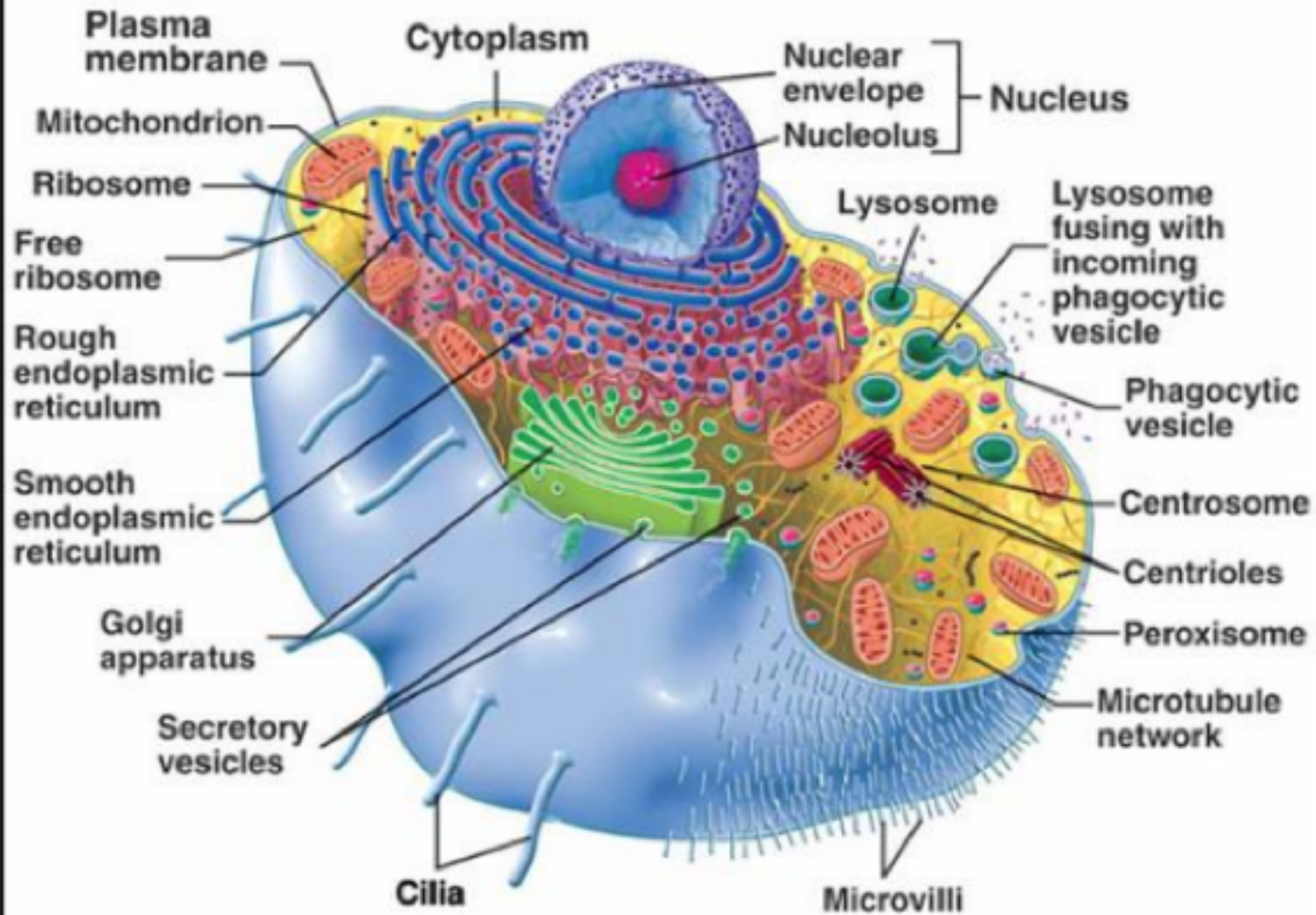


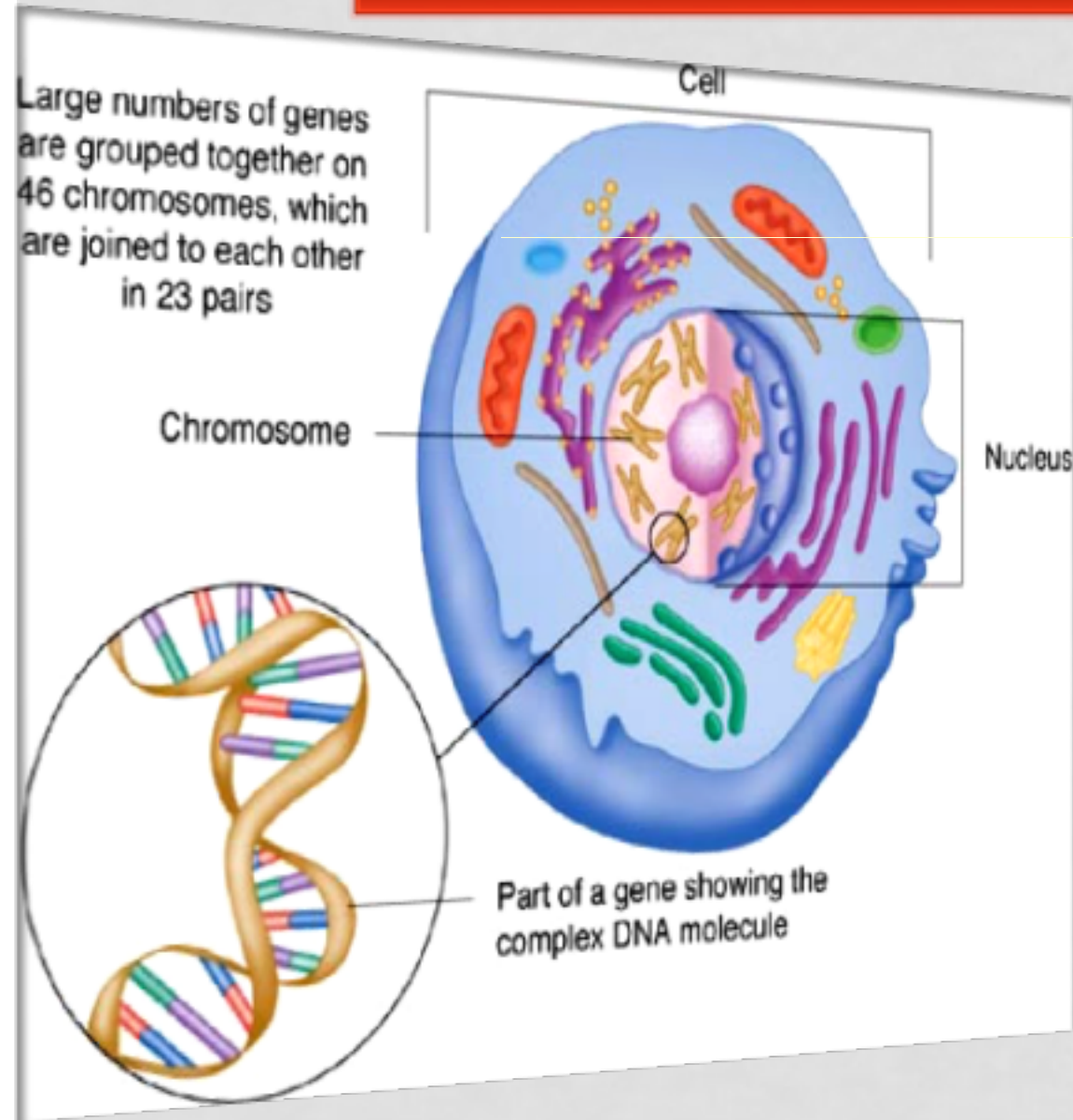


LECTURE 4: CELLS, DNA, CANCER GENE MUTATIONS

The Cell and Genes



The Cell and Genes

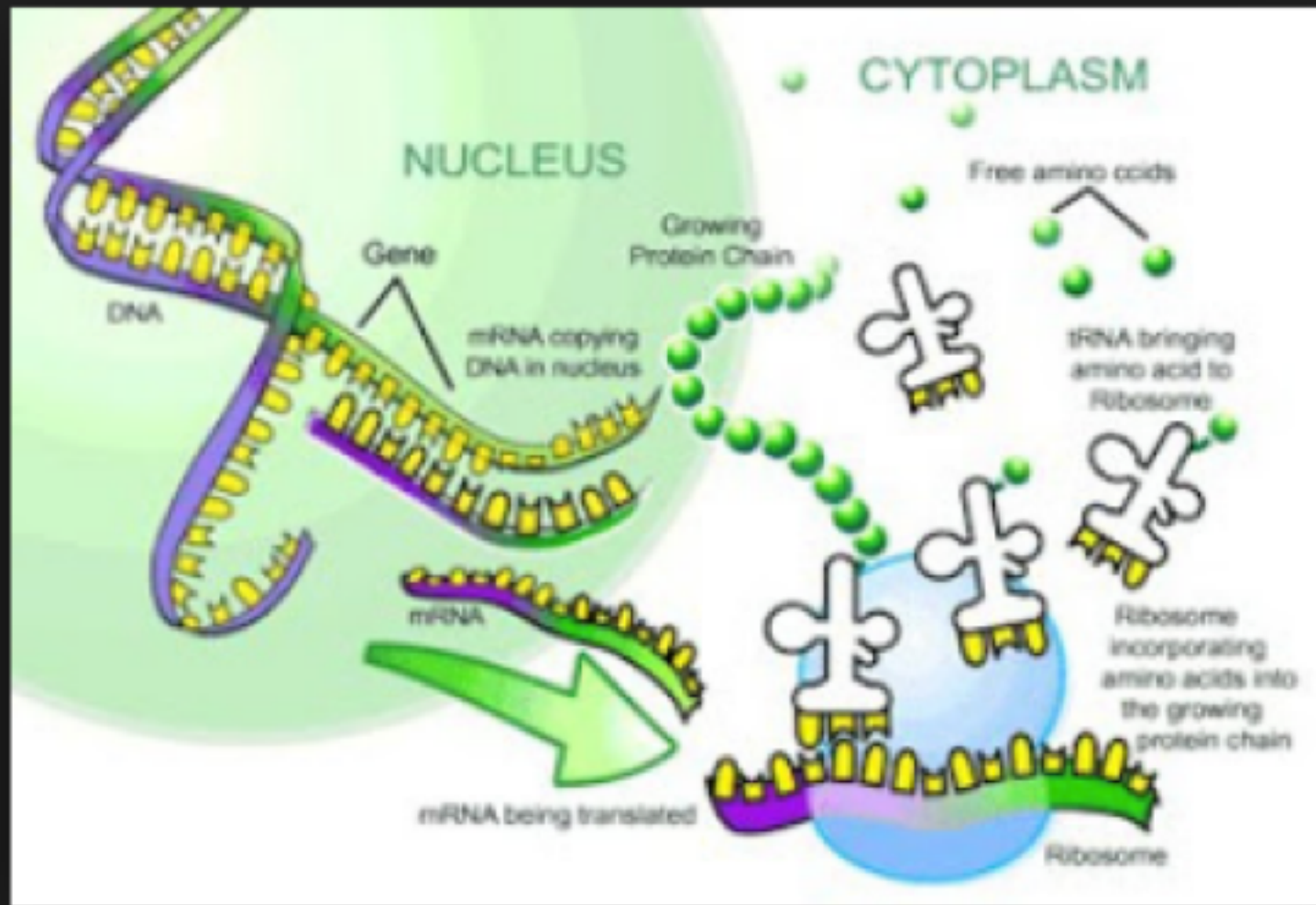


The Human Genome

The instructions (**genes**) the human body needs to function are packaged into **chromosomes**.

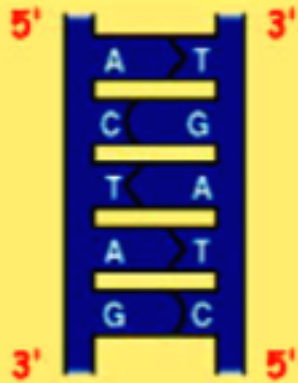
This complete set of instructions is called the **human genome**.

There are **22** pairs of numbered chromosomes plus two sex chromosomes, the **X** and the **Y**



Central Dogma of Molecular Biology: DNA – RNA - Protein

DNA REPLICATION *

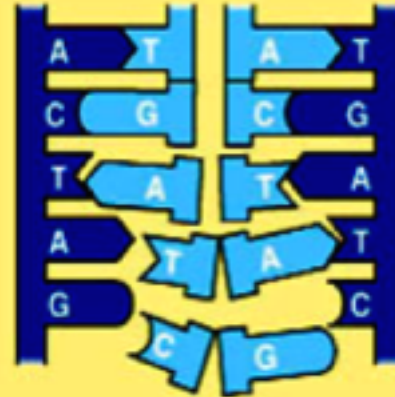


(a) The parent molecule has two complementary strands of DNA. Each base is paired by hydrogen bonding with its specific partner, A with T and G with C.



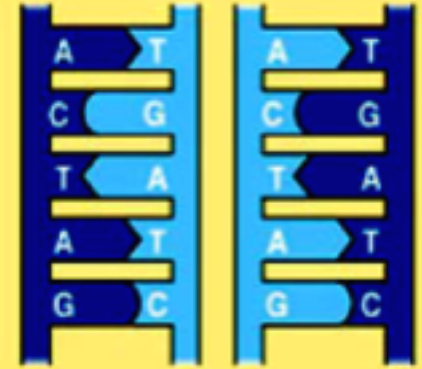
(b) The first step in replication is separation of the two DNA strands.

"melting DNA"



(c) Each parental strand now serves as a template that determines the order of nucleotides along a new complementary strand.

complimentary pairing

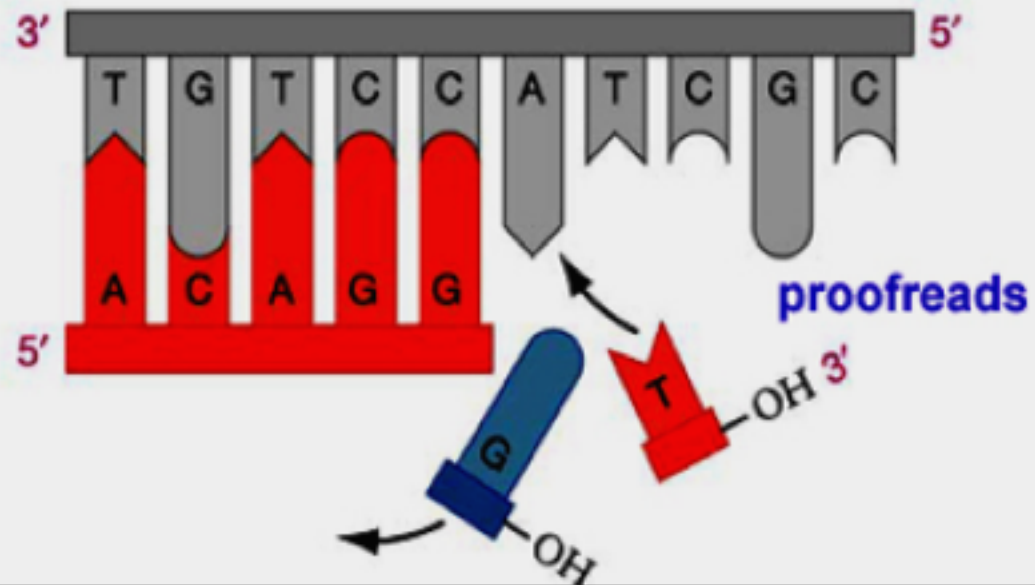
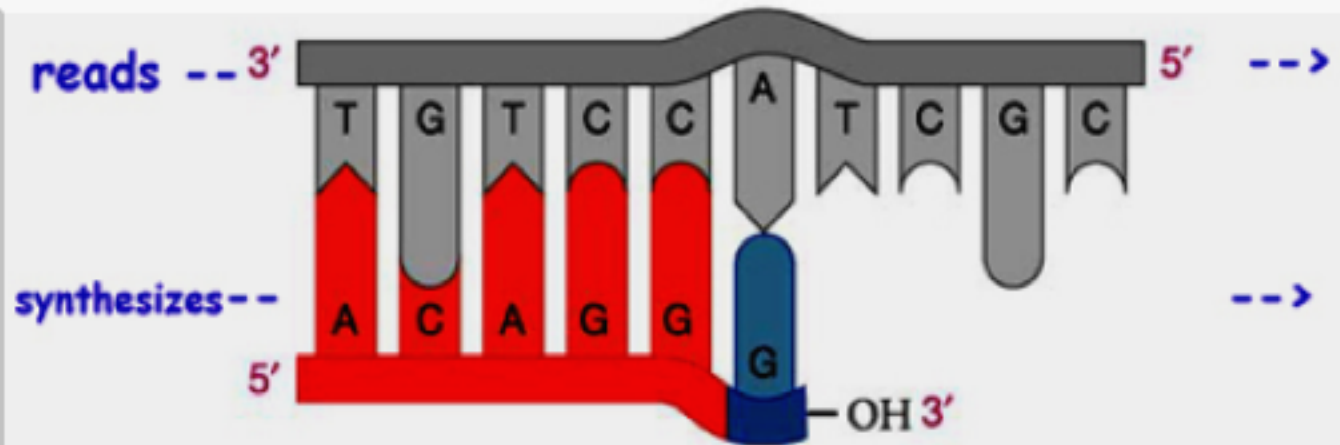


(d) The nucleotides are connected to form the sugar-phosphate backbones of the new strands. Each "daughter" DNA molecule consists of one parental strand and one new strand.

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- Mutations replication mistakes
- Source of genetic diversity and all diversity and future cancers

PROOF READING



COMPARATIVE ERROR RATES

US Postal services on time delivery of local first class mail	13 late deliveries per 100 parcels
Airline Luggage system	1 lost bag per 150
Professional typist typing at 120 words per minute	1 mistake per 250 characters
Driving a car in the United States	1 death per 10^4 people each year
DNA replication (without mismatch repair)	1 mistake per 10^7 nucleotides copied
DNA replication (including mismatch repair)	1 mistake per 10^9 nucleotides copied

The Human genome has over 3 billion nucleotides!

GENES, TRANSCRIPTION, TRANSLATION & PROTEINS

- ❑ DNA → **transcription** → mRNA → **translation** → Protein
- ❑ DNA (deoxyribonucleic acid) is a linear polymer of repeating nucleotide monomers
- ❑ The letters of the DNA genetic alphabet are the nucleotides **A, T, G, & C**
- ❑ **A** always pairs with **T** and **G** always pairs with **C**
- ❑ In RNA (ribonucleic acid) the **T** is substituted for **U**
- ❑ Unit of information is **CODON** = genetic 'word'
- ❑ 3 nucleotides = 1 codon (word) = 1 amino acid

DECIPHERING THE GENETIC CODE

- ❑ We can think about the DNA sequence of a gene as a sentence made up entirely of 3-letter words
- ❑ In the sequence, each 3-letter word is a **codon**, specifying a single **amino acid** in a protein
- ❑ **allthesadboyhadforhisbigolddogwasbadeggandham**
- ❑ The codon would read: “**All the sad boy had for his big old dog was bad egg and ham.**”
- ❑ This sentence represents a gene. Each letter is a nucleotide base, and each word represents a codon.
- ❑ A frame shift mutation could make the sentence look like this: **A llt hes adb oyh adf orh isb igo ldd ogw asb ade gga ndh am**

DNA Mutations

Point Mutations

They change one piece of the DNA sequence.

Healthy protein



Mutation through substitution



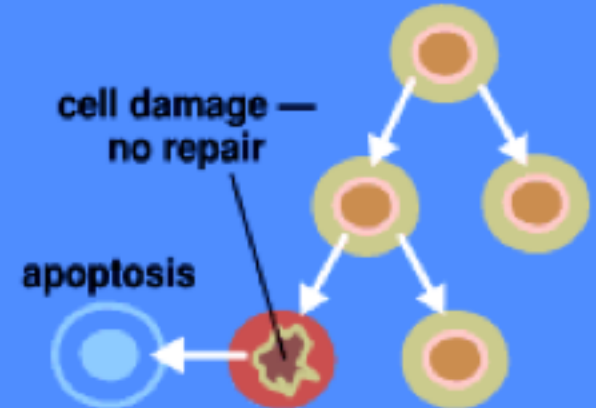
Mutation through deletion



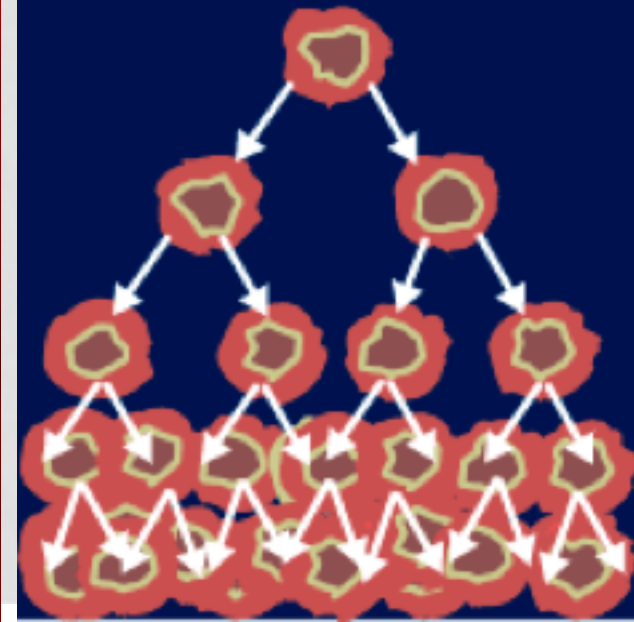
Mutation through addition



Normal Cell Division



Cancer Cell Division



MUTATED GENES IN CANCER

- ❑ Alteration in genes involved in controlling cell proliferation and survival- 3 main categories:
 1. **Oncogenes**- presence contribute to uncontrolled cell proliferation and leading to cancer. Arise from normal **proto-oncogenes** or viral oncogenes
 2. **Tumor Suppressor Genes** – absence (inactivation) contribute to uncontrolled cell proliferation and cancer
 3. **DNA Repair Genes**- mutations in DNA repair genes lead to lack of mismatch repair and can progress to cancer

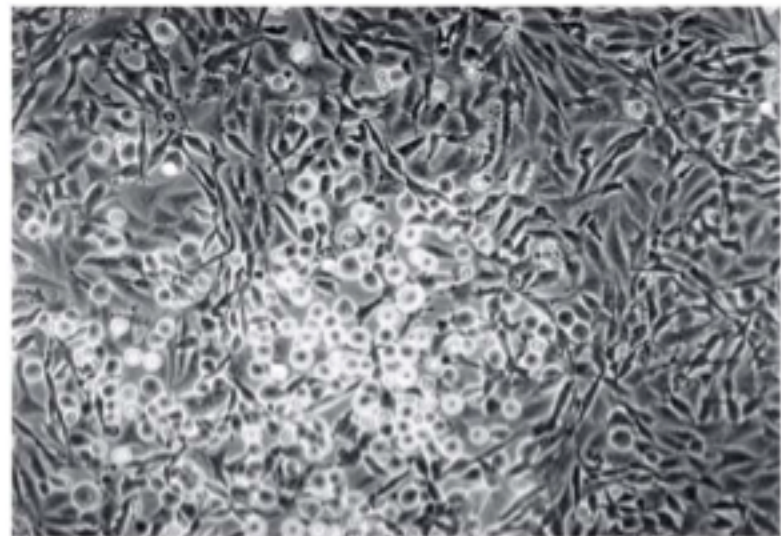
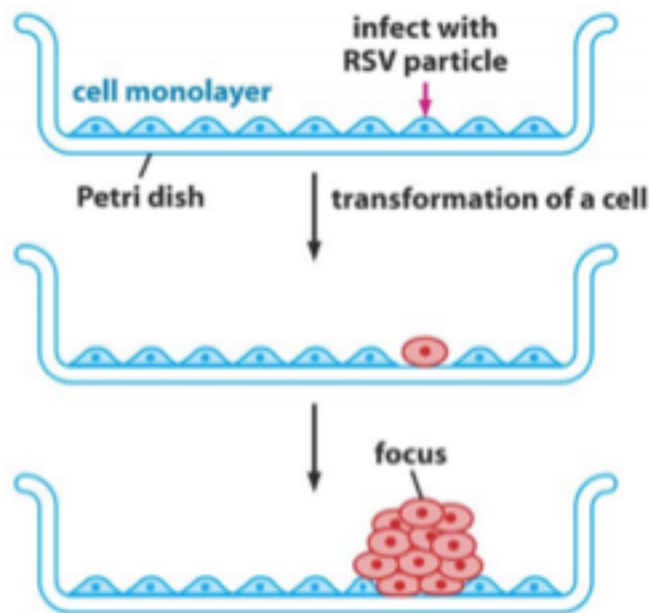
Peyton Rous discovered a chicken sarcoma virus called Rous sarcoma virus (RSV)



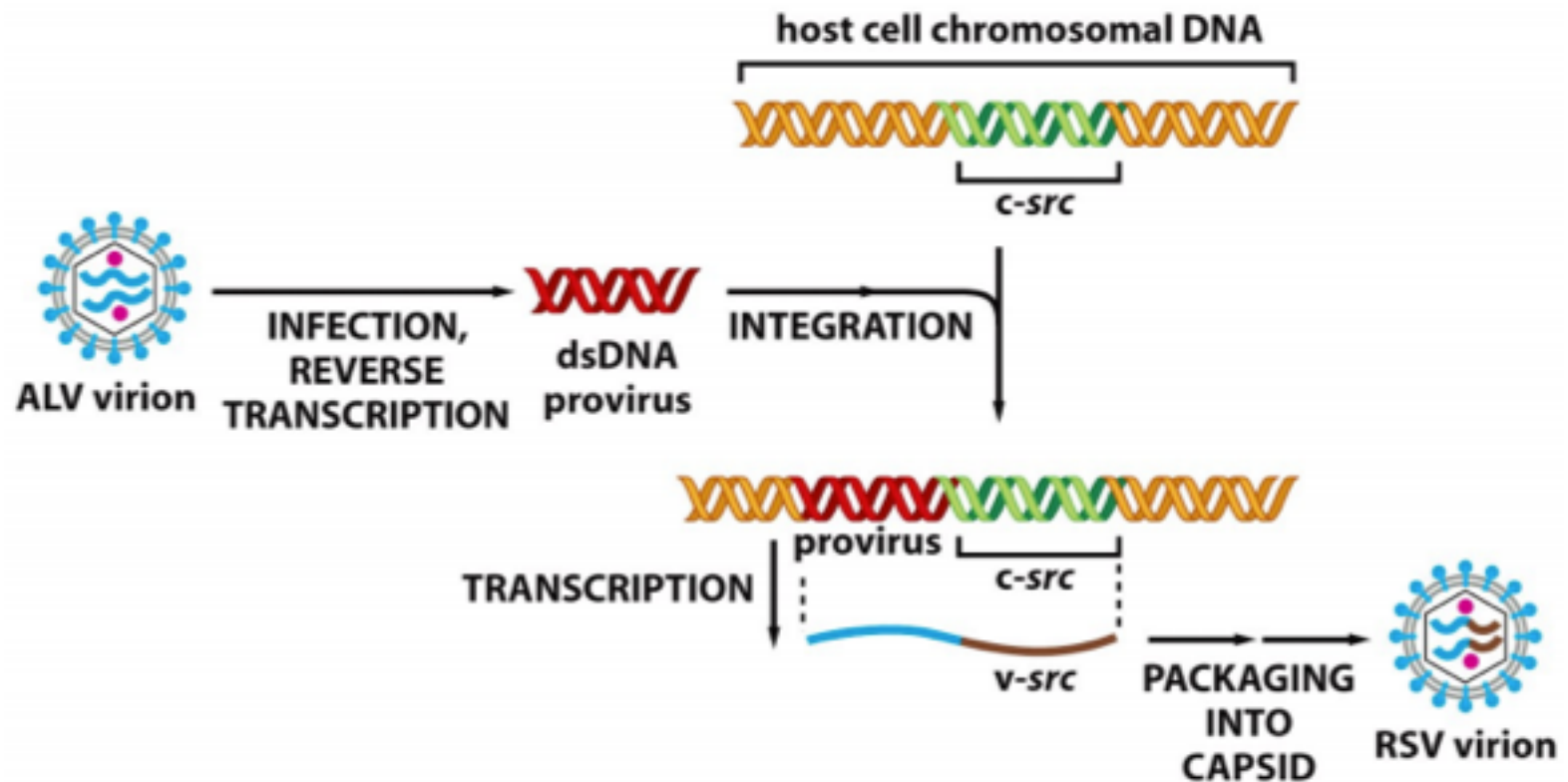
Sarcoma connective tissue tumor
Transformation transmissible
1976 Isolation of first oncogene

Rous sarcoma virus is discovered to transform infected cells in culture

Transformed cells forming foci (clusters) due to loss of cell-contact inhibition



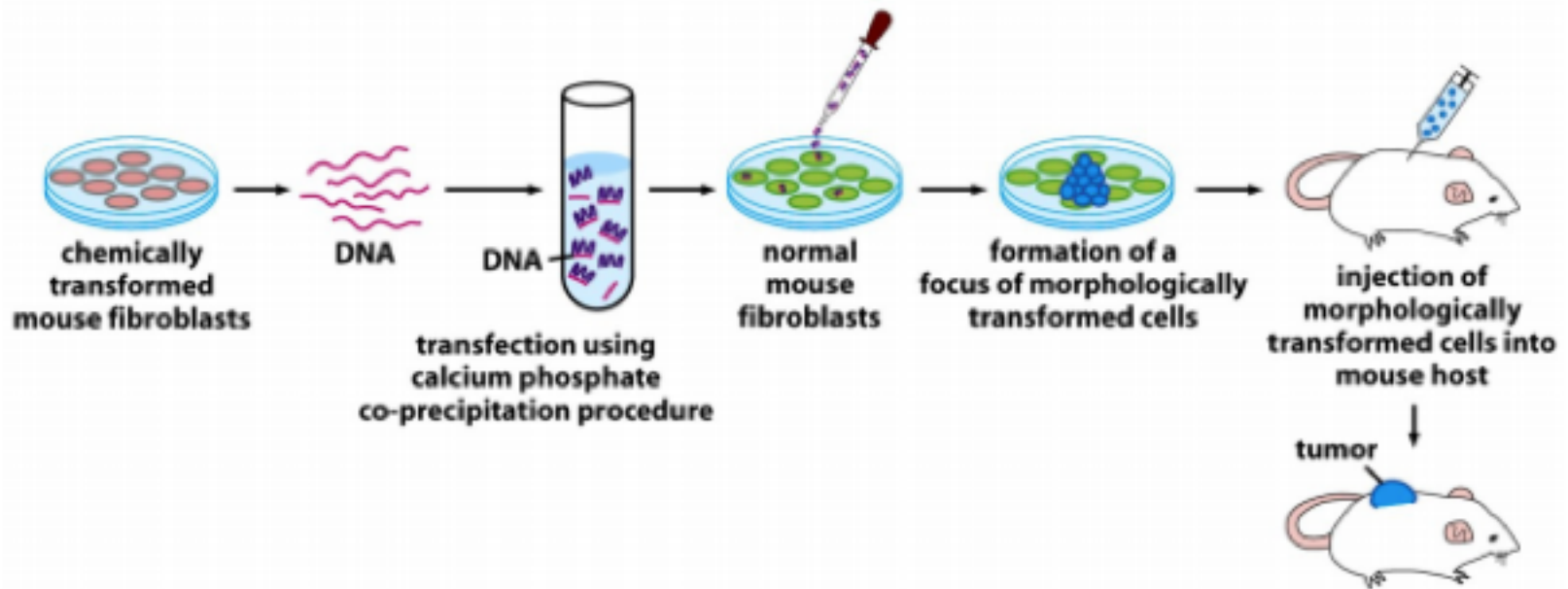
Capture of *src* by ALV leads to formation of RSV



RSV exploits a kidnapped cellular gene to transform cells

c-src- receptor tyrosine kinase

Transfection of DNA provides a strategy for detecting non-viral oncogenes

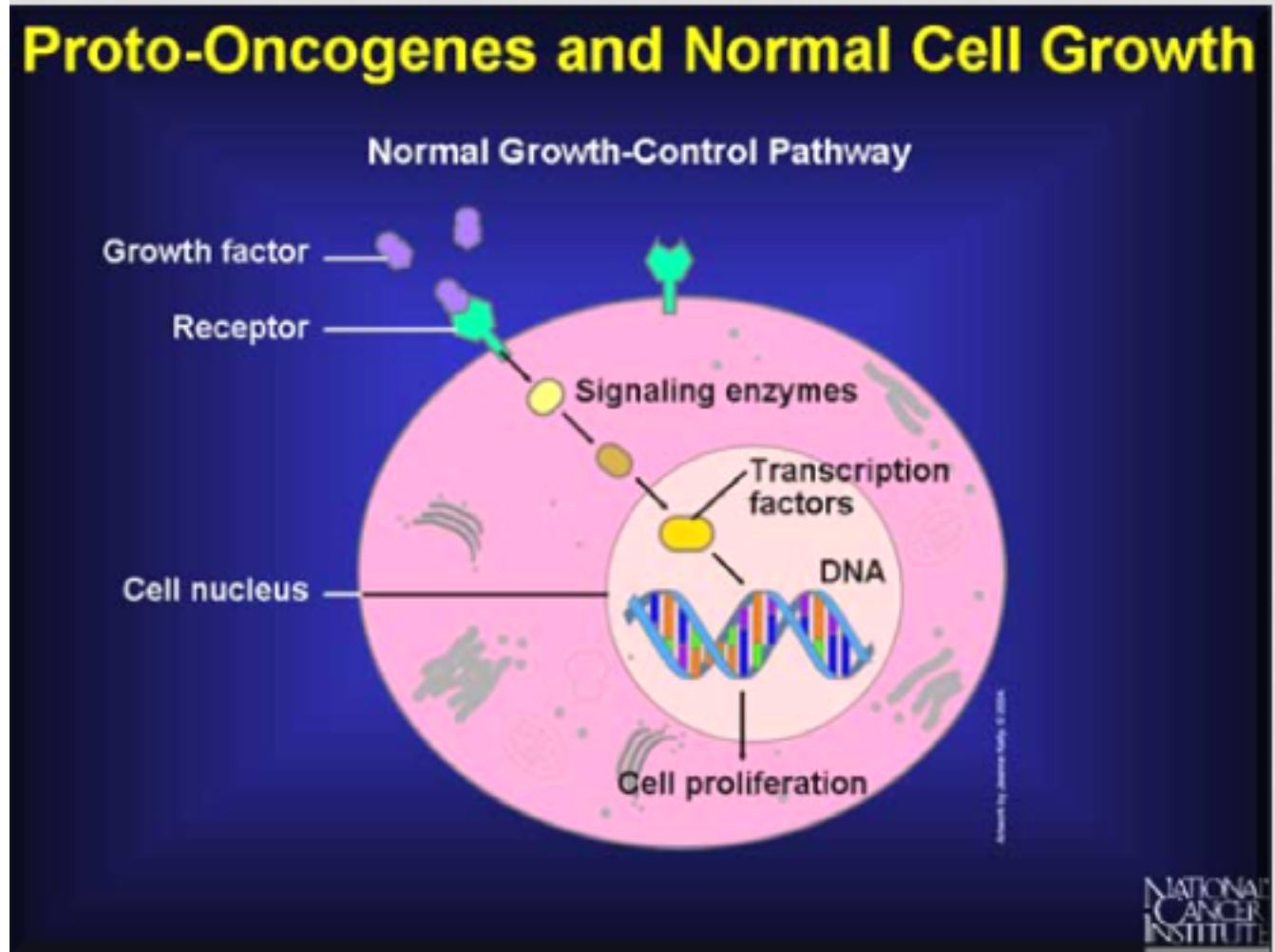


- The donor tumor DNA carried one or several genetic elements that were able to convert non-tumorigenic NIH3T3 recipient cell into a cell that was strongly tumorigenic
- DNA extracted from cell lines derived from human bladder, lung, and colon carcinomas were found capable of transforming recipient NIH3T3 cells.

Transfection = Transformation

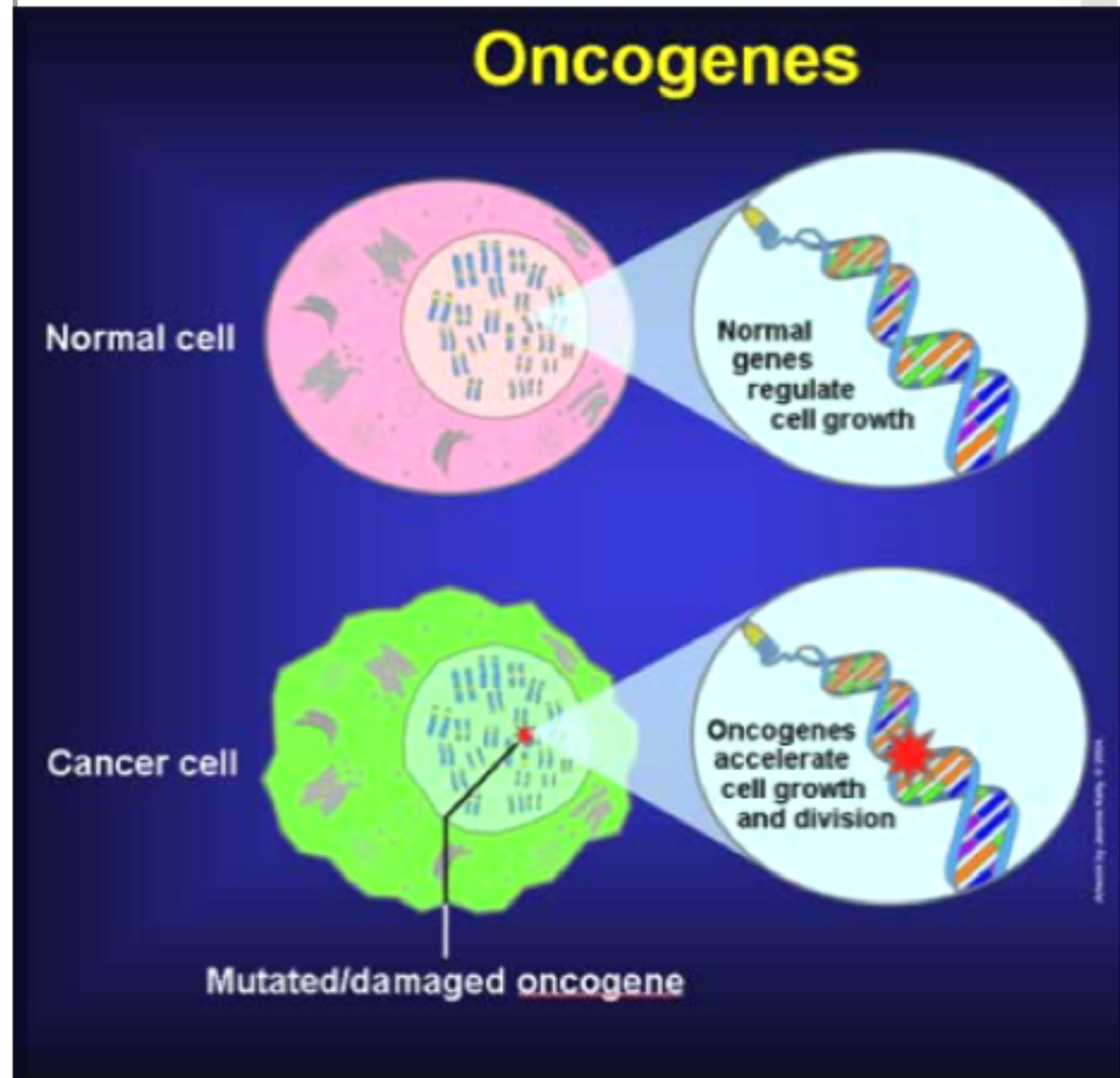
PROTO-ONCOGENES/ONCOGENES

❑ A **proto-oncogene** is a normal gene that can become an oncogene, either after mutation or increased expression.

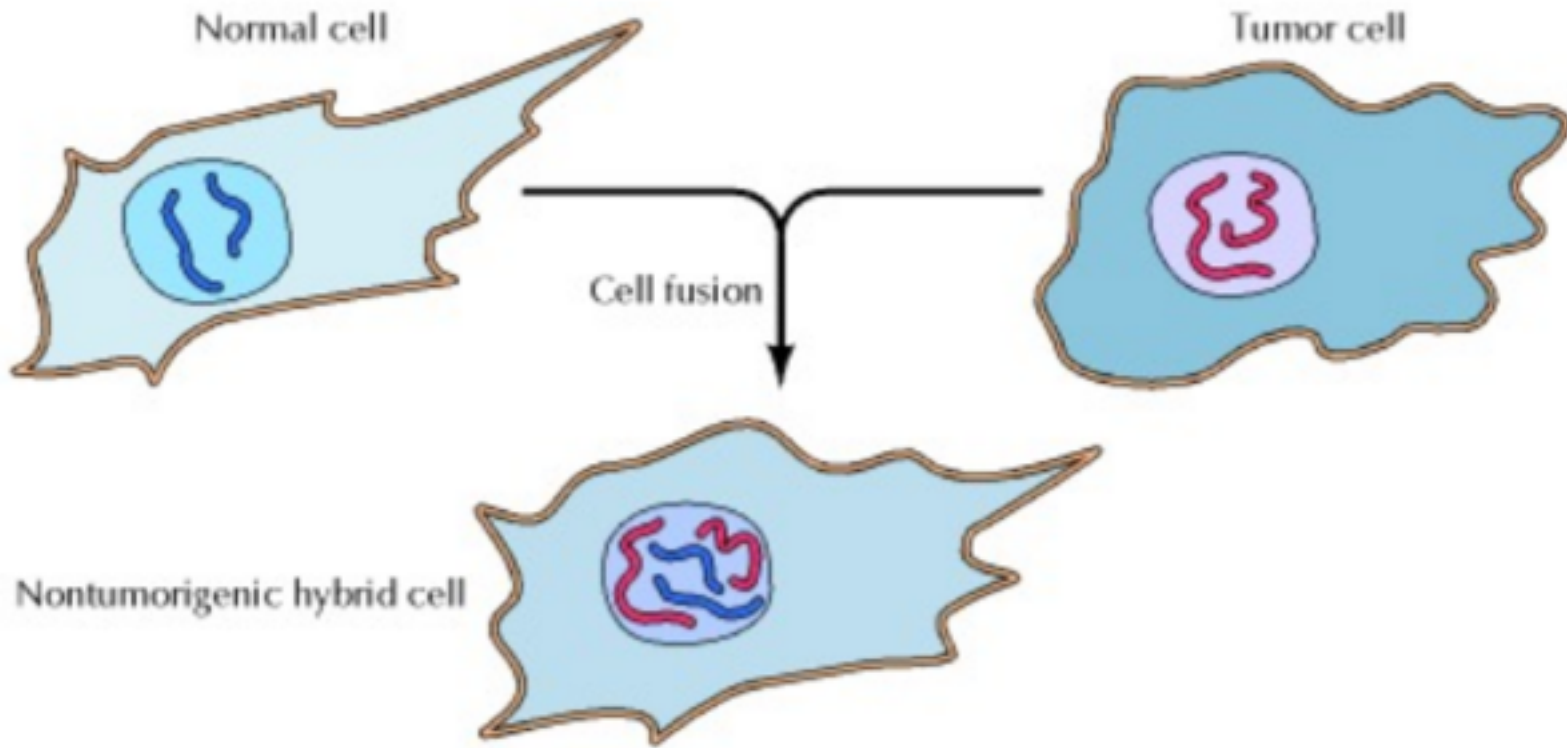


ONCOGENES AND CANCER

- ❑ Proto-oncogenes code for proteins that help to regulate cell **growth** and **differentiation**
- ❑ Proto-oncogenes are often involved in signal transduction and execution of mitogenic signals
- ❑ Oncogenes accelerate cell growth & division



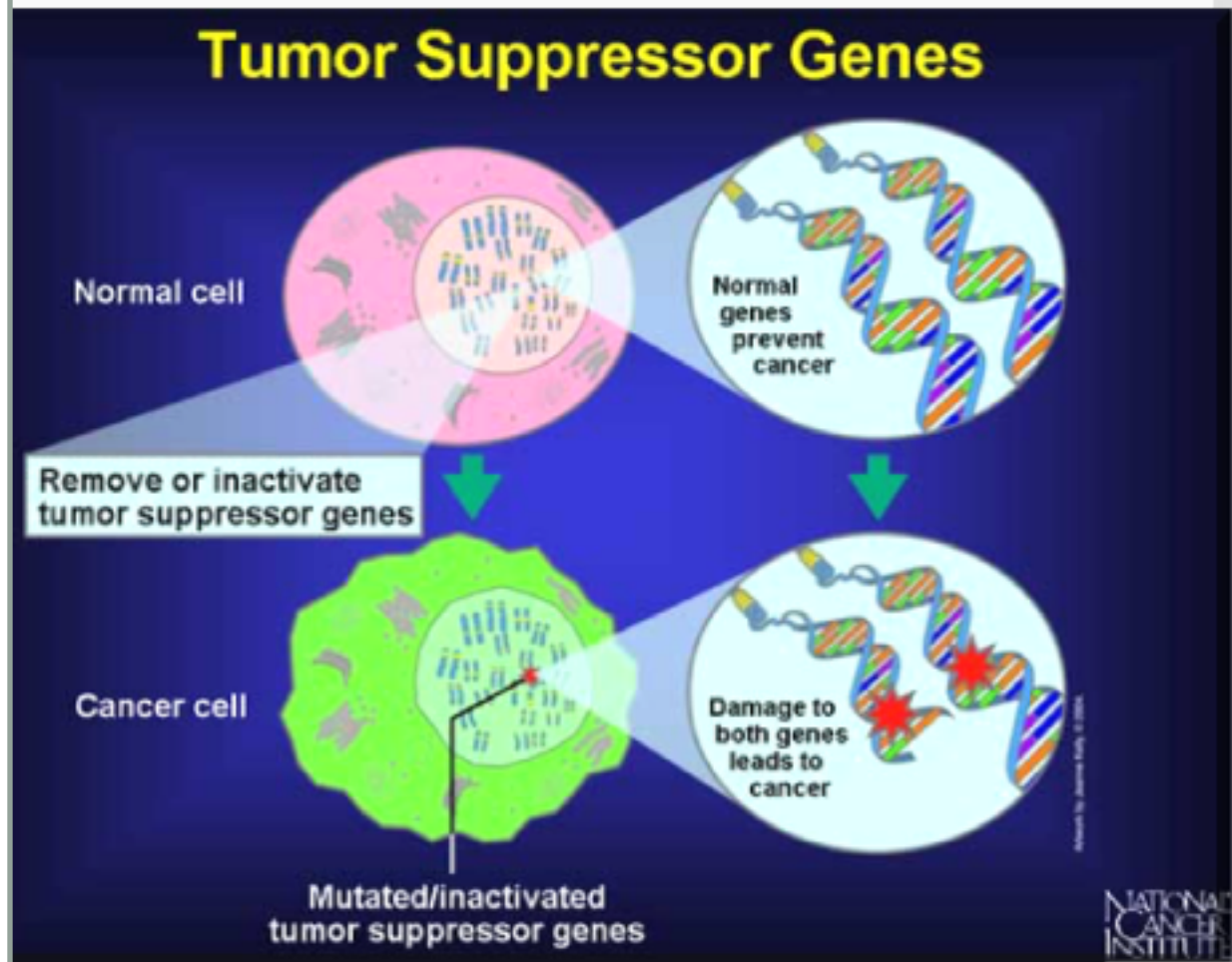
Identification of Tumor suppressor genes



Fusion with normal cell (or chromosome) suppresses tumor formation in mouse

TUMOR SUPPRESSOR GENES

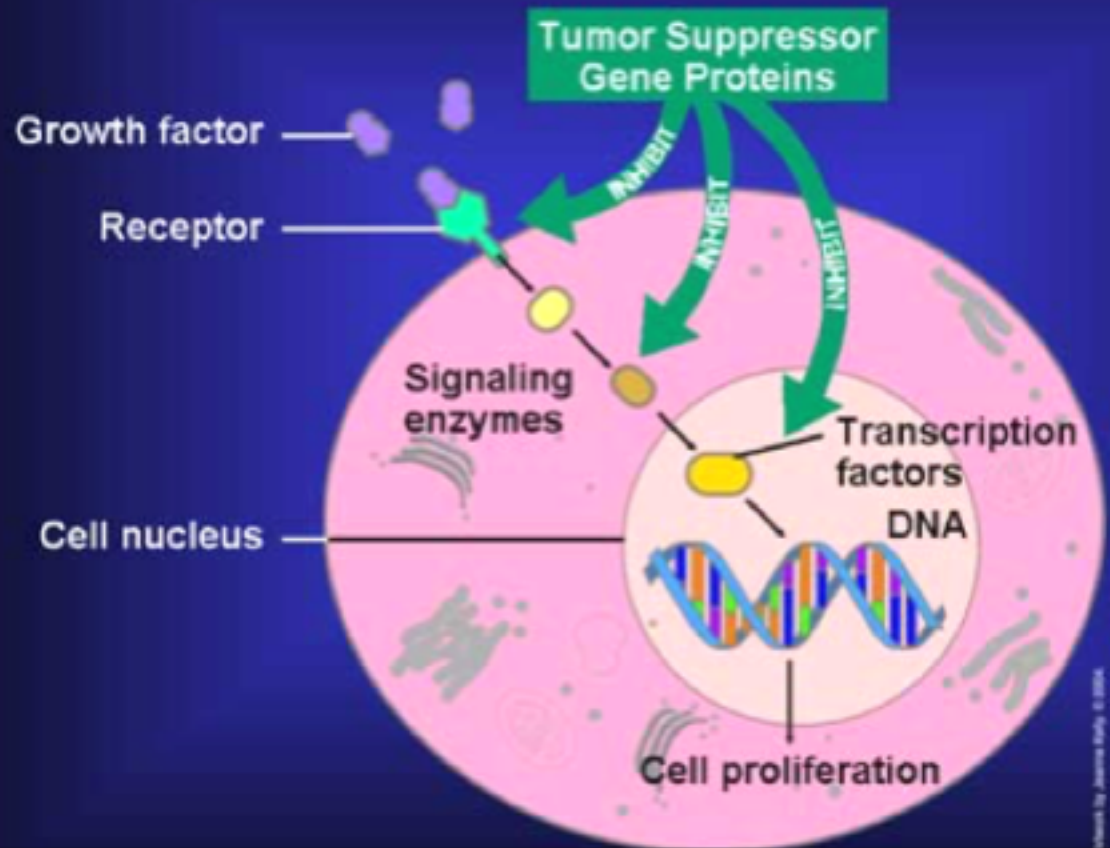
- ❑ Tumor suppressor genes are a family of normal genes that instruct cells to produce proteins that restrain cell growth and division.
- ❑ Since tumor suppressor genes code for proteins that slow down cell growth and division, the loss of such proteins allows a cell to grow and divide in an uncontrolled fashion.



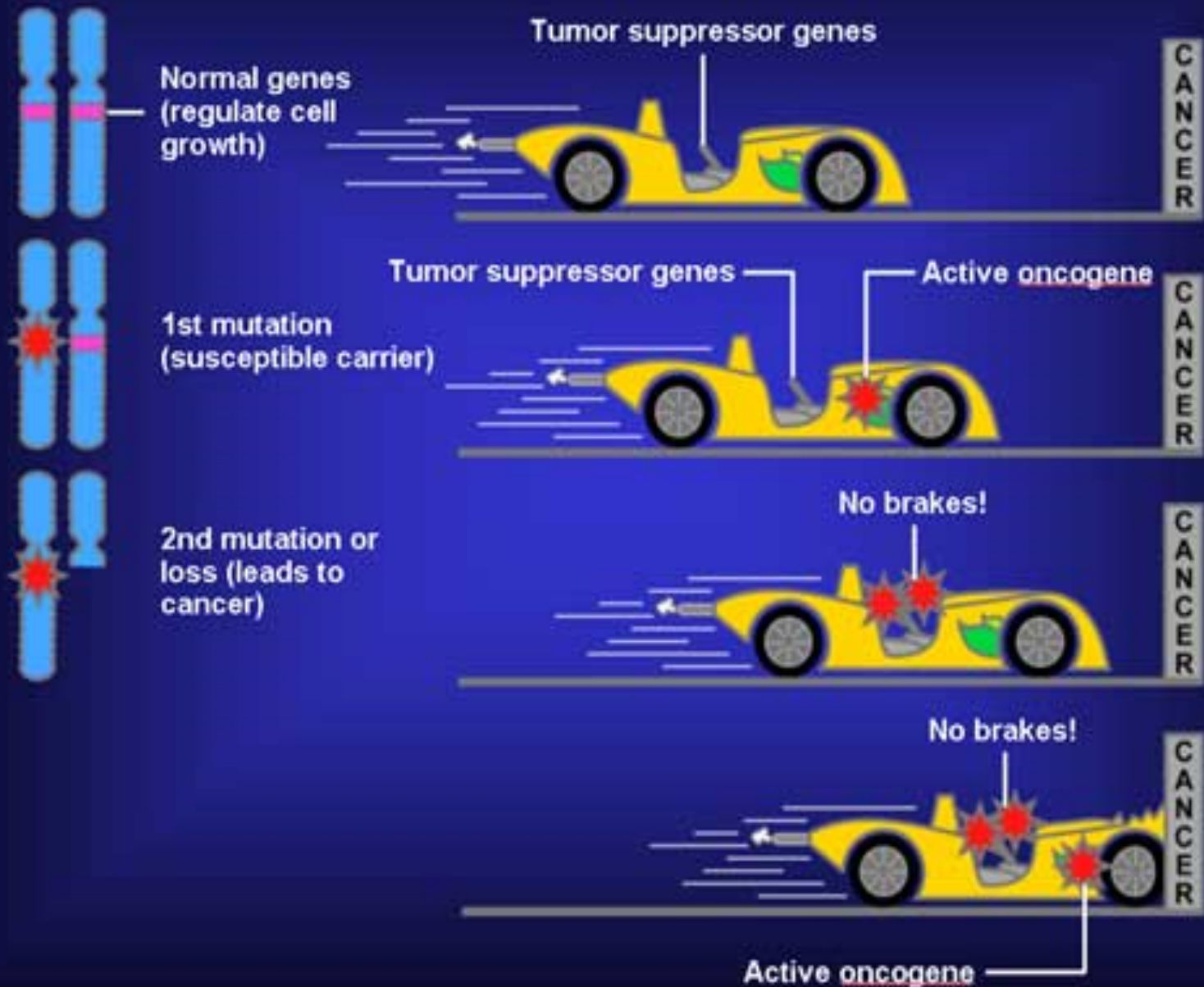
THE BRAKES OF THE CELL CYCLE

- ❑ Tumor suppressor genes are like the brake pedal of an automobile.
- ❑ The loss of a tumor suppressor gene function is like having a brake pedal that does not function properly, thereby allowing the cell to grow and divide continually.

Tumor Suppressor Genes Act Like a Brake Pedal

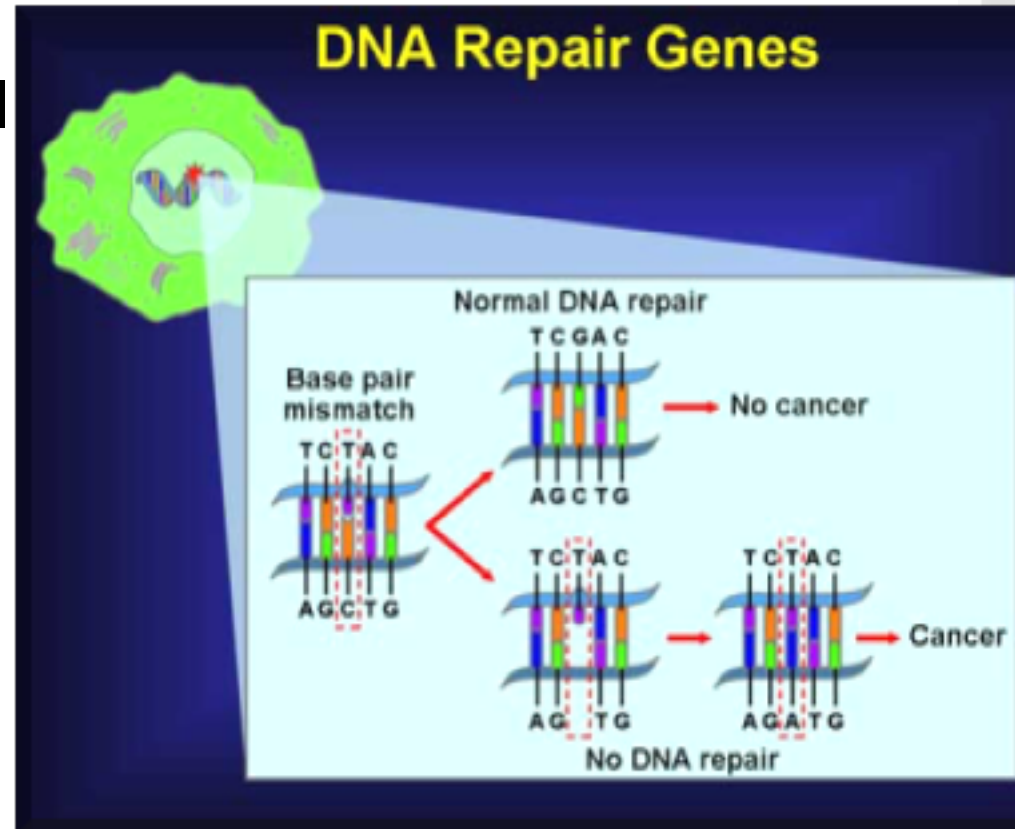


Mutations in Tumor Suppressor Genes

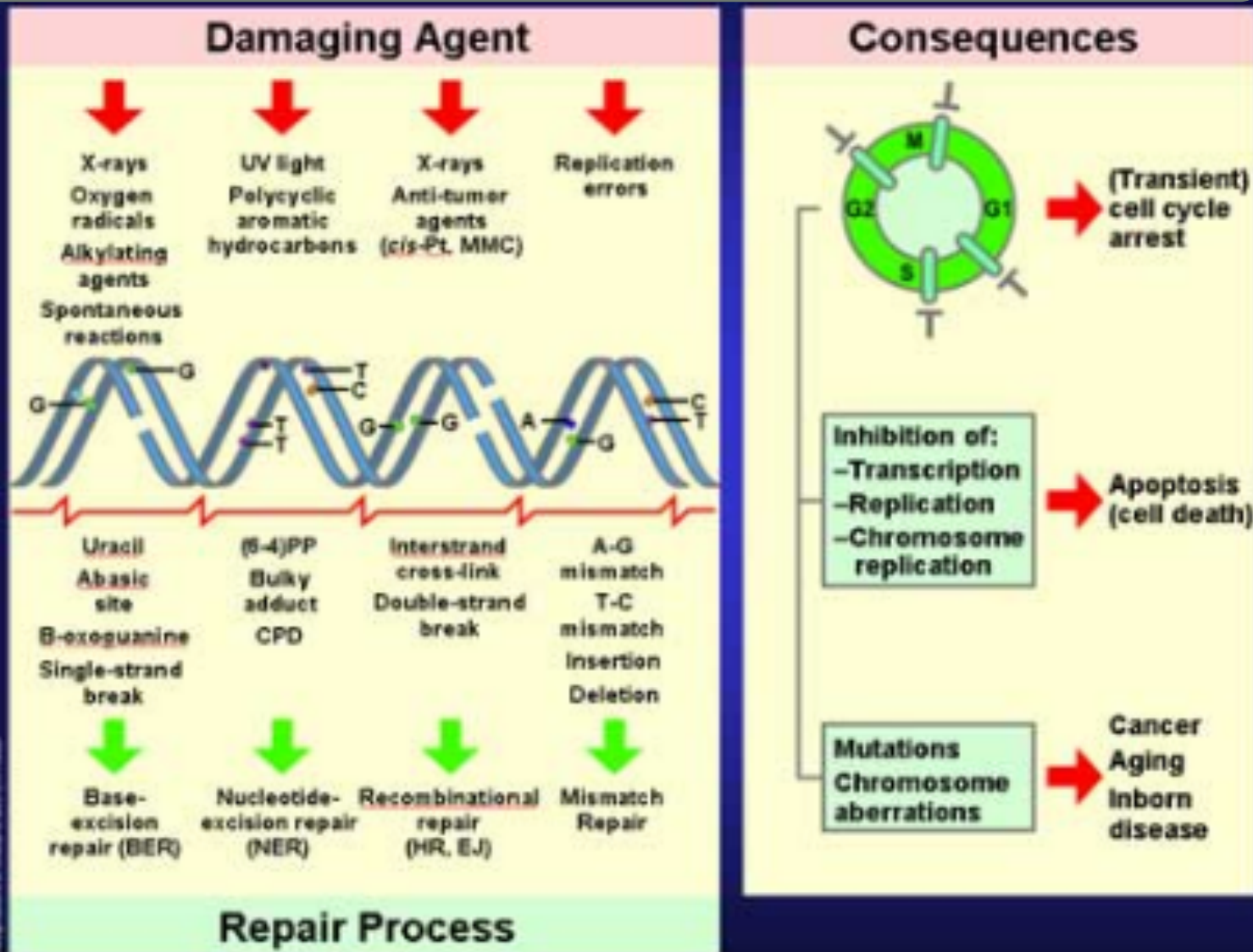


DNA REPAIR GENES

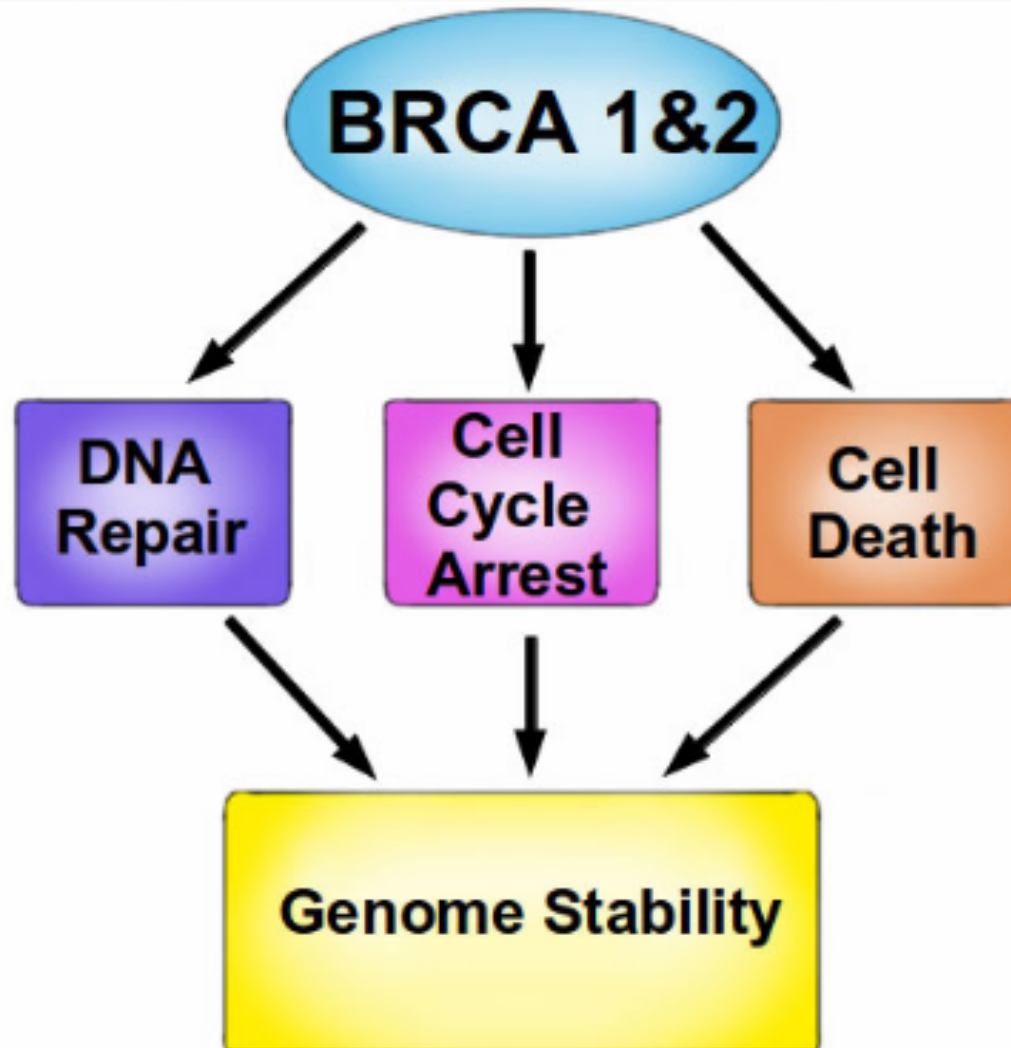
- ❑ DNA repair genes code for proteins whose normal function is to correct errors that arise when cells duplicate their DNA prior to cell division.
- ❑ Mutations in DNA repair genes can lead to a failure in repair, which in turn allows subsequent mutations to accumulate.
- ❑ People with a condition called **xeroderma pigmentosum** have an inherited defect in a DNA repair gene



DNA repair mechanisms: Quality control



BReast **CA**ncer suseptability genes

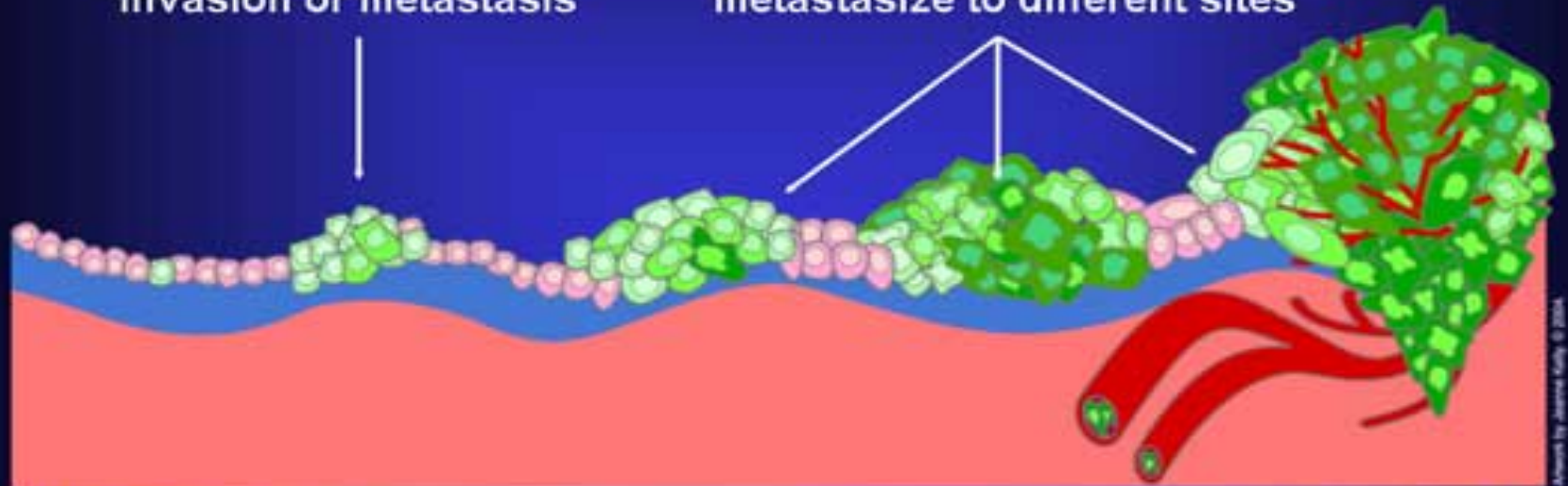


CONSEQUENCE OF MUTATION IN “CANCER GENES”

Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites



Time →

Mutation inactivates suppressor gene

Cells proliferate

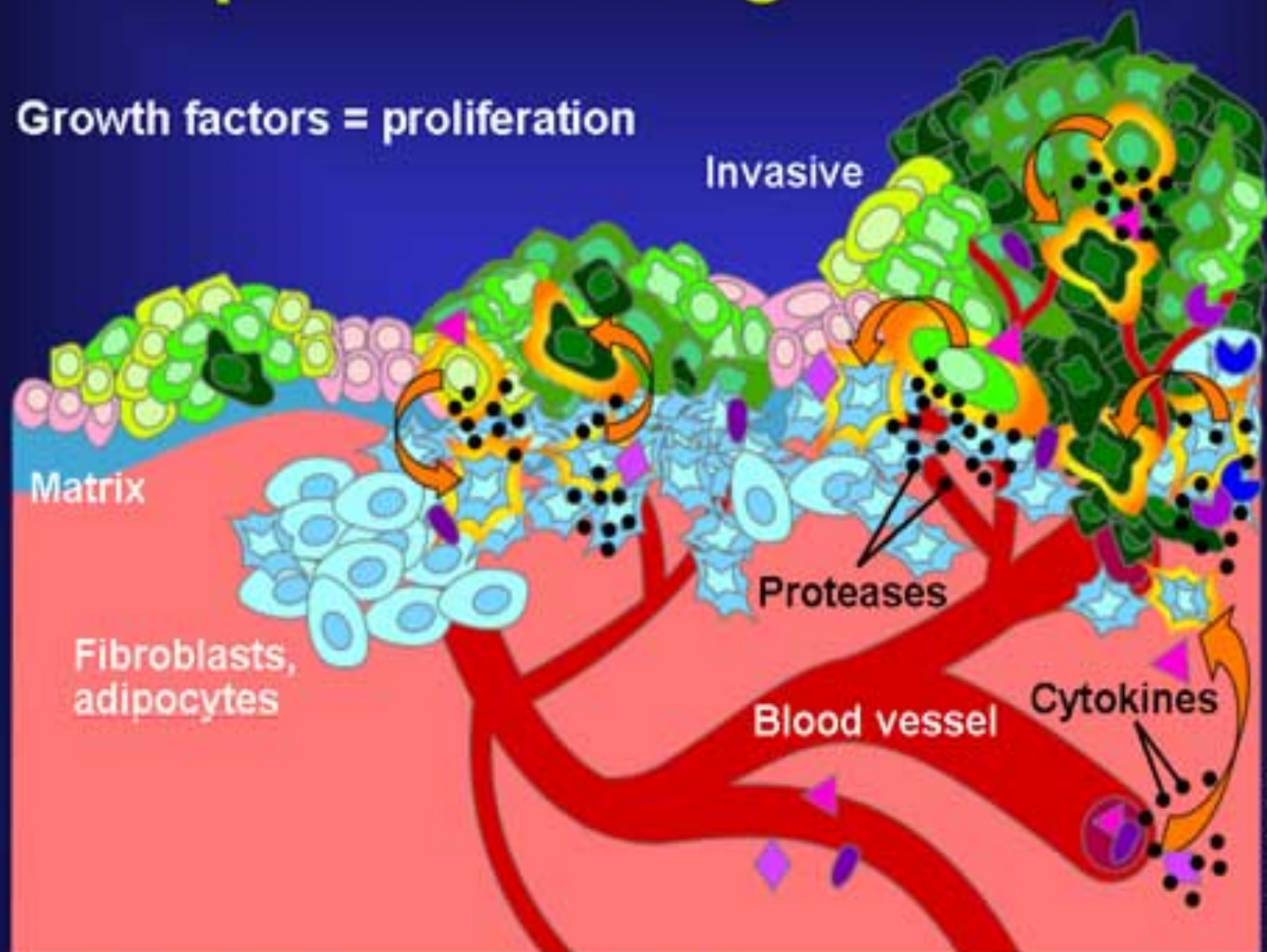
Mutations inactivate DNA repair genes

Proto-oncogenes mutate to oncogenes

More mutations, more genetic instability, metastatic disease

Cancer Tends to Corrupt Surrounding Environment

Growth factors = proliferation



Cytokines, proteases = migration & invasion

GENOME MARVELS

- Queen chromosome
- Burrow designs are genetic
- 45% of human genome is viral **junk**
- **Essential for chromosome shape/gene regulation**
- Replication 50bps/sec
- Replication 5 nts/sec
- Translation 10-20 AA/ sec