

# Advanced Training in understanding the Safety of Nanomaterials



## NANO(materials, technology, medicine) and Human Health

ADVANCED TRAINING IN UNDERSTANDING THE SAFETY OF NANOMATERIAL

Prof.dr. Adrian VOLCEANOV

University POLITEHNICA of Bucharest, Bucharest, ROMANIA



*Nanogentools confidential*



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- What is nano?
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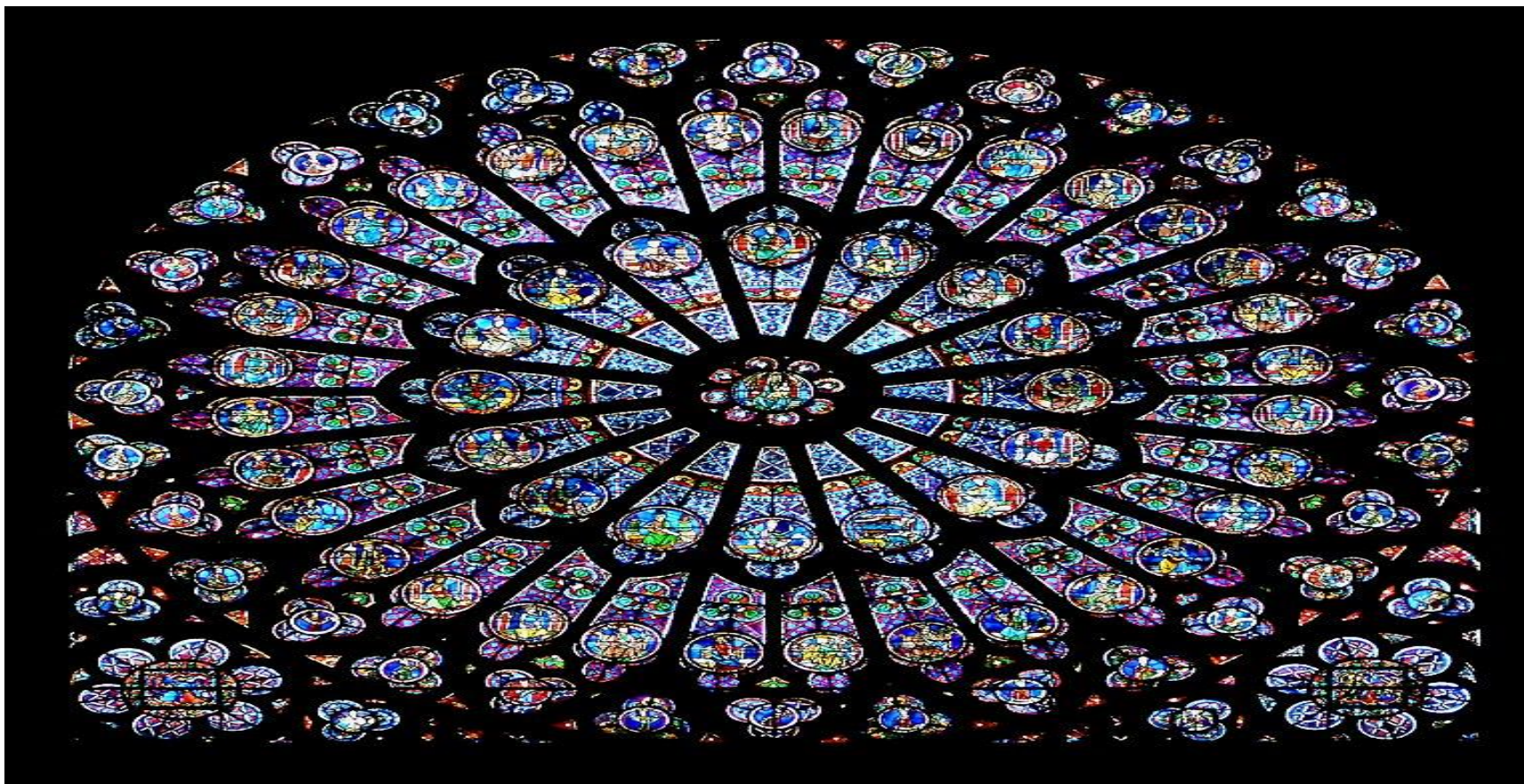


# What is NANO?

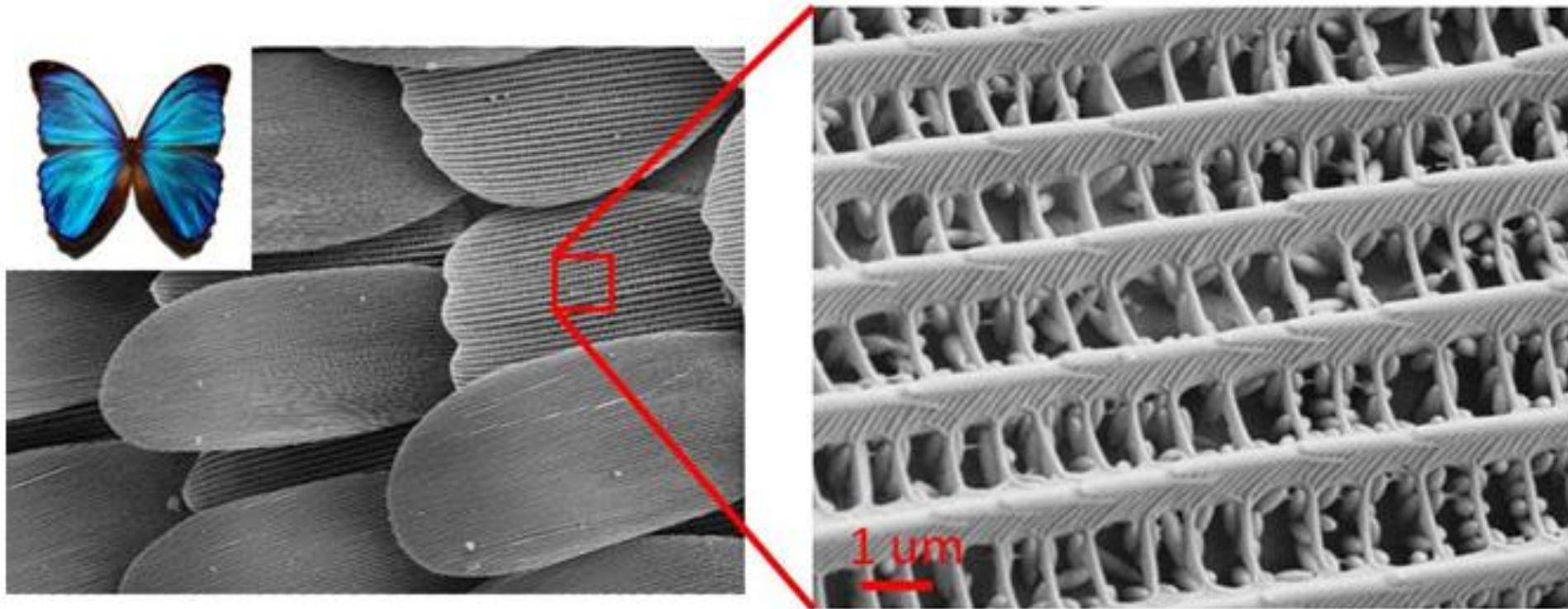


The Lycurgus Cup, as it is known due to its depiction of a scene involving King Lycurgus of Thrace, is a 1,600-year-old jade green Roman chalice that changes colour depending on the direction of the light upon it.

# What is NANO?



# What is NANO?



# What is NANO?



Nano Today (2010) 5, 165–168

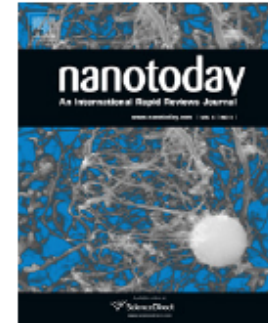


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journal homepage: [www.elsevier.com/locate/nanotoday](http://www.elsevier.com/locate/nanotoday)



NEWS AND OPINIONS

## A complementary definition of nanomaterial

Wolfgang G. Kreyling<sup>a,\*</sup>, Manuela Semmler-Behnke<sup>a</sup>, Qasim Chaudhry<sup>b</sup>



# What is NANO?



- “**Engineered nanomaterial**” means any intentionally produced material that has one or more dimensions of the order of 100nm or less or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100nm but retain properties that are characteristic to the nano-scale.



# What is NANO?



- **Nanotechnology** is the understanding and control of matter at dimensions between approximately 1 and 100 nm, where unique phenomena enable novel applications. . . .
- Dimensions between approximately 1 and 100nm are known as the nano-scale.
- Unusual physical, chemical, and biological properties can emerge in materials at the nano-scale.
- These properties may differ in important ways from the properties of bulk materials and single atoms or molecules.





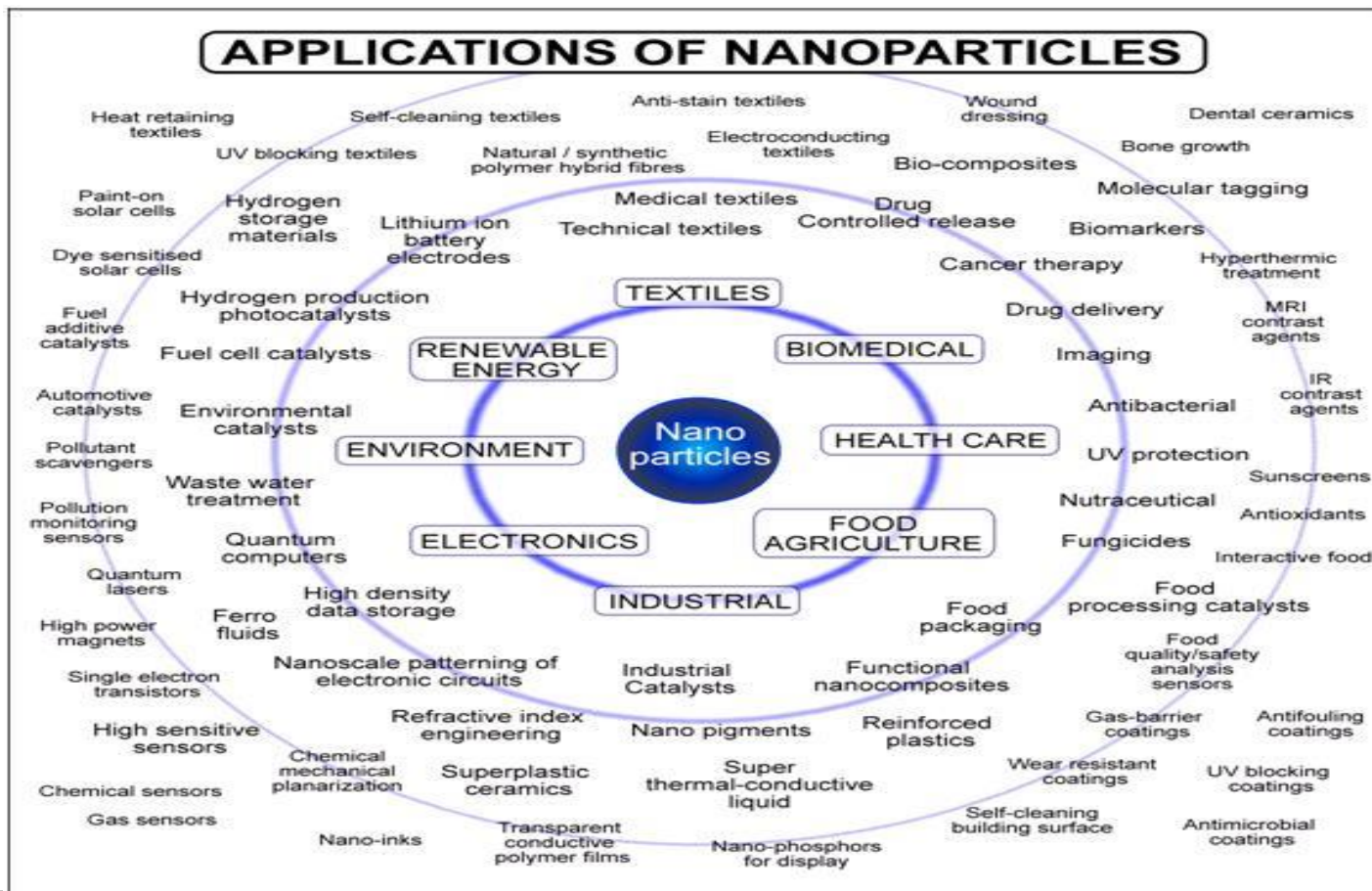
# What is NANO?



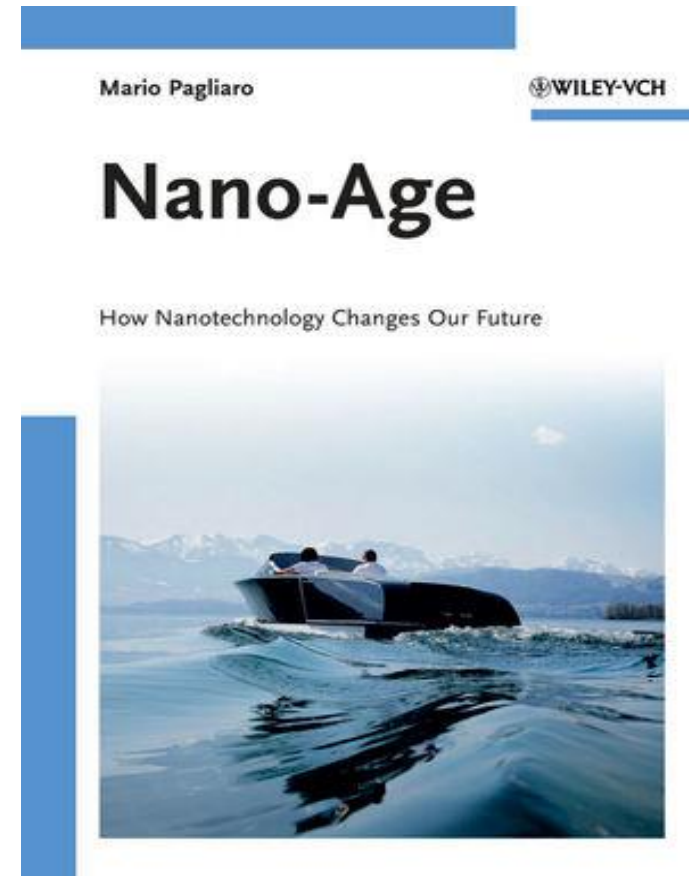
- **Engineered nanomaterial** (ENM) is any material that is deliberately created such that it is composed of discrete functional and structural parts, either internally or at the surface, many of which will have one or more dimensions of the order or 100nm or less.



# What is NANO?



# What is NANO?





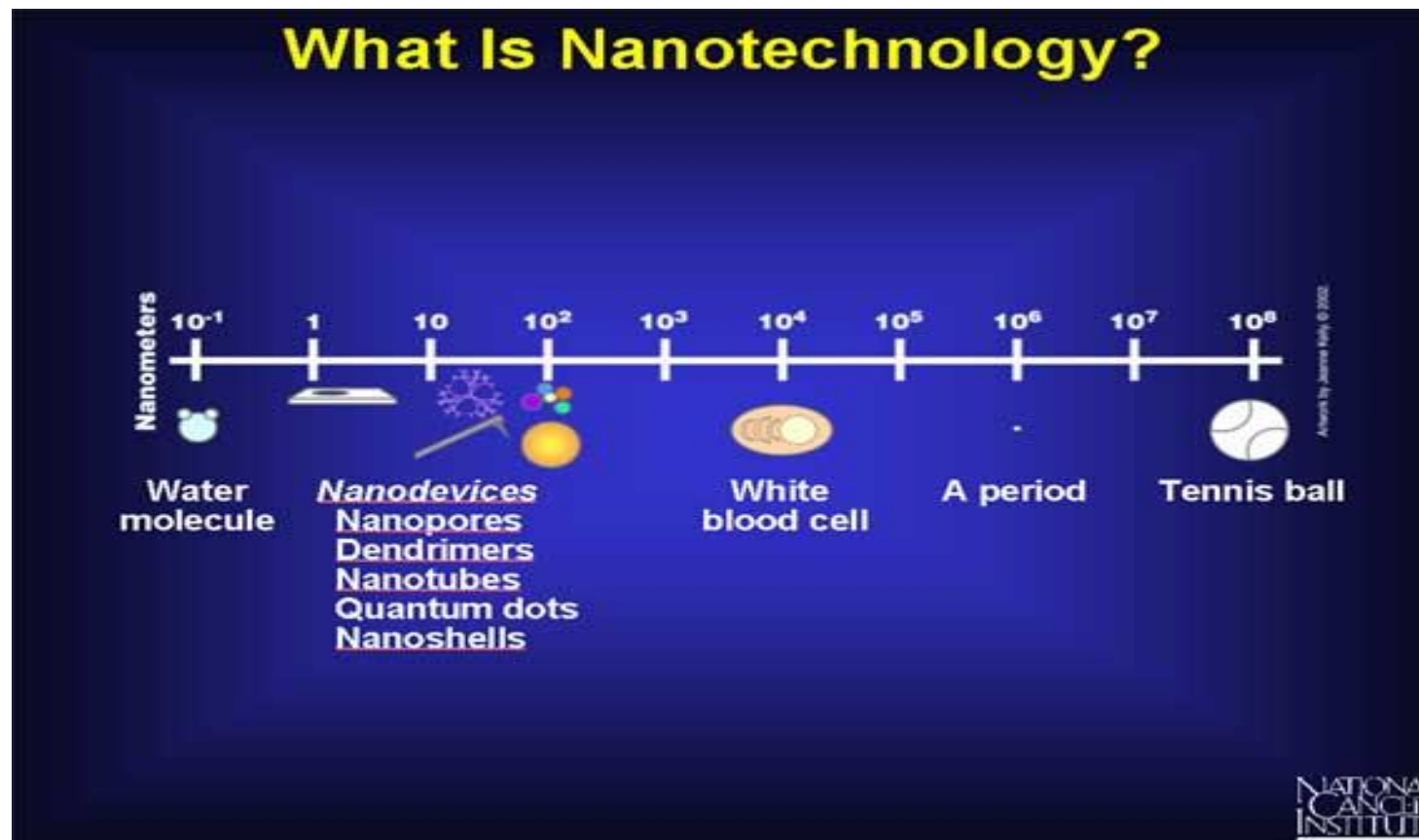
# What is NANOTECHNOLOGY?



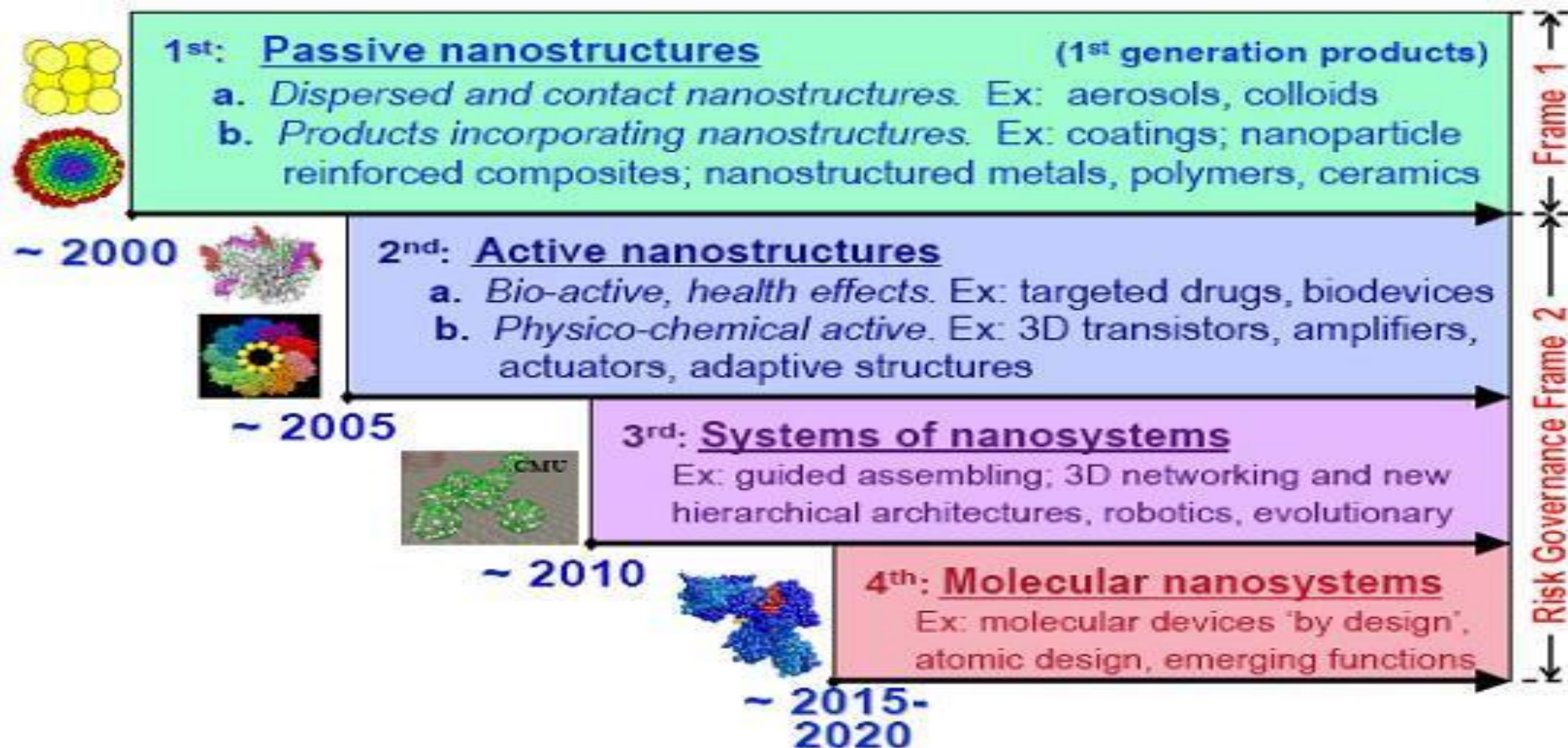
Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nm, where unique phenomena enable novel applications. . . .

*The (US-)National Nanotechnology Initiative Strategic Plan December 2007*

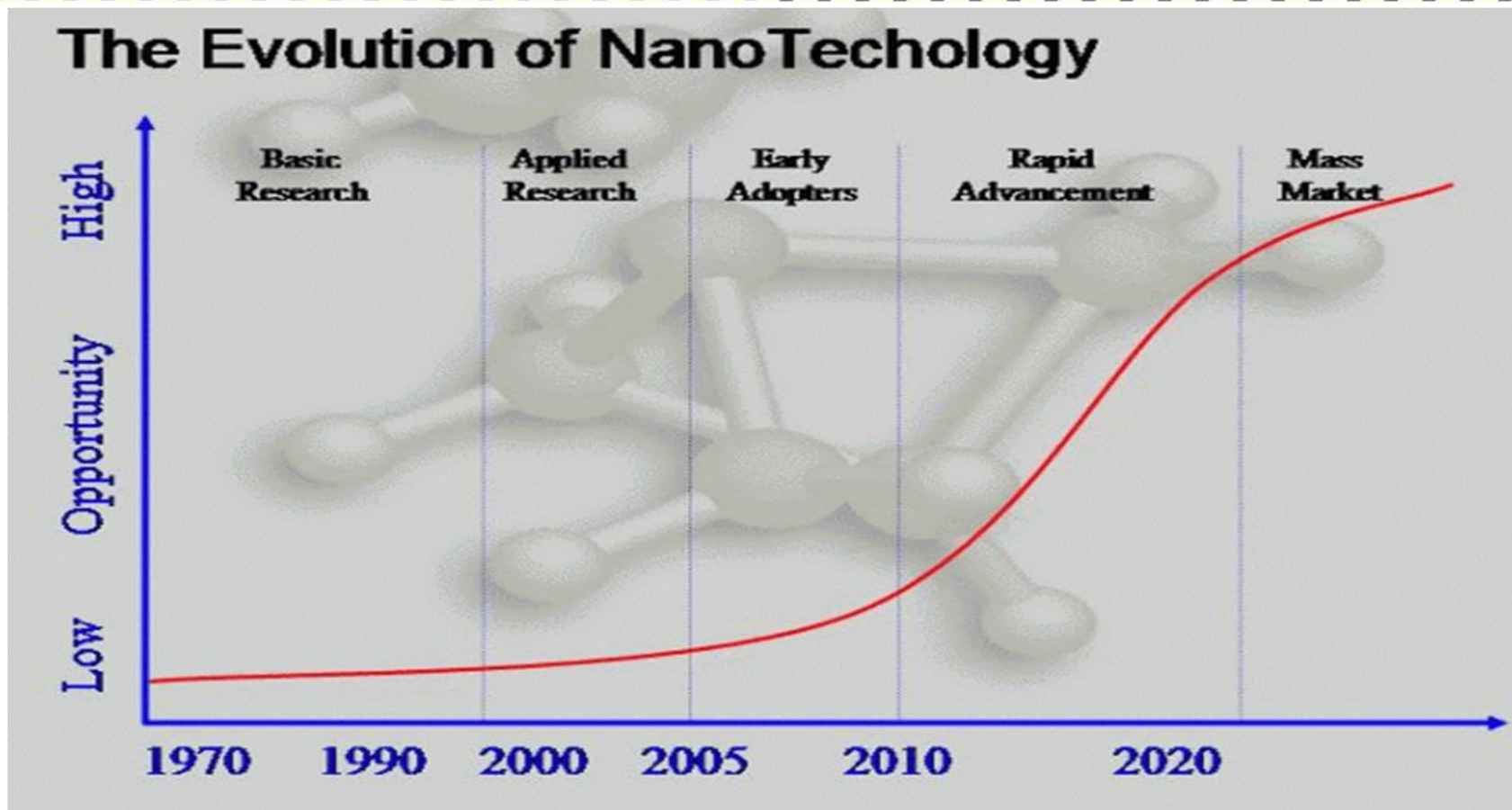
[www.nano.gov/NNI Strategic Plan 2007.pdf](http://www.nano.gov/NNI Strategic Plan 2007.pdf)



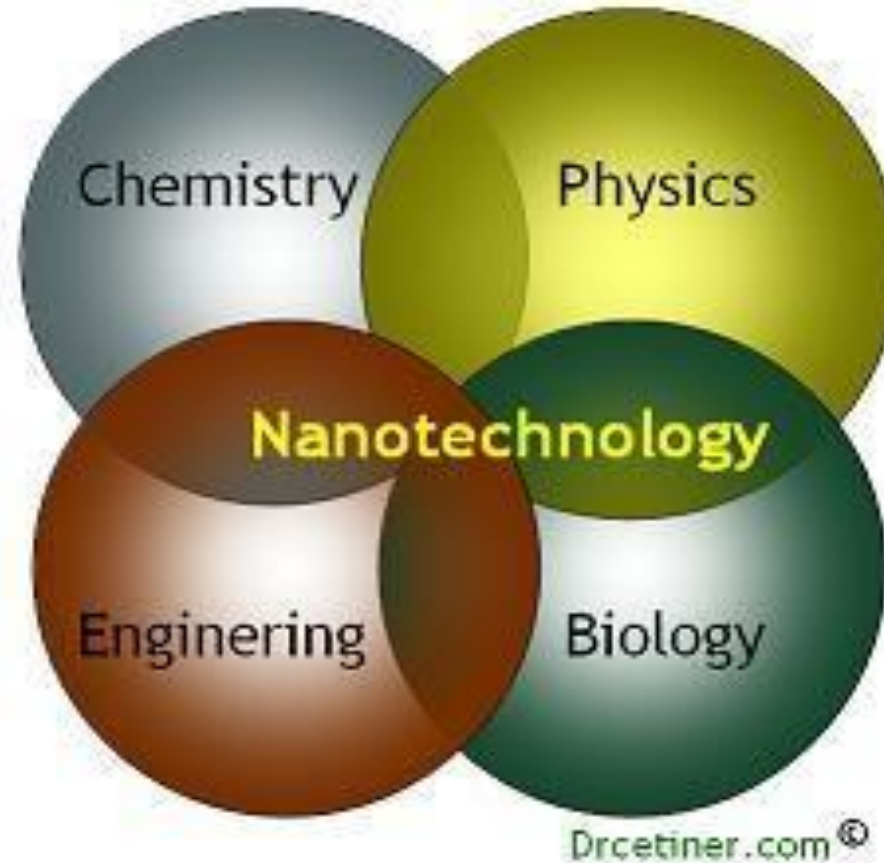
# What is NANOTECHNOLOGY?



# What is NANOTECHNOLOGY?



# What is NANOTECHNOLOGY?





# What is NANOTECHNOLOGY?



# What is NANOTECHNOLOGY?



Nanotechnology has several application on many fields such as :

- o Medicine
- o Electronics
- o Energy production
- o water processing .....



# Nanomedicine



- **Nanotechnology applied medically**
- **New breakthroughs in medicine:**
  - Advanced biomedical research tools
  - Labels to experiments
  - Study of DNA and its component genes
  - Diagnostic tests
  - In bone implants etc...



# Drug Delivery Methods



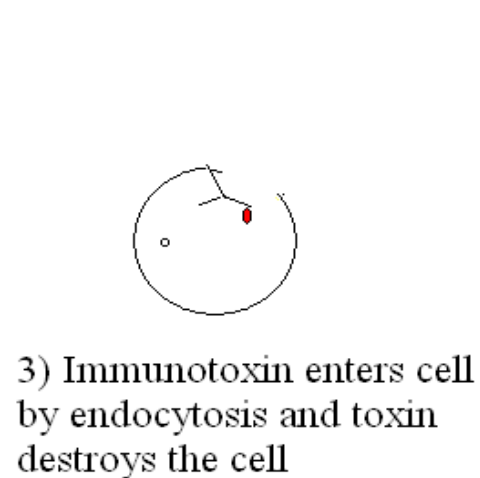
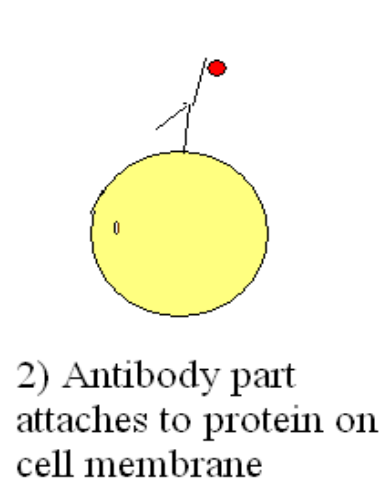
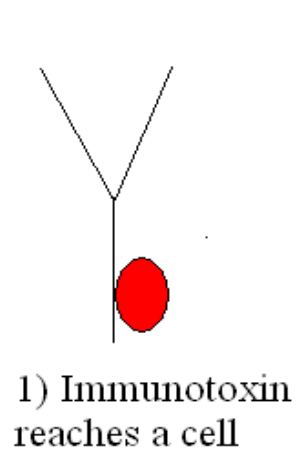
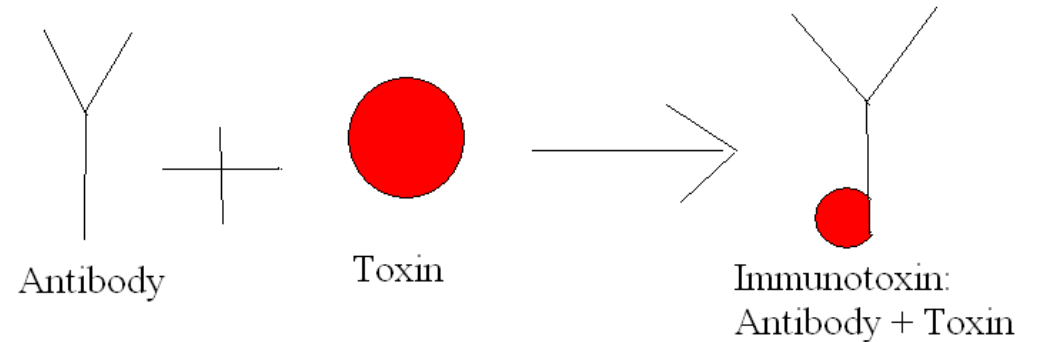
- Systems that deliver drugs to specific sites
- Sample Methods:
  - Smart Drugs
  - Nanocomposite hydrogel systems
  - Magnetic Nanoparticles



# Drug Delivery Methods

- Smart drugs

- Attack specific antigens
- Immunotoxins that are protein in nature
- Consist of an antibody part and toxic part



# Drug Delivery Methods



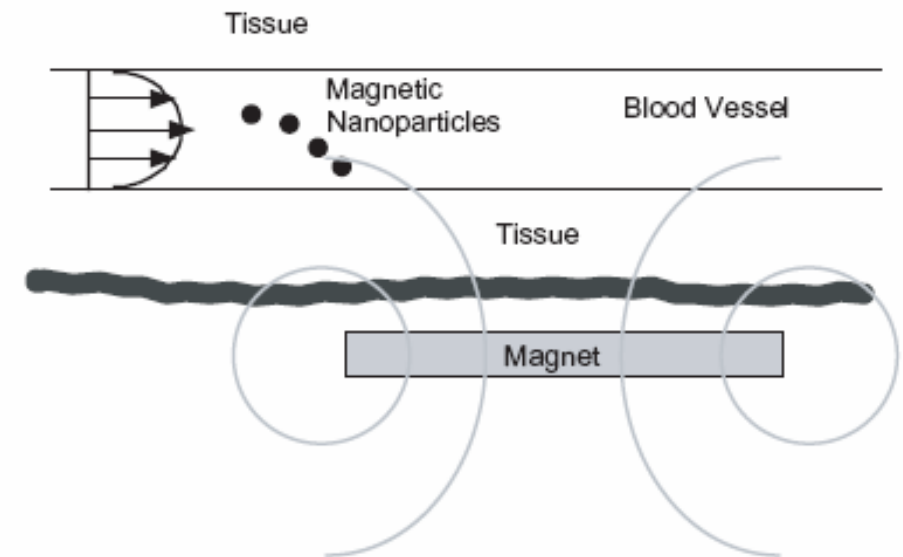
- Nanocomposite hydrogel systems
  - Thermo therapeutic process
  - Releases drugs that are encapsulated on heating
  - Gold nanoshells/nanoparticles can be used
  - Ideal wavelengths of light are infra red i.e 800-1200nm



# Drug Delivery Methods

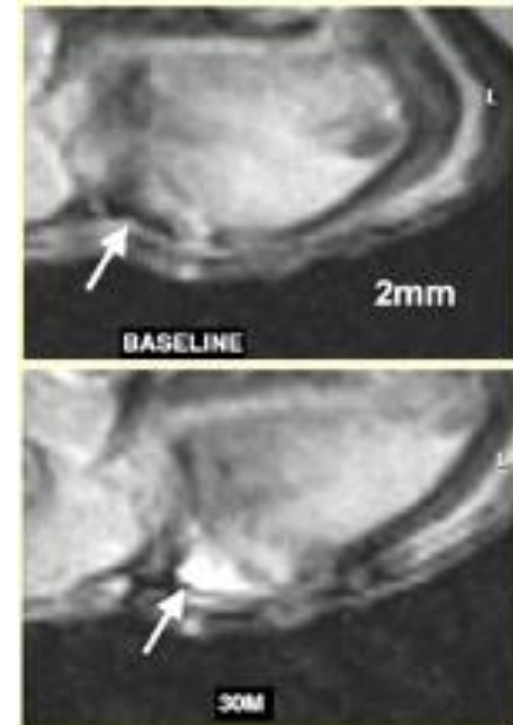
- Magnetic Nanoparticles

- Drugs are bound to magnetic nanoparticles
- Carry drugs to malignant sites with magnetic fields
- Release the drugs by enzymatic activity



# Disease Detection

- Cancer/Virus Detection
  - Carbon Nanotubes
  - Gold nanoparticles & Nanodots
  - Nanowires
- Gene Detection
  - Silicon nanowires



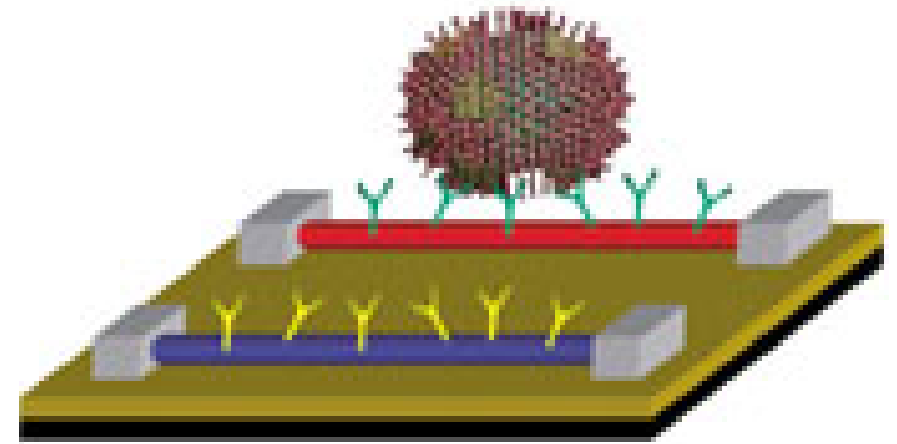
Picture taken from  
<http://mednews.wustl.edu/tips/page/normal/5036.html>



# Cancer/Virus Detection



- **Carbon Nanotubes:**
  - Covered with monoclonal antibodies
  - Antibodies for growth factor receptor commonly found in cancer cells
  - Current increases measured
- **Silicon Nanowires**
  - Similar in use to nanotubes
  - Antibodies attached to wire
  - Current changes measured
  - Can be applied to cancer cells and viruses



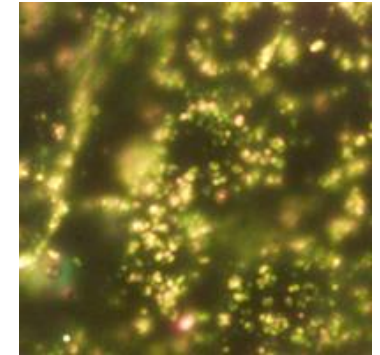
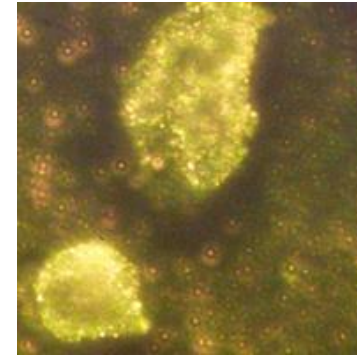
Taken from <http://www.news.harvard.edu/gazette/2004/10.07/01-nanovirus.html>



# Cancer/Virus Detection

- Gold Nanoparticles & Nanodots

- Similar application
- Antibodies attached to nanoparticles
- Nanoparticle antibodies bind to cancer cells
- Colors reflected when light hits particles
- Shapes and sizes affect color



Taken from <http://www.gatech.edu/news-room/release.php?id=561>

# Gene Detection

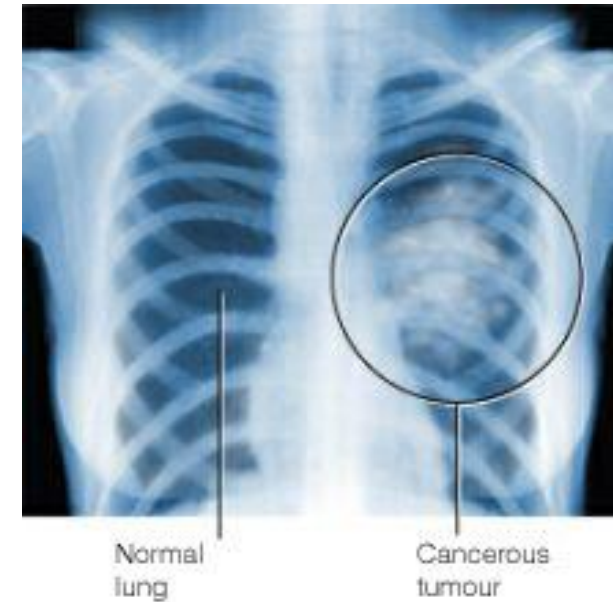


- Silicon nanowire:
  - Can detect specific genes
  - Nucleic acids attached to nanowires
  - Specific sequences can be created
  - Sensor capable of differentiating mutated and nonmutated genes
  - PCR not needed -> detection time lowered



# Imaging Techniques

- Conventional Techniques:
  - X-ray, MRI, Fluoroscopy
  - CAT scan
- Limitations
  - Limited detail
  - Difficult to track movement



Taken from: [http://www.besttreatments.co.uk/btuk/images/lung\\_cancer\\_xray.jpg](http://www.besttreatments.co.uk/btuk/images/lung_cancer_xray.jpg)

# Imaging Applications

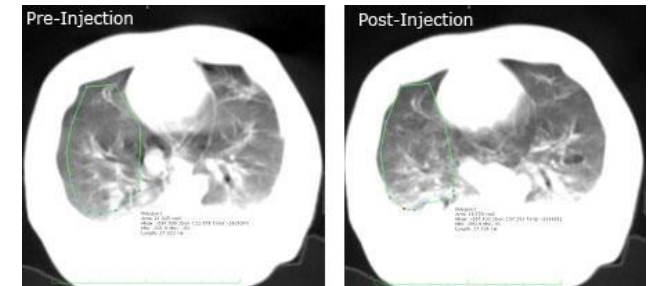


- Molecular Tracking:
  - Use Quantum Dots as labels
    - Dots attached to molecules before injection
  - Fluorescopy used to track movement
    - Colors from dots seen and imaged



# Imaging Applications

- Tracking blood flow:
  - Tag proteins of cells with gold nanoparticles
  - View process of angiogenesis
    - Important for cancer detection and imaging
- Cancer Imaging:
  - Injection of gold nanoparticles
  - Localization around tumors
  - CT scan shows cancerous regions



Taken from <http://www.rsna.org/Publications/rsnanews/oct05/nanoparticles.cfm>

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# POTENTIAL APPLICATION OF NANOPARTICLES IN MEDICINE: Cancer Diagnosis and Therapy

# OUTLINE



- SECTION I
- Nanomedicine overview
- SECTION II
- Nanotechnology potential in medicine
- SECTION III
- Promising works
- SECTION IV
- Assessment





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## SECTION I

# Nanomedicine Review



# Nanomedicine



- Premise:
- Nanometer-sized particles have optical, magnetic, chemical and structural properties that set them apart from bulk solids, with potential applications in medicine.
- Potential applications

**DRUG DELIVERY**

**MEDICAL IMAGING**

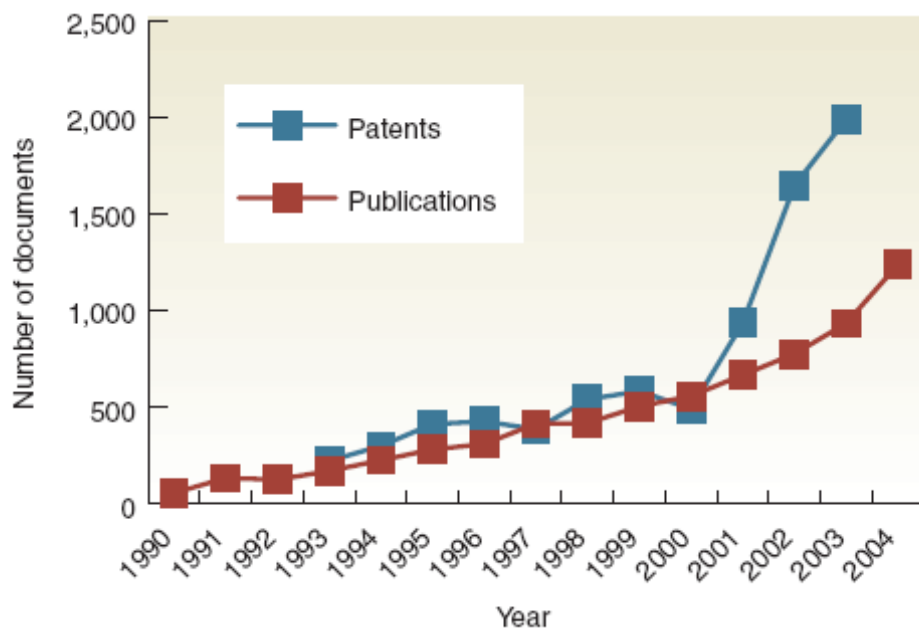
**DIAGNOSIS & SENSING**

**THERAPY**

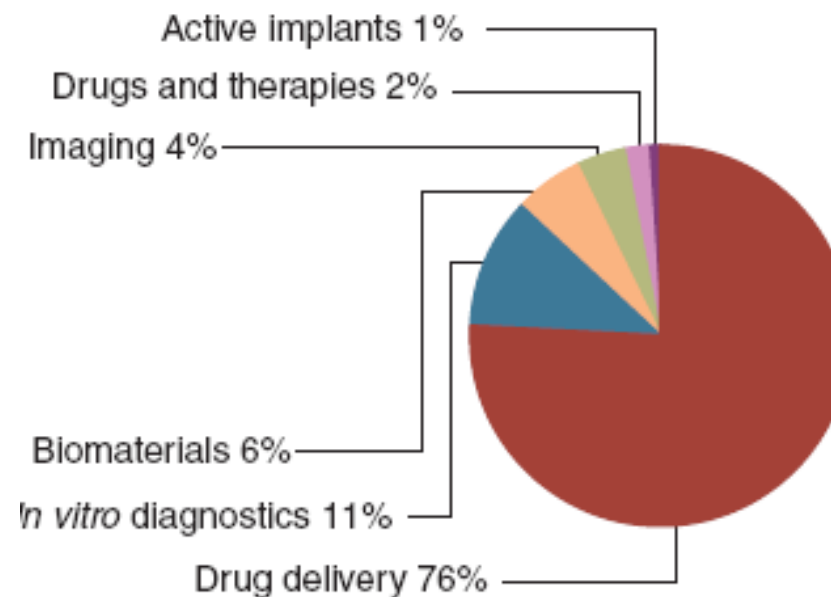


# Interesting facts about nanomedicine

## A. Interest in the area has grown exponentially



## B. Drug delivery is the most productive area



# Interesting facts about nanomedicine



## C. Drug delivery is the most established technology in the nanomedicine market

Table 1 Commercial efforts in nanomedicine<sup>a</sup>

Healthcare sector	Number of products	Sales (\$ billions)	Product pipeline		
			Total	Advanced stages <sup>b</sup>	Companies
Drug delivery	23	5.4	98	9	113
Biomaterials	9	0.07	9	6	32
<i>In vivo</i> imaging	3	0.02	8	2	13
<i>In vitro</i> diagnostics	2	0.78	30	4	35
Active implants	1	0.65	5	1	7
Drugs & therapy	0	0	7	1	7
Total	38	6.8	157	23	207

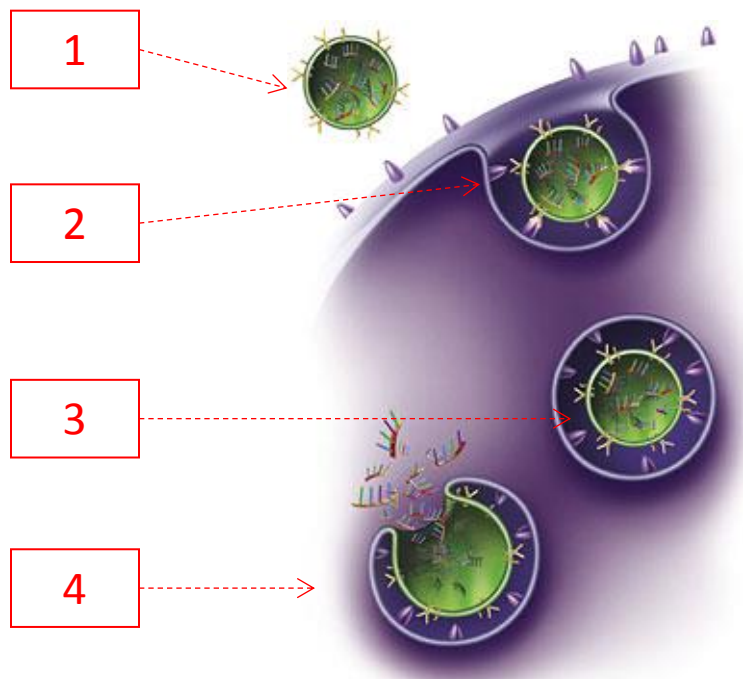
<sup>a</sup>Sales numbers of nanomedicines are estimates for the year 2004. <sup>b</sup>Drugs where the product is in clinical phase 2/3 or 3 and for all other products where market introduction is expected within two years.

Nature Biotechnology 2006, Vol. 4, pp.1212-1217



# Drug Delivery

**A.** Because of their small sizes, nanoparticles are taken by cells where large particles would be excluded or cleared from the body



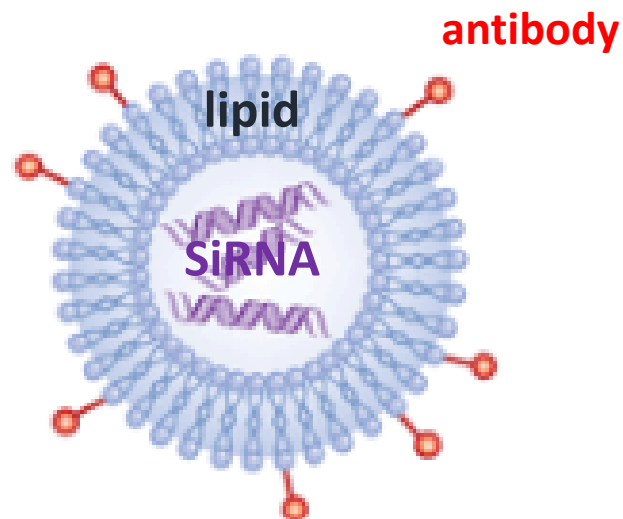
- 1) A nanoparticle carries the pharmaceutical agent inside its core, while its shell is functionalized with a 'binding' agent
- 2) Through the 'binding' agent, the 'targeted' nanoparticle recognizes the target cell. The functionalized nanoparticle shell interacts with the cell membrane
- 3) The nanoparticle is ingested inside the cell, and interacts with the biomolecules inside the cell
- 4) The nanoparticle particles breaks, and the pharmaceutical agent is released

Source: Comprehensive Cancer Center Ohio University

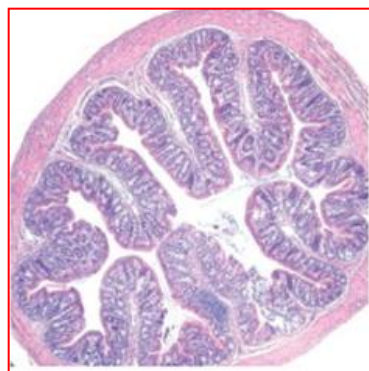
# A Drug Delivery Nanoparticle

A. Nanoparticles for drug delivery can be metal-, polymer-, or lipid-based. Below (left) an example of the latter, containing SiRNA encapsulated, and functionalized with a specific antibody. SiRNA can control often lethal inflammatory body responses, as shown in the microscopic images below (right)

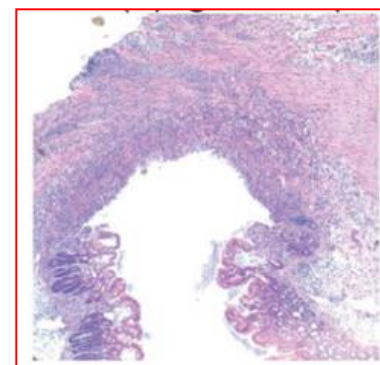
B.



C.



Healthy tissue



Sick tissue treated with non-targeted nanoparticles



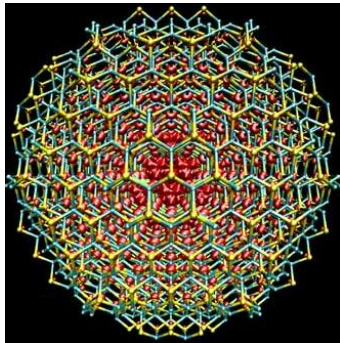
Sick tissue treated with targeted nanoparticles

Science 2008, Vol. 316, pp 627-630

# Medical Imaging

**A.** Optical properties of nanoparticles depend greatly on its structure. Particularly, the color (wavelength) emitted by a quantum dot (a semiconductor nanoparticle) depends on its diameter.

**B.**



*CdSe nanoparticle (QD) structure*

Source: Laurence Livermore Laboratories

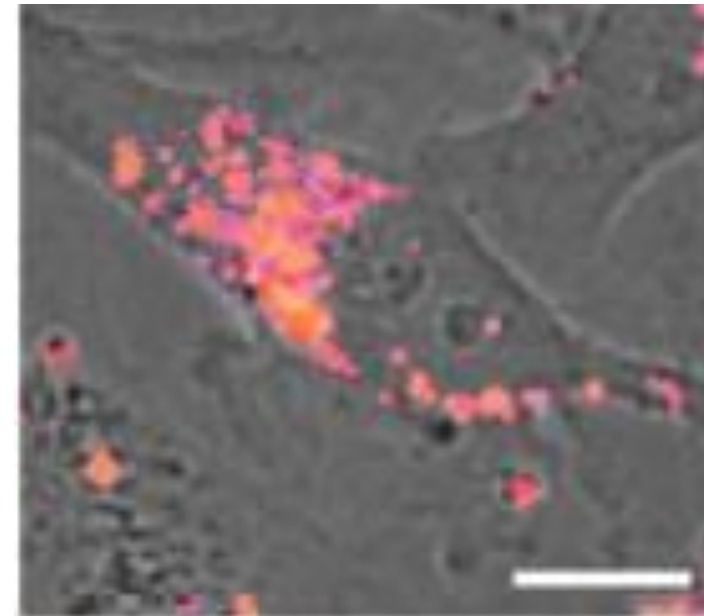
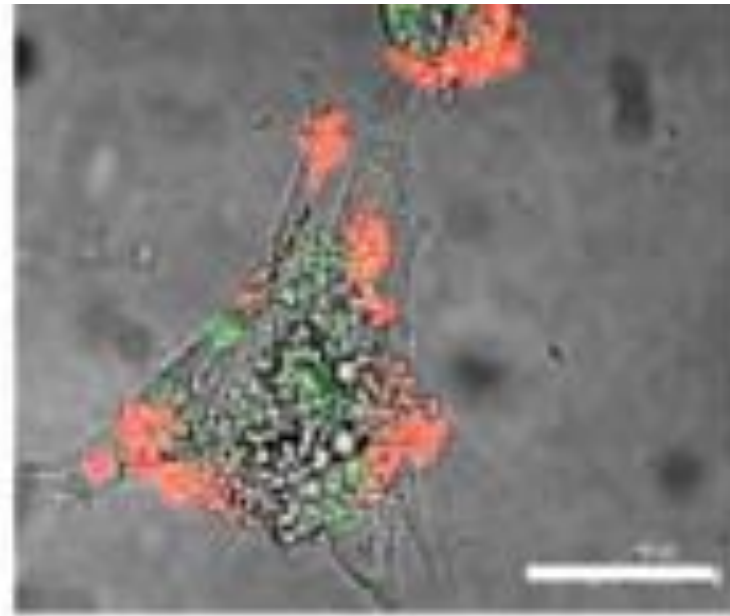


*Solutions of CdSe QD's of different diameter*

Source: Department of immunology, University of Toronto

# Medical Imaging

C. The quantum dots (QD) can be injected to a subject, and then be detected by exciting them to emit light



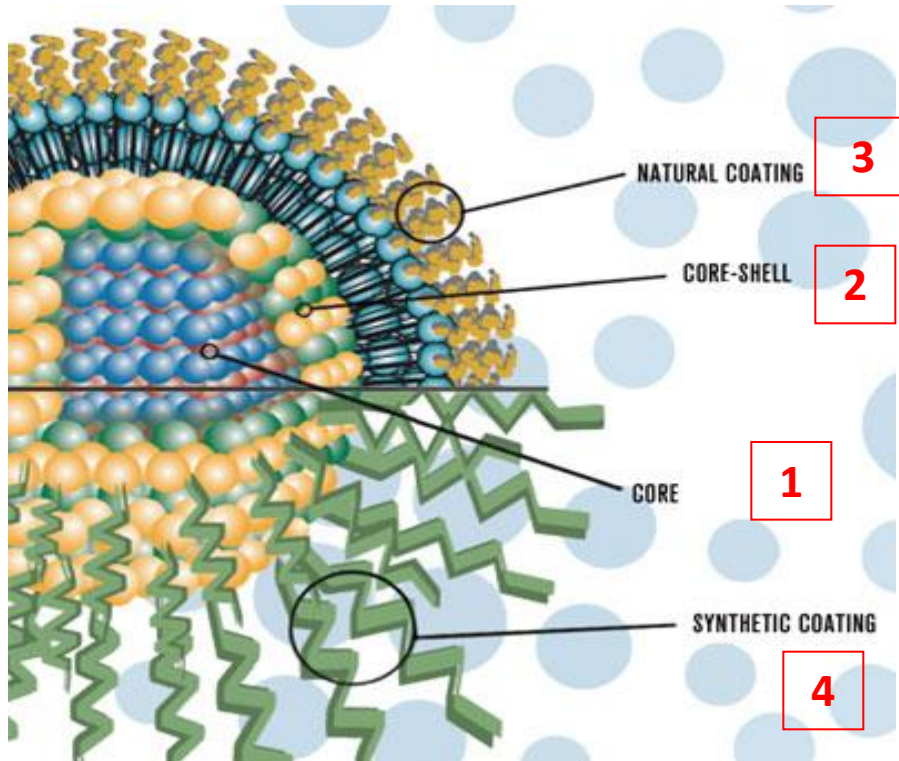
*Imaging of QD's targeted on cellular structures*

Nano Letters 2008., Vol. 8, pp3887-3892



# A Quantum Dot Nanoparticle

**A.** The quantum dot itself (the semiconductor nanoparticle) is toxic. Therefore some typical modifications has to be made for it to become biocompatible.

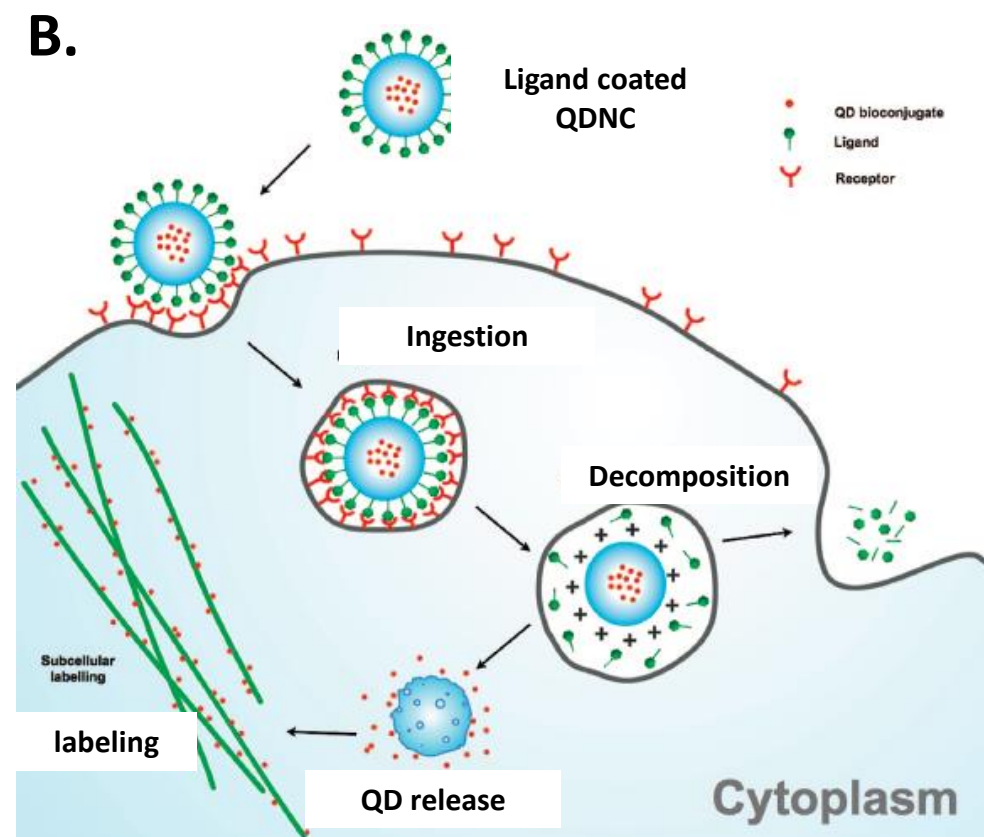


- 1) The core consist of the semiconductor material that emits lights
- 2) The shell consist of an insulator material that protects the light emitting properties of the QD in the upcoming functionalization
- 3) The shell is functionalized with a biocompatible material such as PEG or a lipid layer
- 4) Additional functionalization can be done with several purposes (e.g. embed a drug for drug delivery, or assemble an antibody to become the QD target-specific)

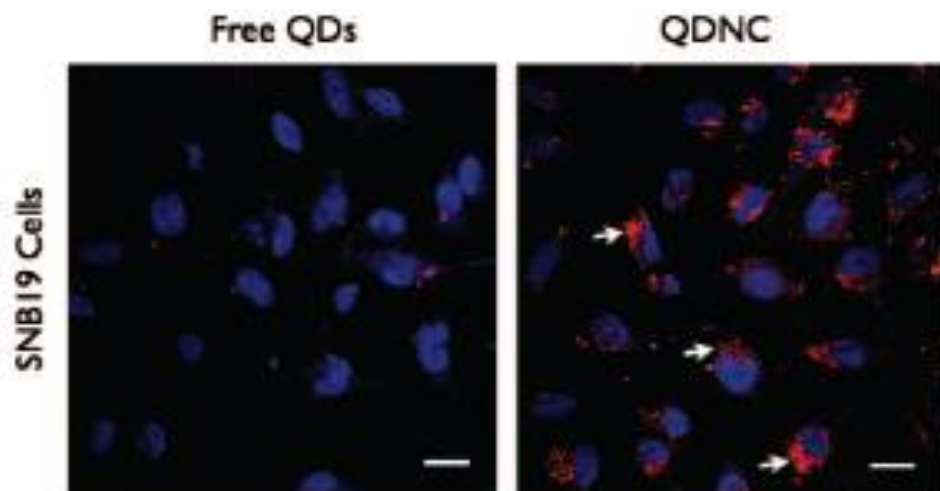
Source: The scientist (2005), Vol. 19, p. 35

# Targeting QD's for intracellular imaging

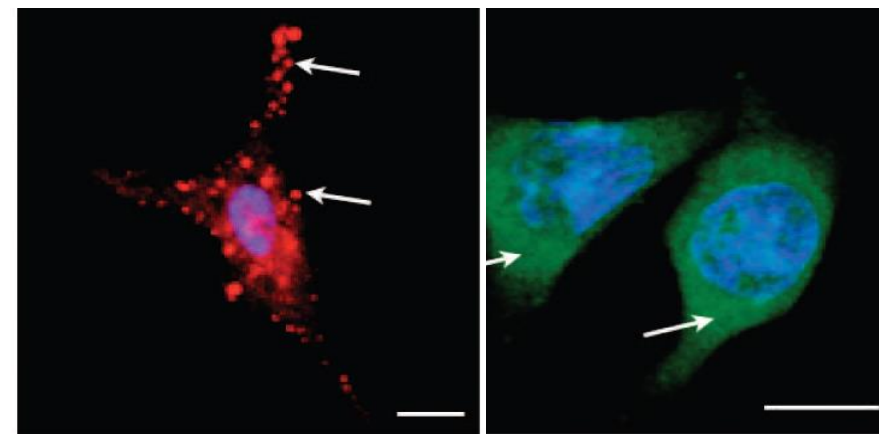
**A.** Using a drug-delivery-like mechanism, a targeted lipid-based nanoparticle (TNP) encapsulating QD's specifically 'attacks' a cell having the receptors that pair with its ligand coating. Upon ingestion and destruction of the TNP, the QD's are set free and accumulate on intracellular structures



# Targeting QD's for intracellular imaging



**C.** QD (red) intracellular uptake is enhanced when using the QDNC instead of the free QD's



**D.** Imaging of nucleus (blue) and cytoplasm (other) after 30 min (left) and 3 hours after uptake

Nano Letters 2008., Vol. 8, pp3887-3892

# Diagnosis and Sensing



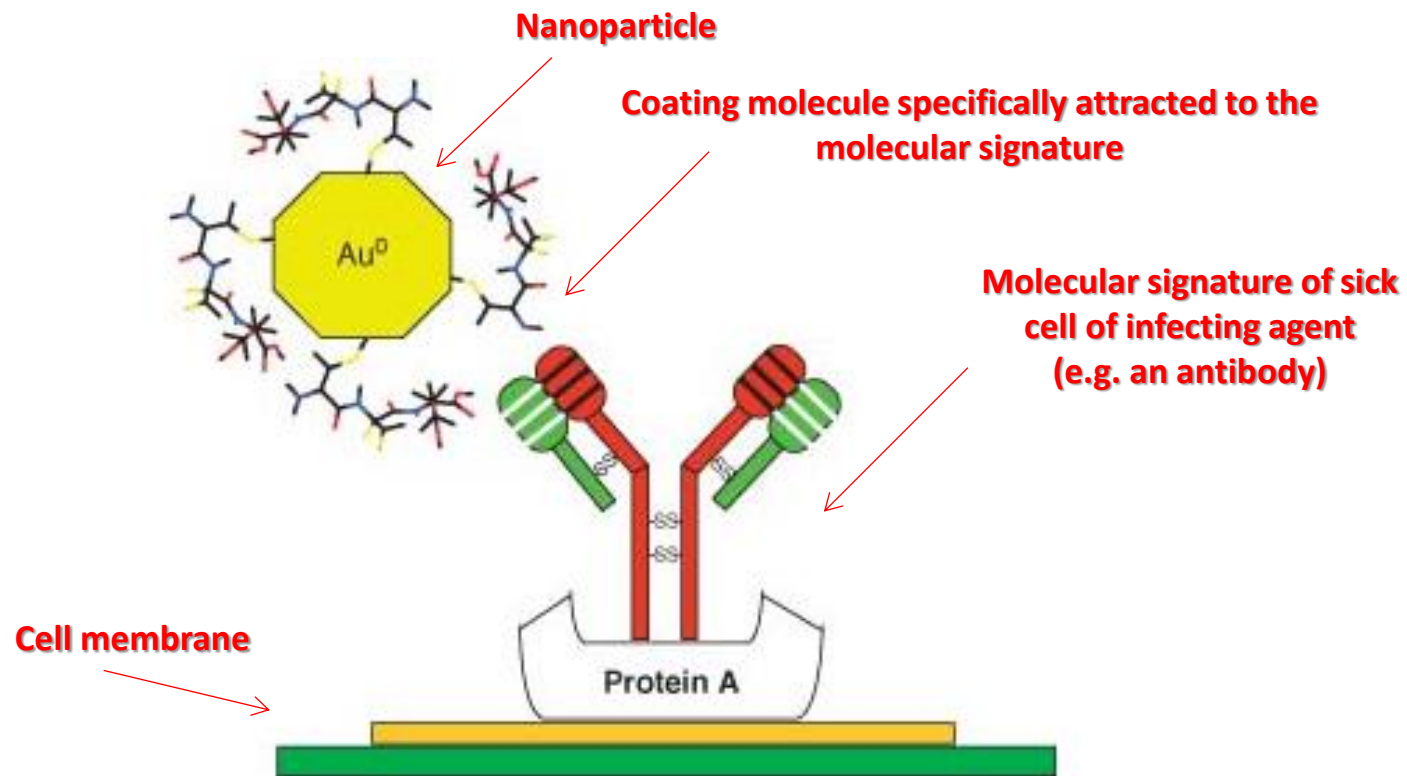
**A.** Diseases can be diagnosed through the (simultaneous) detection of a (set of) biomolecule(s) characteristic to a specific disease type and stage (biomarker).



# Diagnosis and Sensing

B. Each cell type has unique molecular signatures that differentiate healthy and sick tissues. Similarly, an infection can be diagnosed by detecting the distinctive molecular signature of the infecting agent

C. A nanoparticle can be functionalized in such a way that specifically targets a biomarker. Thus, the detection of the nanoparticle is linked to the detection of the biomarker, and to the diagnosis of a disease



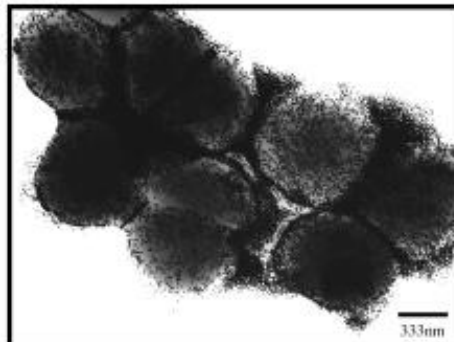
Huffman, Nanomedicine and Nanobiotechnology, Vol. 1, 1, 2009

# Nanoparticles in action

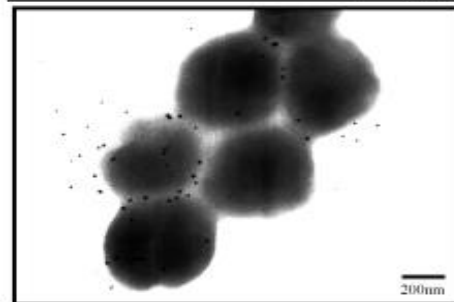
**A.** Modifying a ferromagnetic nanoparticle with human immunoglobulin G (IgG), which specifically binds the protein A in the cellular wall of *staphylococcus*, the bacteria can be detected through a MRI test

**B.**

*Accumulation of functionalized ferromagnetic nanoparticles on staphylococcus*

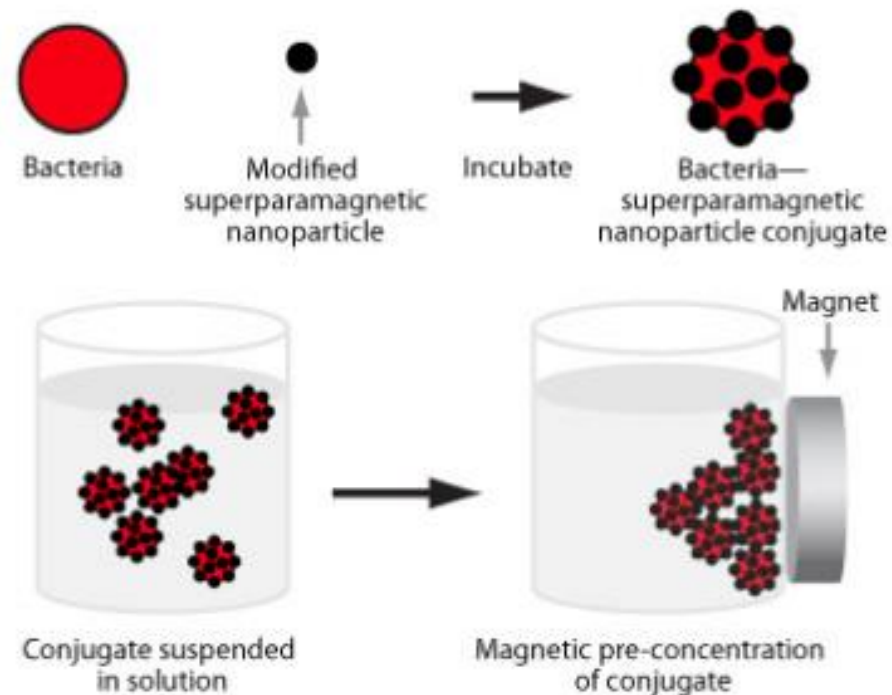


*Negligible accumulation of nanoparticles in absence of functionalization*



Analytical Chemistry 2004, Vol. 76, pp.7162-7168

**C.**



*Directed accumulation of dangerous bacteria by conjugation with functionalized magnetic nanoparticles*

National Research Council, Canada

# Therapy



**A.** Nanometer-sized particles are particularly responsive to electromagnetic and acoustic excitations through a variety of phenomena (e.g. plasmon resonance) that lead to local extreme conditions (e.g. heating). The nanoparticle is able to tolerate this condition, but not so the biological material nearby



# Therapy

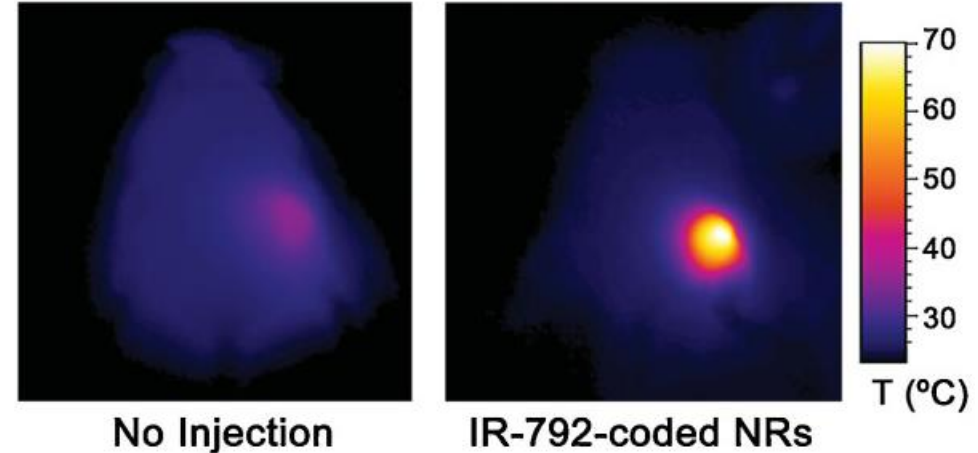


**B.** Intramuscular injections of colloidal gold, a suspension of gold nanoparticles, has been used for decades to alleviate pain linked to rheumatoid arthritis. The mechanism is still unknown

*Colloidal gold*

Source: John Hopkins Center

**C.**



An infrared beam illuminates two mice specimens. The local temperature increases for the mouse that received and injection of gold nanorods.

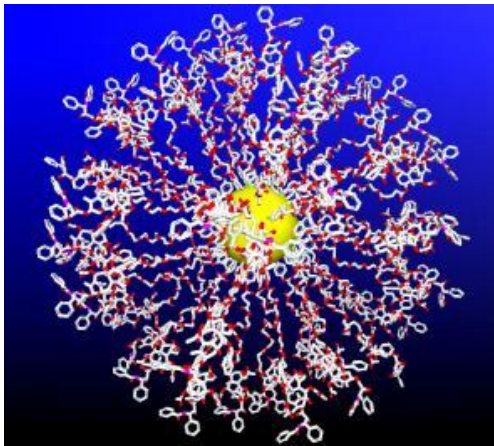
Adv. Mater. 2009, 21, 3175–3180



# Gold Nanoparticles vs. Alzheimer

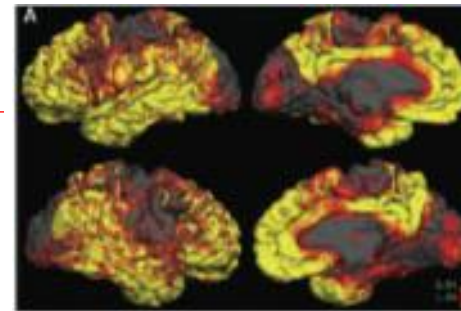
**A.** Alzheimer and other degenerative diseases are caused by the clustering of amyloid beta ( $A\beta$ ) protein.

**C.**

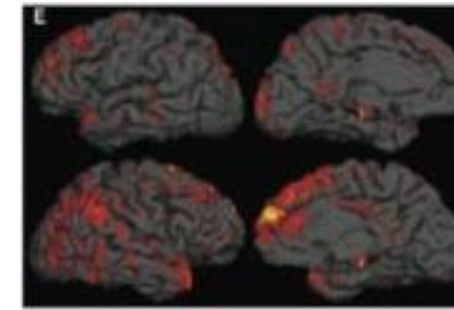


*Functionalized nanoparticle*

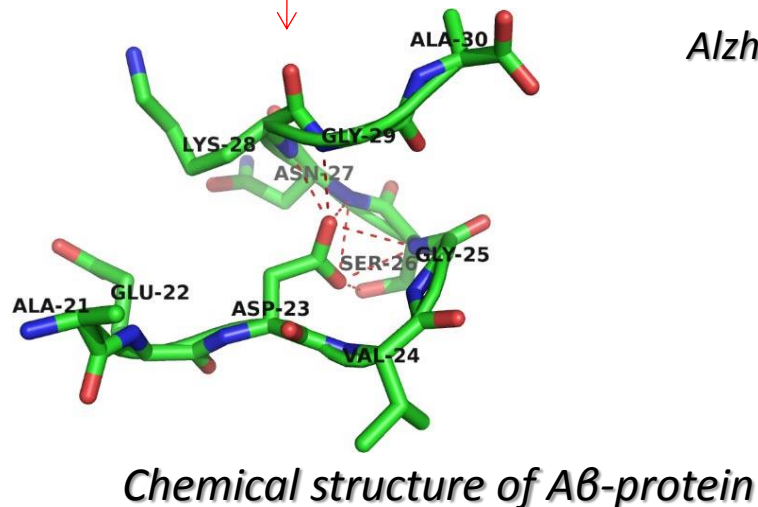
**B.**



*Alzheimer's brain*



*Healthy brain*

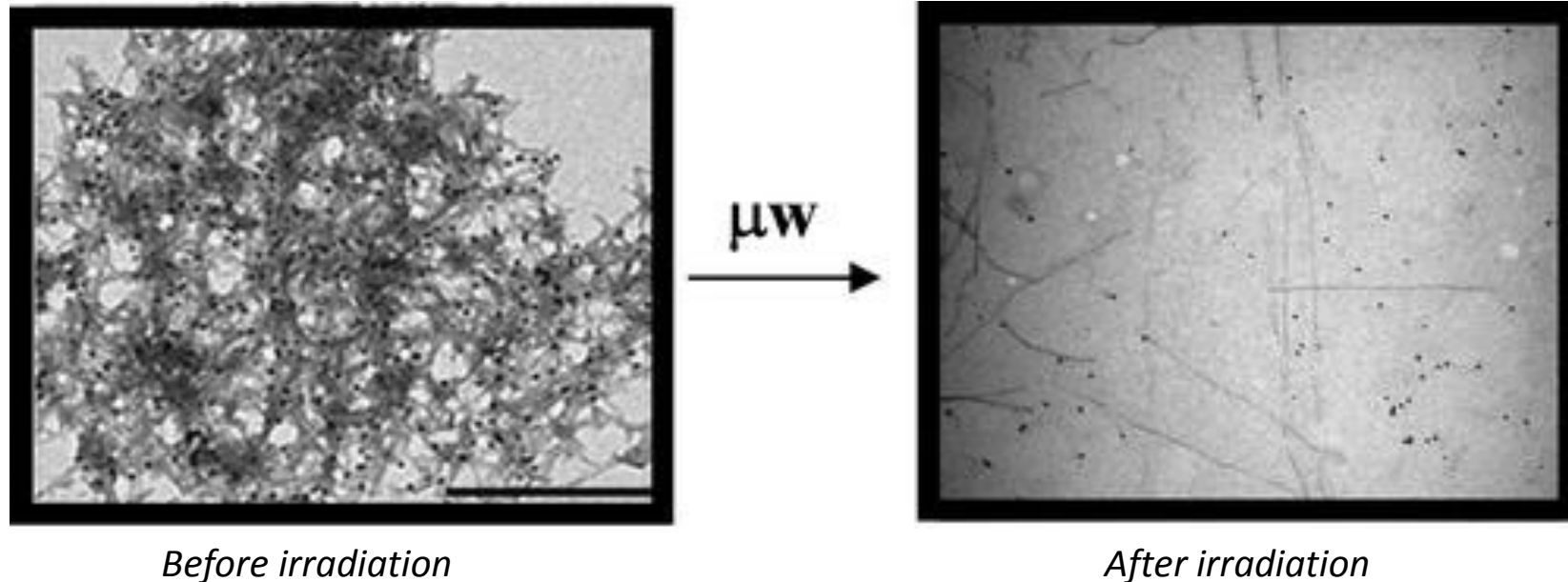


*Chemical structure of  $A\beta$ -protein*

**D.** Gold nanoparticles can be functionalized to specifically attach to aggregates of this protein (amyloidosis)

# Gold Nanoparticles vs. Alzheimer

**A.** The functionalized gold nanoparticles selectively attach to the aggregate of amyloid protein. The microwaves of certain frequency are irradiated on the sample. Resonance with the gold nanoparticles increases the local temperature and destroy the aggregate



Nanoletters 2006,  
Vol. 6, pp.110-115

## SECTION II

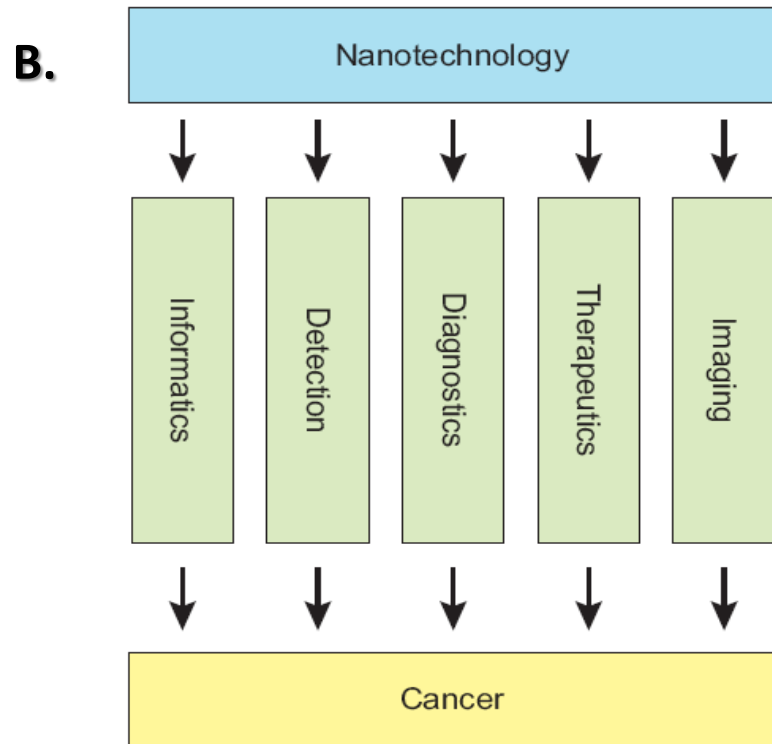
# Nanotechnology potential in medicine



# Cancer Nanotechnology



A. It is an interdisciplinary area merging science, engineering and medicine with the sole purpose of provide humanity new tools to fight cancer



C. **PREMISE**

Cancer nanotechnology, as a particular area of nanomedicine, is based upon the same premise that nanoparticles display unique properties potentially useful in medical (oncological) applications.

Nanoparticles in the size range of 5-100nm have enough surface area to be properly functionalized to bind specific targets, with a variety of ulterior purposes

Annu. Rev. Biomed. Eng. 2007. Vol. 9, pp. 257–88



# Cancer Facts

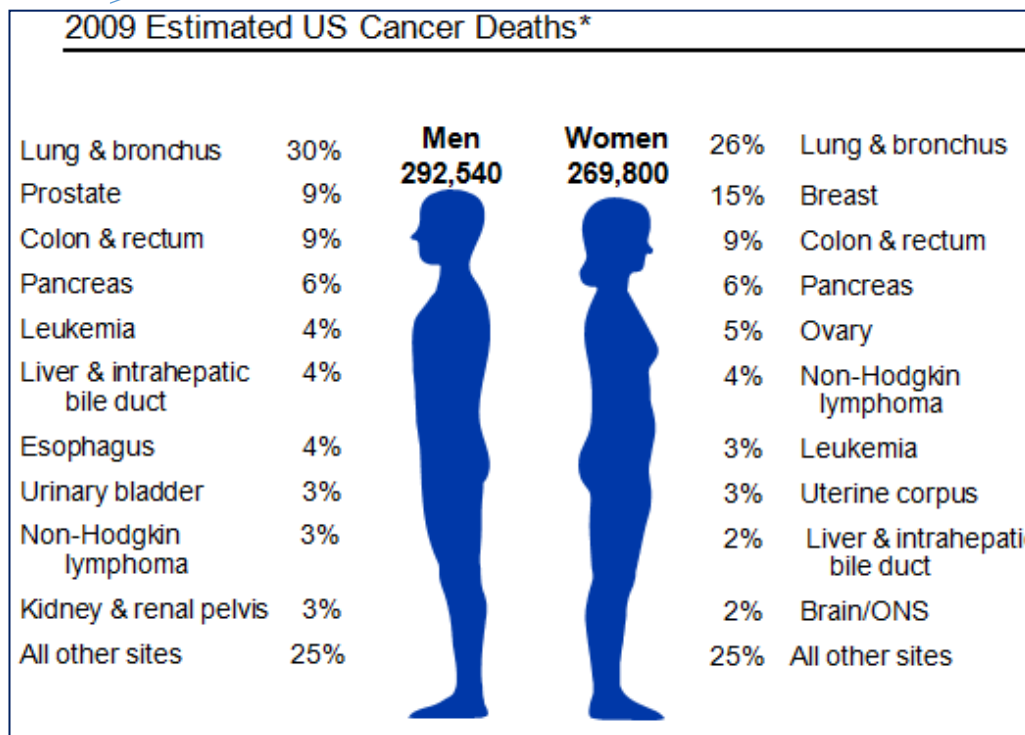
US Mortality, 2006

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	631,636	26.0
<b>2.</b>	<b>Cancer</b>	<b>559,888</b>	<b>23.1</b>
3.	Cerebrovascular diseases	137,119	5.7
4.	Chronic lower respiratory diseases	124,583	5.1
5.	Accidents (unintentional injuries)	121,599	5.0
6.	Diabetes mellitus	72,449	3.0
7.	Alzheimer disease	72,432	3.0
8.	Influenza & pneumonia	56,326	2.3
9.	Nephritis*	45,344	1.9
10.	Septicemia	34,234	1.4

**A.** The second main cause of death in the US, and certainly the diseases that lower the life quality of the patient the most

**B.** Lung cancer is the overwhelming lead cause of cancer-related deaths.

**BEWARE SMOKERS!!!!**



# Motivation



## DIAGNOSIS

A. The only factor that really correlates to the patient survival is early cancer detection



# Motivation



## THERAPY

**B. Chemotherapy and radiotherapy kill healthy and sick cells indiscriminately**



# Motivation

## IMAGING

C. Cancer resurgence after surgery occurs due to failure to recognize and remove all cancerous colonies



# Cancer: Too complex to handle?

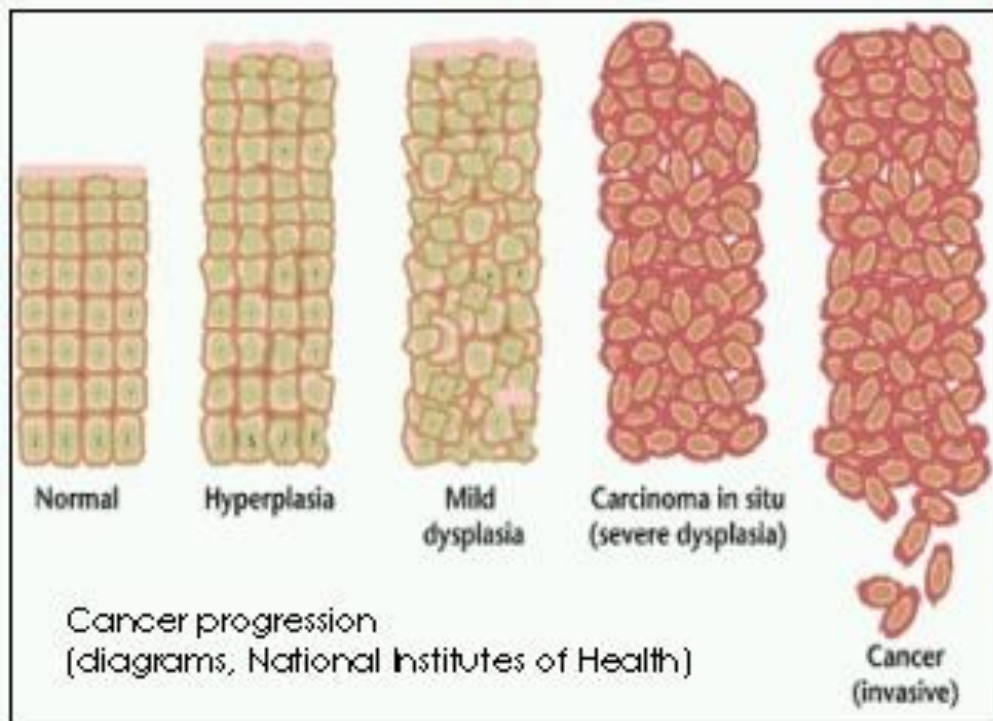


A. If you are an engineer, you can think of cancer as a living organism finally succumbing to entropy. Therefore, cancer is not one disease but million of diseases characterized by the disordered an uncontrolled growth of cells



# Cancer: Too complex to handle?

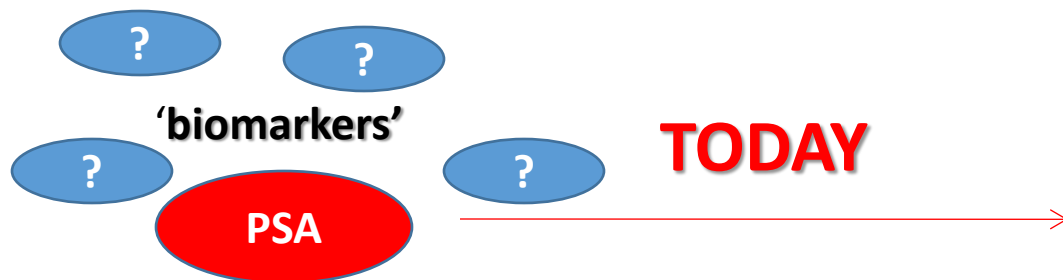
entropy



C. There are a myriad of metabolic/biological events that can unleash the growth of cancer cells. We must completely understand all the complex biochemistry of cancer to improve both diagnosis and treatment

D. The key is full 'biomarker' characterization of a different types of cancer

# Biomarker Research Status



Hmmm!! I see you have abnormal PSA levels. You might have some problems in your prostate. We must check for cancer

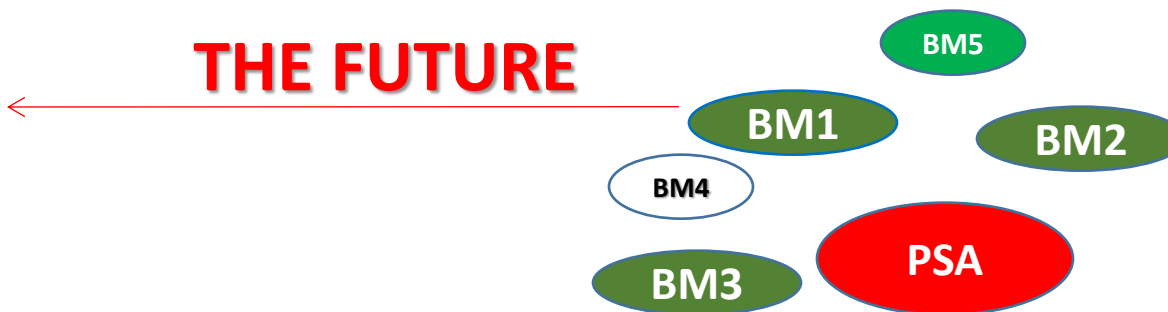


# Biomarker Research Status

Oh!! You have abnormal PSA levels. Also, your levels of BM1, BM2, BM3 are off, and BM4 levels are subnormal. You are starting to develop prostate cancer of the A phenotype. But don't worry your BM5 is fine, so metastasis hasn't occurred yet. Let's start treatment



**THE FUTURE**



# Nanoprobes: The usual suspects

Quantum Dots

Gold Nanoparticles

Nanorods

functionalized  
to achieve  
biocompatibility  
and cell  
targeting

Nanotubes

Liposomes

Polymeric Nanoparticles

# Therapy

**A. There is a search dual-mode nanoparticle that can detect a tumor (imaging) and destroy it (therapy)**

**B. There is two action modes for therapeutical nanoparticles**

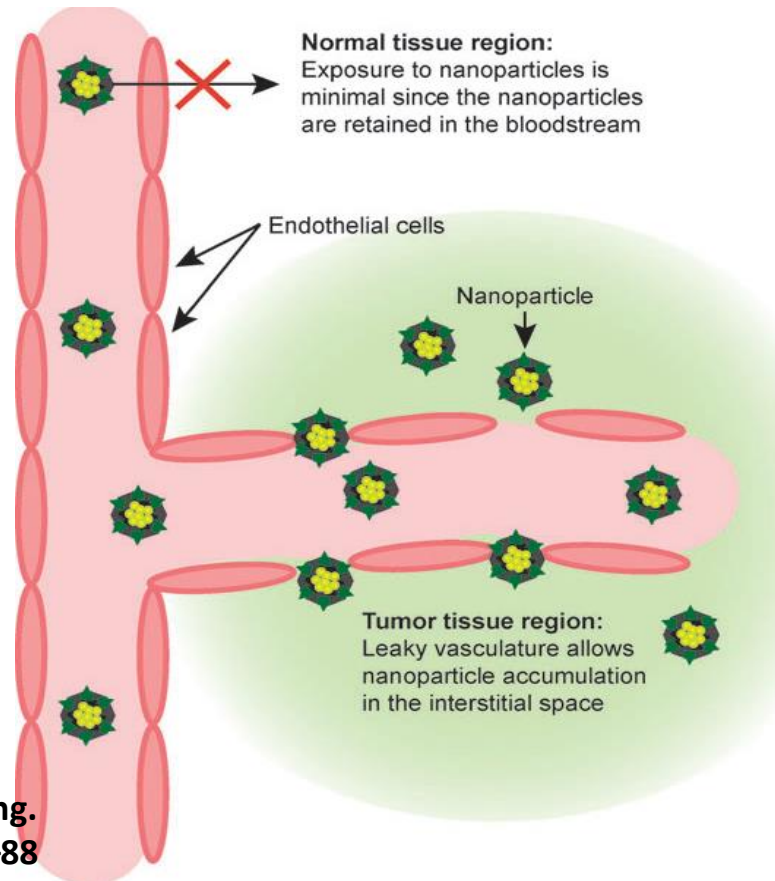
**Passive  
Targeting**

**Based on retention effect of  
particle of certain hydrodynamic  
size in cancerous tissues**

**Active  
Targeting**

**Based on nanoparticle  
functionalization for specific  
targeting of cancerous cells**

# Taking advantage of retention

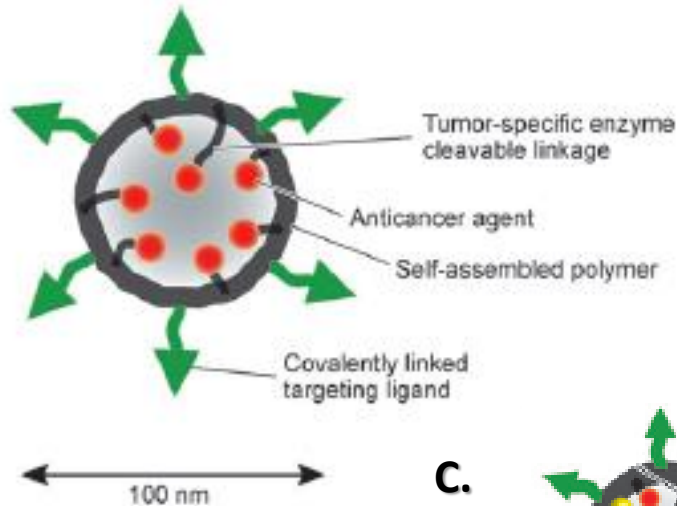


- A.** Tumorous tissues suffer of Enhanced Permeability and Retention effect
- B.** Nanoparticles injected in the blood stream do not permeate through healthy tissues
- C.** Blood vessels in the surrounding of tumorous tissues are defective and porous
- D.** Nanoparticles injected in the blood permeate through blood vessels toward tumorous tissues, wherein they accumulate

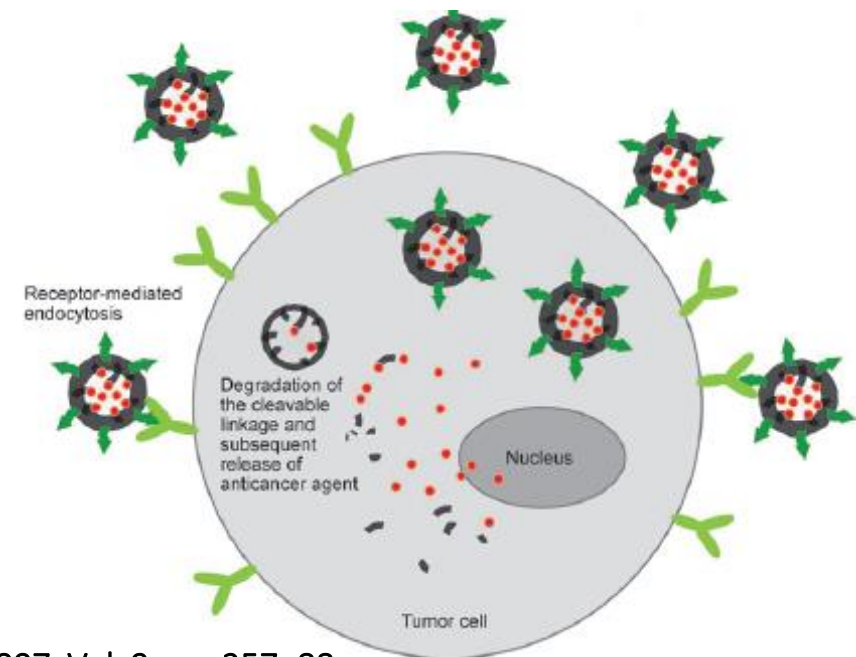
Annu. Rev. Biomed. Eng.  
2007. Vol. 9, pp. 257–88

# A Targeted Polymer Nanoparticle

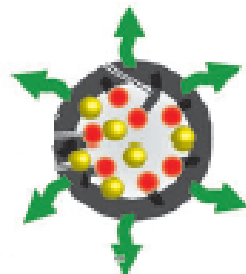
**A.** A dual Nanoparticle, the targeting ligand allow it to diagnose if a cell is healthy or sick, and bind specifically to the tumorous cell



**B.** Once inside the cell, the polymeric nanoparticle degrades and the anticancer agent is set free



**C.**  
Imaging agent



An imaging agent can be added as well

Annu. Rev. Biomed. Eng. 2007. Vol. 9, pp. 257–88



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## SECTION III

# Promising work



# What are the most promising fields of nanomedicine?



- Principles of nanomedicine, including basic research and theoretical applications
- Nanotechnological advances and their potential medical applications
- Disorders/conditions and the benefits of nanomedical tools versus traditional techniques
- Pre-clinical testing of novel nanomedical tools
- Implanted nanodevices for the prevention and treatment of disease and the alleviation of pain
- Nanomedical tools in gene therapy for inherited diseases
- Tissue, cell and genetic engineering involving nanomedical tools
- Drug delivery using nano-particles (natural and artificial) or devices



# Applications of Nanorobots



1. **Drug delivery-** Pharmacytes are the nanorobots designed for the action of drug delivery. The dosage of drug will be loaded into the payload of the pharmacyte. The pharmacyte will be capable of precise transport and targeted delivery of drug to specific cellular targets. The pharmacytes upon arriving at the vicinity of tumor or any target cell would release the drug via nanoinjection or by progressive cytopenetration until the payload delivery is reached.
2. **Body surveillance:** Monitoring continuously of vitals and wireless transmission could be possible using nanorobots, leading to a quantum leap in diagnostics. This would also help in quick response in case of sudden change in vitals, or could warn against a possible risk, such as high blood glucose in case of diabetics.
3. **Dentistry-** The nanorobots designed for dental treatment are referred to as dentifrobots. These nanorobots can induce oral analgesia, desensitize tooth, manipulate the tissues to realign and straighten irregular set of teeth .



# Applications of Nanorobots



- 4. In surgery-** The surgical programmed nanorobot can act as a semi-autonomous onsite surgeon inside the body. It would perform various functions such as detection of pathology, diagnosing, correcting lesions by nano-manipulation coordinated by an on-board computer.
- 5. Cancer detection and treatment-** The nanorobots are made with a mixture of polymer and a protein known as transferrin which is capable of detecting tumor cells. The nanorobots would consist of embedded chemical biosensor that can be used in detection of tumor. The medical nanorobots with chemical biosensors can be programmed to detect different levels of E-cadherin and beta-catenin, aiding in the target identification and drug delivery. The nanorobot could also carry the chemicals employed in chemotherapy to treat the cancer at the site. The robots could either attack tumors directly using lasers, microwaves or ultrasonic signals or as a part of a chemotherapy treatment, delivering medication to the cancer site.



# Applications of Nanorobots



- 6. Diagnosis and treatment of diabetes-** The glucose molecules are carried through the blood stream to maintain the human metabolism. The hSGLT3 molecule can define the glucose levels for diabetes patients. The glucose monitoring nanorobot uses the chemo sensor which involves in the modulation of hSGLT3 protein gluco-sensor activity. These chemical sensors can effectively determine the need of insulin in the body and inject.
- 7. Gene therapy-** The medical nanorobot can treat genetic diseases by comparing the molecular structure of both DNA and proteins found in the cell. The chromosome replacement therapy can carried out using chromalloyocytes



# Applications of Nanorobots



**8. Delicate surgeries:** Nanorobots could be soon used for performing micro surgery of the eye as well as surgeries of the retina and surrounding membranes. In addition, instead of injecting directly into the eye, nanorobots could be injected elsewhere in the body and delivery of the drug can be guided to the eye. Foetal surgery, one of the most risky surgeries today because of the high mortality rate of either the baby or the mother, could soon have a 100% success rate, due to the fact that nanorobots can provide better access to the required area inducing minimal trauma. Similarly, other difficult surgeries could also benefit from advances in nanorobotics



## SECTION IV **Assesment**



# What have we learned?



- Nanoparticles have very special properties that make them attractive for nanomedicine
- Nanoparticles can be functionalized with antibodies to target their binding toward specific cells
- Nanoparticles can be used in diagnosis through the detection of biomarkers





# What have we learned?



- Nanoparticles can respond to external radiation and release heat, killing cells around them
- Nanoparticles can be made of lipids or polymers than decompose once a target is reached and deliver a pharmaceutical agent
- Quantum dots are special nanoparticles that emit light of different colors according to its diameter, and can be used for complex diagnosis



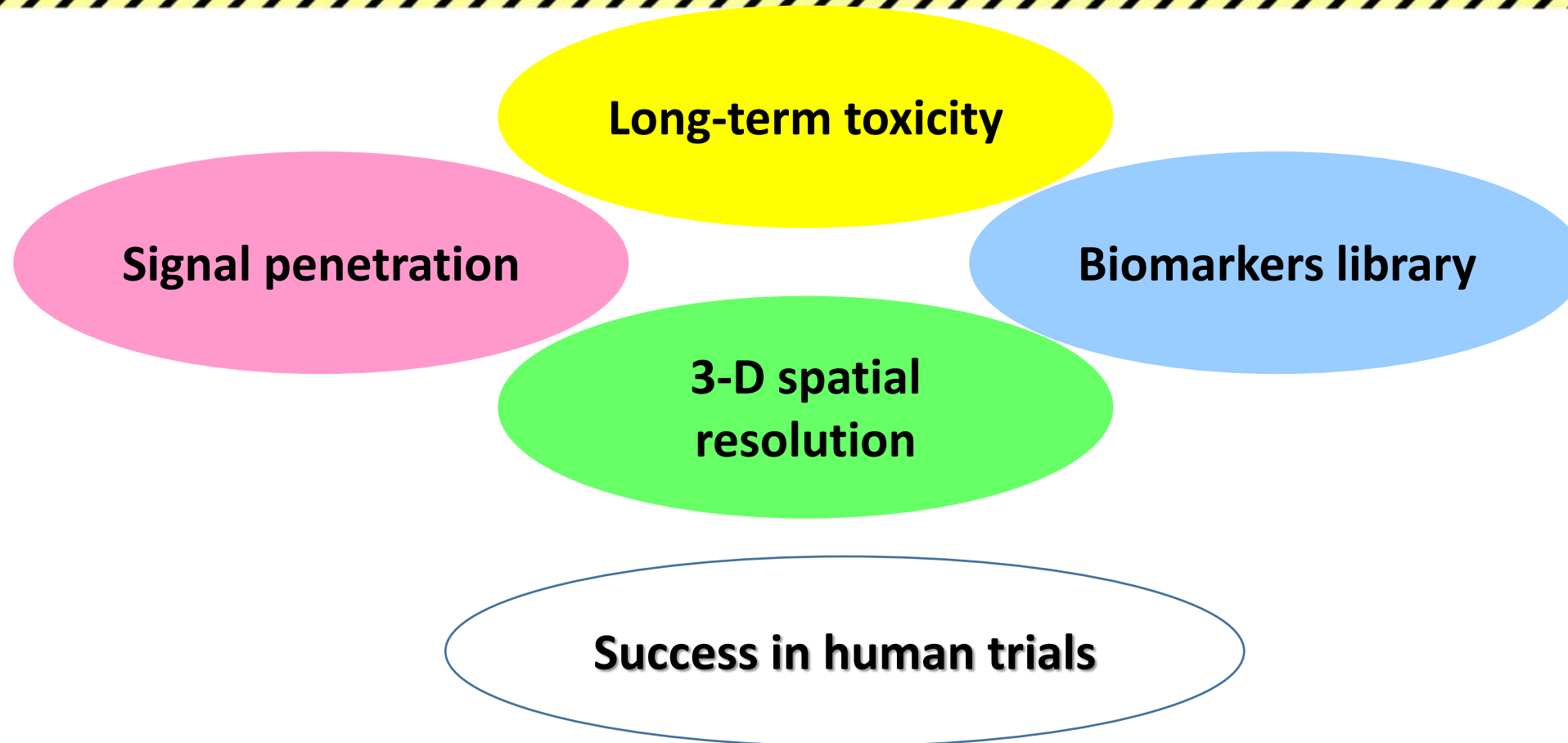
# What have we learned?



- PEG is the most used polymer to coat nanoparticles due to the biocompatibility and biomobility that confers to the nanoparticle
- Targeted nanoparticles offer a light of hope for the fight against cancer
- An ideal nanoparticle is **three-modal**: *detects*, *diagnoses* and *attacks* tumorous cells



# Unsolved issues



# Challenges



- Multiple modality and functional nanoparticles
- Fight against the tendency of nanoparticles to be adsorbed by reticuloendothelial system
- Avoid aggregation of nanoparticles for in vivo viability
- Improve retention times of the nanoparticles inside the body to allow the therapeutic effect
- Substitute potentially toxic elements



# Challenges



- Compromise between coating and hydrodynamic radius
- Eliminate the inflammatory and immune response triggered by some polymer coatings
- Avoid undesired degradation exposing toxic elements (QD) or untimely delivering cargo
- Increase contrast for human medical imaging (tissues are naturally fluorescent)



# Challenges



- Real-time monitoring of drug distribution, action mechanism and patient's response
- Fast detection of biomarkers at lower limits
- Understanding the mechanism of diseases (cancer)
- Diagnosis leading to personalized treatments
- Detection of deep tumors
- Selective targeting in extremely heterogeneous tissues.





# Thank you!



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