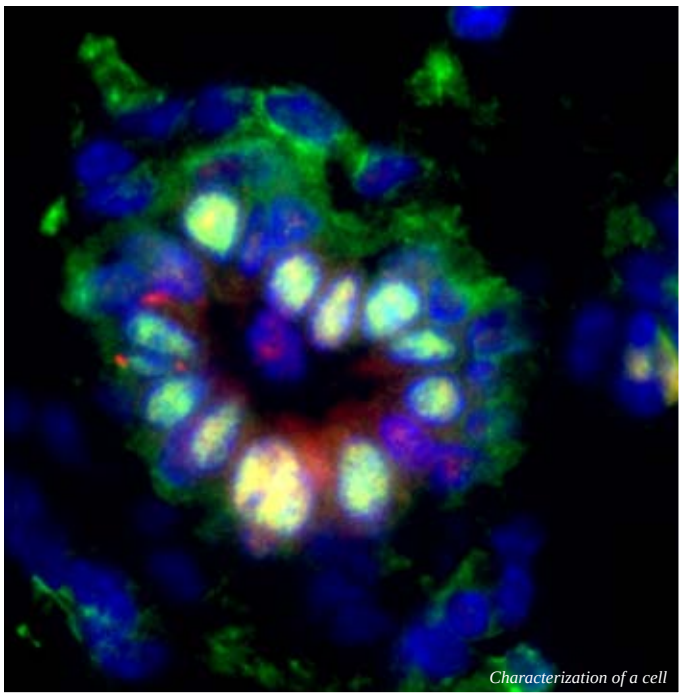
Of Mice and Women: Modeling Breast Cancer and the Environment

SCIENTIFIC GLOSSARY



Characterization of a cell

Developed by the Bay Area Breast Cancer
and the Environment Research Center
Community Outreach Translation Core

The Bay Area Breast Cancer & the Environment Research Center
at the University of California San Francisco
Community Outreach and Translation Core
www.bcerc.org

UCSF Comprehensive Cancer Center

This scientific glossary was developed to accompany the *Of Mice and Women: Modeling Breast Cancer and the Environment* video. Many of the glossary definitions are a combination of content gathered from various sources.

zero breast cancer

The Bay Area Breast Cancer and the Environment Research Center Community Outreach and Translation Core is led by Zero Breast Cancer, a non-profit organization in San Rafael, California, dedicated to finding the causes of breast cancer through community participation in the research process.

Cover design by Kim Huff, Kimber Communications

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INTRODUCTION

"Of Mice and Women: Modeling Breast Cancer and the Environment" video and scientific glossary was developed by the Bay Area Breast Cancer and the Environment Research Center (BABCERC) Community Outreach and Translation Core (COTC) in partnership with Dr. Mary Helen Barcellos-Hoff, PhD. BABCERC is one of four national centers that make up the national collective Breast Cancer and the Environment Research Center (BCERC).

In the *"Of Mice and Women"* video Mary Helen Barcellos-Hoff, PhD, Associate Professor in the Department of Radiation Oncology at New York University Langone School of Medicine, describes why and how different types of mouse models are used in experimental animal studies to study various aspects of breast cancer biology.

Dr. Mary Helen Barcellos-Hoff is co-investigator of the BABCERC animal study, *"Environmental Effects on the Molecular Architecture and Function of the Mammary Gland Across the Life Span"*. The goal of the BABCERC animal study is to determine the effects of low dose ionizing radiation on the mouse mammary gland at different stages of development: pre-puberty, puberty, pregnancy, and aging.

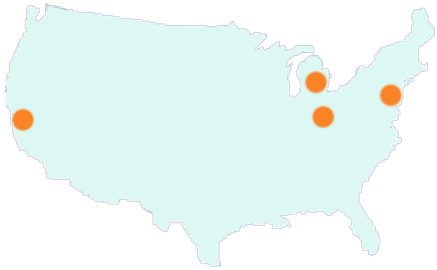
The goal of the video and scientific glossary is to serve as an educational tool for breast cancer advocates and community members to facilitate a greater understanding of why mice models are used in breast cancer prevention research.

The Breast Cancer and the Environment Research Centers
A Nationwide Collaboration

BCERC is a seven-year project jointly supported by the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI) to investigate mammary gland development and early onset of puberty.

The four national research centers that make up the collective are led by:

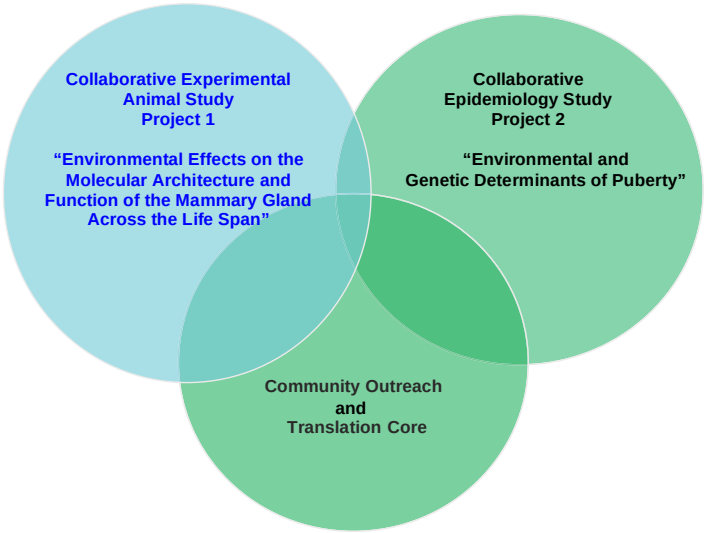
- Fox Chase Cancer Center, Philadelphia, PA
- Michigan State University, East Lansing, MI
- University of California, San Francisco, CA
- University of Cincinnati, Cincinnati, OH



http://www.bcerc.org/index.htm

The BCERC collective functions as a consortium of basic scientists, epidemiologists, and community advocates within and across centers created to investigate potential environmental factors that could increase breast cancer risk.

The Breast Cancer and the Environment Research Centers



The research at each center includes an experimental animal study, an epidemiology study, and a Community-based Outreach and Translation Core (COTC). The joint research being conducted by the centers is based on the hypothesis that environmental exposures during mammary gland development may impact the breast in ways that can alter the risk of breast cancer in later life.

One objective of having these two different research projects interact is to achieve a better understanding in both humans and mouse models of how to prevent breast cancer.

The animal study is examining mammary gland development and how mammary gland development in genetically engineered mice is affected by environmental exposures. The epidemiology study is examining environmental and genetic determinants of puberty by prospectively following three cohorts of young girls to determine how these determinants interact in mammary gland development.

The Community Outreach and Translation Core (COTC) works with the investigators from each of the projects to translate the scientific findings of the Centers into information for the public, policy makers, and clinical professionals to use to develop strategies to prevent breast cancer.

VIDEO TAKE HOME POINTS

The following questions and answers contain the main points of the video, *"Of Mice and Women: Modeling Breast Cancer and the Environment".*

Why do laboratory research scientists study breast cancer in mice?

Like humans, mice are mammals. Like humans, mice mammary glands originate from the milk bud. Like humans, mice mammary glands provide nourishment to their newborns in the form of milk. Like humans, mice can develop breast cancer. Unlike humans, mice have short life spans and go into puberty at about three weeks of age. A woman lives on average 70 to 80 years of age and goes into puberty between eight and ten years of age. A genetically engineered mouse can develop a breast cancer tumor at three months of age. A breast cancer tumor, in humans, can take decades to develop. Both the similarities and the dissimilarities offer invaluable advantages in studying breast cancer. Consequently, breast cancer research invariably deals with animals, in particular mice.

Breast cancer is a process that begins in the epithelial cells that form the tubes (ducts) that carry milk to the nipple or glands (lobules) that make milk. There are multiple genetic changes that need to occur in order for the breast cancer tumor to actually develop and, based on some epidemiological evidence, decades between initiation and progression.

What are the similarities described in the video between the mouse mammary gland and the human breast?

The similarities are:

- Capable of many cycles of growth and milk production
- Cells are organized in a ductal tree
- Development occurs after birth
- Development depends on signals from the ovaries
- Normal function is to make milk
- Organized system of cells
- Tissues are embedded in a fat pad

What is required to make a breast cancer tumor?

Epithelial cells. The epithelial cell is the seed that begins the process. The seed, however, needs to be placed in a hospitable environment and needs "outside" signals in order for the breast cancer to develop. Consequently, an epithelial cell can be initiated but planted in the wrong environment where it can sit dormant for the entire life of a woman. Cells do not become tumors without cooperation from the surrounding cells in the tissue. Just like "it takes a village to raise a child", we say that "it takes a tissue to make a tumor".

What are the similarities described in the video between mouse mammary and human breast cancer development?

The similarities are:

- Development depends on genetic susceptibility
- Development depends on signals from the ovaries
- Frequency of developing breast cancer is modified by life events such as pregnancy and radiation exposure
- Frequency of developing breast cancer increases with age
- Organization of mammary tissue, cells, and expression of particular proteins
- Presence or absence of hormone receptors

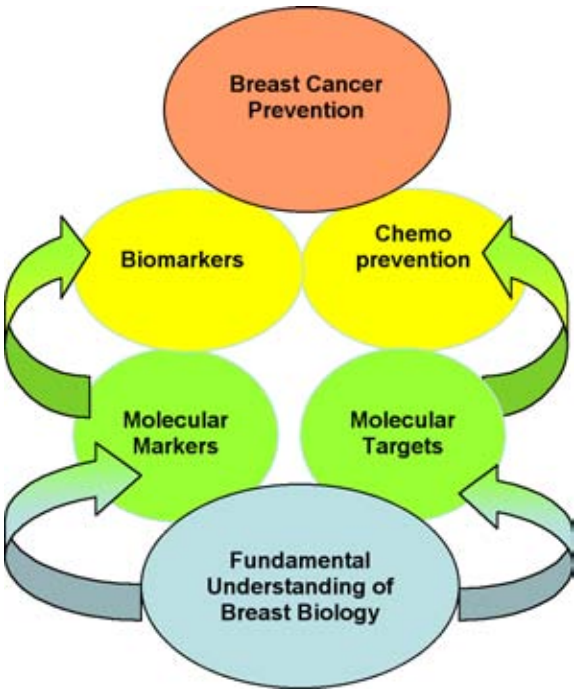
Mice can be "engineered" in multiple ways to take advantage of these similarities. For example, mice can be manipulated by inbreeding to have consistent genetic backgrounds, have their genes replaced with human gene versions, and/or have genes expressed as specific mutant genes. These types of manipulations allow scientists to test different hypotheses about what specifically gives rise to breast cancer.

What is the main take home point of the video?

The main take home point of the video is mice models provide enormous contributions to understanding the fundamental biology of breast development. In mice models, researchers can isolate, “turn on or turn off”, biological processes to understand individual environmental exposures that may or may not contribute to abnormal tissue growth.

The goal of using mice models is to increase our understanding of the fundamental aspects of breast biology. This understanding allows specific molecular markers to be developed to identify a woman’s risk of developing breast cancer, as well as specific molecular targets to be identified that might provide a strategy for chemoprevention.

By identifying specific molecular targets, non-invasive biomarkers can be identified that could be used in a woman’s visit to her doctor’s office to provide information about a woman’s risk of developing breast cancer. And for all this, women can thank mice.



What would help me to engage in a dialogue with researchers?

Researchers are passionate about their research and like to answer questions about their projects and area of expertise. Often a researcher is asked a question about another project not related to their area of expertise, and a missed opportunity occurs, that is, an opportunity to ask researchers more in-depth questions about their research and their next research steps.

The research process is like placing stones on an old-fashioned balance scale. When enough weight accumulates on one side of a question, the scale tips in favor of a particular hypothesis. The more weight there is on one side, the stronger the hypothesis is. The weight supports the next question in the research process, and the research process begins again.

Contradictions in research results will occur. They are an inevitable part of the scientific process. Researchers are constantly performing studies and reporting their results. And when many different scientists study each topic in so many different ways, it's natural that the results won't always be the same. What is key, and what drives health and policy recommendations, is the weight of evidence on a topic, that is, what all the results as a whole point to.

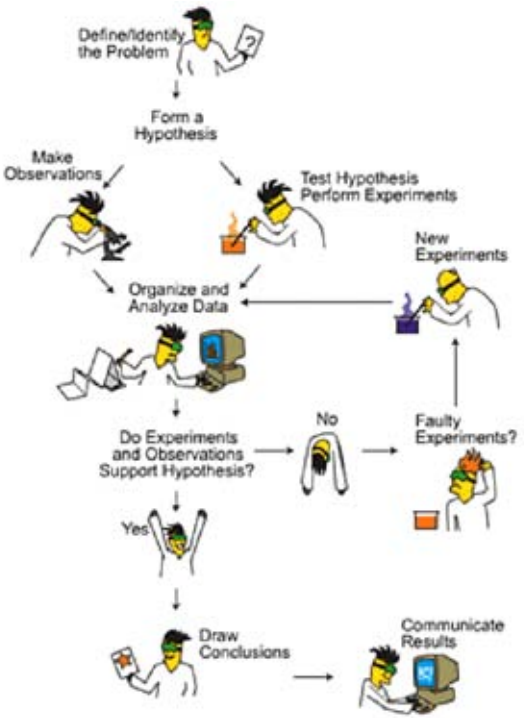
The most important part of a research study is the adherence to the scientific method.

What is the scientific method?

The scientific method is a process of experimentation that is used to answer questions and explore observations in the research process.

The scientific method can be synthesized as occurring in the following phases:

1. Observe, define, and identify the problem
2. Form a hypothesis
3. Make observations or test a hypothesis and perform experiments
4. Organize and analyze data
5. Ask the question: Do experiments and observations support the hypothesis?
    - If No; perform new experiments and/or observations, repeat Step 4
6. Draw conclusions
7. Communicate results



What is the difference between a hypothesis and a scientific theory?

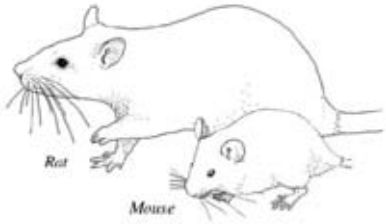
A hypothesis is an educated guess based on observation and/or experiments. A hypothesis can be supported or refuted through more observation and/or experimentation. A hypothesis can be disproven, but not proven to be true.

A scientific theory summarizes a hypothesis or group of hypotheses that have been supported with repeated testing. A scientific theory is valid as long as there is no evidence to dispute it. One definition of a theory is to say it's an accepted hypothesis.

Why do some animal laboratory research projects use mice and some use rats?

In general, it depends upon the research question and the preference or choice of the scientist.

Both mice and rats are mammals that belong to one of numerous species of small, omnivorous rodents. Mice actually are small rodents that resemble very small rats.



Experimental animal studies using rodents play a vital role in advancing our understanding of the molecular biology of mammary gland development and tumor genesis. These studies are important to help predict breast cancer risk when human studies are not possible.

GLOSSARY

Adduct (a-DUK-t)
In biology, an adduct is a compound that forms when a chemical binds to a biological molecule, such as DNA or protein. DNA adducts are altered forms of DNA that occur as a result of exposure to carcinogens.

Adipogenesis (AD-eh-POH-JEN-eh-sis)
Adipogenesis is a multi-step process of the formation of fat cells. The formation of the fat cell occurs by increasing the volume of lipid within its membrane.

Angiogenesis (AN-jee-oh-JEN-eh-sis)
Angiogenesis is the growth of new blood vessels. In order for tumors to grow larger, and for metastases to grow at distant sites, a cancer cell must somehow stimulate growth of new blood vessels.

Apoptosis
Apoptosis is a normal and active process of cell death characterized by cell shrinkage, DNA condensation and DNA degradation. Also referred to as programmed cell death.

Alveolar differentiation (al-VEE-uh-lurr)
The mammary gland contains thousands of milk-producing units called alveoli. Each alveoli consists of a single layer of epithelial cells arranged in a spheroid structure. The alveolar epithelial cells take up a variety of nutrients from the blood that with the hormones of pregnancy are converted into milk.

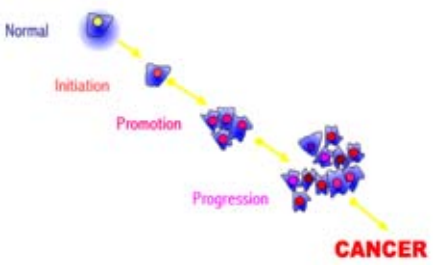
Bacteria (bak-TEER-ee-uh)
Bacteria are one celled microorganisms.

Biomarker
A substance sometimes found in blood, urine, tisses or other body fluids such as breast milk that is associated with an exposure or the presence of a disease. Biomarkers can be used to assess the likelihood of the presence of a cancer. A high level of a biomarker may mean that a certain type of cancer is in the body. Examples of cancer biomarkers are CA15-3 (breast cancer) and CEA (ovarian, lung, breast, pancreas and gastrointestinal cancers). These are also called tumor markers. Some biomarkers indicate exposure to environmental chemicals.

Breast Cancer

Breast cancer is a malignant tumor that forms from the unrestricted growth of abnormal breast cells. It is a process that begins in the epithelial cells that form the tree-like tubes (ducts) that carry milk to the nipple or glands (lobules) that make milk. There are multiple genetic changes that need to occur in order for the breast cancer tumor to actually develop, and, based on some epidemiological evidence, decades between the start and finish of tumor development.

There are three events that categorize the development of a breast cancer:



1. Initiation -
A single **event** where a change in the genetic sequence of DNA gives a cell a potential for becoming a breast cancer. The initiation is not sufficient to move to the next stage if the cell remains a single event.

2. Promotion -
A **multi-event** process where the changed cell reproduces many, many times. During this expansion of the cell population, there still isn't a cancer because these cells still only have one molecular change.

3. Progression -
A **multi-event** process where multiple genetic changes have occurred in a population of cells that promotes malignant behaviors, like invasion.

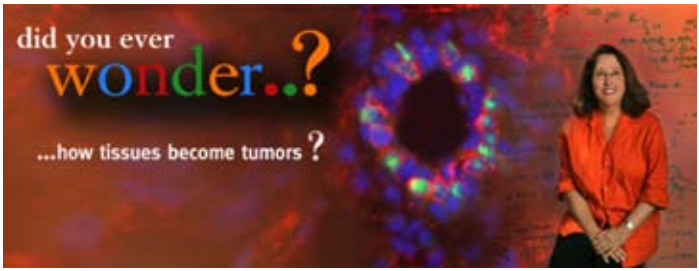
There are various types of human breast cancer, all of which differ significantly in their structure (morphology), their microscopic changes in tissues caused by disease (histopathology), their dependence on endogenous growth factors, their activation/inactivation of specific genes, and most of all their potential for metastasis.

The similarities between human breast and mouse mammary cancer development are:

- Development depends on genetic susceptibility
- Development depends on signals from the ovaries
- Frequency of developing breast cancer is modified by life events such as pregnancy and radiation exposure
- Frequency of developing breast cancer increases with age
- Organization of mammary tissue, cells and expression of particular proteins
- Presence or absence of hormone receptors

Cancer (KAN-ser)
Cancer is a term for any one of a group of diseases that occur when cells in the body become abnormal and divide without control, i.e., cells go from orderly cells to a mass of unorganized cells. Cancer cells can invade nearby tissues and can spread throughout the blood stream and lymphatic system to other parts of the body.

Cancer is not a disease of cells; it is a disease of tissues.



"It takes a tissue to make a tumor. Cells don't become tumors without cooperation from the surrounding cells in the tissue. Therefore, to understand cancer is to understand a process that occurs at the tissue level."

Mary Helen Barcellos-Hoff, PhD.

Carcinogen (kar-SIN-o-jin)
A carcinogen is any cancer-producing substance or organism, such as polycyclic aromatic hydrocarbons, or agents such as in certain types of irradiation.

Carcinogenesis (kar-SIN-o-jin-e-SIS)
Carcinogenesis is a multi-step tissue-level process that results in a malignant tumor. Several genetic alterations in the epithelial cells are necessary to begin the process, as well as the recruitment of normal cells to supply nutrients, and a hospitable environment for the abnormal cells to continue to grow.

Carcinoma (KAR-sih-NOH-muh)
A cancerous growth made up of epithelial cells from tissues that begin in the skin or in tissues that line or cover internal organs, such as the breast.

Cell (SEL)
The cell is the structural and functional unit of all living organisms, and is sometimes called the "building block of life." Some organisms, such as bacteria, are unicellular, consisting of a single cell. Other organisms, such as humans, are multicellular. Humans have an estimated 100 trillion normal cells which make up the tissues of the human body.

Cells discussed in the video are:

Endothelial (en-doe-THEE-lee-ul) **cells -**
Endothelial **cells** are found in the lining of blood vessels, lymph nodes and the heart.

Epithelial (ep-ih-THEE-lee-ul) **cells -**
Epithelial **cells** line the internal and external surfaces of the body. Epithelial cells are the target cells for breast cancer. They form the internal tree-like structure of the duct that is the basis for milk production.

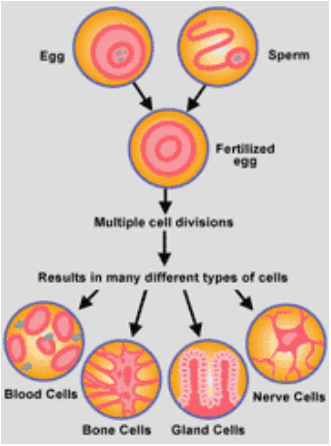
Progenitor (PRO-jen-eh-TUR) **cells -**
Progenitor **cells** are intermediate transitory cells made by a stem cell. A progenitor cell is an early descendant of a stem cell that can only differentiate but not self-renew and is thus more limited in the kind of cell it can become.

Stem cells -
Stem cells are undifferentiated **cells** that retain the ability to divide and differentiate into other cell types. Stem cells have the ability to act as a repair system for the body, replenishing other cells as long as the host organism is alive.

Stromal (STRO-mal) **cells -**
Stromal **cells** are the connective tissue cells of an organ. Stromal cells include fat cells, fibroblasts, connective tissue cells, and blood vessels.

Cell differentiation

Cell differentiation is the process by which a cell becomes specialized in order to perform a specific function, as in the case of a liver cell, a blood cell, or a neuron. There are more than 250 general types of cells in the human body. Differentiation, or maturity, of cells is the process that takes place inside an embryo that determines which genes are expressed and hence what type of cell will result.



[http://genetics.gsk.com/chromosomes.htm]

Chemoprevention (KEE-mo-pre-VEN-shun)

Chemoprevention is the use of drugs, dietary substances, or other agents to reduce or eliminate the development of a tumor.

Chromosome (KRO-mo-some)

Chromosomes are the small bodies in the cell nucleus that carry the chemical “instructions” for reproduction of the cell. They consist of strands of DNA wrapped in a double helix around a core of proteins. Each species of plant or animal has a characteristic number of chromosomes. Human beings have forty-six chromosomes.

Cytokines

Cytokines are a group of non-antibody protein signalling compounds that, like hormones and neurotransmitters, are used extensively for intercellular communication.

> **TGF-beta** is a multifunctional cytokine that is produced in the mammary gland to control growth and differentiation.

DNA (**d**eoxyribo**n**ucleic **a**cid)

DNA is the polymeric macromolecule that is present inside every cell in humans that carries the genetic instructions for making living organisms. DNA is passed from one generation to the next.

Every normal cell in a person's body has the same DNA. Most DNA is located in the cell nucleus. A small amount of DNA can also be found in the mitochondria.

DNA molecules look like a long twisted ladder called the double helix. The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). DNA bases pair up with each other, A with T and C with G, to form units called base pairs.

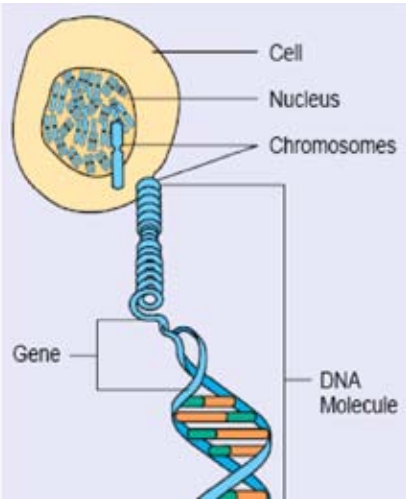


Figure 1

Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people.

An important property of DNA is that it can replicate, or make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide because each new cell needs to have an exact copy of the DNA present in the old cell.

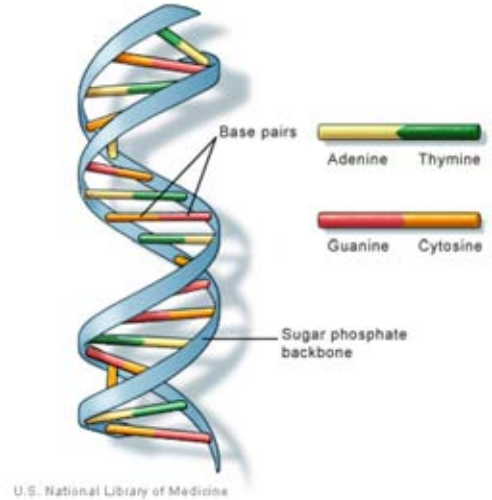
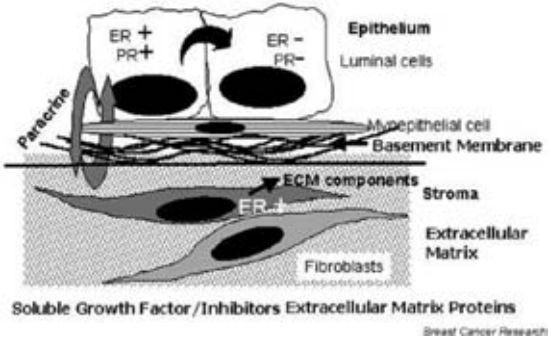


Figure 2

Ductal (DUK-tal) **Tree**
The ductal tree is a tree-like structure formed by epithelial cells to make the milk glands in a breast.

ECM (**e**xtra**c**ellular **m**atrix)
The extracellular matrix is a complex network of watery proteins secreted by cells to form an important mediator of cell behavior. The ECM is the medium through which cells receive materials (e.g., nutrients, hormones) from elsewhere in the body and via which they communicate with other cells. The ECM is situated in between cells of particular types of tissue and is the environment in which cells migrate during tissue development. It contains constituents that bind cells together to maintain tissue integrity.

Cells attach to the ECM via receptors and the intracellular cytoskeleton. The ECM transduces bidirectional signals between the extracellular and intracellular compartments of a cell. ECM adhesion is crucial for control of cell behavior. A specialized ECM called the basement membrane is the barrier that must be breached for breast cancer to become invasive.



The main components of the extracellular matrix are proteoglycans (e.g. aggrecan, perlecan and syndecan) and fibrous proteins (e.g. collagen, elastin, fibronectin and laminin). The extracellular matrix, next to being a scaffold to support cells in a particular tissue, also plays a role in the regulation of processes such as proliferation, differentiation, adhesion and locomotion of these cells.

End buds
End buds are present in the developing mammary gland at the end of the ducts in the breast. From birth to puberty, the mammary gland remains rudimentary. At puberty, ovarian hormones stimulate rapid growth of the end buds.

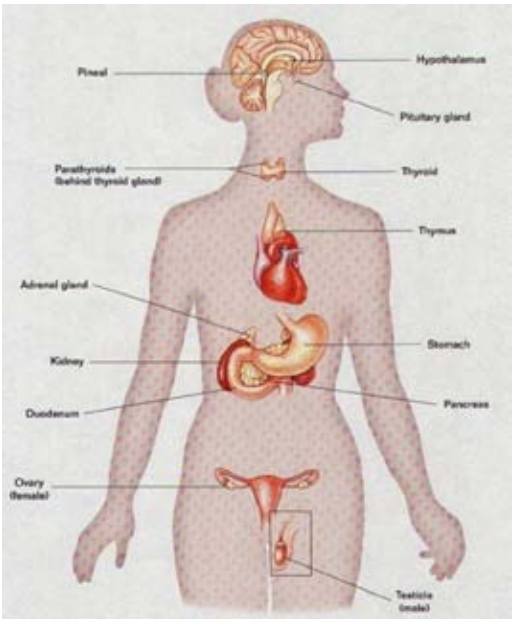
Endocrine (EN-doh-krin) **Disruptors**

An endocrine disruptor is a diverse group of synthetic chemicals that when absorbed into the body either mimics or blocks hormones and disrupts the body's normal functions. This disruption can happen through altering normal hormone levels, halting or stimulating the production of hormones, or changing the way hormones travel through the body, thus affecting the functions that these hormones control. Many chemicals, particularly pesticides and plasticizers, are suspected endocrine disruptors based on limited animal studies. Chemicals that are known human endocrine disruptors include DES (diethylstilbesterol), dioxin, PCBs, and DDT.

The Environmental Protection Agency (EPA) defines endocrine disruptors as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for the maintenance or homeostasis, reproduction, development and or behavior".

Endocrine System (EN-doh-krin SIS-tum)

The endocrine system, also referred to as the hormone system, is a complex system of glands and cells that secrete chemical messages called hormones. The hormones are released by the glands directly into the blood and travel throughout the body until reaching cells that contain matching receptors-proteins within the target cell or located on the surface of the target cell. The hormones, or keys, need to find compatible receptors, or locks, to work properly. Although hormones reach all parts of the body, only target cells with compatible receptors are equipped to respond.



www.eps.gov/scipoly/oscpendo/images/endocrine.jpg

The endocrine system regulates all biological processes from the conception of an organism through adulthood and into old age regulating many functions including metabolism, growth, sexual development, sleep, hunger, and the way the body uses food.

Endogenous
Endogenous describes substances that develop or originate from within an organism, tissue, or cell.

Epithelium (EP-ih-THEE-lee-um)
A thin layer of tissue composed of one or more layers of cells that form the internal and external surfaces of the body. The epithelium forms a covering around the breast.

Epigenetics
Epigenetics, literally “outside” genetic, is the study of reversible heritable changes in gene function or other phenotypes that occur without altering DNA sequence.

Estrogen (ES-truh-jin)
Estrogens are a group of female steroid sex hormones. Estrogen is secreted by the ovaries and is responsible for the development and maintenance of female sex characteristics. Estrogen is largely responsible for stimulating the uterine lining to thicken during the first half of the menstrual cycle in preparation for ovulation and possible pregnancy.

Estrogen is used pharmaceutically as a type of birth control and to treat symptoms of menopause, menstrual disorders, osteoporosis, and other conditions. Estrogen is included in many commercial products.

ER - Estrogen Receptor (ES-truh-jin rih-SEP-ter)
ER is a protein found inside the cells of mammary tissue, female reproductive tissue, and some cancer cells. Estrogen will bind to an ER and stimulate proliferation during normal mammary gland development.

> **ER positive +** (Estrogen receptor positive) -
> Describes breast cells that have a protein to which estrogen will bind. Cancer cells that are ER+ need estrogen to grow, and may stop growing when treated with hormones that block estrogen from binding.
>
> **ER negative -** (Estrogen receptor negative) -
> Describes breast cells that do not have a protein to which the hormone estrogen will bind. Cancer cells that are ER- do not need estrogen to grow, and usually do not stop growing when treated with hormones that block estrogen from binding.

Exogenous (EX-o-JIN-us)
Exogenous describes substances that develop or originate outside an organism, tissue, or cell. An exogenous hormone would be a hormone administered to an organism rather than synthesized within it.

Extracellular
Outside the cell.

GEM (**G**enetically **E**ngineered **M**ice)
A GEM is a genetically manipulated mouse that is generated by gene-targeting (knockout) to study biological function. Researchers create the animal by injecting a selected human gene into an egg from a female mouse right after conception. They are sometimes referred to as “designer mice”.

MMTV-TGF-beta -
A designer **mouse** used to study the function and activity of **TGF-beta. TGF-beta** is a multifunctional cytokine that is produced in the mammary gland to control growth and differentiation.

Transgenic mouse -
A transgenic **mouse** is a mouse whose genome has been altered by the injection of new sequences of DNA into a fertilized embryo at the pro-nuclear stage. The DNA is generally cloned, and may be experimentally altered. It will become incorporated into the genome of the embryo. That embryo is implanted into a foster mother, who gives birth to an animal carrying the new gene. The genetic changes are heritable and are thus passed onto subsequent generations.

Genes

Genes are pieces of DNA that form the hereditary units passed from parent to offspring. Genes are the DNA templates that code for proteins. A gene occupies a specific position on a chromosome. Genetic alterations or mutations that are either environmentally induced and/or inherited are associated with breast cancer risk. The 2 main types of genes that are now recognized as playing a role in cancer are *oncogenes* and *tumor suppressor genes*.

A few of the genes mentioned in the video are:

BRCA 1 gene –

The BRCA1 (breast cancer 1, early onset) **gene** belongs to a class of genes known as tumor suppressor genes. BRCA1 is a gene on chromosome 17 that normally helps to suppress cells from growing and dividing too rapidly or in an uncontrolled way. The BRCA1 gene inhibits the growth of cells that line the milk ducts in the breast. A person who inherits an altered version of the BRCA1 gene has a higher risk of getting breast cancer.

BRCA 2 gene –

The BRCA2 (breast cancer 2, early onset) **gene** belongs to a class of genes known as tumor suppressor genes. The BRCA2 is a gene on chromosome 13 that normally helps to suppress cells from growing and dividing too rapidly or in an uncontrolled way. A person who inherits an altered version of the BRCA2 gene has a higher risk of getting breast cancer.

GATA 3 –

The GATA 3 **gene** is a member of the GATA multi-gene family. These genes play essential roles in activating target genes of specific cell fates and also in repressing target genes of alternate cell fates. Cancer researchers know that breast cancers with high GATA-3 expression have a good prognosis while cancers with low GATA-3 expression tend to be poorly differentiated, with a poor prognosis.

P53 gene –

The P53 (“p” for protein and “53” for its weight) **gene** belongs to a class of genes known as tumor suppressor genes. This protein plays a major role in cell growth. The job of P53 is to prevent (suppress) cells from growing, i.e., ensure that cells respond to DNA damage by dying and thus inhibit the growth of tumors. These functions have lead P53 to be called the guardian of the genome. When the P53 gene has been damaged or altered, P53 loses its ability to block cell growth.

Mutant gene –
A mutant **gene** is a gene that has changed so that the normal transmission and expression of a trait is affected.

Oncogene –
An oncogene is a **gene** alteration (mutation) that promotes uncontrolled cancer growth. Gene alterations can be inherited, occur randomly, or can be caused by an environmental exposure to a carcinogen. They are mutations of certain normal genes of the cell called *proto-oncogenes*.

Proto-oncogenes –
Proto-oncogenes are the **genes** that normally control how often a cell divides and the degree to which it differentiates (or specializes). When a proto-oncogene mutates into an oncogene, it becomes permanently "turned on" or activated when it is not supposed to be. When this occurs, the cell divides too quickly, which can lead to cancer.

Reporter genes –
A reporter (designer) **gene** is a gene in which researchers link a foreign gene to a gene of interest. In this way, the foreign gene 'reports' on the activity of the native gene. For example, green fluorescent protein from jellyfish is used to make the activity or expression of an inherent gene visible using microscopy.

Tumor suppressor genes *(anti-oncogene)* **–**
Tumor suppressor **genes** are normal genes that suppress the development of cancers in living cells, slow down cell division, repair DNA mistakes, and tell cells when to die (a process known as *apoptosis* or programmed cell death). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer. About 30 tumor suppressor genes have been identified, including p53, BRCA1, BRCA2, APC, and RB1.

> An important difference between tumor suppressor **genes** and oncogenes is that oncogenes result from the *activation* (turning on) of proto-oncogenes, but tumor suppressor genes cause cancer when they are *inactivated* (turned off). Another major difference is that while the overwhelming majority of oncogenes develop from mutations in normal genes, abnormalities of tumor suppressor genes can be inherited as well as acquired.

Gene Expression
Gene expression is the conversion of DNA to RNA to protein. Not all genes are active in all cells. Gene expression is evidence of activation of a gene. When a gene is expressed, the DNA sequence of that gene is copied into the RNA and the information is translated into a protein that performs a specific function.

Genetics (jeh-NEH-tiks)
Genetics is the branch of biology concerned with heredity. It is a study of the manner in which genes operate and are transmitted from parents to offspring.

Genetic (jeh-NEH-tik) **markers**
Genetic markers are a phenotypically recognizable genetic trait that can be used to identify a genetic locus, a linkage group, or a recombination event.

Genome (jeh-NOH-m)
Genome is the general term for all the genes carried by a cell. Humans have two genomes; a chromosonal genome and a mitochondrial genome.

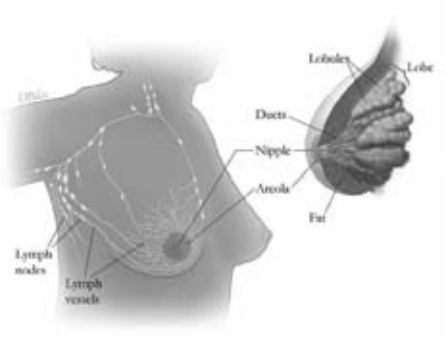
Genomics (jeh-NOH-miks)
Genomics is the comprehensive study of whole sets of genes and their interactions.

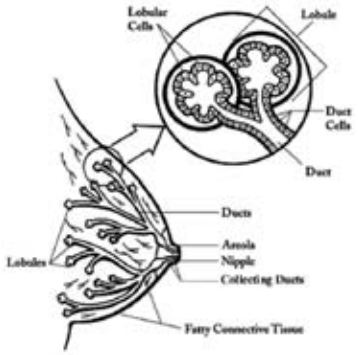
Herceptin® (trastuzumab (*tras-to-zoo-mab*)
Herceptin® is the drug name for trastuzumab. Herceptin® has been shown to be an effective targeted therapy designed specifically to address the kinds of tumors that are over expressed with the protein called EGFR (epidermal growth factor receptor). It is a type of monoclonal antibody, not a chemotherapy. Monoclonal antibodies are treatments that target particular proteins within the body.

Hormone (HOR-mone)
A substance secreted by specialized cells that affects the metabolism or behavior of other cells possessing functional receptors for the hormone. Hormones may be hydrophilic, like insulin, in which case the receptors are on the cell surface, or lipophilic, like steroids, where the receptor can be intracellular.

Human Mammary Gland

The human mammary gland is a ductal epithelial glandular organ that contains two mature epithelial cell types: the luminal epithelial cells, which line the ductal lumen and secrete milk proteins, and the myoepithelial cells, which line the basal surface of the luminal cells.





www.cancer.gov/templates/

The mammary gland is located on the chest and is made up of connective tissue, fat, and breast tissue that contains the glands that can make milk, also called the **breast.** The mammary gland is the milk-producing gland of females. Milk production is hormonally controlled.

Hyperplasia (hye-per-PLAY-zha)

Hyperplasia is an increase in the number of normal cells in a tissue or organ, excluding tumor formation.

Inflammation (IN-fluh-MAY-shun)

Inflammation is a localized tissue response to injury, irritation and/or infection involving a phagocytic cell and other white blood cells that mediate removal of microorganisms, and healing of the damaged tissue. The key observable reaction is redness, warmth, swelling, pain, and/or a feeling of heat. This is a protective reaction to injury, disease, or irritation of the tissues.

Cellular inflammation involves the movement/influx of white blood cells from blood vessels into inflamed tissue. The white blood cells, or leukocytes, take on an important role. The white blood cells filter out from the capillaries into tissue, and act as phagocytes, picking up bacteria and cellular debris. They may also aid by walling off an infection and preventing its spread.

Inflammation has been demonstrated by many breast cancer studies to correlate with increased aggressive tumor behavior, including angiogenesis and metastasis.

Phagocyte –
A phagocyte is a cell that ingests and destroys foreign matter such as microorganisms or debris via a process known as phagocytosis.

Phagocytes are extremely useful as an initial immune system response to tissue damage.

Intracellular
Inside the cell.

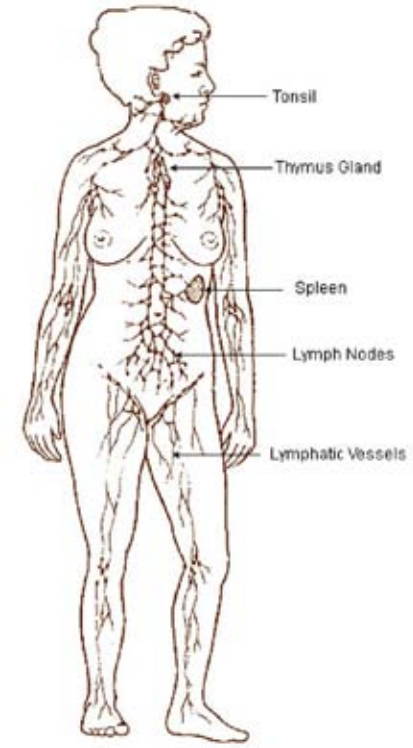
In vitro
Literally means "in glass". In science, *in vitro* describes the biological processes that are made to occur outside the living body in a laboratory apparatus, such as a cell culture dish or test tube.

In vivo
Literally means "in life". In science, *in vivo* describes the biological processes as they are observed to occur in the natural environment, i.e., within a living organism. Animal testing and clinical trials are forms of *in vivo* research.

Ionizing radiation (I-uh-NIZE-ing ray-dee-AY-shun)
Ionizing radiation is high-energy radiation capable of producing ionization in substances through which it passes. When a person is exposed to radiation, the incoming photons interact with macromolecules like DNA or protein, or with the water molecules that make up most tissue. (The human body is approximately 80% water.) The interaction with water molecules creates electrically charged atoms or "ions" that are also highly energized and harmful to living cells. Ionizing radiation is used for both diagnostic and therapeutic medical applications, which mean that people are exposed over a very large dose range. While cancer therapy may deliver cumulative doses of up to 80 Gy (Gy is a unit of dose), much of radiation biology has been conducted in the range of 1-10 Gy. Epidemiological studies of cancer incidence have shown significant risk for some cancers at doses above 0.5 Gy. Understanding the carcinogenic effect of radiation is one of the interests of Dr. Barcellos-Hoff.

Latency
Latency is the time between the first exposure to a cancer-causing agent and clinical diagnosis of the disease.

Lymphatic System (lim-FAT-ik SIS-tem)
The lymphatic system is a network of exceedingly thin-walled capillaries in almost all the organs and tissues except the brain and bones, that produce, store, and circulate lymph. Lymph is a colorless liquid that contains white blood cells.



The breast consists of lobes, lobules, and bulbs that are connected by ducts. The breast also contains blood and lymph vessels. Along lymph vessels are small bean-shaped glandular nodules called lymph nodes. Clusters of lymph nodes are found under the arm, above the collarbone, in the chest, and in other parts of the body.

http://training.seer.cancer.gov/

Lymphoma (lim-FO-ma)
Lymphoma, or lymphatic cancer, is a cancer that begins in cells of the lymphatic system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma. The other category is non-Hodgkin's lymphoma.

Matrix
A matrix is a term to describe the surrounding substance or environment.

Menarche
Menarche is the time of the first menstrual period in females, usually occurring during puberty.

Metastasis (meh-TAS-tuh-sis)
Metastasis is a metastatic tumor formed by cells that have spread from one part of the body to another. The metastatic tumor contains cells that are like those in the original tumor. The plural form of metastasis is metastases (meh-TAS-tuh-SEEZ).

Metastasize (meh-TAS-ta-size)
Metastasize is a term that usually refers to the spread of malignant tumors from one part of the body to another. When cancer cells metastasize and form secondary tumors, the cells in the metastatic tumor are like those in the original (primary) tumor.

Microenvironment
A microenvironment describes the local and systemic architecture surrounding a cancer cell. A microenvironment includes other cells, growth factors, enzymes, and parts of the blood and lymphatic systems.

Niche -
A niche is a specialized **microenvironment**. It is the local environment, the neighborhood within, that provides services to insure survival and protection. An example would be stem cells residing in the liver. The stem cells are the niche, the neighborhood within.

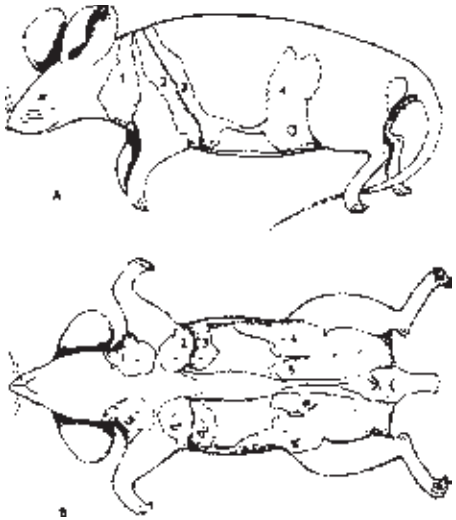
Signaling environment -
The signaling environment is a **microenvironment** in which tumors reside. It appears to strongly influence the initiation and maintenance of a malignancy. Studies of normal body cells as well as stem cells have established the essential role of signals emanating from surrounding tissue and the supportive extracellular matrix in sustaining a given cell's identity and in directing it's behavior.

Molecular (muh-LEH-kyuh-ler) **marker**
A molecular marker (biomarker) in biology can be a substance native to the organism whose detection indicates a particular disease state. For example, the presence of an antibody may indicate an infection.

A molecular marker (genetic marker) in genetics is a fragment of DNA sequence that is associated to a part of the genome.

Mouse mammary (MA-muh-ree) **gland**

The mouse mammary gland is a complex tissue, which is continually undergoing changes in structure and function. Like the human, the mouse mammary gland originates from the milk bud. The mouse has five to six pairs of mammary glands that extend from the neck to the groin. At puberty, the mammary ducts extend into the mammary fat pad in an orderly manner.



Structure of the Normal Mouse Mammary Gland

KEY:
Diagram A
1. Mammary Gland-Left Cervical
2. Mammary Gland-Left Thoracic
3. Mammary Gland-Left Thoracic
4. Mammary Gland-Left Thoracic

Diagram B
1. Mammary Gland-Left Cervical
2. Mammary Gland-Left Thoracic
3. Mammary Gland-Left Thoracic
4. Mammary Gland-Left Abdominal
5. Mammary Gland-Left Inguinal
6. Mammary Gland-Left Cervical
7. Mammary Gland-Left Thoracic
8. Mammary Gland-Right

http://ccm.ucdavis.edu/bcancercd/22/mouse_figure.html
http://www.niaid.nih.gov/Dir/services/animalcare/MouseNecropsy/mammary.gif

Mouse mammary glands have cell, functional and tumor characteristics similar to human mammary glands. Mouse mammary glands can host human cells and genes for analysis.

The following are similarities between a human breast and a mouse mammary gland.

- Capable of many cycles of growth and milk production
- Cells are organized in a ductal tree
- Development occurs after birth
- Development depends on signals from the ovaries
- Normal function is to make milk
- Organized system of cells
- Tissues are embedded in a fat pad

Morphogenesis (mor-FOE-oh-jen-eh-sus)
Morphogenesis is the organization of cells into a functional unit to allow for differentiation and growth of tissues and organs during development. Morphogenesis is concerned with the shapes of tissues, organs and entire organisms, as well as the positions of the various specialized cell types.

Neoplasia (NEE-o-PLAY-zha)
Neoplasia literally means “new growth”. Neoplasia in cancer research refers to abnormal and uncontrolled growth of new cells, and thus has the same meaning as tumor. The neoplasia may be benign or malignant.

Phenome
Phenome refers to all the biochemical, physiological, and morphological characteristics of an organism.

Phenotype
Phenotype refers to the observable characteristics, at the physical, morphologic, or biochemical level, of an individual, as determined by the genotype and environment.

Polymorphism
Polymorphism in biology, means having a common variation or mutation in DNA sequence. An example is a single nucleotide polymorphism or SNP.

www.bioteach.ubc.ca/Bioinformatics/DeCODE/dna.gif

Protein (PRO-teen)
Proteins are large complex molecules made up of amino acids arranged in a linear form and joined together by a peptide bond. Proteins are everywhere in the body and are necessary for the structure, function, and regulation of cells, tissues, and organs.

A few proteins mentioned in the video are:

Antibody -
An antibody is a **protein** produced by the body's immune system that recognizes and helps fight infections and other foreign substances in the body.

A protein Collagen gel -
Collagen gel is a **protein** matrix with a layer of collagen underneath the cells.

Cytokine -
Cytokines are a group of **proteins** and peptides that are used in organisms as signaling compounds. These chemical signals are similar to hormones and neurotransmitters and are used to allow one cell to communicate with another. While hormones are released from specific organs into the blood and neurotransmitters are released by nerves, cytokines are released by many types of cells. The cytokines includes the interleukins, lymphokines and cell signal molecules, such as tumor necrosis factor and the interferons, which trigger inflammation and respond to infections.

EGFR (**E**pidermal **G**rowth **F**actor **R**eceptor) -
EGFR is one of a family of receptors that help regulate cell growth, division, and death. Normal epithelial cells contain two copies of the EGFR gene and produce low levels of EGFR **protein** on the surface of their cells. In a variety of cancers, there is an increased amount of EGFR protein present in the tumor tissue. This can be due to too many copies of the gene are produced (amplification), an increased amount of the protein are produced (over-expression), and/or a decreased protein destruction. Tumors that have an increased EGFR protein tend to grow more aggressively, are more likely to metastasize, and are more resistant to standard chemotherapies.

Receptors are particular **proteins** that are present on the surface of, or within, cells. Other proteins or chemicals that circulate in the body can attach to these receptors to bring about change within a cell (for example, to make it reproduce or repair itself). Growth factors are chemicals that attach to these receptors and stimulate cells to grow.

Inactivation of EGFR family members represents a promising strategy for the development of selective therapies against epithelial cancers.

Enzyme -
An enzyme is a protein that accelerates the rate of chemical reactions. Enzymes are catalysts that promote reactions repeatedly, without being damaged by the reactions.

Green fluorescent protein -
A **protein** found in jellyfish that is used as a marker to highlight something within a cell.

HER2 -
HER2 (also termed ErbB) is a **protein** found on the surface of certain cancer cells. It is made by a specific gene called the HER2/neu gene. HER2 is a receptor for a particular growth factor called human epidermal growth factor, which occurs naturally in the body.

Laminin -
Laminin is a cell adhesion **protein** secreted by cells to function as an extracellular matrix.

P53 protein (PRO-teen) -
P53 is a **protein** that regulates whether or not a cell undergoes a DNA damage response; it decides to divide or it decides to die. P53 ("p" for protein and "53" for its weight) is also referred to as P53 gene. P53 is deleted at 50% of all human breast cancers.

TGF-beta -
TGF-beta is a **protein** that inhibits proliferation, differentiation, and many other functions of various cell types, and is a member of a "superfamily" which consists of at least 26 different proteins.

Proteomics (PRO-TEE-OM-iks)
Proteomics is the large-scale study of protein, particularly their structures and functions.

Puberty (PYOO-ber-tee)
Puberty is the stage of adolescence in which a child develops secondary sex characteristics as his or her hormonal balance shifts strongly towards an adult and becomes physiologically capable of sexual reproduction. The onset of puberty is triggered by the pituitary gland, which secretes a surge of hormones into the blood stream and begins the rapid maturation of the gonads: girl's ovaries and boy's testicles.

Tanner Stage
Tanner stage is a stage of puberty based on pubic hair growth, development of genitalia in boys, and breast development in girls.

Thelarche
Thelarche is the beginning of breast development in females.

Tissue (TISH-oo)
Tissue is a collection of different types of cells held together by an extracellular matrix that perform specific functions within an organism. There are four basic types of tissue in the body of all animals. They are the epithelium, connective tissue, muscle, and nervous tissue.

Tumor (TOO-mer)
A tumor is an abnormal mass of tissue that has lost its usual architecture as a result of abnormal cell division. Strictly, a tumor refers to any abnormal swelling. Tumors perform no useful body function. They may be benign (non-cancerous) or malignant (cancerous).

Virus (VYE-rus)
A virus is a microscopic particle that is smaller than a single cell or bacteria. A virus can infect cells and cause infectious diseases, but cannot reproduce on their own.

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