(Selected slides)

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Understanding the roots of cancer

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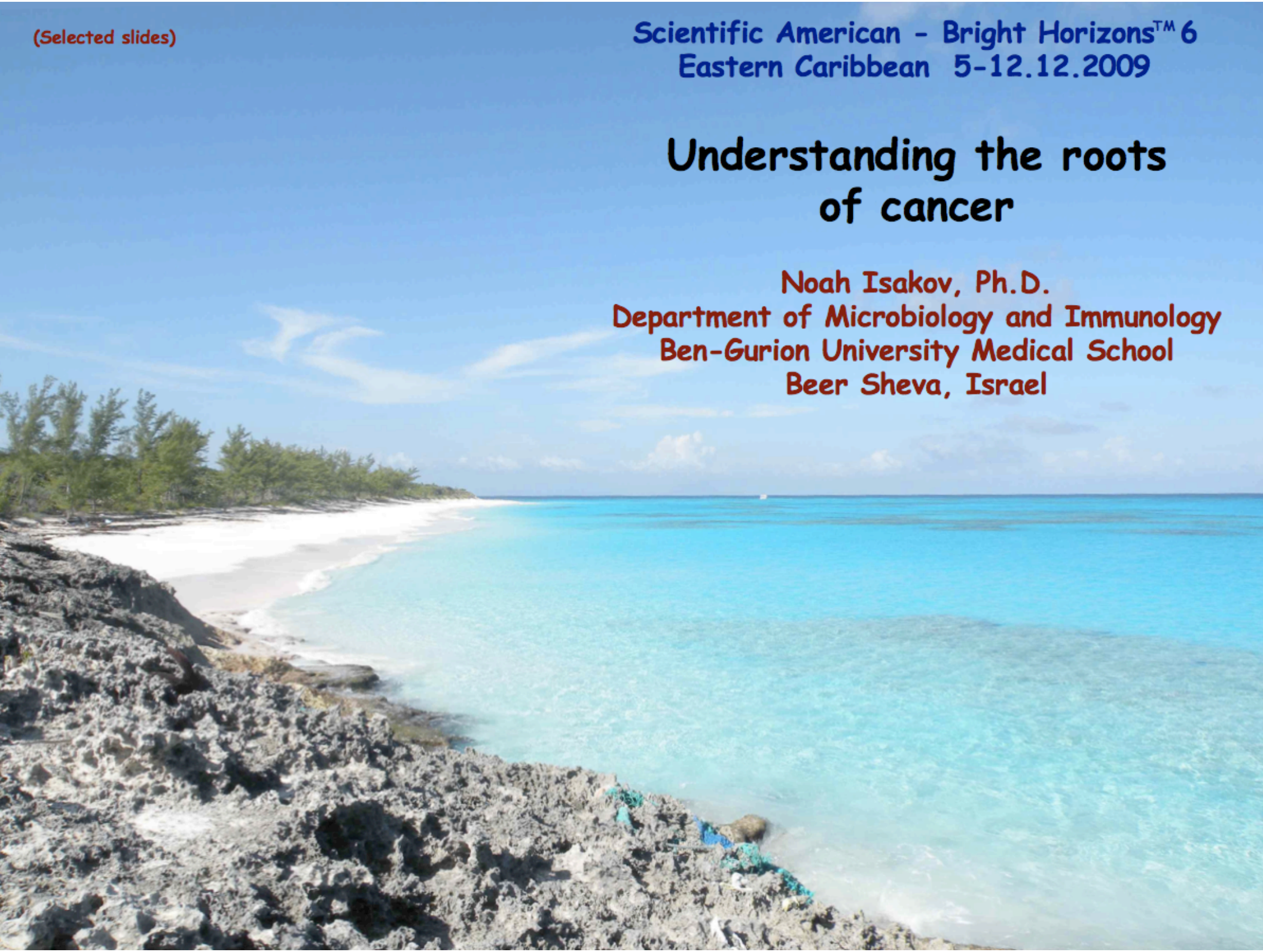


Cancer can occur at almost any organ in the body

There are many different types of cancers affecting different parts of the body. A cancer, or tumor, can occur in any organ or tissue of the human body. Solid tumors form lumps, while liquid tumors flow freely in the blood.

Cancer starts by mutations in a single cell. The mutations are in the cell's DNA. Mutations are inherited in >10% of all cancers. Most mutations arise as a result of environmental factors.

The DNA mutation may be a single nucleotide change or a deletion or duplication of DNA sequence. A change in the genetic sequence can then lead to the production of a mutant protein.

Although in rare cases one mutation is enough, it is usually an accumulation of mutations that irreversibly transforms a normal cell into a cancerous one. As we age, we accumulate more and more mutations; this explains why cancer incidence increases with age.

Mutations in DNA can disrupt the cell's life cycle of growth, proliferation, and death. This leads to the accumulation of more aggressive type of cancer cells and the development of a tumor mass.

Cancer cells have to learn how to grow in the presence of growth inhibitory signals that normally succeed in stopping the proliferation of normal cells.

Survival of cancer cells depends on their ability to evade apoptosis

Just as signals regulate cell growth and division, signals control cell death. Cancers can result from cells that do not die when they should.

Cancer cells have to learn how to avoid the process of programmed cell death, or suicide, otherwise known as apoptosis.

A cell may die because it is damaged or old. Killing of selected normal cells by a mechanism of apoptosis is also important for sculpting tissue and organ structure during development of the embryo (including the metamorphosis of a tadpole), but may occur at any time even in adult cells when a tissue needs to be remodeled.

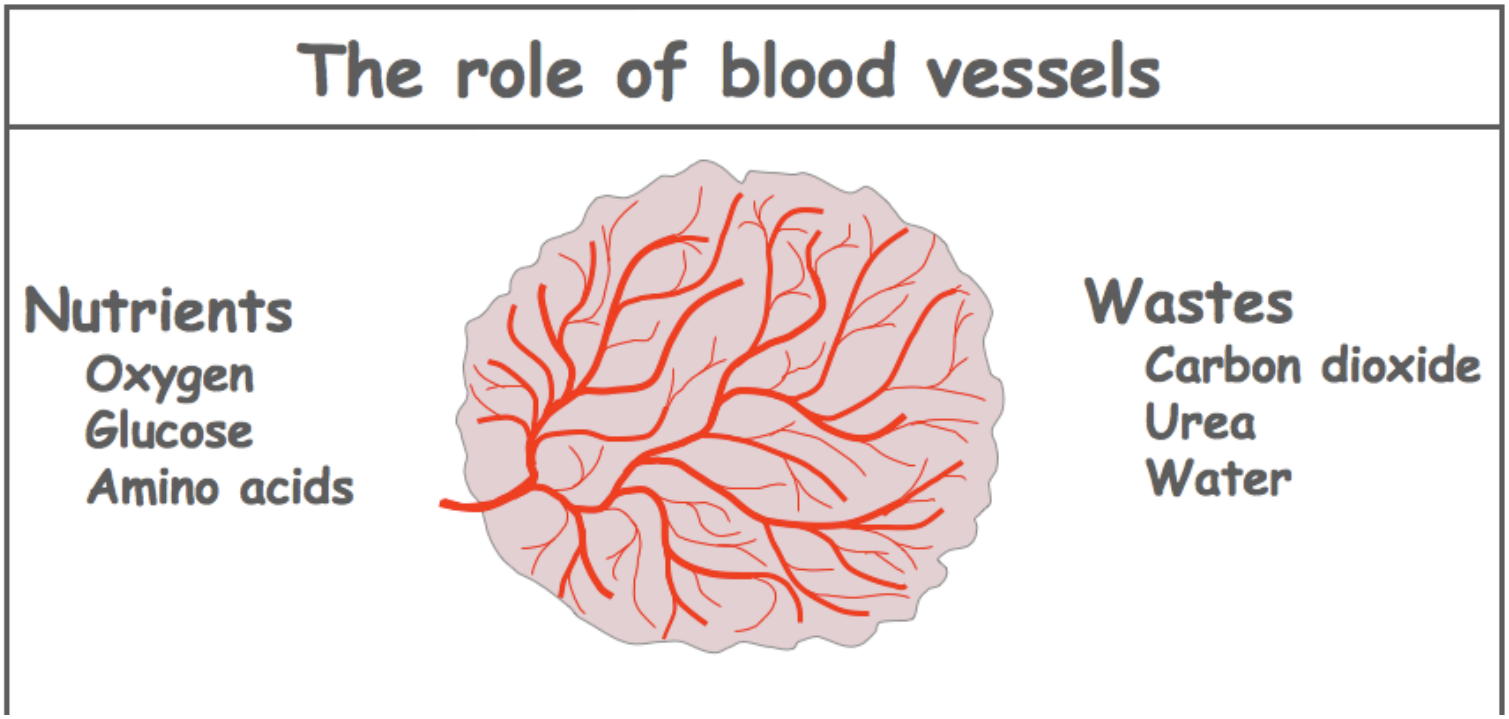
Apoptosis is one of the body's normal mechanism for disposing off damaged, unwanted, or unneeded cells.

Once a cell is signaled to die, the cell makes proteases and additional enzymes that degrade its components. The DNA in the nucleus is fragmented, the cell membrane shrinks, and, eventually, a neighboring cell engulfs the cellular remains.

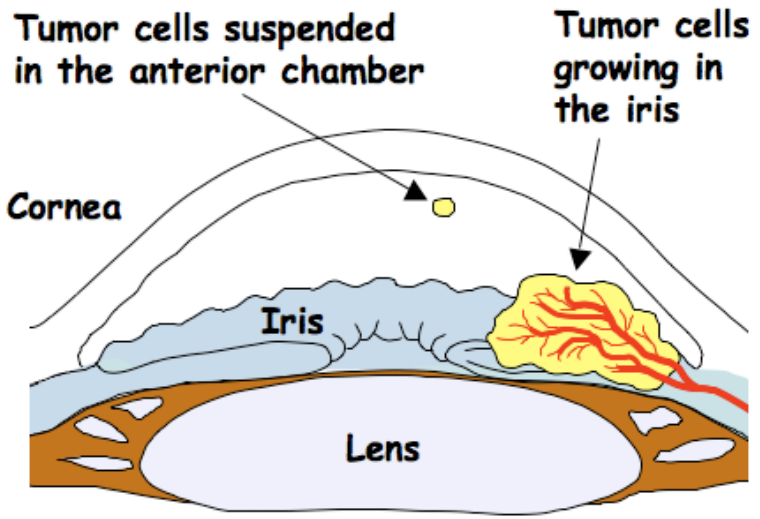
Tumor cells promote angiogenesis

To grow beyond a certain size, tumors need a system to bring in nutrients and oxygen and take out wastes. The cancer cells that make up a tumor learn how to become angiogenic, that is to say attract blood vessels to grow into the tumor mass. The blood vessels then nourish the tumor just like any organ in the body. They provide the tumor with nutrients, glucose and oxygen, and evacuating metabolic wastes and carbon dioxide.

Angiogenesis is regulated by specific factors, such as 'vascular endothelial growth factor' (VEGF), which are produced by the tumor cells and promote new blood vessel formation. Tumor angiogenesis enables the developing tumors to establish an independent blood supply, consequently facilitating tumor growth.

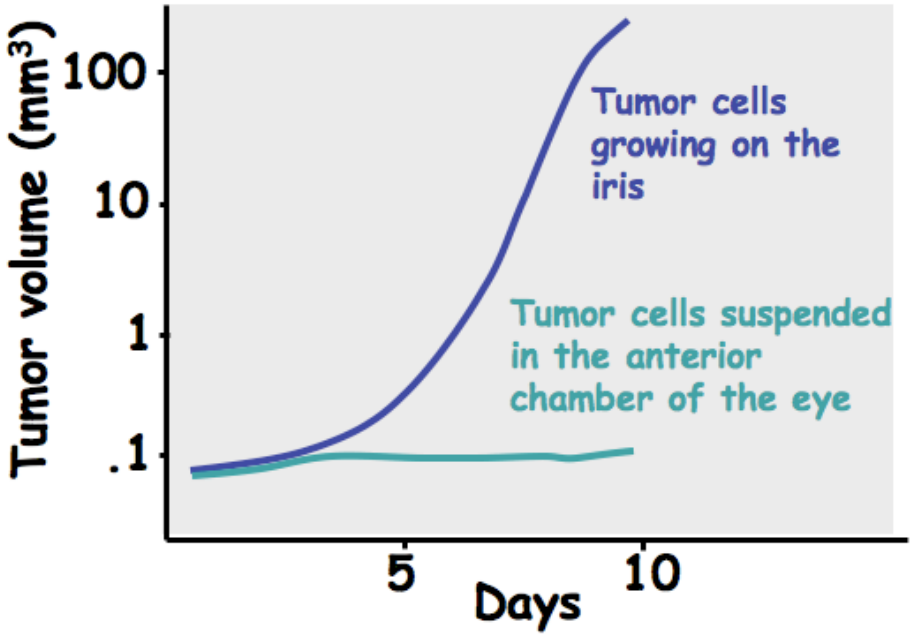


The ability of tumor cells to attract blood vessels to grow into the tumor mass is critical for tumor growth



In the following experiment, 10^6 tumor cells injected into the anterior chamber of the eye form a small tumor mass and stop growing due to lack of blood supply.

In contrast, the same number of tumor cells injected into the iris, promote neo-angiogenesis (formation of new blood vessels) and develop into a large tumor mass.



Cancer cells are immortal

Normal cells have a lifespan. They can only double a certain limited finite number of times.

In contrast, cancer cells learn how to proliferate indefinitely, i.e, they are becoming immortalized.

The machinery for controlling how often a cell may grow and divide, how many generations a lineage of cells may pass through, is determined by elements, called telomeres, found at the ends of chromosomes.

The telomeres are specialized sequences at the ends of each chromosome and they operate to prevent end-to-end fusion of chromosomes. These telomeres protect the ends of chromosomal DNA from such accidents.

When normal cells go through cycles of growth and division, their telomeric DNA gets shorter and shorter, and ultimately it can no longer protect the ends of chromosomal DNA.

Telomeres start fusing. Chromosomes start fusing in those cells, leading to their death.

Cancer cells must avoid that problem because they want to grow indefinitely. They do it by turning on an enzyme called telomerase that is normally expressed only early in embryologic development and in a small number of so-called stem cells in the body.

The telomerase enzyme is able to extend the telomeres, making them longer and longer thereby enabling the cancer cell to go through many cycles of growth and division without worrying about the imminent collapse of its telomeres. The telomerase ensures the telomeres stay very long.

Cancer cells can metastasize.

They can leave the primary tumor and colonize remote tissues and organs

Most of the deaths from human cancers (90%) are due to cancer cells spreading and establishing colonies in other parts of the body.

Cancer cells also have to learn how to invade and metastasize. And that, in fact, is involved in the inactivation of a whole series of controls that normally confines a cell to the site and the tissue where it normally grows – enabling these cells to move to other sites in the body.

During the metastatic process, cancer cells proceed through a series of distinct steps to form an overt, secondary tumor. These steps include the growth of the primary tumor, promotion of angiogenesis, tumor cell invasion into adjacent tissues, intravasation into neighboring blood vessels, survival in the circulation, arrest in a new organ, extravasation, and formation of secondary tumors.

Cancer cells learn to avoid detection by immune cells

Cancer cells are often different in shape and size compared to normal cells, and they no longer respond to signals that control normal cellular functions.

Our body's immune response is constantly surveying for these emerging pre-cancers or pre-tumor cells. Successful cancers have to avoid detection long enough to grow into a tumor.

There is constant surveillance of the cells in our body so that emerging pre-cancers or pre-tumor cells would be eliminated by the immune response.

Causes of cancer and cancer prevention

About 10% of all cancers are inherited.
Synthetic chemicals, including pollution, food additives, and industrial wastes account for less than 5% of cancers in the U.S.
Additional causes can be identified by epidemiological studies, by looking for "hot spot" regions with high cancer rates, and correlating them with environmental, dietary, cultural, or lifestyle factors that are common to the regions where cancers are most frequent.

Tobacco smoking increases the risk for lung cancer

Lung cancer is the leading cause of cancer deaths in the United States. Lung cancer is almost entirely preventable, since the vast majority of cases are due to cigarette smoking. Although tobacco has been used by American Indians for 2,000 years and in western societies since the 16th century, cigarette smoking is mainly a 20th century phenomenon.

The highest rates of lung cancer are found in developed countries, where people can afford the luxury of a cigarette habit. Lung cancer cases rose in men following WWII, but have fallen in recent years. Unfortunately, smoking - and lung cancer - are on the rise in women. Lung cancer is the leading cause of cancer deaths in the US, but deaths would drop 85% if no one smoked.

Comparison between the curves showing tobacco consumption in the last decade, and death due to lung cancer shows that cancer deaths lag behind increases in cigarette consumption by about 20 years.

Cancer predisposition can be inherited

A cancer gene alters the normal functioning of a protein. All cancer causing genes can be grouped into three major categories of cancer genes.

Oncogenes - genes that normally signal cells to grow. When an oncogene is mutated the cells grow in a constitutive manner. An analogy for an oncogene is the accelerator in a car. A mutation in an oncogene is like having an accelerator pushed to the floor. Car keeps going even though the driver takes his foot of the accelerator.

Tumor suppressor genes - they are like the breaks of a car. In the absence of breaks, an accelerating car will continue to move.

A car has more than one break. Similarly, a combination of mutations in oncogenes and tumor suppressor genes, and the sequential accumulation of those mutations, which lead to the formation of a full blown cancer.

Stability genes - they are not directly involved in cell growth or death. Instead, they control the rate of mutation. If someone has defective stability genes, his genes, including oncogenes and tumor suppressor genes, are mutated more frequently. As a result, the entire process of cell transformation is accelerated.

Products of microorganisms may serve as chemical carcinogens:

Food crops such as peanuts, corn, and wheat are susceptible to contamination by molds – *Aspergillus flavus* and *Aspergillus parasiticus*. Aflatoxin, a metabolic byproduct of these molds, is a potent cancer-causing agent. Long-term exposure to aflatoxin has been linked to increased incidence of liver cancer.

Ear rot of corn is frequently caused by *Aspergillus flavus* and *Aspergillus parasiticus*. These fungi may colonize only a few kernels on each ear, but the colonization is a cause for concern nevertheless because of the aflatoxin they produce, which is a potent carcinogen. The disease is most severe in areas with high temperatures and drought.

Crops which are frequently affected include cereals (maize, sorghum, pearl millet, rice, wheat), oilseeds (peanut, soybean, sunflower, cotton), spices (chile peppers, black pepper, coriander, turmeric, ginger), and tree nuts (almond, pistachio, walnut, coconut, brazil nut).

Human cancer can be caused by viruses and bacteria

Virus	Type of Cancer	% Virus positive
Human papiloma virus (HPV)	Cervical cancer	100
Hepatitis B virus (HBV)	Liver cancer	50
Hepatitis C viruse (HCV)	Liver cancer	25
Epstein-Barr Virus (EBV)	Burkitt's lymphoma	>90
	Hodgkin's lymphoma	>50
	Nasopharyngeal carcinoma	100
Kaposi sarcoma virus (KSHV)	Kaposi sarcoma	100
	Multi Castleman's disease	>50
Human T cell leukemia virus (HTLV)	Adult T cell leukemia	100

Bacterial infection (helicobacter pylori infection) causes inflammation of the stomach lining, which increases the risk of gastric carcinoma and MALT (mucosa-associated lymphoid tissue) lymphoma.

Additional causes of cancer

Physical carcinogens

Ionizing radiation (most organs and tissues)

Ultraviolet radiation (skin)

The ultraviolet (UV) radiation in sunlight is the major cause of skin cancer. Some types of skin cancer, such as squamous cell carcinoma, can be directly attributed to damage from exposure to UV-B. However, the incidence of skin cancers such as melanoma is more complex, being influenced by genetics and additional factors such as the type and frequency of UV exposure.

Genetic background (some cancer genes can be inherited).

Age (enables accumulation of mutations).

Cancer 'parasitic'-like cells were observed in the Tasmanian devil in Eastern Tasmania, where sick individuals can transfer cancer cells by bite.

Devil facial tumor disease (DFTD)

DFTD is an aggressive non-viral transmissible parasitic cancer that affects Tasmanian Devils. The first "official case" was described in 1996, in Australia. In the subsequent decade the disease ravaged Tasmania's wild devils, with estimates of decline ranging from 20% to 50% of the devil population, across over 65% of the state. Affected high-density populations suffer up to 100% mortality in 12–18 months. The cancer is passed from devil to devil through biting. The live tumor cells aren't rejected by their immune system because of a lack of genetic diversity among Tasmanian devils. Visible signs of DFTD begin with lesions and lumps around the mouth. These develop into cancerous tumors that may spread from the face to the entire body. The tumors interfere with feeding, and the affected animal may starve to death.

Transmissible cancer in animals is extremely rare. There is only one other known type - canine transmissible venereal tumor (CTVT), which is spread in dogs through sexual activity and has been known to science for about 100 years.

Tasmanian Devil

Immunotherapy using Abs

- Passive immunization (i.e., against snake venom)

- Infusion of anti-Rh Abs to pregnant women to eliminate future hemolytic disease of the newborn

- Utilization of Abs for negative selection of T cells from a transplantable bone marrow

- Infusion of anti-cancer cell Abs

  Infusion of anti-cancer cell Abs bound to toxins, isotopes, or drugs

  Infusion of Abs against viral antigens (i.e., HIV), to neutralize viruses

  Infusion of Abs against cellular receptors for viruses (i.e., HIV), block the receptor and prevent further infection

  Infusion of Abs against TNF or other cytokines (or their corresponding receptors), to prevent autoimmune disorders (i.e., RA)

Cancer therapy and immunotherapy

using anti-angiogenic drugs

Anti-angiogenic drugs inhibit the growth of tumors by cutting off their blood supply, usually by disabling cellular signaling pathways that are essential for blood vessel growth, such as the vascular endothelial growth factor (VEGF) pathway.

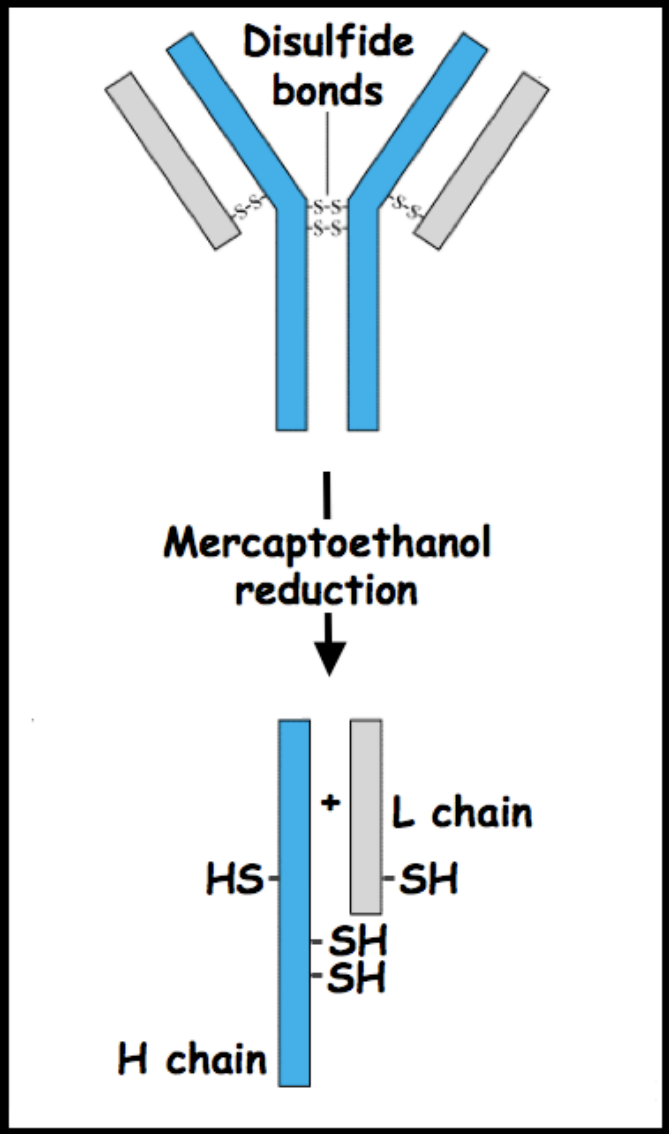
The current VEGF-targeting drugs were found to have unanticipated and undesirable effects on tumor behavior that explain their limited clinical efficacy.

Most drugs tested inhibited primary tumor growth, but stimulated tumor cells to develop a more invasive and metastatic phenotype.

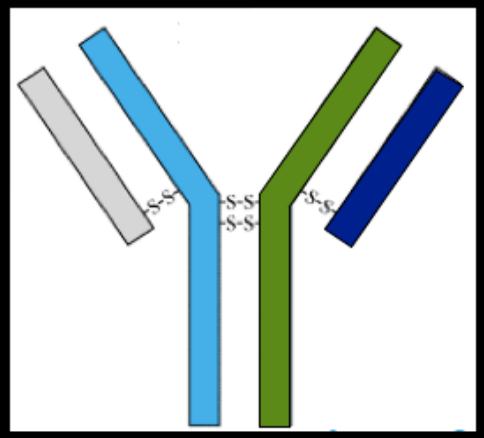
This might occur because the drugs cause hypoxia (oxygen deficiency), which in turn selects for more malignant cells, or because the drugs increase the leakiness of blood vessels, thereby facilitating the entry of tumor cells into the circulation.

A chimeric monoclonal antibody (mAb)

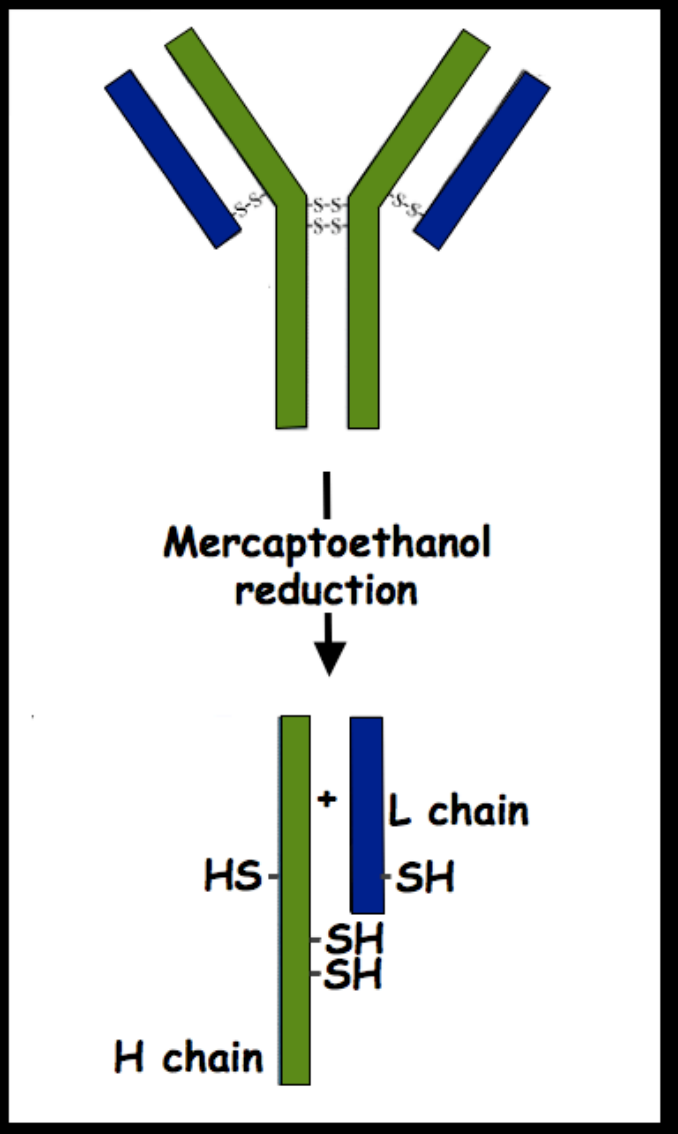
Anti-tumor cell Ab



Dual specificity Ab



Anti-T cell Ab

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