BIOLOGY

CENTRAL DOGMA OF CELL BIOLOGY

CELL DIVISION (phases)

NUCLEUS, DNA-code and MUTATION

(+ Cancer as problem of cell division and mutation)

„META-BACKROUND“ for the all organels

(central dogma of cell biology of eukaryotic cells)

- *DNA is form of genetic infromation. DNA can be replicated and exportedto daughter cells. (in nucleus)*
- *DNA can be transcribed to RNA code.(in nucleus)*
- *RNA code can be translated to protein.*

(in Ribosomes)

- Complex scheme of transcritpiton and translation:

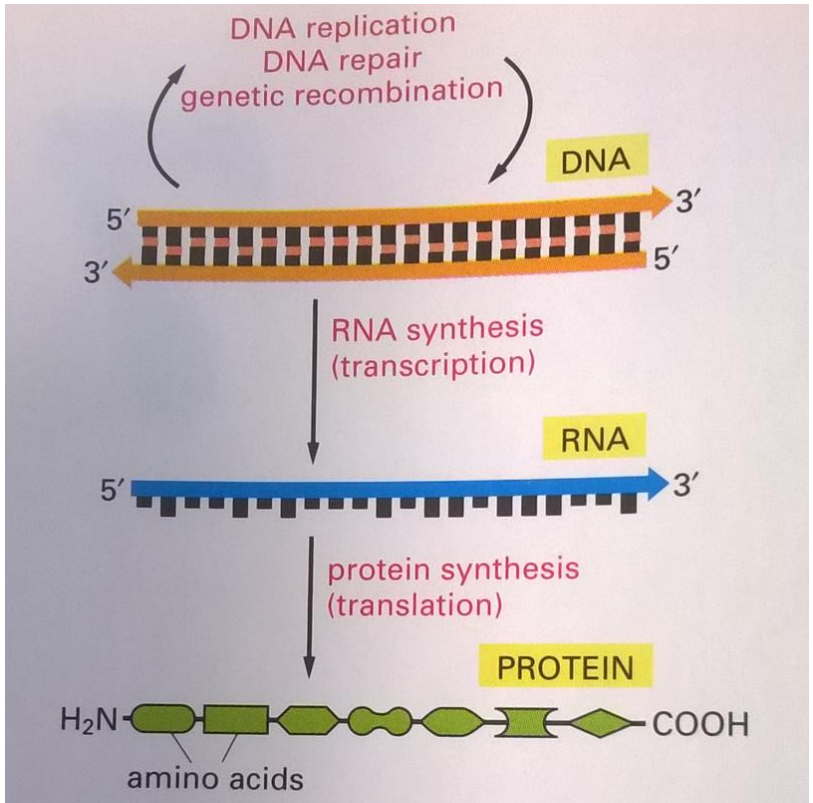


Figure 7–1 Genetic information directs the synthesis of protein. The flow of genetic information from DNA to RNA (transcription) and from RNA to protein (translation) occurs in all living cells.

- Technical details of DNA structure and RNA structure:

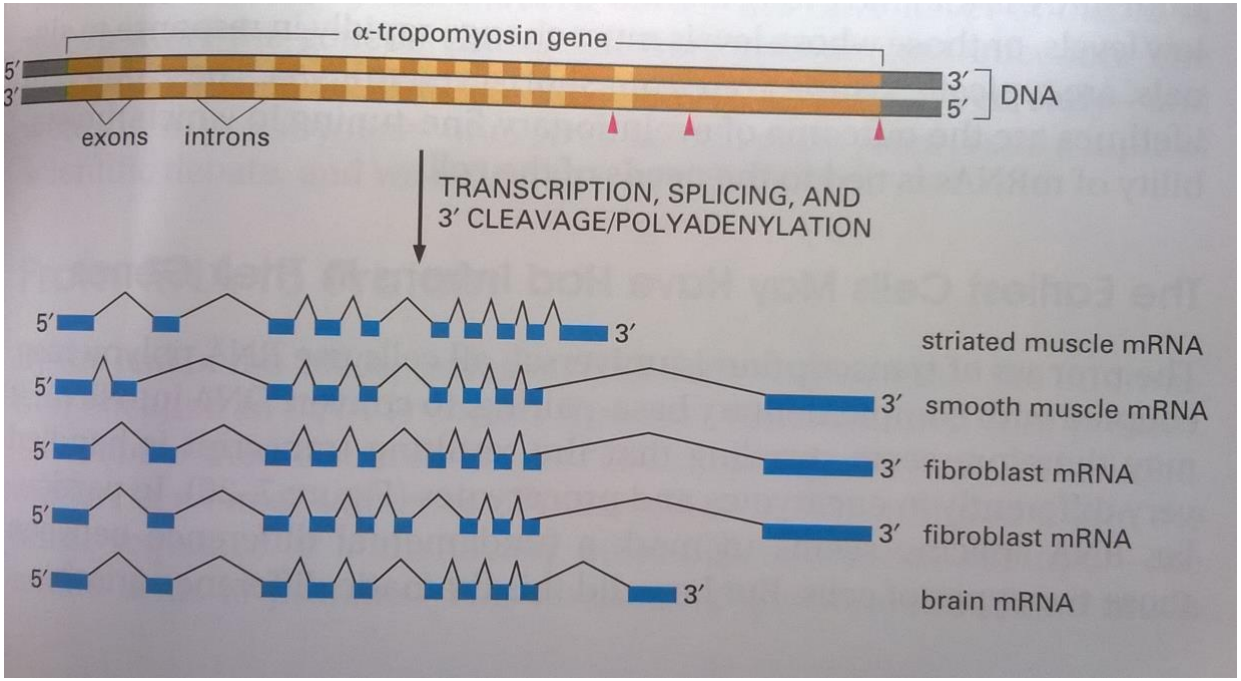
Adenine(A), Guanine(G), Cytosine(C), Uracil (U) and Thymine (T)

DNA: A, G, C, T

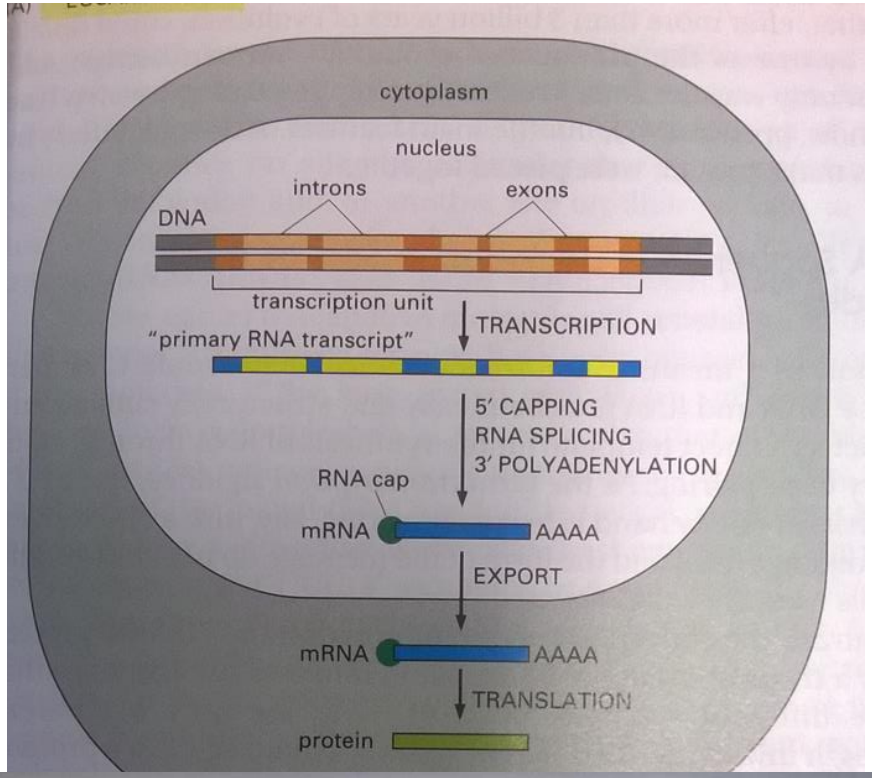
RNA: A, G, C, U

- !!! Different cells in the body produce different final protein from DNA code:

How it is possible? The trasncription of many genes cen be spliced in various ways to produce different mRNA.



How is the code of RNA recoded to amino-acid



GCA GCC GCG GCU	AGA AGG CGA CGC CGG CGU	GAC GAU	AAC AAU	UGC UGU	GAA GAG	CAA CAG	GGA GGC GGG GGU	CAC CAU	AUA AUC AUU	UUA UUG CUA CUC CUG CUU	AAA AAG	AUG	UUC UUU	CCA CCC CCG CCU	AGC AGU UCA UCC UCG UCU	ACA ACC ACG ACU	UGG	UAC UAU	GUA GUC GUG GUU
Ala	Arg	Asp	Asn	Cys	Glu	Gln	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val
A	R	D	N	C	E	Q	G	H	I	L	K	M	F	P	S	T	W	Y	V

NUCLEUS
AND CELL DIVISION

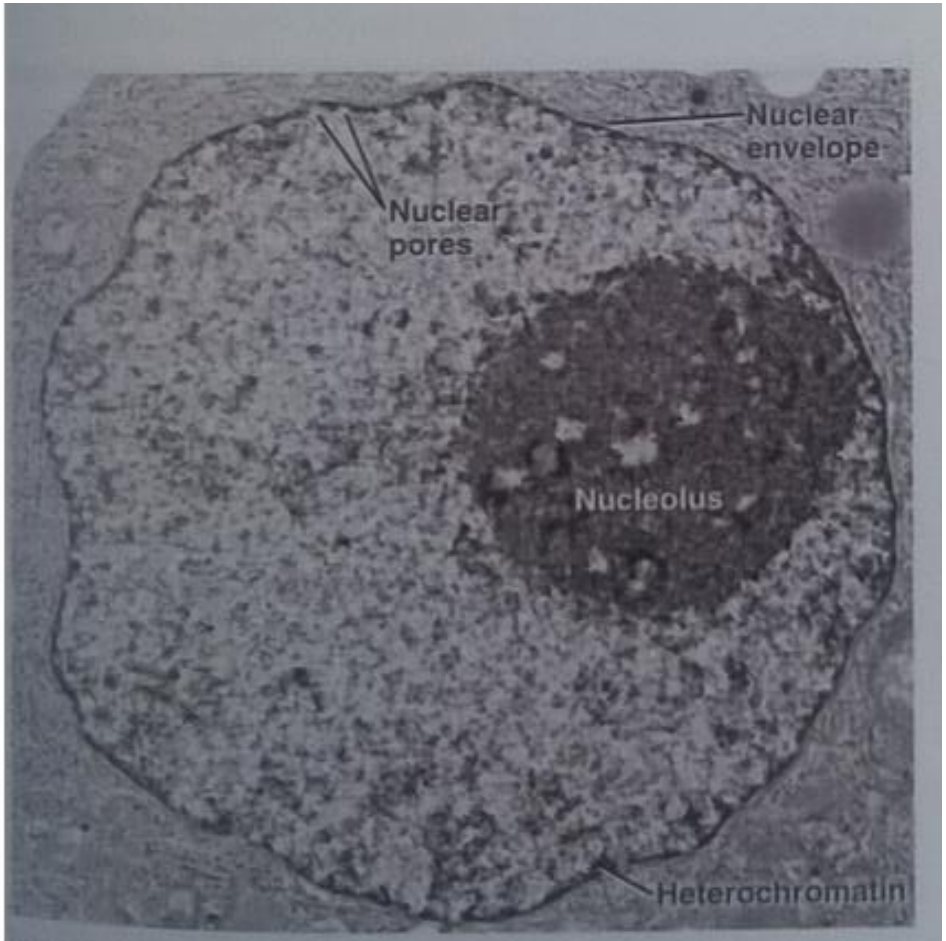


FIGURE 9.1 ELECTRON MICROGRAPH OF A THIN SECTION OF A CANCER CELL NUCLEUS WITH MAJOR FEATURES LABELED. (Courtesy Scott Kaufmann, Mayo Clinic, Rochester, MN.)

- DNA chains in nucleus are not like single molecules of water in cup. DNA in nucleus is divided into several „macro-molecules“ which are conncetd with protein scaffolds
- this components create:

„DNA+protein“ = CHROMOSOMES

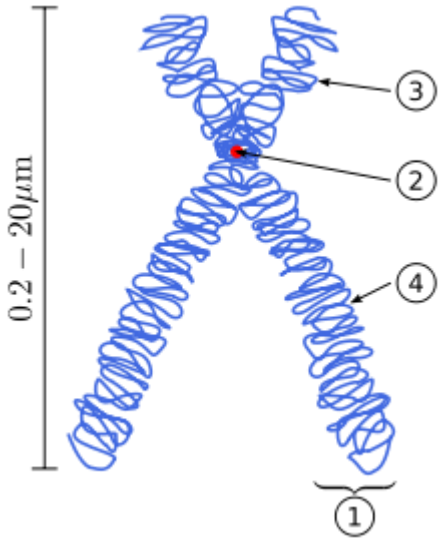
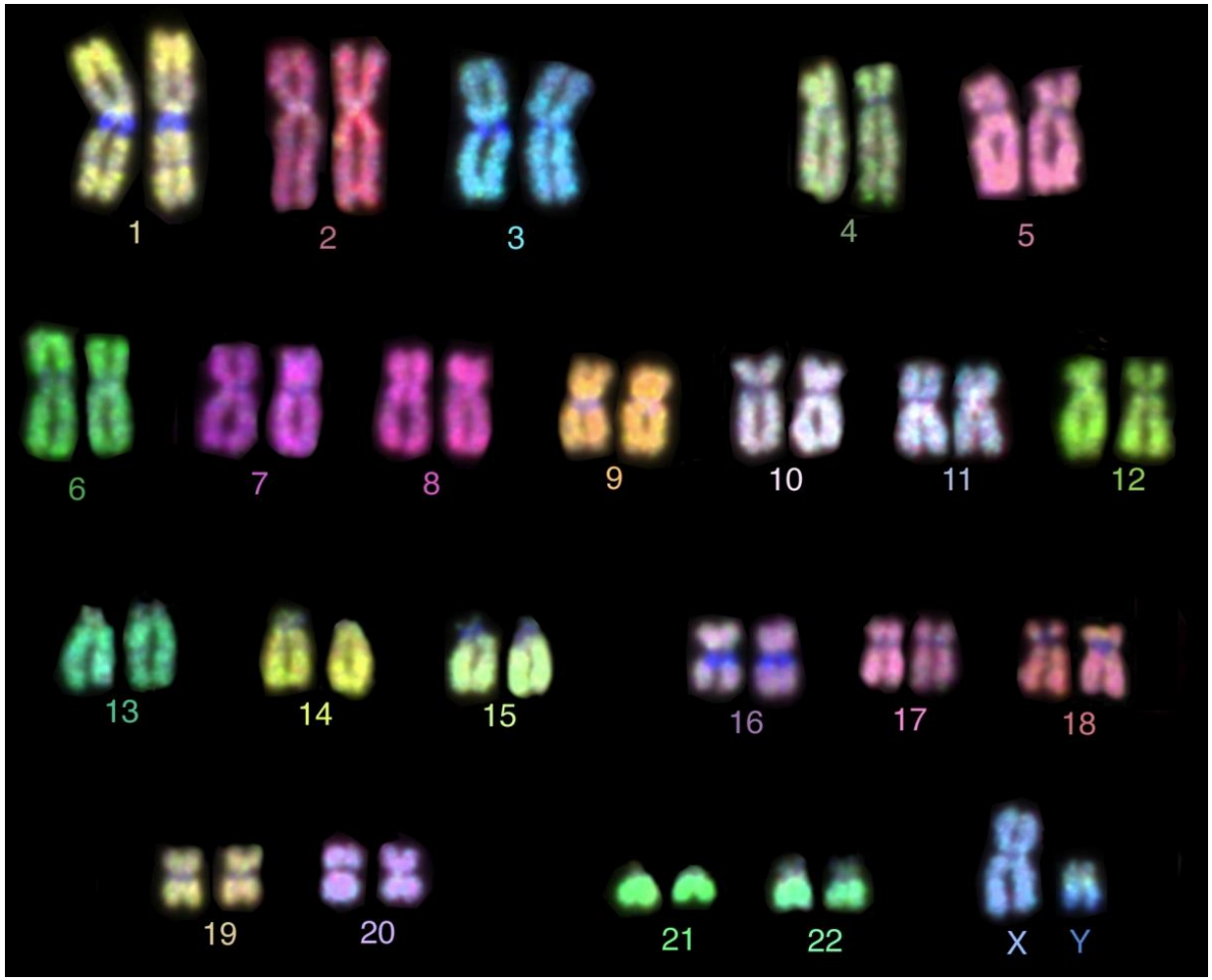
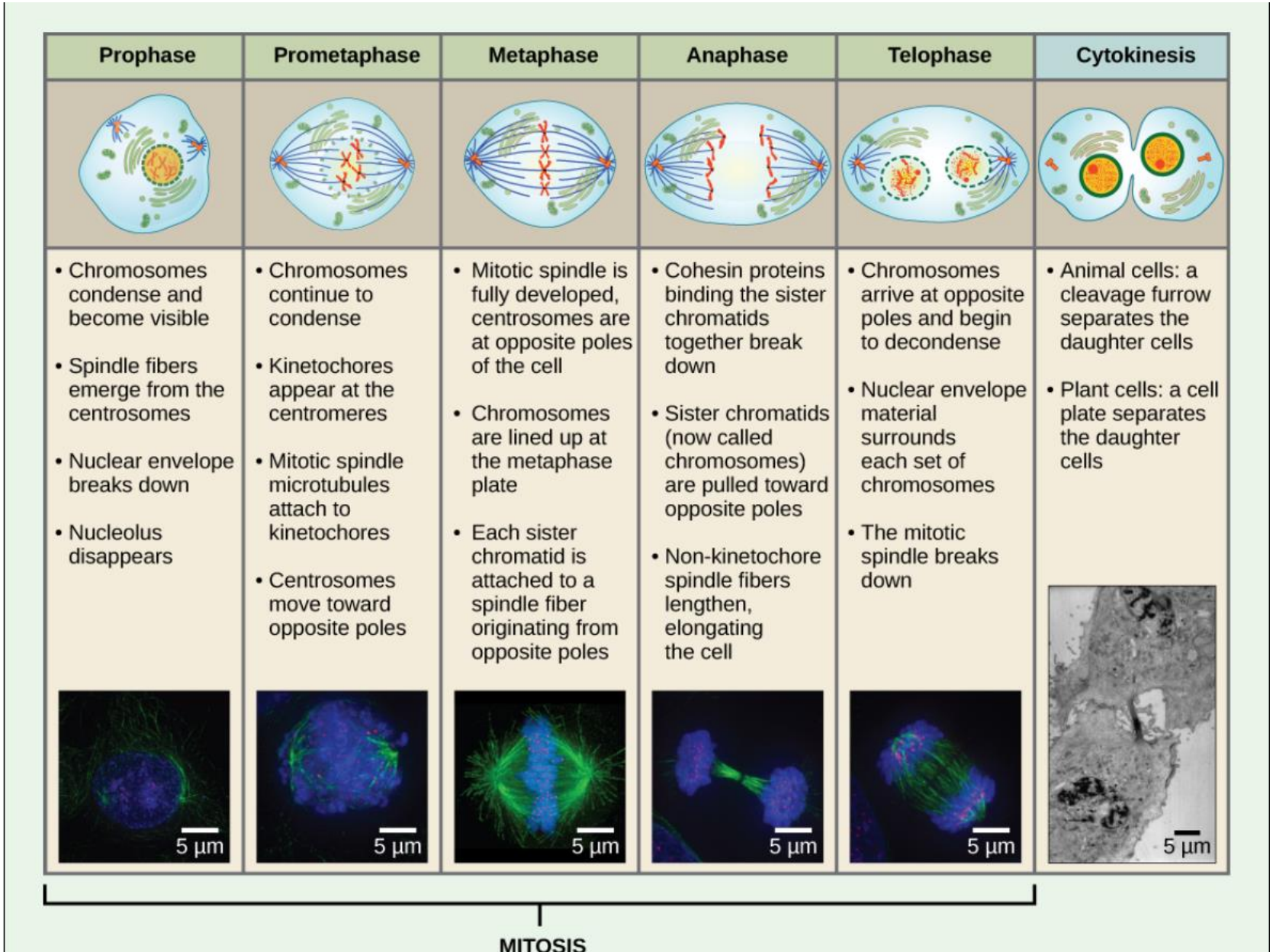


Diagram of a replicated and condensed metaphase eukaryotic chromosome. (1) Chromatid – one of the two identical parts of the chromosome after S phase. (2) Centromere – the point where the two chromatids touch. (3) Short arm (p). (4) Long arm (q).

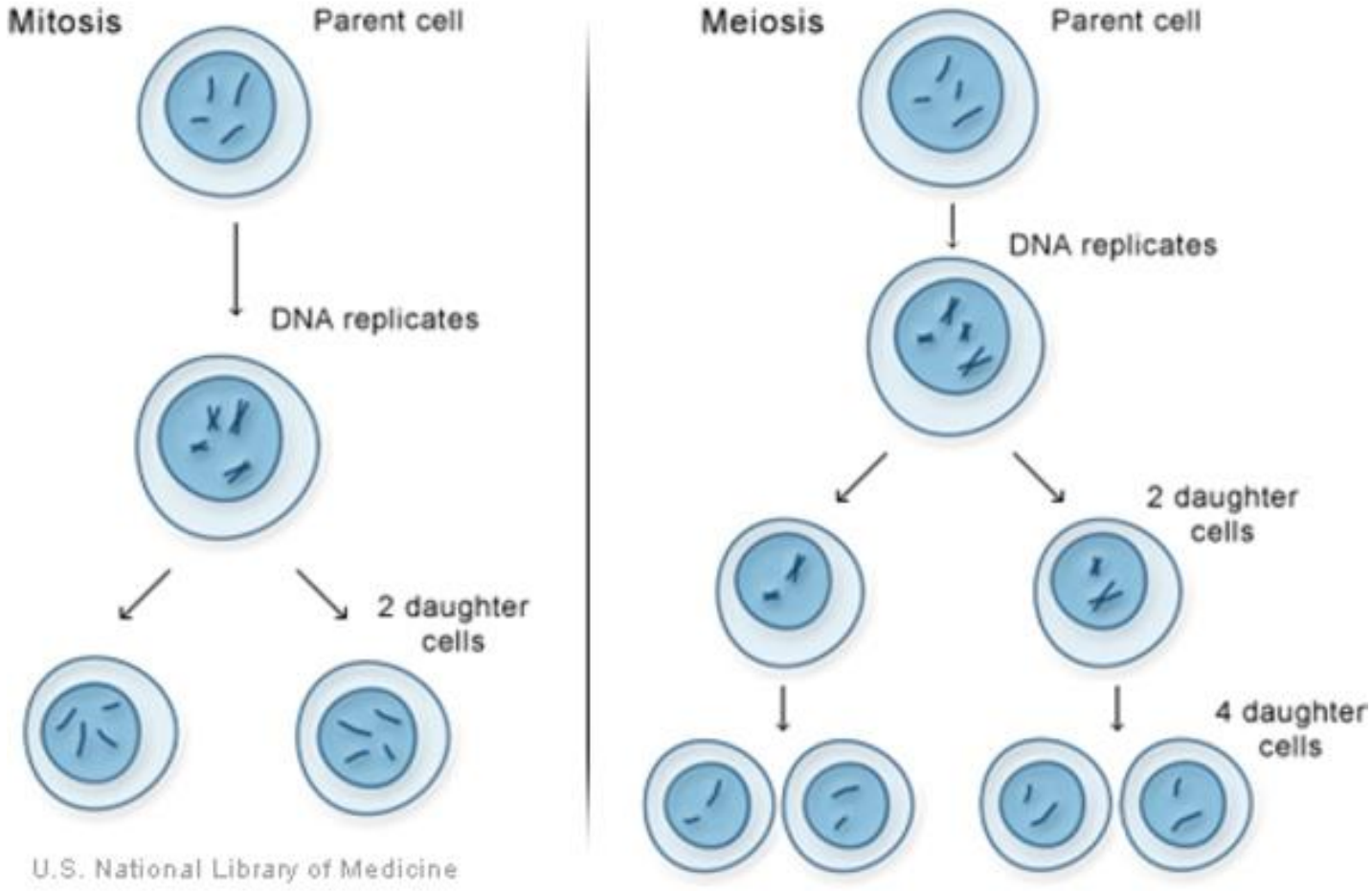
- Human cells normally contains 23 pairs of chromosomes, for a total of 46. Twenty-two of these pairs, called autosomes, look the same in both males and females. The 23rd pair, the sex chromosomes, differ between males and females. Females have two copies of the X chromosome, while males have one X and one Y chromosome.

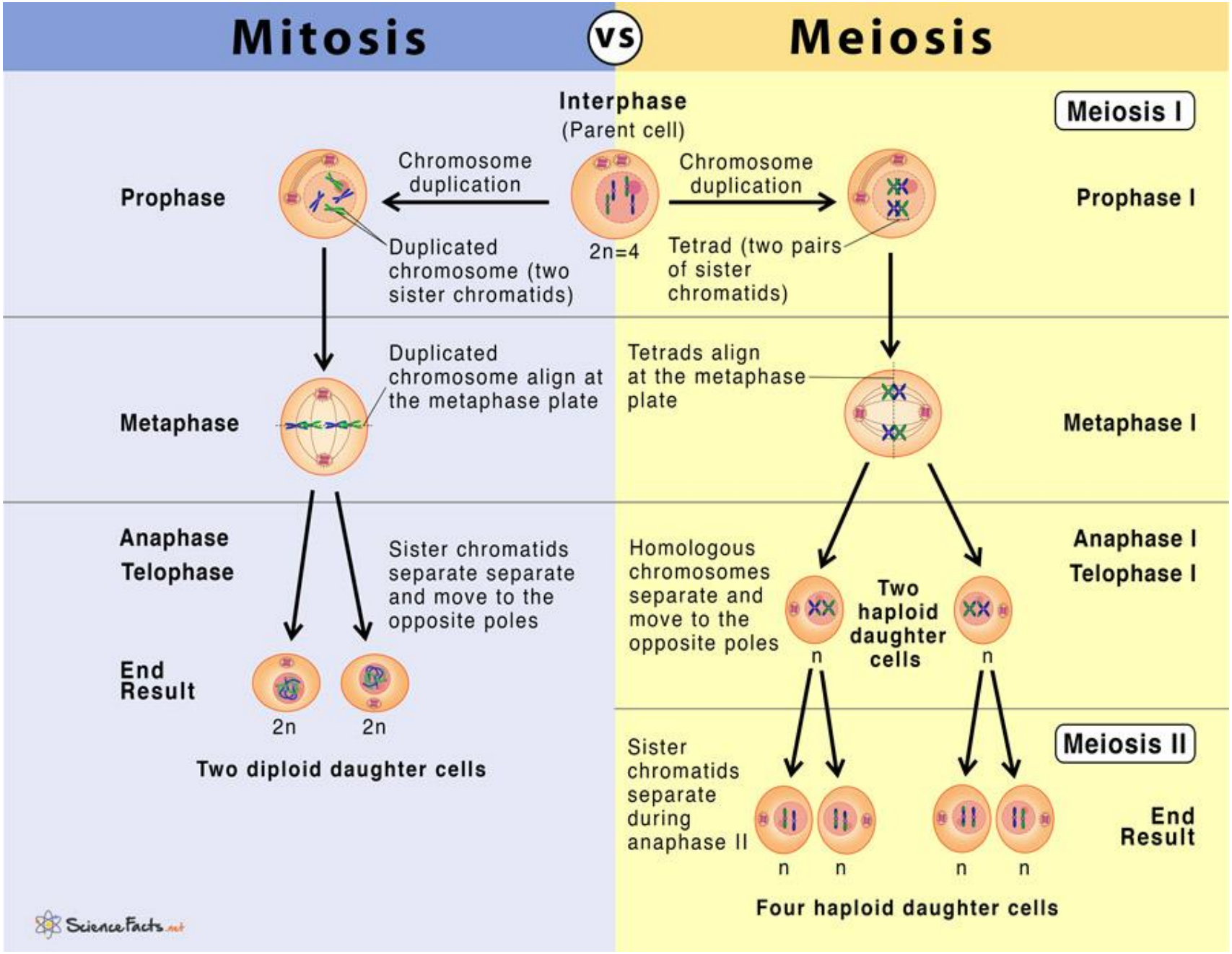


Human somatic cells undergo cell-dividing, this somatic cell nuclear and cell dividing is called MITOSIS --- 6 steps:



Two types of **cell division**



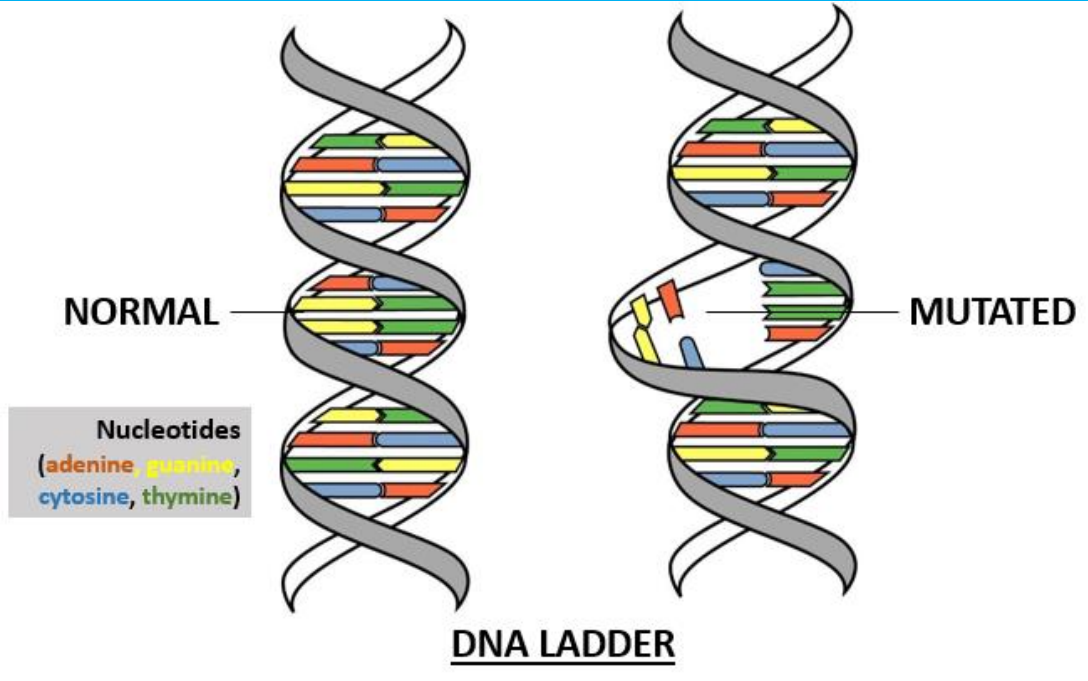

Mitosis
vs
Meiosis
Interphase
(Parent cell)
Meiosis I
Chromosome duplication
Chromosome duplication
Prophase
Prophase I
Duplicated chromosome (two sister chromatids)
2n=4
Tetrad (two pairs of sister chromatids)
Duplicated chromosome align at the metaphase plate
Tetrads align at the metaphase plate
Metaphase
Metaphase I
Anaphase
Telophase
Sister chromatids separate separate and move to the opposite poles
Homologous chromosomes separate and move to the opposite poles
Two haploid daughter cells
Anaphase I
Telophase I
End Result
2n
2n
n
n
Two diploid daughter cells
Meiosis II
Sister chromatids separate during anaphase II
End Result
n
n
n
n
Four haploid daughter cells
ScienceFacts.net

MUTATION

- *A mutation is a change that occurs in our DNA sequence, either due to mistakes when the DNA is copied or as the result of environmental factors (Gamma radiation, UV light and cigarette smoke…)*
- Often cells can recognise any potentially mutation-causing damage and repair it before it becomes a fixed mutation.
- Not all mutation had to be negative (positive mutation are axis of evolution in hisgtorical pariod)

MUTATION

- Mutation can be crated during the DNA replication:



(on the picture: one possible type of mutation, several another types exist – overview in next pages)

(Ad. Mutation)

- Each eukaryotic cells have systems for „error“ founding and elimination of part of DNA (or self-killing of the whole cells)
- „The body must survive, each one single cells had to be prepared for mutation elimination or selfkilling“

- Types of mutation from the view of the tissue:

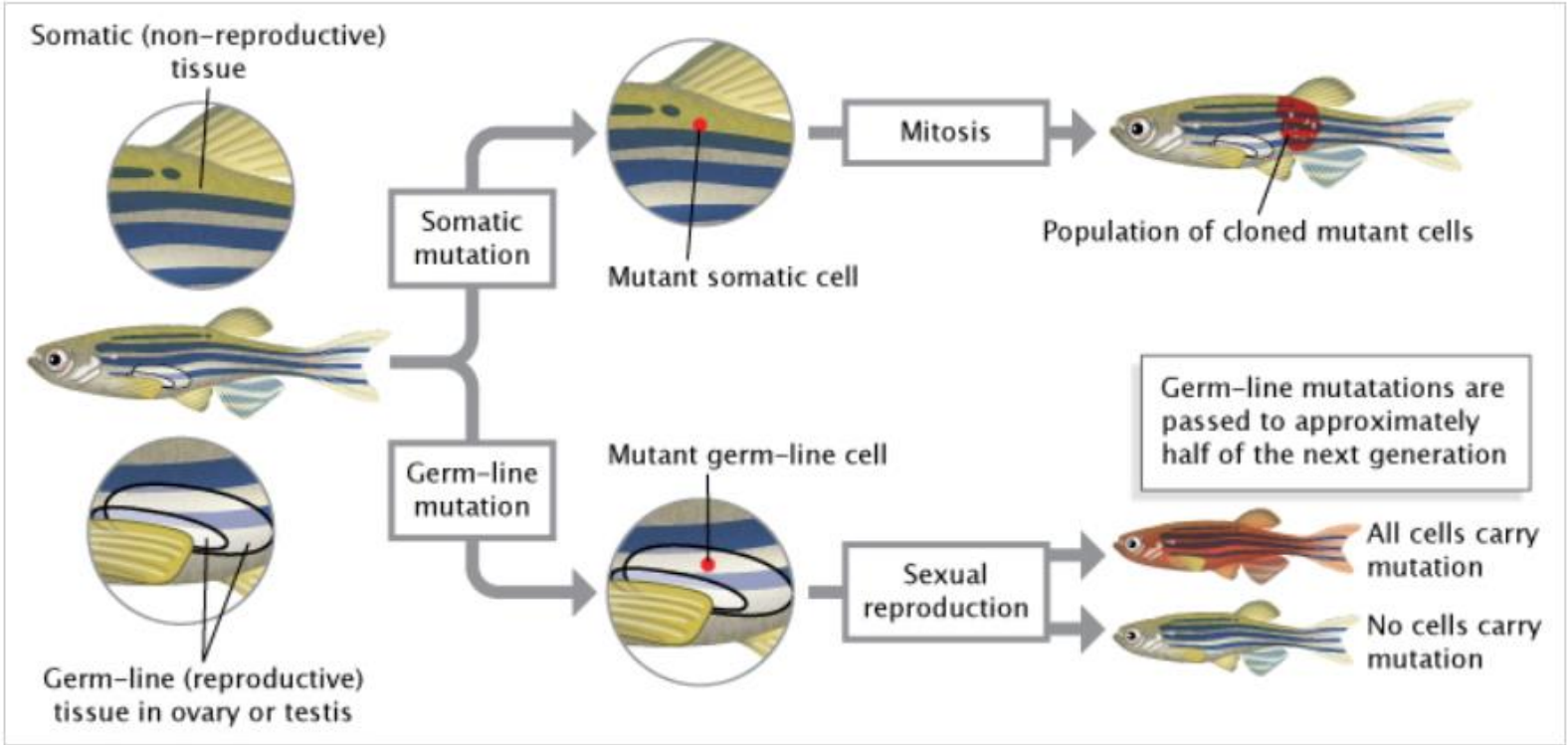


Figure 2: Mutations can occur in germ-line cells or somatic cells.
Germ-line mutations occur in reproductive cells (sperm or eggs) and are passed to an organism's offspring during sexual reproduction. Somatic mutations occur in non-reproductive cells; they are passed to daughter cells during mitosis but not to offspring during sexual reproduction.

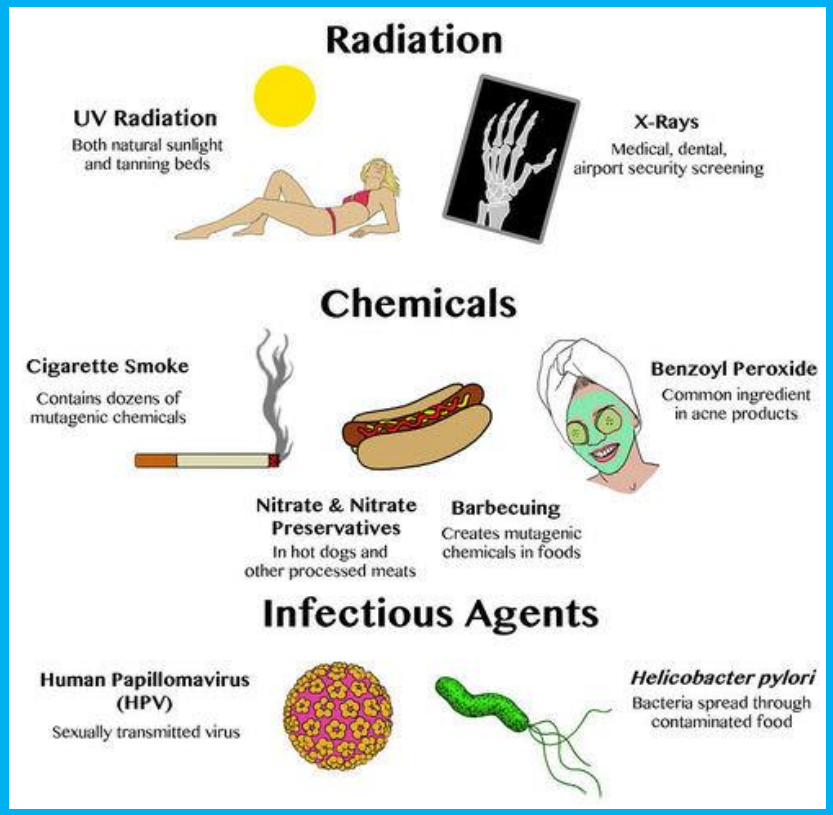
Spontaneous versus induced mutation

We can list 5 type of the SPONTANEOUS mutation

There are five common types of spontaneous mutations. These are described in the **Table**

Mutation	Description
Tautomerism	a base is changed by the repositioning of a hydrogen atom
Depurination	loss of a purine base (A or G)
Deamination	spontaneous deamination of 5-methycytosine
Transition	a purine to purine (A to G, G to A), or a pyrimidine to pyrimidine (C to T, T to C) change
Transversion	a purine becomes a pyrimidine, or vice versa

INDUCED MUTATION: some external factor play role in increasing of mutation:



- !!There exist several types of mutation of DNA chain !!

Major types of mutations

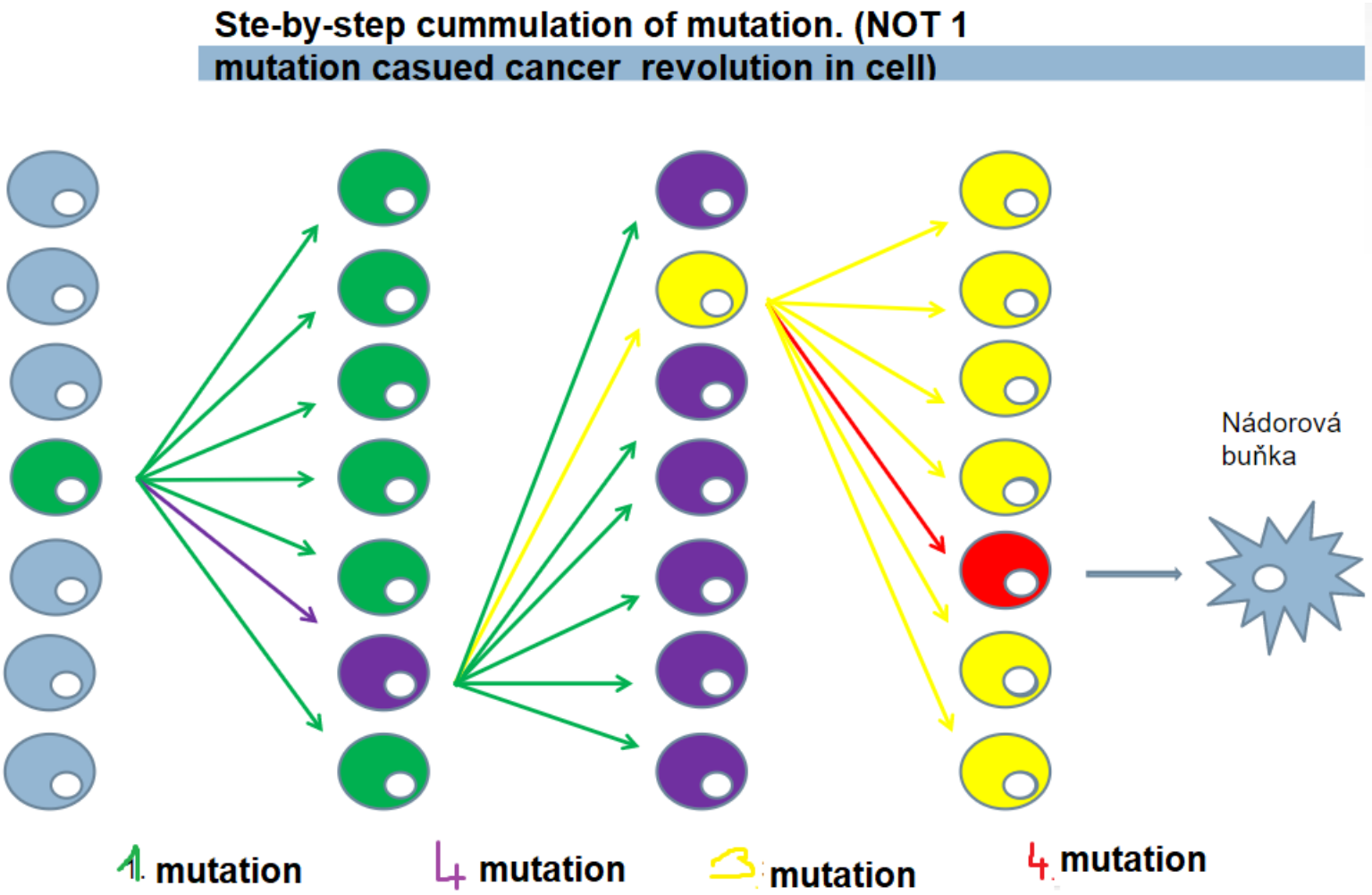
Basis of classification	Mutation type	Major features
Origin	Spontaneous Induced	Absence of known mutagen Presence of known mutagen
cell type	Somatic Germ-line	Non-reproductive cells Reproductive cells
expression	Conditional Unconditional	Under restrictive conditions Under permissive conditions
Effect on function	Loss-of-function Hypomorphic Hypermorphic Gain-of-function	Eliminating normal function Reducing normal function Increasing normal function Expressed at incorrect time or in inappropriate cell type

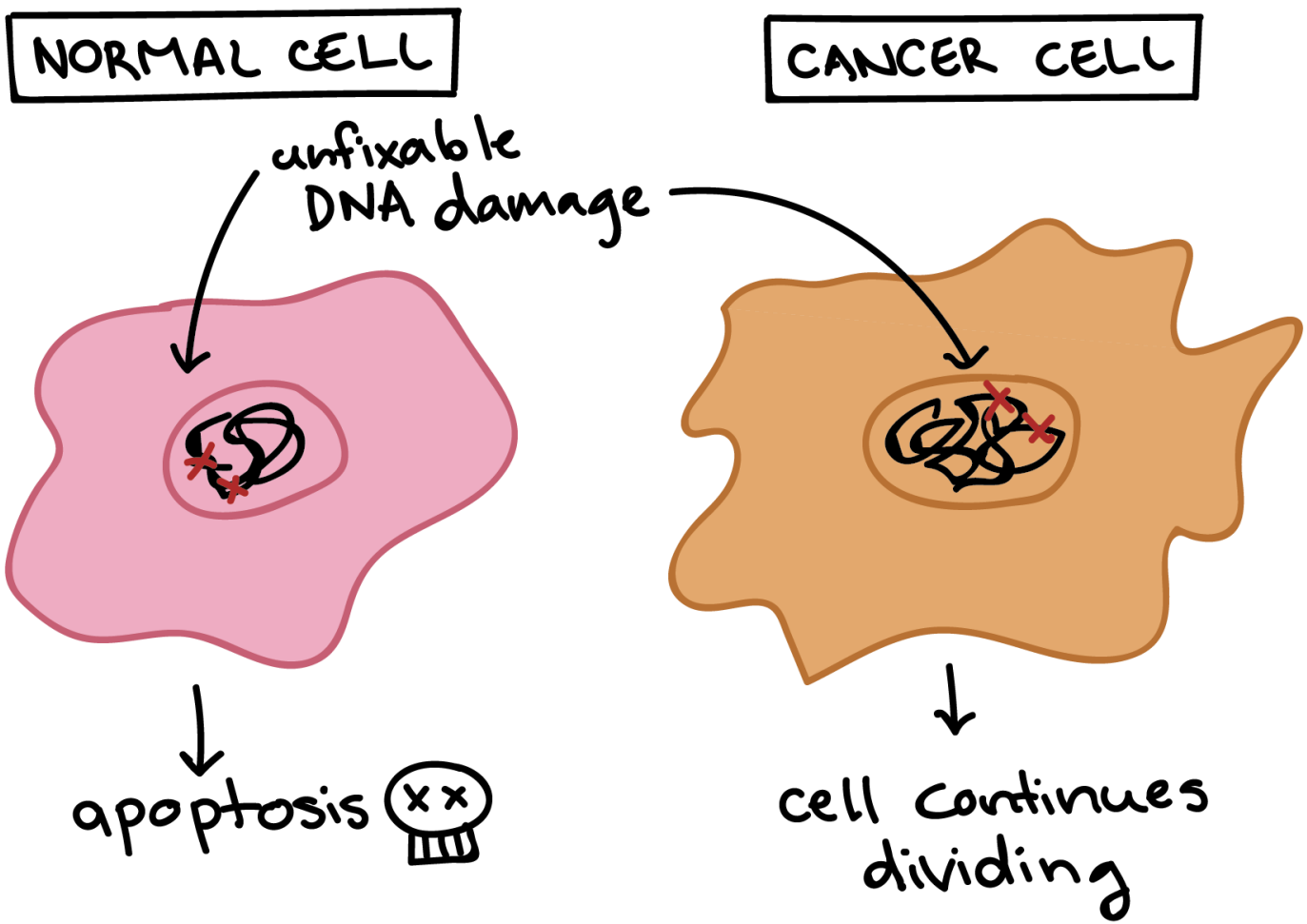
Types and frequency of mutations

Typy mutací a jejich odhadované frekvence

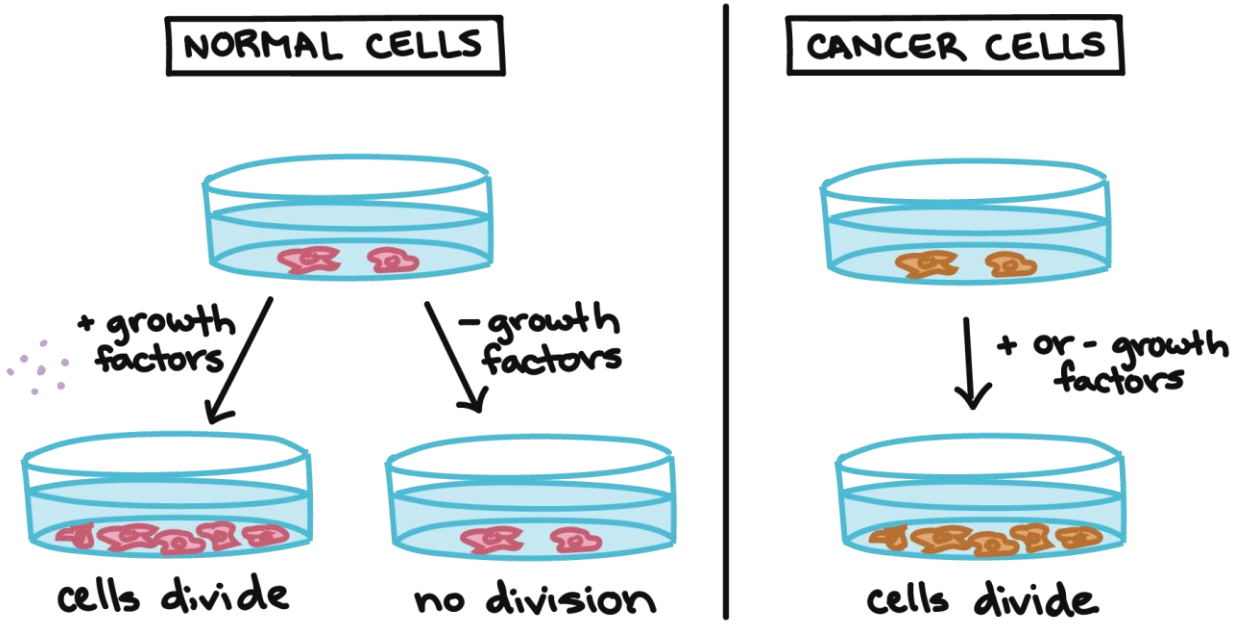
Typ mutace	Mechanismus	Četnosti
Bodová mutace	1. chyba při replikaci DNA 2. poškození DNA zářením či chemickými mutageny	~ 10^{-10}/pár bazí/buň. dělení ~ 10^{-5}/gen/generaci 0,5/buňku
Submikroskopická delece či inzerce	1. nerovnoměrný crossing-over 2. vychýlení při replikaci 3. inzerce mobilních elementů 4. poškození DNA zářením či chemickými mutageny	
Mikroskopicky viditelná delece, translokace nebo inverze	1. nerovnoměrný crossing-over 2. poškození DNA zářením či chemickými mutageny	6×10^{-4}
Ztráta či zisk celého chromozomu	1. chyby při meióze, mitóze	1 na 100


CANCER = illness conected with mutation




NORMAL CELL
CANCER CELL
unfixable DNA damage
apoptosis
cell continues dividing

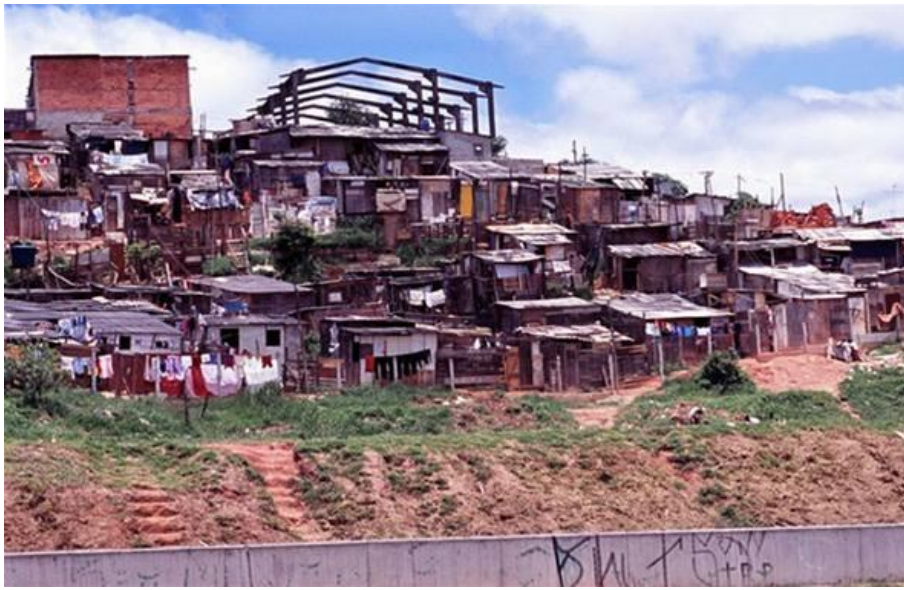
Due to the mutation: „cancer cells have shifted rules of metabolism“



And shifted expansion and dividing strateg: analogy to rational and chaotic overgrow of cities

Rational and organised x

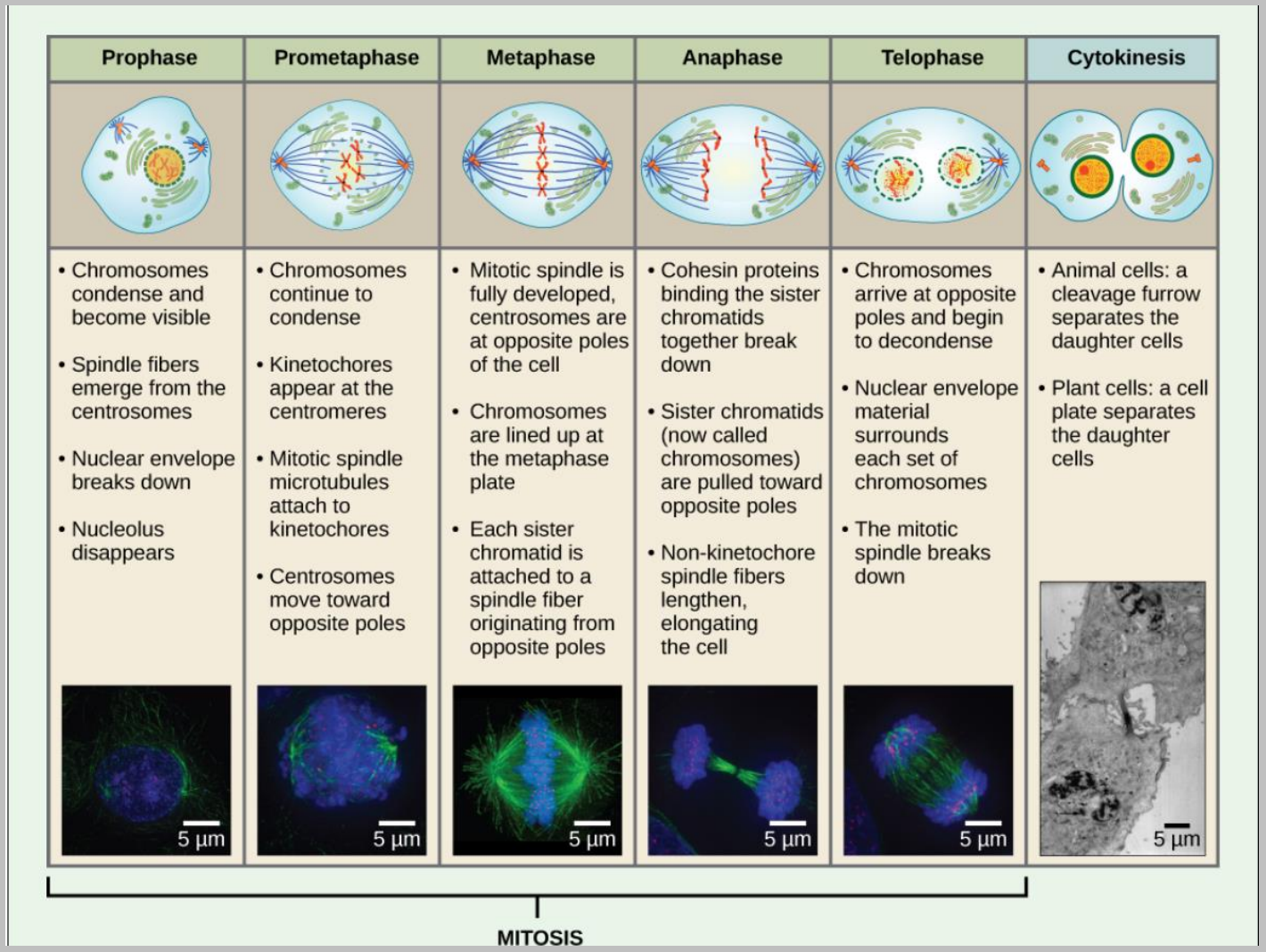
Overgrowing and selfkilling



LONG TERM SURVIVING:
Sustainable development

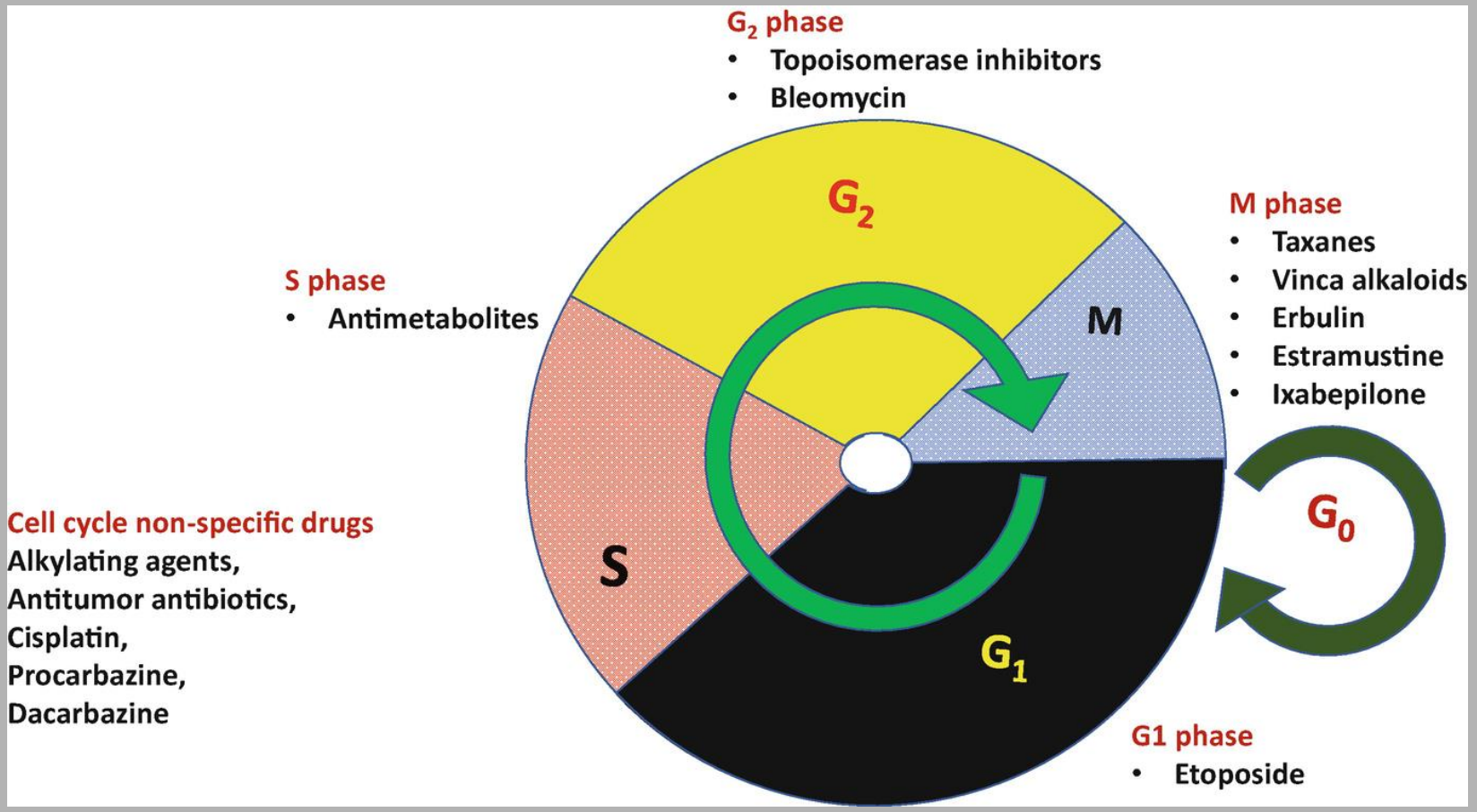
vs. Unsustainable development

Cancer from antoher site: Cell divison and chemotherapy



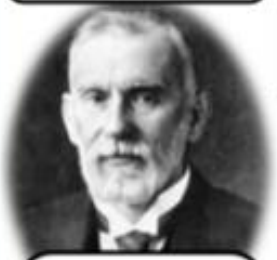
Cell divison and chemotherapy

(some cytostatic agent arrests the cell cycle at G1 or G2 or S or M phase:



Timeline history of chemotherapy development

1908- Discovery of Arsphenamine

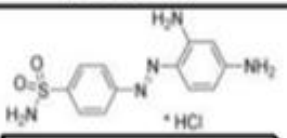


Paul Ehrilich
Father of Chemotherapy

1900- *Paul Ehrilich* Chemotherapy Animal model developed

Alexander Fleming 1928- Penicillin

Gerhard Domagk 1939- Sulfonamidochrysoidine (Prontosil)



1932- Prontosil- First sulfonamide- Bayer's Laboratory

1959- Antitumor antibiotics

1958- Methotrexate

1957- 5-Fluorouracil

1951- Thiopurines

1948- Anitfolates

1944- Waksman *et al.*, discovered streptomycin.

1943- Nitrogen mustard in

1963- Vinca alkaloids

1962- nalidixic acid

1963 to 1970- Treatment for Hodgkin's disease

2007- Target specific screens

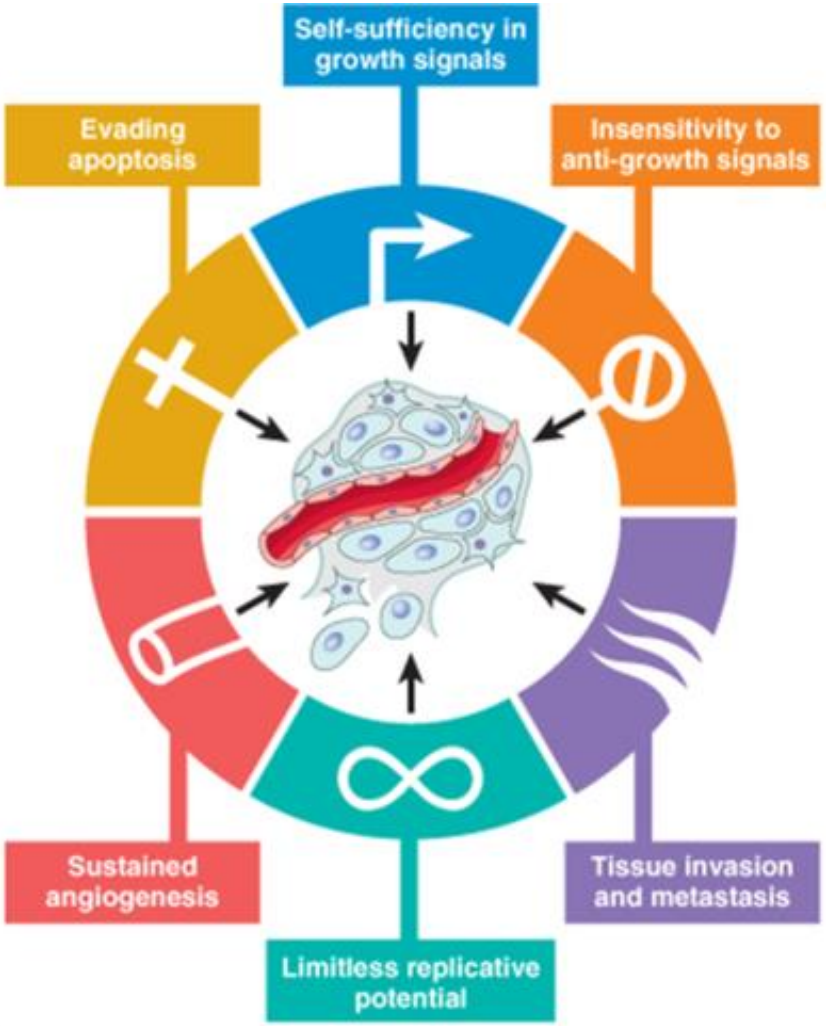
2005- Tyrosine kinase inhibitors

1997- Monoclonal antibody approved for the treatment of tumor.

1996- Imatinib

2015

Global overview of „un-rational“ changes in genetic code of cancer cells (…reason why the selfelimination and external fighting is not easy).



Another illnesses caused by mutation

- ANEMIA

Table 1: Single-Base Mutation Associated with Sickle-Cell Anemia

Sequence for Wild-Type Hemoglobin												
ATG	GTG	CAC	CTG	ACT	CCT	GAG	GAG	AAG	TCT	GCC	GTT	ACT
Start	Val	His	Leu	Thr	Pro	Glu	Glu	Lys	Ser	Ala	Val	Thr
Sequence for Mutant (Sickle-Cell) Hemoglobin												
ATG	GTG	CAC	CTG	ACT	CCT	GTG	GAG	AAG	TCT	GCC	GTT	ACT
Start	Val	His	Leu	Thr	Pro	Val	Glu	Lys	Ser	Ala	Val	Thr

Molecules of sickle-cell hemoglobin stick to one another, forming rigid rods. These rods cause a person's red blood cells to take on a deformed, sickle-like shape, thus giving the disease its name. The rigid, misshapen blood cells do not carry oxygen well, and they also tend to clog capillaries, causing an affected person's blood supply to be cut off to various tissues, including the brain and the heart. Therefore, when an afflicted individual exerts himself or herself even slightly, he or she often experiences terrible pain, and he or she might even undergo heart attack or stroke—all because of a single nucleotide mutation (Figure 1).

- Goode overview: https://www.nature.com/scitable/topicpage/genetic-mutation-441/

- **Some examples of single-gene disorders include**

1. cystic fibrosis,
2. alpha- and beta-thalassemias,
3. sickle cell anemia (sickle cell disease),
4. Marfan syndrome,
5. fragile X syndrome,
6. Huntington's disease, and
7. hemochromatosis.