Introduction to Cancer basics?

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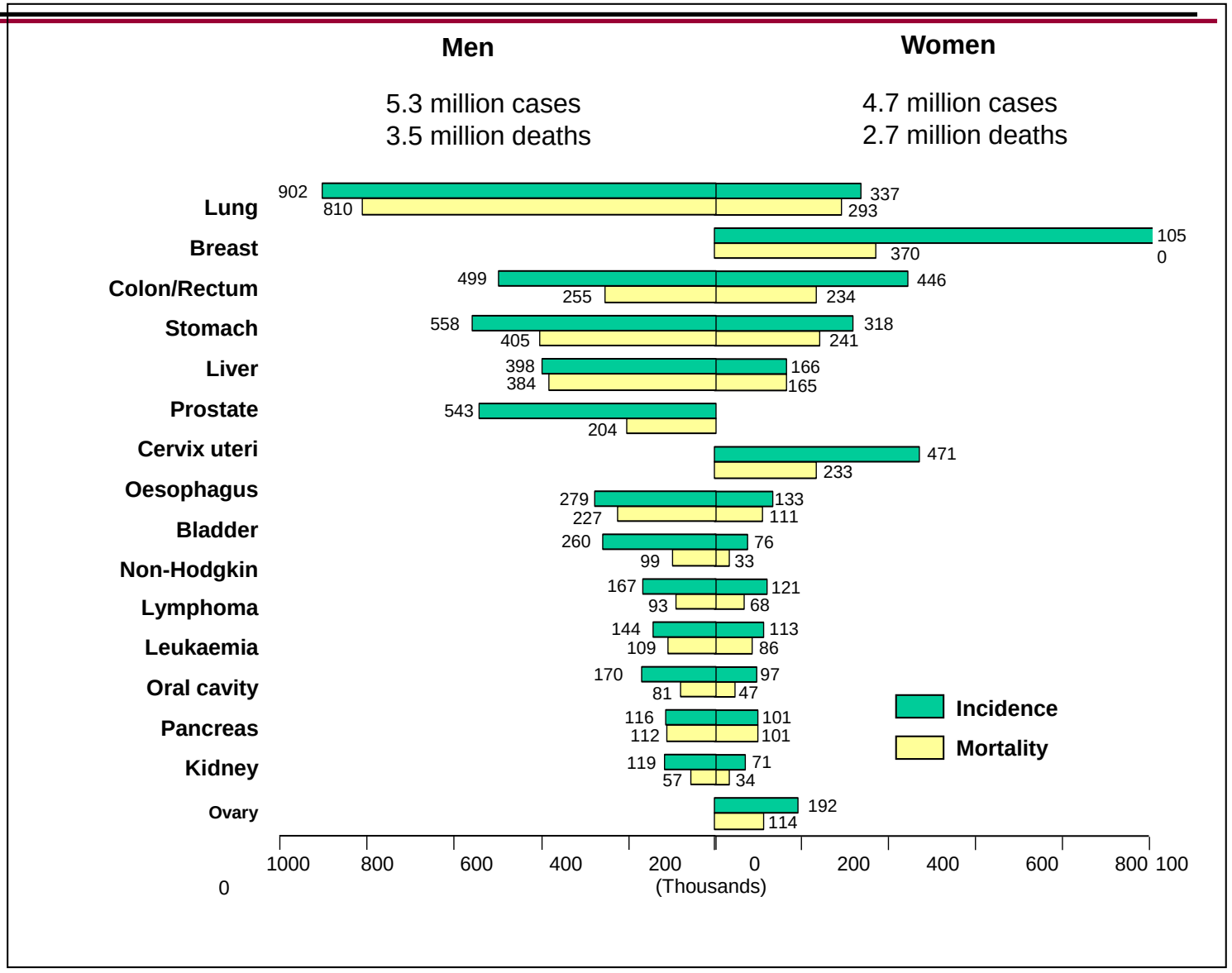
Statistics

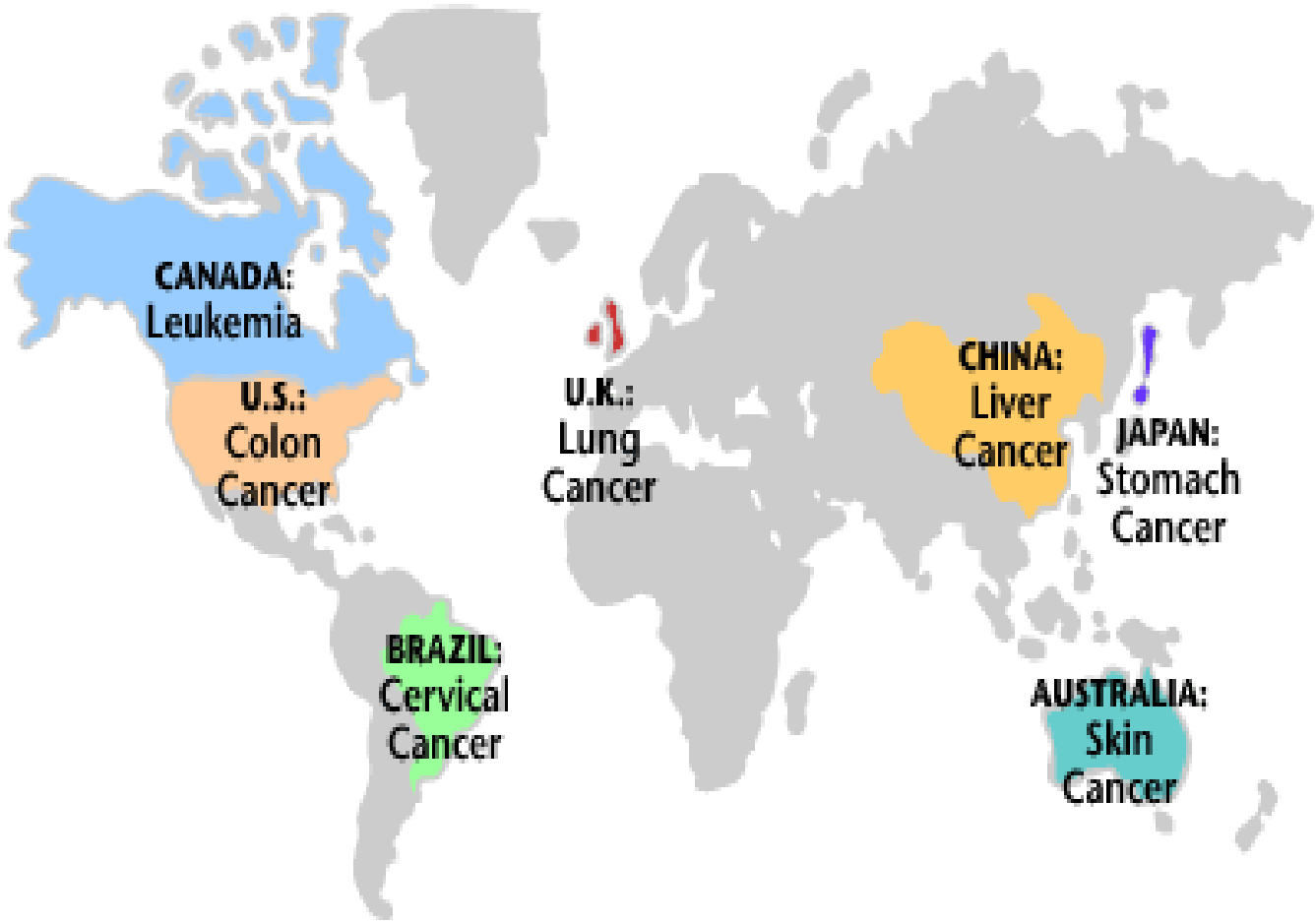
- >9.7 million cases are detected each year
- 6.7 million people will die from cancer
- Every day, around 1700 Americans die of the disease
- 20.4 million people living with cancer in the world today
- 1 in 3 people will be diagnosed with cancer in the UK and 1 in 4 will die from their disease

The Global Burden of Cancer 2000



From: D.M. Parkin *The Lancet Oncology* 2: 533-543 (2001)

Regions of Highest Incidence



What is Cancer?

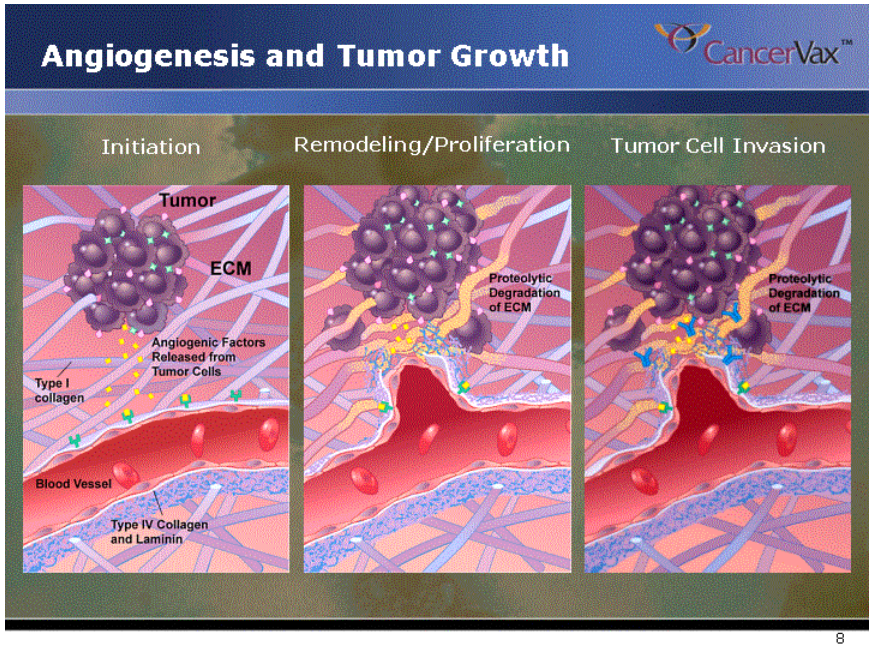
- Division – uncontrolled cell division
- Growth – formation of a lump (tumour) or large numbers of abnormal white cells in the blood
- Mutation – changes to how the cell is viewed by the immune system
- Spread – ability to move within the body and survive in another part

Growth

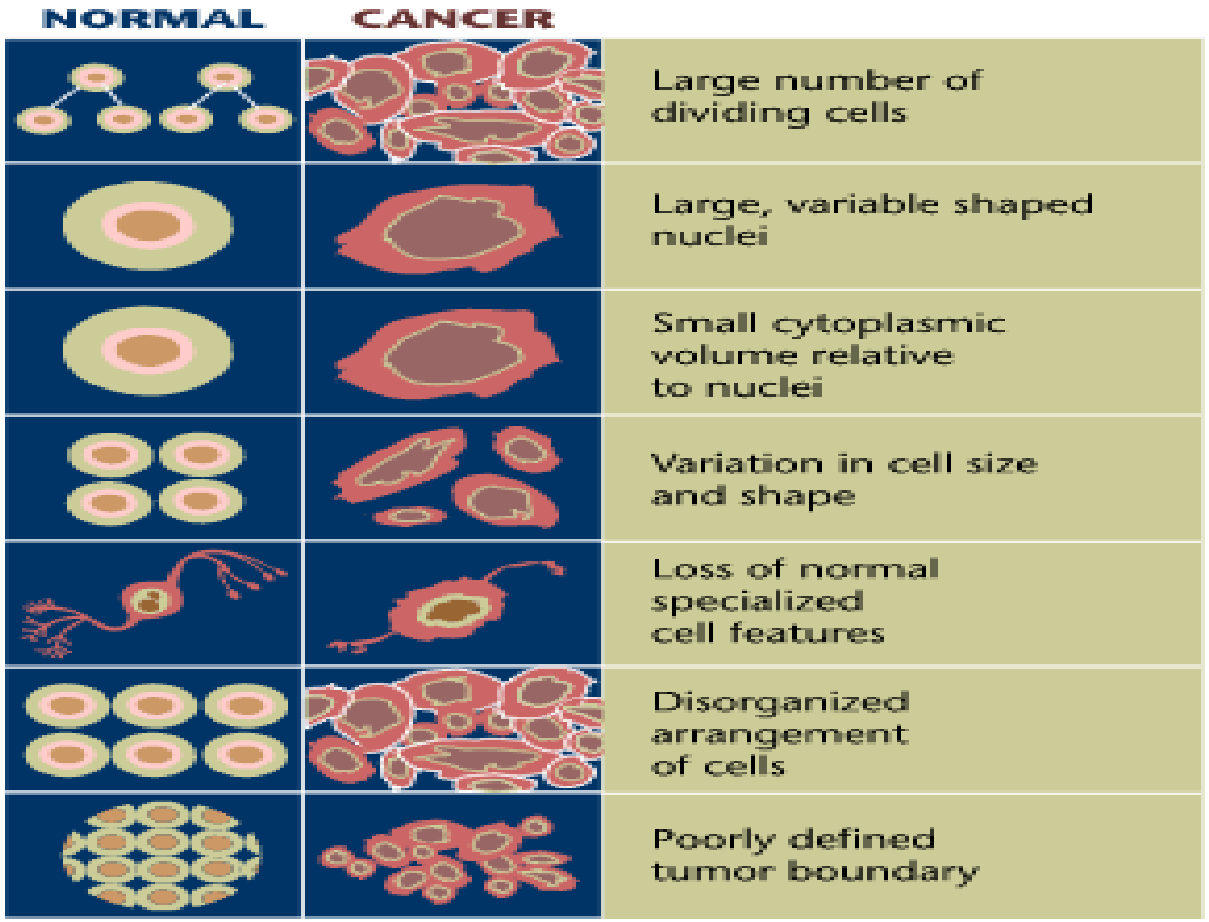
- Tumour
  - Pressure on nerves
  - Blocking organs
  - Stopping normal function
  - Altering nerve signals
  - Fungating

Mutation and Spread

- Invasion
- Angiogenesis
- it must be able to leave its usual environment and travel through the blood or lymph system, a process called **invasion** .
- when it arrives at its new location, it must be able to make new blood vessels grow around it and supply it with oxygen and nutrients, a process known as **angiogenesis**.

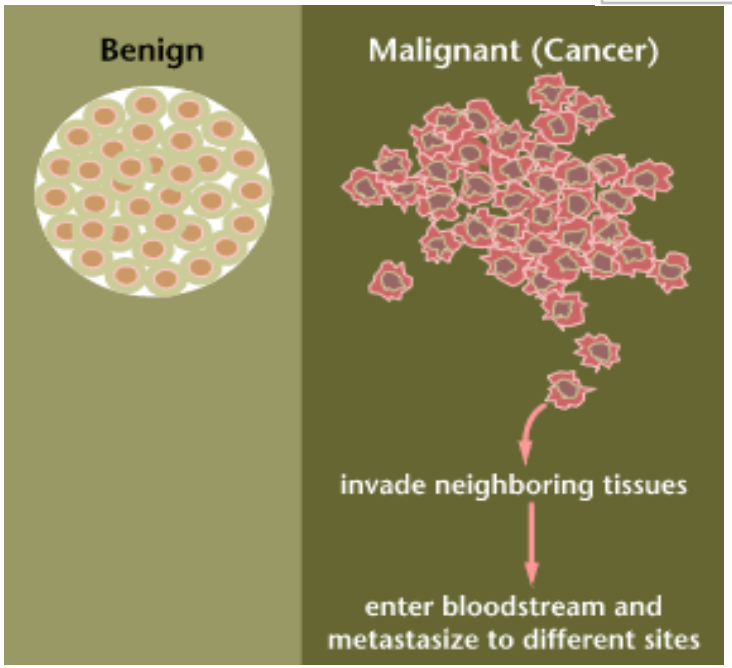


What are the differences in the features of normal and cancer cells?

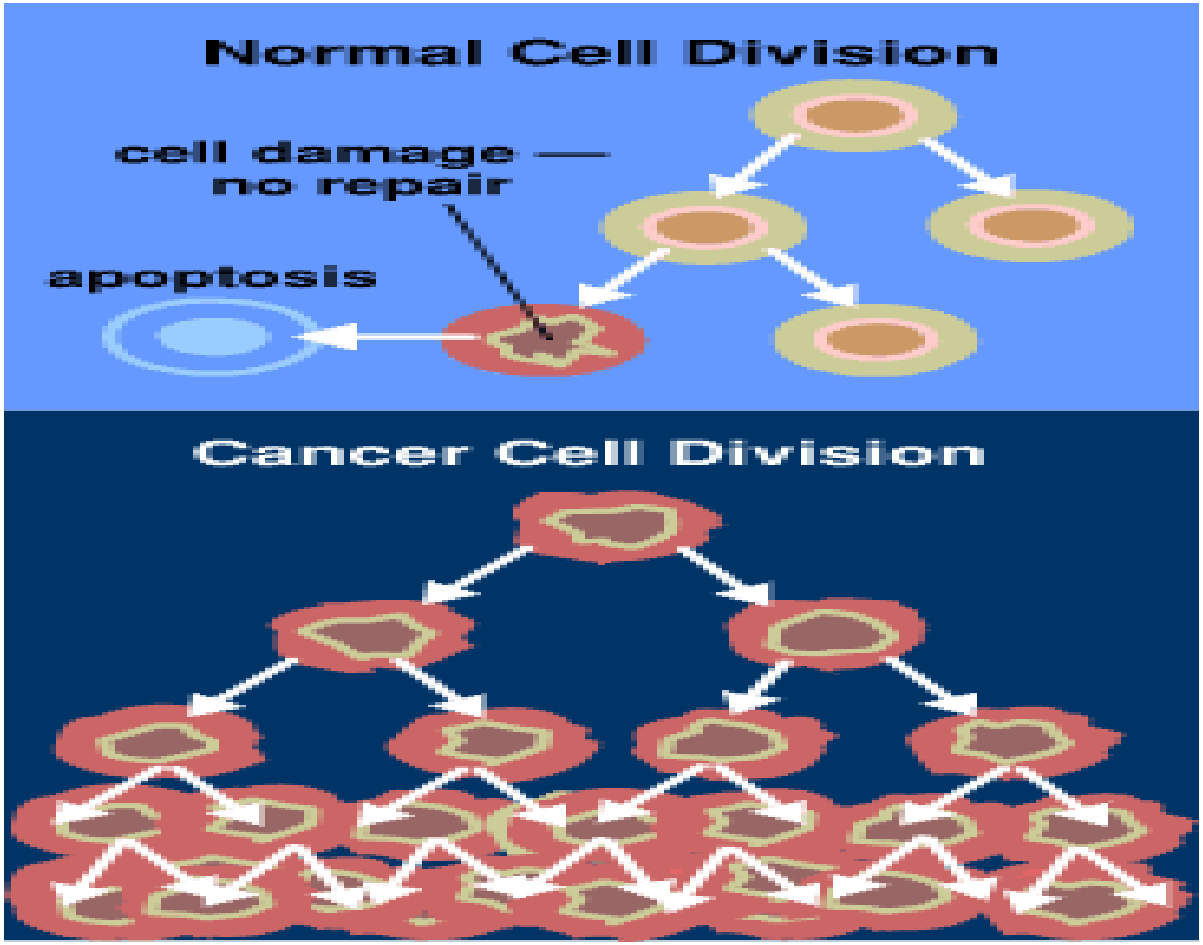


Malignant versus benign tumours

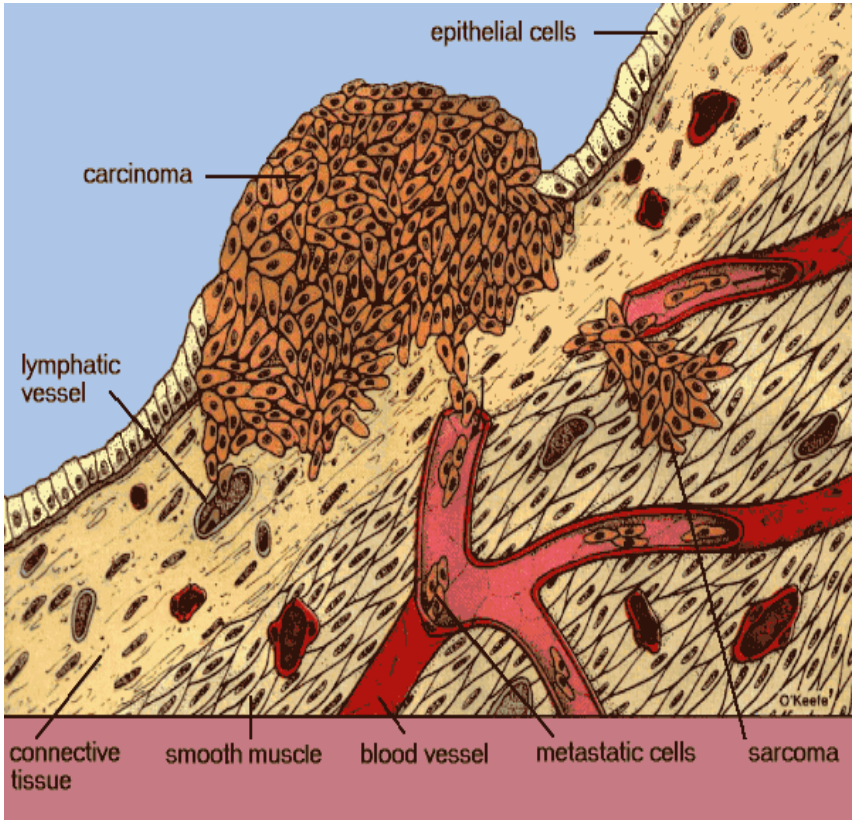
مشخصه	تومور بدخیم	تومور خوش‌خیم
کپسول‌دار بودن	به‌ندرت	اغلب
تمایز یافتگی	اندک	تاحدودی
متاستاز	غالباً	ندارد
عود	مکرر	به‌ندرت
عروق	متوسط تا زیاد	اندک
مشخصات سلولی	غیرطبیعی و بی شباهت به سلول والد	نسبتاً طبیعی و مشابه سلول والد

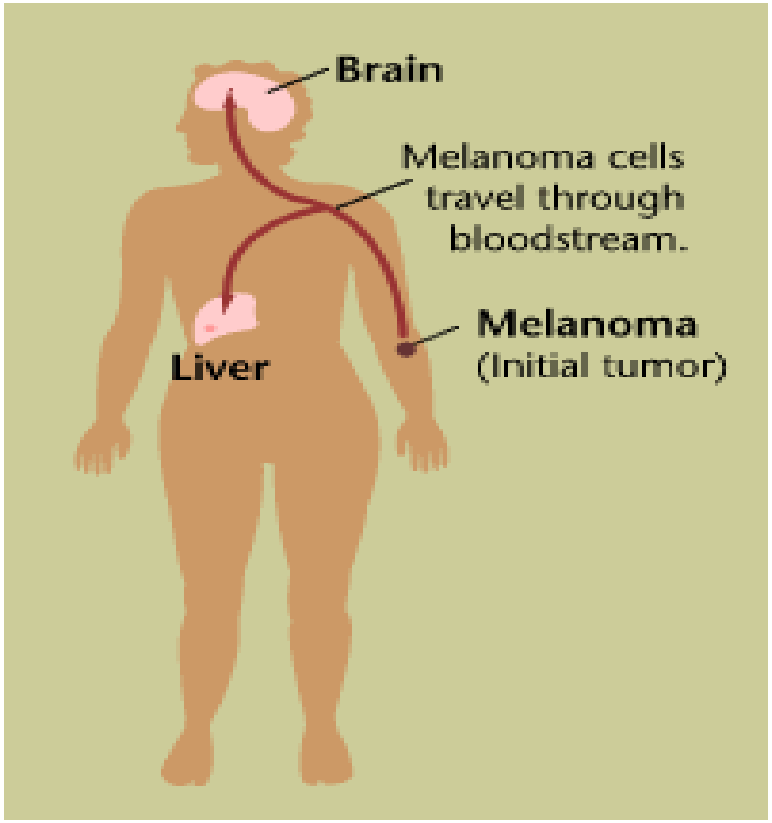


Normal and abnormal cell growth

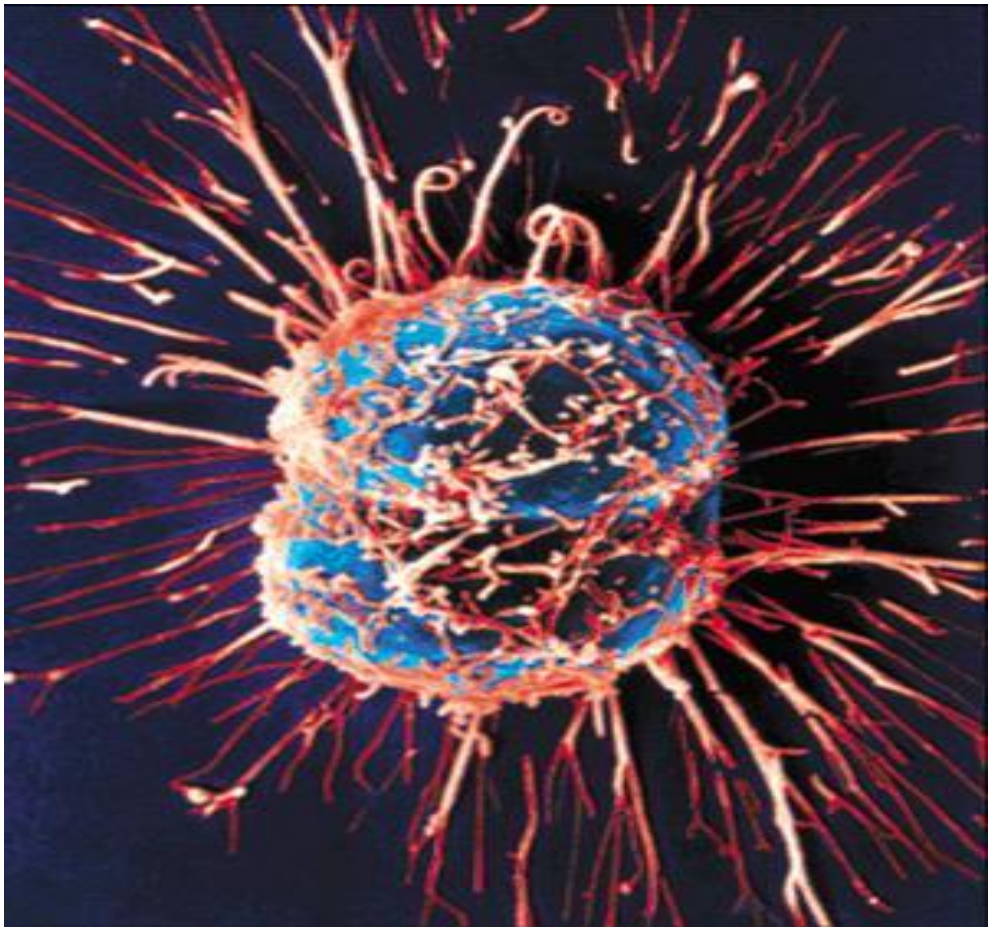


Metastatic cancer



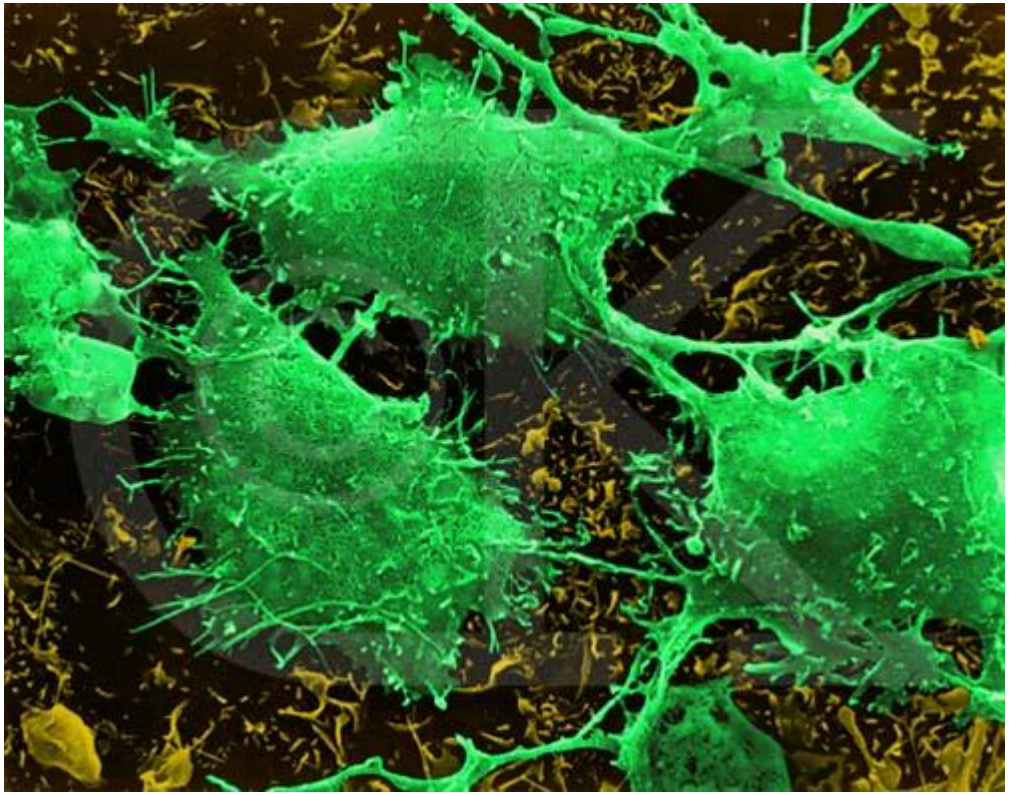


What causes cancer?



Carcinogenesis.
Some factors to consider…

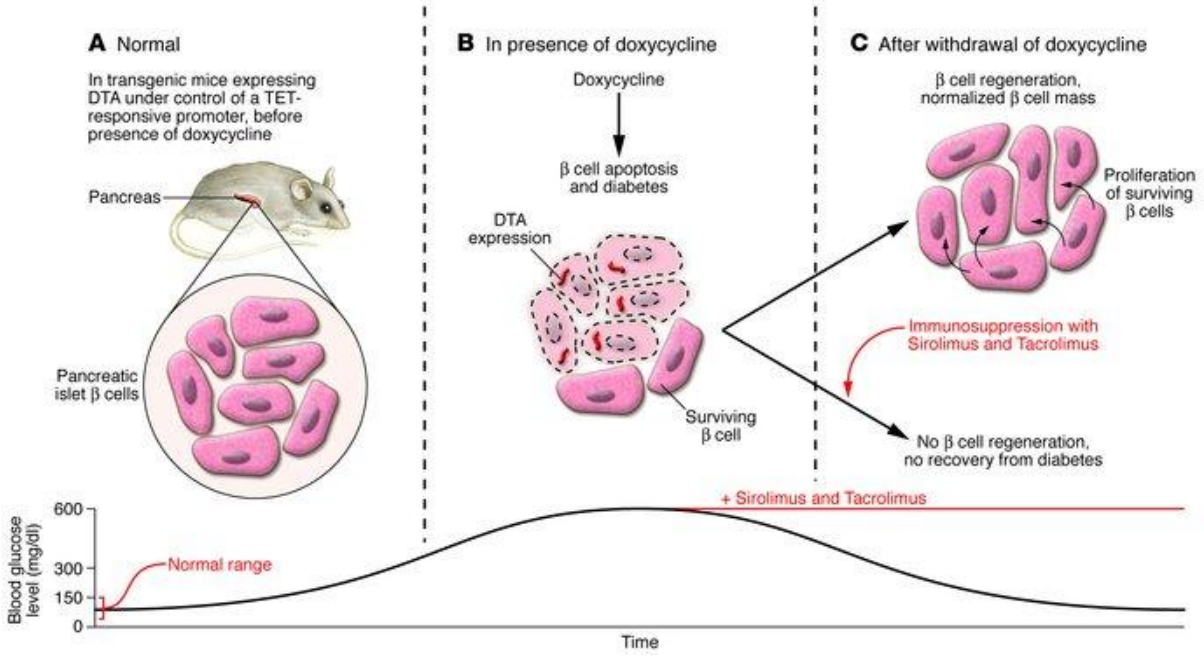
- Heredity
- Immunity
- Chemical
- Physical
- Viral
- Bacterial
- Lifestyle



Immunity

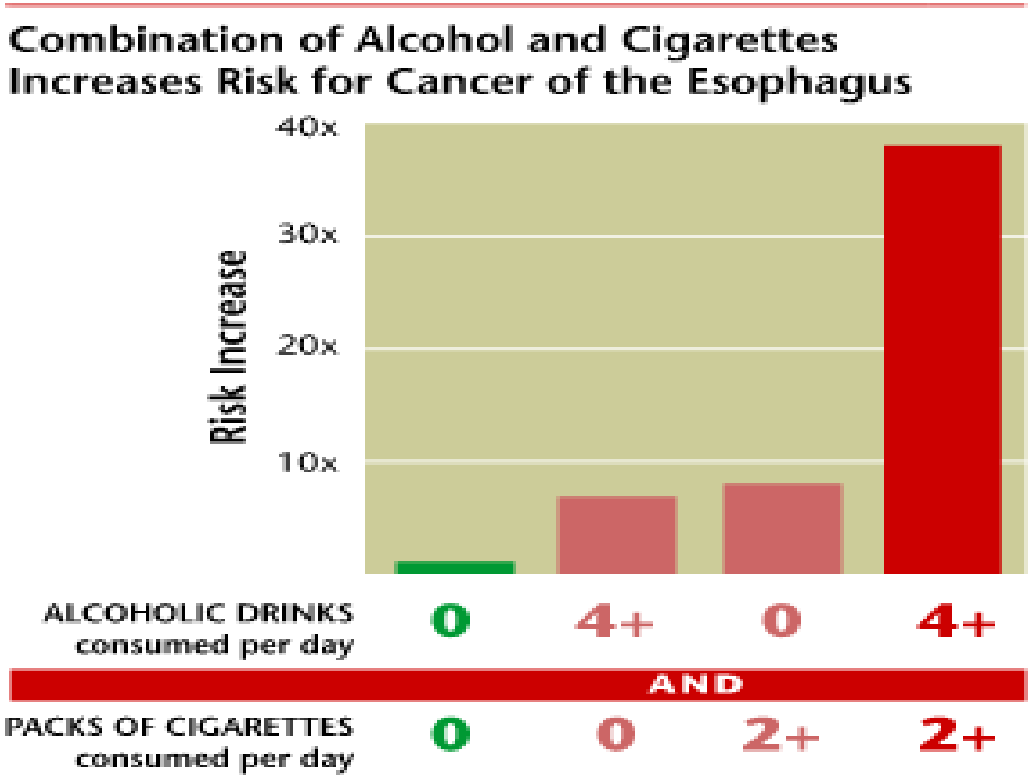
- HIV / AIDS
- Immunosuppression

A person who is undergoing immunosuppression, or whose immune system is weak for other reasons (for example, chemotherapy or HIV), is said to be *immunocompromised*. An **immunosuppressant** is any agent that weakens the immune system, including immunosuppressive drugs and some environmental toxins.



Smoking and alcohol

Smoking: Single biggest cause of cancer



Physical causes

- Ultraviolet radiation
  - Sunlight
  - Certain industrial sources

- Radiation
  - Radon
  - Cancer treatment

Obesity

Lifestyle:

- Highly caloric diet, rich in fat, refined carbohydrates and animal protein
- Low physical activity

Consequences:

- **Cancer**
- Diabetes
- Cardiovascular disease
- Hypertension

Lifestyle

- Age
- Occupation
- Ethnicity
- Deprivation

Diagnosis and staging

- Clinical History
- Normal diagnostic procedures
  - Scans, xrays
  - Blood tests
  - Biopsy
- Pathological staging

- تست های غربالگری سرطان میتواند در تشخیص آن در مراحل اولیه و حتی قبل از شروع علایم بالینی کمک کننده باشد. انواع روش های تشخیصی سرطان ها عبارت است از:

معاینه فیزیکی، تست های آزمایشگاهی، انواع عکس برداری ها و تست های ژنتیکی که خود شامل انجام بیوپسی از بافت های درگیر سرطان، CTاسکن، MRI، سونوگرافی، ماموگرافی، کولونوسکوپی، آندوسکوپی، پاپ اسمیر، تست های کبدی، آزمایش شمارش سلول های خونی CBCو ...

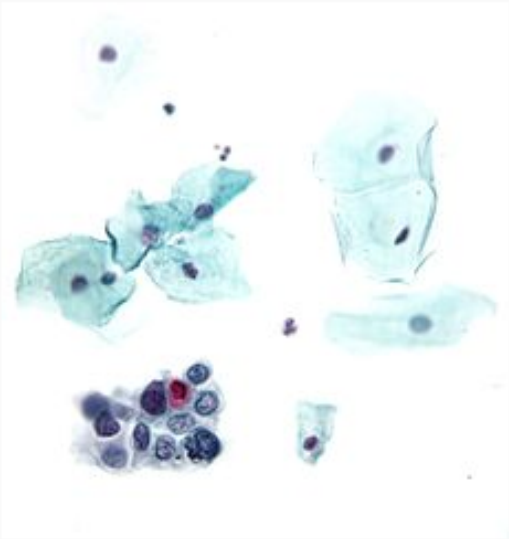
آزمایش پاپ اسمیر یا **آزمایش اسمیر** جز آزمایش‌های غربال‌گری است که برای تشخیص سرطان یا عواملی که منجر به سرطان خواهند شد، در گردن رحم دستگاه تولید مثلی زنان انجام می‌گیرد. این روش توسط پزشکی یونانی به نام جورجیوس پاپانیکولائو ابداع شد.

روش انجام آزمایش

در این روش پزشک توسط اسپکولوم دهانه دستگاه تناسلی را باز کرده و نمونه‌ها از رحم و گردن رحم برداشته می‌شود. نمونه‌ها برای تشخیص سلول‌های ناهنجار زیر میکروسکوپ مشاهده می‌شوند. [۱] این روش جز تشخیص سلول‌های سرطانی مرتبط با HPV[۲]، نشان‌دهنده عفونت‌های رحمی نیز است.

آزمایش پاپ اسمیر

مداخله درمانی



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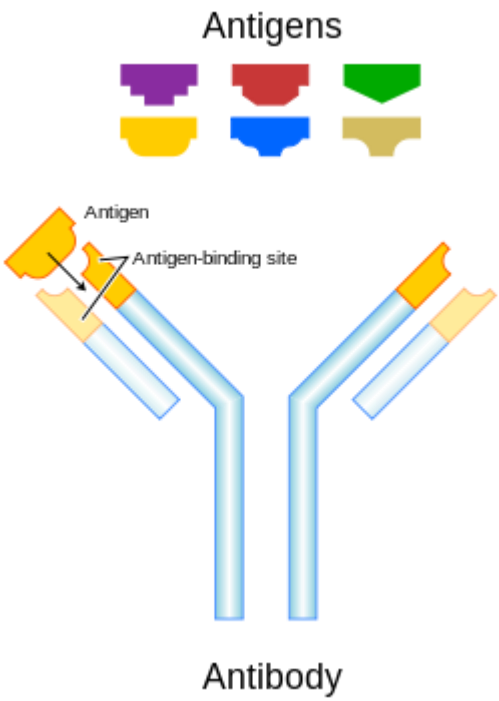
سمپ	D014626
مدلاین پلاس	003911

تکرار آزمایش

در سال‌های اخیر توصیه شده است که در خانم‌های زیر ۳۰ سال، هر دو سال یک‌بار و در خانم‌های بالای ۳۰ سال هر سه سال یک‌بار پاپ اسمیر انجام شود. [۳]


Antigens
Antigen
Antigen-binding site
Antibody

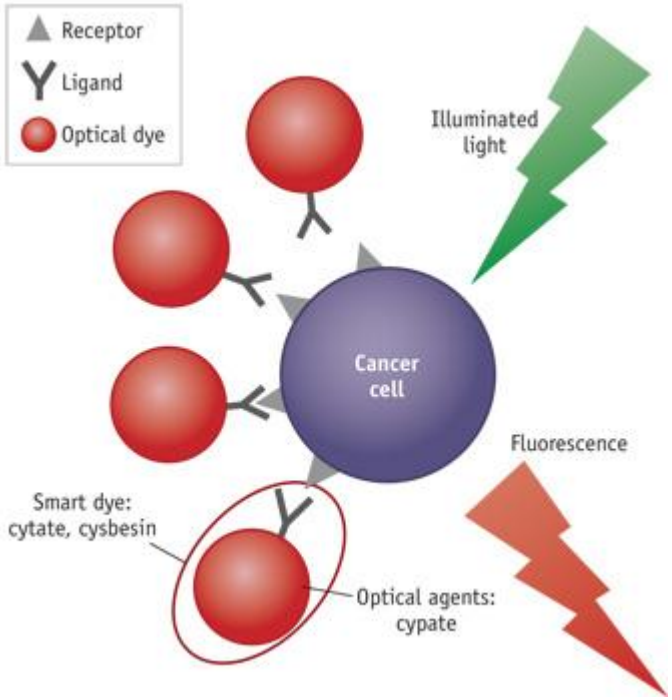

Receptor
Ligand
Optical dye
Illuminated light
Cancer cell
Fluorescence
Smart dye: cytate, cysbesin
Optical agents: cypate

Table 1 FDA approved therapeutic monoclonal antibodies for cancer therapy

Generic name	Proprietary name	Target	Technology	Isotype	Additional manipulations	Year FDA approved	Approved clinical indication
Rituximab	Rituxin®/ Mabthera®	CD20	Mouse Hybridoma	IgG1-kappa	Chimeric	1997	NHL; later CD20+CLL, FL, RA
Transtuzumab	Herceptin®	HER-2	Mouse Hybridoma	IgG1-kappa	Humanized	1998	HER-2$^+$ MBC
Alemtuzumab	Campath®/ Mabcampath®	CD52	Rat Hybridoma	IgG1-kappa	Humanized	2001	CL L, T-cell Lymphoma
Ibritomomab tiuxitan	Zevalin®	CD20	Mouse monoclonal	IgG1-kappa	Conjugated to Yittrium-90	2002	NHL
Tositumomab	Bexxar®	CD20	Mouse monoclonal	IgG2a-lambda	Conjugated to I-131	2003	NHL
Cetuximab	Erbitux®	EGRF, HER-1	Mouse monoclonal	IgG1- kappa	Chimeric	2004	EGRF$^+$ MCC
Bevacizumab	Avastin®	VEGF	Mouse monoclonal	IgG1- kappa	Humanized	2004	MCC
Panitumumab	Vectibix™	EGRF, HER-1	Human monoclonal	IgG2-kappa	Human	2006	MCC
Ofatumumab	Arzerra™	CD20	Human monoclonal	IgG1-kappa	Human	2009	Refractory CLL
Ipilimumab	Yervoy™	CTLA-4	Human monoclonal	IgG1-kappa	Human	2011	MMel
Pertuzumab	Perjeta™	EGFR2, HER-2	Mouse monoclonal	IgG1-kappa	Humanized	2012	BC

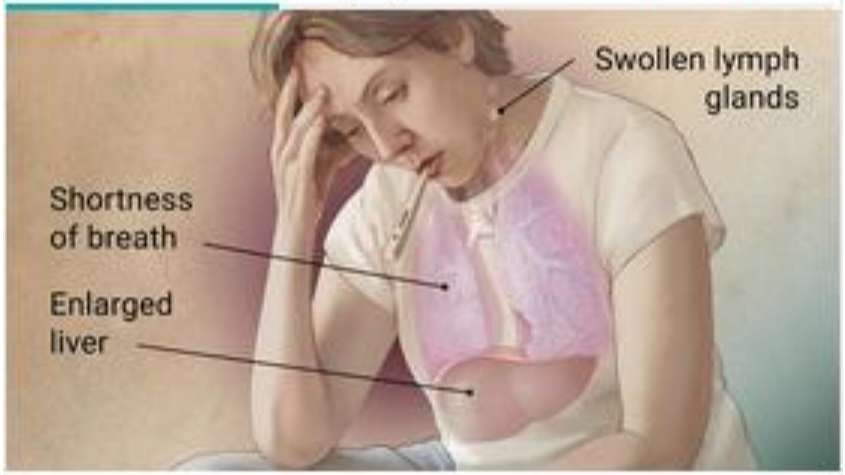
BC, Breast cancer; MBC_Metastatic breast cancer; NHL, Non-Hodgkin's Lymphoma; CLL, Chronic Lymphocytic leukemia; FL, Follicular Leukemia; RA, Rhematoid arthritis; MCC, Metastatic colorectal cancer; MMel, metastatic melanoma.

Lymphoma is a cancer of a part of the immune system called the lymph system

Leukemia

Also called: blood cancer

About Symptoms Treatments

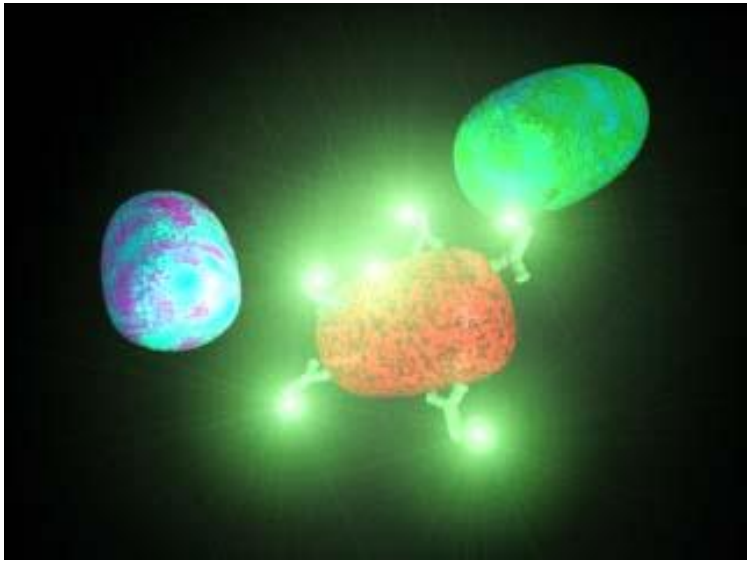


A cancer of blood-forming tissues, hindering the body's ability to fight infection

تشخیص in-vivo

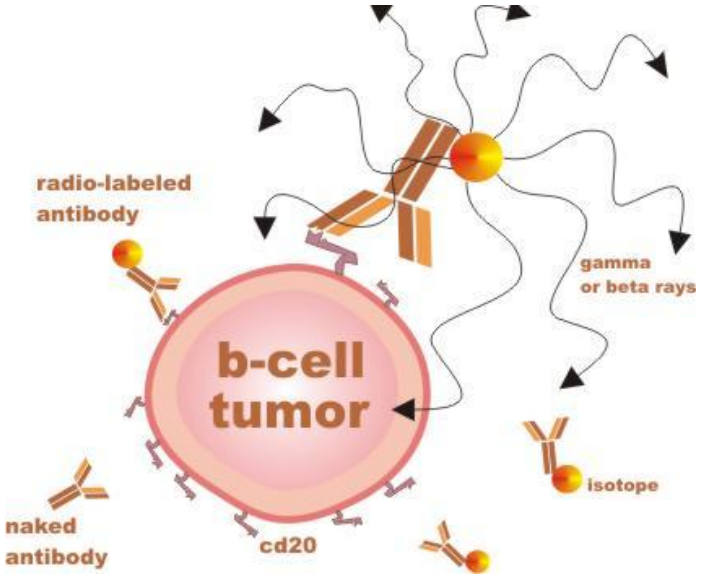
در حال حاضر آنتی بادیهای منوکلونال متعددی برای ردیابی موارد بیماری مانند: انواع تومورها (سرطان ریه، پروستات، کلون، تخمدان)، بیماری قلبی، التهابات و عفونت در بدن انسان وجود دارد. در اینگونه موارد از آنتی بادی ضد آنتی ژن اختصاصی بافت بیمار که معمولاً تغییر یافته آنتی ژن طبیعی و یا نوعی از آن است که در حالت طبیعی در سطح سلول بیان نمی شود (میوزین)، استفاده می شود بدین ترتیب که این آنتی بادی را با یك رادیوایزوتوپ نشاندار می کنند و پس از تزریق این آنتی بادی نشاندار شده محل قرارگیری آنرا در بدن ردیابی می کنند.

از این روش برای تعیین محل توده های سرطانی قبل از عمل جراحی استفاده کرد.



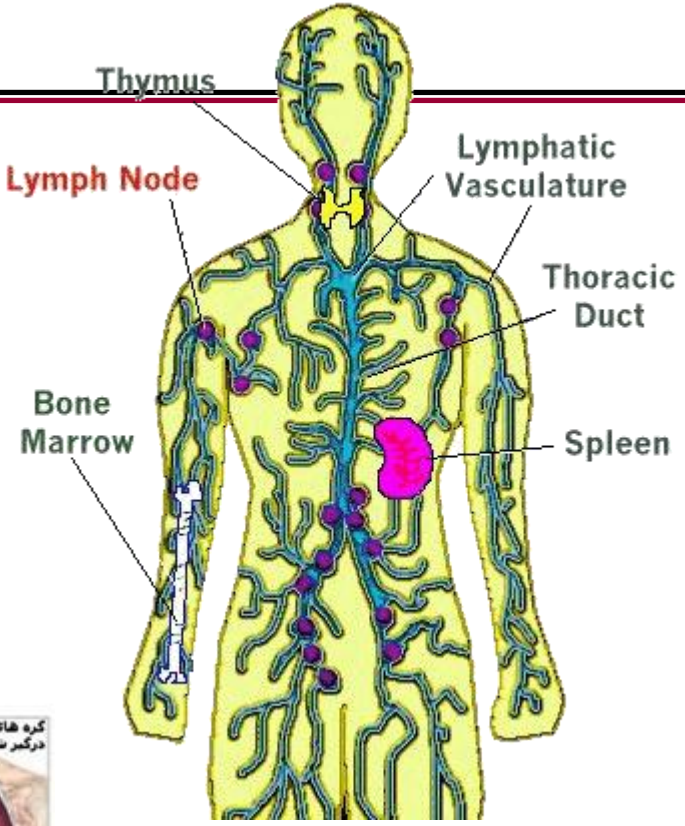
hematological cancer

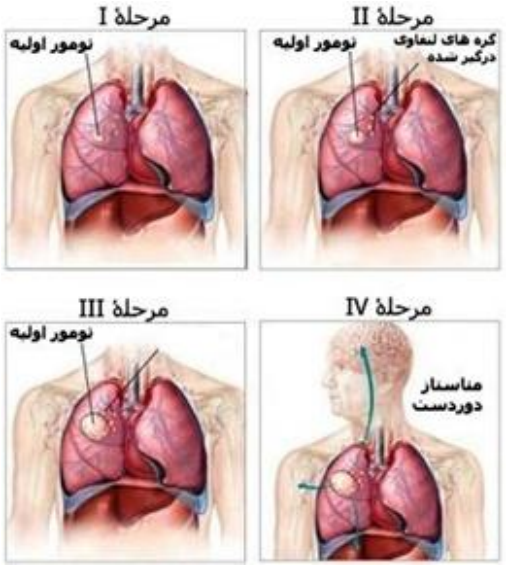
- Ibritumumab is a murine anti-CD20 monoclonal antibody conjugated to the yttrium isotope (90Y-Ibritumumab tiuxetan). This intense β-radiation releasing immunoconjugate was approved in 2002 for use in patients with NHL but has also shown efficacy in Rituxin-refractory lymphoma [20]. Another immunoradioisotope, tositumomab- I131, was approved in 2003 for treatment of patients with CD20+ FL. Both drugs are efficacious but induce hemato-toxicity and have been the subject of several comparison clinical trials

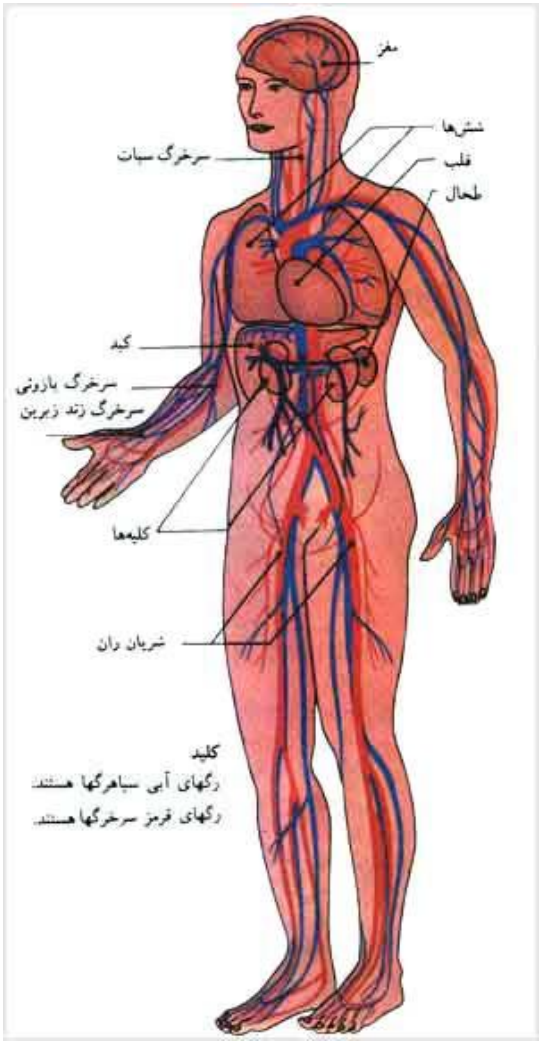


Staging

- Size
- Invasion
- Lymph nodes
- Metastasises







TNM Staging

- **T** (a,is,(0),1-4): size or direct extent of the primary tumor
- **N** (0-3): degree of spread to regional lymph nodes
  - N0: tumor cells absent from regional lymph nodes
  - N1: tumor cells spread to closest or small number of regional lymph nodes
  - N2: tumor cells spread to an extent between N1 and N3.
  - N3: tumor cells spread to most distant or numerous regional lymph nodes
- **M** (0/1): presence of metastasis
  - M0: no distant metastasis
  - M1: metastasis to distant organs (beyond regional lymph nodes)

- **Other parameters**
- **G** (1-4): the grade of the cancer cells (i.e. they are "low grade" if they appear similar to normal cells, and "high grade" if they appear poorly differentiated)
- **R** (0/1/2): the completeness of the operation (surgery-boundaries free of cancer cells or not)
- **L** (0/1): invasion into lymphatics
- **V** (0/1): invasion into vein
- **C** (1-4): a modifier of the **certainty** (quality) of the last mentioned parameter

Examples

- Small, low grade cancer, no metastasis, no spread to regional lymph nodes, cancer completely removed, resection material seen by pathologist - pT1 pN0 M0 R0 G1; this would be considered Stage I.

- Large, high grade cancer, with spread to regional lymph nodes and other organs, not completely removed, seen by pathologist - pT4 pN2 M1 R1 G3; this would be considered Stage IV.

- Most Stage I tumors are curable; most Stage IV tumors are not.

Summary

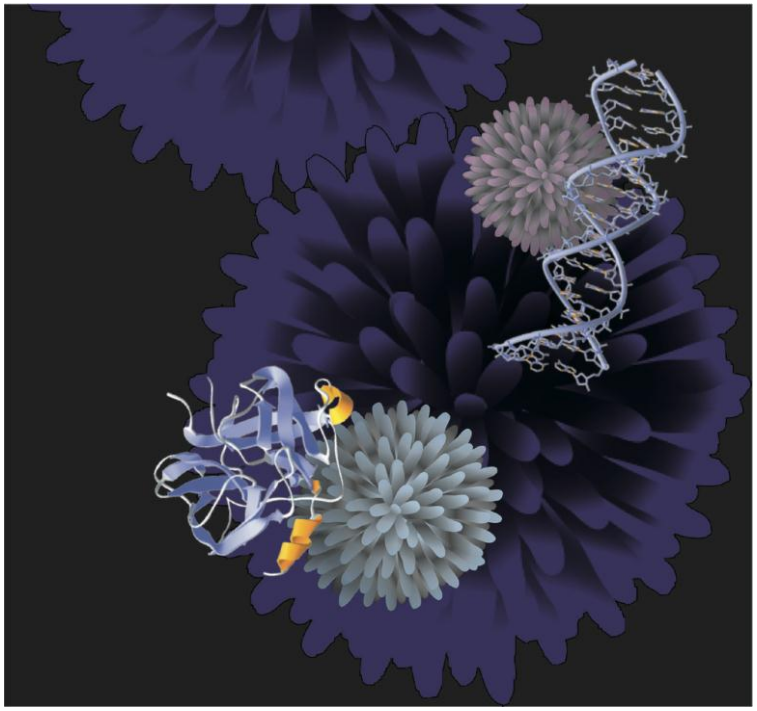
- Cancer is a disease of Division, growth and spread
- It has a number of causes many of them preventable
- The survival of the patient is determined by the stage of the disease, the earlier the detection or the smaller the tumour the better the survival

10 Rules to Avoid Cancer

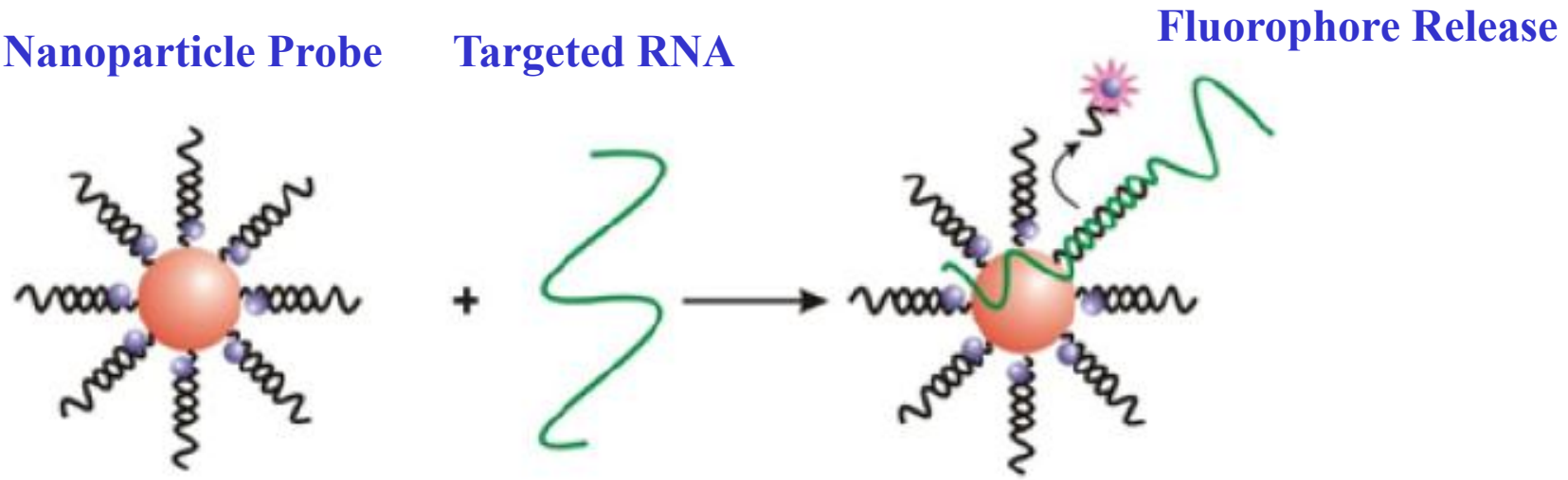
1. Don’t smoke
2. Don’t smoke.
3. Don’t smoke.
4. Avoid exposure to other known carcinogens, including aflatoxin, asbestos and UV light.
5. Enjoy a healthy diet, moderate in calories, salt and fat, and low in alcohol.
6. Eat fresh fruit and vegetables several times a day.
7. Be physically active and avoid obesity.
8. Have vaccination against, or early detection/treatment of, cancer causing chronic infections.
9. Have the right genes.
10. Have good luck !

Introduction

- What is nanomedicine?
  - It is nanotechnology used for the treatment, diagnosis, monitoring and control of biological systems
  - It includes the delivery and targeting of pharmaceutical, therapeutic, and diagnostic agents using nanoparticles to cancer and other cells

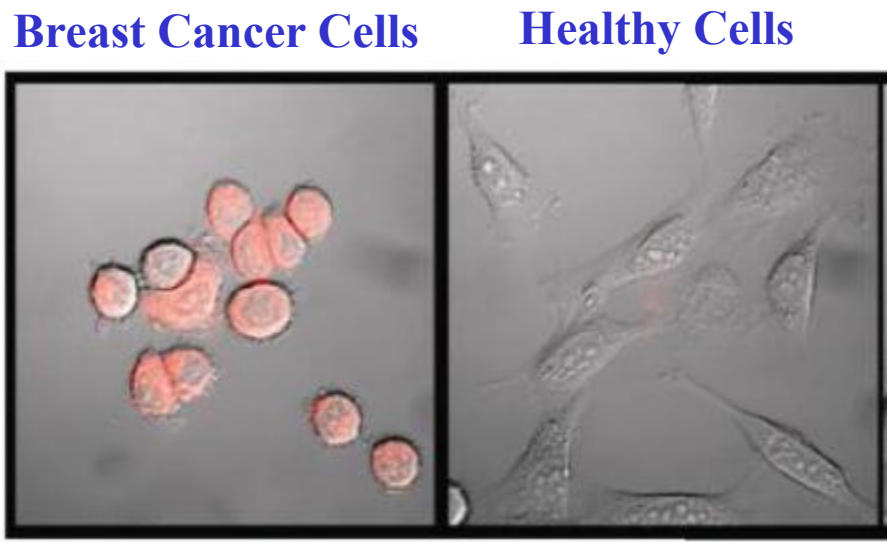


Nanoparticles for Pathogen Detection



- Gold nanoparticles can be functionalized with thiolated oligonucleatides.
- Bound to the oligonucleatides are fluorophores which are quenched by their proximity to the nanoparticle.
- When the targeted RNA (H2N2, HIV or a cancer) bindes to the oligonucleatide, the fluorophore is released and becomes fluorescence.
    - The fluorescence can be detected in a BioMEMS device.
- Challenge is developing oligonucleatides with high selectivity for the target RNA.

Nanoparticles for Targeted Detection of Cancer

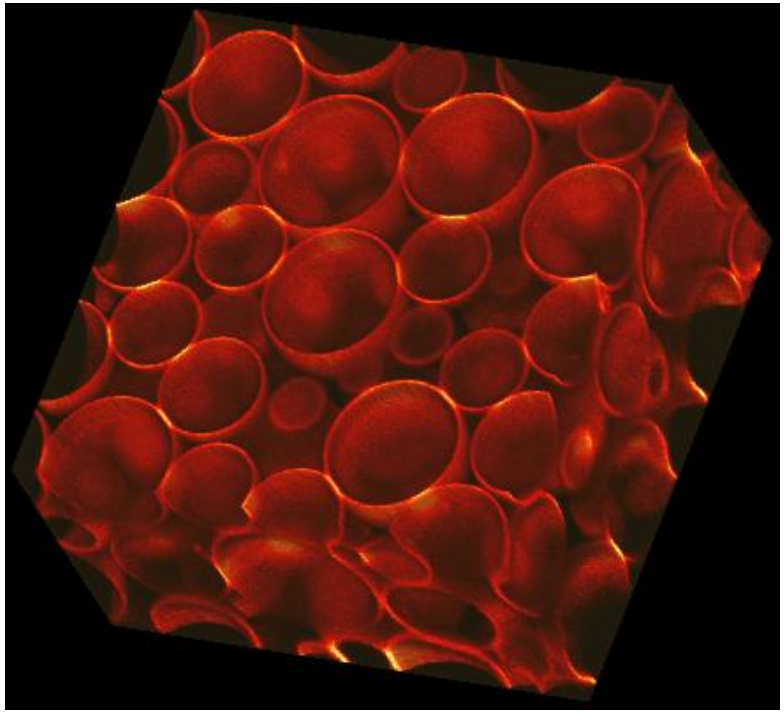


- As an example, nanoparticle probes were developed by Chad Mirkin at Northwestern Univ. that target the survivin RNA sequence known to exist in a certain breast cancers.
- Experiments are done ex-vivo.
- On the left, cancer cells fluoresce.
- On the right, healthy cells show minimal fluorescence.

Nanoparticle Encapsulation for Drug Delivery

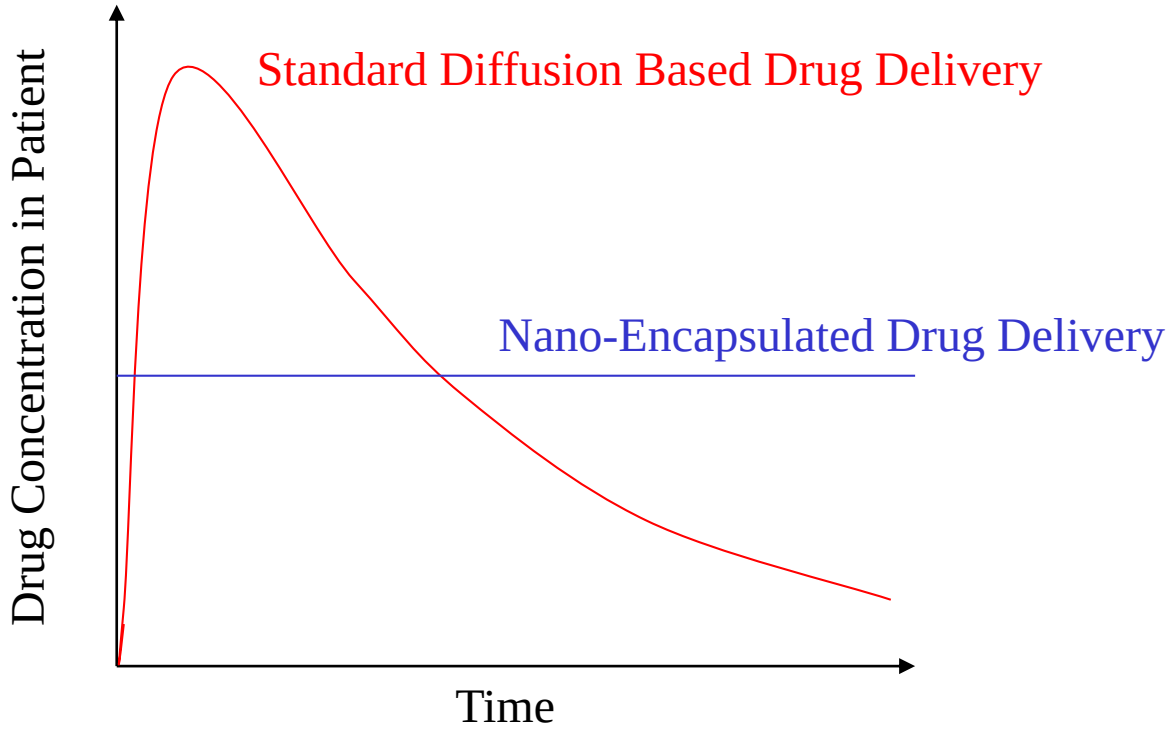
- Nanoparticle shells can be formed around spherical droplets
  - A.D. Dinsmore, *et al., Science* 298, 1006 (2002), Y. Lin, *et al., Science* 299, 226 (2003)

- Shells are porous at lengthscales much smaller than size of nanoparticle.



Nano-Encapsulation for Drug Delivery

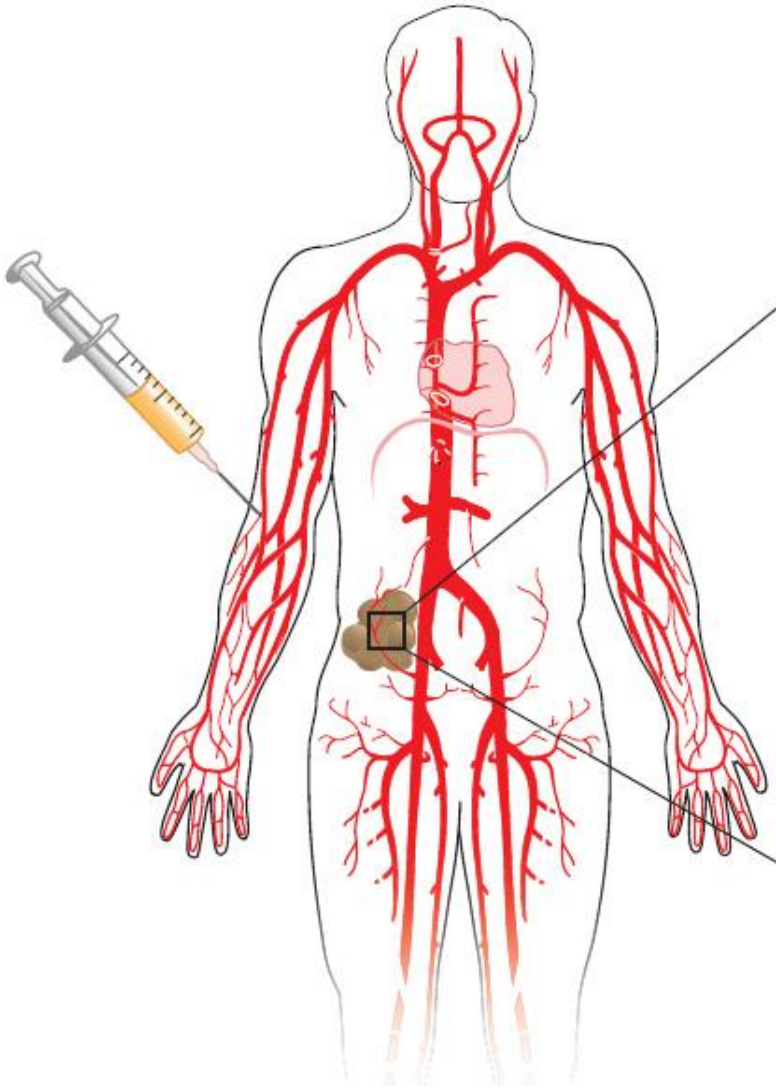
- By making the holes between nanoparticles approximately the same size as the drug you want to administer you can get a constant release rate – avoids spikes in dosage.

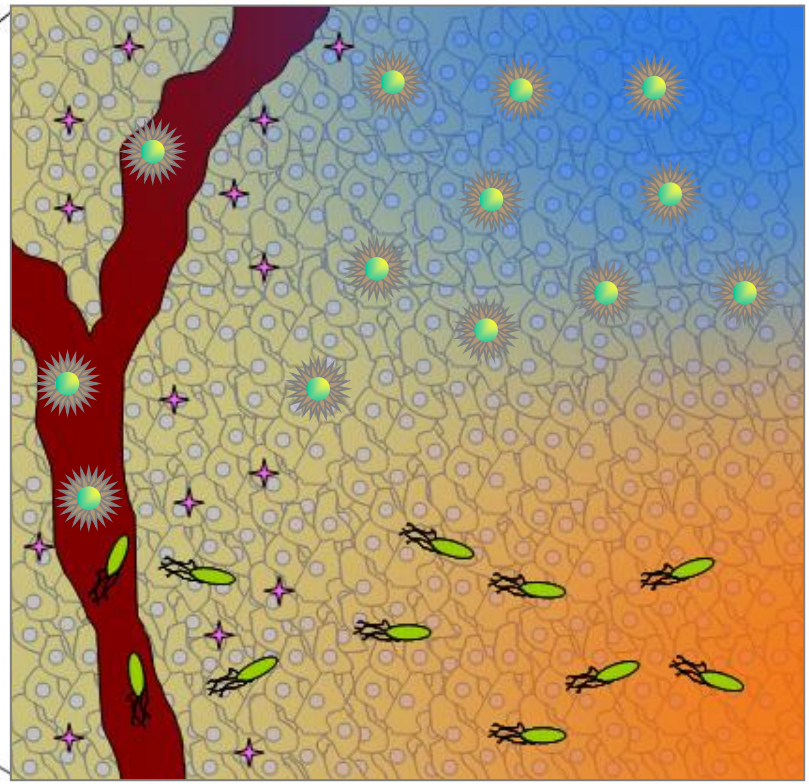


- Can also allow encapsulation of hydrophobic drugs which are difficult to get into you mostly water body.

Targeted Delivery to Tumors

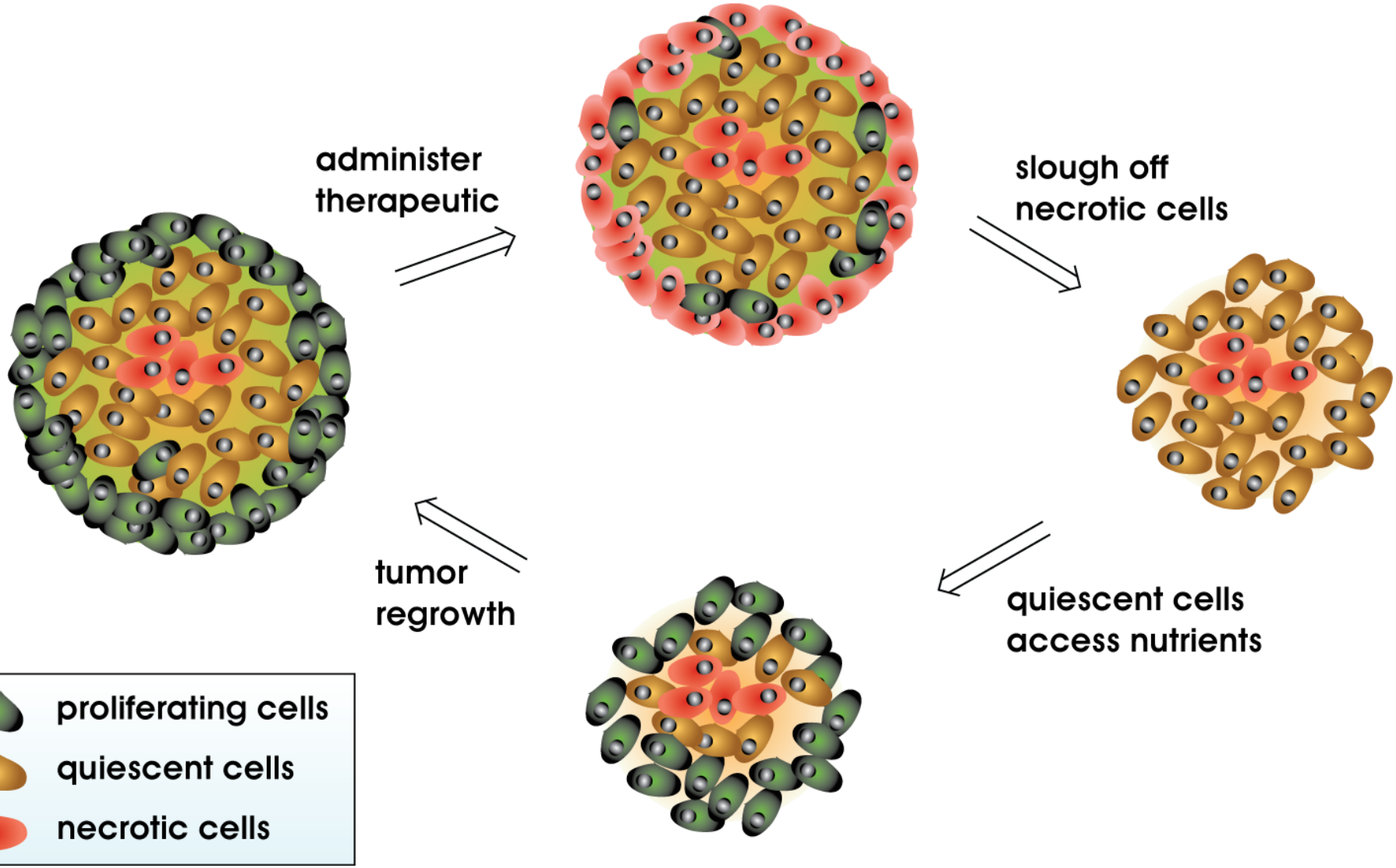
- Goal is to inject treatment far from tumor and have large accumulation in tumor and minimal accumulation in normal cells/organs.





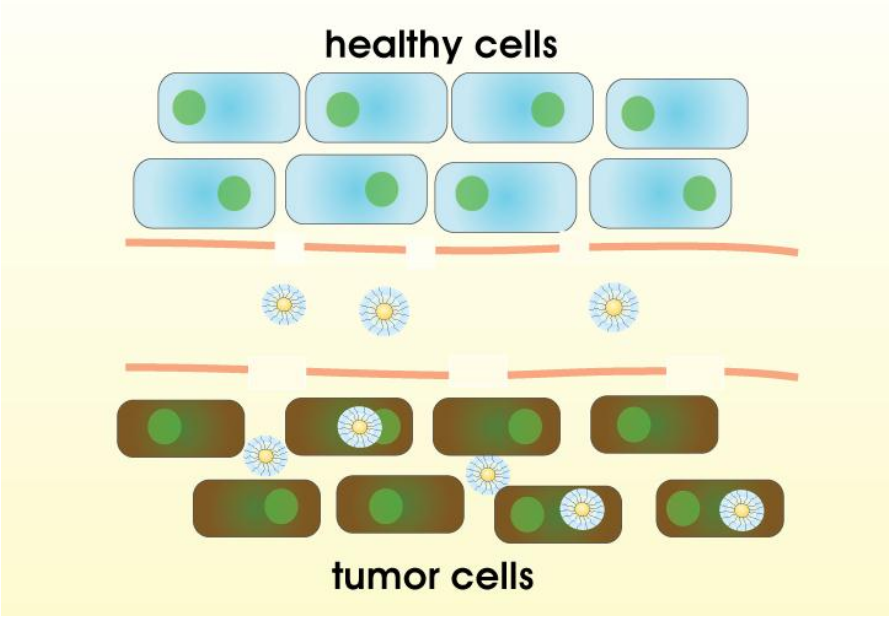
Cancer Treatments

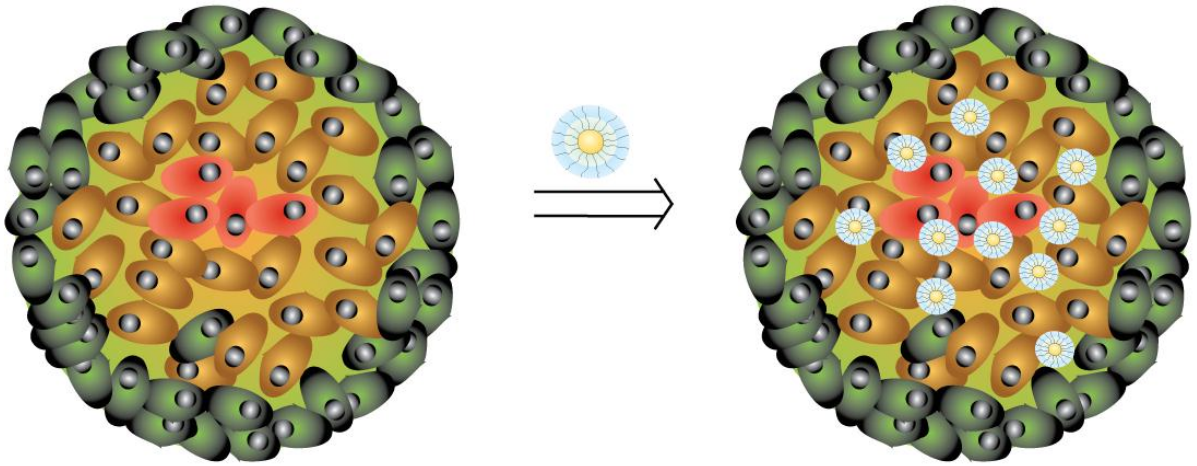
- Tumor penetration is a key issue for successful chemotherapy



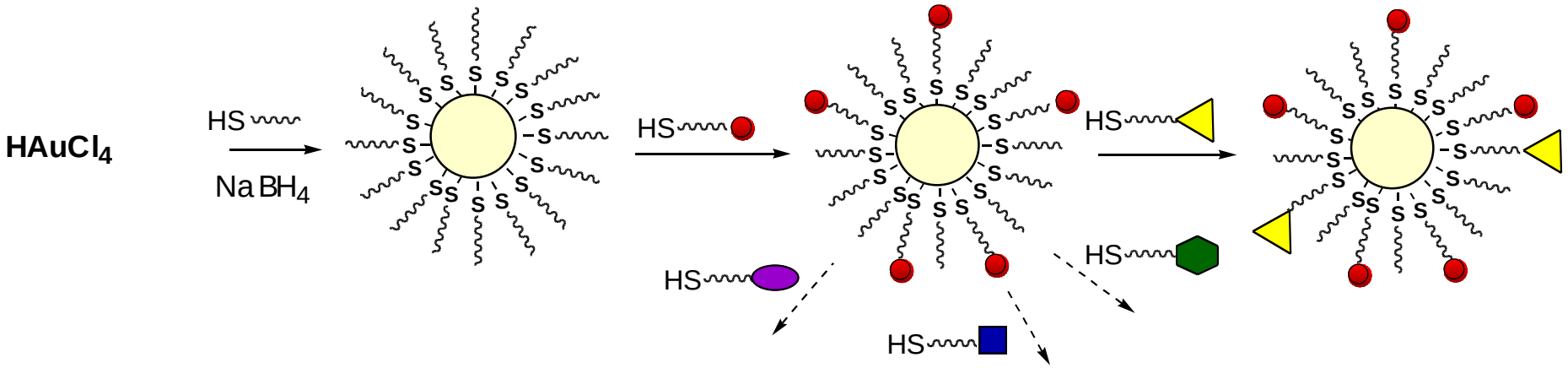
Nanoparticle use in Cancer Treatments

- Because of their small size, nanoparticles can pass through interstitial spaces between necrotic and quiescent cells.
- Tumor cells typically have larger interstitial spaces than healthy cells
- Particles collect in center bringing therapeutics to kill the tumor from inside out.





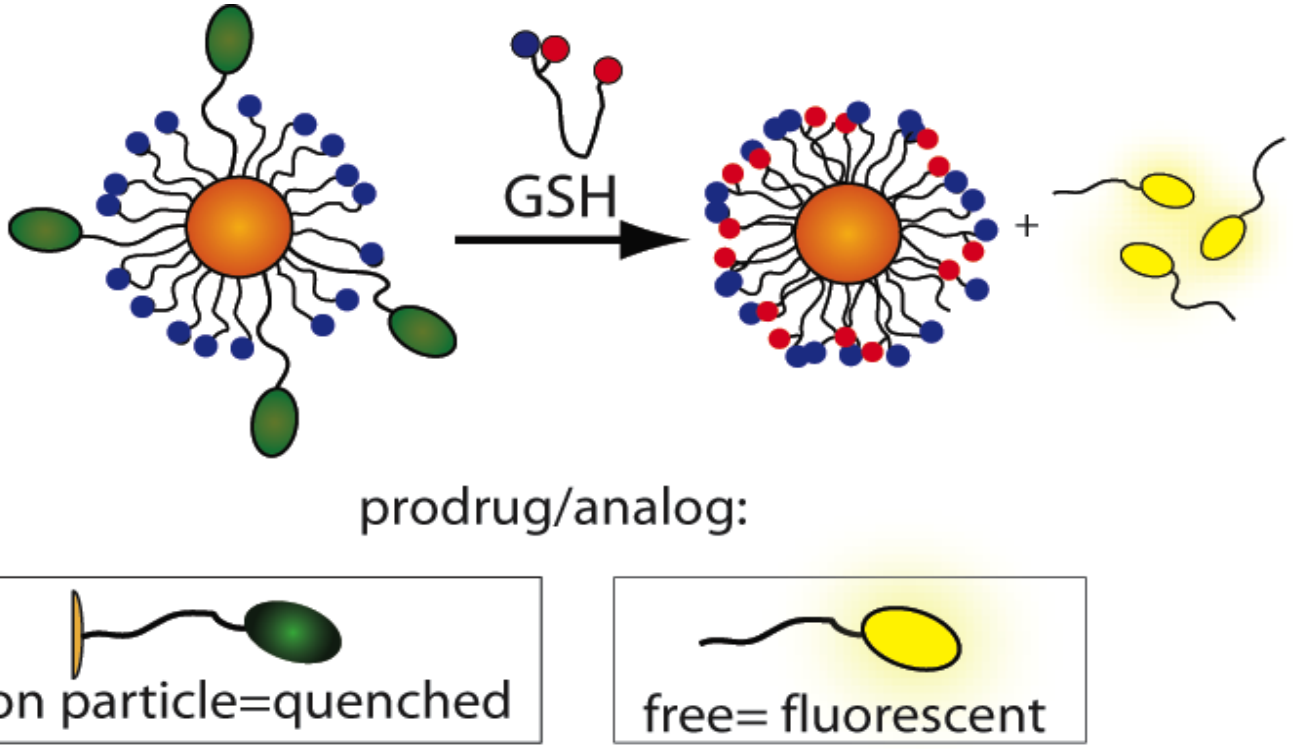
Making Gold Nanoparticles



- AuCl4- salts are reduced using $NaBH_4$ in the presence of thiol capping ligands
- The core size of the particles formed can be varied from <1 nm to ~ 8 nm
- The surface functionality can be controlled through the choice of thiols
- Diffusion speed can be controlled by length of thiols

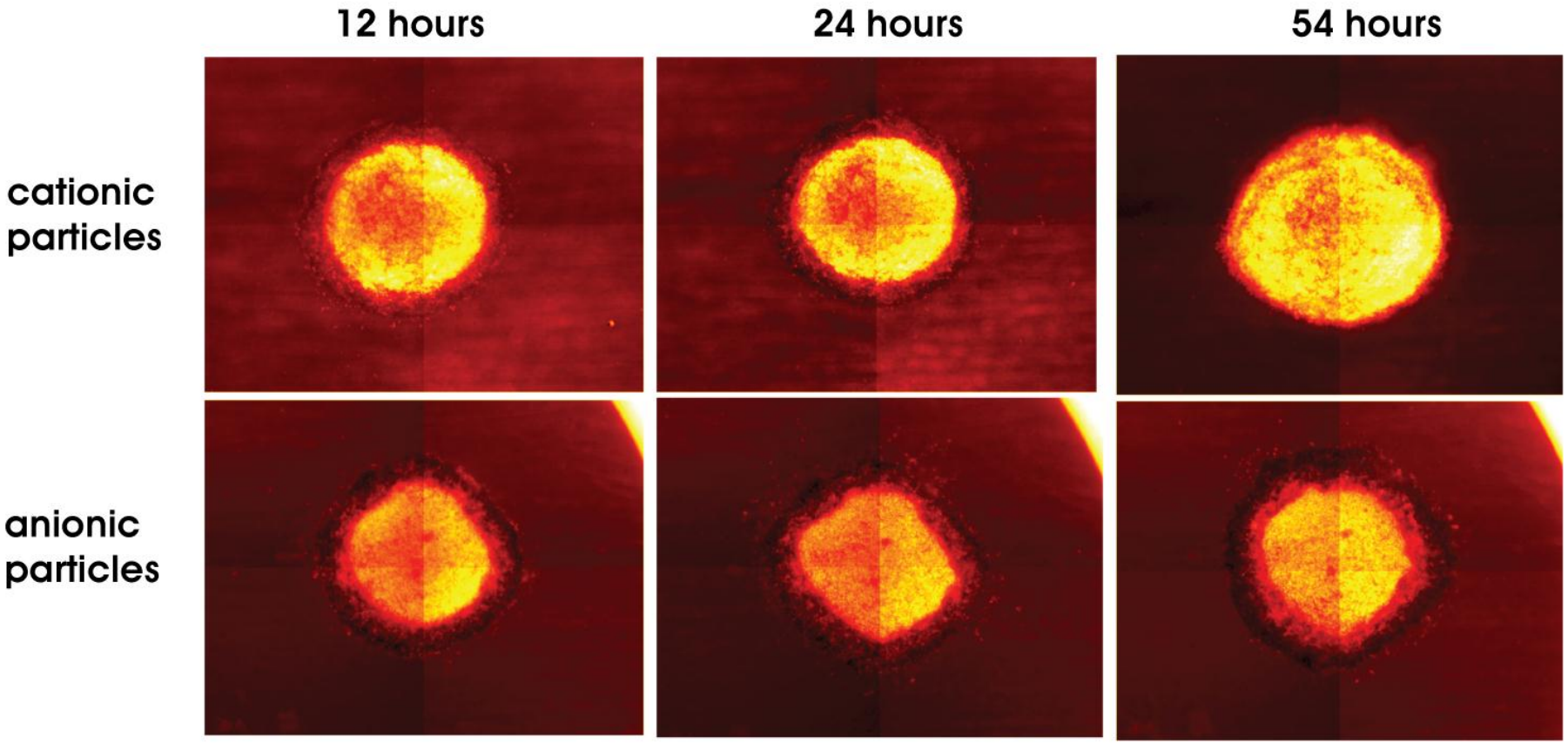
Nanoparticles as Sensors and Therapeutics

- Glutathione (GSH) provides a selective and tunable release mechanism
- Once inside cells, fluorophores and drugs selectively dissociate



Nanoparticle Success

- Both cationic and anionic particles penetrate and accumulate in tumors.
- However, only cationic particles diffuse fully throughout the tumor.



- Work of Neil Forbes and Vince Rotello at UMASS

Nanoparticle Targeting and Accumulation

- To maximize their effectiveness, the microenvironment of the tumor must be quantified and vectors developed to specifically target the tumor.
- These treatment approaches have shown great promise in mice.