Universita deglli Studi di Milano
- LLP / ERASMUS - 2008

Nanotechnologies and drug delivery devices in medical sciences

Romeo-Teodor Cristina

Faculty of Veterinary Medicine Timisoara

Pharmacology, Pharmacy and Therapeutics Depts.

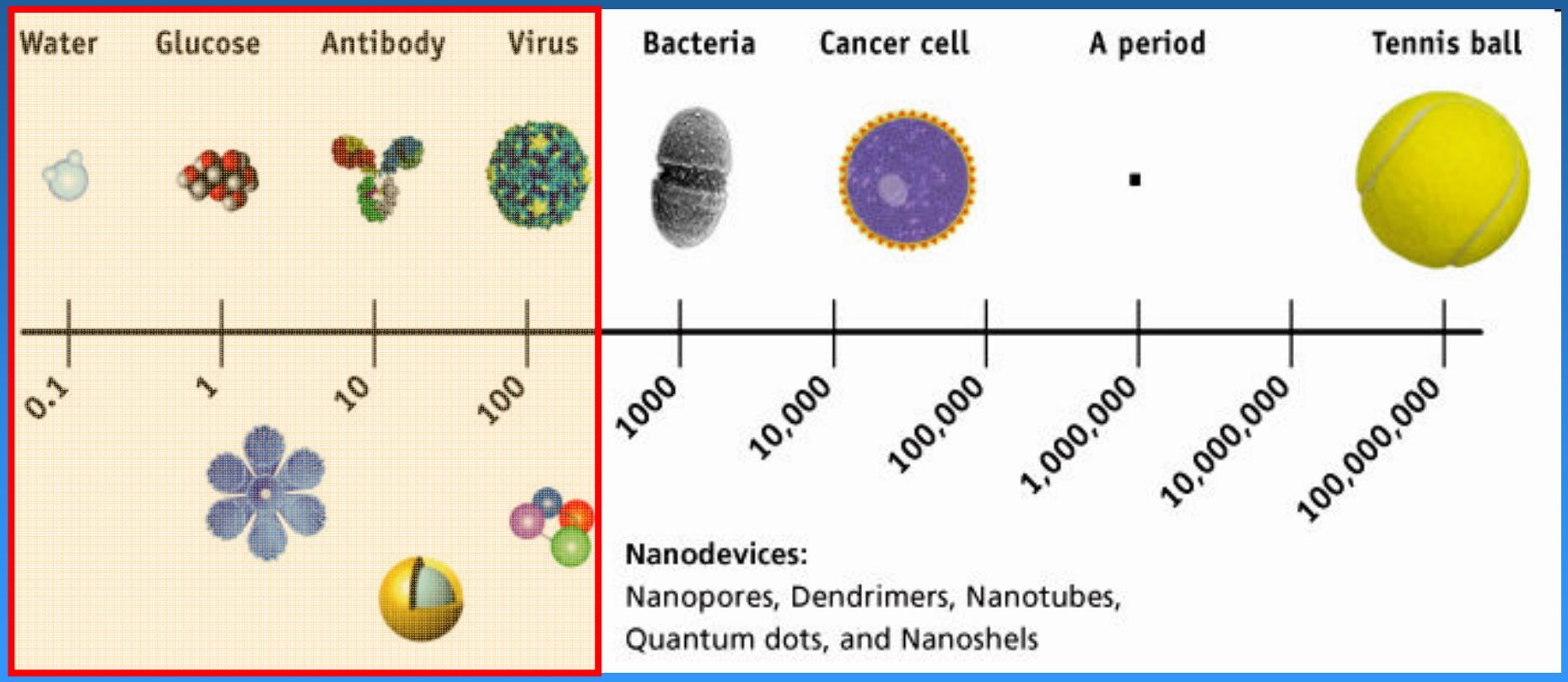
Image: http://biomed.brown.edu/Courses/BI108/BI108_2004_Groups/Group04/tissues2.jpg

Introduction

Nanobiotechnology is a thriving new area of research at the interface between the life sciences and nanotechnology, which deals with structures of dimensions ranging from:

1 nm to 100 nm (below lithographic fabrication techniques range)

Nanobiotechnology aims to exploit biomolecules and the processes carried out by them for the development of novel functional materials and devices, nanomachines, perhaps nanorobots.



Source: www.fda.gov/consumer/ updates/nanotech072507.html

Drugs are substances that generally cause favourable changes to the body…

But

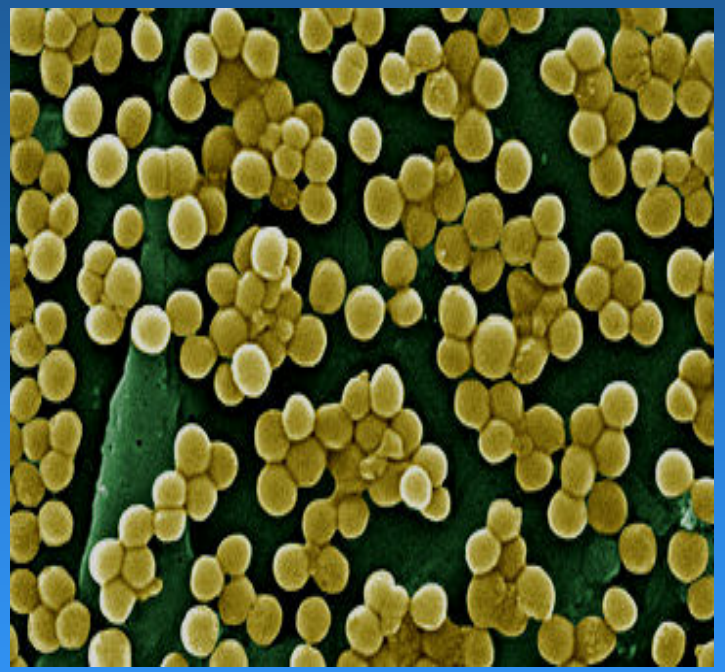
Drugs can also harm it especially following of:

- undesired effects
- residues
- resistance

….

For example:

Numerous clumps of Methicillin-Resistant *Staphylococcus aureus* (MRSA) by Scanning Electron Micrograph (SEM)

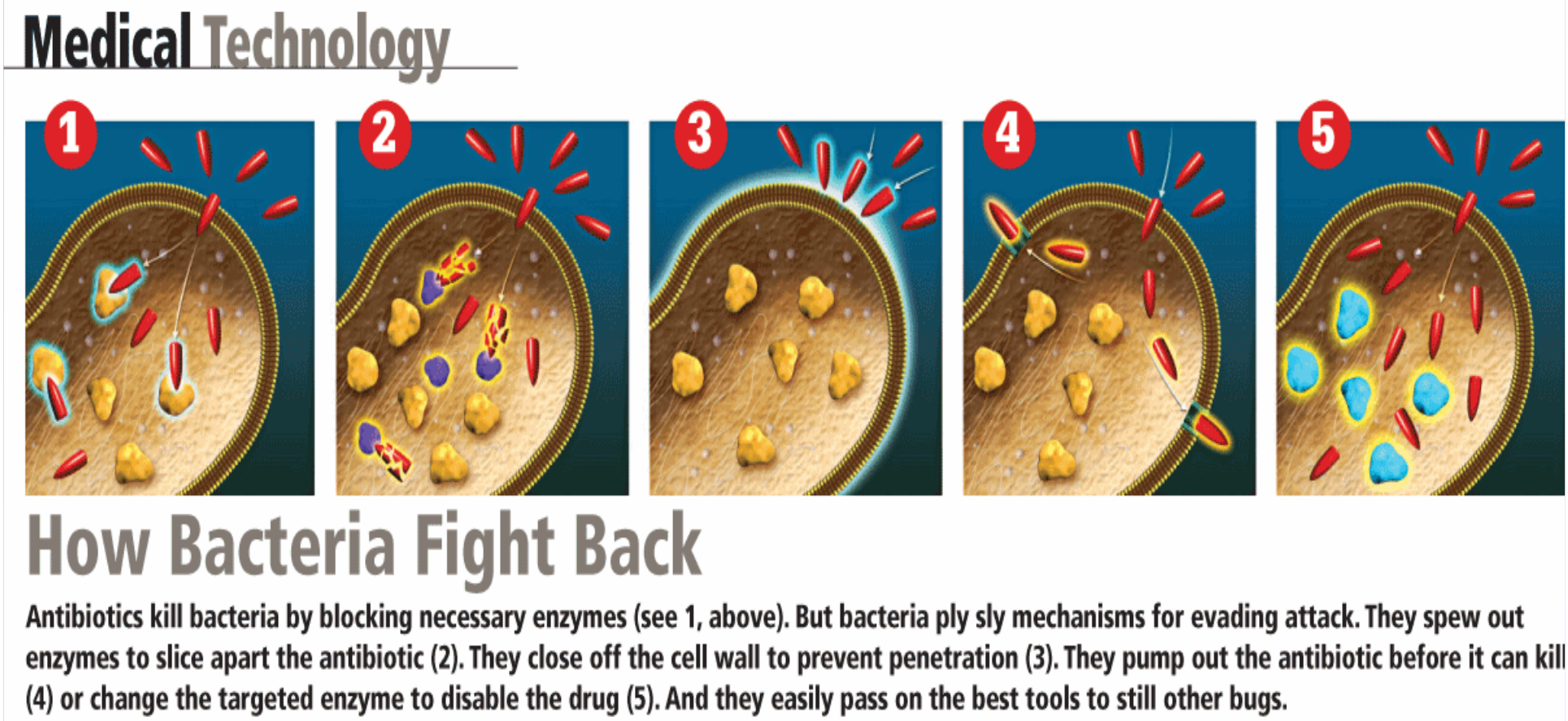


Fact:

More than 70% of the bacteria that cause infections in hospitals are resistant to at least one antibiotic: Methicillin-Resistant *Staphylococcus aureus* (MRSA) !!!

Source: http://img.timeinc.net/time/daily/2007/0706/a_lantibiotics_0618.jpg

The ply sly mechanism:



Source: http://s3.amazonaws.com/readers/healthmad/2007/07/22/43701_0.jpg

As we can see

drug - resistant bugs are smart,

so new types of drugs are finding ways to be smarter !

Therapeutic nanotechnology offers features that may reduce patient morbidity and mortality:

- ► minimally invasive therapies
- ► high densities of function
- ► concentrated in small volumes

A definition of a drug delivery system device after the FDA can be:

"an article intended to diagnose, cure, treat, prevent, or mitigate a disease or condition, or to affect a function or structure of the body, that does not achieve its primary effect through a chemical action and is not metabolized“…

Early application of nanotechnology

enabled products involved drug reformulation to deliver some otherwise toxic drugs (e.g. antifungal and anticancer agents) in a safer and more effective manner.

Nano-devices first-generation included:

- liposomes
- albumin bound nanoparticles
- gadolinium chelates
- iron oxide particles
- silver nanoparticles (antibacterial wound dressing
- nanoparticulate restoratives (dentistry)

Among the great number of researches on the topic, magnetic fluids are considered as being among primary verified nanoscience applications.

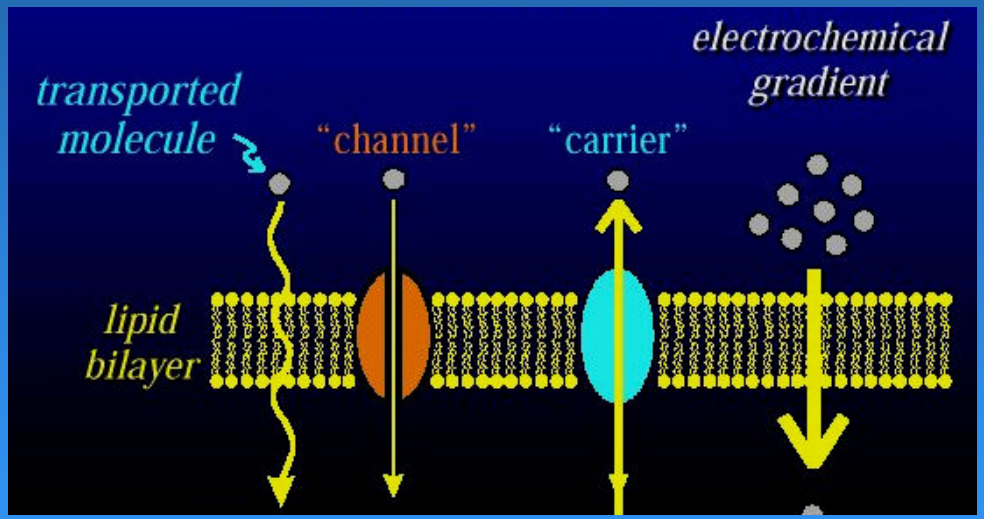
A good example is the successful use of the magnetic fluids in AIDS:

Second-Generation Nanotechnologies

Second generation nanotechnologies are more sophisticated than first generation nanotechnologies due to novel molecular engineering that enables the devices to:

- target,
- image,
- deliver a therapeutic agent, and
- monitor therapeutic efficacy in real time.

General known mechanisms of drug's passage used also as delivery mechanisms and / or ways



Source: http://www.pharmacology2000.com/General/Introduction/chan_trans1.jpg

Top of last decade preoccupations:

Human	Veterinary
Diabetes ◄	► Infectious diseases
Cancer ◄	► Parasitary diseases
Hearth attack ◄	► Diabetes in dogs
Hormonal disorders ◄	► Hormonal disorders
CNS modulators ◄	► Stem cells (bone)
Stem cells ◄	► Monitoring
Immune suppression ◄	► Immune suppresion
Allergy ◄	
Eye deficiencies ◄	
Angioplasty ◄	
Monitoring ◄	

Biomaterials for delivery systems in them evolution

A great range of materials have been employed to control the release of drugs and other active agents.

The earliest of polymers were originally intended for other, non biological uses, and were selected because of their desirable physical properties, for example:

Polymer type	Main activity
Polyurethanes	- elasticity
Polysiloxanes	- insulating ability
Polymethyl methacrylates	- physical strength and transparency
Polyvinyl alcohols	- hydrophilicity and strength
Polyethylenes	- toughness and lack of swelling
Polyvinyl pyrrolidones	- suspension capabilities

To be successfully used in controlled drug delivery formulations, a material must be:

- chemically inert
- free of leachable impurities
- with minimal undesired aging
- readily processable
- with an appropriate structure

The materials that are currently used for drug delivery includes:

Poly
- hydroxy-ethyl-methacrylate
- N-vinyl-pyrrolidone
- methyl-methacrylate
- vinyl-alcohol
- acrylic acid
- acryl-amide
- ethylene-co-vinyl-acetate
- ethylene-glycol
- methacrylic acid
- lactides(PLA)
- glycolide (PGA)
- lactide-co-glycolide (PLGA)
- anhydride
- orthoester

There are also to mention the main factors that can affect polymers' biodegradation:

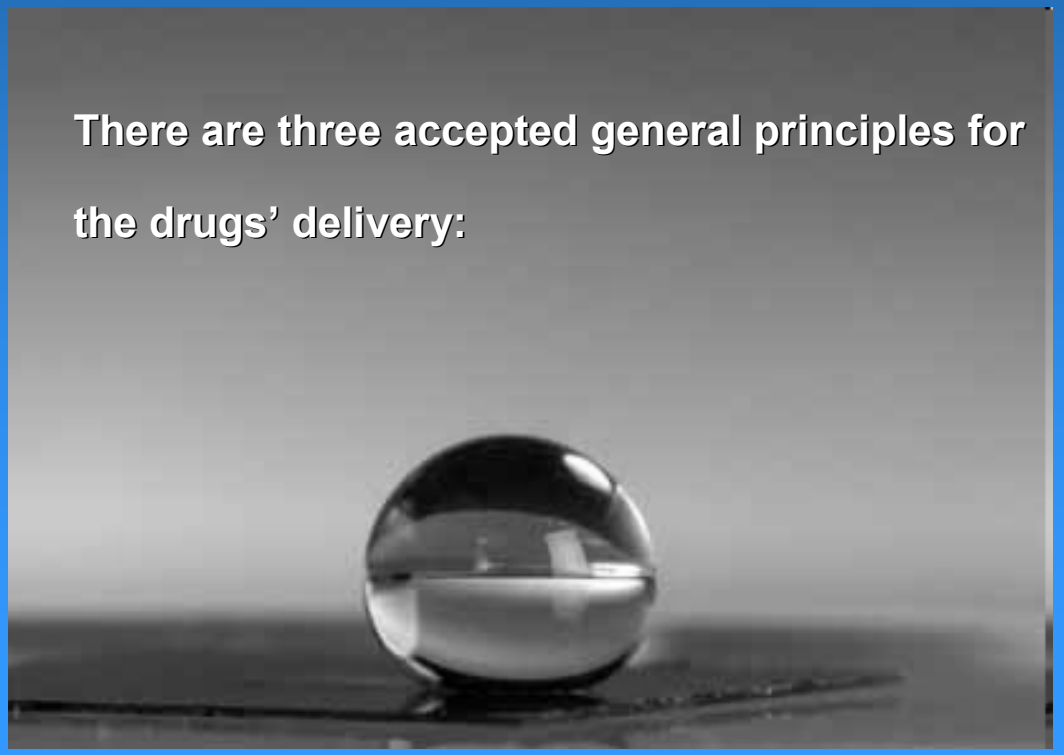
- chemical structure
- chemical composition
- distribution of repeat units in multimers
- ionic groups presence
- unexpected units (or chain defects) presence
- molecular weight and molecular - weight distribution
- morphology (amorphous/semi crystalline, microstructures)
- presence of low-molecular-weight compounds

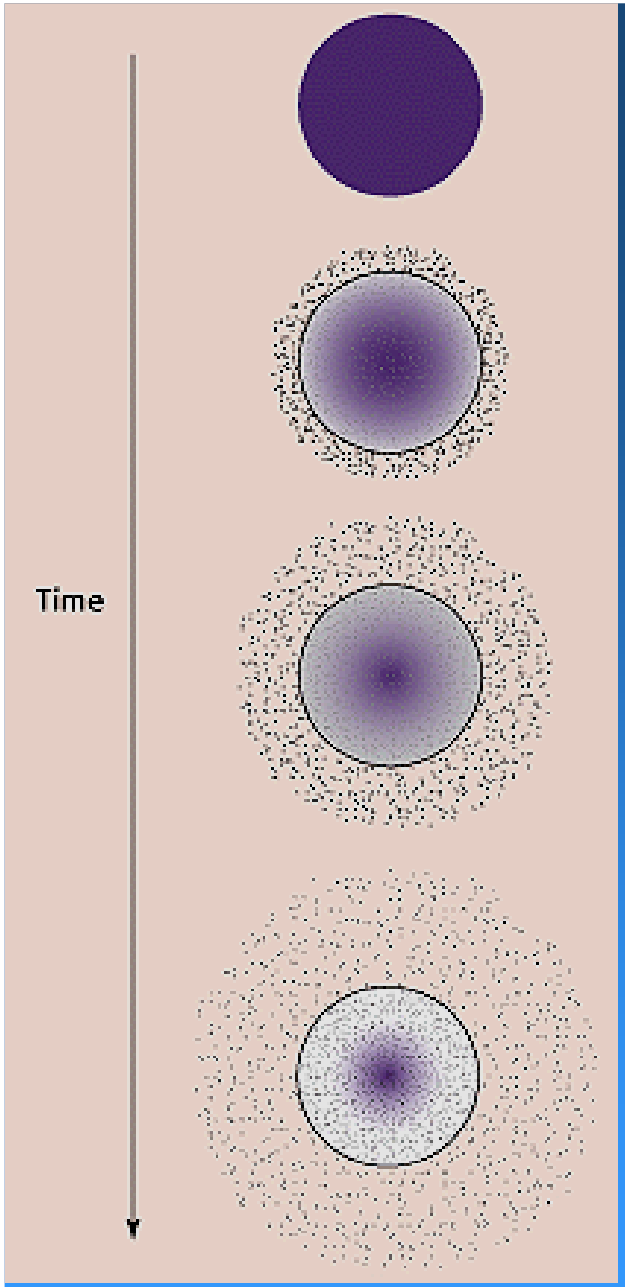
… and also technological and medical ones:

- Processing conditions
- Annealing
- Sterilization process
- Storage history
- Shape
- Site of implantation
- Adsorbed and absorbed compounds (water, lipids, ions)
- Physicochemical factors (ion exchange, ionic strength, pH)
- Physical factors (shape and size changes, diffusion's coefficient variations, mechanical stresses, and solvent-induced cracking)
- Mechanism of hydrolysis (enzymes vs. water)

Known and Applied principles:

There are three accepted general principles for the drugs' delivery:



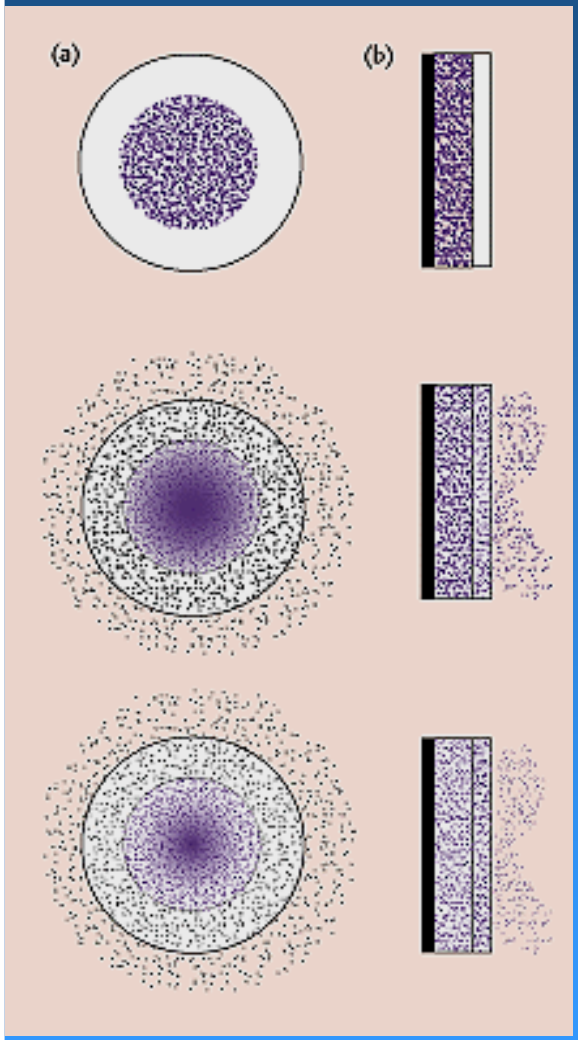


1. Drug delivery from

a typical matrix drug delivery system

- a polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system
- diffusion occurs when the drug passes from the polymer matrix into the external environment
- as the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release

Source: http://www.devicelink.com/mpb/archive/97/11/9711b34c.gif



2. Drug delivery from typical reservoir devices:

(a) implantable or oral systems, and

(b) transdermal systems

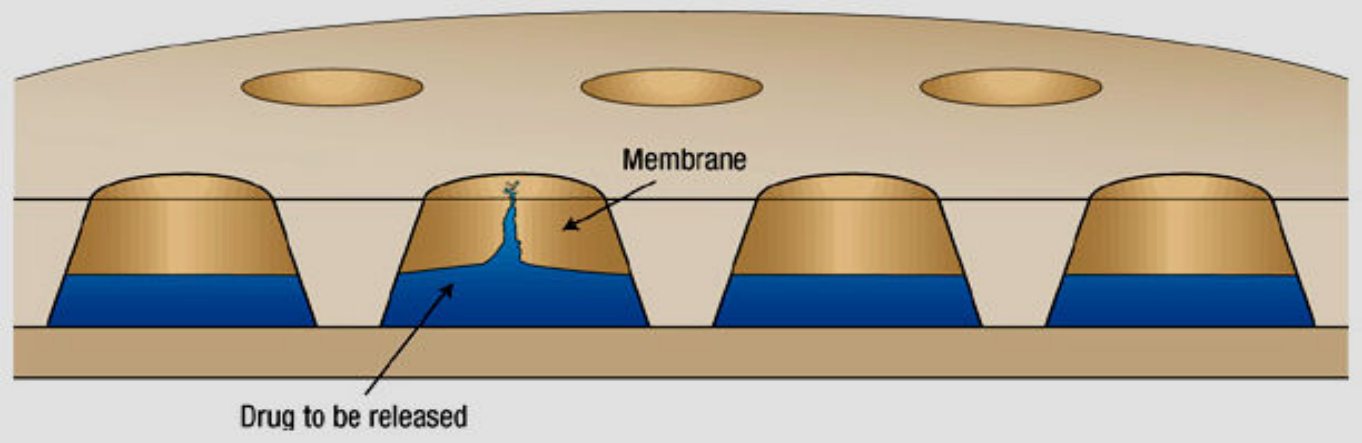
click

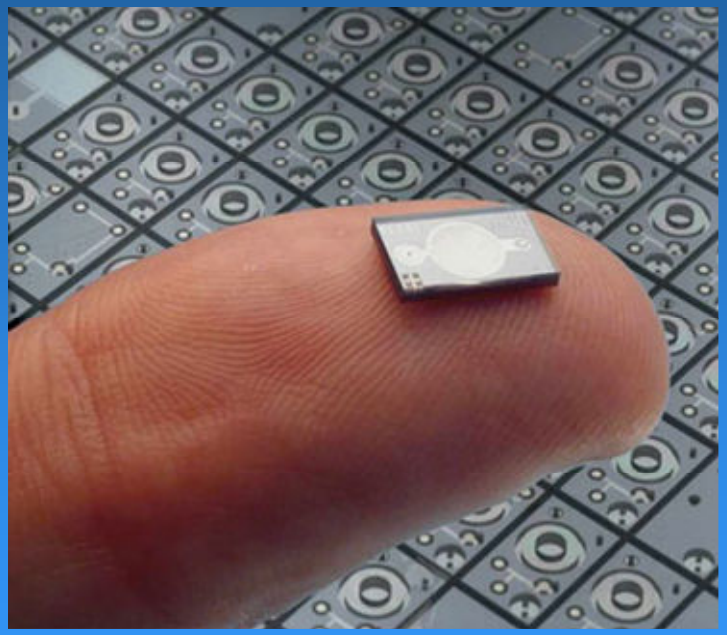
For the reservoir systems shown in figures **a** and **b**, the drug delivery rate can remain fairly constant.

In this design, a reservoir - whether solid drug, dilute solution, or highly concentrated drug solution within a polymer matrix is surrounded by a film or membrane of a rate - controlling material.

Source: http://www.devicelink.com/mpb/archive/97/11/9711b34c.gif

3. Polymer-based microchip drug-delivery





Debiotech of Lausanne, Switzerland (2007) has produced the first prototypes of the company's tiny insulin pump device

The working principle is a volumetric membrane pump, with a pair of check valves, integrated in a MEMS chip.

Source: http://www.medgadget.com/archives/img/524deb1.jpg

Limitations that can embezzle the earliest drug-delivery systems

- under-optimal bioavailability
- limited effective targeting
- potential cytotoxicity
- long and frequent treatments that are often required

but …

- **nanocarriers** overcome these limitations.

Nanocarriers are able to:

- maximize therapeutic activity
- minimize toxic side effects
- target specific cells rather than tissues
- allow for easy surface movement.

Functional groups may be placed on the nanocarrier to:

- ► increase / decrease solubility
- ► cellular membranes' easy penetration
- ► increase of immuno-compatibility
- ► encourage the cellular uptake
- ► determine the drug's final destination

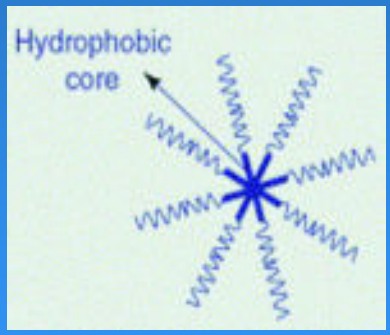
Types of nanocarriers

1. The polymeric micelles

There are spherical conglomerations of amphiphylic molecule, ranging from 50 nm to 220 nm. Generally, micelles encapsulate non-water soluble drugs to be administered i.v.

► in aqueous environment, the molecules form a tight ball with:
- the hydrophobic groups on the inside and with
- the hydrophilic groups on the outside.

► in non-aqueous environment, reverse occurs

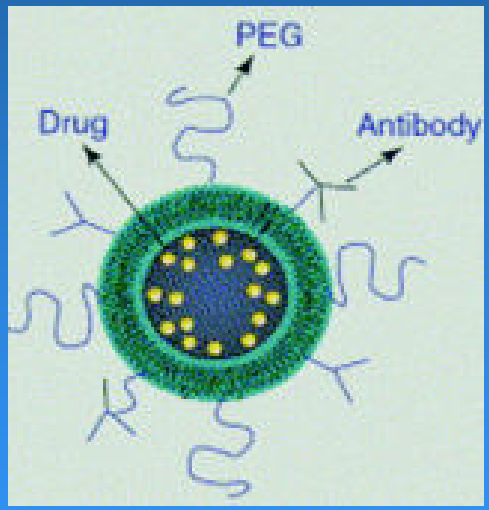


Source: http://s3.amazonaws.com/readers/healthmad/2007/07/22/43701_0.jpg

2. Liposomes

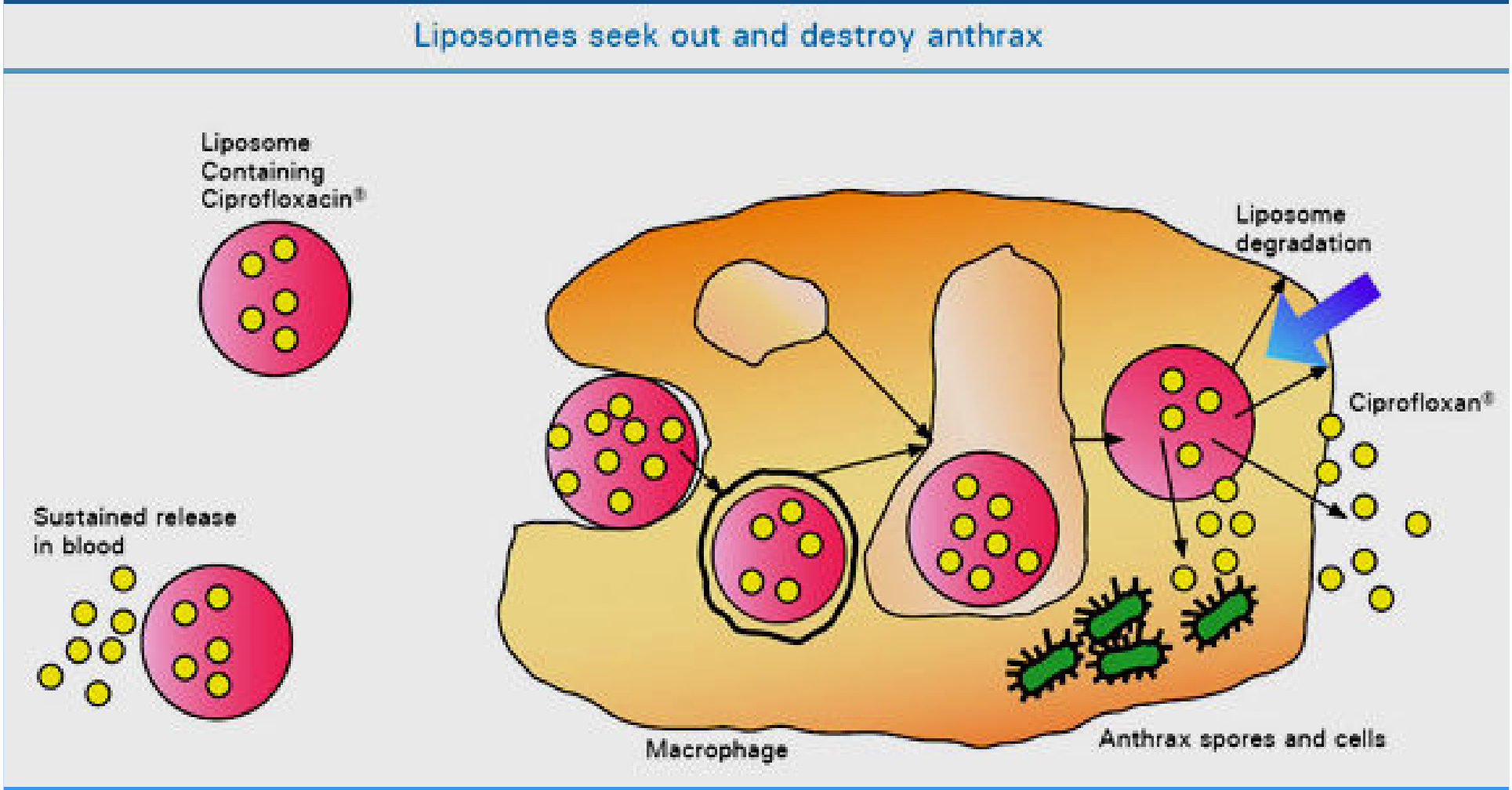
Are spherical vesicles comprised of one or more lipid bilayer structures enclosing an aqueous core.

- ► they are high-potency carriers and do an excellent job of protecting encapsulated drugs from the early degradation
- ► they can also be functionalized to improve cell targeting and solubility having many medical applications



Source: http://s3.amazonaws.com/readers/healthmad/2007/07/22/43701_0.jpg

Examples:

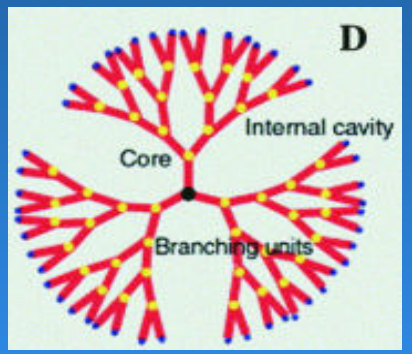


Source: http://s3.amazonaws.com/readers/healthmad/2007/07/22/43701_0.jpg

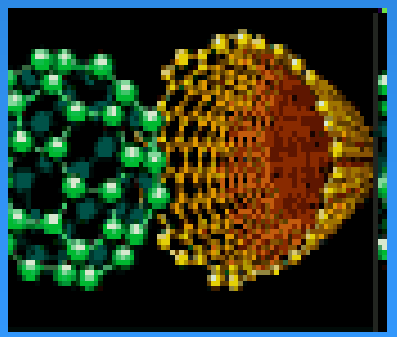
3. Dendrimers

Are highly branched polymers of 5 to 20 nm with a controlled 3D structure around a central core.

The flexibility they offer in terms of their size, shape, branching, length, and surface functionality gives dendrimers great potential as nanocarriers.



- the most versatile of all nanocarriers are easily functionalized
- can easily accommodate more than 100 terminal groups
- dendrimers have been studied extensively for:
  - targeting
  - treating tumors
  - treating drug resistance



This particle holds significant promise for cancer treatment

Its many branches allow other molecules to easily attach to its surface

The creators of these dendrimers have had successful tests with cancer cells in culture and try them also in living animals

Researchers have fashioned dendrimers into sophisticated anti-cancer machines carrying five chemical tools:

- a molecule designed to bind to cancer cells
- a second that fluoresces upon locating genetic mutations
- a third to assist in imaging tumor shape using X-rays
- a fourth carrying drugs released on demand
- a fifth that would send a signal when cancerous cells are dead

Newest slow release devices

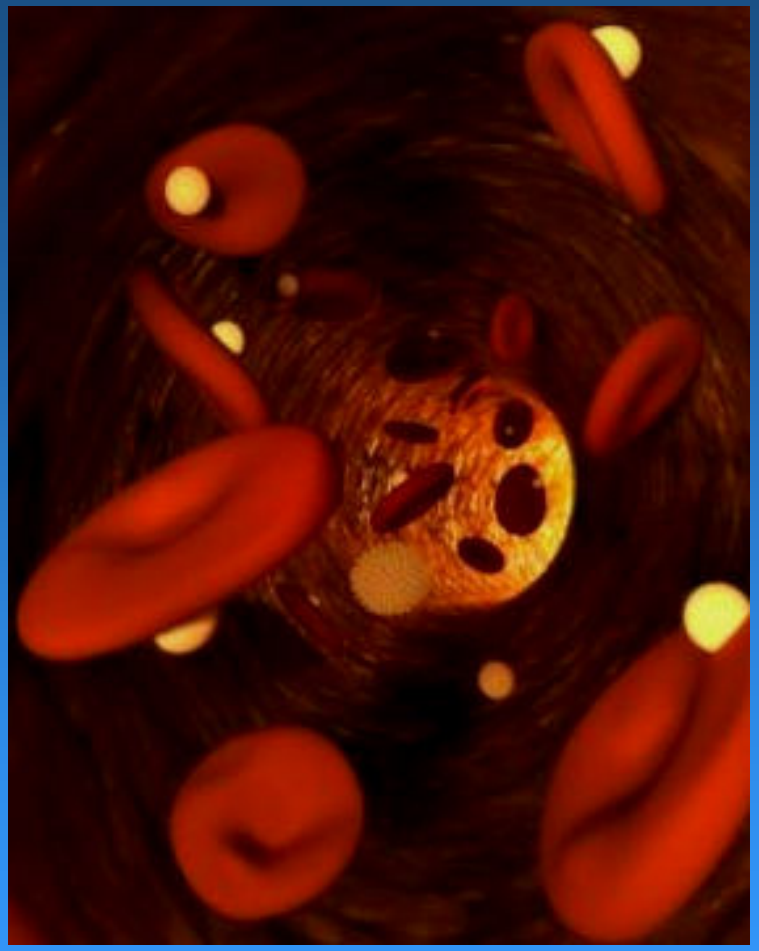
- Human medicine

Researchers from the University of California at Santa Barbara (UCSB) have found that ‘nanoparticles can be forced to remain in the circulation when attached to red blood cells

In other words, these nanoparticles hitchhike on red blood cells

Apparently, these nanoparticles could stay with their hosts for their life time about 120 days

So this could lead to new treatments for heart disease

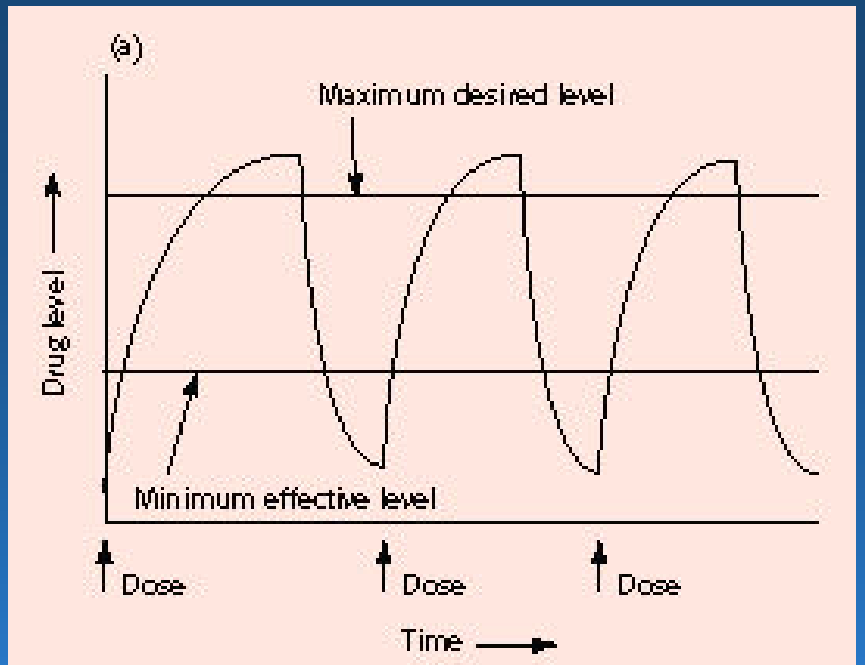


Source: http://blogs.zdnet.com/emergingtech/?m=200706

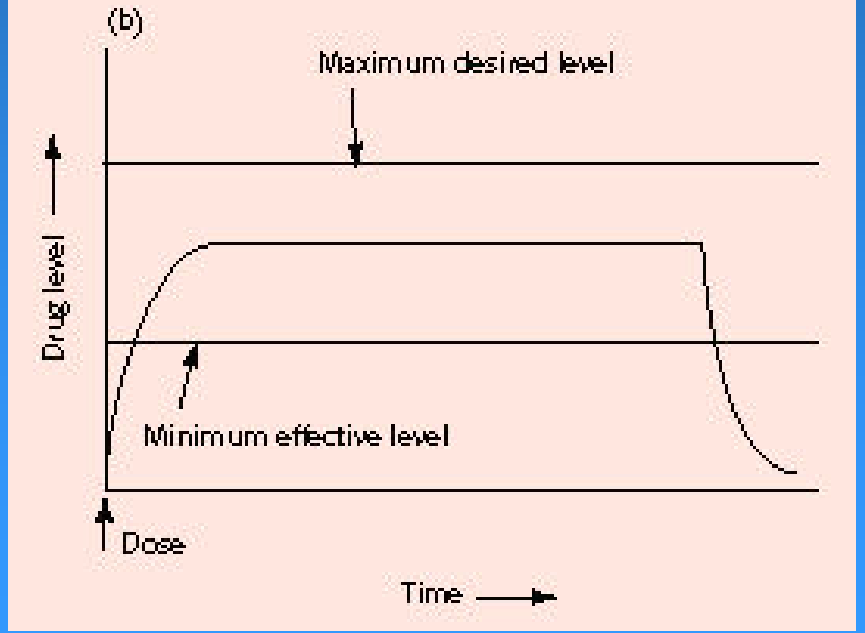
advantage:

the drug levels in the blood:

(a) Traditional drug dosing

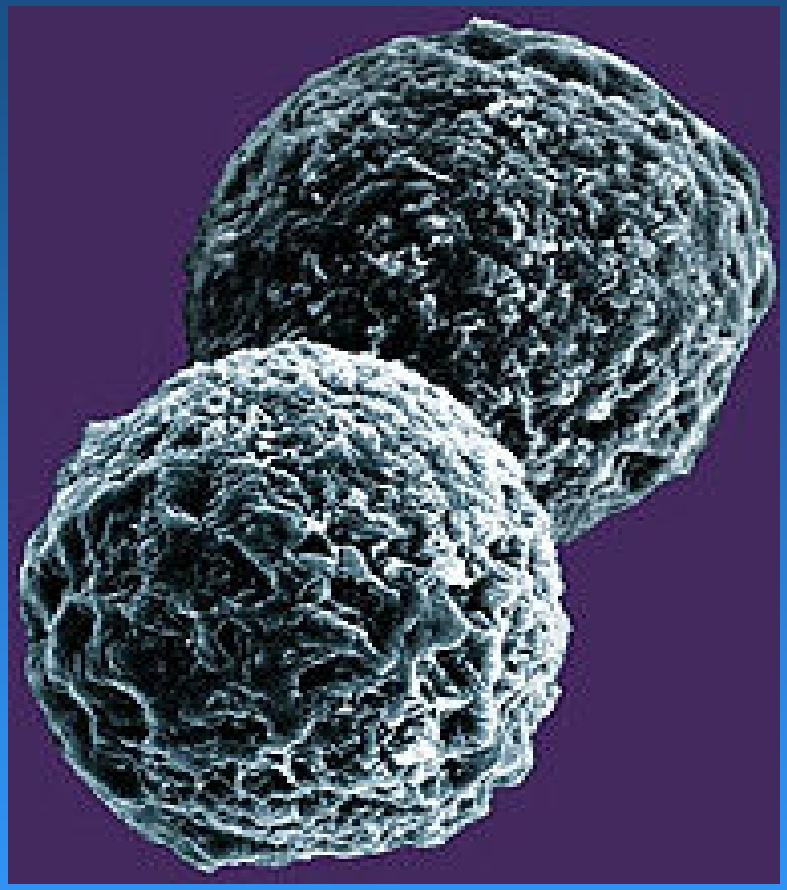


(b) Controlled - delivery dosing



Source: http://www.devicelink.com/mpb/archive/97/11/9711b34b.jpg

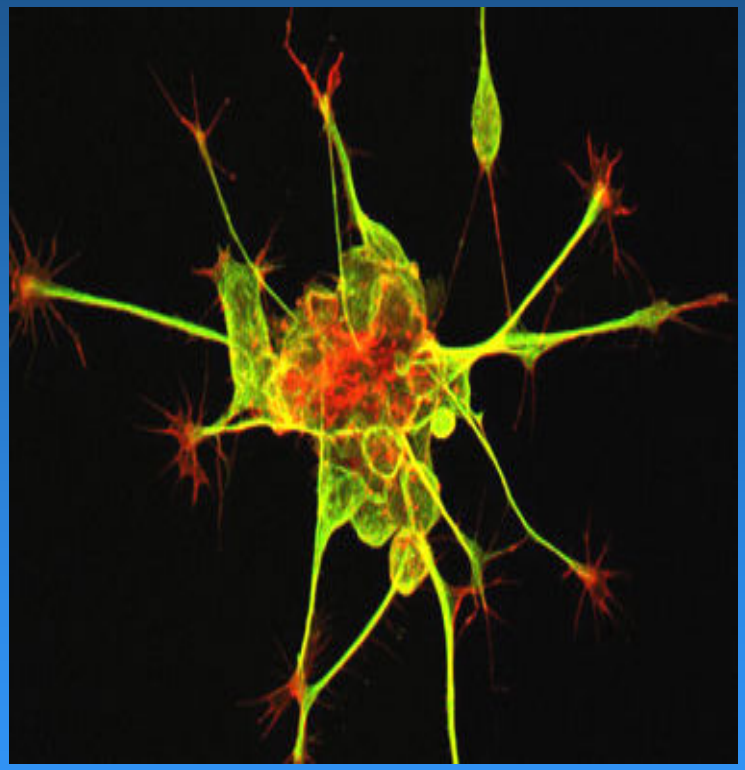
Micrograph of particles used to carry drugs to the lung



These are providing control over the drug delivery can be the most important factor at times when traditional oral or injectable drug formulations cannot be used

Photo: Courtesy of R. Langer, Massachusetts Institute of Technology, Cambridge (MA)

- Researchers at the Burnham Institute for Medical Research in La Jolla, CA have for the first time converted stem cells to nerve cells, and implanted them into mice.
- Transplantation and accommodation of these cells was successful, and the scientists did not get into the common problems associated with transplanted cells, such as resulting formation of tumors.



Source: http://www.medgadget.com/archives/img/45345wer.jpg

Retisert is the first FDA approved intravitreal implant for the treatment of chronic posterior non-infectious uveitis

It is a sterile implant that releases fluocinolone initially at a rate of **0.6** micrograms per day to the posterior segment of the eye decreasing over the month to **0.3-0.4** micrograms/day over approximately **30 months**

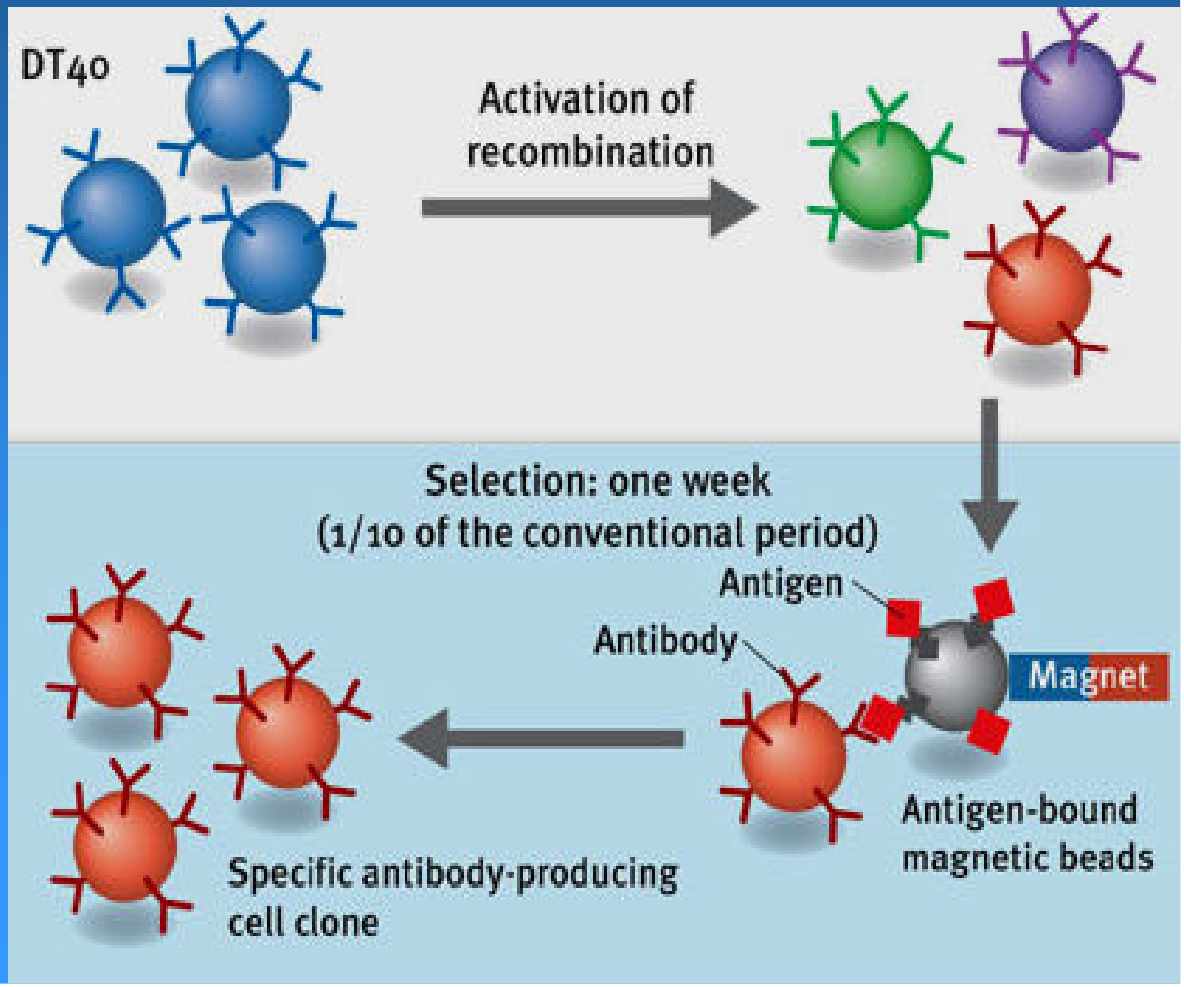
Source: http://s3.amazonaws.com/readers/healthmad/2007/07/22/43701_0.jpg

Source: www.health-news-blog.com.

- Medidur is an injectable non-erodable intravitreal device for the treatment of diabetic macular edema (DME).
- Diabetic macular edema is a common complication of diabetic retinopathy and is a leading cause of visual loss for old humans and animals.
- Similar to Retisert, Medidur also contains the corticosteroid fluocinolone.
- Unlike Retisert, Medidur implants are injectable, releasing a constant amount of fluocinolone into the back of the eye and is estimated to last for 18 to 36 months.

- the ADLib system can offer a way to produce the antibodies against any human biological molecules.
- This feature of the ADLib system is also expected to open up applications to diagnostic products for 'personalized medical treatment' (patients can select the medical treatment that is most suitable for them).

Source: www.rikenresearch.riken.jpg



- Valera's Hydron implant technology is a: subcutaneous drug delivery reservoir
- Employing micropores for drug diffusion, the implants are non-biodegradable and are capable of long-term (one year or more)
- It was used to suppress premature puberty in young girls

Source: http://www.medgadget.com/archives/img/524deb1.jpg

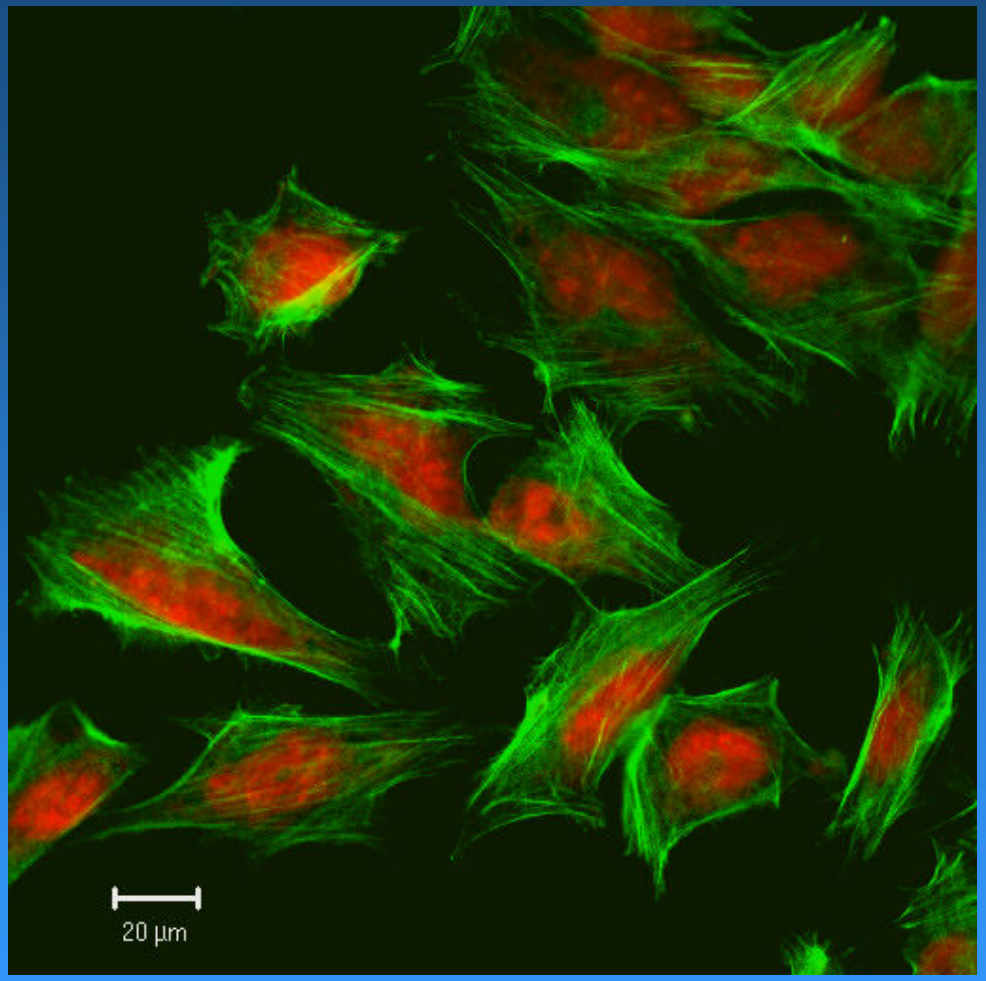
- and… veterinary medicine examples

The Smart - Pill

is a wireless medical device that measures:

- temperature
- pressure and
- pH of the gastrointestinal tract, as well as
- the rate at which the pill moves through the stomach and bowel of large animals

Source: http://media.knoxnews.com/kns/content/img/photos/2008/04/30/050108smartpill3_t220.jpg

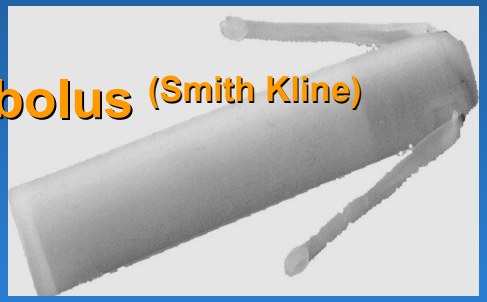


Mouse Osteoblast-Like Cells

Source: www.eng.uwo.ca/research

Albendazole
continuous slow release device

Proftril bolus (Smith Kline)

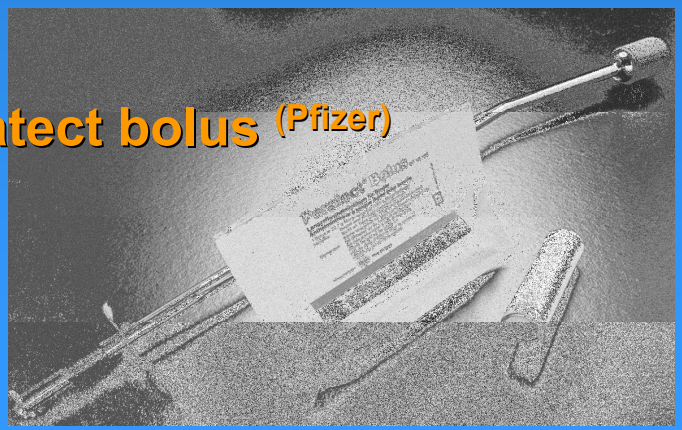


Oxfendazole
continuous slow release device

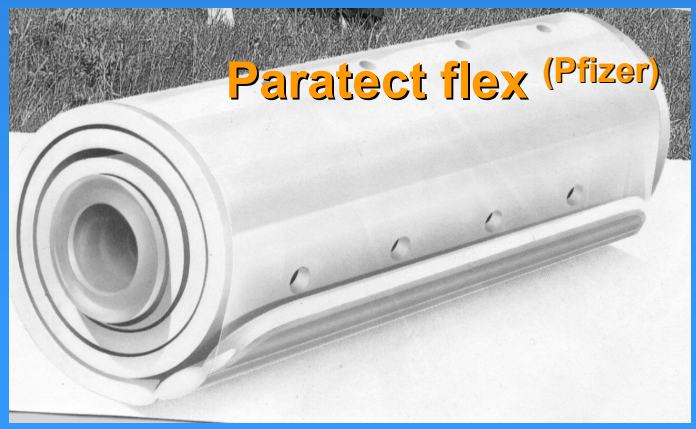
Synanthic multidose bolus (Pitman Moore)

Contiuous slow release device for morantel tartrate

Paratect bolus (Pfizer)



Paratect flex (Pfizer)



Ivermectine
slow release bolus

Ivomec SR Bolus (Merial)

Fenbendazole
slow release bolus

Panacur Bolus (Hoechst Roussel)

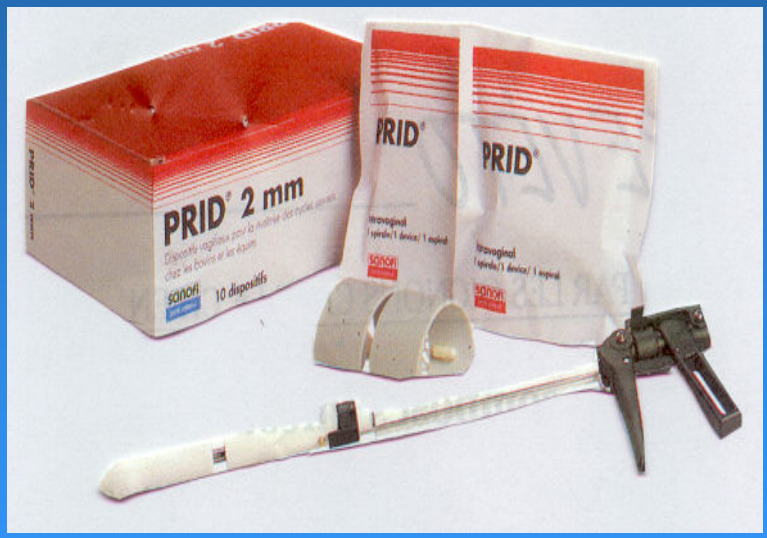
Another devices:

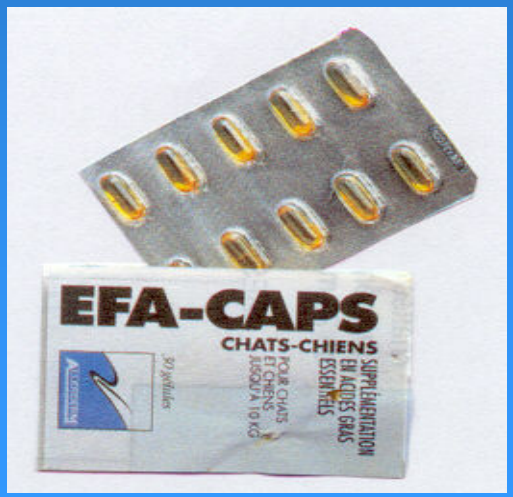
- Enzec and Alzet- Osmotic-pump (MSD)
- Repidose (Autoworm)
- Intra Ruminal Pulse Release Electronic Device (I.R.P.R.E.D)
- Oxfendazole Pulsed Release Bolus)(Pitman Moore)

Difloxacin
palatable microcapsules

Dicural (Fort Dodge)

Prid (Sanofi)





Efa-Caps chats et chiens (Virbac)

and…

the future

make us

to…

see

small…

really

small…

Facts:

Nanotechnology employs devices with dimensions of 1,0 to 1,000 nm

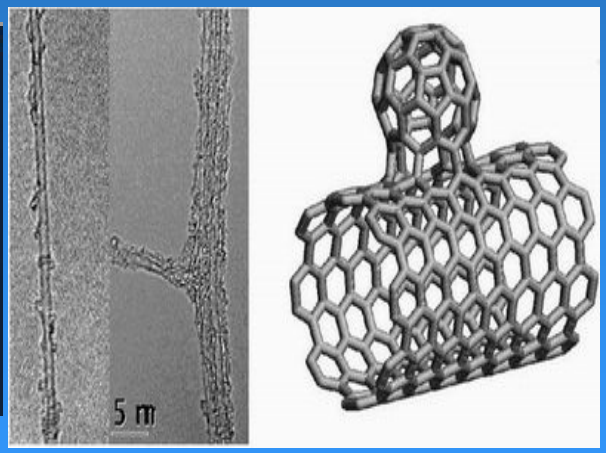
To put this in perspective, consider the following:

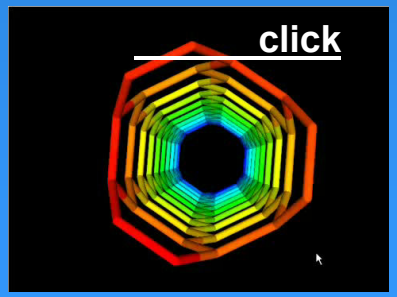
- a nanometer is 1/80,000th the width. of a human hair
- it is the length of 10 hydrogen atoms placed end to end
- it is less than one third the height of a single twist on a strand of DNA

1. Nanotubes

Cancer was the initial key area of medical nanotechnology research

Nanotubes can transform cancer's diagnosis, treatment, and prevention





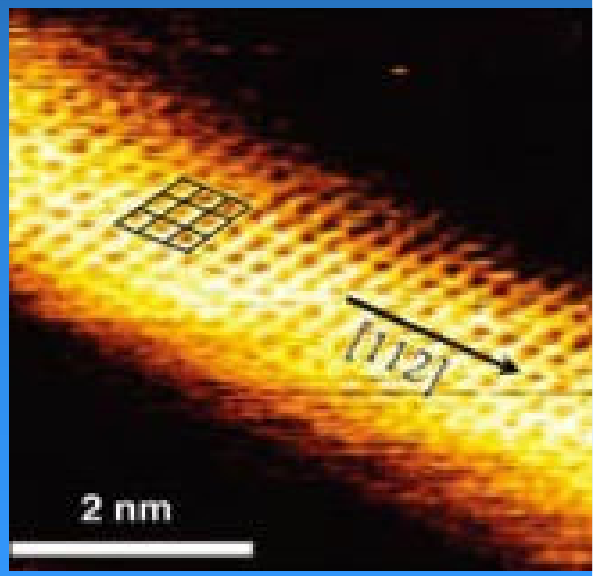
2. Nanowires

are so small that doctors could one day implant them into the body as permanent health detectives that continuously monitor molecular levels.

It looks delicate it is about five times smaller than a virus but it is several times stronger than spider silk

Researches had developed coated nanowires that bind to certain proteins that can indicate the presence of prostate cancer before conventional tests can

Other potential applications for nanowires include the early sensing of breast and ovarian malignancies



3. Nanocantilever

Cantilevers are beams anchored at only one end, they function as **sensors** ideal for detecting the presence of extremely small molecules in biological fluids

Arrays of nanocantilevers coated with antibodies, for example, will bend from the changes in surface tension when substrates that signal a malignancy bind to it.

The honeycomb mesh behind this tiny carbon cantilever is the surface of a fly's eye

4. Nanoshells

are hollow silica spheres covered with gold.

Scientists can attach antibodies to their surfaces, enabling the shells to target certain cells such as cancer cells

In tests, research team directed infrared radiation through tissue and onto the shells, causing the gold to superheat and destroy tumor cells while leaving healthy ones intact

Nanoshells could one day also be filled with drug - containing polymers

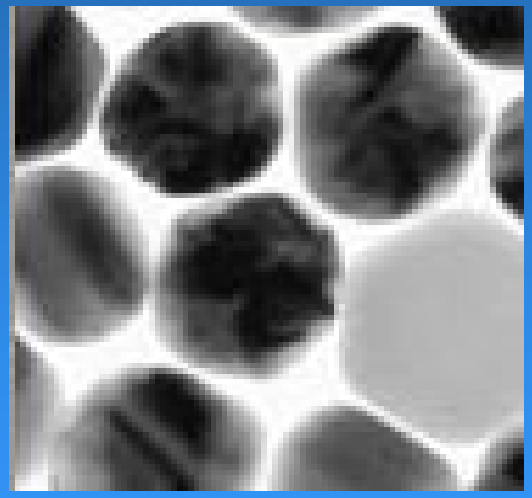
Heating them would cause the polymers to release a controlled amount of the drug

5. Gold nanoparticles

Researchers are using gold nanoparticles to develop ultrasensitive detection systems for DNA and protein markers associated with many forms of cancer, including breast and prostate cancer.

The nanoparticles can hunt for hundreds of different cancer targets simultaneously.

Tests with cancer molecules in solution revealed that gold nanoparticles are up to one million times as sensitive as conventional cancer-detection approaches

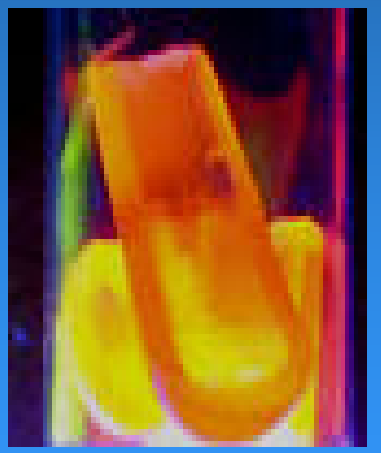


These nanoparticles, seen in a transmission electron micrograph image, are similar in structure to nanoshells, but they have a solid core.

6. Nanopores

They are holes that are so tiny that DNA molecules can pass through them one strand at a time, allowing for highly precise and efficient DNA sequencing

As a DNA strand moves through a nanopore, scientists can monitor each "letter" on it, deciphering coded information, including mutations associated with cancer



By engineering nanopores into the surface of a drug capsule that are only slightly larger than the medicine's molecular structure, drug manufacturers can also use nanopores to control the rate of a drug's diffusion in the body

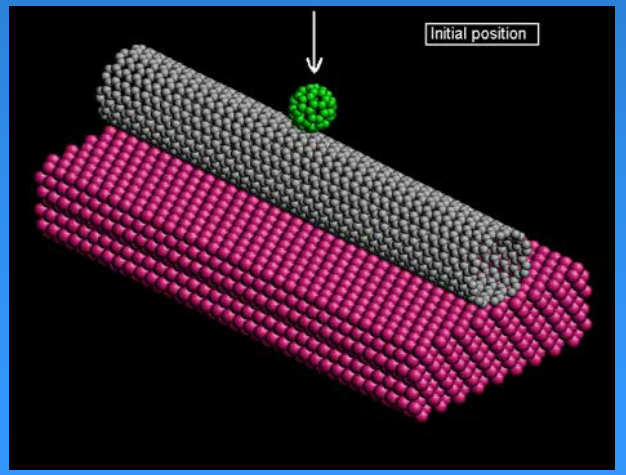
and finally….

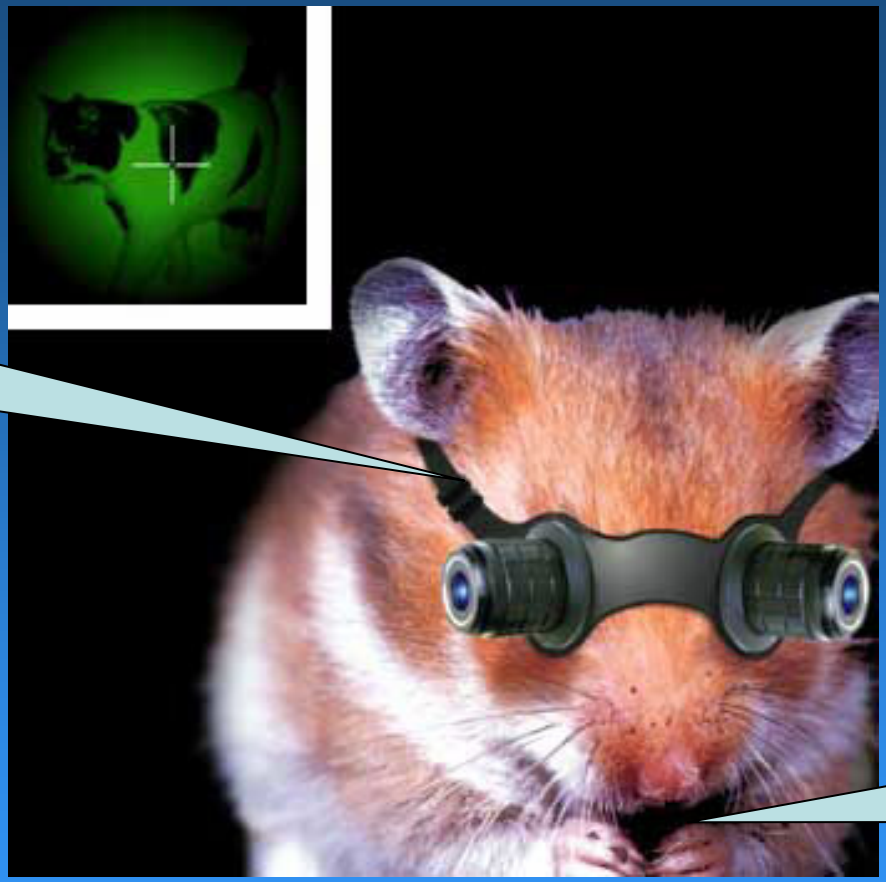
7. Fullerenes

These crystalline particles are a form of carbon atom whose molecular architecture is arranged in a soccer ball-like structure.

This trait can be important for cancer treatment compounds that are dangerous to healthy cells

For example, fullerene drug delivery particles that contain radioactive atoms would allow for the complete removal of radiation from the body following treatment





click

D’ont miss the point,

Knowing the identity you can see diversity

http://tbn0.google.com/images?q=tbn:x5BeCr9wnEe7rM:http://www.wired.com/news/images/full/augmented1_f.jpg