Cancer Medicine and Action Mechanisms (MoA) of Drugs

Vural Tagal, PhD

1-31-2025

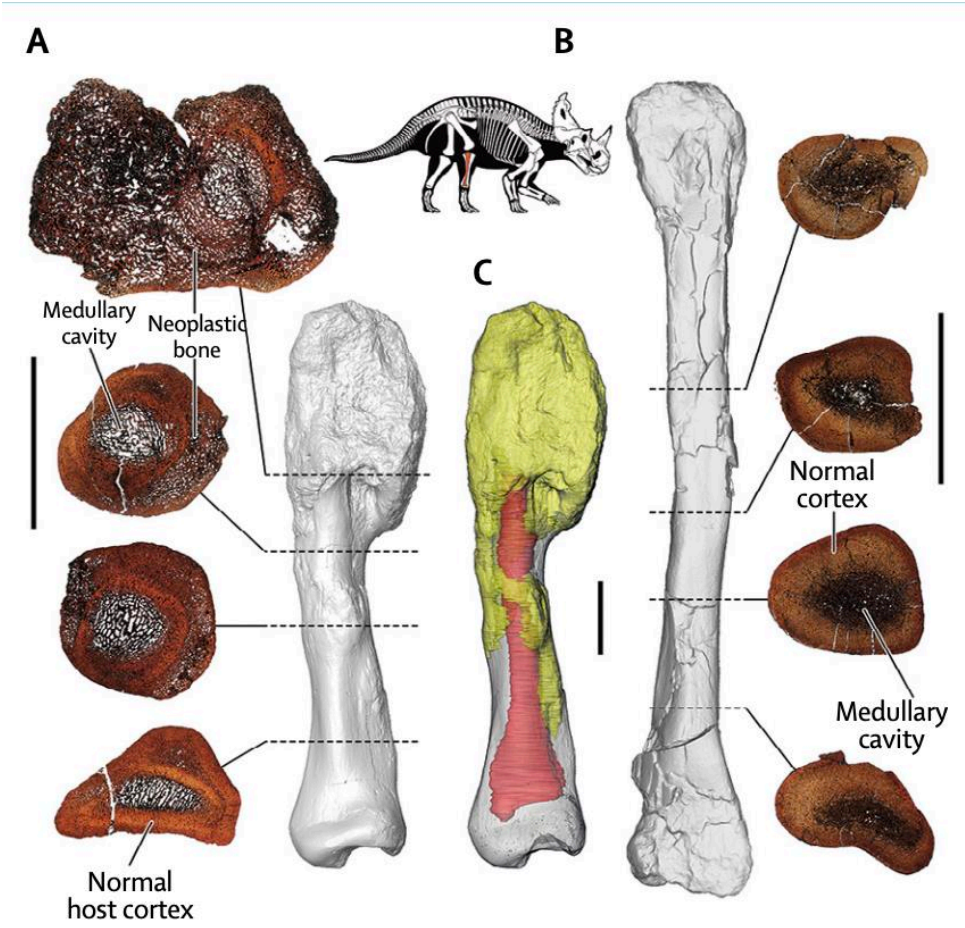
IMAT Lecture

Department of Integrated Mathematical Oncology

H. Lee Moffitt Cancer Center and Research Institute

Cancer is an ancient disease

77-million year old *Centrosaurus apertus*



Ekhtiari et al, Lancet Onc., 2020

The Evolution of Cancer Therapeutic Agents

Examples for The First Chemotherapy Agents
Herbal teas
Fruit juices
Salts
Figs
Boiled cabbage
Egg white
Pastes of arsenic, iron, mercury, copper
…

3500 years

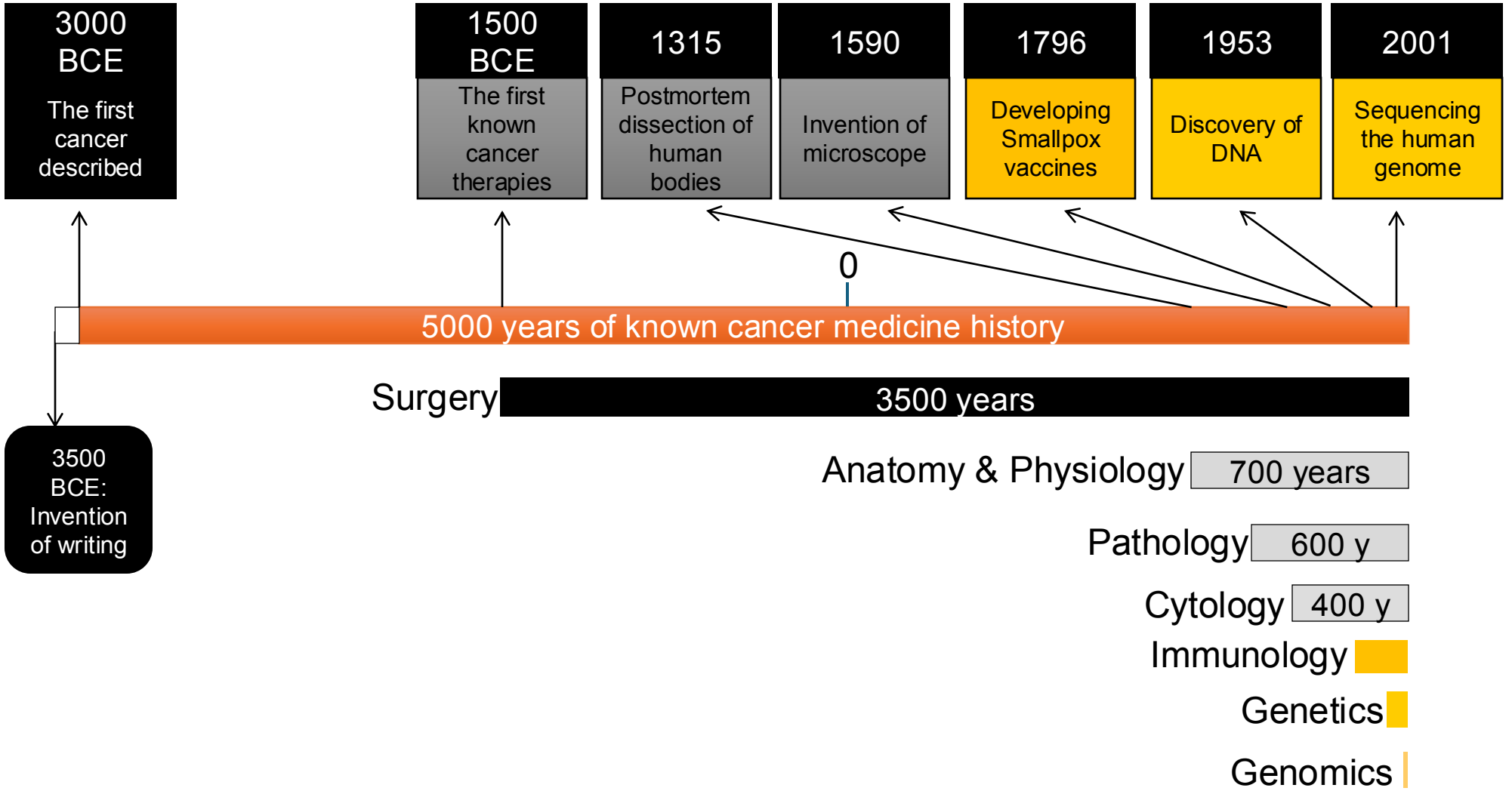
Modern Targeted-Therapy Agents
Kinase inhibitors
Receptor inhibitor/activators
Apoptosis enhancers
PARP inhibitors
…

Modern Chemotherapy Agents
Anti-metabolites
Alkylating agents
DNA-intercalating agents
Microtubule poisons
Nucleotide analogs
…

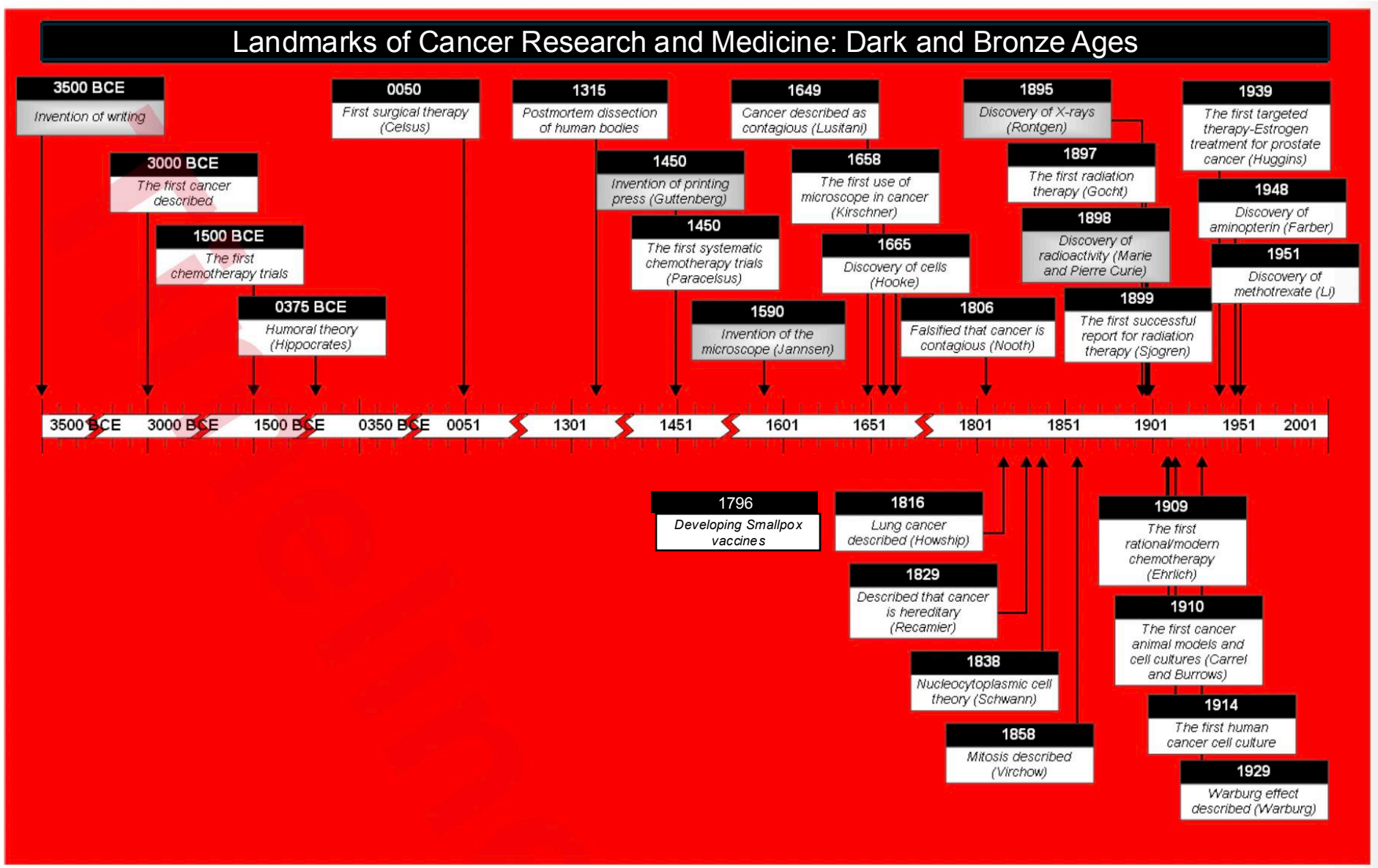
Immunotherapies
Immune checkpoint inhibitors
CAR-T cell antibodies
…

The hieroglyphic for the word *tumor* as described in the Edwin Smith papyrus. For details, refer to Breasted's translation of the document [1]. Reproduced with permission from Marcel Dekker, Inc., New York – Pitot HC (1986) Fundamentals of oncology, 3rd edn

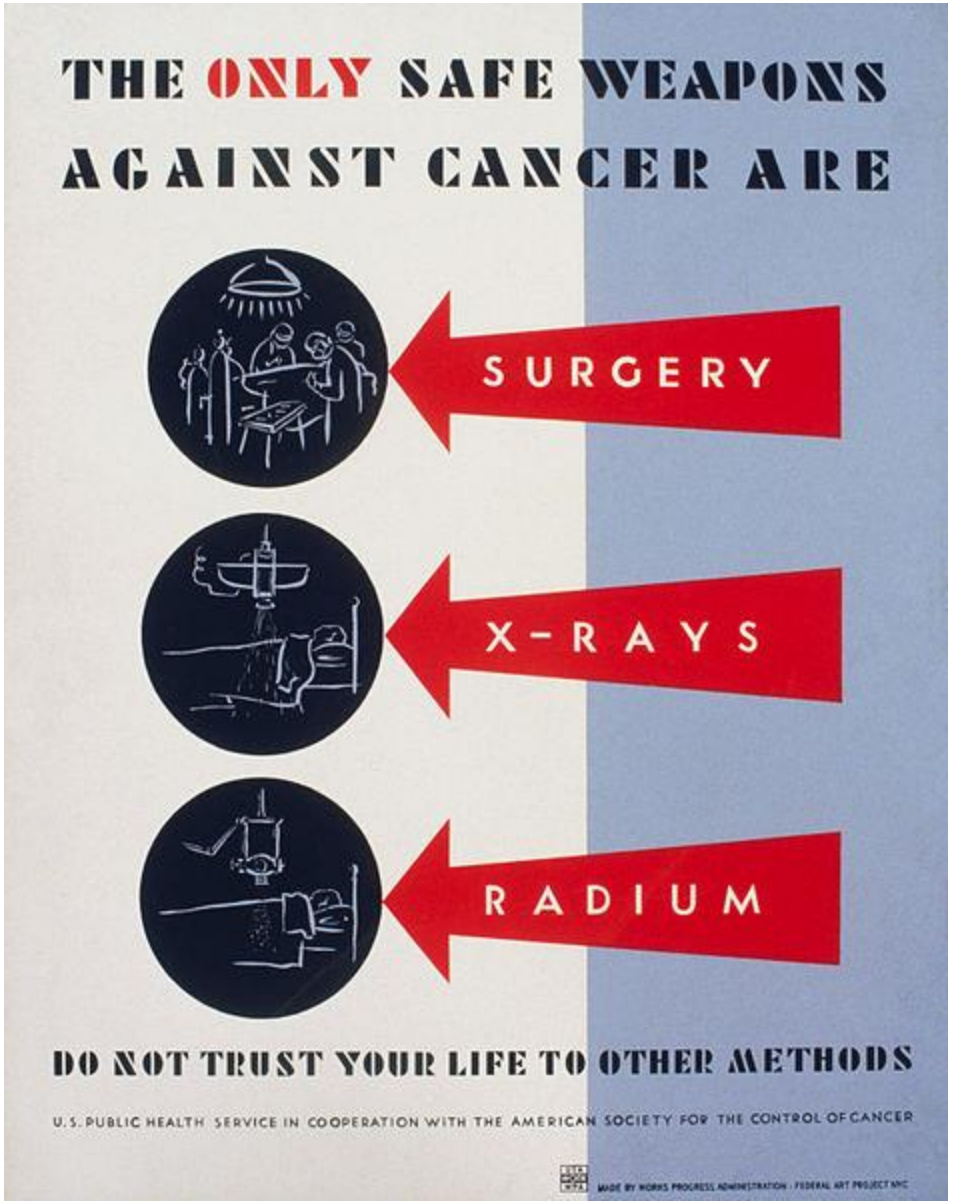
Emerging Disciplines for Cancer Medicine



Milestones in cancer research and medicine

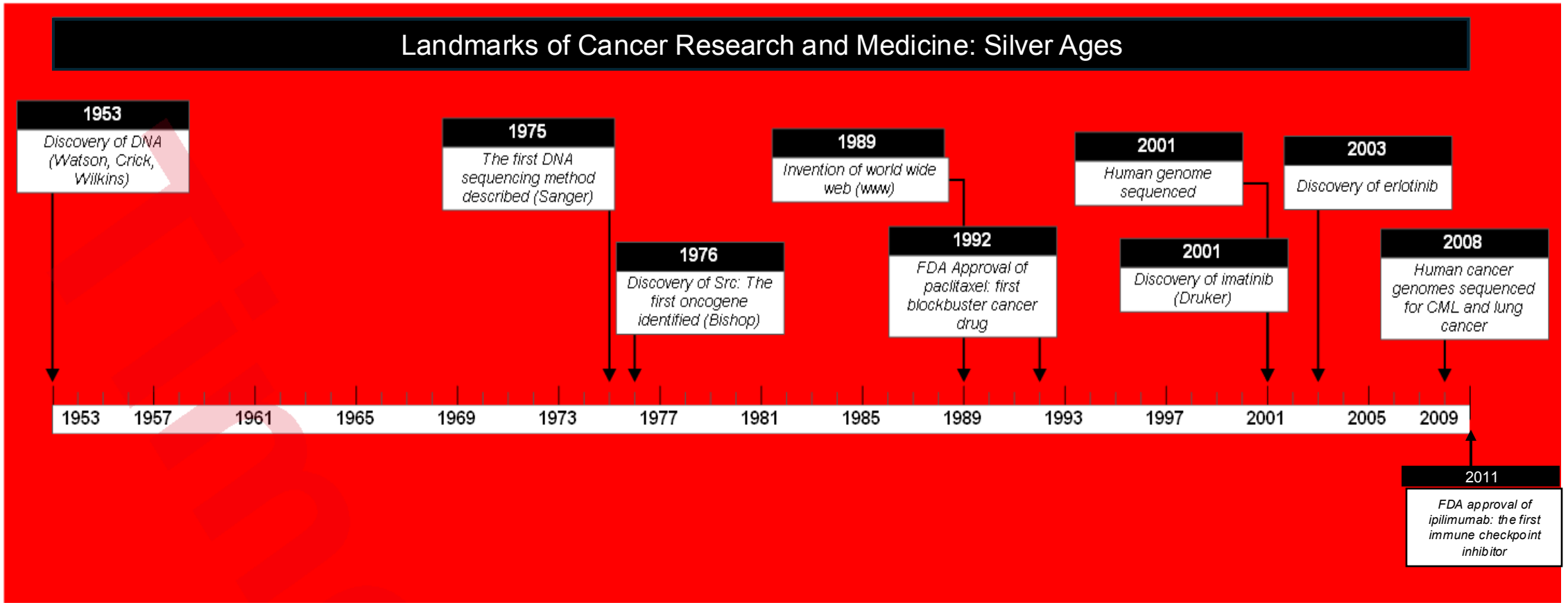


1938



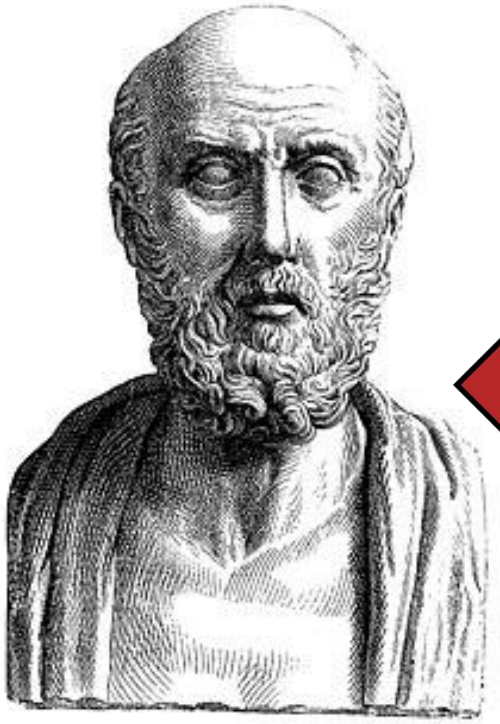
American Cancer Society

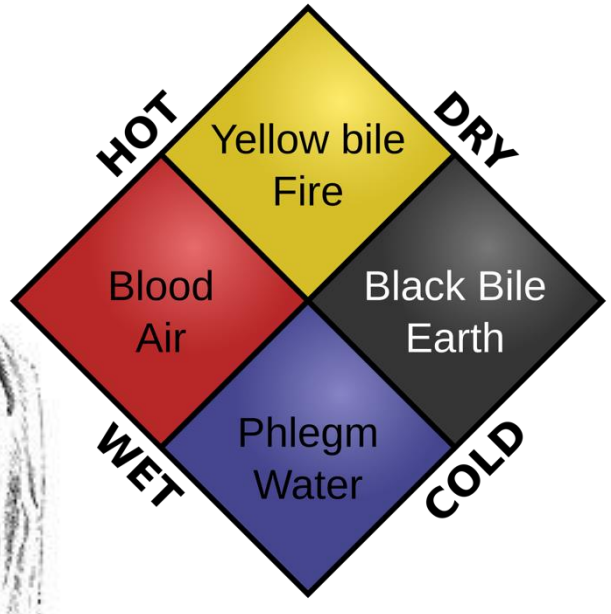
The New Era of Cancer Medicine

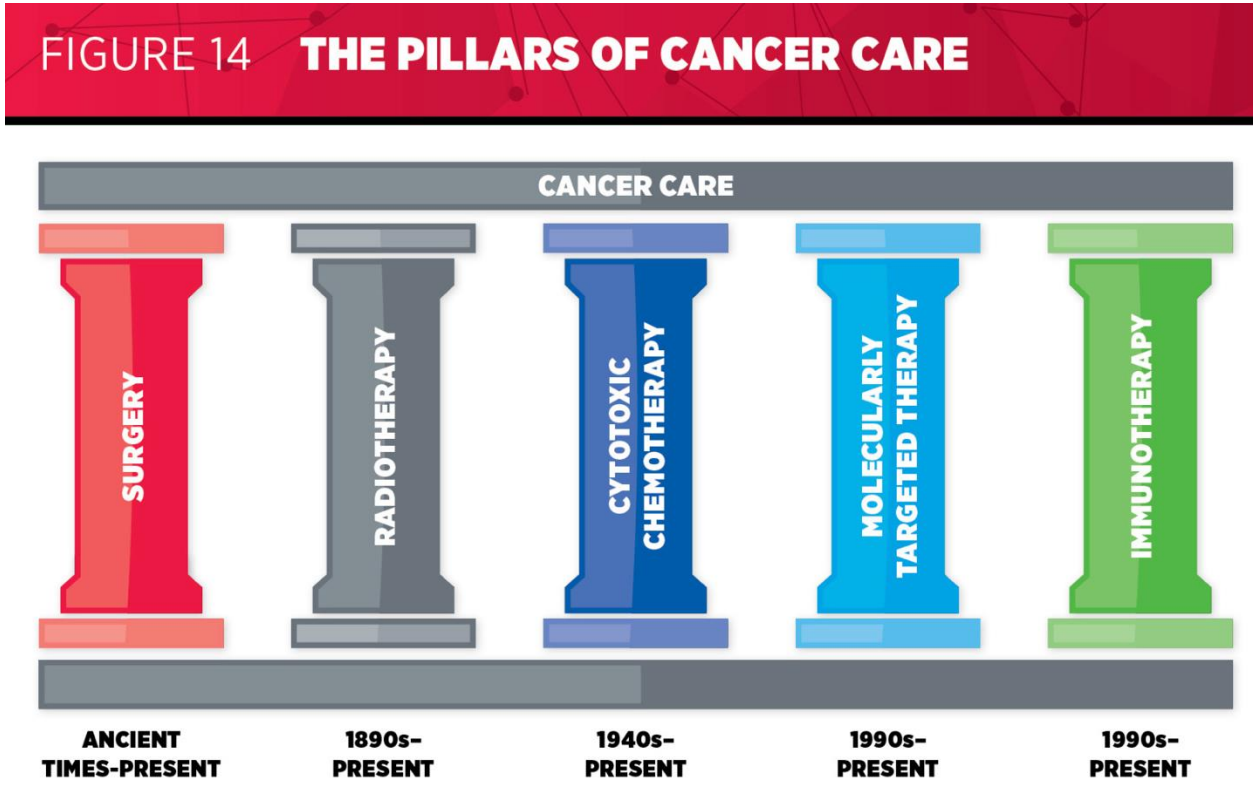


History of Cancer Research and Medicine

- Hippocrates (460-370 BC) and humoral theory







AACR Cancer Progress Report, 2020

Surgery

- Celsus (50 CE)

Spencer, Proc R Soc Med, 1926

Celsus “After excision, even when a scar has formed, none the less the disease has returned.”

The first systematic use of chemotherapy

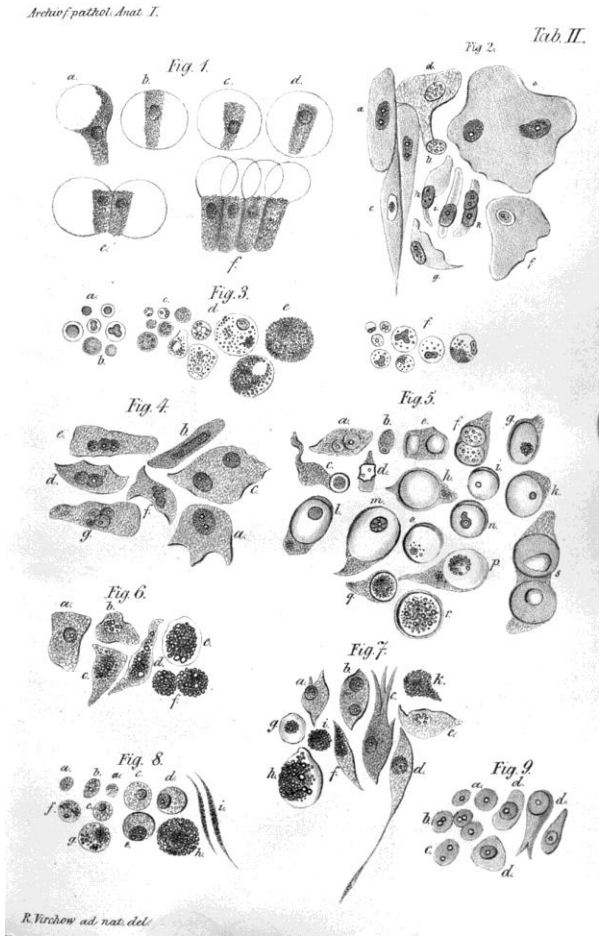
- Paracelsus (~1500) (Swiss physician-chemist)
  - Combination and pastes of
    - Mercury
    - Lead
    - Sulfur
    - Iron
    - Zinc
    - Copper
    - Arsenic
    - Iodine
    - Potassium

Cell theory (1839-1855)

Matthias Jakob Schleiden

Rudolf Virchow

Theodor Schwann

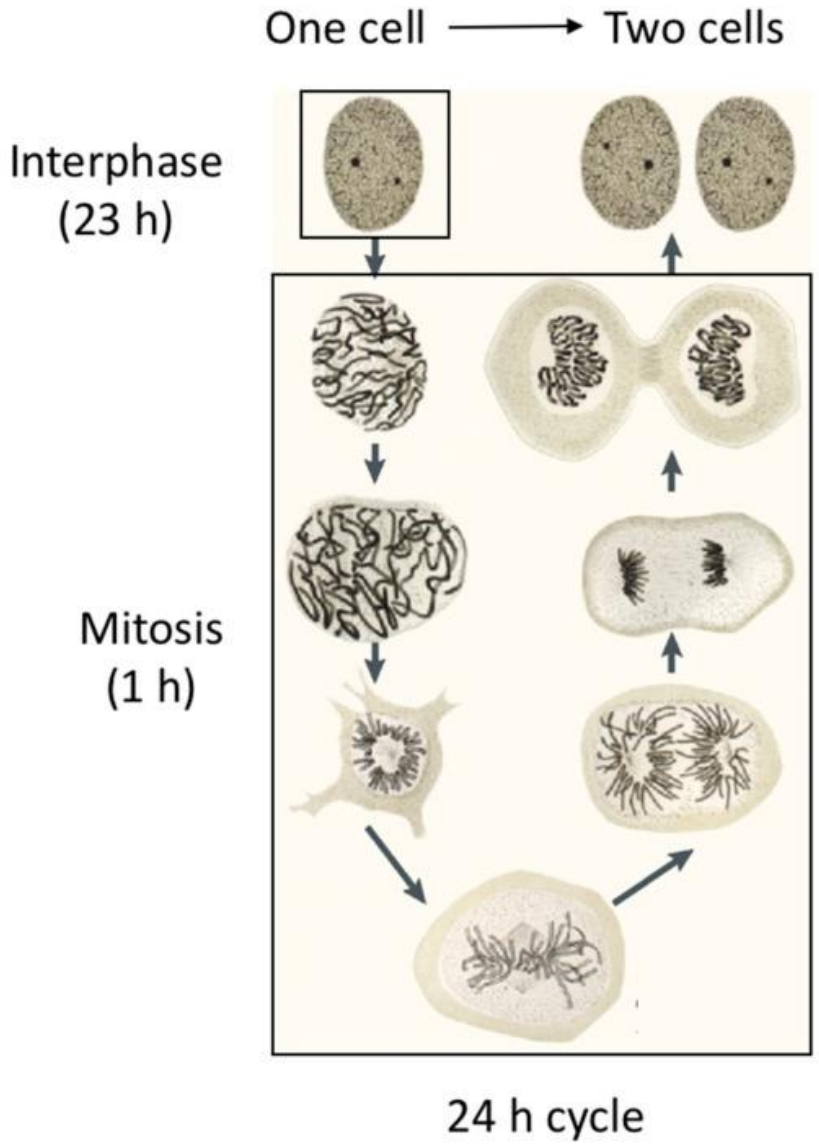


Archiv für Pathologische Anatomie und Physiologie , 1847

Three tenets of cell theory:

1. All living organisms are composed of one or more cells.
2. The cell is the most basic unit of life.
3. All cells arise only from pre-existing cells.

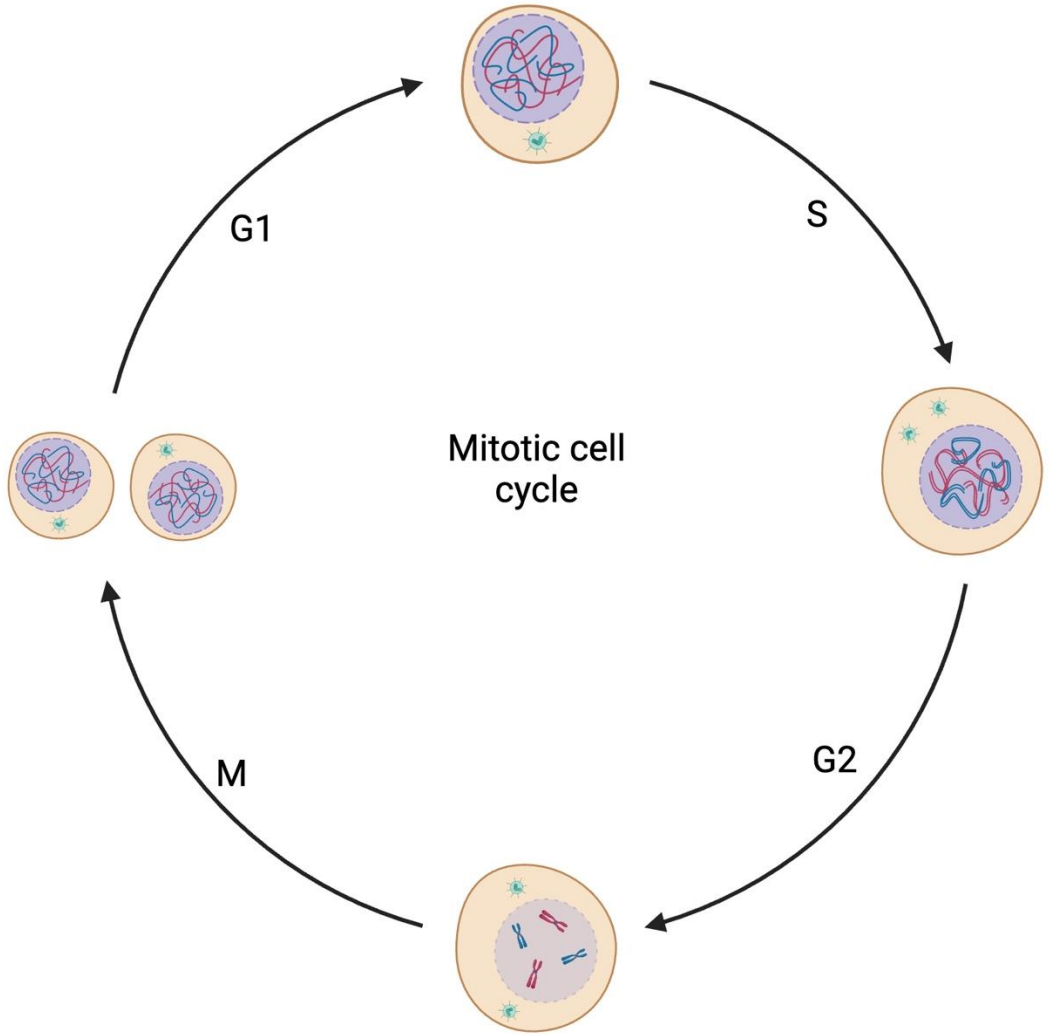
Discovery of mitosis



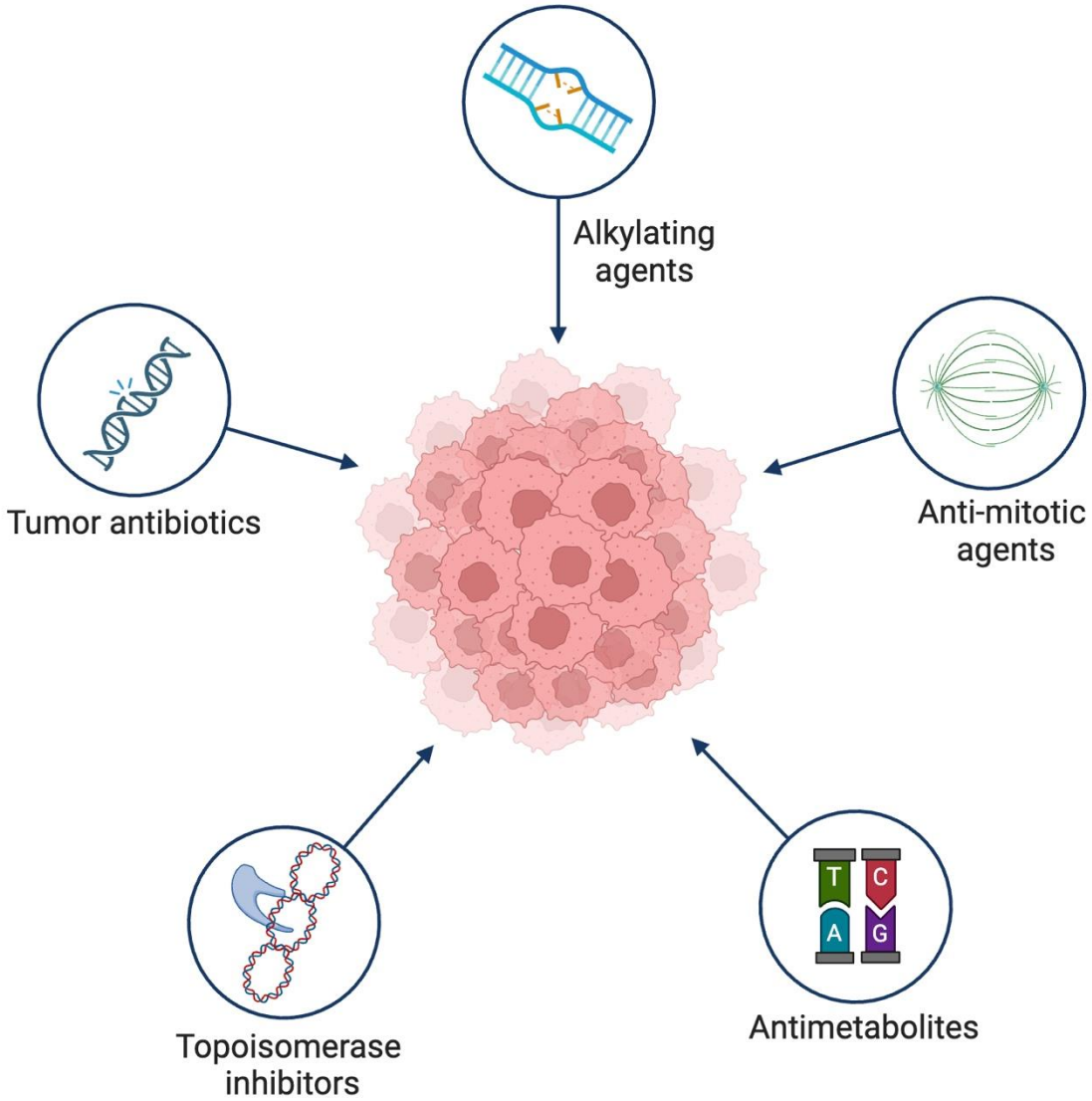
Walther Flemming
1843 - 1905

Adapted from Flemming, Zellsubstanz, Kern und Zelltheilung, 1882
Uzbekov and Prigent, Cells, 2022

Stages of cell cycle



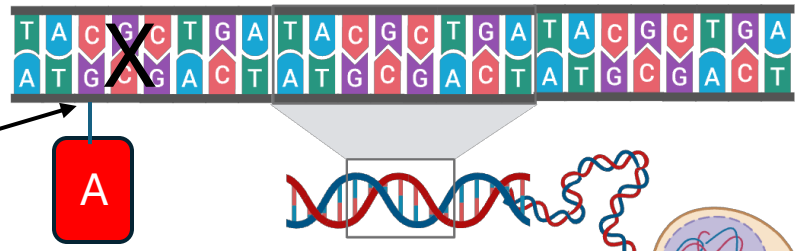
Classification of chemotherapeutic agents

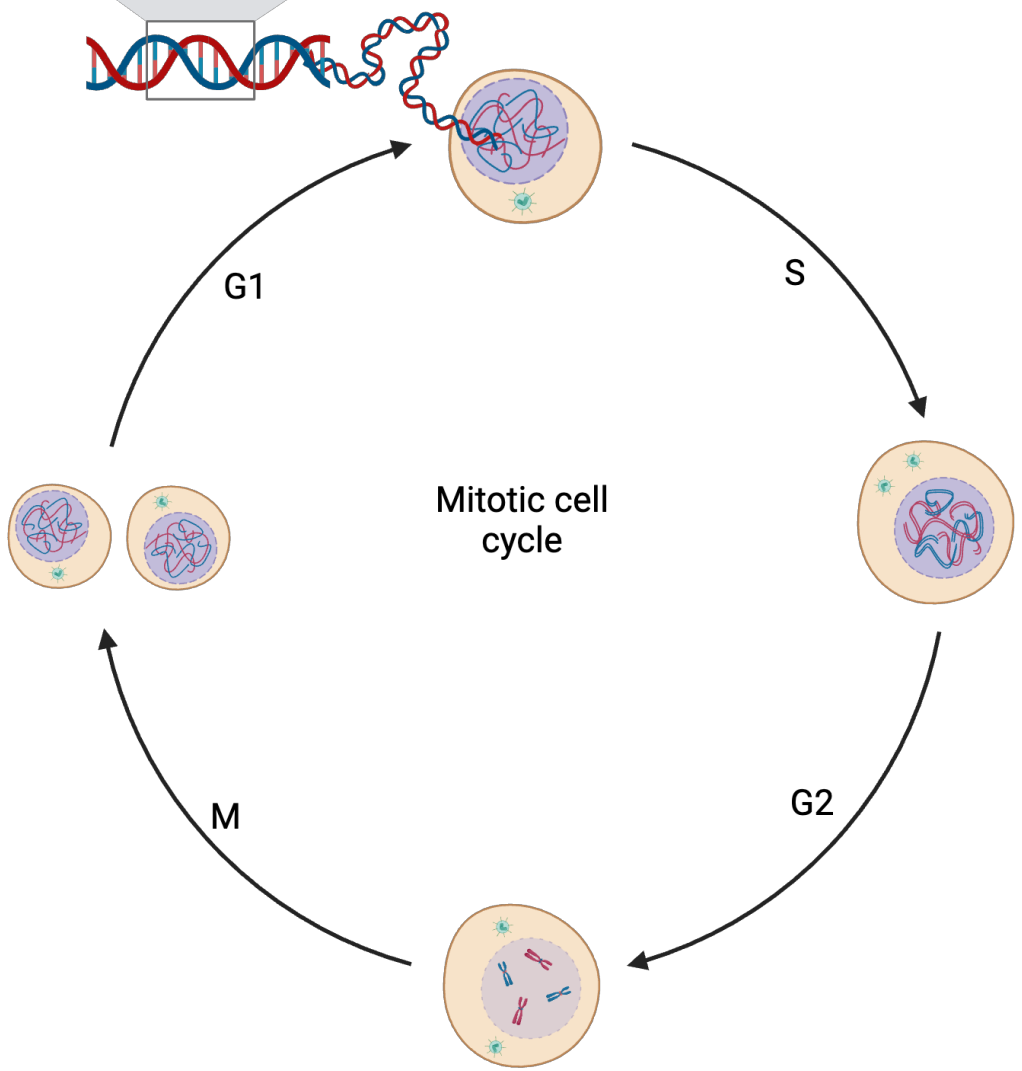


Alkylating agents

Nitrogen mustards (Discontinued)	Cisplatin
Cyclophosphamide	Carboplatin
Ifosfamide	Oxaliplatin
Bendamustine	Dicycloplatin
Chlorambucil	Eptaplatin
Melphalan	Lobaplatin
Uramustine	Miriplatin
Carmustine	Nedaplatin
Lomustine	Picoplatin
Streptozocin	Satraplatin
Busulfan	Triplatin tetranitrate
Altretamine	Procarbazine
	Temozolomide

DNA damage



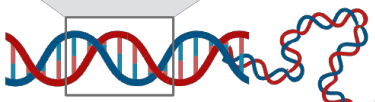


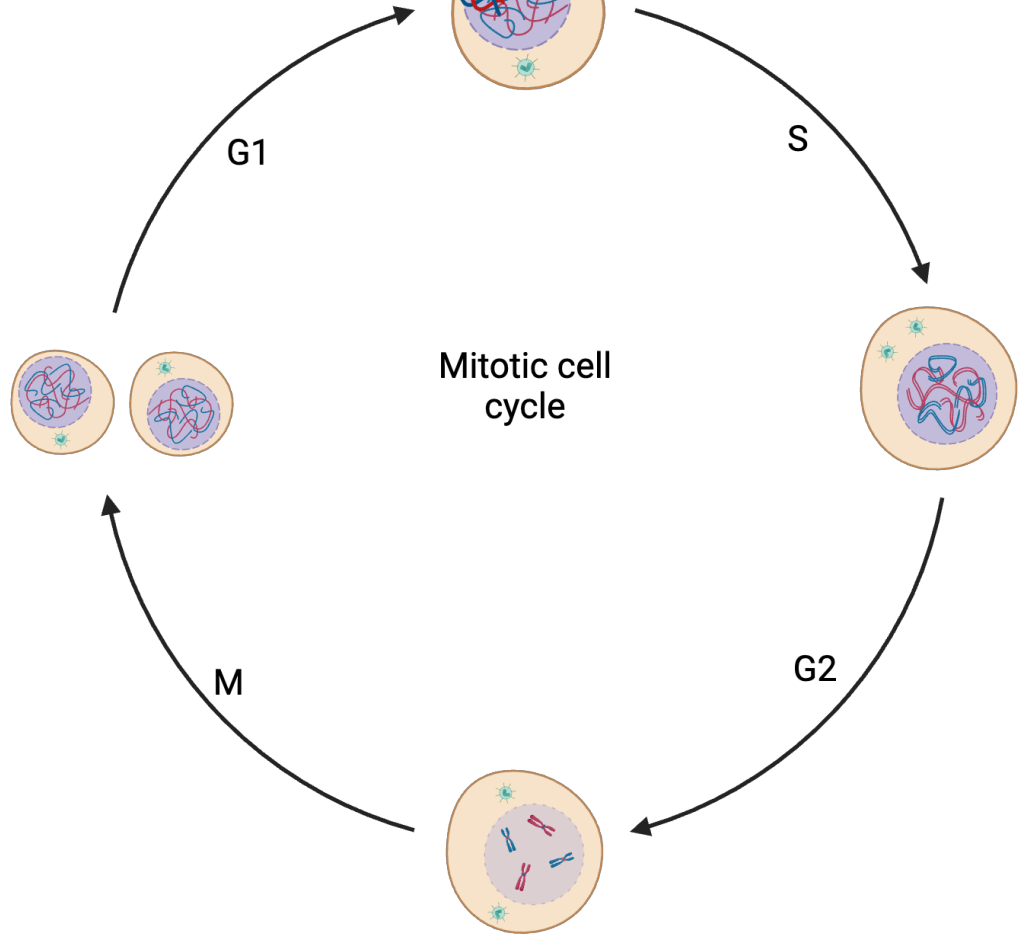
Anti-tumor antibiotics

1) Alkylating agents

Bleomycin
Dactinomycin
Mitomycin-C
Mitoxantrone

DNA damage

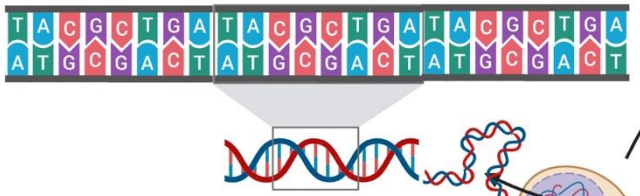


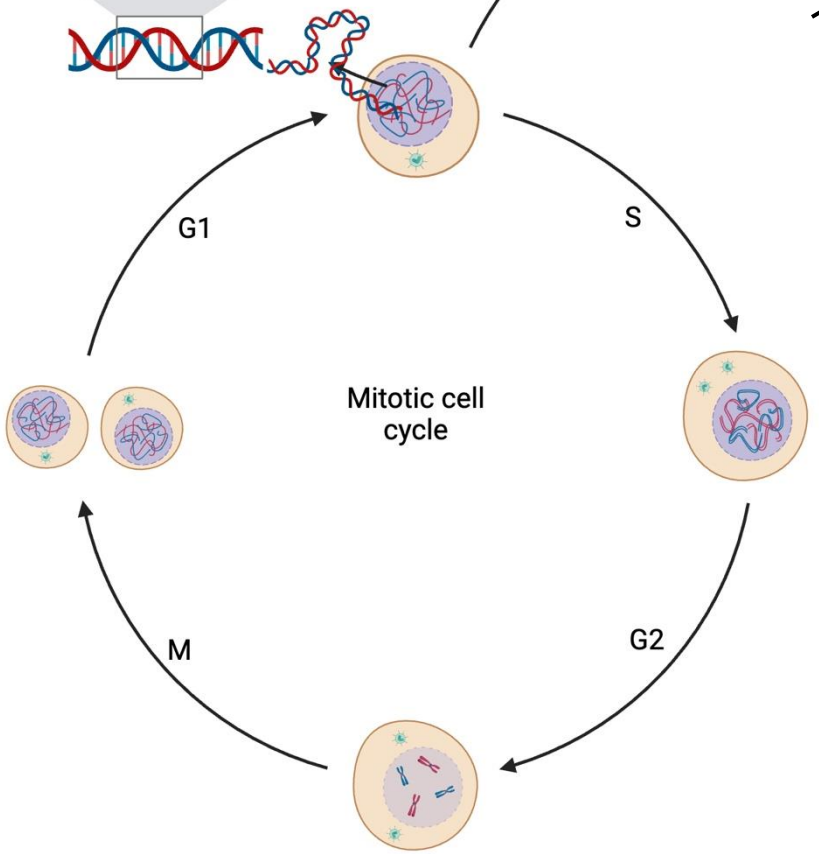


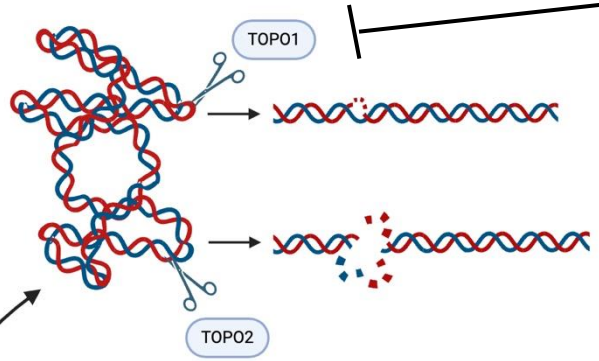
Topoisomerase inhibitors

1) Alkylating agents

2) Anti-tumor antibotics







DNA REPLICATION
Overview of the eukaryotic process

Topoisomerase I inhibitors
Camptothecins:
Topotecan
Irinotecan
Belotecan

Topoisomerase II inhibitors
Doxorubicin
Daunorubicin
Epirubicin
Idarubicin
Etoposide
Teniposide
Dexrazoxane
Novobiocin
Merbarone
Aclarubicin

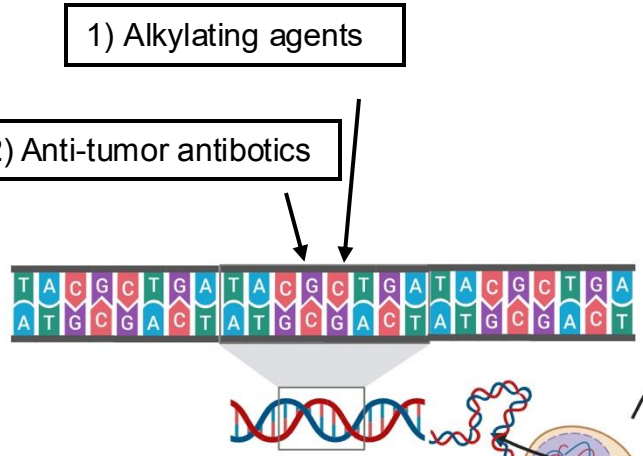
DNA damage

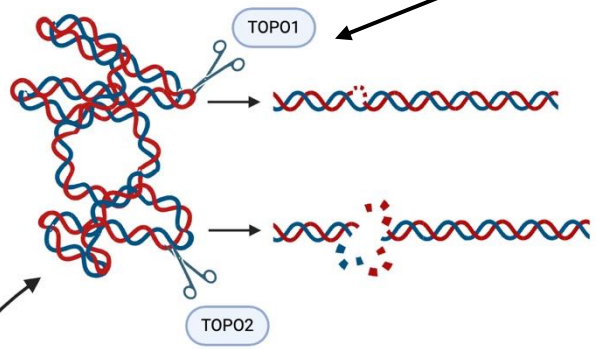
Antimetabolites

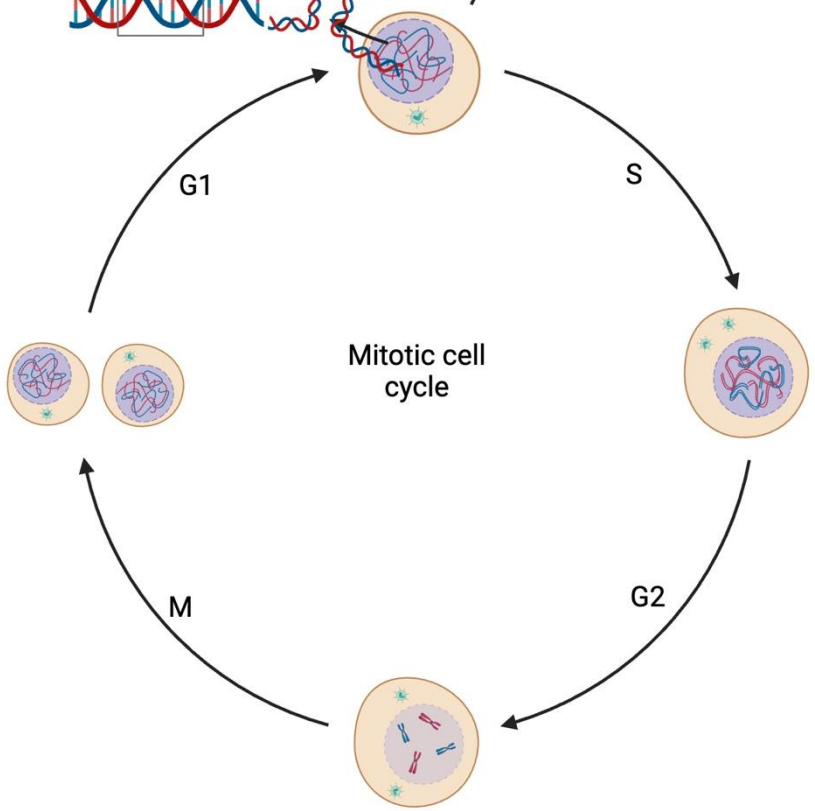
1) Alkylating agents

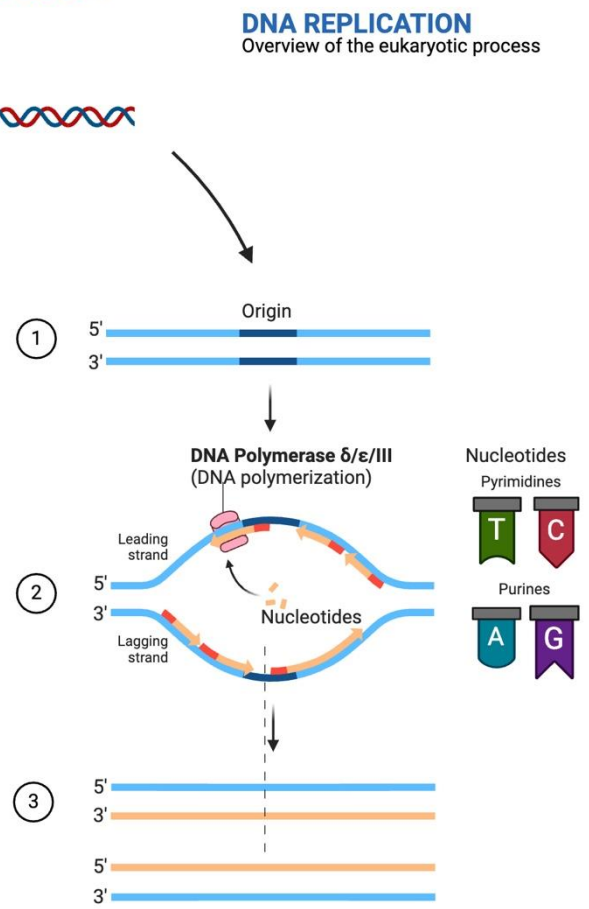
2) Anti-tumor antibotics

3) Topoisomerase inhibitors









Cell cycle arrest and DNA damage

Antipyrimidines	*Antipurines*
5-fluorouracil	Mercaptopurine
Capecitabine	
Cytarabine	*Antifolates*
Floxouridine	Methotrexate
Fludarabine	Pemetrexed
Gemcitabine	Phototrexate

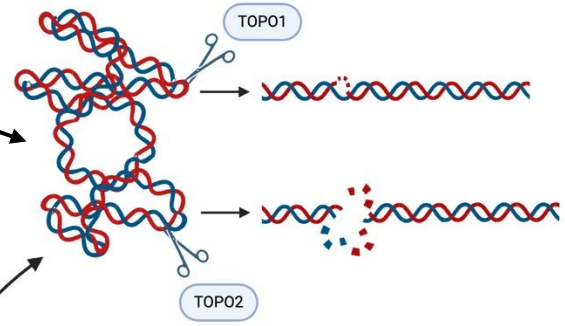
(Nucleotide analogs)

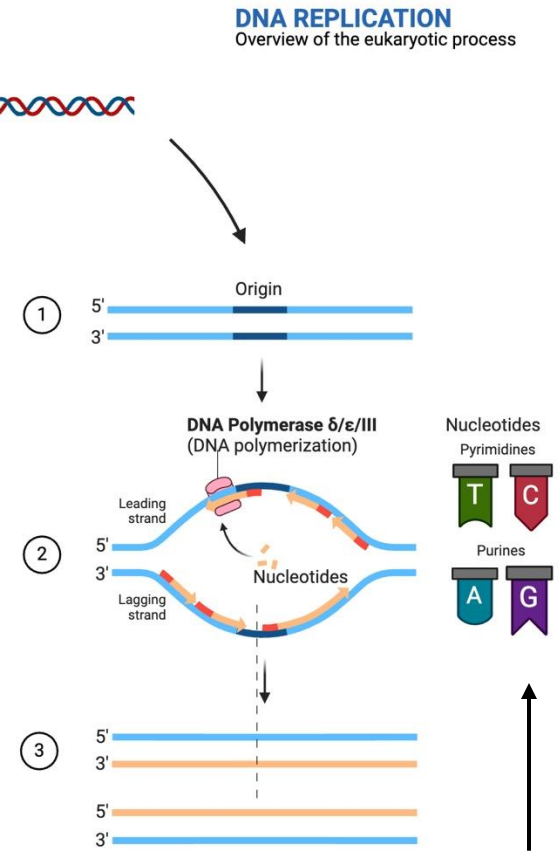
Anti-mitotic agents

1) Alkylating agents

2) Anti-tumor antibotics

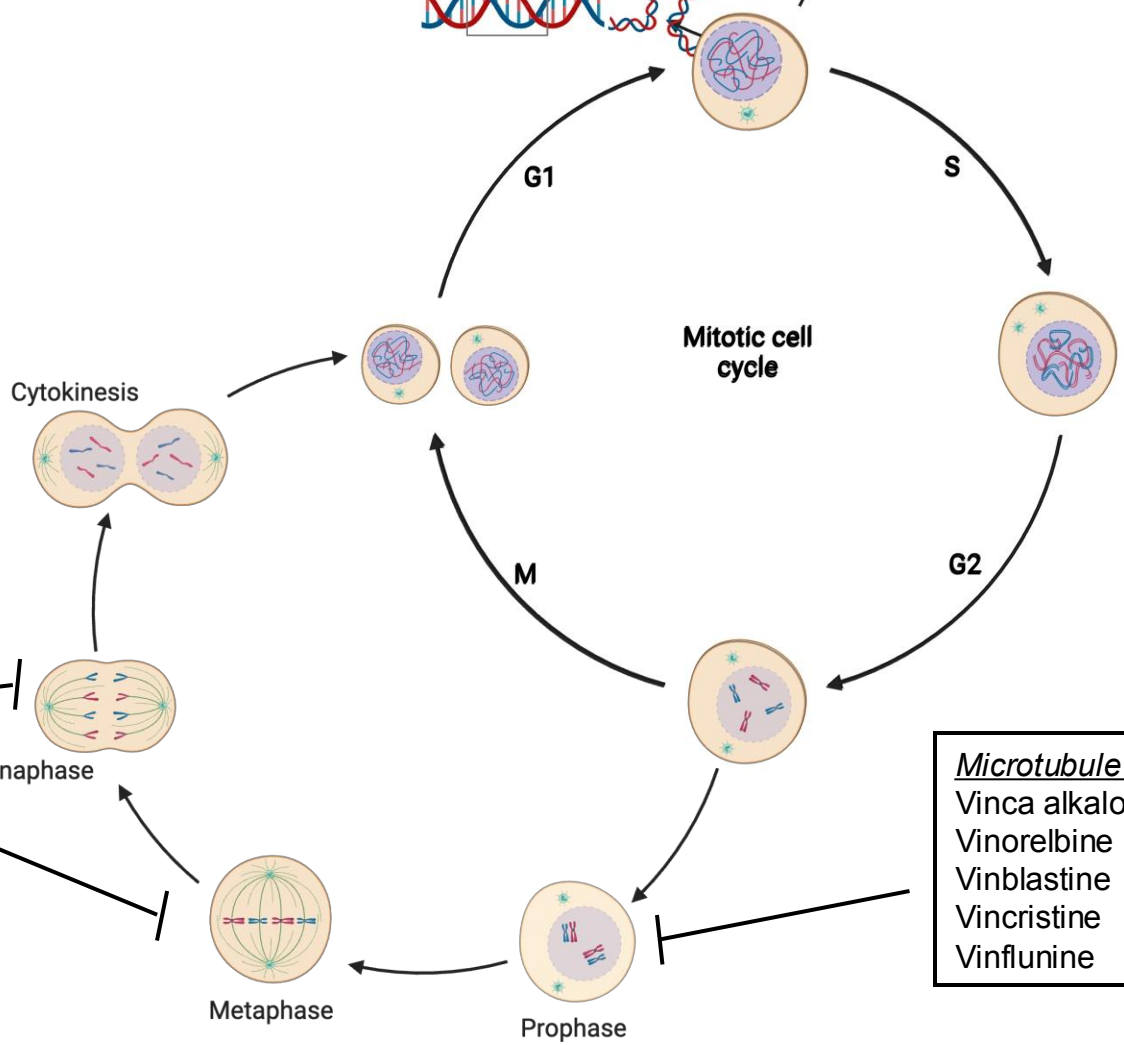
3)Topoisomerase inhibitors





4) Antimetabolites

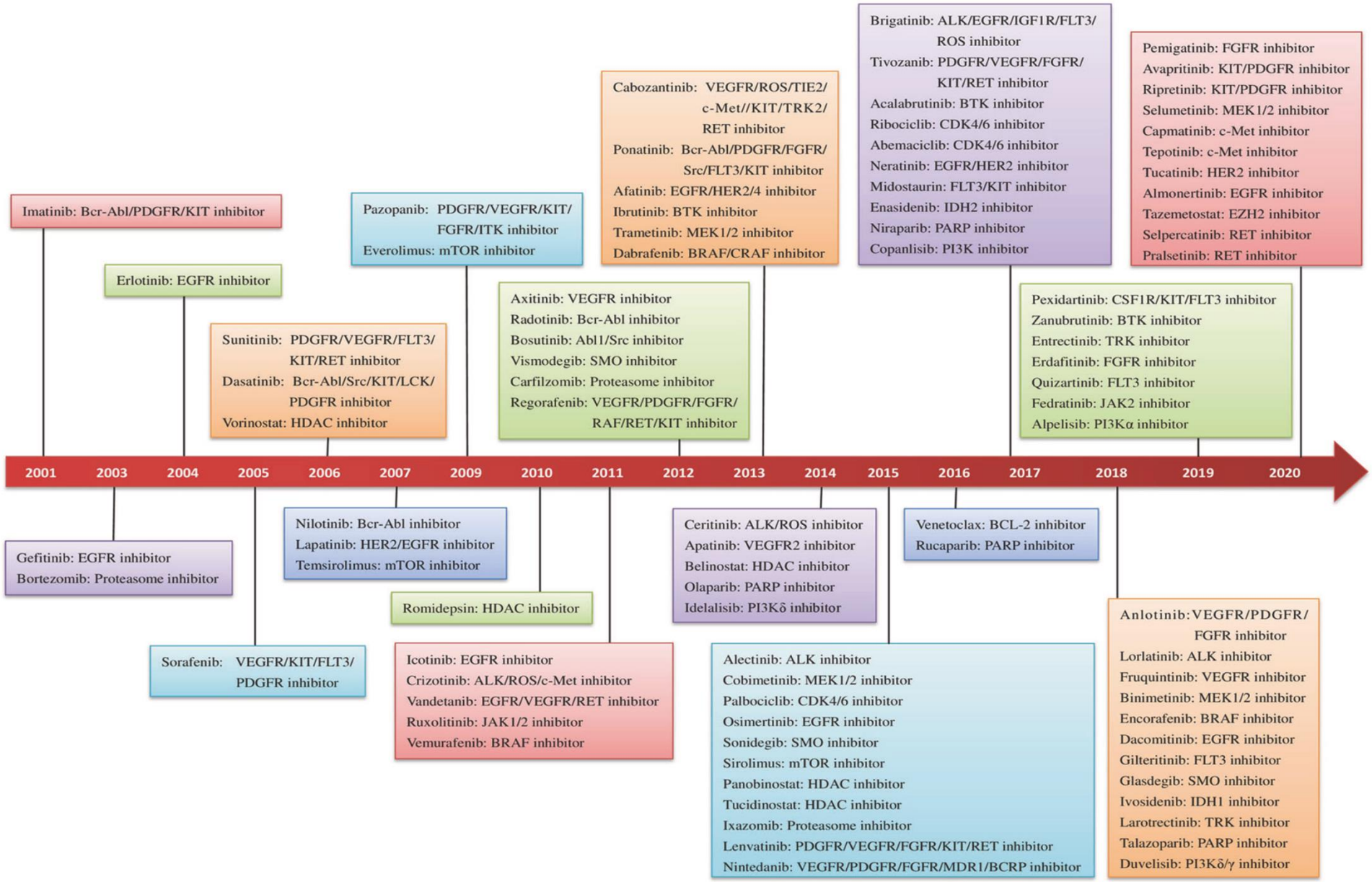
Mitotic catastrophe



Microtubule stabilizing agents
Taxanes:
Paclitaxel
Docetaxel
Cabazitaxel

Microtubule destabilizing agents
Vinca alkaloids:
Vinorelbine
Vinblastine
Vincristine
Vinflunine

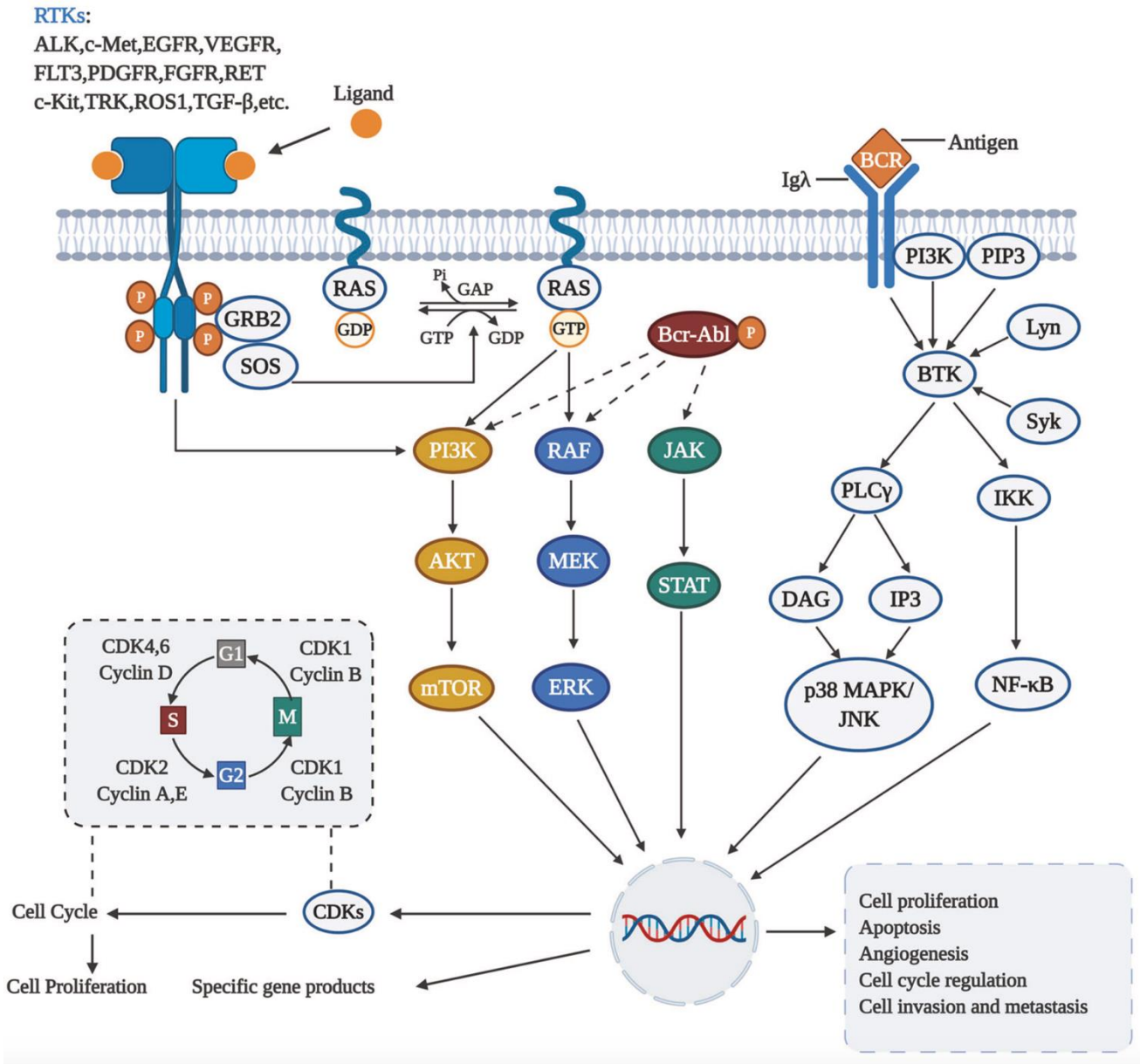
Timeline of the approved targeted therapies



Zhong et al, Sig. Trans. Tar. Ther., 2021

Kinase inhibitors

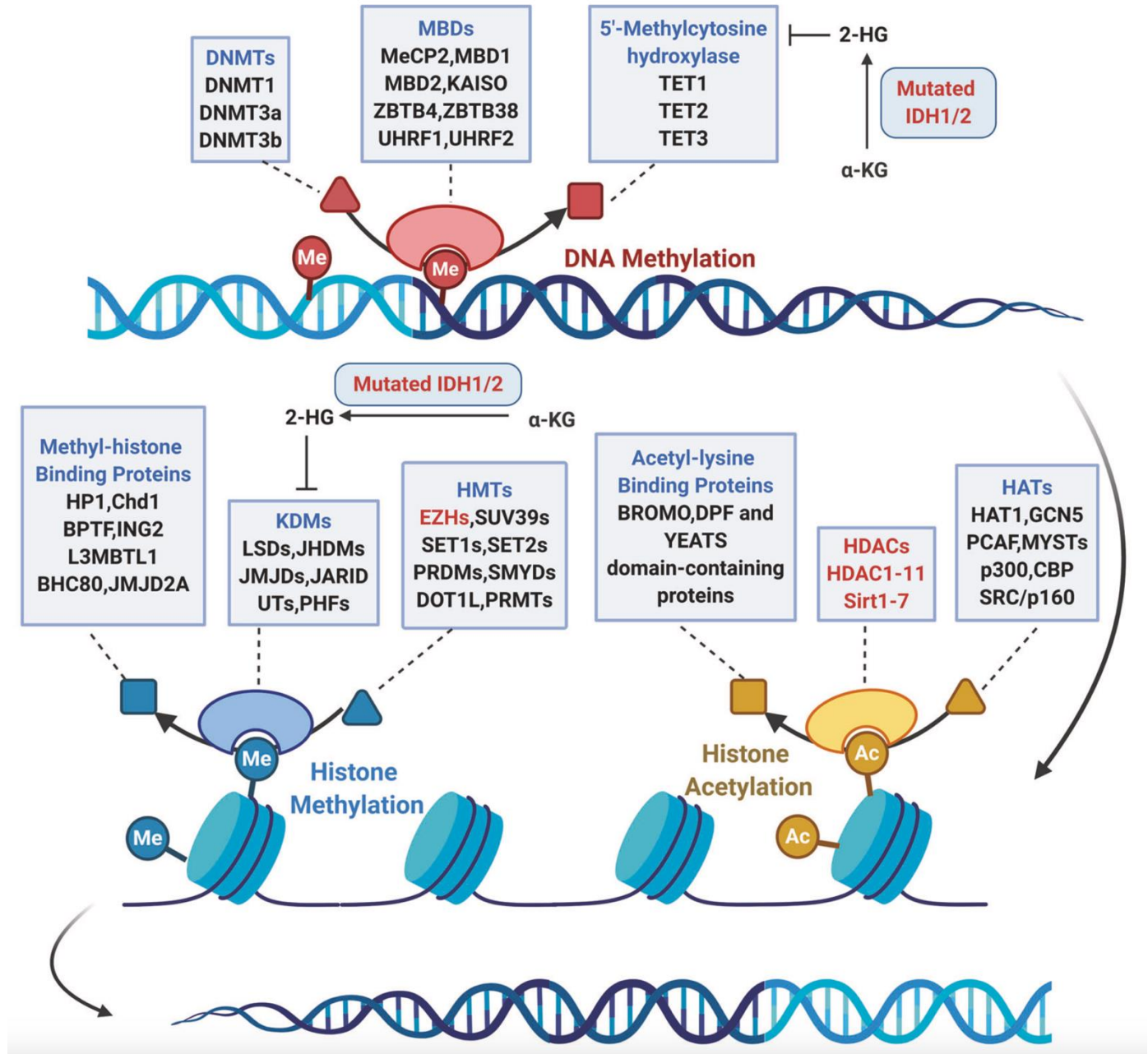
1. Receptor Tyrosine Kinase Inhibitors
2. Non-receptor Tyrosine Kinase Inhibitors
3. Serine/Threonine Kinase Inhibitors



Zhong et al, Sig. Trans. Tar. Ther., 2021

Epigenetic inhibitors

1. Writers: Modify DNA or histones
2. Erasers: Remove modifications
3. Readers: Recognize the modifications

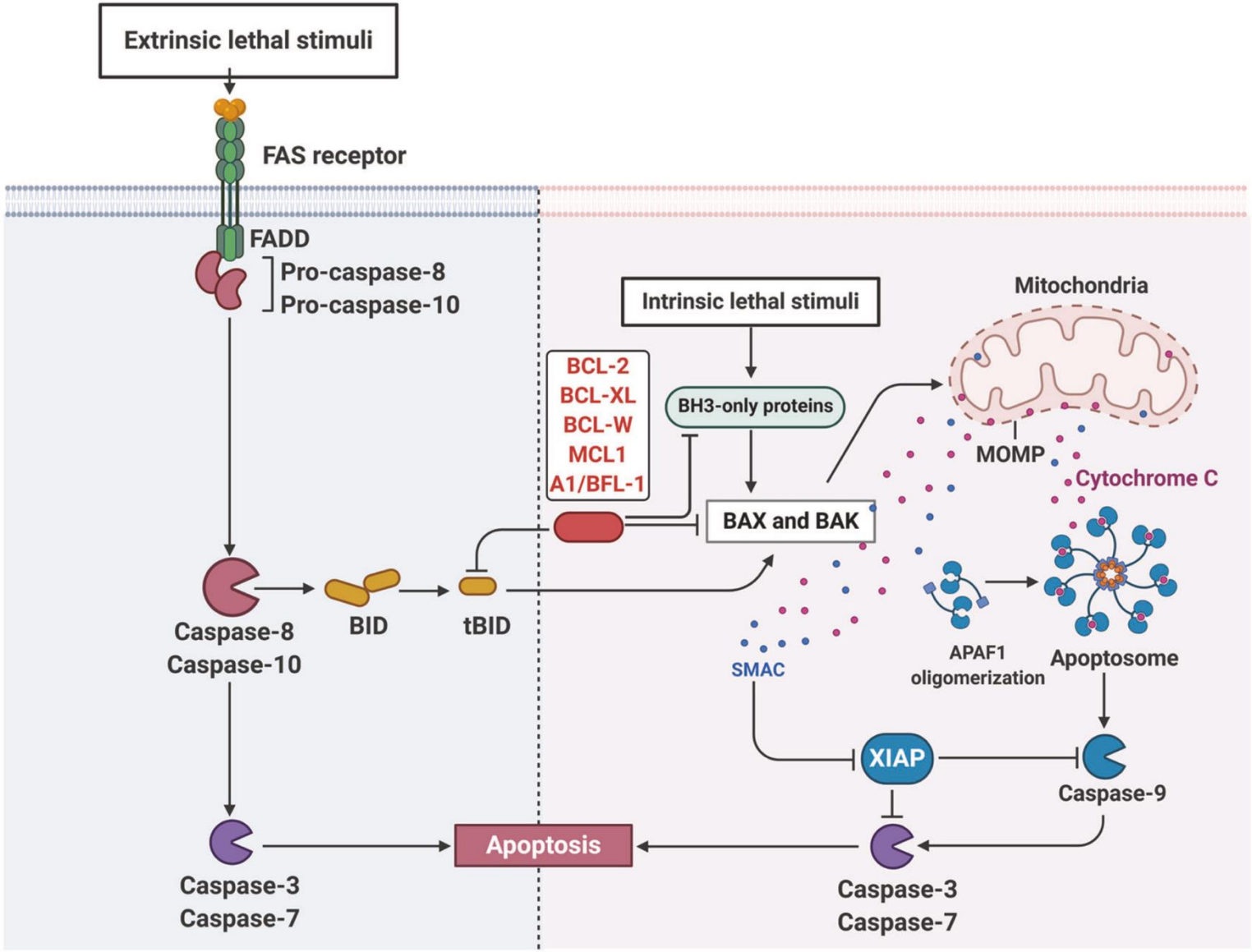


Zhong et al, Sig. Trans. Tar. Ther., 2021

BCL-2 inhibitors (Pro-apoptotic agents)

1. BCL-2 family of proteins: Inhibits apoptosis (programmed cell death) or anti-apoptotic proteins

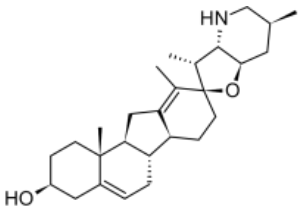
2. Pro-apoptotic effector proteins (BAX and BAK) and BCL-2 homology 3 (BH3)-only pro-apoptotic proteins

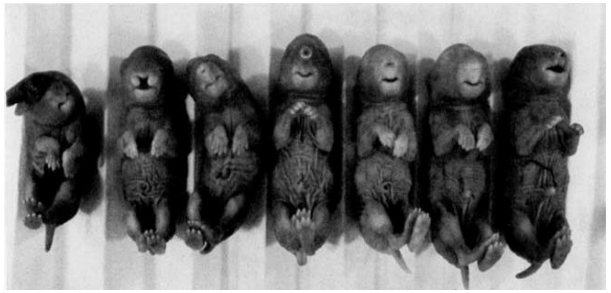


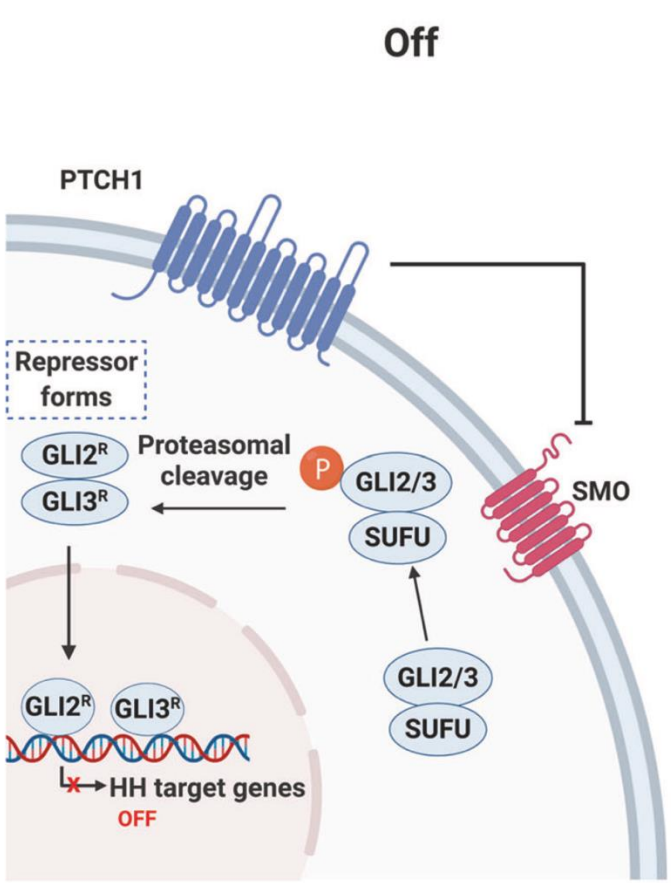
Zhong et al, Sig. Trans. Tar. Ther., 2021

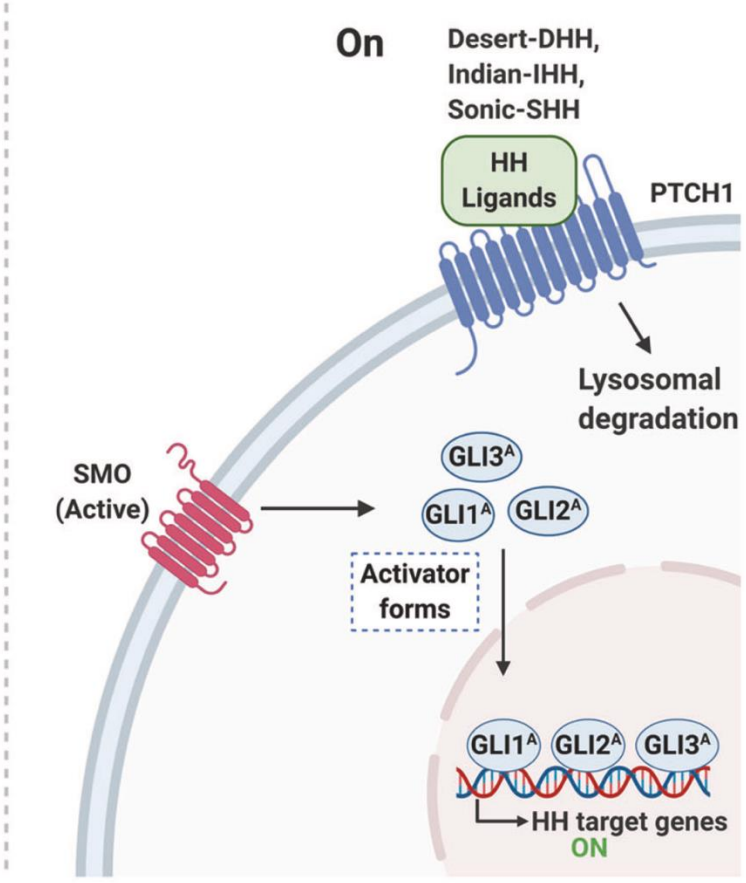
Hedgehog pathway inhibitors

Embryonic development
and tissue regeneration





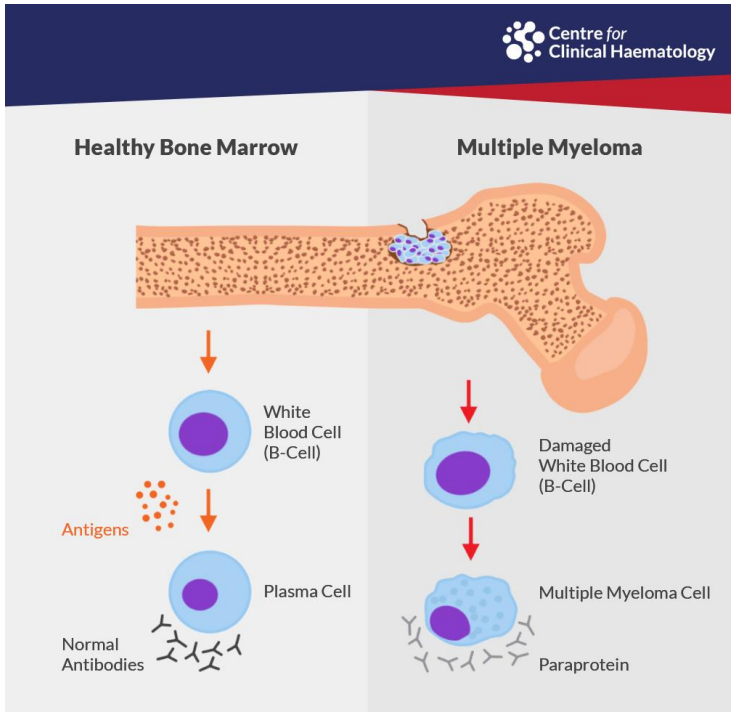


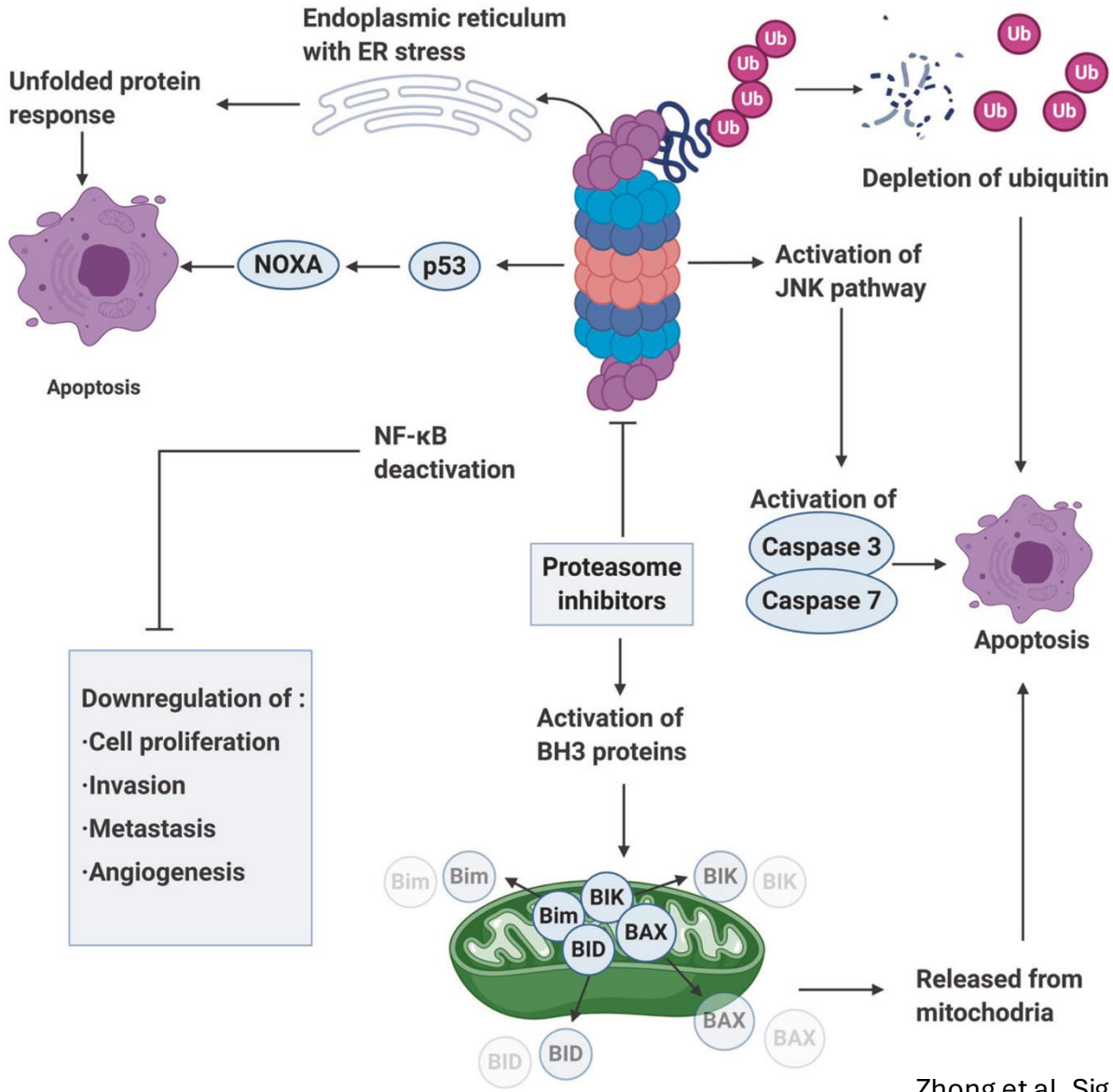


Zhong et al, Sig. Trans. Tar. Ther., 2021

Proteosome inhibitors

1. Ubiquitin-proteosome system (UPS): Misfolded, unassembled, or damaged proteins form toxic aggregates

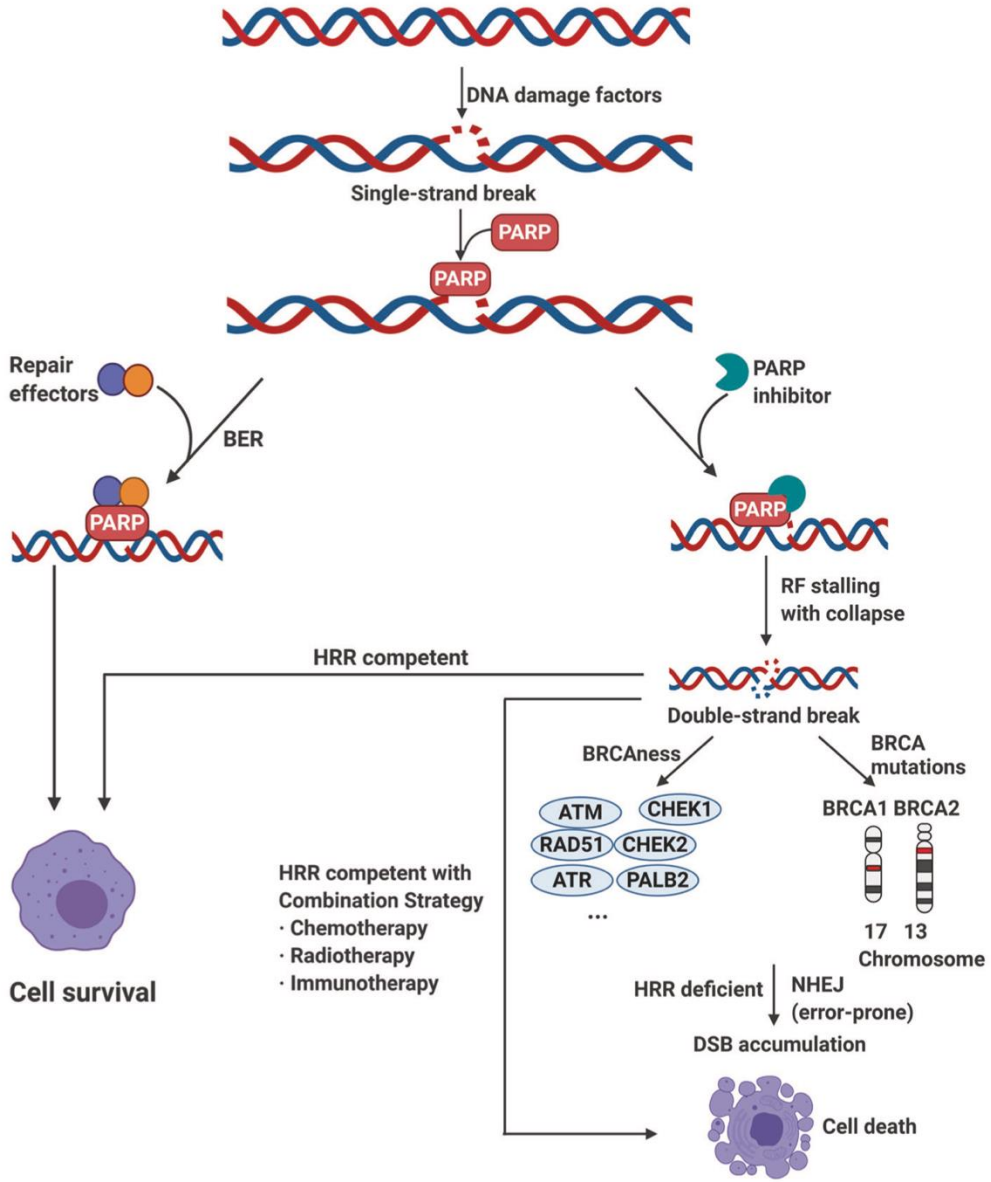




Zhong et al, Sig. Trans. Tar. Ther., 2021

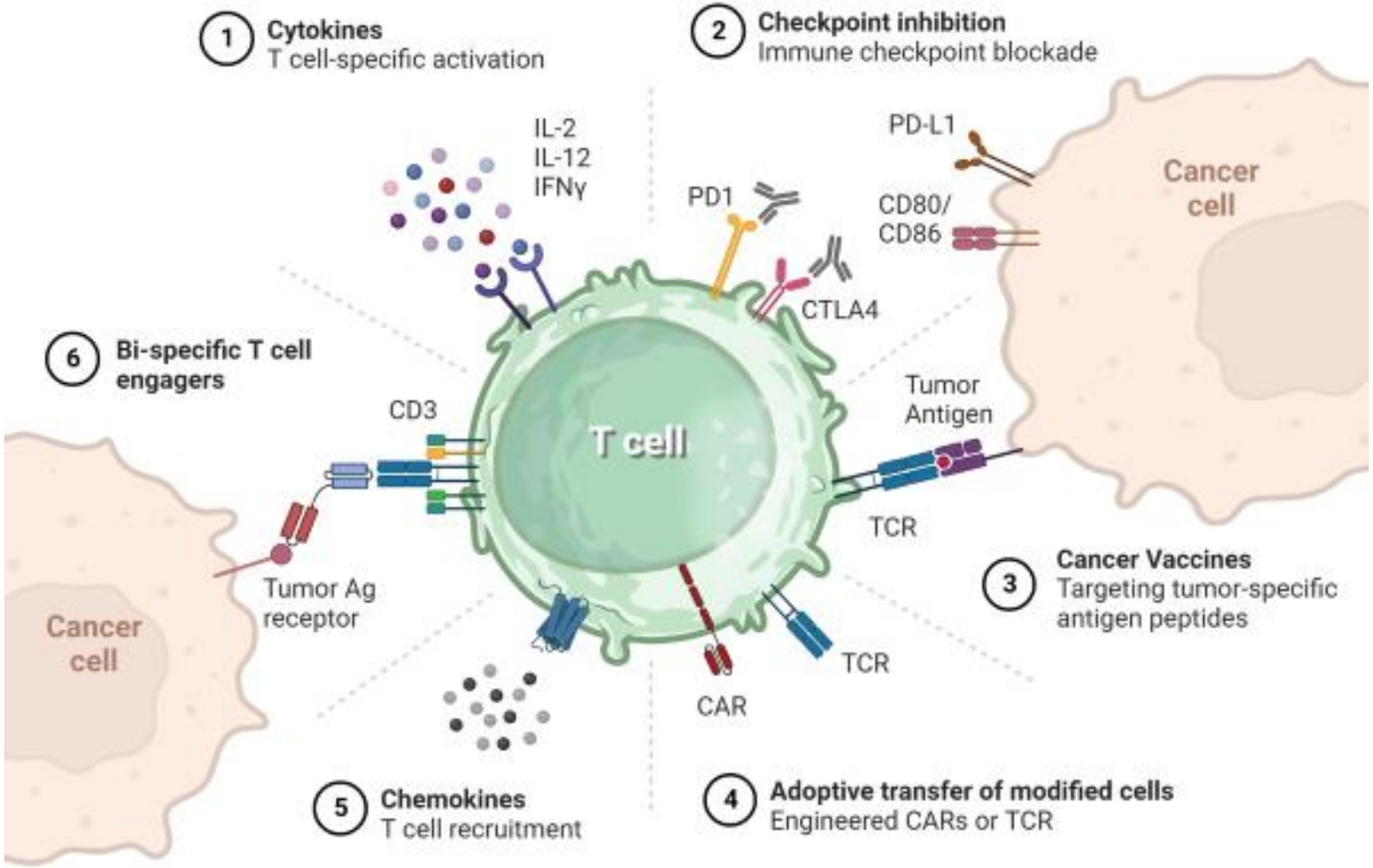
PARP inhibitors (DNA Damage Repair inhibitors)

1. Genomic instability and chronic DNA damage is common in cancers.
2. Single strand and double-strand break repair.

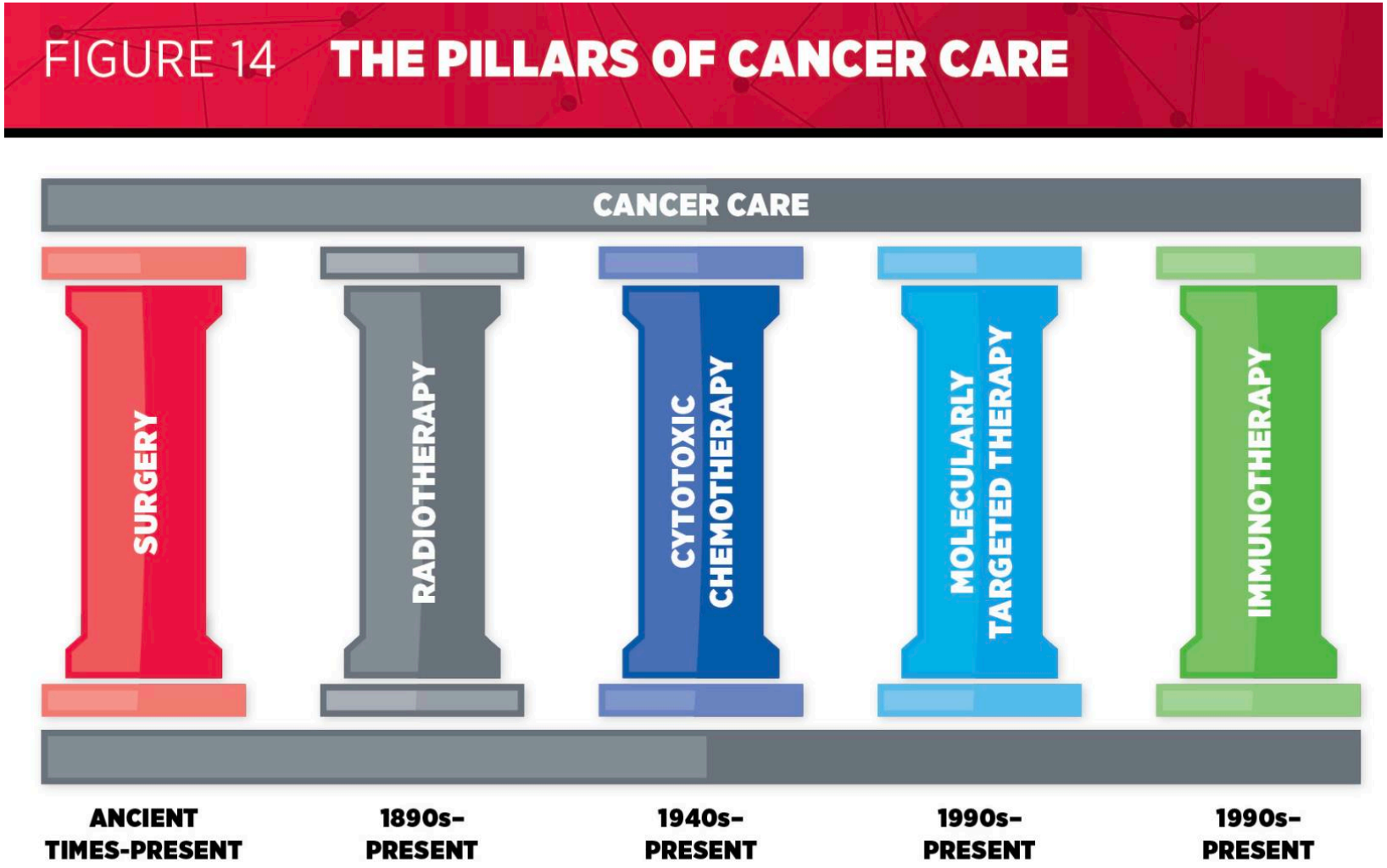


Zhong et al, Sig. Trans. Tar. Ther., 2021

Immunotherapy

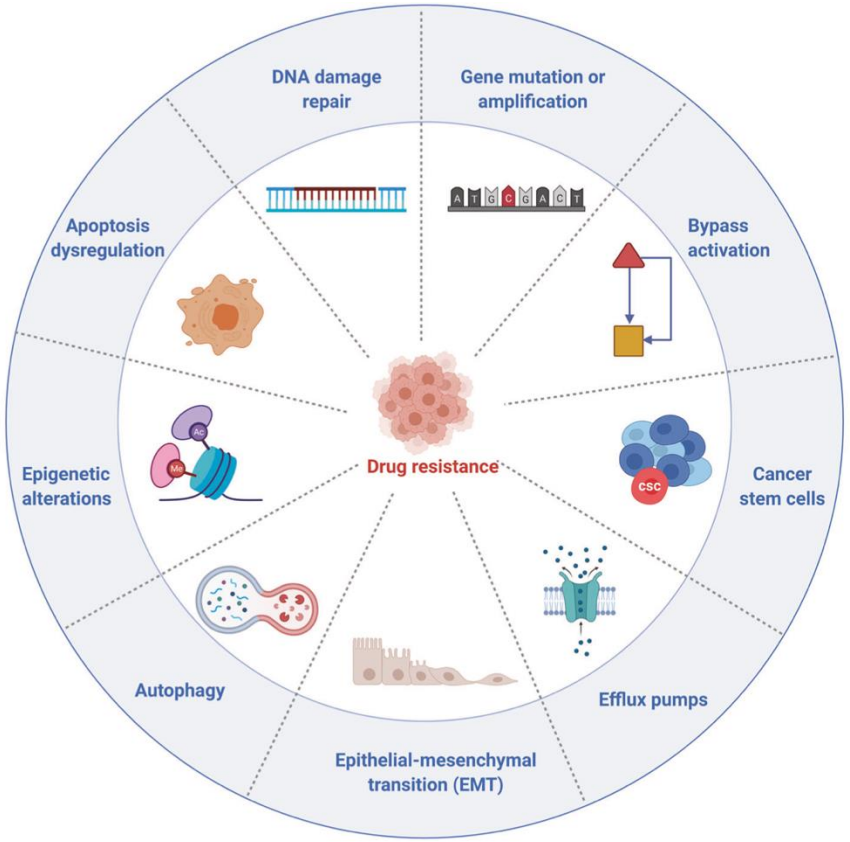


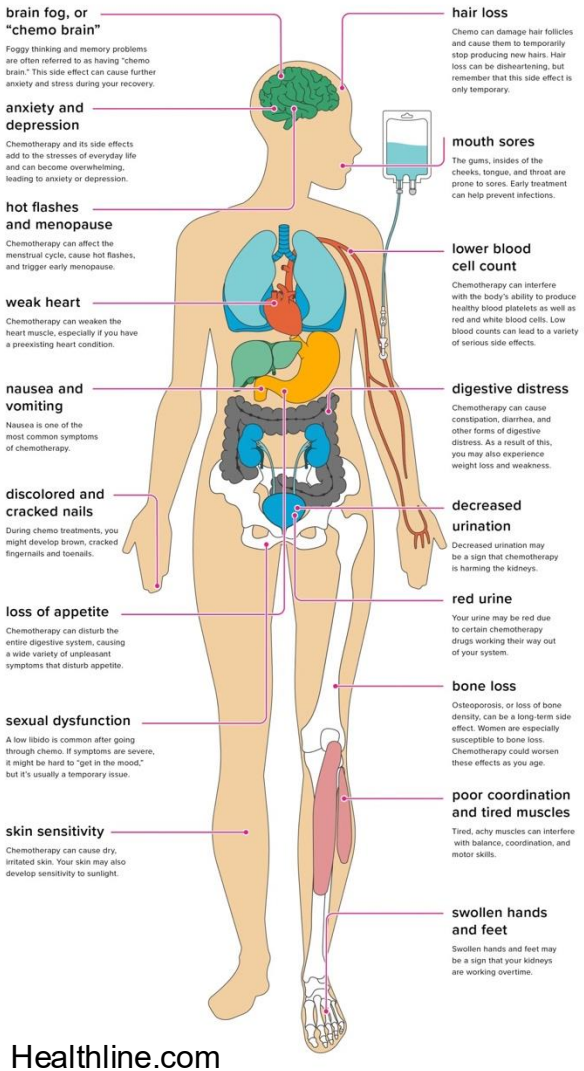
The pillars of cancer care



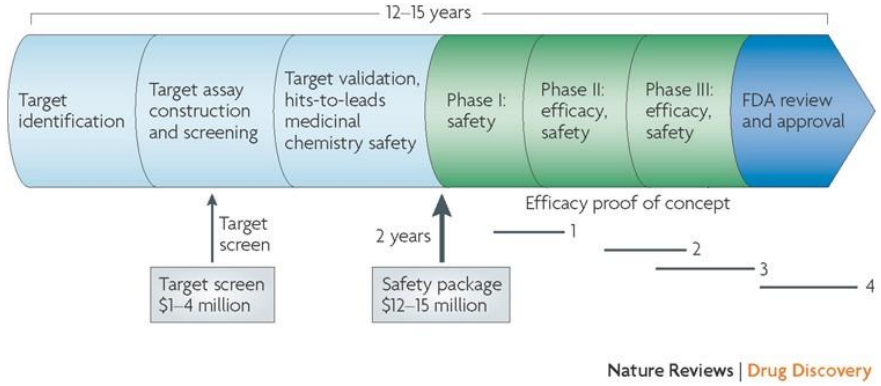
AACR Cancer Progress Report, 2020

Next: Drug resistance, adverse effects and drug discovery process





Healthline.com



Roses, Nature Rev. Drug Disc., 2008