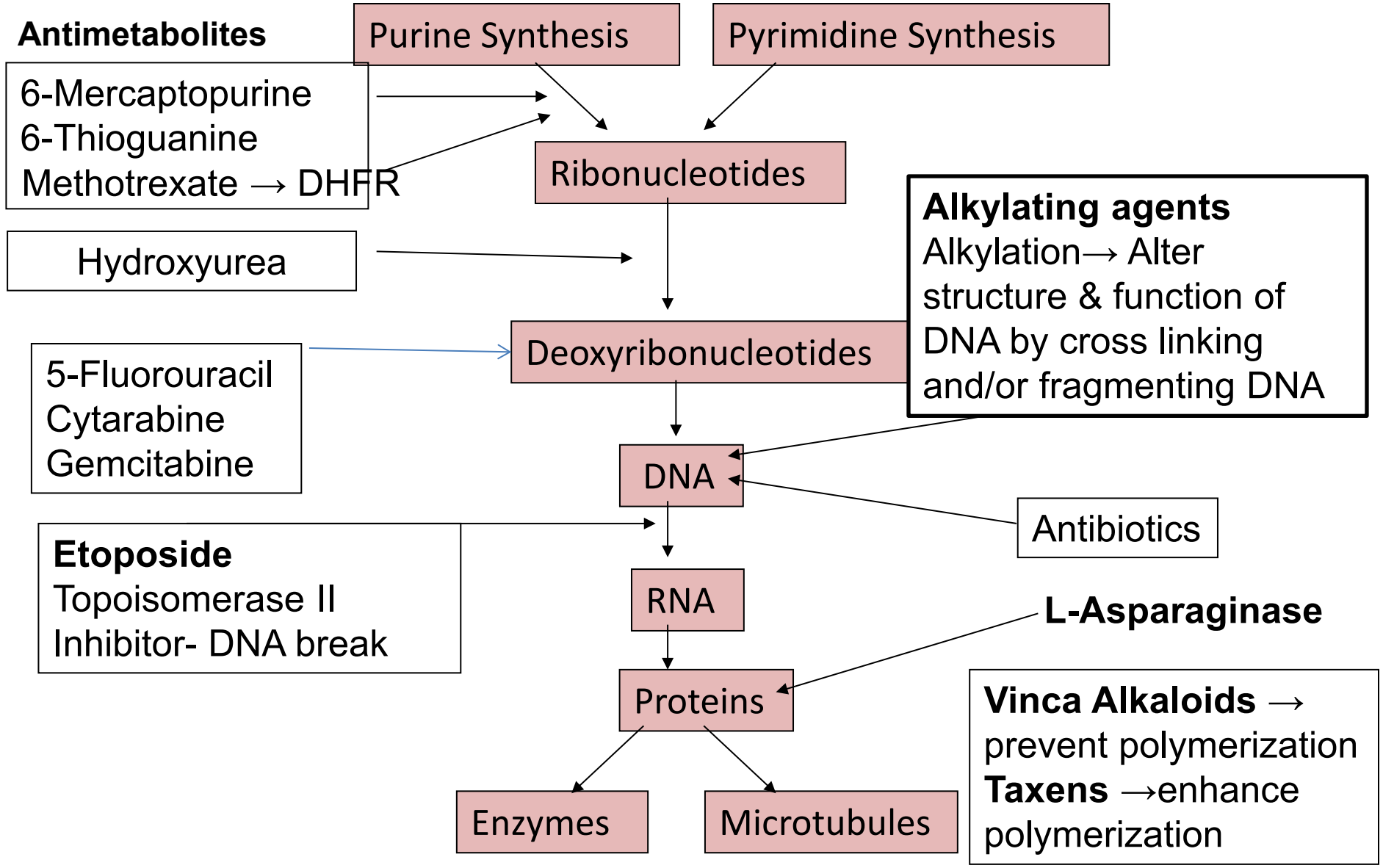
Risk factors

- Dose (< 450-550mg/m2 , 1-10% CHF , 270 mg/m2 less cardiotoxicity)
- 900 to 1000mg/m^2
  - CHF refractory to medical therapy.
  - Cardiac irradiation or the administration of Cyclophosphamide may increase the risk of cardiotoxicity.
- Bolus
- Extreme young, advanced old
- Previous mediastinal radiation
- Malnutrition
- Pre-existing cardiac disease

Mechanisms of Anthracycline-Induced Injury to Cardiac Cells.



N Engl J Med 2013; 368:1154-1156


Antimetabolites
Purine Synthesis
Pyrimidine Synthesis
6-Mercaptopurine
6-Thioguanine
Methotrexate → DHFR
Ribonucleotides
Hydroxyurea
Alkylating agents
Alkylation→ Alter structure & function of DNA by cross linking and/or fragmenting DNA
Deoxyribonucleotides
5-Fluorouracil
Cytarabine
Gemcitabine
DNA
Antibiotics
Etoposide
Topoisomerase II Inhibitor- DNA break
RNA
L-Asparaginase
Proteins
Vinca Alkaloids → prevent polymerization
Taxens →enhance polymerization
Enzymes
Microtubules

Side effect profiles and nursing considerations
(副作用特徵和護理考量)

. Role of the Nurse Practitioner

- Drug administration and monitoring
- Treatment
  - Response rate
  - Managing side effects: nausea, myelosuppression, neuropathy
- Patient education and adherence
- Symptom management and survivorship care

Conditions when Cytotoxic Chemotherapy may be withheld (不適進行化療)

- Infection (感染)
- Previous chemotherapy given < 2 weeks (前化療在2周內)
- Leukopenia and thrombocytopenia (血球低下)
- Severely debilitated patients (身體虛弱)
- Pregnancy (1st trimester)(懷孕第一期)
- Major surgery < 2 weeks (兩周內有大手術)
- Poor patient follow-up (無好的追蹤)
- Psychological problems (精神疾病)

Choice of chemotherapeutic agent
（化療選擇）

- 不是所有人都可忍受化療，也不是所有化療處方都適用病人Not all patients can tolerate drugs, and not all drug regimens are appropriate for a given patient.
- 藥物選擇依賴Choice of drug depends on following factor
  - Tumour type (腫瘤型態)
  - General performance status of patient (病人狀態)
  - Renal and hepatic function（肝腎功能)
  - Bone marrow reserve (骨髓造血功能)
  - Concurrent medical problems（目前疾病)
  - Patient‘s willingness（病人意願)
  - Patient‘s physical and emotional tolerance for side effects (身體與心情)

Toxicity (毒性)

- Rapidly multiplying cells (分裂快速細胞)
- Nausea & Vomiting (噁心嘔吐)
- Bone marrow depression（骨髓抑制)
- Alopecia (掉髮)
- Gonads: Oligospermia, impotence, ↓ ovulation (精子減少、性功能減少)
- Fetus: Abortion, fetal death, teratogenicity
- Carcinogenicity（致癌)
- Hyperuricemia（高尿酸血症)
- Hazards to staff

General toxicity of cytotoxic drugs

Dermatological toxicity	Drugs
Alopecia	Cyclophosphamide, Ifosfamide Vincristin ,Methotrexate , Paclitaxel,
Local necrosis- extravasation	Dactinomycin, Doxorubicin, vinca alkaloid
Hyperpigmentation of skin	

Gastrointestinal toxicity	Drugs
Nausea and vomiting	Carmustin,cisplatin,cyclophosphamide,dacarbazine, cytarabine,lomustine,thiotepa
Stomatitis	Capecitabine,5 FU,methotrexate,mercaptopurine
Diarrhea	Irinotecan, 5FU
Constipation	Vincristine
Anorexia, taste change,etc	

Bone marrow suppression

- Cause by almost all anticancer drugs except Bleomycin, Vincristin and Asparginase.
- **Most serious toxicity and often limit dose of chemotherapy**
  - Granulocytopenia
  - Agranulocytosis
  - Thrombocytopenia
  - Aplastic anemia
  - Lymphocytopenia
  - immunosppression

Complications :

- Opportunistic infections
- Bleeding

Drug causing severe myelosuppression
Carmustin
Cytarabine
Daunorubicine
Paclitaxel
Alkylating agents
Antimetabolites

General toxicity of cytotoxic drugs

Toxicity	Drugs
Neuropathy	Oxaliplatin,Paclitaxel, Cytarabine,5FU,
Renal toxicity	Cisplatin, Ifosfamide, Methotrexate
Hemorrhagic cystitis	Cyclophosphamide, Ifosphamide
Hepatotoxicity	Asparginase, Cytarabine, Mercaptopurine,Thioguanine, Methotrexate
Cardio toxicity	Daunorubicin, Doxorubicin,Epirubicine, Mitoxantrone,Transtuzumab, Bevacizumab
Pulmonary toxicity	Bleomycin, Melphalan, Chlorambucil, Busulphan,
Infertility	Alkylating agents
Hypersensitivity reaction	Asparginase, Platinum compound, etoposide

Toxicity amelioration and supportive care

Drugs	Use
Filgrastim (G-CSF)	■ Prevent neutropenia, ■ Increases neutrophil count, ■ prevent infection.
Sargramostim (GM-CSF)	
Oprelvekin (IL-11)	■ Prevent thrombocytopenia
Thrombopoietin	

Toxicity amelioration and supportive care

Drugs	Use
Folinic acid	Methotrexate toxicity
Mesna	Cyclophosphamide induced cystitis
Dexrazoxane	Doxurubicine /Daunorubicine cardiotoxicity
5HT3 inhibitors , Aprepitant (NK1 receptor antagonist) Dexamethasone, Lorazepam, olanzapine	Vomiting
Allopurinol, Alkalization of urine	Hyperuricemia
Hydration , Bisphosphonates	Hypercalcemia

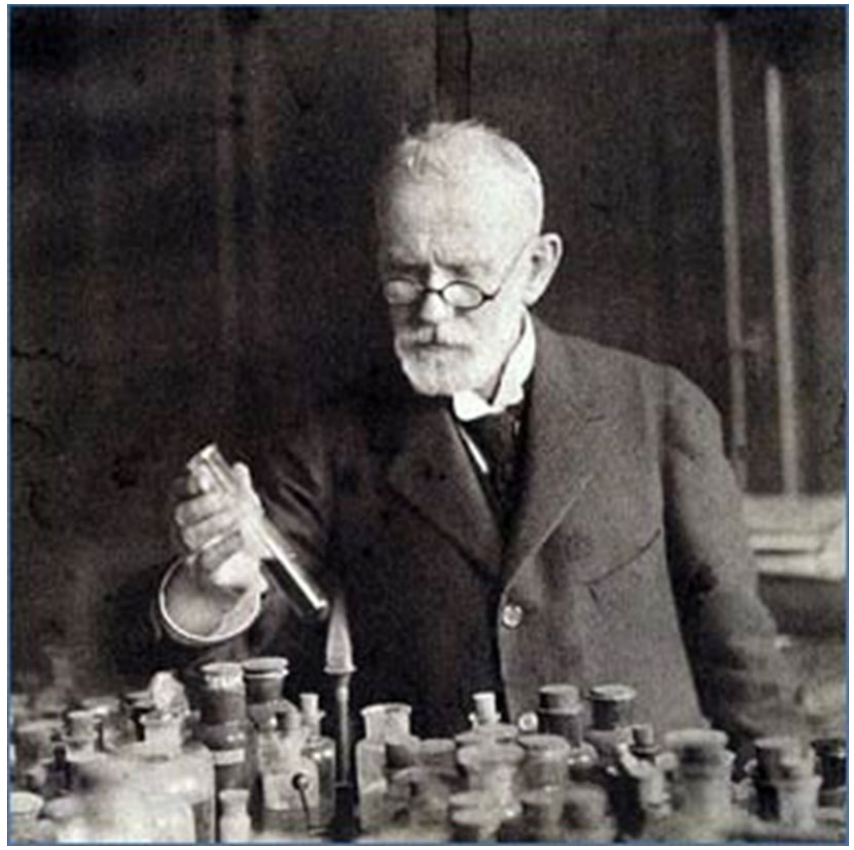
WHO response scale to chemotherapy

1. **Complete response (全癒)**– disappearance of disease on imaging test.
2. **Partial response(部分反應)** – size decrease of 50% or more from original tumor. No new lesions.
3. **Stable disease (穩定)**– less than 50% response without actual progression of disease.
4. **Disease progression (疾病進展)**– 25% increase in the size of the original tumor. Or new lesions developed.

Target therapy

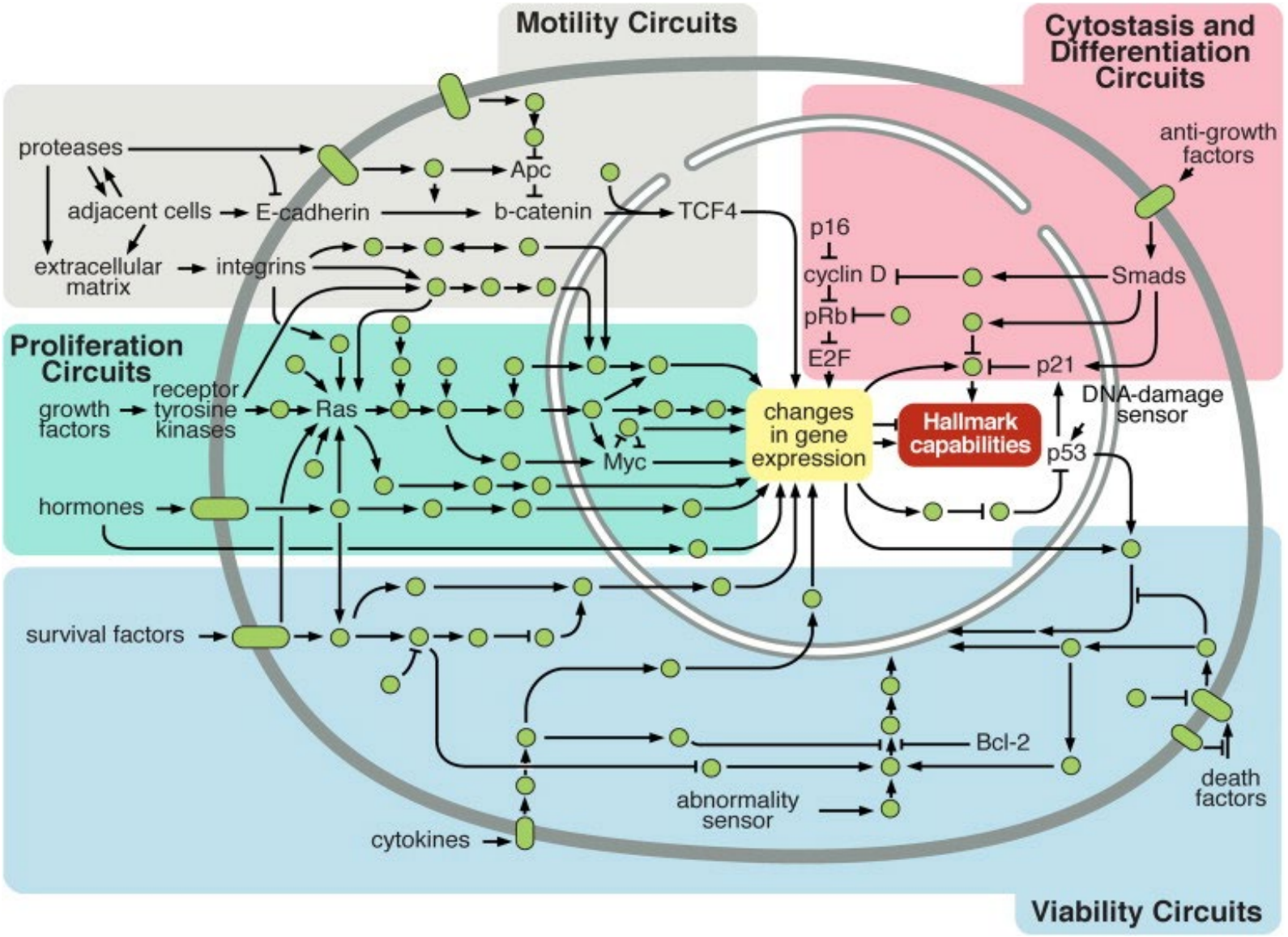
- Targeted therapy introduction 標靶療法介紹
- Immunotherapy overview (checkpoint inhibitors, CAR-T) 免疫療法概述（檢查點抑制劑，CAR-T）

Paul Ehrlich : Magic Bullet (神奇子彈)



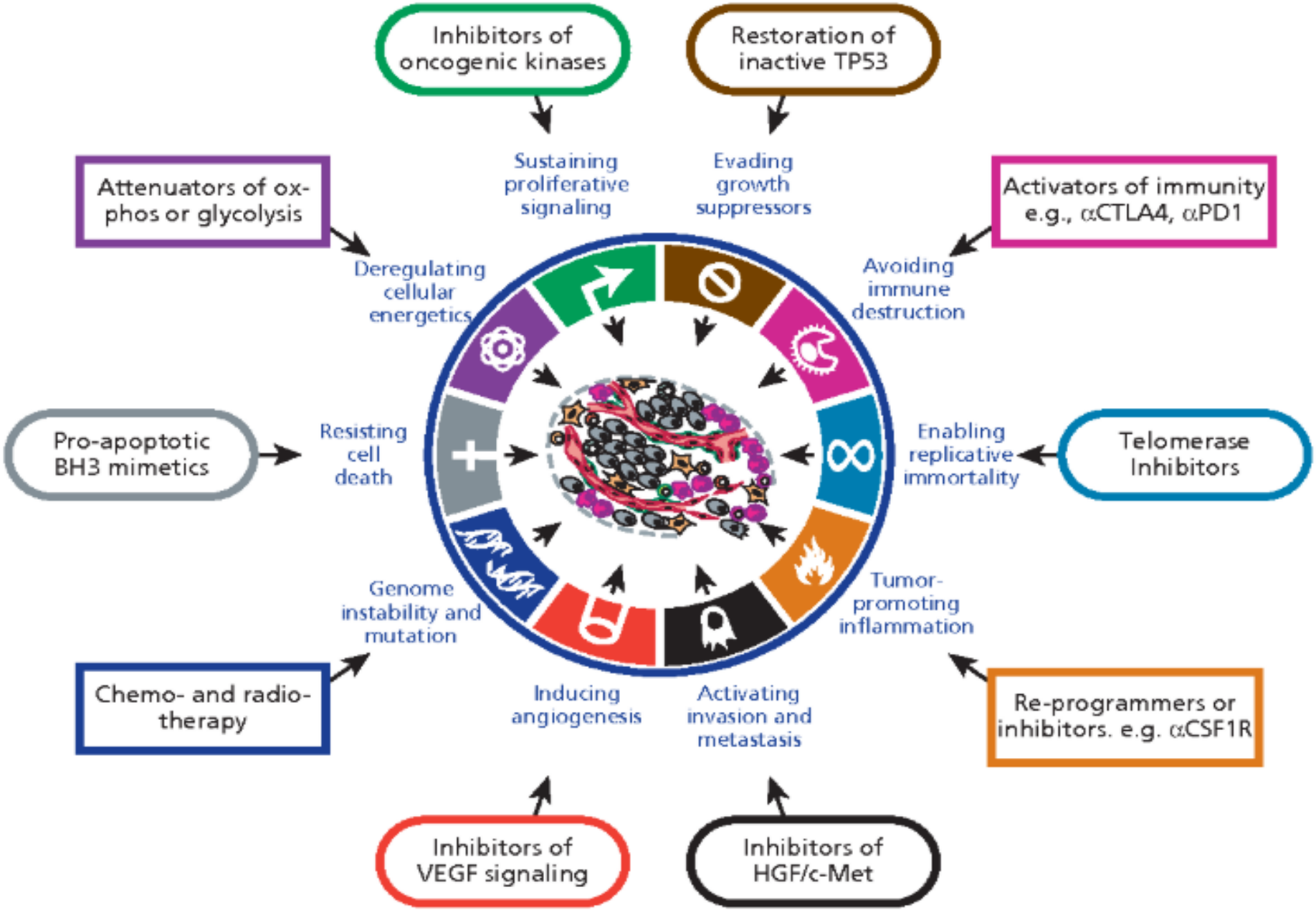
Multimodal Cancer Treatment

Surgery, radiation, chemotherapy,
targeted therapy, immunotherapy

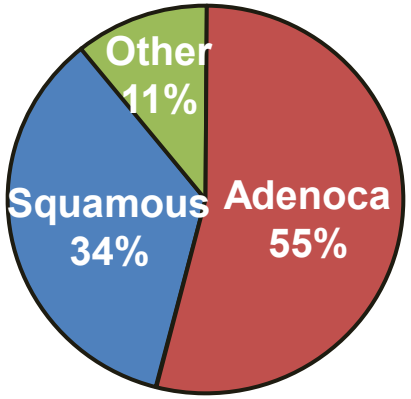


Cell 2011 Mar 4;144(5):646-74

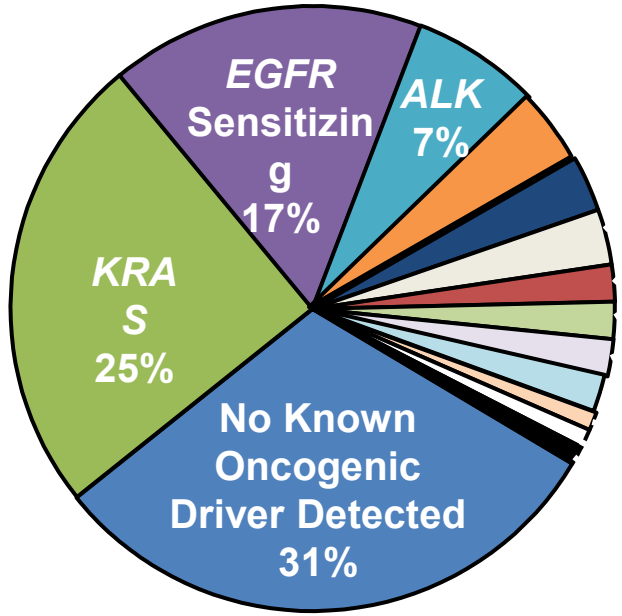
正常細胞內運行如同精細的集成電路，並經過重新編程以調節癌細胞內的標誌性功能。 單獨的子電路（此處在不同顏色的區域中進行了描述）專用於協調各種功能。 一方面，這種描述是簡單的，因為在這些子電路之間存在相當大的串擾(crosstalk)。 此外，由於每個癌細胞都暴露於來自其微環境的信號的複雜混合物，因此這些子電路中的每一個都與來自腫瘤微環境中其他細胞的信號相連。


Inhibitors of oncogenic kinases
Restoration of inactive TP53
Sustaining proliferative signaling
Evading growth suppressors
Attenuators of ox-phos or glycolysis
Activators of immunity e.g., αCTLA4, αPD1
Deregulating cellular energetics
Avoiding immune destruction
Pro-apoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability and mutation
Tumor-promoting inflammation
Chemo- and radio-therapy
Inducing angiogenesis
Activating invasion and metastasis
Re-programmers or inhibitors. e.g. αCSF1R
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Non-Small-Cell Lung Cancer: Not One Disease, but Many!



Adenocarcinoma



MET **3%**

EGFR **Other 4%**

> 1 Mutation 3%

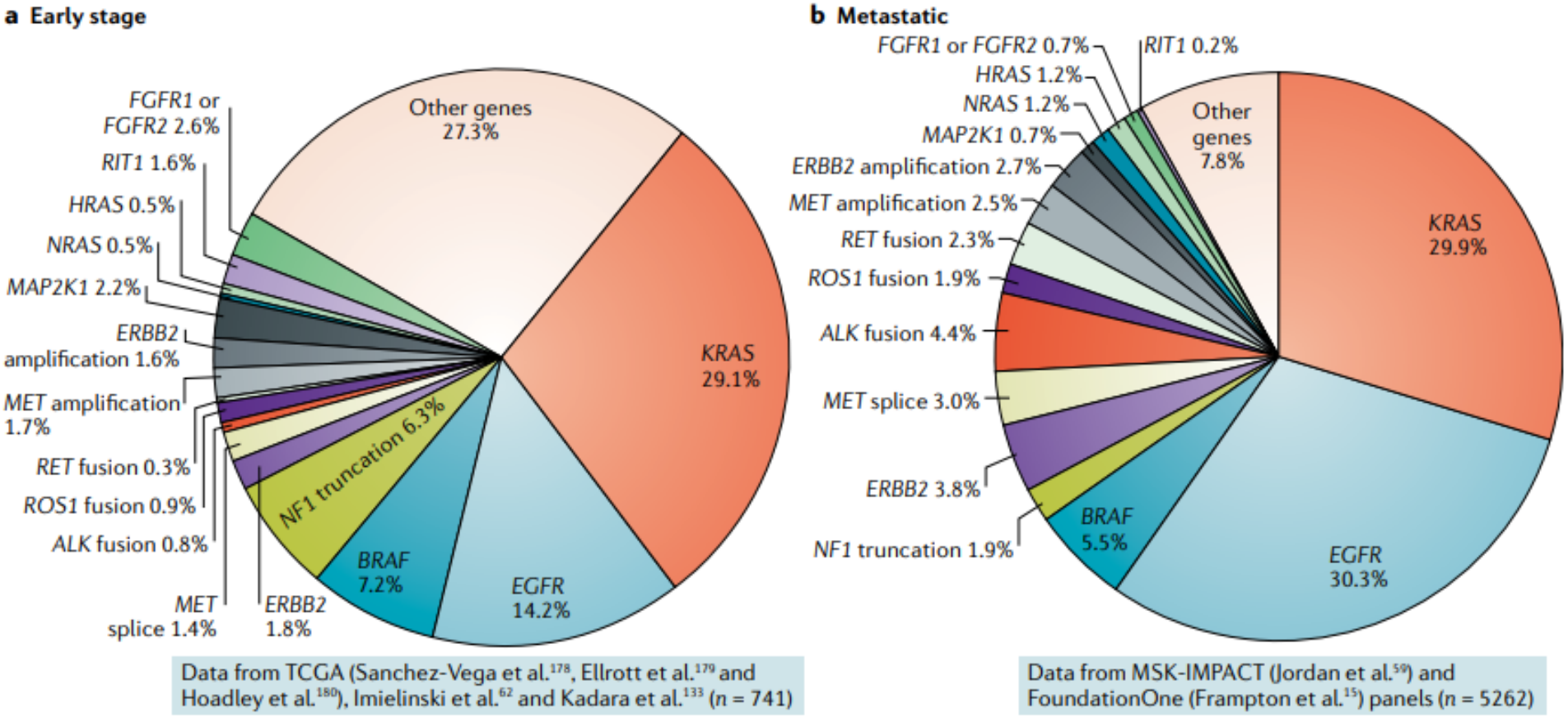
HER2 **2%**
ROS1 **2%**
BRAF **2%**
RET **2%**
NTRK **< 1%**
PIK3CA **1%**
MEK1 **< 1%**

Then → **Histology-Based Subtyping** → **Now**

Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

Slide credit: clinicaloptions.com

Single oncogenic driver paradigm of lung adenocarcinoma molecular classification

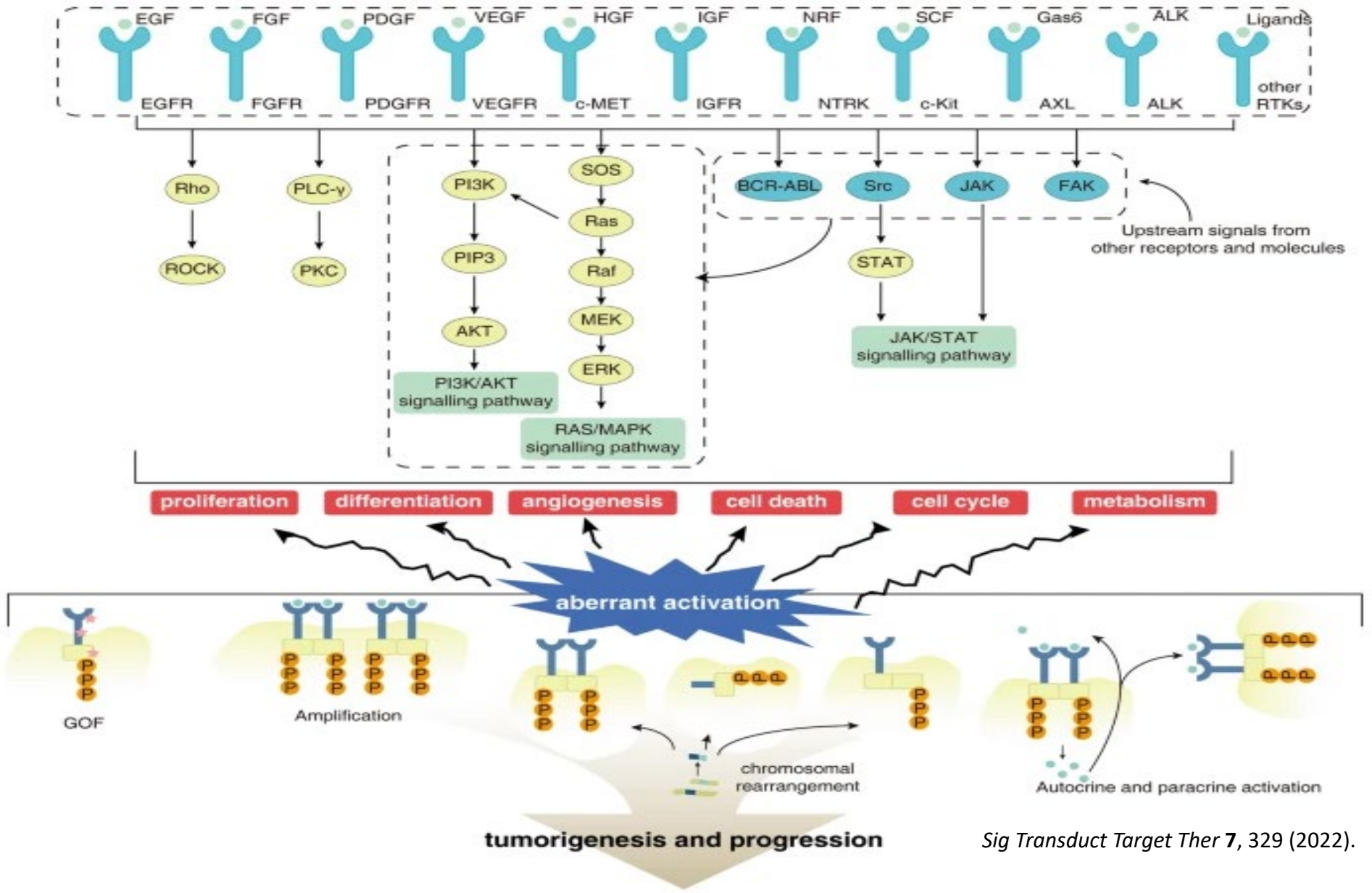


Nat Rev Cancer **19**, 495–509 (2019)

Target therapy classification (Small molecular inhibitors : kinase inhibitors)

- 跨膜受體酪氨酸激酶 (Receptor tyrosine kinase)
  - ALK inhibitor
  - EGFR inhibitors
  - FGFR inhibitors
  - FLT3 Inhibitor
  - Her2 inhibitor
  - NTRK
  - Multikinase Inhibitors
  - CSF-1R inhibitors
  - MET Inhibitor
  - RET Kinase Inhibitor
  - PDGFRA Inhibitor (platelet-derived growth factor receptor α)
- 非跨膜細胞內酪氨酸激酶
  - BCR-ABL inhibitor
  - BRAF inhibitor
  - BTK inhibitor
  - JAK inhibitor
  - FLT3 inhibitor
- 非跨膜細胞內絲氨酸/蘇氨酸蛋白激酶 (serine/threonine kinase)
  - MEK inhibitor
  - PI3K Inhibitors
  - mTOR inhibitor
  - CDK 4/6 inhibitors
  - Akt inhibitor (protein kinase B)

The relationship between PTK and tumors.



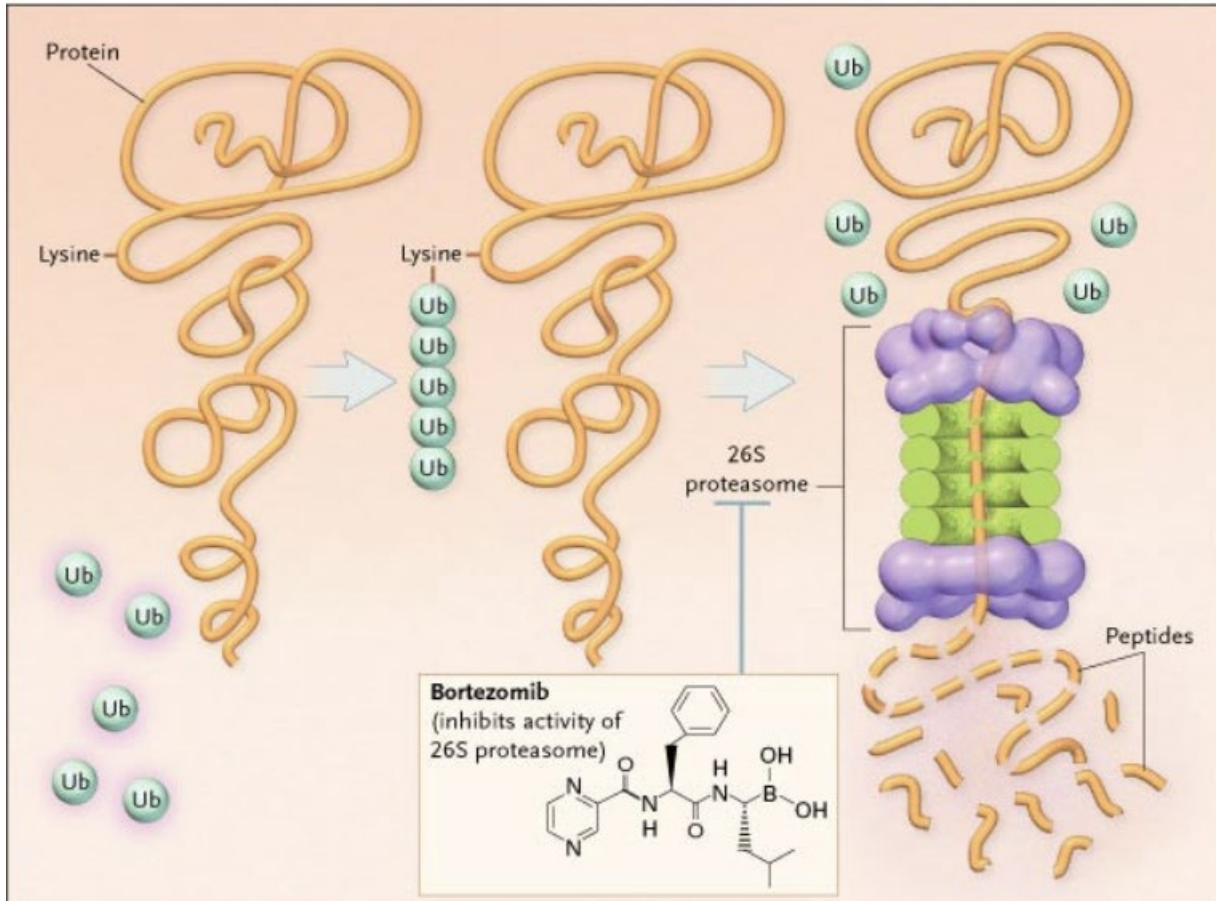
Sig Transduct Target Ther **7**, 329 (2022).

The main TKI drugs on the market in recent 20 years.

Cell Death Discovery **volume 8**, Article number: 488 (2022)

Target therapy classification (Small molecular inhibitors)

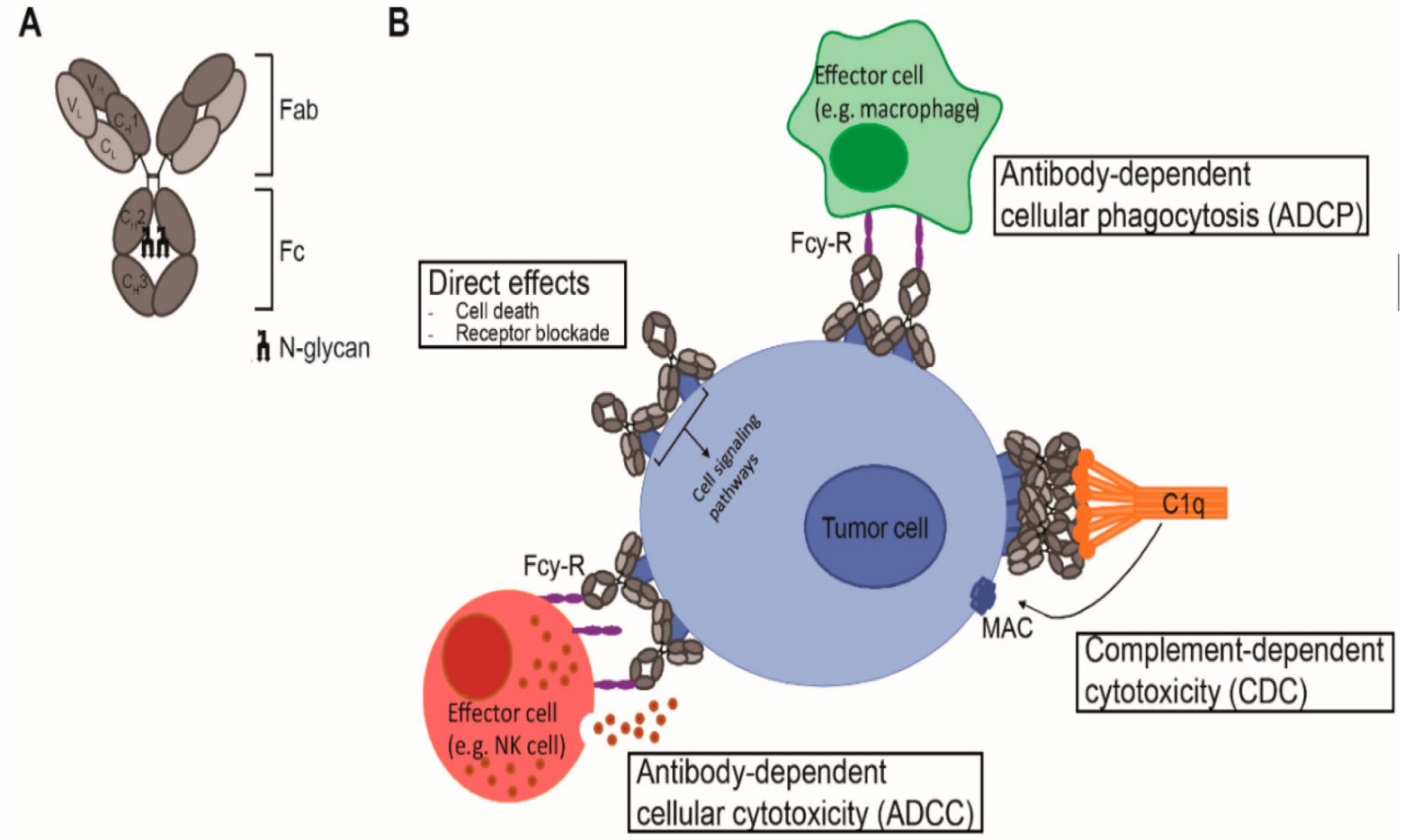
- 訊號阻斷 (ib)
  - Hedgehog pathway inhibitors
  - HDAC Inhibitors
  - PARP Inhibitor
  - Proteasome inhibitors
  - IDH2 Inhibitor
  - BCL2 Inhibitor
  - XPO1 Inhibitor(exportin 1 (XPO1))
  - STAMP Inhibitor
  - KRAS Inhibitor



N Engl J Med 2003;348:2597-2598

Target therapy classification (monoclonal antibodies)

- Monoclonal antibodies
- Antibody Drug conjugate



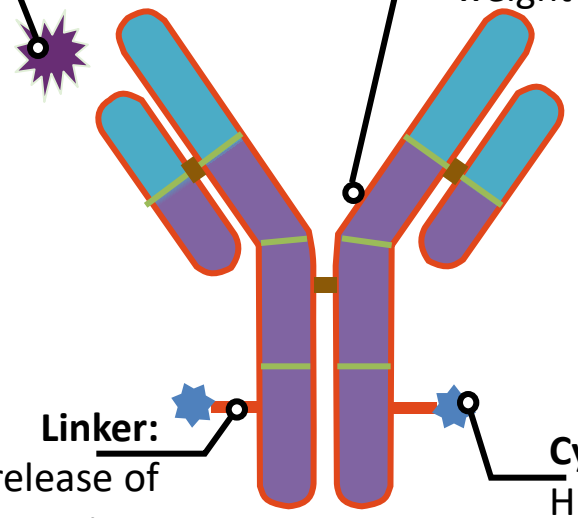
Antibody–Drug Conjugates

- Also known as **immunoconjugates**
- Represent a **new class** of targeted chemotherapeutic drug
- Composed of **monoclonal antibodies (mAbs)** tethered to a **cytotoxic drug** (known as the "payload" or "warhead") via a **chemical linker**

Antigen:
High homogenous expression on tumor cells with low expression on healthy cells; high affinity/avidity for mAb recognition

Tumor Antigen

mAb:
High affinity/avidity for tumor antigens; chimeric or humanized to decrease immunogenicity with long half-life and high molecular weight



Linker:
Stable in circulation; efficient release of payload in target cell; no premature release of payload at nontarget tissue; efficient linker technology (cleavable vs noncleavable); site of conjugation affects drug distribution and PK data

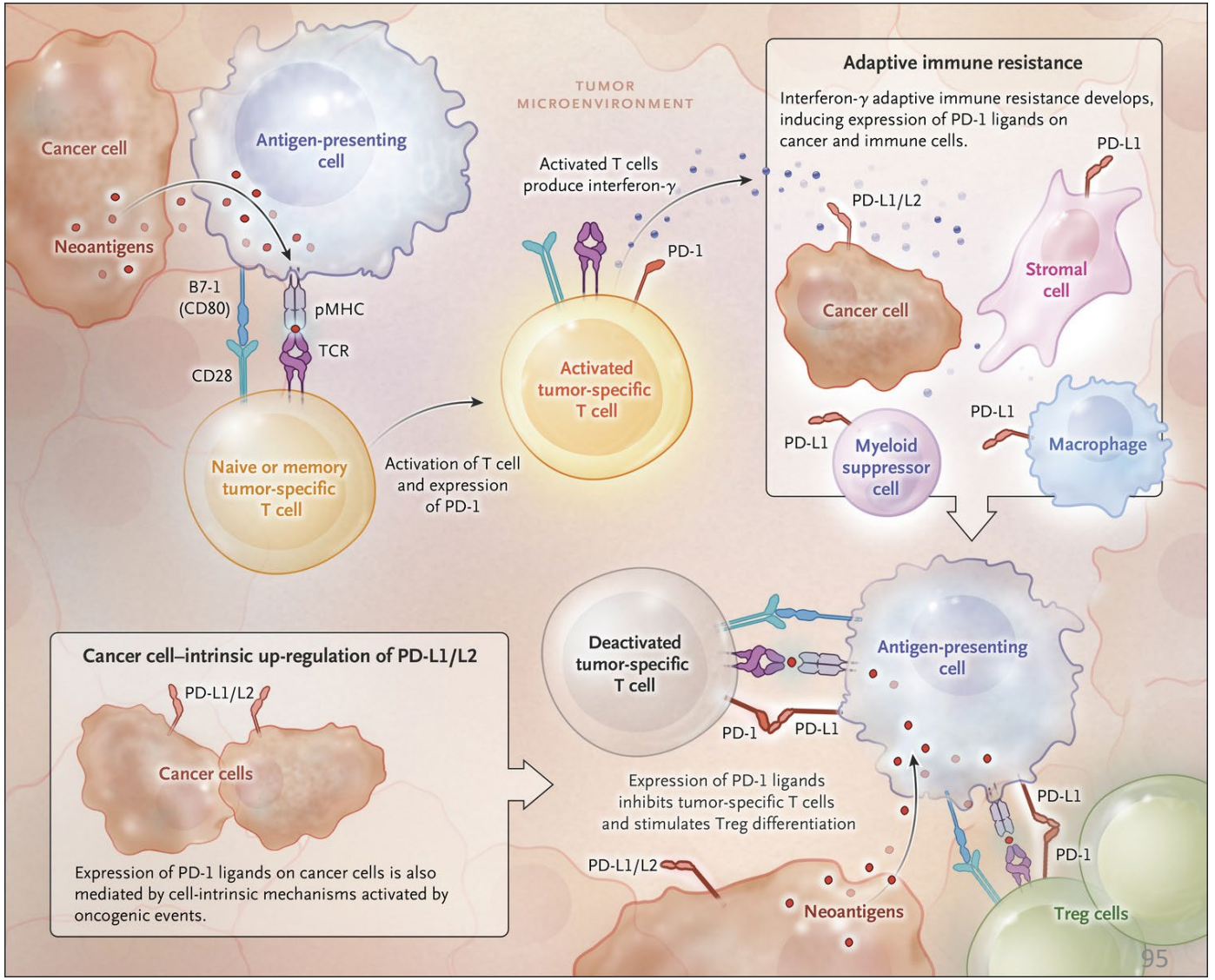
Cytotoxic Agent:
Highly potent agent (IC_{50} in subnanomolar range) with optimal DAR

Chau. Lancet. 2019;394:793.

Slide credit: clinicaloptions.com

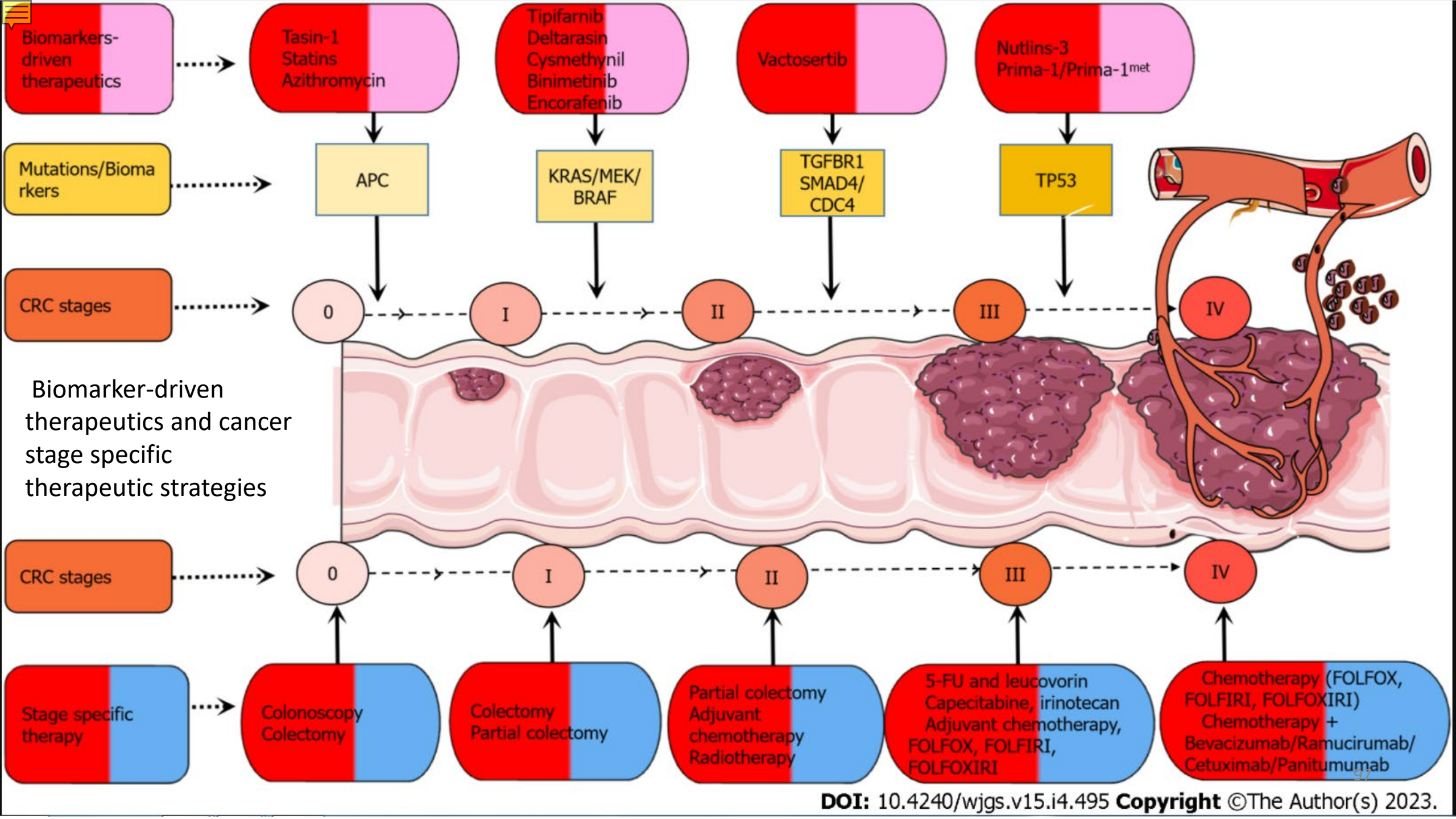
Target therapy classification (monoclonal antibodies)

- Immunotherapy
  - CTLA inhibitor
  - PD1 inhibitor
  - PDL1 inhibitor
  - CART cell
- IrAE monitoring



https://cancerinfo.org.tw/CancerInfoPro/Clinical

免疫檢查點抑制劑病人自我評估	輸注反應	口腔黏膜發炎
噁心與嘔吐	嗜中性白血球低下	食慾降低
疲勞	化療外滲的處理 (專業版)	腹瀉 (專業版)
化療藥物造成周邊神經病變 (專業版)	癌症治療藥物的常見毒性分級 (CTCAE)第五版 (專業版)	癌症藥物副作用症狀解釋與自我照顧 (專業版)
化學治療藥物的基本專用名詞與常識 (專業版)	手足症候群 (專業版)	單株抗體輸注反應與過敏性休克不同
痤瘡樣皮疹照顧處理	免疫治療副作用評估與處理2023 (專業版)	腎功能不全下化療藥物的調整與處理
抗癌藥物相關指甲毒性評估與處理 (專業版)	T細胞免疫療法副作用處理原則	



Biomarker-driven therapeutics and cancer stage specific therapeutic strategies

DOI: 10.4240/wjgs.v15.i4.495

Chemotherapy regimens of colon cancer

Adjuvant chemotherapy for *High risk stage* II

- mFOLFOX6
- CapeOX
- FLOX
- 5-FU & LV
- Capecitabine

Adjuvant chemotherapy for stage III

- mFOLFOX6
- CapeOX
- FLOX
- 5-FU & LV
- Capecitabine

Chemotherapy of Metastatic disease

- FOLFIRI
- Irinotecan
- mFOLFOX6
- CapeOX
- Capecitabine
- 5-FU & LV
- IROX
- FOLFOXIRI
- TS-1,UFT, Lonsurf

+/-

- bevacizumab
- Ramucirumab
- ziv-aflibercept
- Cetuximab
- Panitumumab

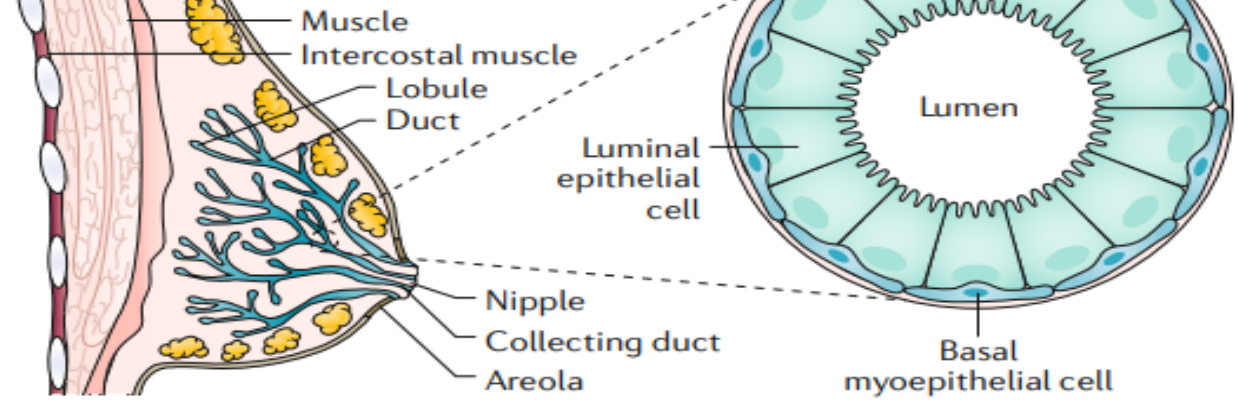
☐ Regorafenib

☐

Case : 64 y/o male with Diagnosis: Stage III colon cancer, with regional lymph node involvement

- Surgery: Total colectomy with lymph node dissection to remove the primary tumor and affected nodes.
- Adjuvant Chemotherapy: FOLFOX (folinic acid, fluorouracil, and oxaliplatin) regimen:
  - Administered over a cycle of 2 weeks for a total of 12 cycles:
- Day 1: Oxaliplatin and leucovorin infusion, followed by a bolus of 5-FU and then a 46-hour continuous infusion of 5-FU. (Combined cetuximab or bevacizumab)
- Progression Scenario:
  - After 6 cycles of chemotherapy, follow-up imaging indicated a reduction in tumor markers and no visible metastases. However, during the subsequent cycles, the patient began experiencing increased abdominal pain and weight loss. Further imaging revealed new hepatic lesions suggestive of metastatic disease, indicating progression despite initial therapy.

- Modified Chemotherapy Regimen:
- Switched to FOLFIRI (folinic acid, fluorouracil, and irinotecan) due to progression:



Preinvasive

Ductal carcinoma in situ (DCIS)
- Spreads through ducts and distorts ductal architecture; can progress to invasive cancer; unilateral

Lobular carcinoma in situ (LCIS)
- Does not distort ductal architecture; can be bilateral
- Risk factor rather than precursor

Invasive

Ductal carcinoma no special type (NST)
- Develops from DCIS; fibrous response to produce a mass; metastasizes via lymphatics and blood

Lobular carcinoma (ILC)
- Isolated tumor cells (*CDH1* mutations) minimal fibrous response; metastasizes preferentially via viscera

Intrinsic subtypes (PAM50)

Basal-like
TP53 mutations; genetic instability; *BRCA* mutations; medullary-like histology poorly differentiatied

Claudin-low
Largely triple-negative; metaplastic

HER2-enriched
HER2 amplification; *GRB7* amplification; *PIK3CA* mutations; *TOPO2* and/or *MYC* amplification; NST, pleiomorphic lobular and micropapillary histology

Normal-like[b]

Luminal B
PI3KCA mutations (40%); *ESR1* mutations (30–40%)[a]; *ERBB2* and *ERBB3* mutations; NST, micropapillary and atypical lobular histology

Luminal A
Activation of *ERS1*, *GATA3*, *FOXA1*, *XBP1*; NST, tubular cribriform and classic lobular histology

Breast cancer. *Nat Rev Dis Primers* **5,** 67 (2019).

Surrogate intrinsic subtypes

Triple-negative
ER–, PR–, HER2–; high grade; high Ki67 index; NST histology; special type histology (metaplastic, adenoid cystic, medullary-like and secretory); poor prognosis except for some special types

HER2-enriched (non-luminal)
ER–, PR–, HER2+; high grade; high Ki67 index; NST histology; aggressive disease but responds to targeted therapies; intermediate prognosis

Luminal B-like HER2+
ER+ but lower ER and PR expression than luminal A-like; HER2+; higher grade; high Ki67 index; NST and pleiomorphic; responds to targeted therapies; intermediate prognosis

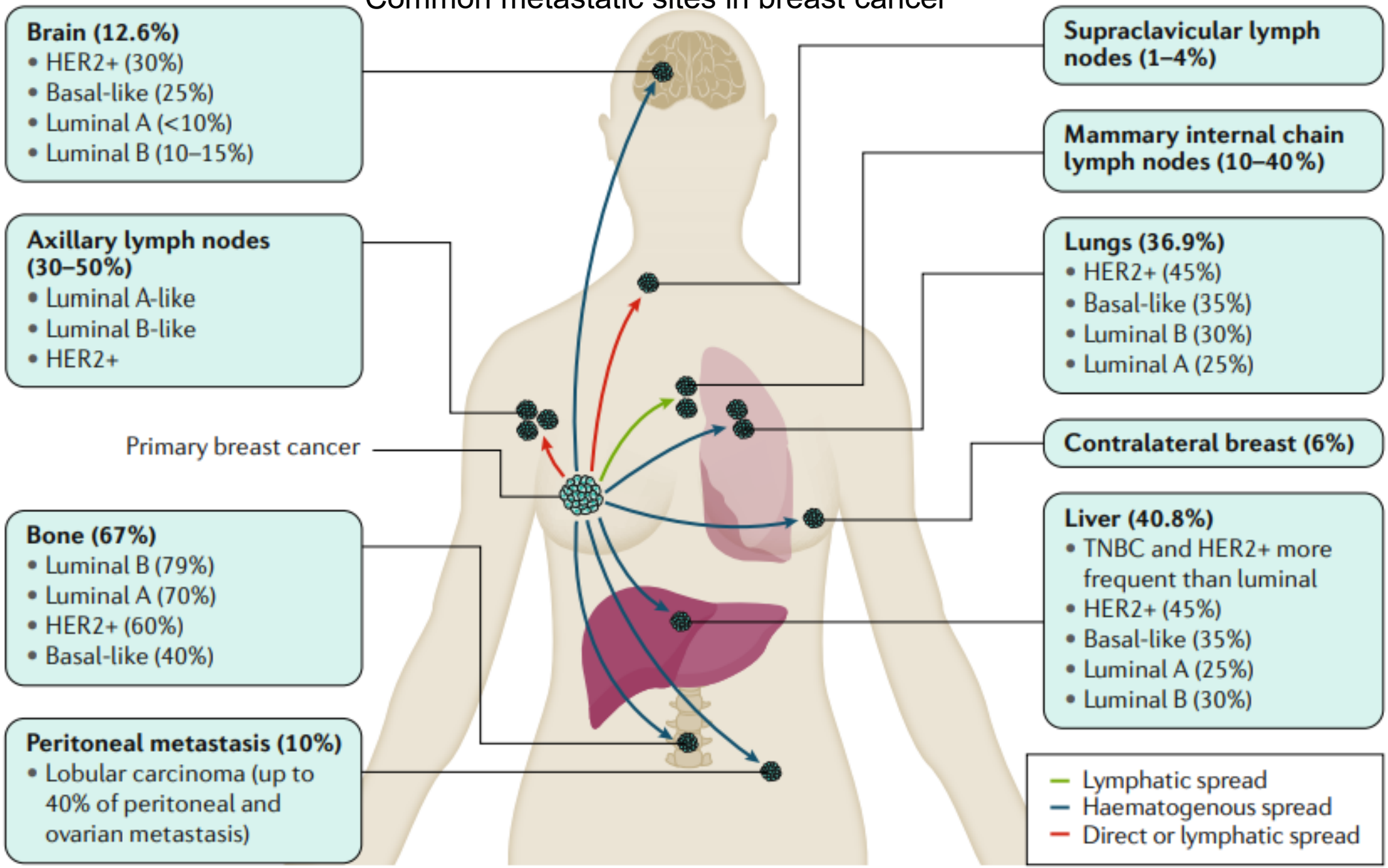
Luminal B-like HER2–
ER+ but ER and PR expression lower than in luminal A-like; HER2–; higher grade; high Ki67 index; high-risk GES; NST, micropapillary and lobular pleiomorphic histology; intermediate prognosis

Luminal A-like
Strongly ER+ and PR+; HER2–; low proliferation rates; typically low grade; low Ki67 index; low-risk GES; NST, tubular cribriform and classic lobular histology; good prognosis

10–15% **13–15%** **10–20%** **60–70%**

Proliferation
High grade
Basal-like genes
ER expression
HER2 expression
Low grade

Common metastatic sites in breast cancer



Breast cancer the most important Drugs : Her2 and hormone therapy

- Monoclonal antibody
  - Trastuzumab, Pertuzumab
  - Margetuximab (Fc engineered)
- New oral tyrosine kinase inhibitors (HER2)
  - Lapatinib (HER2/HR3 reversible)
  - Tucatinib (HER2, irreversible, less side effect)
  - Neratinib (HER2, HER1 (EGFR) and HER4, irreversible)
  - Pyrotinib (China)
- Antibody drug conjugates (HER2 antibody+ chemotherapy)
  - Tratuzumab Emtansine (taxane)
  - Trastuzumab deruxtecan (topoisomerase 1 inhibitor)
  - Trastuzumab duocarmazine
- Hormone therapy
  - Tamoxifen
  - Anastrozole, Letrozole (aromatase inhibitor)
  - Exemestane
  - Fulvestrant
- CDK4/6 Inhibitors
  - Palbociclib, Abemaciclib, Ribociclib
- mTOR inhibitor
  - Everolimus +endocrine therapy
- PI3K inhibitor
  - Alpelisib+ Endocrine therapy
- PARP inhibitors
  - Olaparib, Rucaparib, Niraparib, Talazoparib

Breast cancer : Case

- 61 y/o female, diagnosed with Breast Cancer ,T1cN0M1, BH:164.80cm BW:52.20kg BSA:1.55(m2) BMI:19.22 , who is going to receive therapy of Trastuzumab deruxtecan.

- #Brief history
- ** Breast cancer with bone metastasis, ER(8)PR(0)HER2(1+), liver, brain mets
- * PIK3CA mutation (-)
- * TMB-L

- left breast cancer s/p SM + SLNB on 2020/03/24 , ER(8)PR(0)HER2(1+)Ki67(20%), pT1c(m)(1.2cm)N0(0/1)M0, Nottingham grade (Modified SBR grade): 3, CEA 30.76, CA153: 41.3
  - microarray: Oncotype >=45 (high risk); subtype IV
  - (2020/05/27) PET CT scan: 3 bone metastasis
  - FNA of sternum metastasis: ER(8)PR(0)HER2(1+)
  - s/p CAF x 6 (2020/05/05~2020/8): improvement by PET CT
  - s/p anastrozole and palbociclib (NHI) (2020/9/21~2022/1/2)
  - (2021/06) s/p RT for sternum mets, improvement of pain
  - (2021/12/23) PET CT: mild progression of bone metastases; so we stop anastrozole (2020/09/21~2022/01/03) and change to letrozole.

Breast cancer : Case

- s/p letrozole and palbociclib (2022/01/03~2022/3): PET CT: disease progression at bone
- s/p everolimus + exemestane (2022/04/11~2023/02/24, side effect of ILD s/p steroid)
- s/p gemcitabine and paclitaxel (2023/02/24~2023/05/05): liver progression
- s/p Xeloda x 4 (2023/05/19~2023/07/21): liver & bone progression, marker increased, pain stable
- s/p Eribulin (2023/08/11~2024/01/05): progression, brain mets
- (2024/01/12) PET CT, brain MRI: disease progression, brain mets(new), increaesd tumor marker
- s/p palliative RT 30 Gy/10 Fr/2 weeks to the whole brain (2024/01/22~2024/02/02)
- s/p weekly oral Vinorelbine (2024/01/19~2024/03/15): marker elevation
- start liposomal doxorubicin (2024/03/22~)
  - @ cardiac echo every 3 month (2024/03/22 LVEF: 71 %)
  - @ denosumab every 6 weeks (2022/04/29~), last on 2024/03/22
  - @ (2024/03/22) s/p #1 liposomal doxorubicin, 75% dose because of jaundice
  - @ (2024/04/05) explain poor prognosis, discussion about DNR. explain the risk of hepatic failure and hepatic encephalopathy (husband, son accompanied)
  - @ marker today, decide if change to T-DXd

Breast cacner : case

- 1. Plan: next line: T-DXd for low-HER2, self-pay; Taxotere and cisplatin; tamoxifen)
- 2. T-spine X-ray: Destruction of Rt 4th rib.
  - R't T4 pedical osteolytic lesion. Erosion of Rt margin of T3 vertebral body.
  - (2022/04/14) dentist for denosumab (oral condition is stable)

- 3. history of DVT
  - (2021/05/06): thrombus in right subclavian vein and axillary vein.
  - (2021/12) color doppler: no DVT
  - s/p Rivaroxaban (2021/05/07~2022/01/03)
- 4. cardiac assessment
  - ECG: V3, V4 T inversion, R/I ischemic change or RV strain/dysfunction
  - echocardiography: unremarkable
  - myocardial perfusion scan: normal

Thank you for listening