Basic Cancer Genetics

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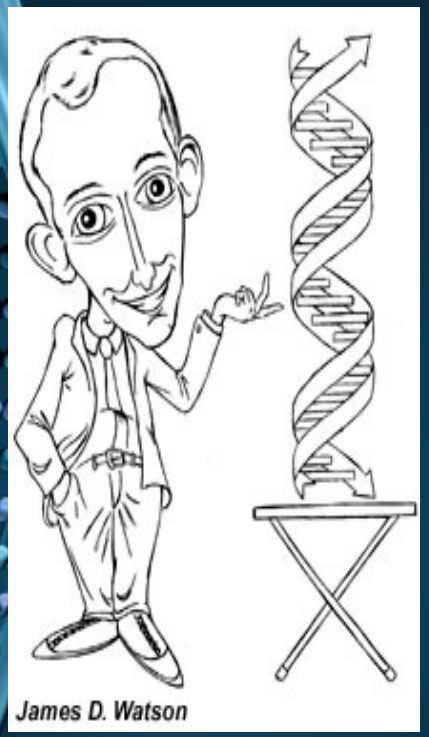
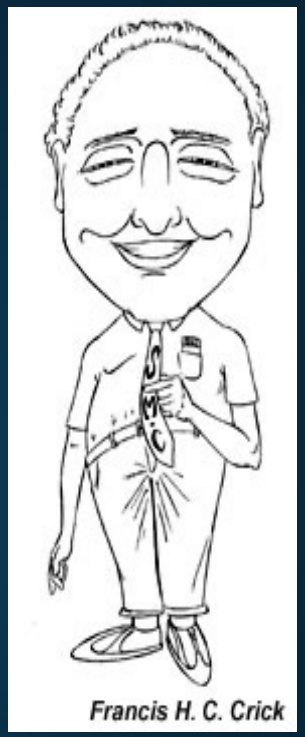
“Anything found to be true of *E.coli* must also be true of elephants.”

Jacques Monrod, pioneer molecular biologist, 1954

- The biological revolution of the 20th century reshaped all fields of biomedical study, including cancer research.
- This began with Watson and Crick’s discovery of the DNA double helix.
- After this the field of molecular biology grew by asking “how does the genetic makeup of a cell and organism determine it’s appearance and function?”

Watson and Crick

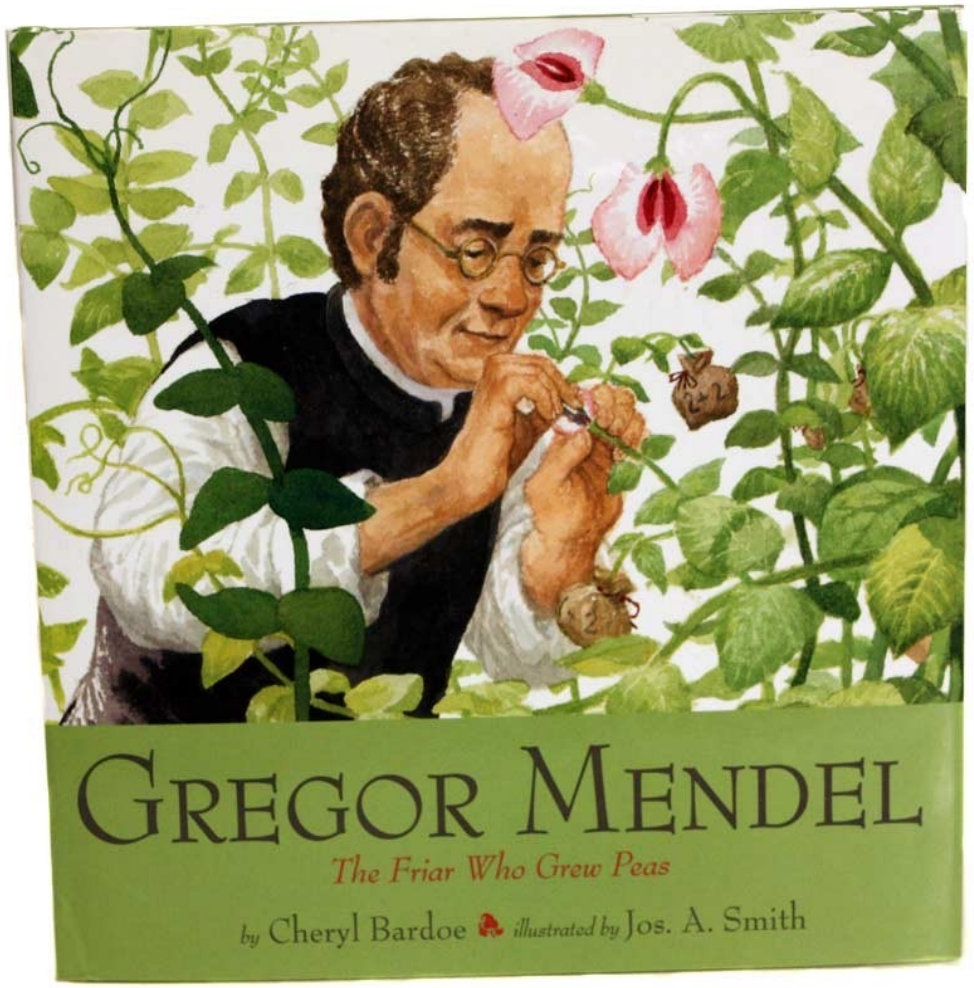


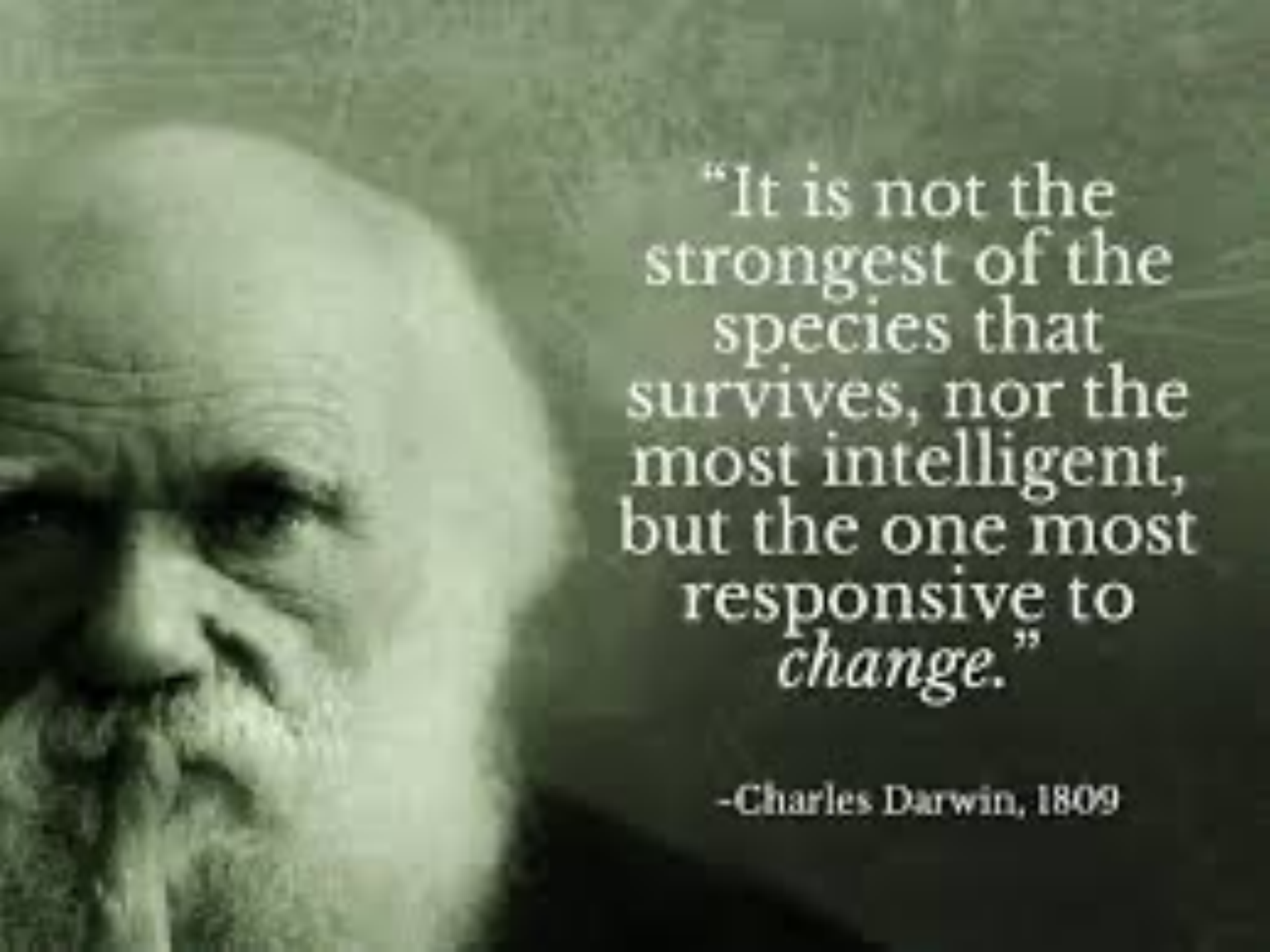


- Watson and Crick made a model of the DNA molecule and proved that genes determine heredity

- Without this molecular foundation, cancer research would not be possible.
- Gregory Mendel was the father of genetic research.
  - Though farmers had known for centuries that crossbreeding of animals and plants could favor certain desirable traits, Mendel's pea plant experiments conducted between 1856 and 1863 established many of the rules of heredity , now referred to as the laws of Mendelian inheritance.
  - To explain this phenomenon, Mendel coined the terms “recessive” and “dominant” in reference to certain traits.
  - He published his work in 1866, demonstrating the actions of invisible “factors”— now called genes —in providing for visible traits in predictable ways.
  - The profound significance of Mendel's work was not recognized until the turn of the 20th century.

Mendel's work was actually based upon the prior writings off Charles Darwin.




"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to *change*."
-Charles Darwin, 1809

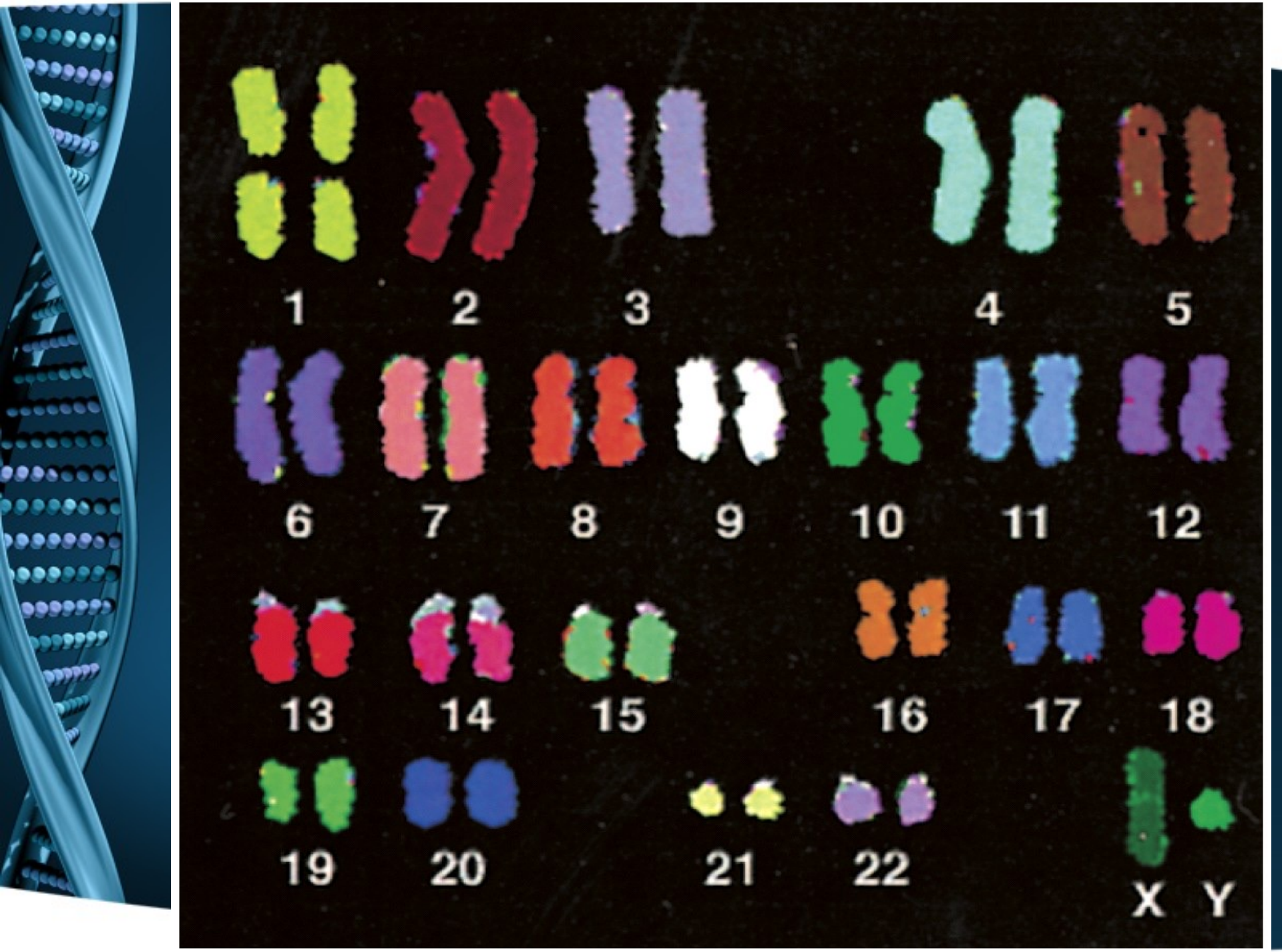
Mendel established the basic rules of genetics

- Mendel's work focused on the genetics of pea plants and his results and conclusions were soon forgotten, only to be discovered in the early 1900's by other researchers.
- Mendel's most fundamental insight came from realizing that genetic information is passed on to an offspring.
- He called this information discrete separate information packets, which latter became known as **genes.**

- Now we have studied the human genome, which states that we have 22,000 genes.
  - Barely more than the 19,000 of a fruit fly !!!
- Basically, each observable trait can be directly traced to a separate gene that is the blueprint.
- Mendel's research implied that the genetic information – genotype – could be divided into thousands of packets.
- Phenotypes came to be described as the outward appearance of physical and chemical traits.

Medelian genetics governs how both genes and chromosomes behave

- Individual genes are to small to be seen with a light microscope, thus most cancer mutations cannot be visualized.
- Normal chromosomes are euploid karyotype, which means they are normally in structured pairs.
- The next slide shows normal chromosome pairs or euploidity.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- Cancer cells often have altered chromosome structure, such as to many or to few chromosomes, or extra arms or fusions.
- Deviation from a normal euploid karyotype is called aneuploidy.
  - Single or with extra arms or off by themselves
  - This weird genetic configuration benefits the cancer cell and its agenda of runaway growth.
- Check out the breast cancer chromosomes in the next slide.

Figure 1.11c *The Biology of Cancer* (© Garland Science 2007)

- An abiding theme in cancer research is the notion that carcinogens - cancer causing agents – act through their ability to enter the tissues and to damage specific genes inside previously normal cells.
- IE – carcinogens are mutagenic and can mutate genes.
- Basic concept is that cancer cells have mutated genomes.
- What are some examples of carcinogens that could could mutagenesis?


Cadmium
Batteries
Butane
Lighter
Fluid
Stearic Acid
Candle Wax
Hexamine
Barbecue
Lighter
Toluene
Industrial
Solvent
Nicotine
Insecticide
Ammonia
Toilet Cleaner
Acetic Acid
Vinegar
Methane
Sewer Gas
Arsenic
Poison
Carbon
Monoxide
Methanol
Rocket Fuel
PAINT


SHAMPOO
HAIRSPRAY
EYE SHADOW
BLUSHER
LIPSTICK
FOUNDATION
NAIL VARNISH
DEODORANT
PERFUME
BODY LOTION
FAKE TAN

- Obviously we get the connection with smoking and lung cancer, although 10% of lung cancers are in people who never smoked.
- The truth is that the vast majority of cancers are NOT caused by specific mutagenic chemicals that enter the body.
- Most of the carcinogens do not act as agent as that are mutagenic, but they can act through other mechanisms to provoke cancer.
  - For example that certain viral infections, such a Hepatitis B, produce a very high incidence of liver cancer.

There are two basic types of genetic mutations:

- **Acquired mutations** are the most common cause of cancer.
  - These occur from damage to genes during a person's life.
  - They are not passed from parent to child.
  - Factors such as tobacco, ultraviolet (UV) radiation, viruses, and age cause these mutations.
  - Cancer that occurs because of acquired mutations is called sporadic cancer.

- **Germline mutations**, which are less common.
- Passed directly from a parent to a child.
  - In these situations, the mutation can be found in every cell of a person's body, including the reproductive sperm cells in a boy's body and egg cells in a girl's body.
  - Because the mutation affects reproductive cells, it passes from generation to generation.
  - Cancer caused by germline mutations is called inherited cancer, and it makes up about 5% to 10% of all cancers.
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Mutations and cancer

- Mutations happen often, and the human body is normally able to correct most of them.
- One mutation alone is unlikely to lead to cancer.
- Usually, it takes multiple mutations over a lifetime to cause cancer.
- This is why cancer occurs more often in older people who have had more opportunities for mutations to build up.
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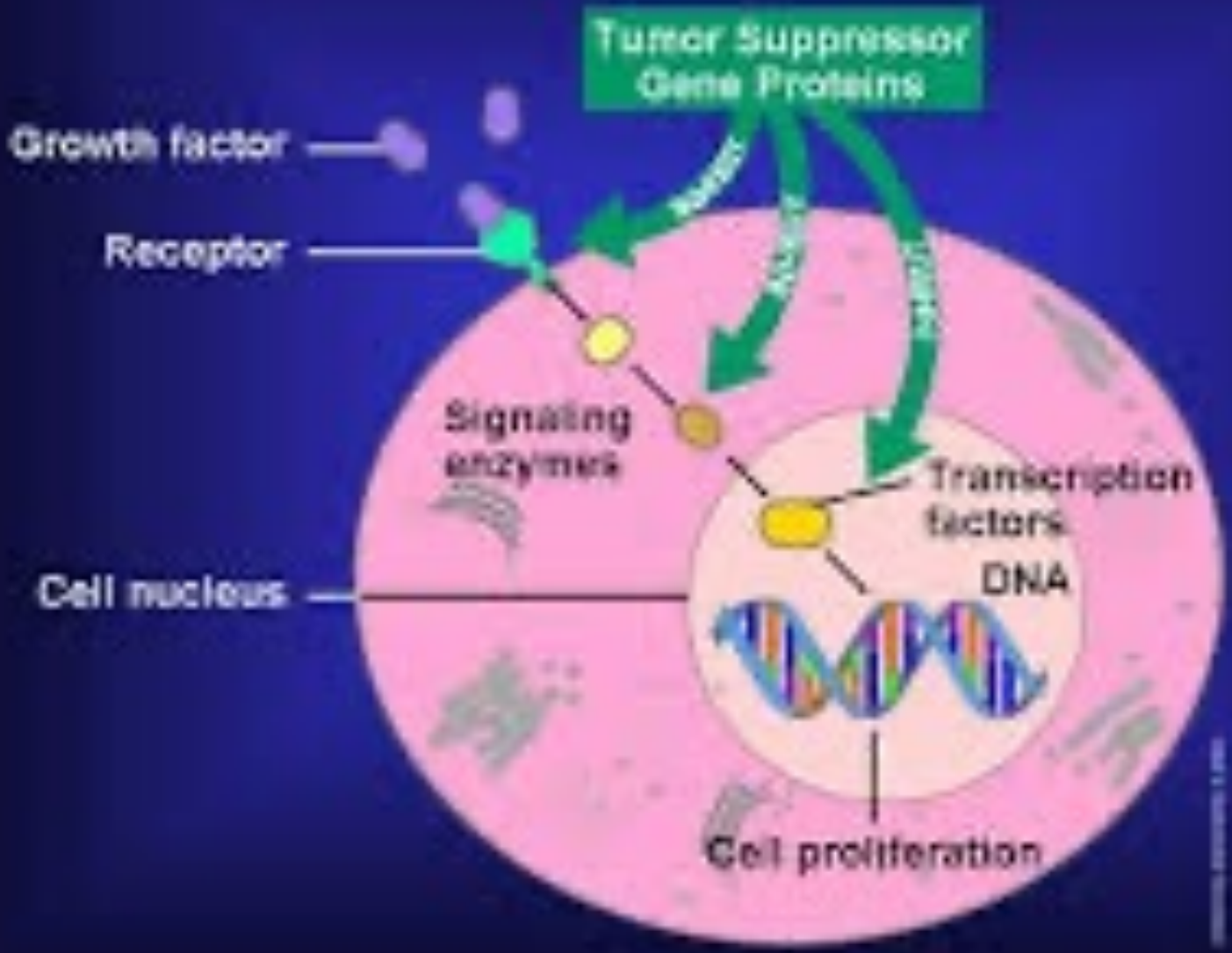
Types of genes linked to cancer

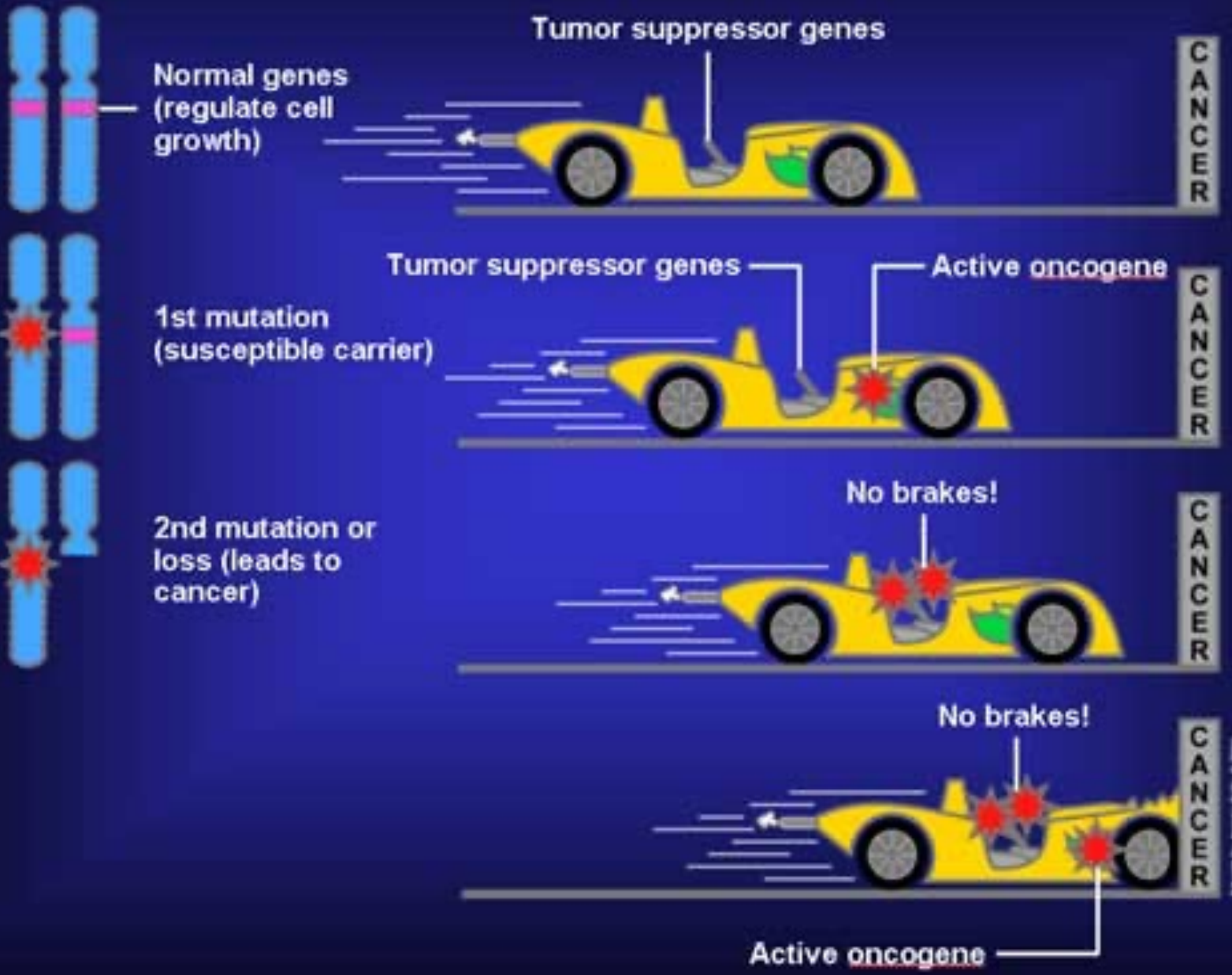
- Tumor suppressor genes are protective genes.
  - They limit cell growth by monitoring how quickly cells divide into new cells, repairing mismatched DNA, and controlling when a cell dies.
  - When a tumor suppressor gene is mutated, cells grow uncontrollably and may eventually form a mass called a tumor.

Tumor Suppressor Genes Act Like a Brake Pedal



- *BRCA1*, *BRCA2*, and *p53* are examples of tumor suppressor genes.
- *BRCA1* or *BRCA2* genes (which are germline mutations) increase a woman's risk of developing hereditary breast or ovarian cancers.
- The most commonly mutated gene in people who have cancer is *p53*.
- More than 50% of all cancers involve a missing or damaged *p53* gene
  - Most *p53* gene mutations are acquired mutations.
    - *P53* is often referred to as the "guardian of the genome."

Mutations in Tumor Suppressor Genes



Types of genes linked to cancer

- Oncogenes turn a healthy cell into a cancerous cell.
- Mutations in these genes are not inherited.
- Two common oncogenes are:
  - *HER2*, which is a specialized protein that controls cancer growth and spread, and it is found on some cancer cells, such as breast and ovarian cancer cells.
  - *T*he *ras* family of genes, which make proteins involved in cell communication pathways, cell growth, and cell death.
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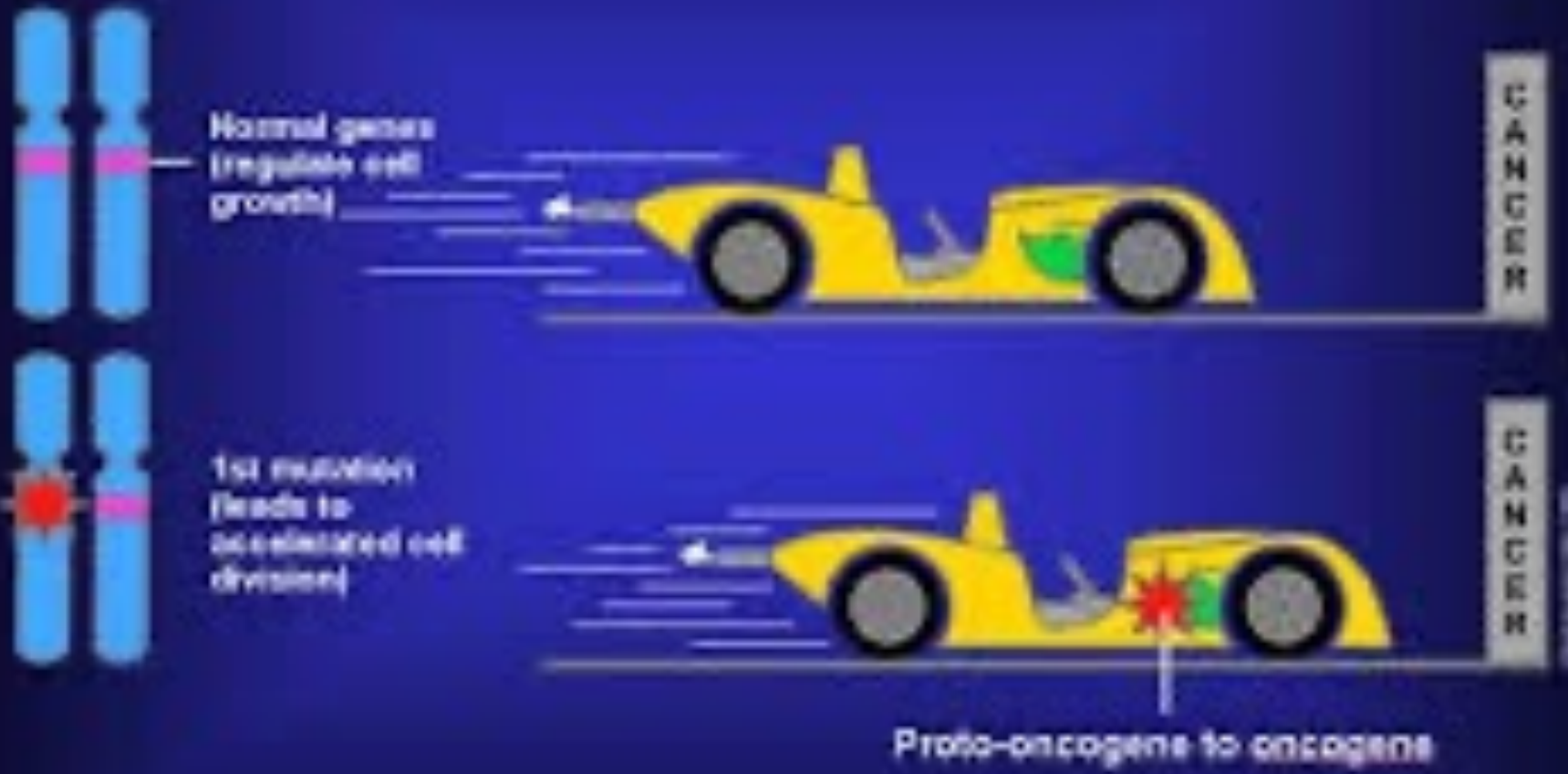
Abnormal Cell Growth: Oncogenes



Types of genes linked to cancer

- DNA repair genes fix mistakes made when DNA is copied.
  - If a person has an error in a DNA repair gene, these mistakes are not corrected.
  - Then they become mutations, which may eventually lead to cancer.
  - This is especially true if the mutation occurs in a tumor suppressor gene or oncogene.

- Despite all that is known about the different ways cancer genes work, many cancers cannot be linked to a specific gene.
- Cancer likely involves multiple gene mutations.
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Cancer Genetics Animation