Cancer – Definition:

Growth (enlargements) composed of clonal populations of cells that acquired the ability to expand in defiance of the checks and balances that would normally control the proliferation and survival of normal cells.

Malignant growths take control of whole organs, turning them into non-functional organs. Moreover, they consume a great deal of the body energy, often causing death. The concept of cancer as we see it today began with Nowell and Co.'s research in the 1960's.

Development of cancer is an evolutionary process. When a normal cell gains mutations that provide it with an evolutionary advantage, it proliferates faster and this population takes control of the cell medium. The ability to expand independently of cell cycle control is such an advantage, since it provides the cells with better fitness and adaptability to their surroundings. Usually a series of mutations and/or chromosomal aberrations is needed for the development of a cancerous cell.

Nowell and Co. used chromosome staining in order to inspect leukemia (CML) cells. Chromosome staining produces different banding (cytobands) patterns for each chromosome, and therefore reveals chromosomal aberrations. They found a reciprocal translocation between chromosome 9 and 22, producing the Philadelphia chromosome. This chromosome contains a fusion between a growth factor named Abl (which originates from chromosome 9) and a regulation site of a housekeeping gene, bcr (which originates from chromosome 22). The fusion site is very specific, as well as the fusion protein formed. At the present, there is a drug that specifically attacks this protein.
Oncogenes and tumor suppressors

**Oncogene**: the hyperactive version of a gene whose normal form (proto-oncogene) is involved in the regulation of cellular proliferation and/or survival. This alteration is a dominant genetic event.

Abl is an example for such gene. When existing normally in chromosome 9, Abl is a proto-oncogene, while Abl translocated to chromosome 22 becomes an oncogene.

**Tumor suppressor**: a gene whose normal function involves the inhibition of cell growth and/or survival. The loss of both copies of this gene results in the uninhibited growth of the cell. This is a recessive genetic event.

Retinoblastoma is an example for cancer that develops as a result of one mutation. The mutated gene is Rb, a gene located in chromosome 13 that regulates the cell cycle. A single normal copy of this gene is necessary for normal function, and yet, individuals that carry the mutation in a single allele are most likely to gain the mutation in the second allele and develop the disease.

In 1909 Rous and Co. used an extract from a tumor of a chicken who had Rous sarcoma (so it is called today) to infect a healthy chicken. Although the extract did not contain tumor cells, the healthy chicks developed Rous sarcoma consequently. This experiment produced the assumption that cancer is an infectious disease.

Today it is known that the reagent that causes the Rous sarcoma is a virus that possesses a gene, very similar to one of the chicken's genes that controls the cell cycle. The chicken's gene is therefore a proto-oncogene, and the virus' version is an oncogene.

The infection is of course indirect, while the cancer itself is not infectious.
Cell cycle

The cell cycle is the main process in the cell in which the pathogeny of cancer begins.

Normal cells are in G\textsubscript{0} phase most of the time, and leave this phase when there is a cell cycle stimulation. In contrast, malignant cells replicate all the time.

From G\textsubscript{0} a cell can turn to G\textsubscript{1}, a phase in which the cell increases in mass and produces essential materials for growing and replicating. When the cell has gathered enough materials for replication it enters S phase, in which DNA replication occurs. G\textsubscript{2} is again a phase of growing, and in M phase the cell reproduces into two daughter cells.

Between the phases there are checkpoints: the phase transit does not take place if specific conditions aren't present.

Example of two genes that control the cell cycle: p34, a proto oncogene and p53, a tumor suppressor.

p53 is responsible for finding DNA damage at the end of G\textsubscript{1}, if such damage exists. In this case, levels of p53 increase and repair genes are recruited. BRCA1 is such a gene. A mutation in BRCA1 causes breast cancer. Another function of p53 causes cell apoptosis by activating p21, a repressor of cdk2. When cdk2 is repressed, the cell does not transit from G\textsubscript{1} phase to S phase, causing apoptosis shortly after.

A mutation or deactivation of p53 causes cells to enter into S phase, even when DNA damage exists.

In S phase the DNA replicates, when each strand is used as a template for a new strand. The replication is carried out in a specific order. Housekeeping genes, for example, are synthesized early in the S phase because they should be activated at an early stage in the daughter cells. Replication begins in sites called ORI, origin of replication.
**CDKs** – Cyclin dependant Kinase. There are many cdks. They check if specific conditions exist, and if they do, they activate other proteins. For example, cdks that are responsible for transition from S to G₂ phase check whether the cell has grown enough and whether replication has occurred appropriately.

p34 (cdc2) is responsible for transition to M phase. p34 is a proto oncogene. Great amounts of p34 will cause transition to M phase when the cell is not ready for reproduction. A high level of p53 inhibits p34 through p21.

**M-phase**

During M phase, organelles called centrioles pull the cell to two poles while it divides.

The M phase is divided into different stages:

- **Prophase**: The centrioles begin to move to two poles and the chromatin starts condensing. The spindle begins to form.
- **Pro-metaphase**: Chromosomes begin to migrate towards the cell center.
- **Metaphase**: The chromosomes are aligned on the equatorial plate. The chromosomes assume a "classic" chromosome shape and can be easily distinguished from one another. This is the only time when we can clearly see the chromosomes since they are usually unfolded.
- **Anaphase** – the centrioles move farther apart and the spindle starts "stretching" between them, moving the sister chromatids in different directions.
- **Telophase** – Nuclei begin to form around the two sets of chromosomes in the emerging daughter cells.

The cell then reenters the resting phase, G₀.

In cancer data, an irregular activity in cell cycle control genes is usually associated with the cancer.
Bcl1 (Cyclin D1) is a proto-oncogene involved in G2/M transition. Its oncogene form is associated with mantle cell lymphoma. This oncogene is caused by a translocation that transfers the gene for D1 into juxtaposition to the enhancer region of the immunoglobulin heavy chain gene on chromosome 14. This results in enhanced cyclin D1 gene activation with subsequent cell cycle deregulation. Cyclin D1 amplification is also present in a range of solid tumors (lung, breast, bladder).

DNA copy number variation is a duplication / amplification of chromosome parts. An amplification of the Bcl1 gene is another case in which it becomes an oncogene. One of the ways of recognizing proto-oncogenes is identifying genes which are amplified in cancerous cells. For this purpose, 10-15% of cancerous cells are enough for such recognition.

**Resources:**

1. The Biology Project:  
   [http://www.biology.arizona.edu/DEFAULT.html](http://www.biology.arizona.edu/DEFAULT.html)
2. General glossary of cancer terms:  
3. Cancer related genes:  
4. Cell cycle game:  