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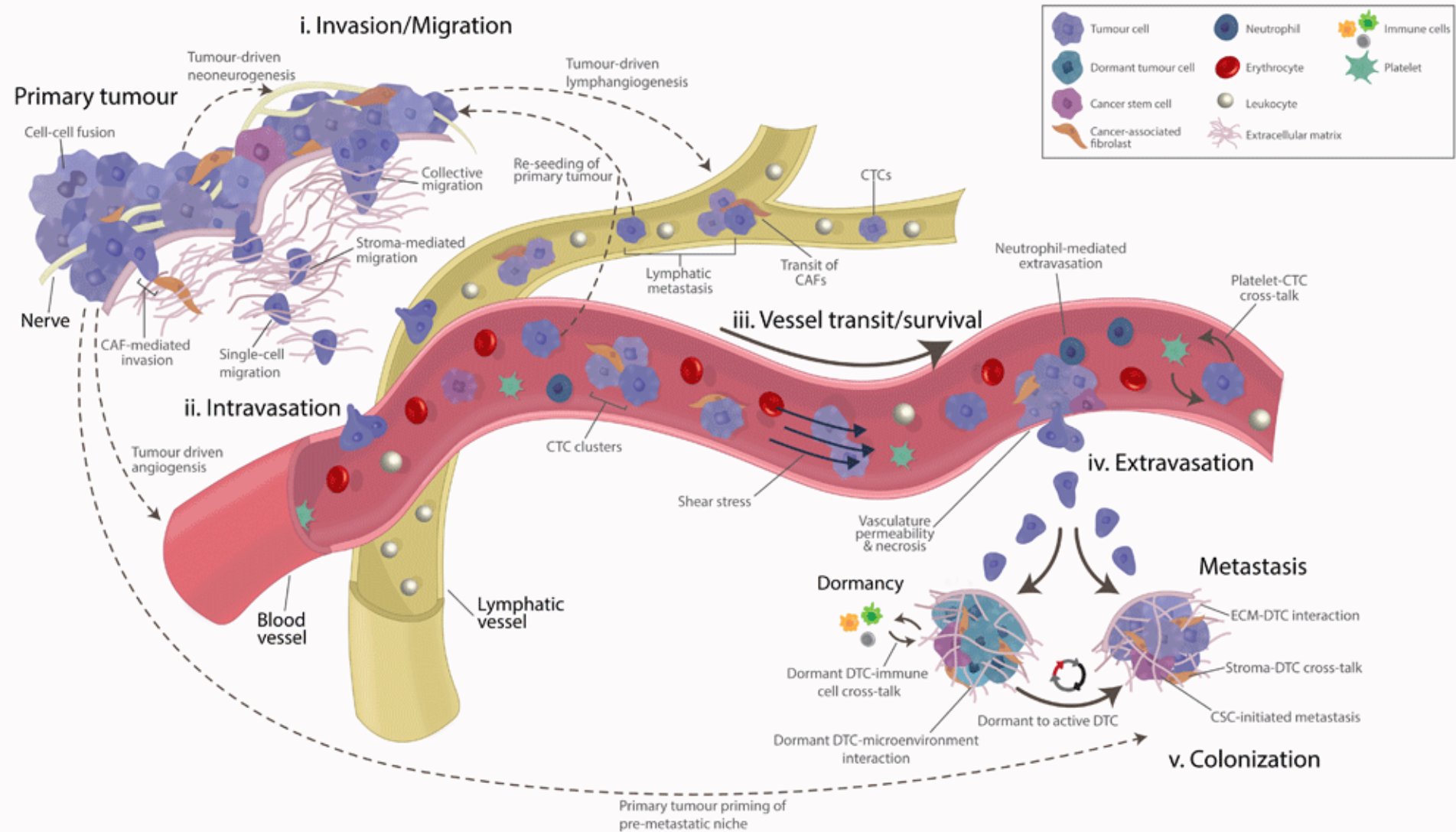
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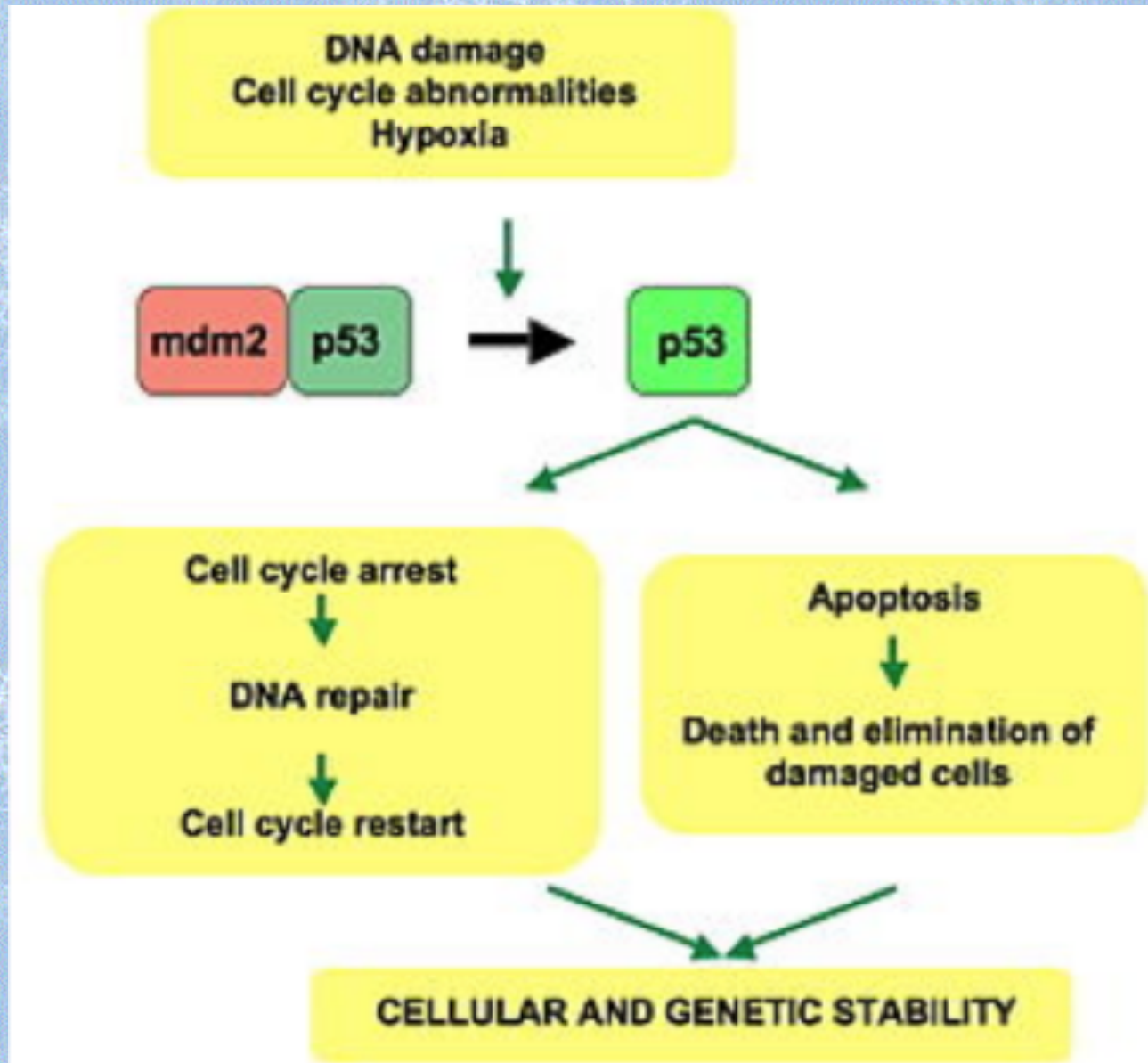
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...How Cancer spreads: Metastasis

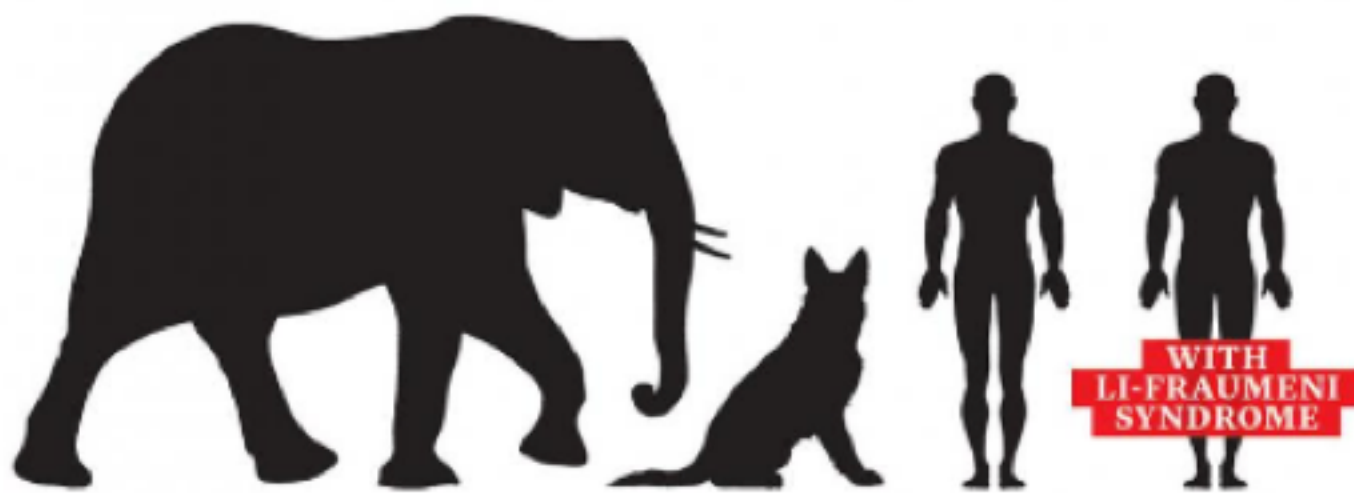


P53 Guardian Angel of the cell/genome



MAGIC GENE IN A BOTTLE

A tumor suppressor gene, TP53 is the police officer of the cellular world. If a cell with faulty DNA is replicating, it can arrest the process and allow it to move forward only once the DNA is fixed. Or it can shoot to kill, getting rid of the cell with bad DNA.



LIFETIME RISK OF CANCER	<5%	25%	33-50%	90%
CANCER MORTALITY RATE	<5%	50%	25%	n/a*
TP53 GENE	40	2	2	1

*Not Available /// SOURCE: Joshua Schiffman

Primary and Secondary Cancer

- ❑ The main reason cancer can be difficult to cure is that it can spread to another part of the body from where it started.
- ❑ The cancer that is growing where it started in the body is called the '**primary cancer**'.
- ❑ The place a cancer spreads to and starts growing is called the '**secondary cancer**' or 'metastasis'.
- ❑ In order to spread, some cells from the primary cancer must break away, travel to another part of the body and start growing there.

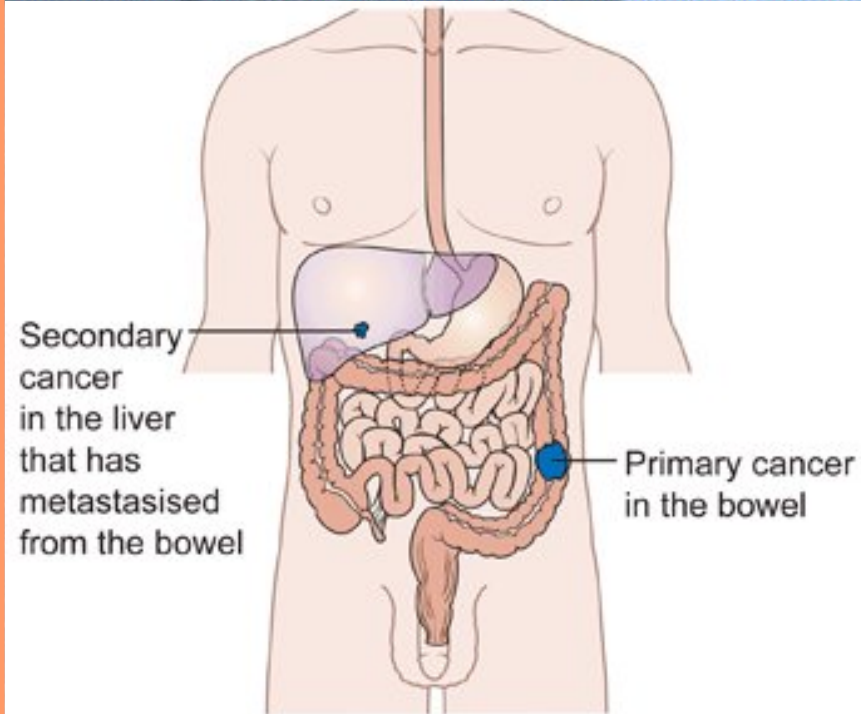


Diagram showing a primary and a secondary cancer
Copyright © CancerHelp UK

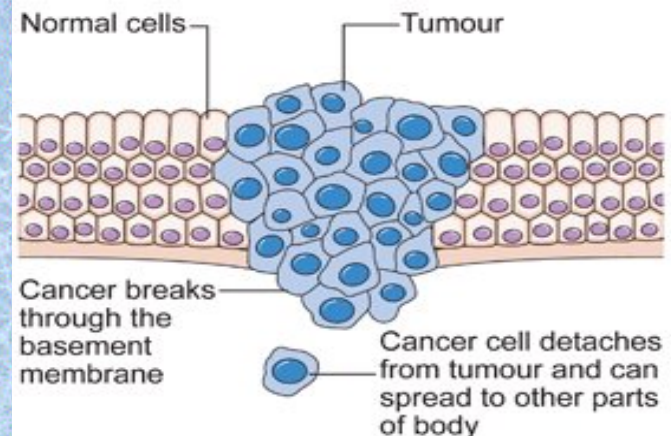
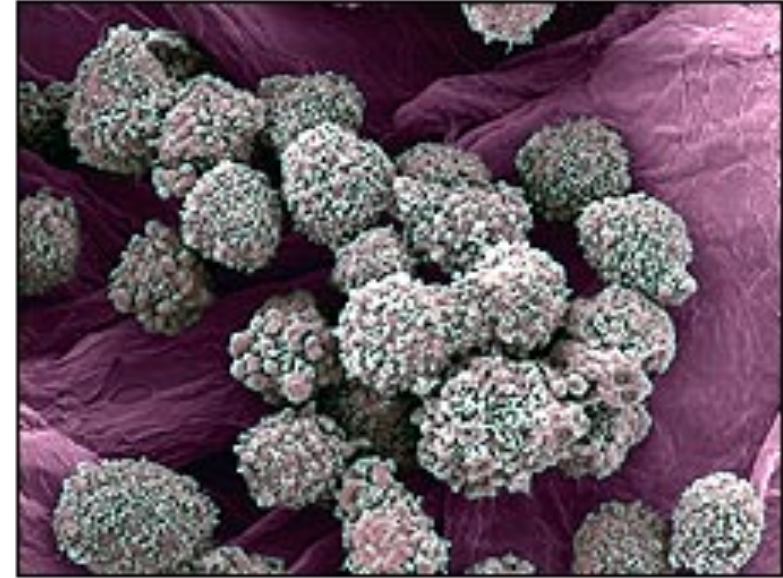


Diagram showing a malignant tumour
Copyright © CancerHelp UK

Cancer Spread and Mortality

- ❑ **90% of Cancer Deaths Occur Because of Where Cancer Ends Up, Not Where It Begins**
- ❑ Research shows that most metastatic cancers induce pre-metastatic niches or landing pads, allowing cancerous cells to colonize a secondary organ
- ❑ When cancer cells travel to a vital organ, they often overwhelm the cells and cause it to shut down



It was thought cancer cells stayed put until advanced stages of the disease

- ❑ By the time a tumor is found, cancer cells may have been present for some years, but the immune system has controlled their proliferation.

How Hematologic Cancers Cause Death

- ❑ “Non-solid” tumors
- ❑ Hematologic (blood) cancers kill because the components of the blood are no longer fulfilling their duties
- ❑ The immune system is no longer working effectively
- ❑ The **platelet count drops** causing **hemorrhage**
- ❑ Red cells are significantly reduced, causing **reduced oxygen** and the patient has a **heart attack**



- ❑ Increased white blood cells lead to really viscous blood, effectively clogging the arteries

How Solid Tumors Cause Death

- ❑ Solid tumors kill in very **mechanical ways**
- ❑ Ovarian cancer kills you by **obstructing your bowel**, as does colon cancer and most other cancers of the GI tract
- ❑ Lung cancers usually kill **by eroding into an artery or obstructing the airway**
- ❑ Breast cancers typically kill by **metastases in the brain** causing increased **intracranial pressure**
- ❑ **More than 40 percent of cancer patients die from malnutrition**, not the cancer itself
- ❑ Tumors induce a **hypermetabolic state** and secrete a substance called Tumor Necrosis Factor alpha ($\text{TNF}\alpha$) that results in **weakness and weight loss**

Most common sites of
Cancer metastasis
and their symptoms

Brain

- Headaches
- Seizures
- Vertigo

Lymph nodes

- Lymphadenopathy

Respiratory

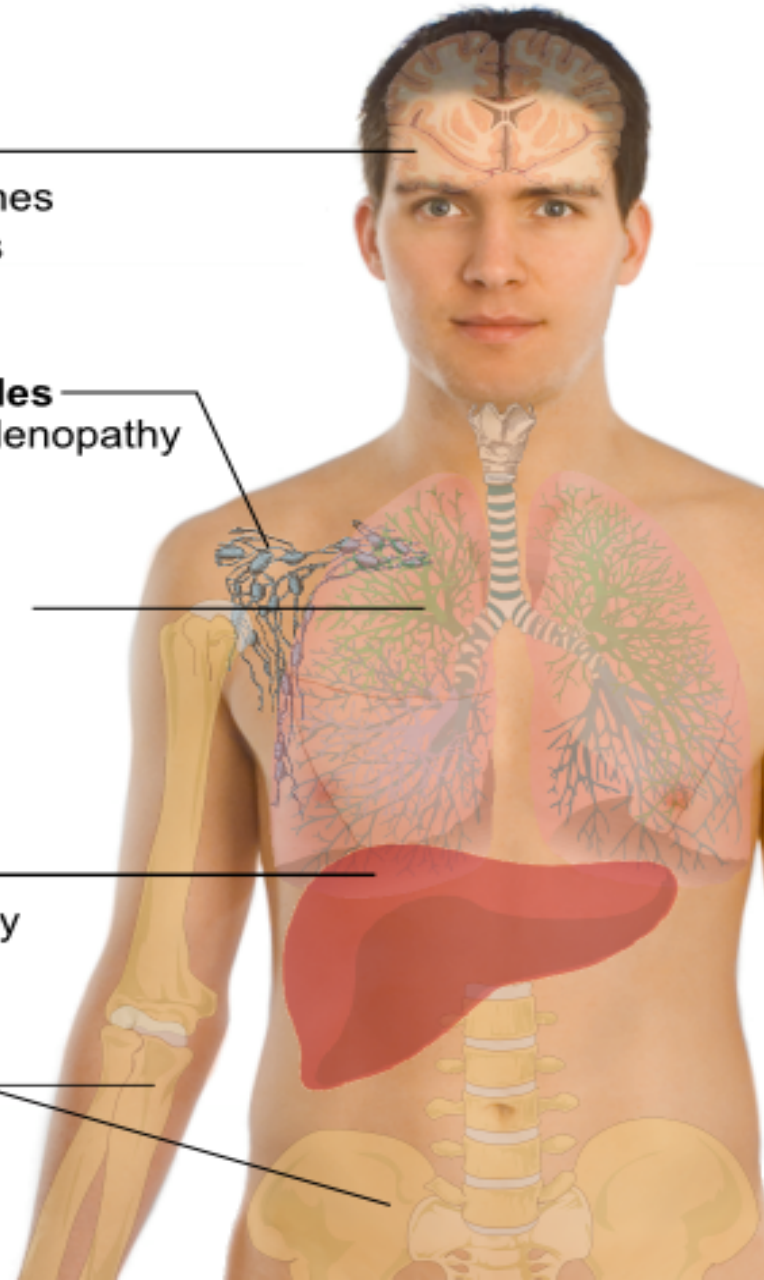
- Cough
- Hemoptysis
- Dyspnea

Liver

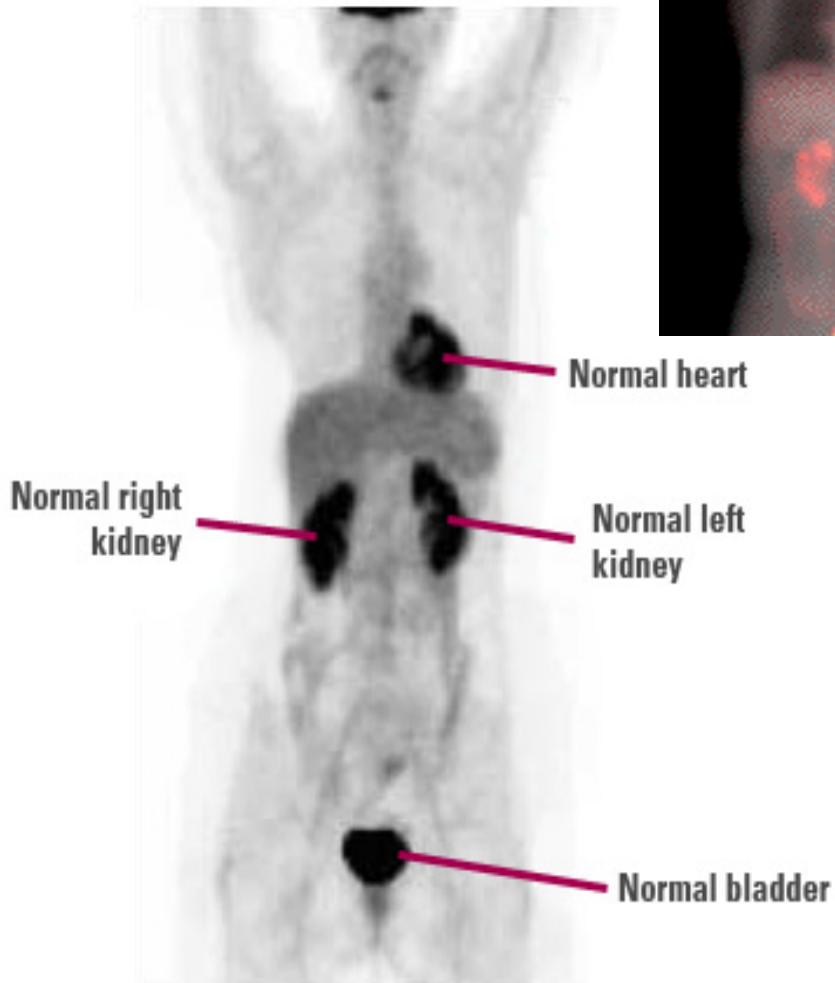
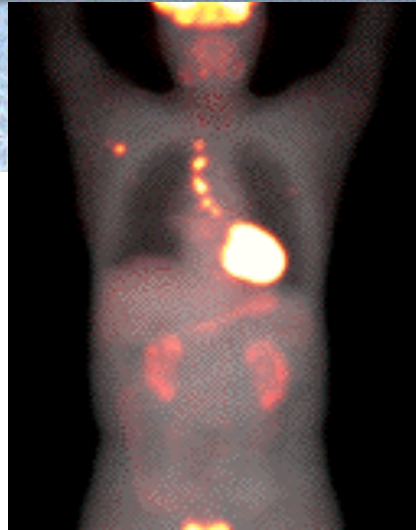
- Hepatomegaly
- Jaundice

Skeletal

- Pain
- Fractures



Metastasis: Cancers Deadly Weapon

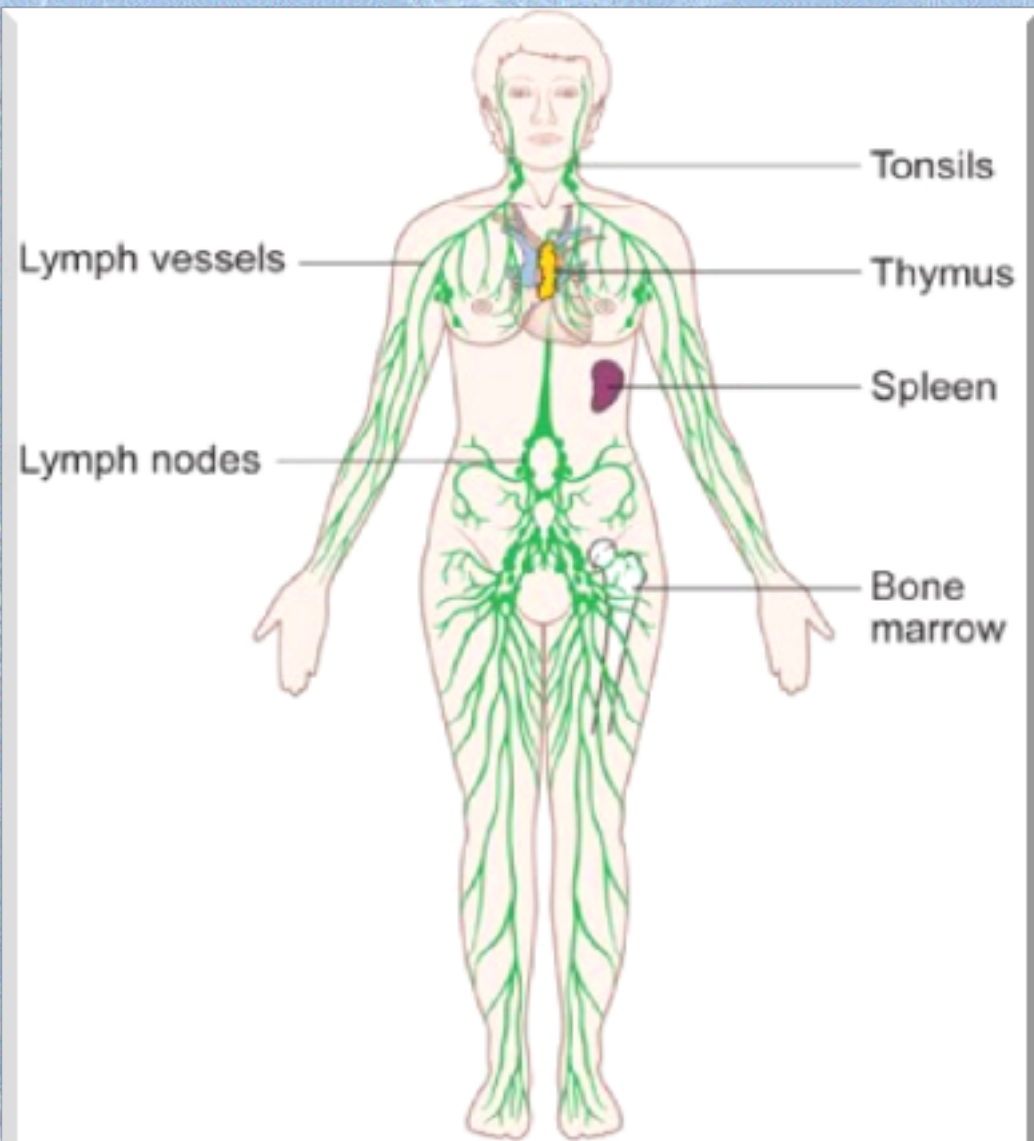
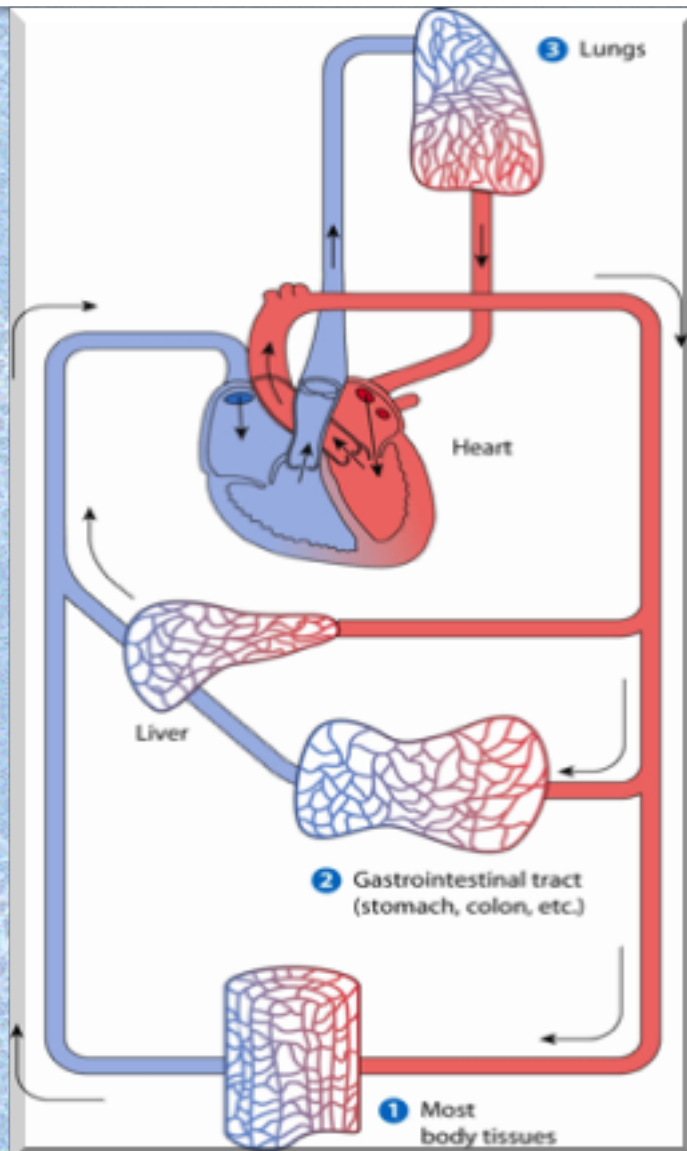


Normal PET scan



PET scan showing abnormal lymph nodes

Blood and Lymph Flow Patterns



From L. J. Kleinsmith, *Principles of Cancer Biology*.
Copyright (c) 2006 Pearson Benjamin Cummings.

Diagram of the lymphatic system
Copyright © CancerHelp UK

There are three main ways a cancer spreads

- ❑ Local spread
- ❑ Through the blood circulation
- ❑ Through the lymphatic system



Local spread

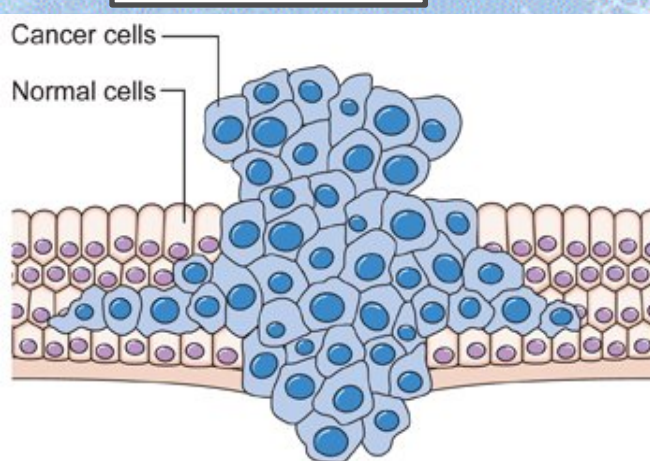


Diagram showing a tumour forcing its way through normal tissue
Copyright © CancerHelp UK

Blood

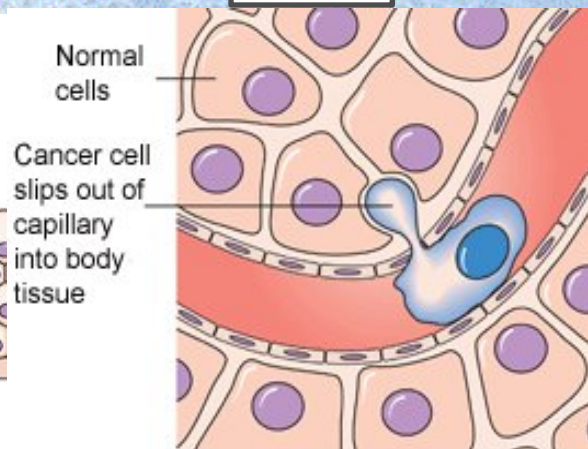


Diagram showing how cancer cells get into the bloodstream
Copyright © CancerHelp UK

Lymphatics

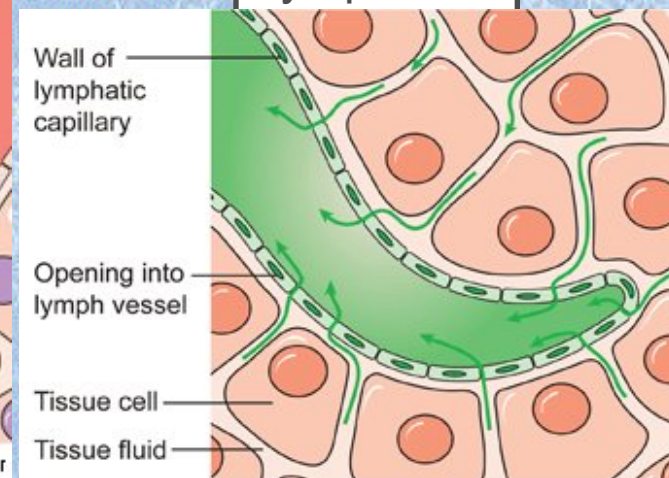
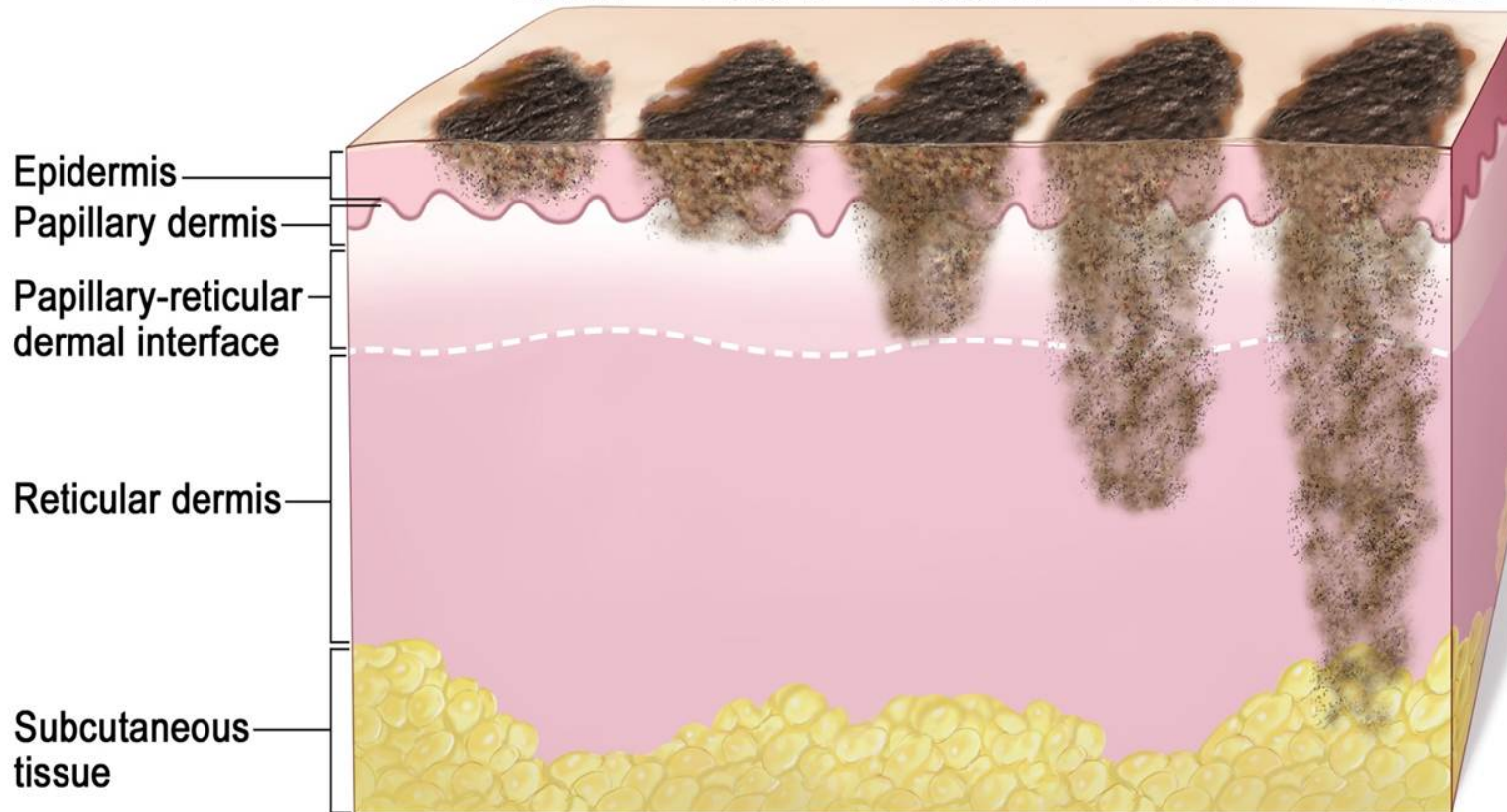


Diagram of a lymphatic capillary
Copyright © CancerHelp UK

How Cancer Spreads: Melanoma

Clark Levels

Level I Level II Level III Level IV Level V



Vasculogenesis and Angiogenesis

Undifferentiated cells

Endothelial cells

Vasculogenesis

Dividing cells

Dividing cells

Angiogenesis

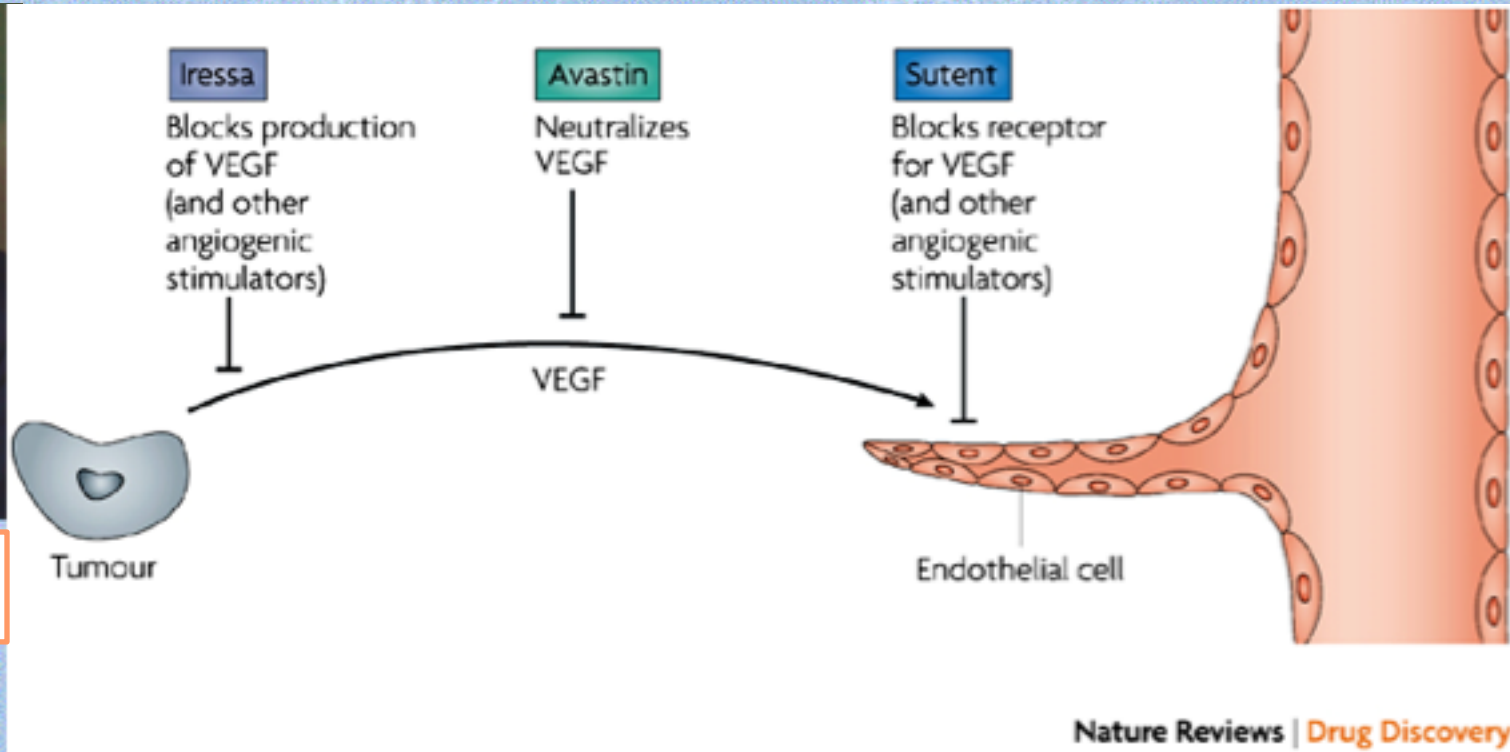
❑ **Vasculogenesis** is the term used for the formation of new blood vessels when there are no pre-existing ones.

❑ The term **angiogenesis** denotes the formation of new blood vessels from pre-existing ones.

Dr Judah Folkman – Pioneer in Tumor Angiogenesis

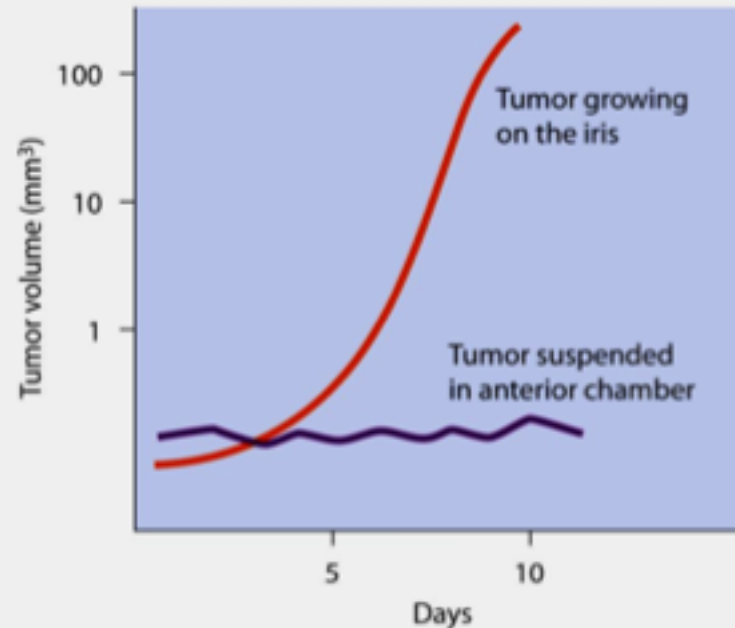
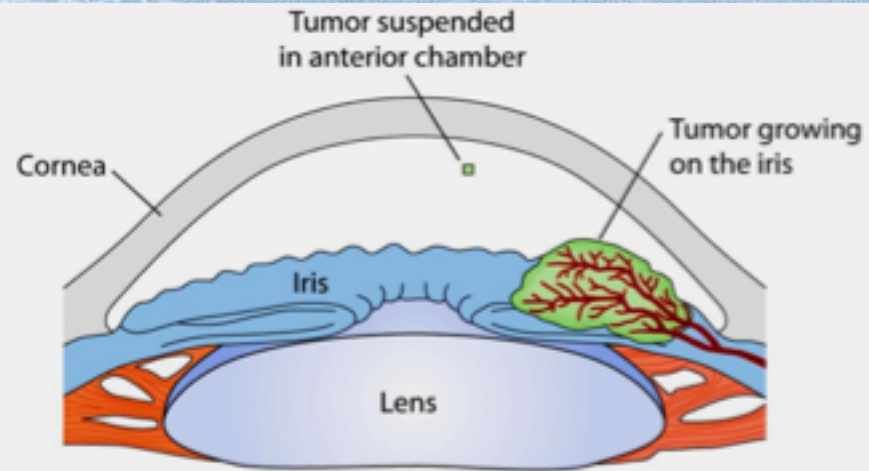
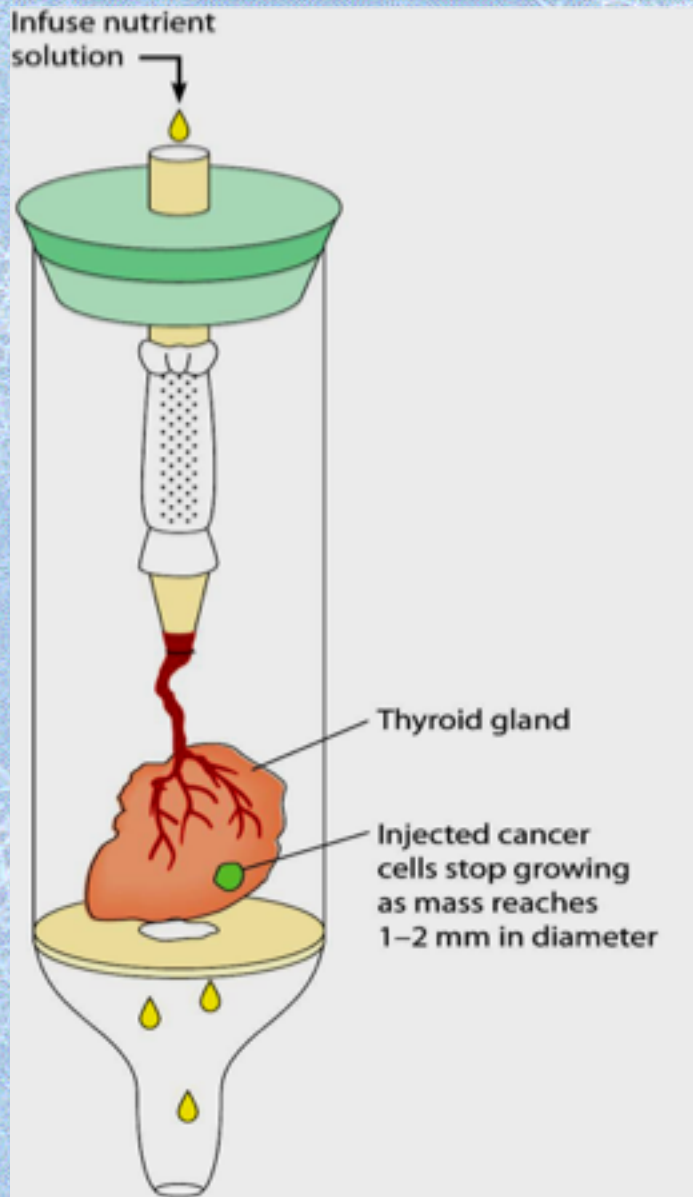


(February 24, 1933 –
14 January 2008)



- While working for the Navy in 1960's on blood substitutes, he began experimenting with tumors and found that all grew to the same size and stopped.
- Hypothesized that the tumors could not grow beyond a certain size without a blood supply and that tumors must have some mechanism to induce the formation of blood vessels.

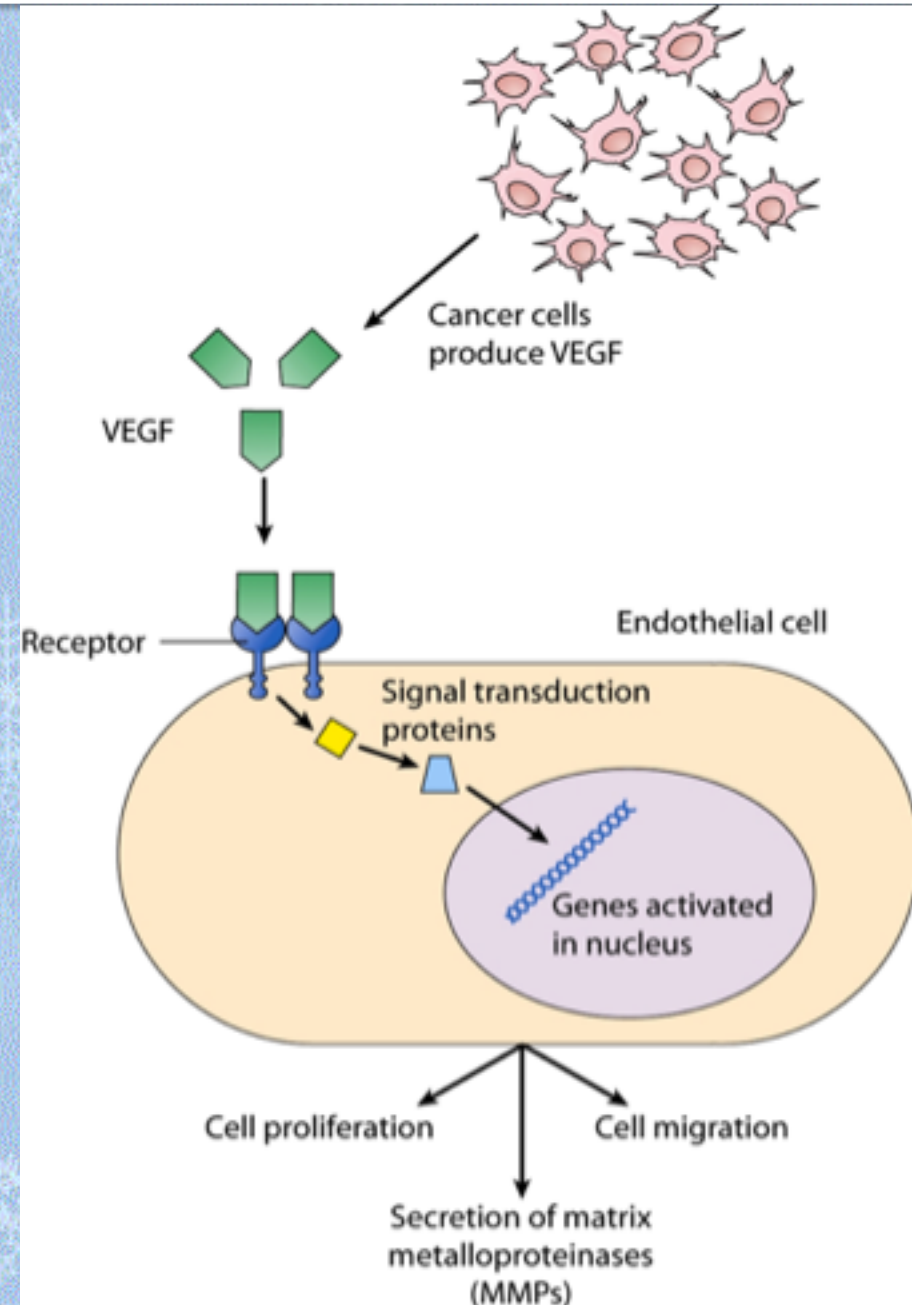
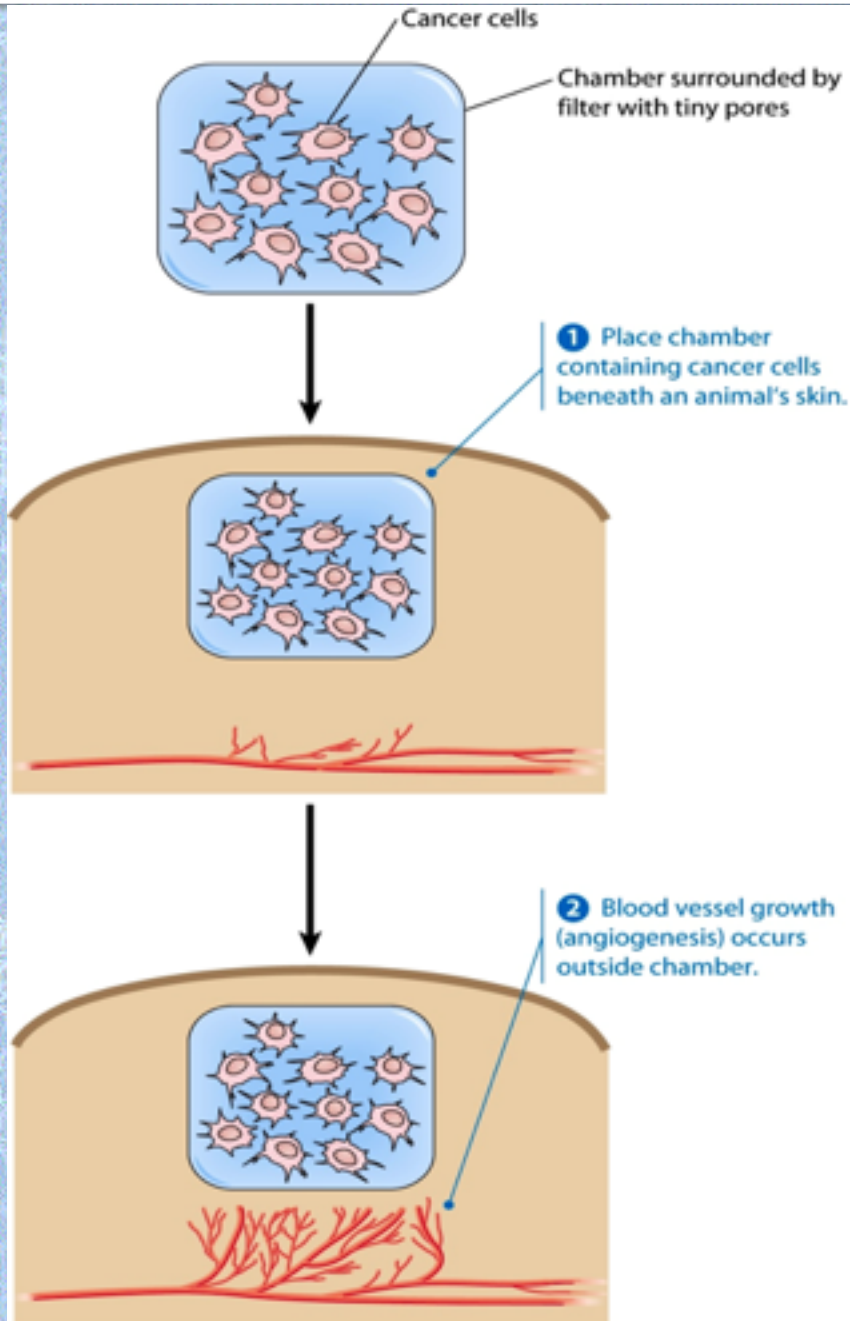
Experiments Showing That Tumor Growth Depends on Angiogenesis



From L. J. Kleinsmith, *Principles of Cancer Biology*.
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Cancer Cells Produce Angiogenesis stimulating Molecules

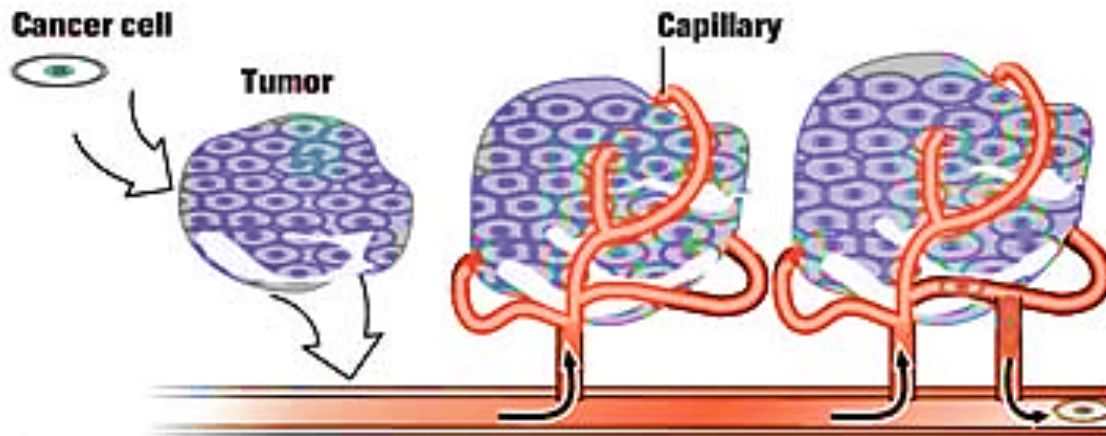
From L. J. Kleinsmith, *Principles of Cancer Biology*. Copyright (c) 2006 Pearson Benjamin Cummings. Pages 48 & 49



Avastin Inhibits Angiogenesis

Blood vessel blockers

Genentech received federal approval Friday to market its drug Avastin for late-stage breast cancer. The drug is designed to block the supply of blood to cancerous tumors by attacking Vascular Endothelial Growth Factor (VEGF), a protein that causes the growth of new blood vessels to cancerous tumors.



❶ Cancer cells multiply and grow into a tumor. The tumor releases VEGF in a process called angiogenesis.

❷ Capillaries form a network that feeds the tumor oxygen and nutrients, and the tumor grows larger.

❸ Cancer cells break off from the tumor and enter the bloodstream, allowing the cancer to spread to other parts of the body.

How Avastin works: The drug attaches to VEGF and prevents the protein from working, thereby stopping the growth of new blood vessels to the tumor.

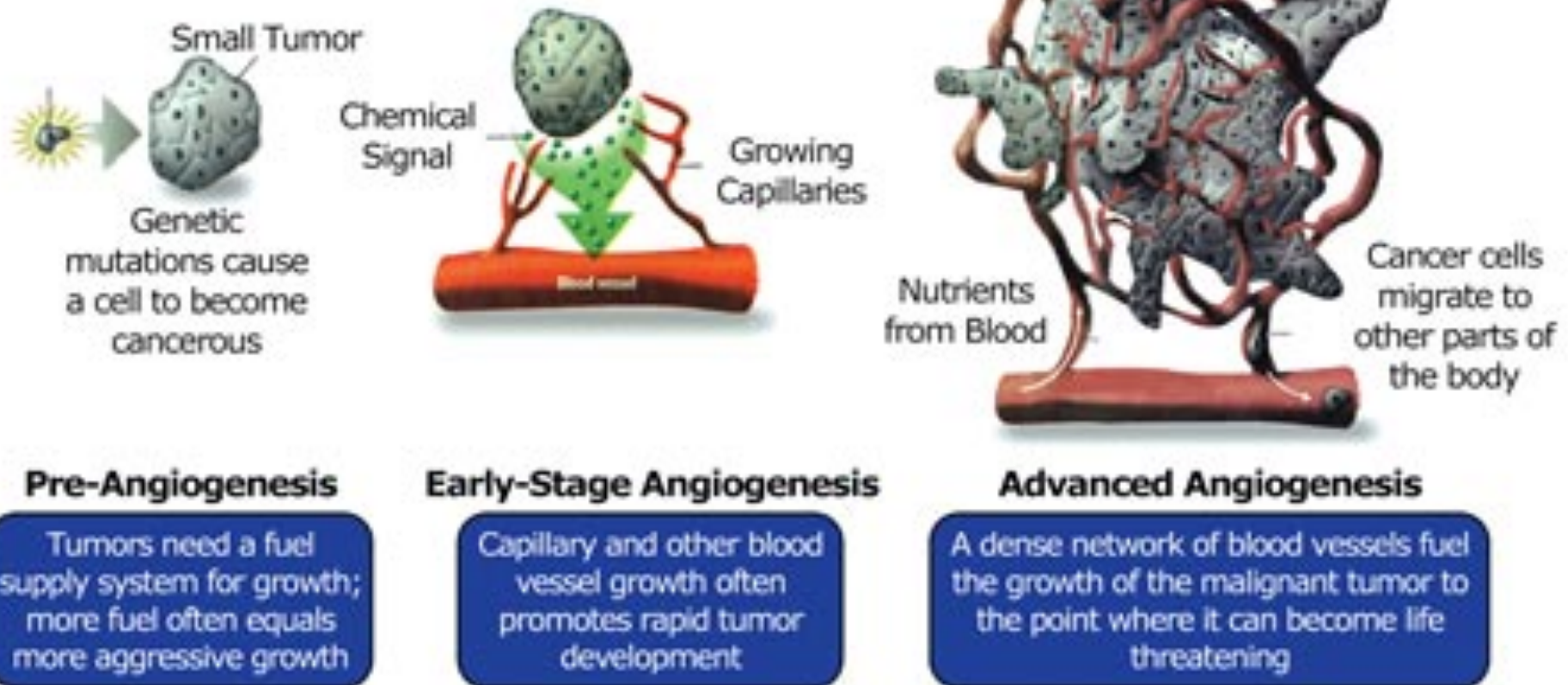
Lucentis and Avastin have been called "miracle drugs" because they are the first treatments that can actually reverse some vision loss from advanced macular degeneration.

Avastin ~ Lucentis

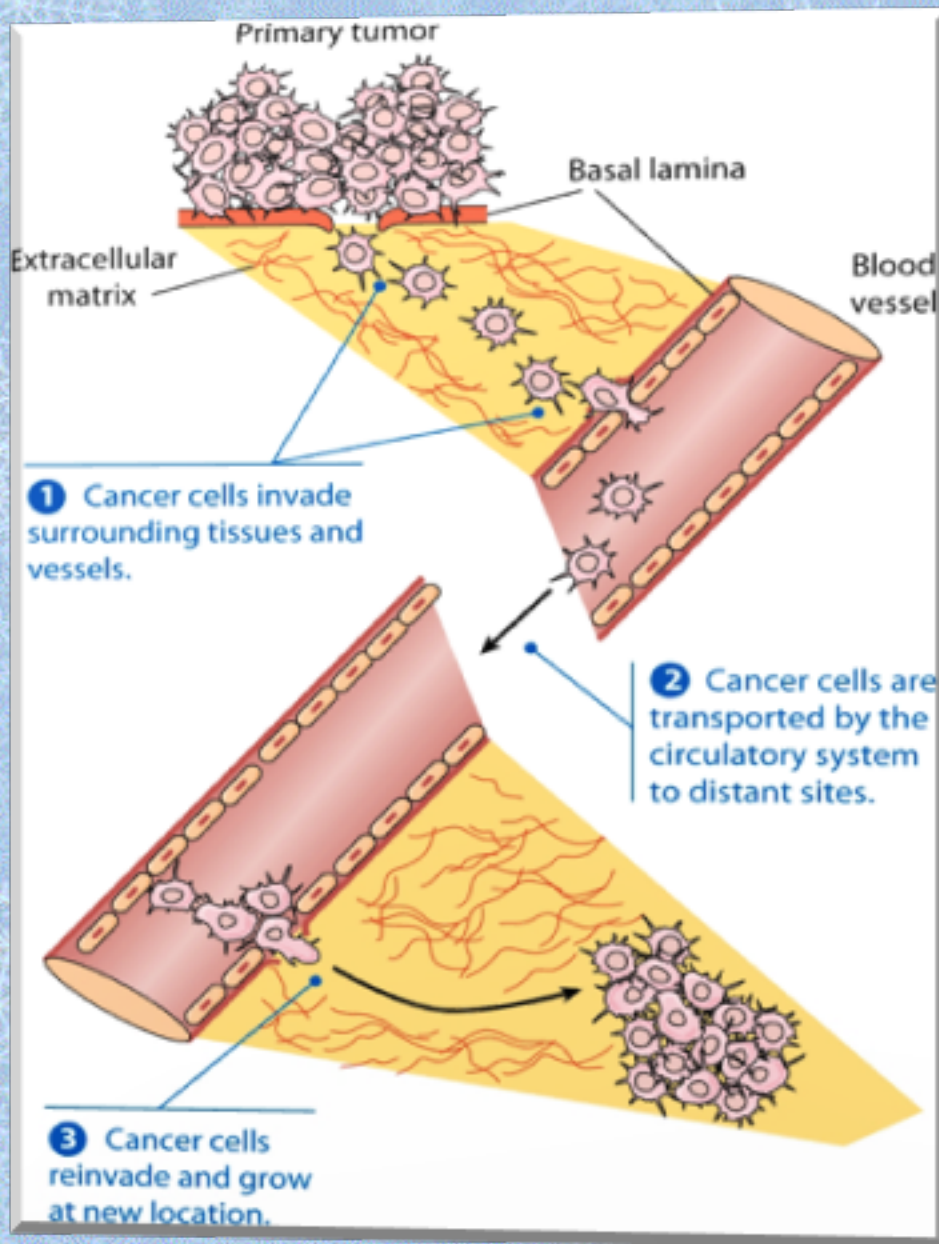
- proteins
- Humanized antibodies

Stages of Angiogenesis

Source: Graphics from Time Magazine

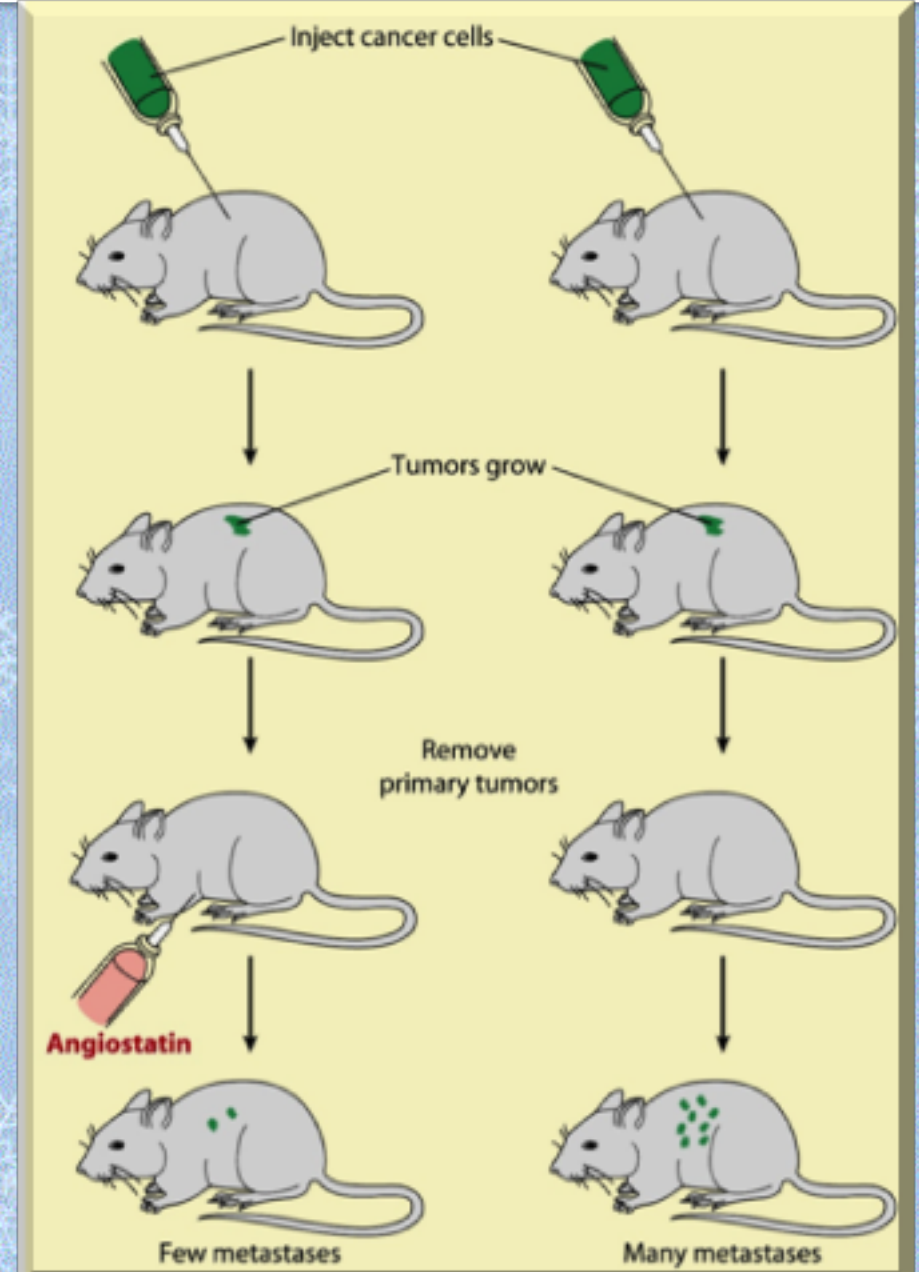
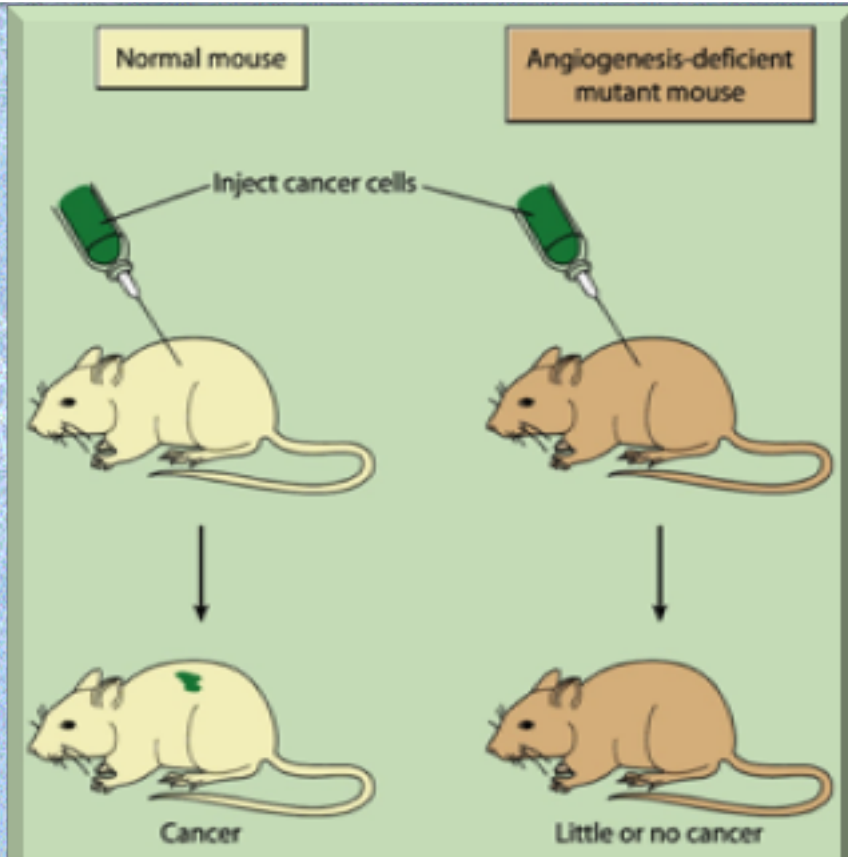


Steps Involved in The Metastatic Process

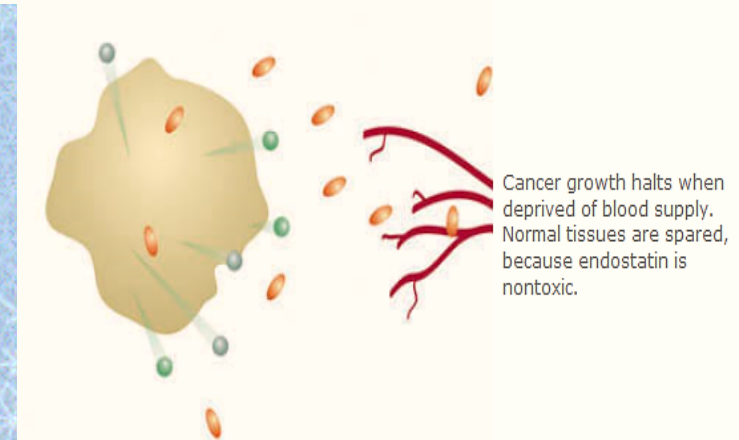
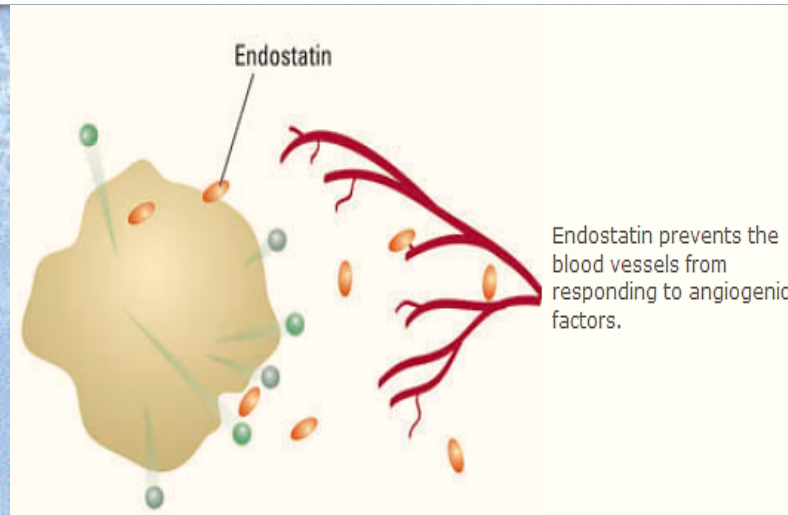
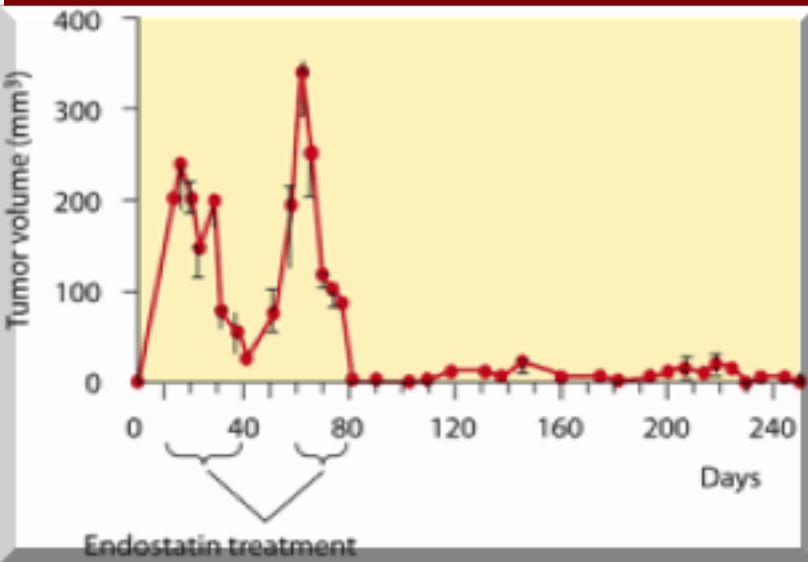


- ❑ The ability to invade differs among cancer cells and tumors
- ❑ Blood flow patterns often dictate where cancers will spread to
- ❑ Relatively few cancer cells survive the voyage through the blood stream
- ❑ Cancer cells are able to invade because:
 1. Decreased adhesiveness
 2. Activated motility
 3. Protease production

Treating Cancer by Inhibition of Angiogenesis



Treating Cancer by Inhibition of Angiogenesis



Endostatin **IS** part of collagen, enzyme cleavage product
Collagen (cartilage, tendons, *jello*) is part of the extra cellular matrix/space
Tumors use Extra Cellular Matrix proteases to metastasize
To date Endostatin has *not* proven to be successful antiangiogenic treatment in Humans

Modern Medicine ... Modern problems

Counterfeit Avastin: FDA Warns Of New Batch Of Fake Cancer Drug

02/06/13 11:56 AM ET EST **AP**

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AP

- Biomedicine/Immunologics
- avastin(bevacizumab) mab
monoclonal antibody
- 5 billion USD/yr world wide
- Chemo ~250K
- Chemo plus avastin ~500K
- Difference in time without progression - months

More Money Medicine

The New York Times

Business Day

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- Macular degeneration
- Lucentis is a purified form of Avastin
- \$2000/dose VS \$20 dose
- Off-label use
- Infections with Avastin due to sloppy procedure?

Genentech Offers Secret Rebates for Eye Drug

By ANDREW POLLACK
Published: November 3, 2010

[Genentech](#) has begun offering secret rebates to eye doctors as an apparent inducement to get them to use more of the company's expensive drug Lucentis rather than a less costly alternative.

[Enlarge This Image](#)



Madalyn Ruggiero for The New York Times

Dr. Greg Rosenthal, a retina specialist, said the rebates on Lucentis amounted to bribery.

Under the program, which started on Oct. 1, medical practices can earn up to tens of thousands of dollars in rebates each quarter if they use a lot of Lucentis and if their usage increases from the previous quarter, according to a confidential document outlining the program that was obtained by The New York Times.

Lucentis, approved in 2006, is mainly used to treat age-related [macular degeneration](#), the leading cause of [blindness](#) in the elderly. It costs about \$2,000 for each

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Hope for an Avastin Biomarker

Anti-angiogenic therapy may be more beneficial in ER-negative subset; data very limited

Chicago—An exploratory analysis of patients in the Eastern Cooperative Oncology Group 2100 trial has shown that a 13-gene signature may help identify breast cancer patients who will gain a survival advantage from bevacizumab. Investigators caution that the study is an underpowered analysis of a subset of patients in the trial and additional studies are needed. The molecular signature is not ready to be used in clinical practice.

“The search for biomarkers continues, as we try to resurrect anti-angiogenic therapy for breast cancer out of the ashes. It’s not dead yet,” said Hope S. Rugo, MD, a professor of medicine at San Francisco’s Helen Diller Family Comprehensive Cancer Center at the University of California, who was not involved with the study.

- **Biomarker** – gene mutation(s) shown to be associated with “good” response to a given treatment
- “Good” = 5 months without increase in tumor size
- Avastin was once used to treat breast cancer
- Colon and lung cancer biomarkers are still being evaluated

Bevacizumab in Colorectal Cancer: Current Role in Treatment and the Potential of Biosimilars.

Rosen LS¹, Jacobs JA², Burkes RL³.

⊕ Author information

Abstract

Colorectal cancer (CRC) is a leading cause of tumor-related morbidity and mortality worldwide, with mortality most often attributable to metastatic disease. Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor, has a significant role in the treatment of metastatic CRC (mCRC). However, patient access to bevacizumab may be limited in some regions or circumstances, owing to factors related to insurance coverage, reimbursement, patient out-of-pocket costs, or availability. As a result, outcomes for patients with mCRC may be worsened. Additionally, counterfeit bevacizumab has infiltrated legitimate supply chains, exposing patients to risk. Oncologists may also be affected detrimentally, since resolving access issues can be time-consuming and demoralizing. The imminent expiry of patents protecting bevacizumab provides other manufacturers with the opportunity to produce highly similar versions known as biosimilars. High-quality, safe, and effective biosimilars have the potential to expand access to bevacizumab. Most of the bevacizumab biosimilars currently in development are in clinical trials in patients with non-small-cell lung cancer, and future authorization for mCRC indications will, therefore, be based on extrapolation. This article reviews the current role of bevacizumab in the management of mCRC, the possible barriers associated with diminished access to bevacizumab, and the potential bevacizumab biosimilars in development. How biosimilars may impact the treatment of mCRC is also discussed.

AVASTIN = Bevacizumab: monoclonal antibody = biologic / immunologic treatment

Biosimilar: generic version of a biologic treatment