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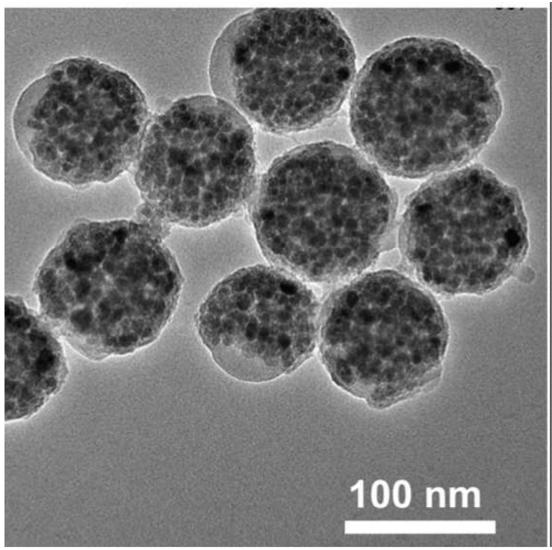
Lectures on Medical Biophysics
Department of Biophysics, Medical Faculty,
Masaryk University in Brno

Nanomedical Devices

(a lecture for future)



Carmel J Caruana, BioMedical Physics, Institute of Health Care, University of Malta
Vladan Bernard Deparment of Biophysics Lf MU

Basics

- Nanomedical devices - definition: biomedical devices at the scale 1 – 100 nm
- Very multidisciplinary issues
- Promise of nanomedical devices (why we develope it?):
  - New methods for prevention, diagnosis, therapy
  - Daily screening of health (very fast devices for monitoring of patient - Point Of Care – POC - testing)
  - Therapy targeted to the individual patient
- Origin from Greek language : νάνο – „dwarf“
- dynamic evolution

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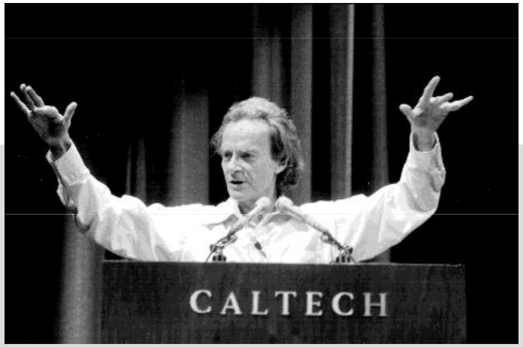
At the beginning...

- 1959 R. Feynman (1918/88) - „There's plenty room at the bottom"- presentation on meeting of American Physical Society – show the possibility to deals with material on molecular size.



There's Plenty of Room at the Bottom

An invitation to enter a new field of physics.

by Richard P. Feynman

I imagine experimental physicists must often look with envy at men like Kamerlingh Onnes, who discovered a field like low tempe… be bottomless and in which … down. Such a man is then a… temporary monopoly in a scie… Bridgman, in designing a way… sures, opened up another new…

nothing; that's the most primitive, halting step in the direction I intend to discuss. It is a staggeringly small…

"There's Plenty of Room at the Bottom" is a transcript of a talk given by Dr. Feynman on December 29 at the annual meeting of the American Physical Society at Caltech.

Engineering and Science

Challenge for $ 1,000 – 1985

(text 1/25,000 smaller in linear scale)

Pioneer ...

Norio Taniguchi – University of Tokio – 1974 first use term nanotechnology

"Nano-technology" mainly consists of the processing of separation, consolidation, and deformation of materials by one atom or one molecule."

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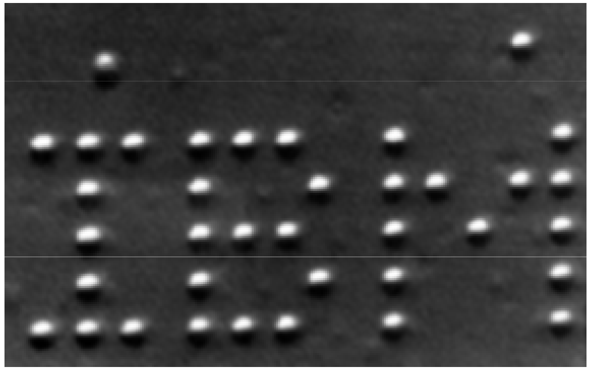
Pioneers company ...

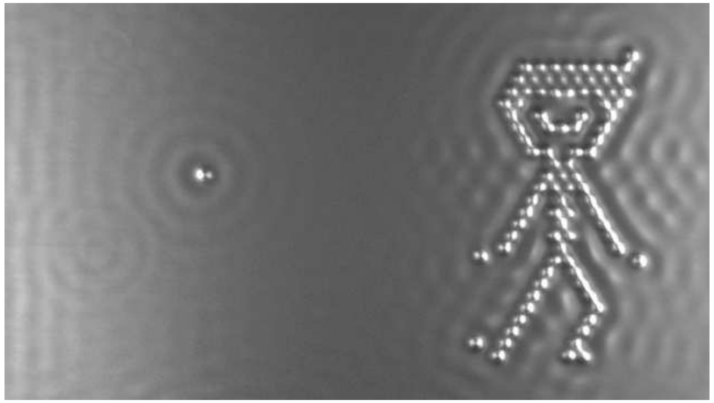
- Company **IBM**, has invested considerable finance in „nano“ development and commercial exploitation.



Logo IBM, 1990 (nikl, xenon, SEM)

„A boy and his atom“ 2013
The "smallest film" was created as part of experimental outputs. This was done using a scanning tunnel microscope. (www.CSFD.cz – 63% :c))

http://www.youtube.com/watch?v=oSCX78-8-q0



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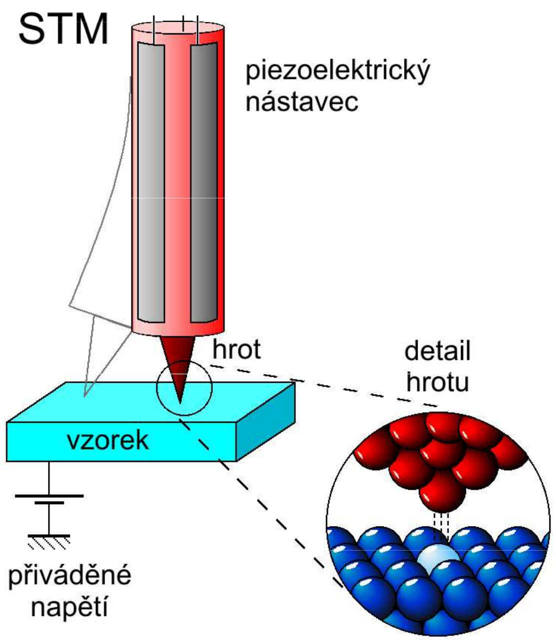
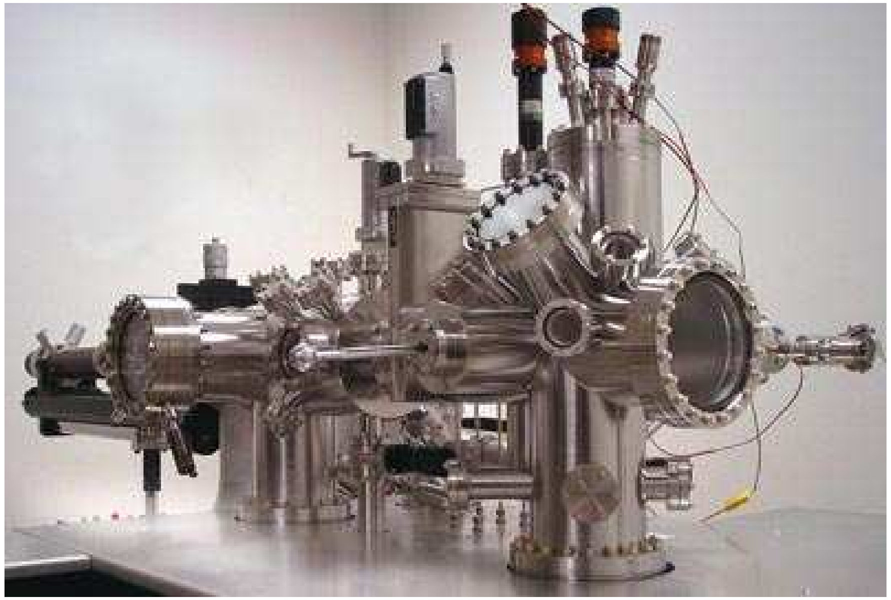
IBM and „nanoworld“ ...

IBM - Scanning Tunneling Microscope – how to observe nanoworld

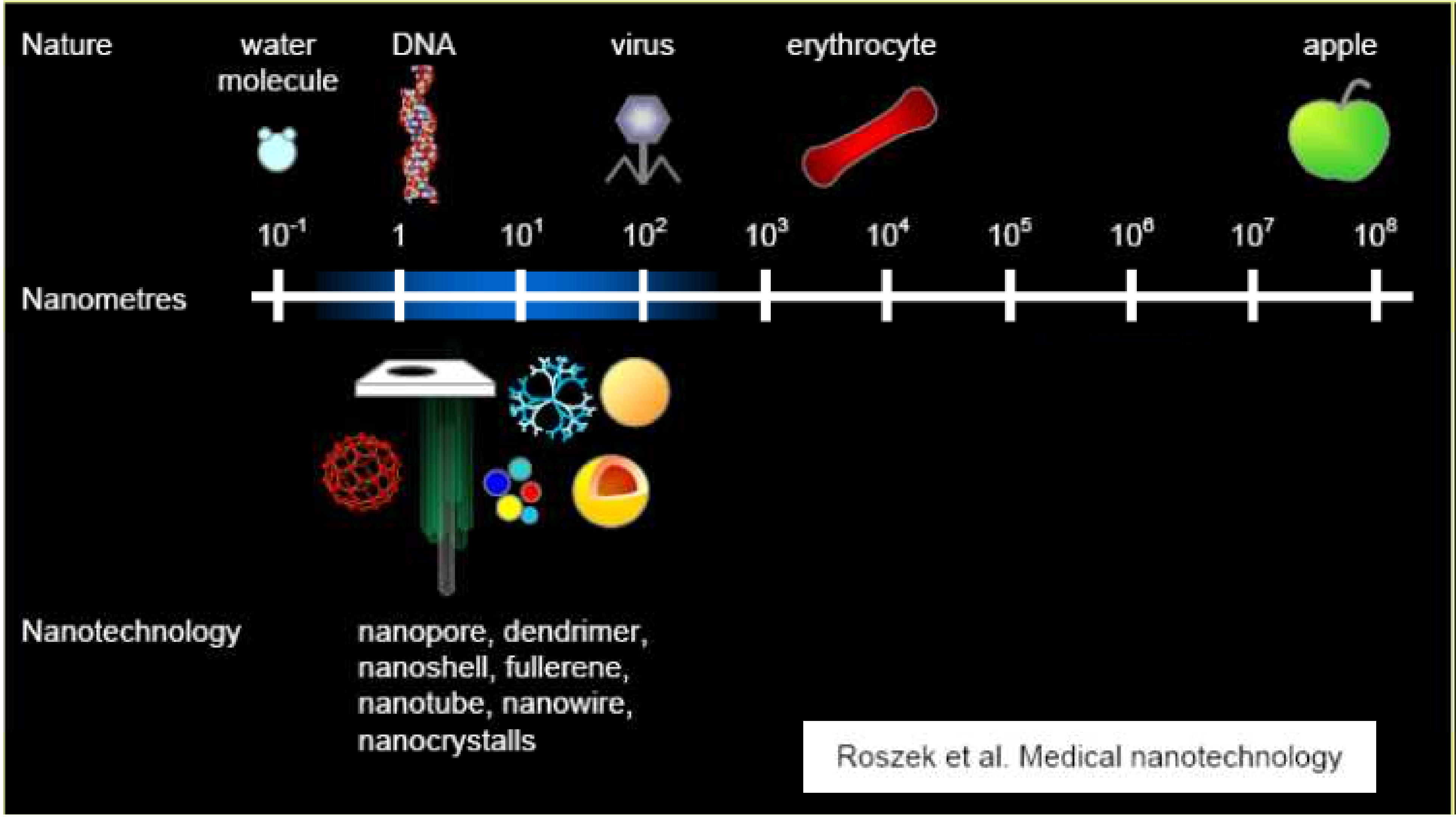




IBM.com

M U N I

..ow much is a nanometer?



Notice much smaller than RBC

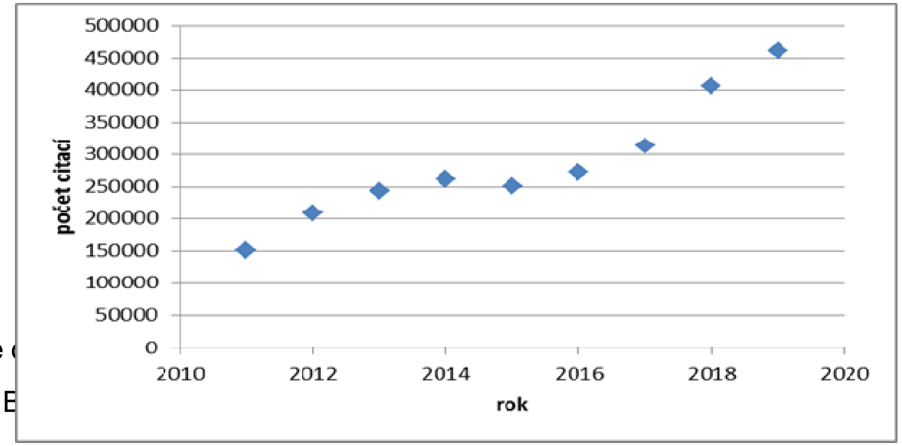
Nano ... in the world, web, science and articles

Number of references to (articles, books) in ScienceDirect database published in 2011 x 2013 x 2014 x 2015x 2016 x 2017 x 2018 x 2019 x 2020 connected with the phrase:

nano – 151 x 209 x 244 x 262 x 251 x 272 x 313 x 406 x 461 x 528 t
nanomaterials 23 x 35 x 37 x 47 x 64 x 71 x 85 x 101 x 121 x 147 t
nanoparticles – 90 x 128 x 135 x 167 x 206 x 227 x 266 x 327 x 378 x 442 t
brain - 1.148 x 1.286 x 1.378 x 1.419 x 1.380 x1.433 x1.510 x1.612 x1.688 x 1.782 t

Google in 2011, 2012, 2013, 2014, 2015, 2016 x 2017 x 2018 x 2019 :

Nanomaterials – 2.580, 5.230, 4.720, 5.490, 4.990, 5.420, 6.320,15.000,14.300, 40.700 t
Nanoparticles – 5.670, 12.500 , 11.600, 13.500, 12.800, 14.700, 17.000 , 29.000, 38.200, 35.300 t
Brain – 264.000, 649.000, 605.000, 557.000, 509.000, 526.000, 652.000 , 958.000, 1240.000, 917.000t



Definition of nanotechnology

Nanotechnology is the applied science dealing with the production and using of materials and particles, whose origin is to be targeted at the manipulation of individual atoms or relatively small groups of atoms.

Nanotechnology (sometimes shortened to "**nanotech**") is the study of manipulating matter on an atomic and molecular scale. Generally, nanotechnology deals with developing materials, devices, or other structures possessing at least one dimension sized from 1 to 100 nanomethers. Quantum mechanical effects are important at this quantum-realm scale.

The criteria of nanotechnology

- Focus on the objects smaller than 100 nm (in one diameter)
- Ability to handle and active use these objects and their functions
- The different behavior of nano-technology compared to macro-technology (quantum phenomena, atomic forces, chemical bonds, ...)

Nanomedicine definition

- is currently inconsistent
- According to the **US National Initiative:** Nanomedicine is the application of nanotechnology in medicine
- Definitions by **Europe Science Foundation** is more explicit. It says that "the field of scope of nanomedicine are science and technology, diagnostic, treatment and prevention of diseases and injuries leading to pain relief, preserving and improving human health, using tools and molecular level knowledge of the human body."

Nanomedicine can be generally defined as a comprehensive monitoring, management, repair, protection and improvement of all human biological systems, operating at the molecular level - and this purposefully created by using nanodevices and nanostructures, ultimately leading to improved health status of individuals.

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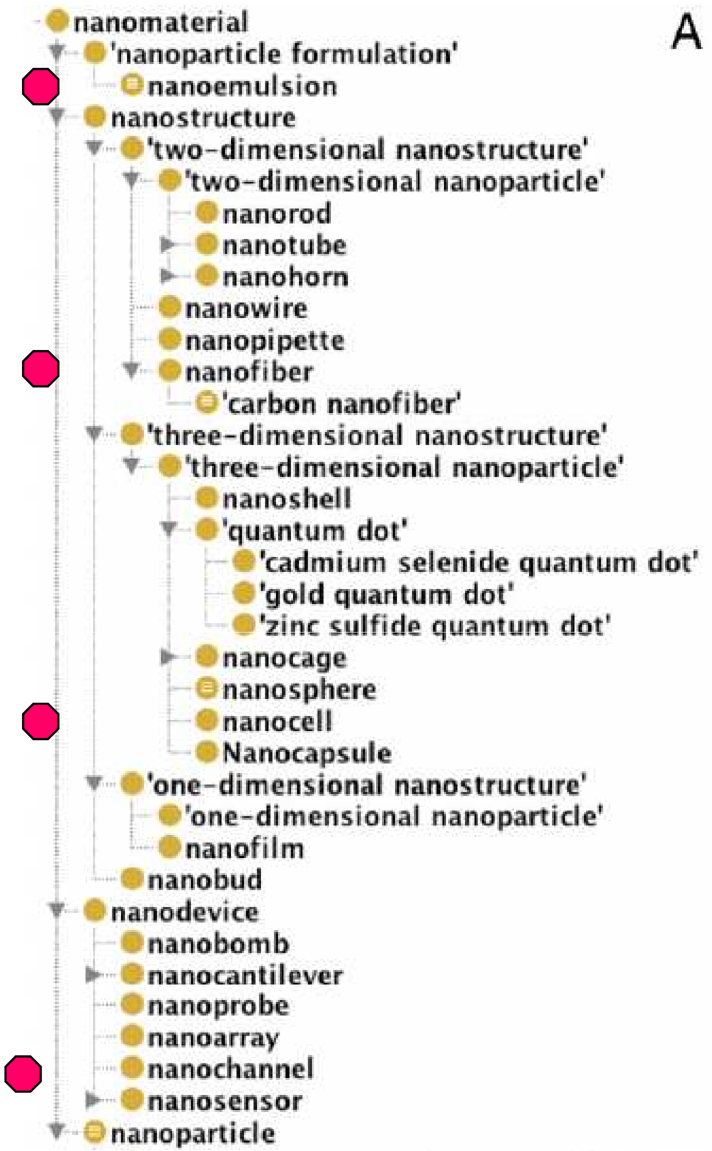
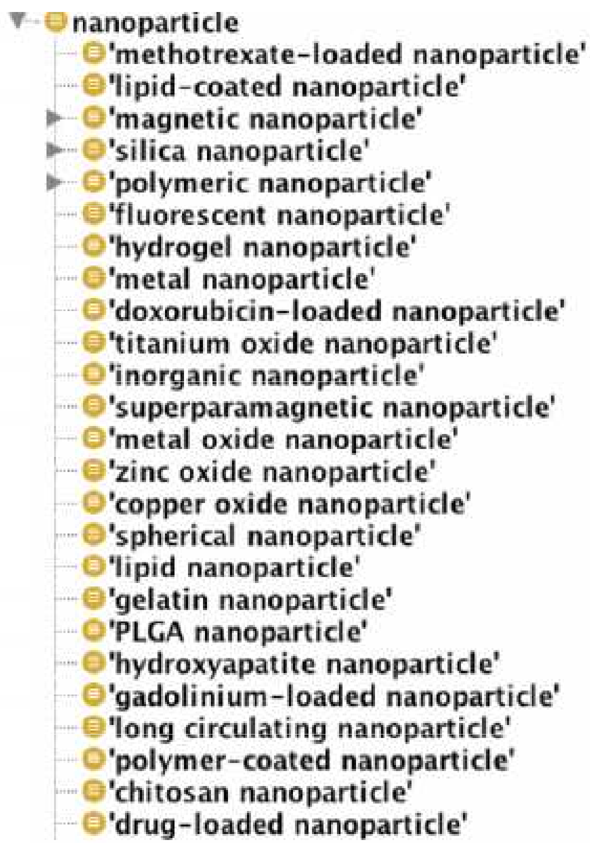
Categorization of nanomaterials which is used in medicine and "bio-sciences," by D.G. Thomas et al. / Journal of Biomedical Informatics 44 (2011) 59–74





Examples

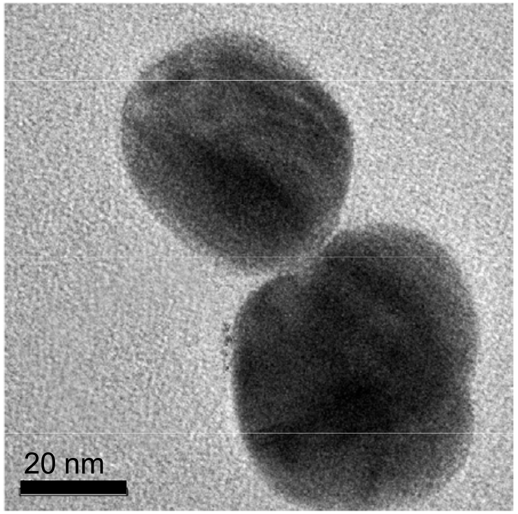
… definitely not all existing, only a small percentage of all ...

Nanoemulsions

- Nanoemulsions are known as dispersion systems consisting of a liquid dispersion medium and liquid dispersive fraction (inmixible) with the size of dispersion droplets below 100 nm.
- nanodroplets (usually fats, oils), forming a nanoemulsion system can serve as carriers of drugs or other substances (e.g. vitamins). Advantages - targeted delivery, increased absorption of the drug
- Preparation of nanoemulsions is done particularly by an ultrasonic field (e.g. by ultrasonic desintegrator) or "by extrusion" dispersion through the thin piezoelectric layers with pores

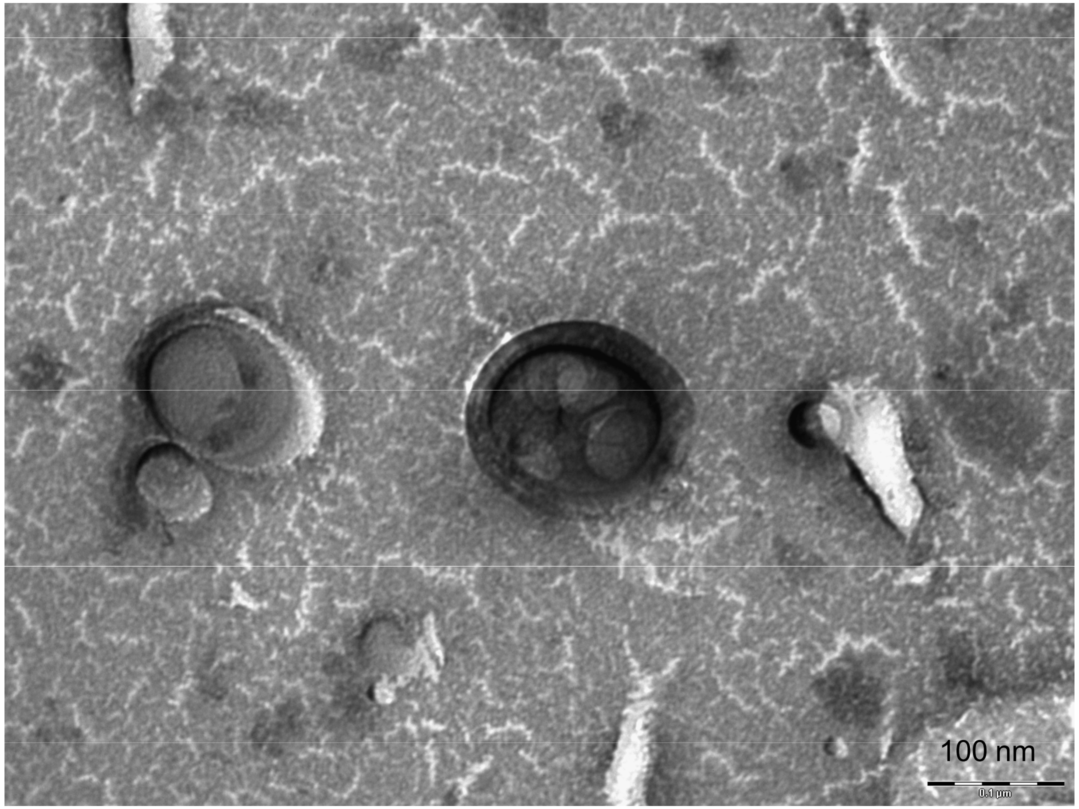
Usability:

Many contemporary publications present the possibility of using nanoemulsions as carriers of anticancer drugs with targeted delivery (subject to the existence of an increased uptake of lipid droplets in tumor tissue).



S. Swarnalatha, Nanoemulsion drug delivery by ketene based polyester synthesized using electron rich carbon/silica composite surface, Colloids and Surfaces B: Biointerfaces 65 (2008) 292–299

Nanoemulsions

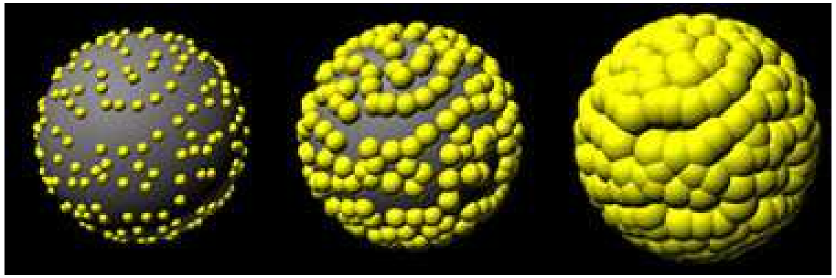


N. Vaškovicová, 2010,
Department of Biophysics Lf MU

Nanoemulsion consisting of: dispersion medium - distilled water, dispersed fraction - lipids and cholesterol + immunosuppressive agents, emulsifier - alcohol.

Nanoshell

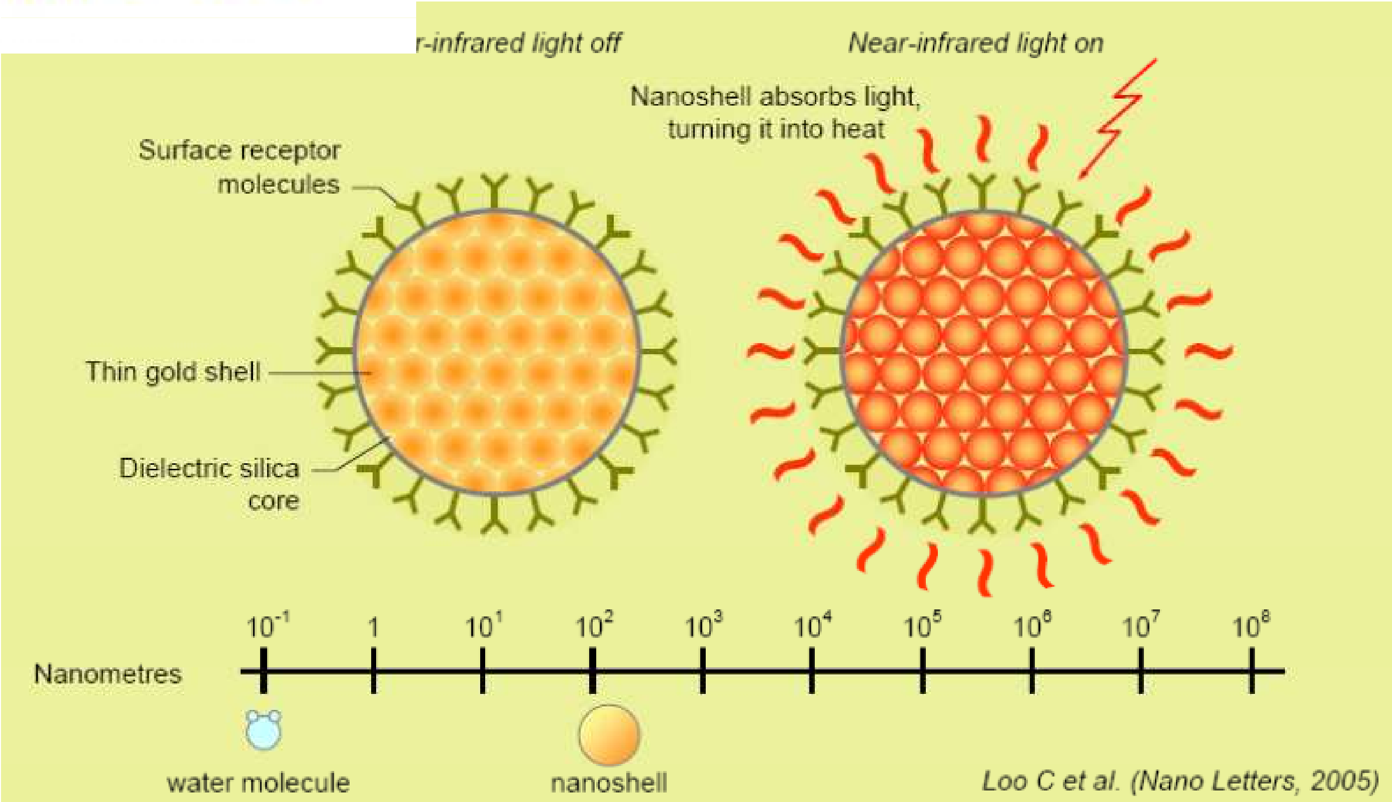
- A nanoshell is composed of a spherical hollow shell of insulator surrounded by a conducting shell of a few nanometer in thickness (gold).
- By varying the thickness of the conducting shell one can precisely tune the electric and optical properties of nanoshells e.g., make them absorb a certain wavelength of light



Computer simulation depicts growth of gold nanoshell: a silica (glass) spherical core covered with a layer of gold. Gold is a biocompatible compound, making it a useful material for medical applications.

Courtesy N. Halas

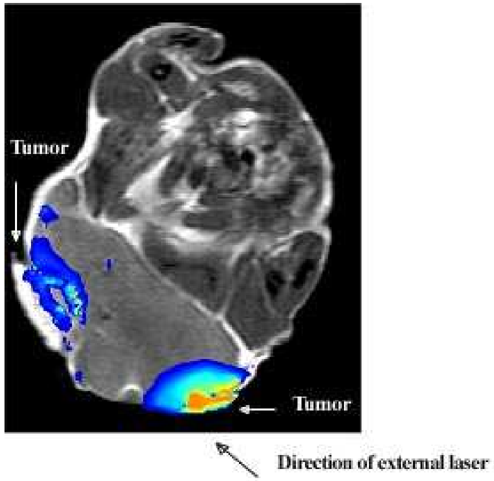
Nanoshells: Medical Applications - Photothermal Tumor Ablation



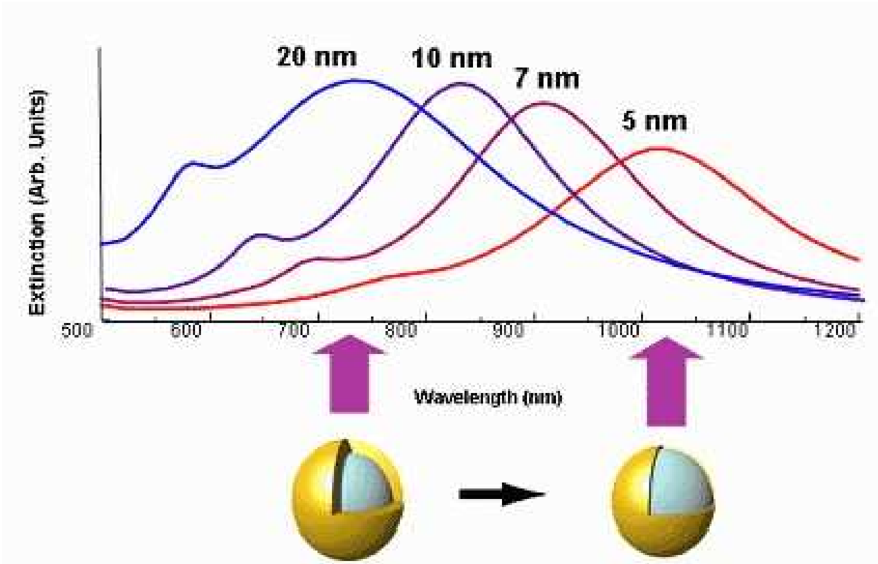
- The nanoshells are coated with receptors that bind to tumor cells and are simply injected into the bloodstream. Once delivered to a tumor, near infrared light is shone through the skin (near IR is not attenuated much by tissue). The nanoshells absorb the IR and convert it to heat with incredible efficiency. This raises the temperature of the local environment of the tumor cells by 10-20 degrees and the cells die. Advantage: zero toxic effects (unlike chemotherapy) no ionizing radiation (like radiotherapy).

Nanoshell...

Studies with photo thermal ablation of the tumor were performed by a team of researchers Jennifer West, Houston. The core of the used nanoshell was large 110 nm and gold coating of thickness 10 nm. By application of nanoshells on the suspension of tumor cells and subsequent laser irradiation of IR light, temperature increased to 55 ° C and subsequently the viability of the cell suspension decreasied. Attempts were also done with modified nanoshells, whose surface was modified by antibodies that allow specific binding of nanoshell only to cancer cells anywhere in the body.



Two tumors in the mouse body "saturated" by specially made "nanoshells" under the influence of laser light are heated (blue denotes places with higher temperature) and tumor cells die.



Thickness of the gold coating determines sensitivity of nanoshells to different wavelengths. The picture shows the results of theoretical calculations.

Nanoshells: Medical Applications - Single Molecule Raman Spectroscopy

- Scientists have long known that they **could boost the Raman light emissions** from a sample **by the addition of colloidal particles** to a sample. Nanoshells are colloids and can increase the Raman signal by *1000 million* times. In this way it is possible to characterize *single* molecules (such as environmental contaminants, chemical or biological toxins and even viruses).
- Advantages: very high sensitivity, high levels of multiplexing (simultaneous measurement of many biomolecules), ability to perform detection in blood and other biological matrices.

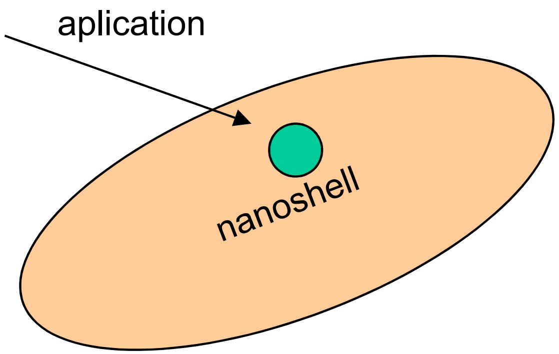
1000 million times increasing

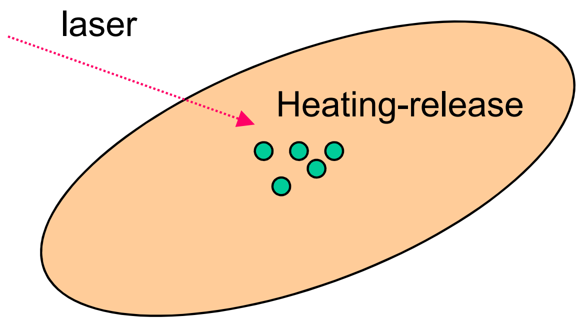
Carmel J Caruana, BioMedical Physics, Institute of Health Care, University of Malta

Vladan Bernard Deparment of Biophysics Lf MU

Nanoshells: Medical Applications - Delivering Insulin – in future???

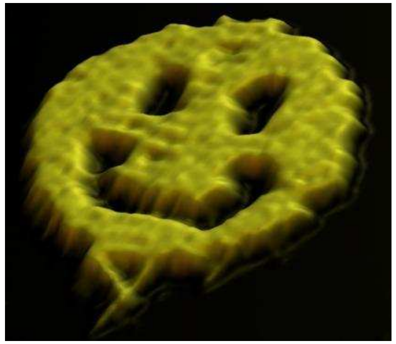
- Nanoshells loaded with insulin would be injected under the skin, where they would stay for months. To release the drug, patients would use a pen-sized IR laser over the skin at the injection site.



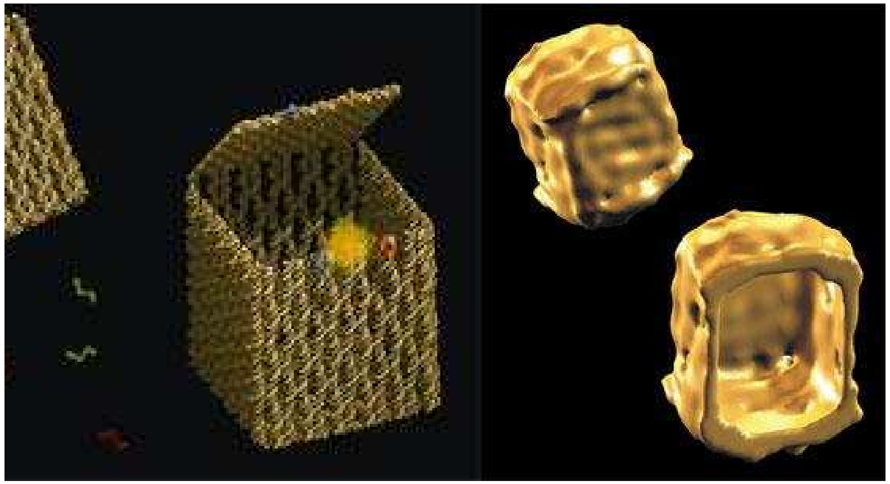


DNA nanocage, nanoorigam

- The basis of these structures are two-dimensional "surfaces" formed by chain molecules of DNA. Another layer of complementary DNA strands can be attached to this matrix thus forming a relief structure.
- The horizontal structure (appropriate combination of complementary DNA strands) can be "put together" as a cube with an internal cavity (a cage).

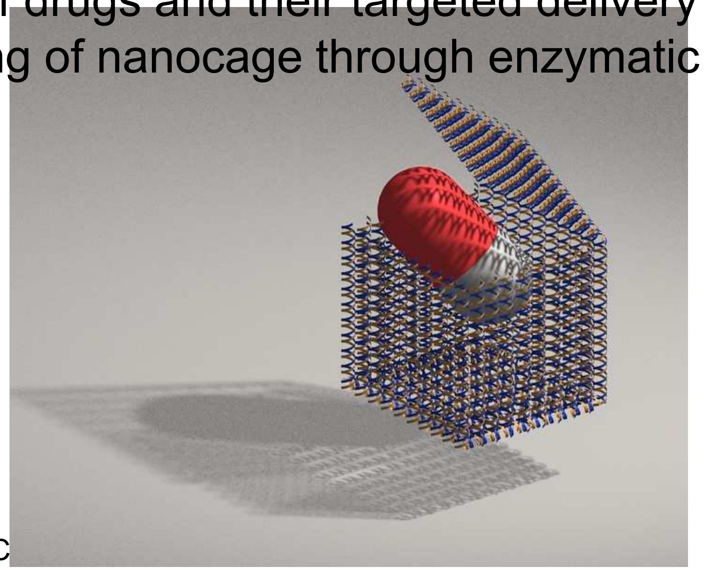


Relief created by a horizontal structure of the DNA layer height of 2-4 nm (Nick Papadakis, P.W.K.R)



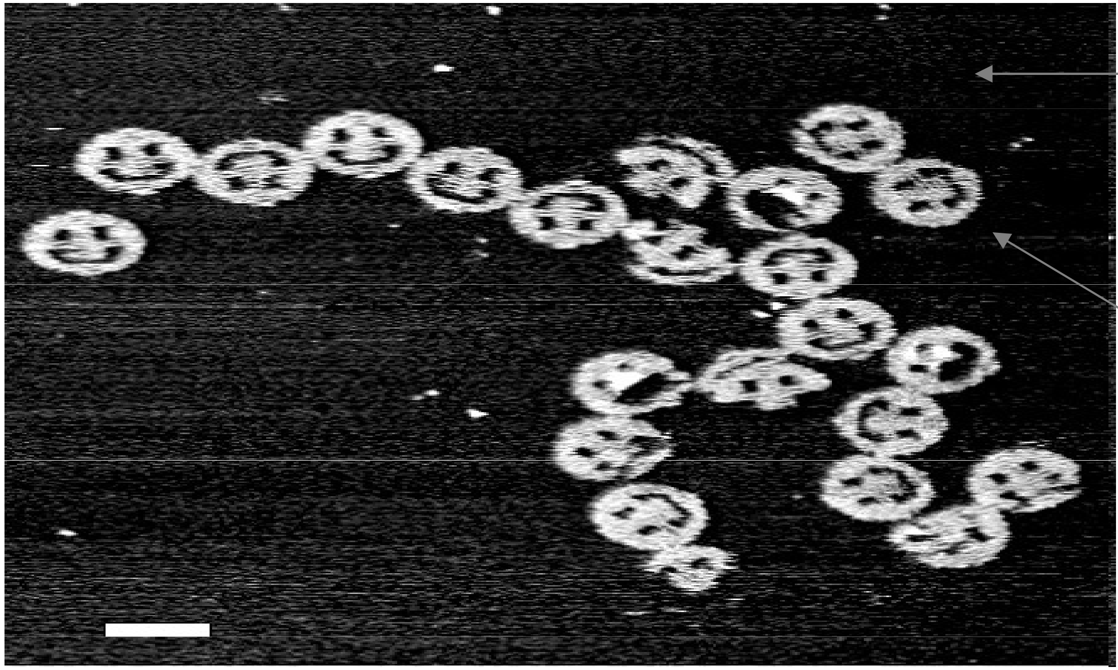
3D model of the structure and its real cryoelectron microscopic image (author of image: Andersen EC)

One possibility is to use these structures as carriers of drugs and their targeted delivery by opening of nanocage through enzymatic locks.



DNA nanocage, nanoorigam

… when a scientist has a free time …

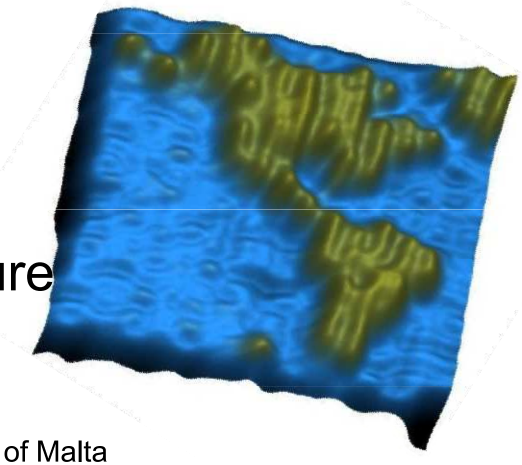


flat structure consisting of chain molecules of DNA

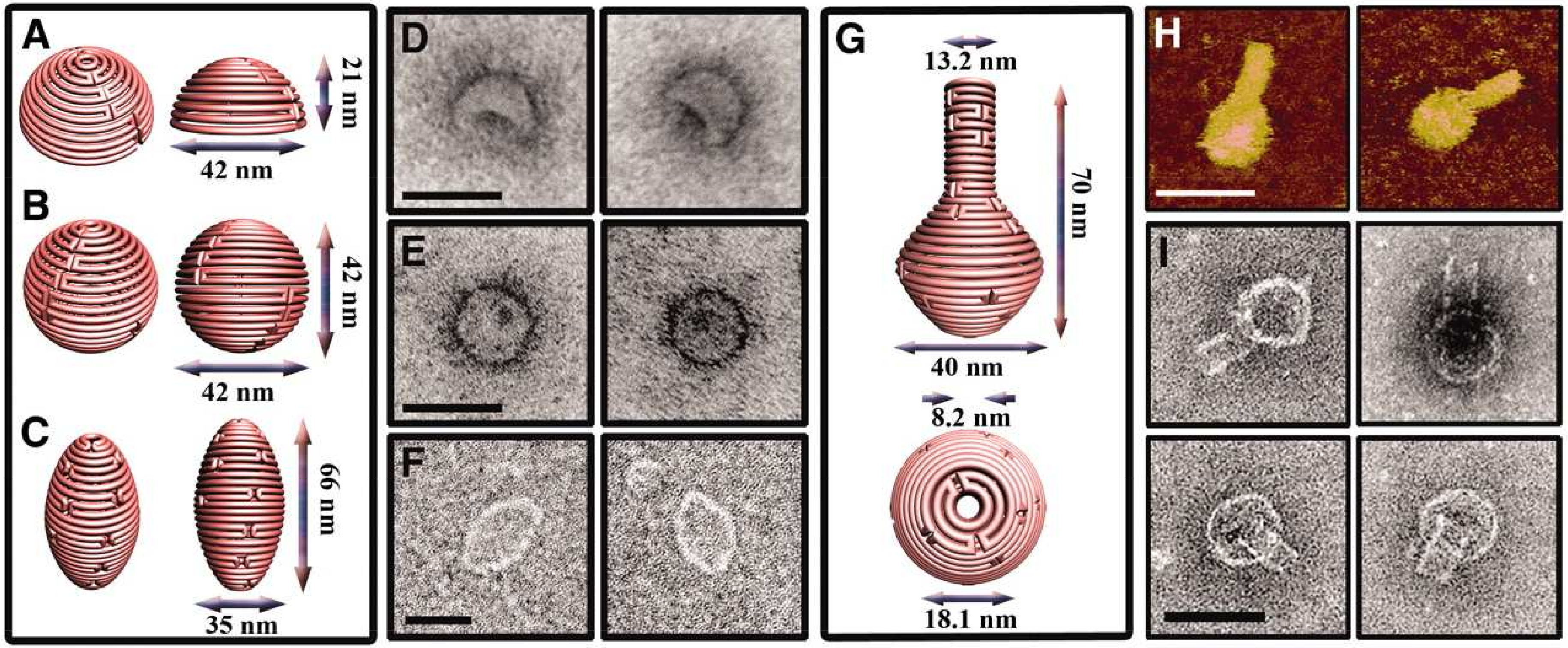
complementary chain of molecule DNA, formed to „smile“

Paul W. K. Rothemund

Map of Americas formed by DNA flat structure (secundary coloured)



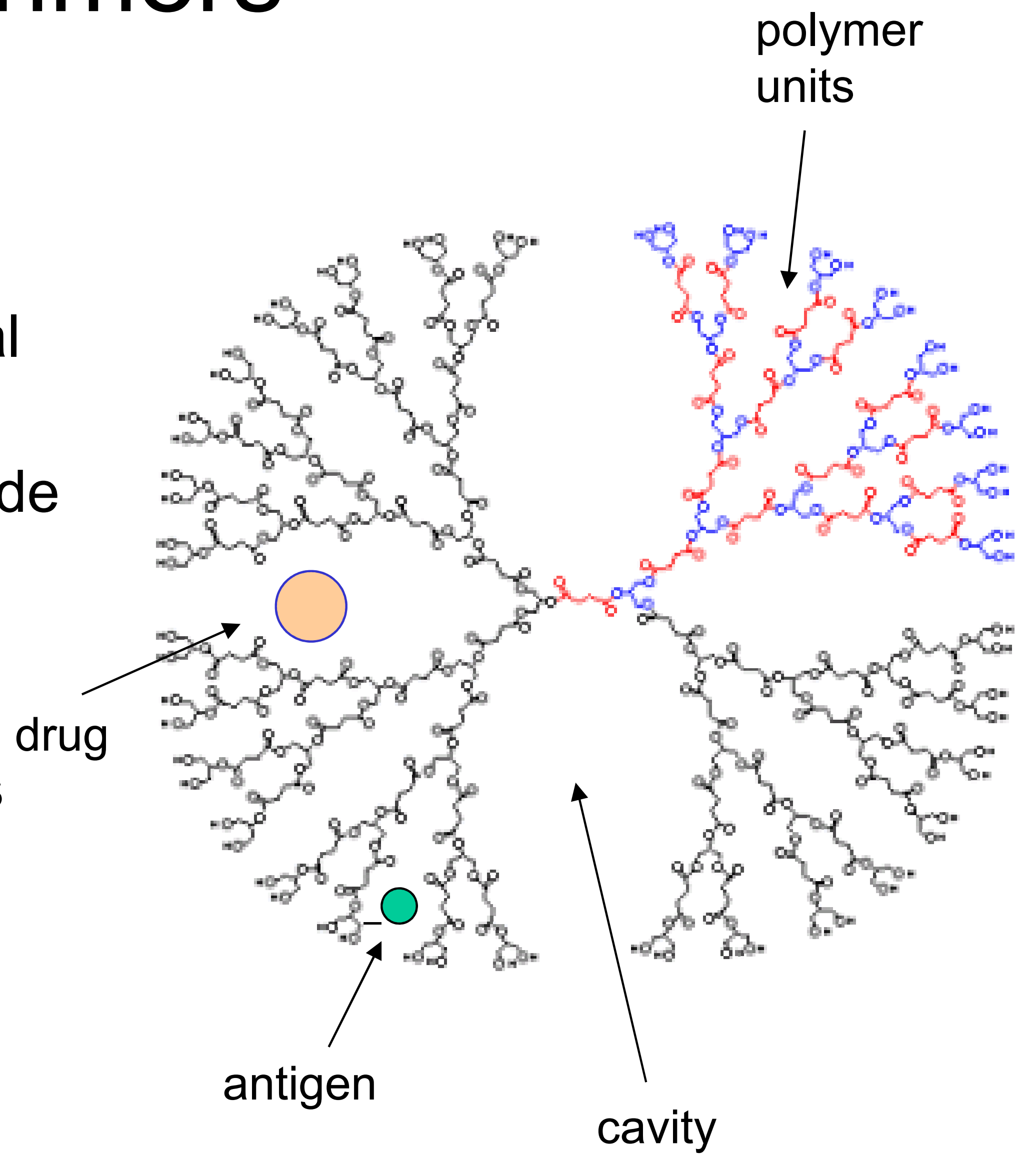
DNA nanocage



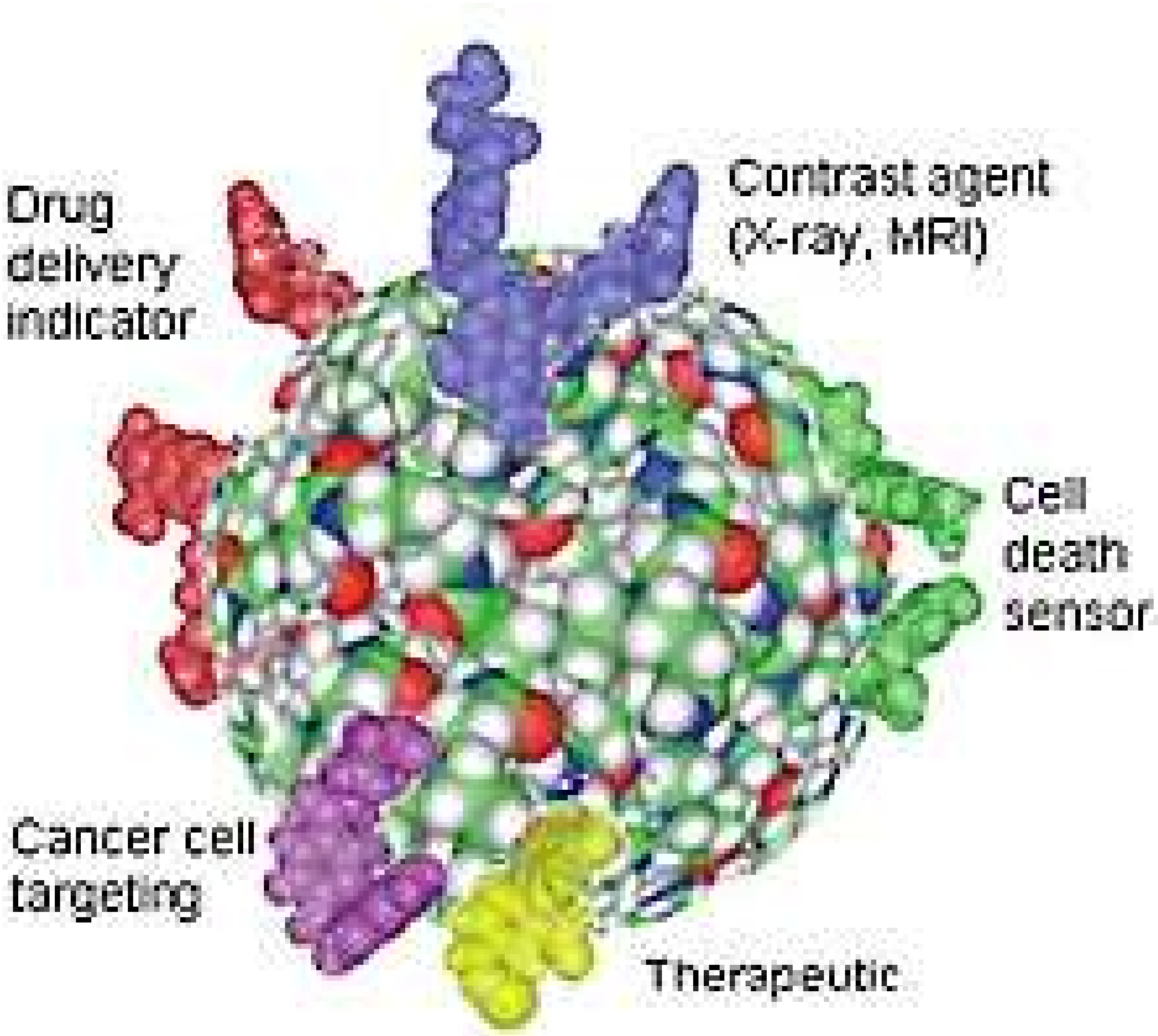
- DNA nanostructures with complex 3D curvatures. (A) Schematic representation of the hemisphere. (B) Schematic representation of the sphere. (C) Schematic representation of the ellipsoid. (D) TEM images of the hemisphere, randomly deposited on TEM grids. The concave surface is visible as a dark area. (E) TEM images of the sphere, randomly deposited on TEM grids. Due to the spherical symmetry, the orientation can not be determined. (F) TEM images of the ellipsoid. The outline of the ellipsoid is visible. Scale bar for the TEM images in (D), (E) and (F) is 50 nm. (G) Schematic representation of the nanoflask. (H) AFM images of the nanoflask. Scale bar is 75 nm. (I) TEM images of the nanoflask, randomly deposited on TEM grids. The cylindrical neck and rounded bottom of the flask are clearly visible in the images. Scale bar is 50 nm.
- **Han, D. et al. DNA Origami with Complex Curvatures in Three-Dimensional Space. Science 332, 342–346 (2011).**

Dendrimers

- Dendrimers are globularly shaped polymers composed of branched repeating units leading off a central core (like a tree, snowflake).
- Biodendrimers are dendrimers made of repeating units known to be biocompatible or biodegradable in vivo to natural metabolites.
- The cavities present in dendrimers can be used as binding sites for smaller molecules - effectively the dendrite becomes a nanosized 'container' for various molecules.

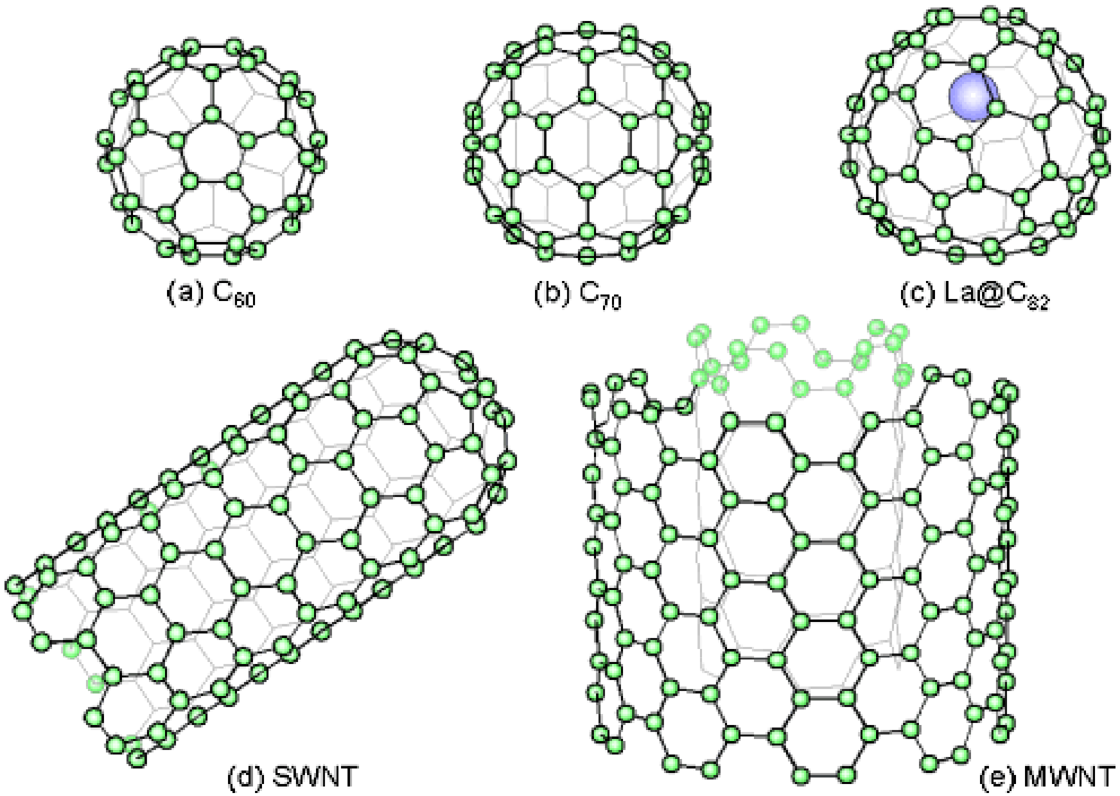


Dendrimers: Medical Applications – Multifunctional nanosized containers (‘Platforms’)



Fullerenes (and nanotubes)

- Carbon molecules in the shape of a **hollow sphere, ellipsoid, tube or ring**.
- Cylindrical fullerenes are often called nanotubes.
- The smallest fullerene is C_{60} (i.e., 60 C atoms)
- Other atoms can be trapped inside fullerenes e.g., La@C_{82} (lanthanum)
- SWNT - single walled nanotubes
- MWNT - multiwall carbon nanotube

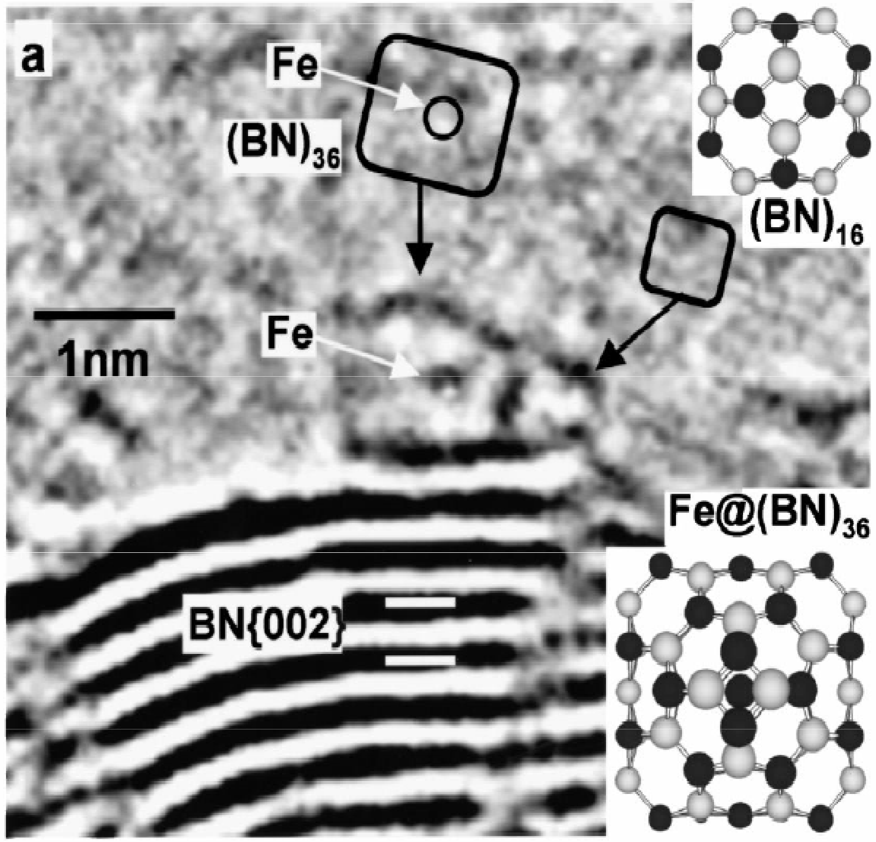


Fullerenes and nanotubes

- The first fullerene molecule was discovered and prepared in 1985 by Richard Smalley et al.
- Nanotubes are cylindrical fullerenes. These tubes of carbon are usually only a few nanometres wide, but they can range from less than a micrometer to several millimeters in length. They often have closed ends, but can be open-ended as well. There are also cases in which the tube reduces in diameter before closing off. Their unique molecular structure results in extraordinary properties, including high tensile strength, high electrical conductivity, high ductility, high heat conductivity, and relative chemical inactivity
- Fullerenes can be made to be absorbed by HeLa cells. The C60 derivatives can be delivered to the cells by using the functional groups L-phenylalanine, folic acid, and L-arginine among others. The purpose for functionalizing the fullerenes is to increase the solubility of the molecule by the cancer cells. Cancer cells take up these molecules at an increased rate because of an upregulation of transporters in the cancer cell, in this case amino acid transporters will bring in the L-arginine and L-phenylalanine functional groups of the fullerenes. Once absorbed by the cells, the **C60 derivatives would react to light radiation by turning molecular oxygen into reactive oxygen which triggers apoptosis** This research shows that a reactive substance can target cancer cells and then be triggered by light radiation, minimizing damage to surrounding tissues while undergoing treatment.

Fullerenes (and nanotubes)

Creating three-dimensional nanounits is not just the property of carbon, this ability have other atoms too, e.g. molecules such as boron nitride (BN). This material also produces similar formations such as carbon tubes, rings or fullerenes, including the possible closure of an atom of another element into the created „cage“ (in this case the atom of Fe).



T. Oku et al. / *International Journal of Inorganic Materials* 3 (2001) 597 –612

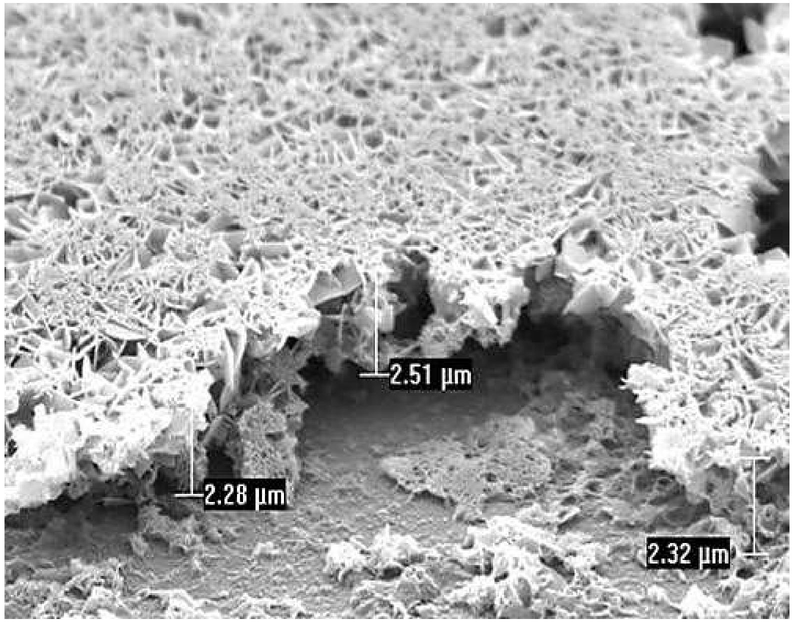
Nanotubes – aplication (future???)

Bone tissue

Utilization of nanotubes in medicine is experimentally demonstrated in experiments with **bone tissue substitutes**. In this case the nanotubes (with modified surface compounds of phosphorus and sulfur) are a substitute of collagen, which binds to crystalline hydroxyapatite and so creates a **very strong** and **compact** bone tissue.

The benefit of this technology is far **greater strength** of the structures.

A possible disadvantage is the potential toxicity of fullerens and derived compounds (R E. Oberdörster, Southern Methodist University, Dallas, New Scientist, March 2004), but it can be avoided by the re-modification of surfaces (eg, by atoms of Fe).

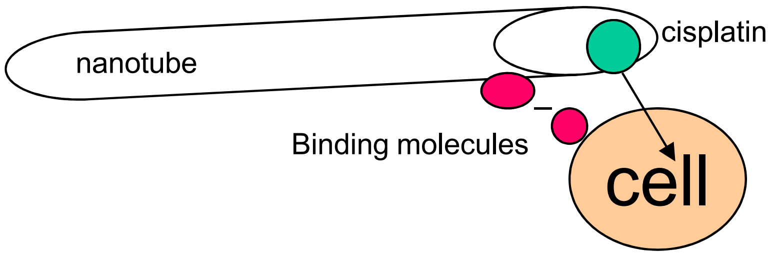


Crystallized hydroxyapatite on the surface of modified nanotubes (University of California, osel.cz)

Nanotubes – aplication (future???)

Antibacterial effects
Results of studies show that surfaces treated with carbon nanostructures (fullerens, graphens) themselves exhibit antibacterial properties.
Another use of carbon nanostructures is reatment of surfaces (eg, surgical instruments, equipment of hospital rooms, ...) in conjunction with enzymes. By attaching nanotubes enriched with enzymes on surfaces various medical instruments its own surface will increase, which corresponds to the increasing interaction of the enzyme and subsequent enzymatic degradation of bacteria.

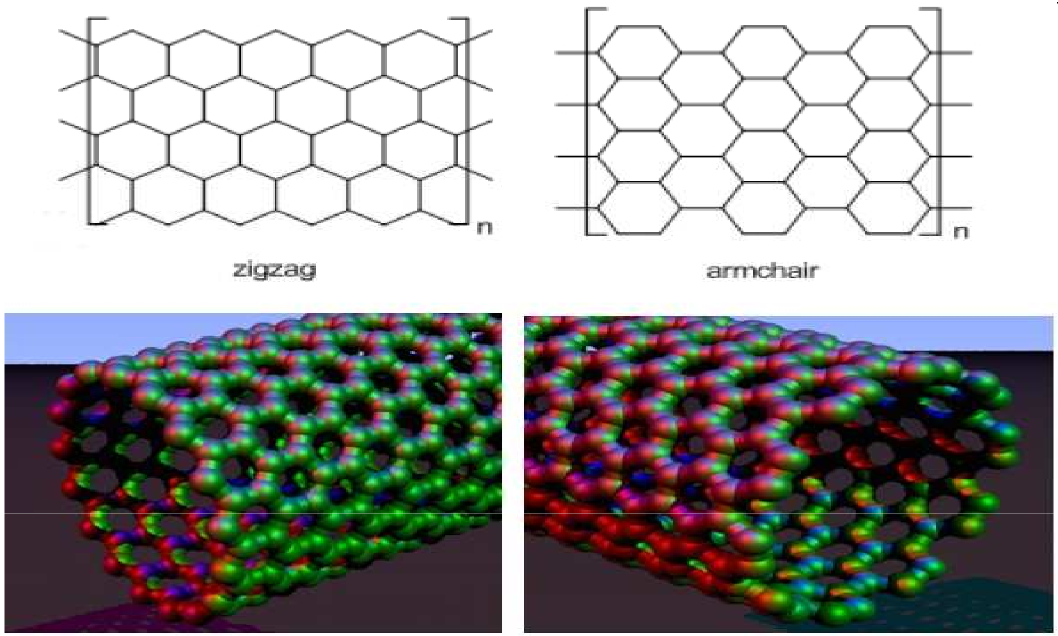
Cytostatic therapy
Bhirde et al., In *Targeted killing of cancer cells in vivo and in vitro with EGF-directed carbon nanotube-based drug delivery*, ACS Nano 3 (2009) describes the use of multiple wall nanotubes for targeted cytostatic treatment. The principle is the linking of cisplatin with epidermal growth factor by using nanotubes and subsequent binding of this complex to the receptors of growth factor on tumor cells.



Fullerenes: Medical Uses

- Carbon nanotube involving **catheters** (nanotubes have Young’s modulus 5 times greater that of steel!)
- Nanotube-based “cold” **cathodes** (emit electrons freely without need of thermionic emission). It will change conventional x-ray tube technology because of no need of a high power source and are exceptionally durable. Nanotube based small X-ray tubes for radiation therapy inside the body (brachytherapy) can be expected.
- Fullerenes with gadolinium are 5 times better **MRI contrast agents** than those used presently.
- Multifunctional platforms: binding specific antibiotics to the fullerene to target resistant bacteria and cancer cells. Fullerenes are not very reactive and are insoluble in many solvents.

Nanotubes as wires



Depending on the structure of carbon nanotubes, the nanotube behaves as a metal or as a semiconductor (or even a superconductor!). See so called "Armchair Quantum Wire„ elsewhere.

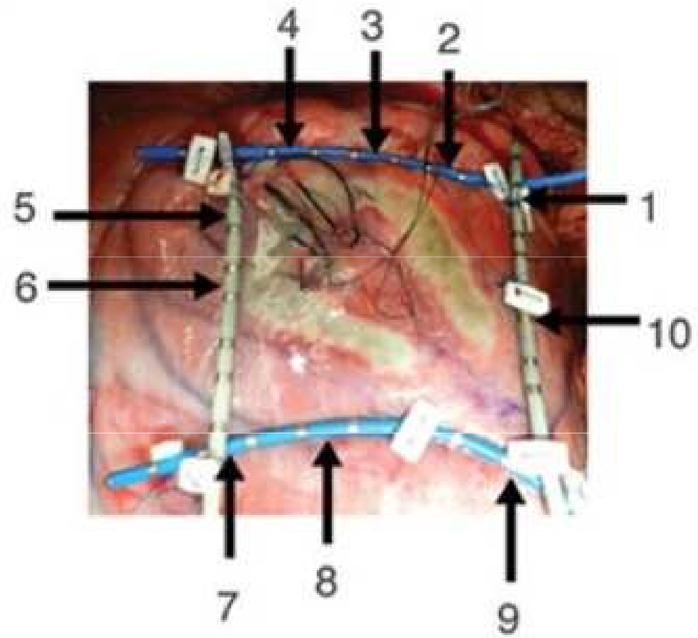
They can be also used (as superconductors) for generation of strong magnetic field, i.e. for MRI

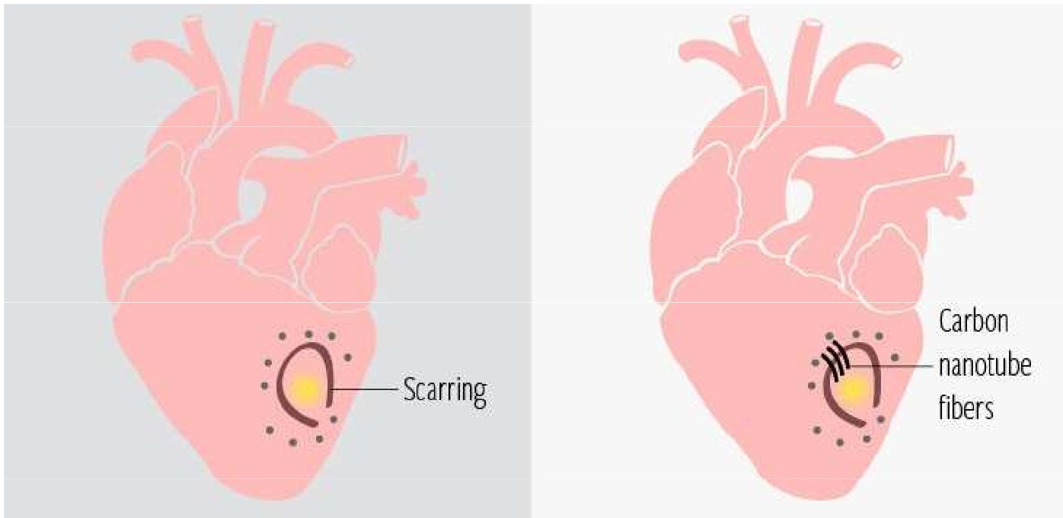
Nanotubes are currently the strongest material. The diameter of Single Wall Carbon Nanotubes (SWCNT) is from 1 nm to 50 nm. Electrical properties are different according to the arrangement of atoms C in the tube (the molecular structure influences the orientation of bonds). Depending on the structure of bonds between carbons we can have Z (zigzag) or a A (armchair) configuration. "Z" acts as a metal, "Armchair" as a semiconductor.

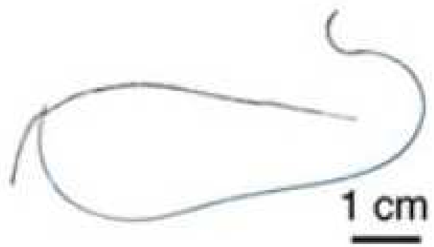
Rice University - http://www.ece.rice.edu/~irlabs/aqw.htm

Carbon nanowires

- carbon nanowires, conductive, entangled nanofibers for "bridging" scarred heart tissue after a heart attack and acting as an electrical signal transfer



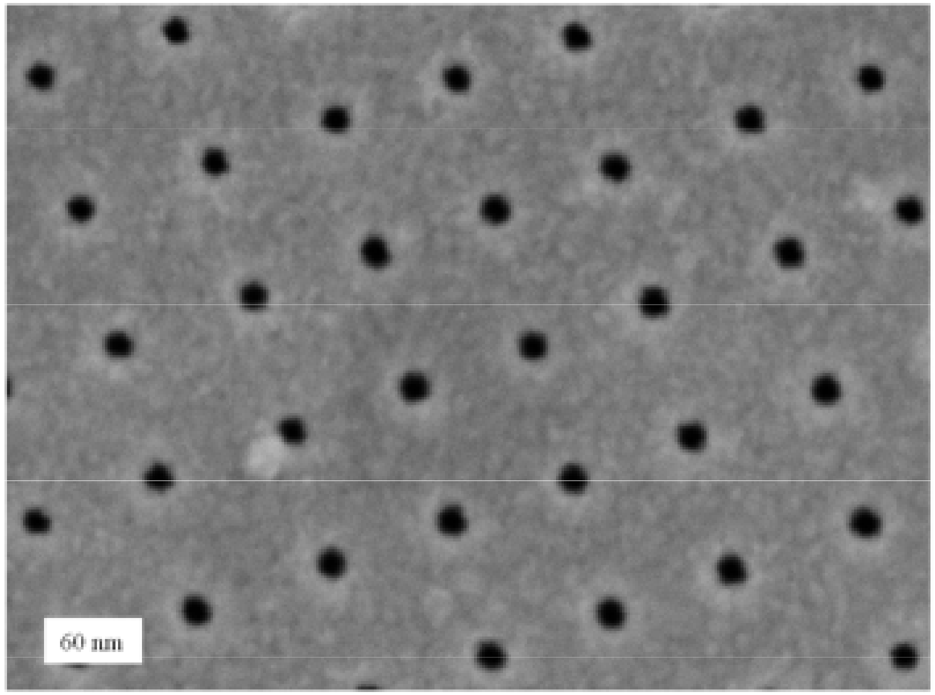




McCauley et al.,Circulation: Arrhythmia and Electrophysiology (2019).

Nanopores

- The pores of nanometer diameter become exploited in biology.
- **They are used to regulate the flow of ions or molecules through the otherwise impermeable membranes**.

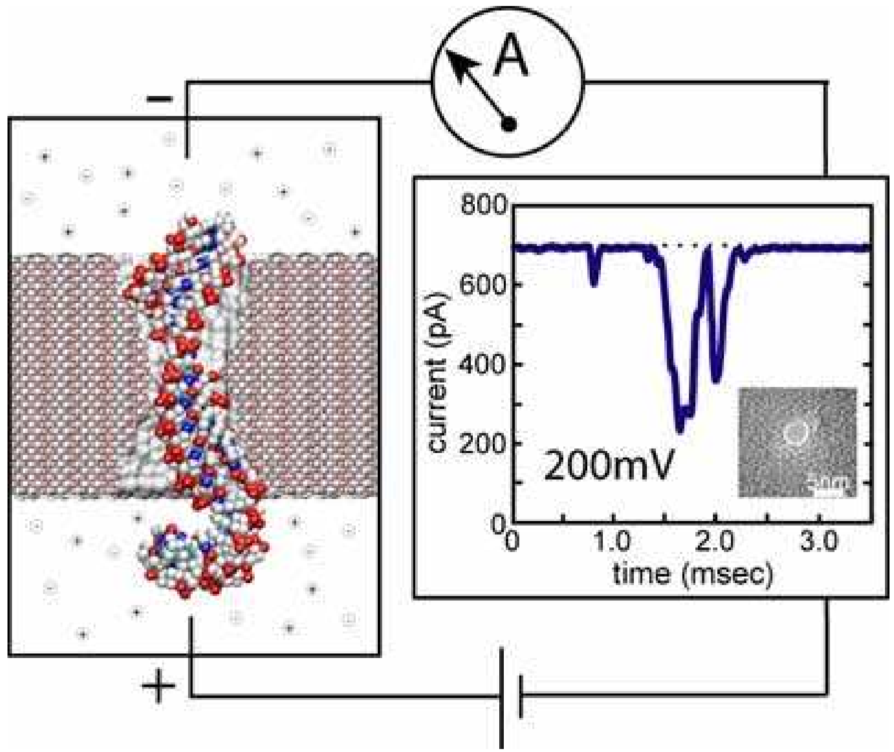


Nanopores drilled by a focused-ion-beam in a 10 nm thick silicon nitride membrane. The scale bar is 60 nm.

Ref: H.D. Tong, H.V. Jansen, V.J. Gadgil, C.G. Bostan, J.W. Berenschot, C.J.M. van Rijn, and M. Elwenspoek, Nano Lett. 4, 283, (2004).

Nanopores: Medical Applications: DNA sequencing

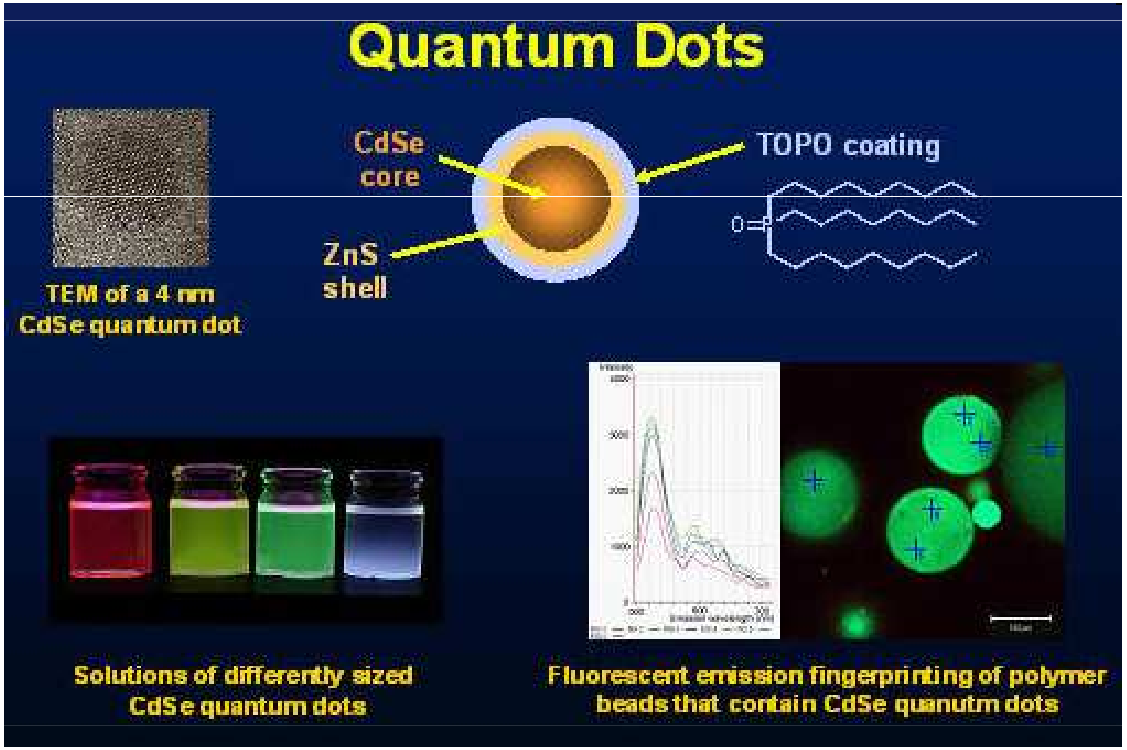
- As the DNA molecule passes through the nanopore, different bases lead to different drops in the current and hence can be identified.
- Such sequencing, could revolutionize the field of genomics, as sequencing could be carried out in a matter of seconds – very fast
- Other applications of this technique include separation of single stranded and double stranded DNA in solution, and the determination of length of biopolymers.



http://www.ks.uiuc.edu/Research/nanopore/

Nanocrystal

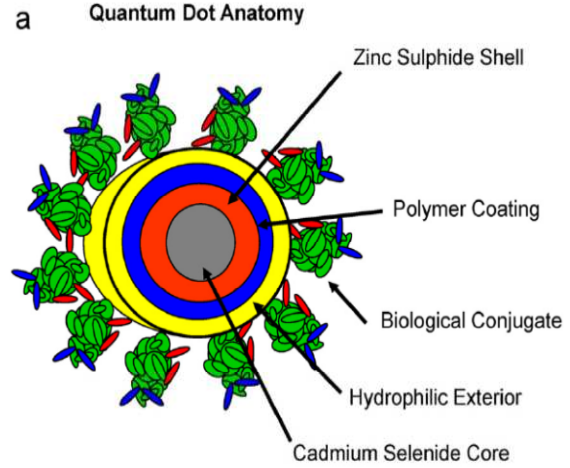
- A nanocrystal is a crystalline particle **with at least one dimension less than 100 nm.**
- Semiconductor nanocrystals in the sub-10nm size range are often referred to as ‘quantum dots’. A quantum dot has a discrete quantized energy spectrum.

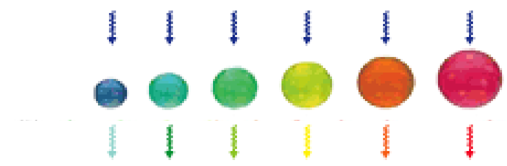


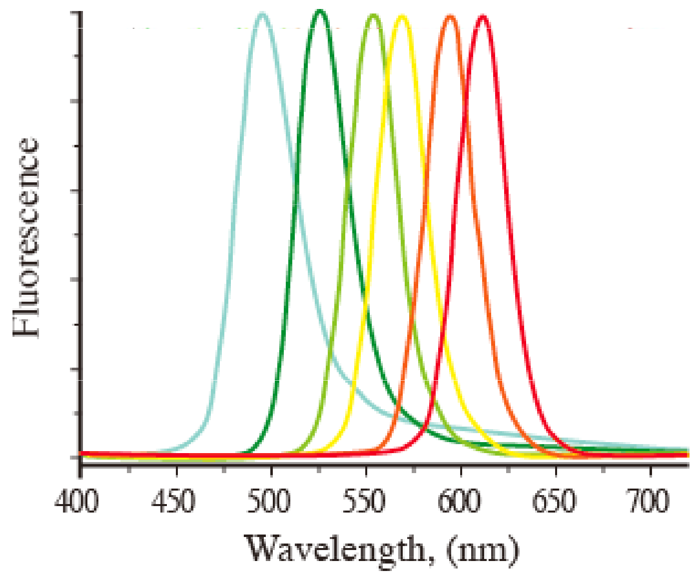
http://www.elec-intro.com

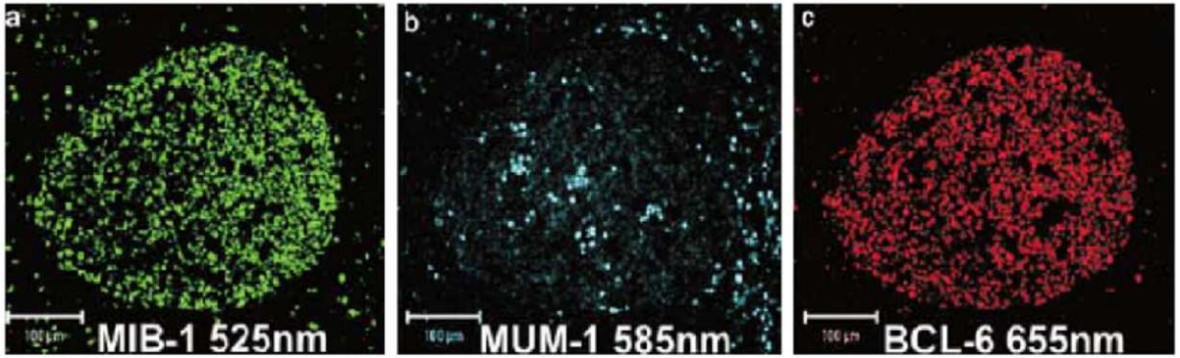
Nanocrystal – Quantum dots

- Clusters of atoms forming the regular monocrystalline structures
- As quantum dots can be also called clusters of atoms created on suitable ground (use in electronics, communication technologies, ...)
- They have discrete energy levels
- **Fluorescence properties** – wavelength of the excitation radiation is chosen according to the size of core of quantum dots.
- Use – cell mapping, immunomapping, MRI contrast





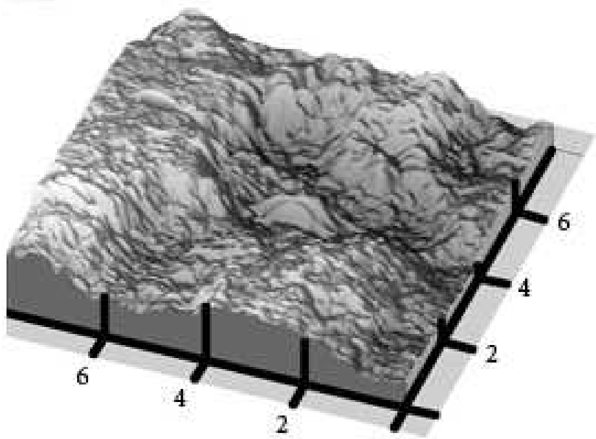




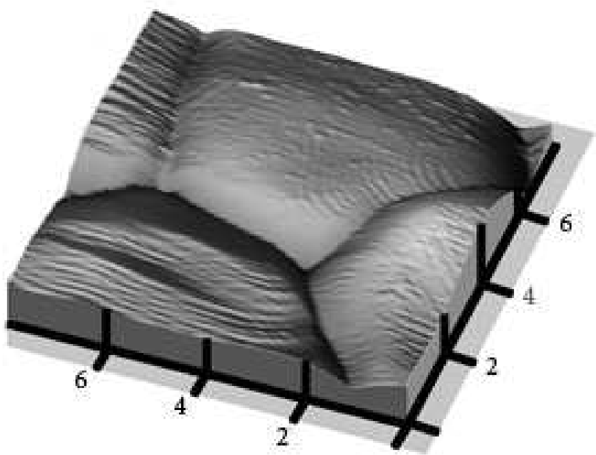
Triple immunofluorescence using the quantum dots, Fountaine *et al*, Mod Pathol 2006, 19, 1181-1191

Nanocrystals : antibacterial effects

According to Thomas J. Webster from Brown University, USA, it is possible to use nanocrystals of titanium and zinc oxides to modify the surface of implants - nanostructuring method. Its nature lies in multiple magnification of the surface of material by applying layers of nanocrystals (proces of roughening), such as in the case orthopaedic implants. It helps to increase adhesion of the tissue cells and accelerate the "healing". Another important function of such a modified surface is the antimicrobial function, where the presence of zinc oxide nanocrystals suppresses the formation of microbial films.



implants effected by nanomaterials



nature implants without nanomaterials

Nanocrystals: liquid glass

- Liquid glass - the source material in this case is ordinary silica sand (**silicon oxide**) nanoparticles, which are added to the mixture with water or ethanol - according to the surface on which liquid glass is applied (using spray). Nothing other is needed, the liquid glass at the site sticks by physical forces (which are ubiquitous in nanoworlds).
- Sprayed liquid glass creates a waterproof layer with thickness of about 100 nanometers, which represents only 15-30 molecules.
  Liquid glass has a very durable antibacterial effects. It is antimicrobial, because **liquid glass reduced adhesion of microbes** on the treated surface.
- Liquid glass was been tested in a hospital in Lancashire, where the staff used surgical equipment, implants, catheters, … all threated by this interesting nanomaterial. The result of the tests was an increase in antibacterial protection

Nanofibers – recently existing and often used

- Nanofibers are fibers with diameters in the nanometer range.
- Nanofibers can be generated from different polymers and hence have different physical properties and application potentials.
- Biodegradability, biocompatibility
- Examples of natural polymers include collagen, cellulose, silk fibroin, keratin, gelatin and polysaccharides
- Examples of synthetic polymers include poly(lactic acid) (PLA), polycaprolactone (PCL), polyurethane (PU) …

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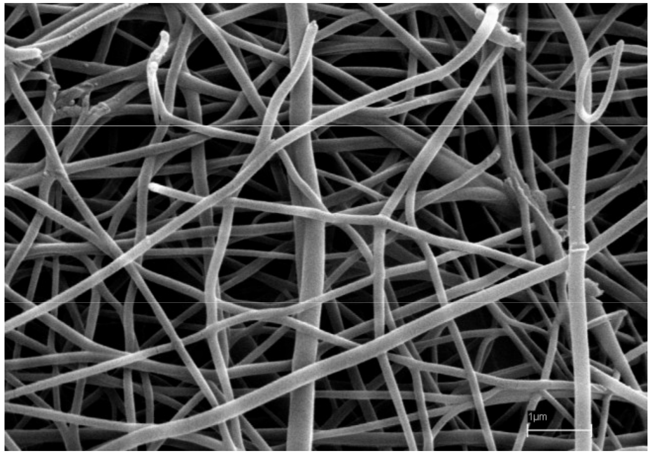
Nanofibers

- There exist many different methods to make nanofibers, including drawing, electrospinning, self-assembly, template synthesis, and thermal-induced phase separation.



Nanofibers

Applications :

- **Tissue engineering (**extracellular matrix)
- **Drug delivery** (antibiotics and anticancer drugs have been successfully encapsulated)
- **Cancer diagnosis** (chips)
- **Optical sensors**

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Nanofibers

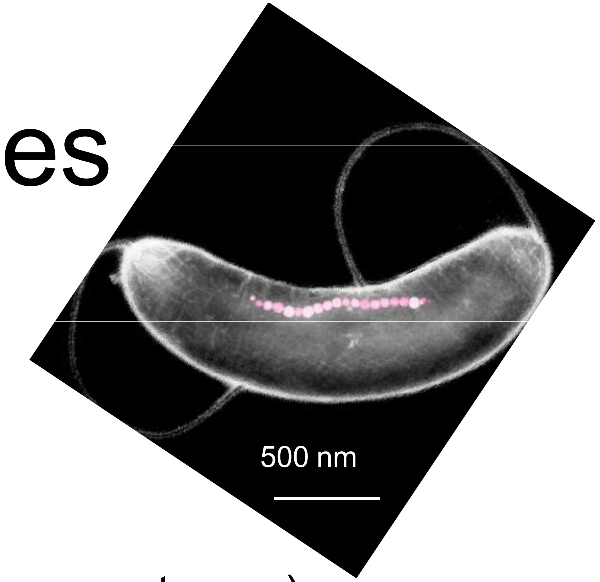
skeleton of trachea

surface protection „new skin“

Carmel J Caruana, BioMedical Physics, Institute of Health Care, University of Malta

Vladan Bernard Deparment of Biophysics Lf MU

Magnetic nanoparticles



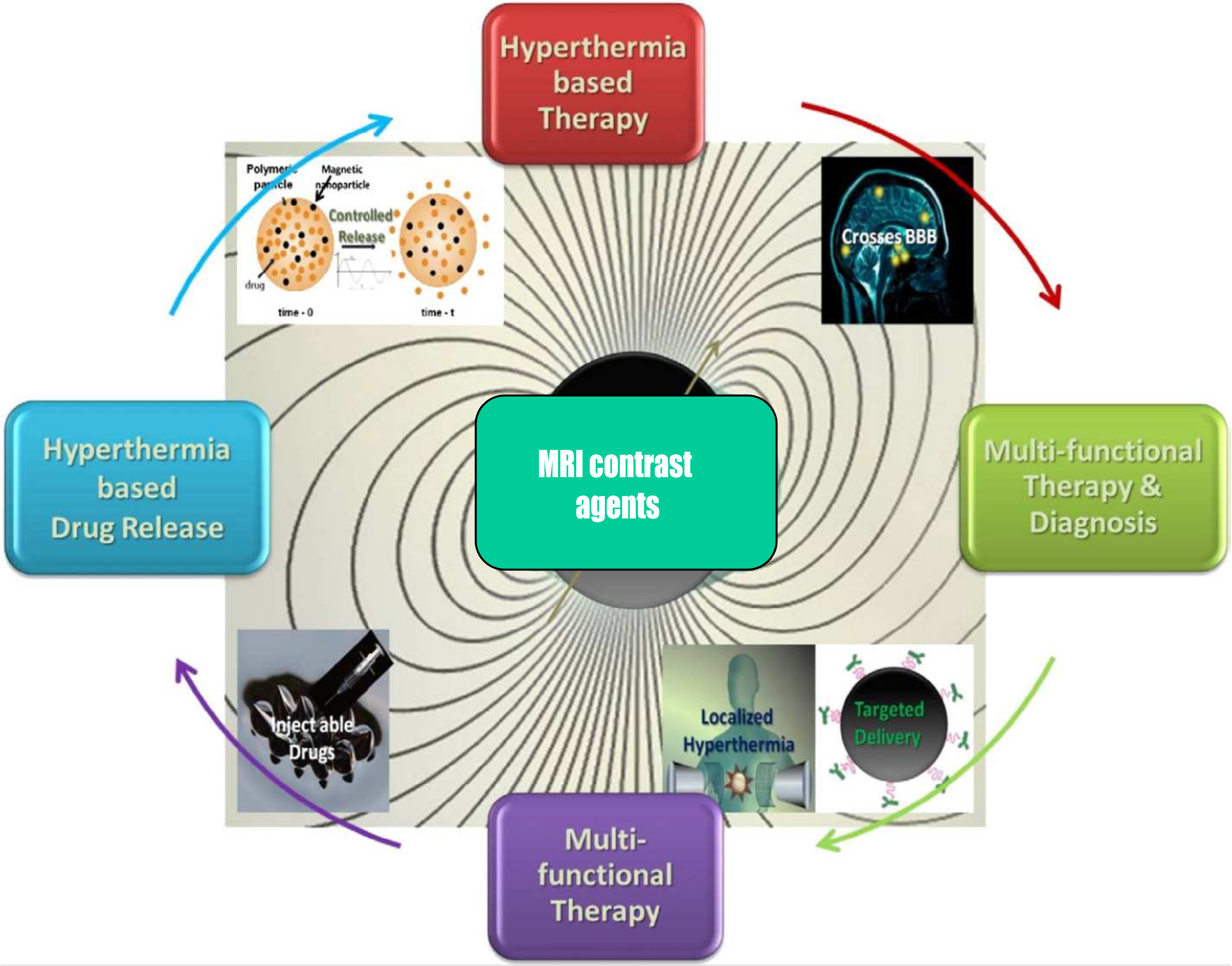
- Magnetic nanoparticles - characterized by magnetic moment **μ** and by interaction with the external magnetic field **H**
- The natural incidence of magnetic nanoparticles in nature - Magnetospirillum magnetotacticum - magnetite (organelle magnetosom) bee, termite, pigeon, dolphin

The use in medicine, biomedicine:

- **transport / separation / immobilisation** of magnetic nanoparticles or molecules conjugated with the nanoparticles by an external magnetic field - the separation of DNA / RNA, targeted drug delivery
- **heating** (energy transfer from the external magnetic field on magnetic nanoparticles) - eg magnetic intercellular hyperthermia for cancer treatment
- **increasing** MRI contrast signal - as a contrast agent Resovist ® (iron oxide coated karboxydextranem) for examination of the liver

MUNI

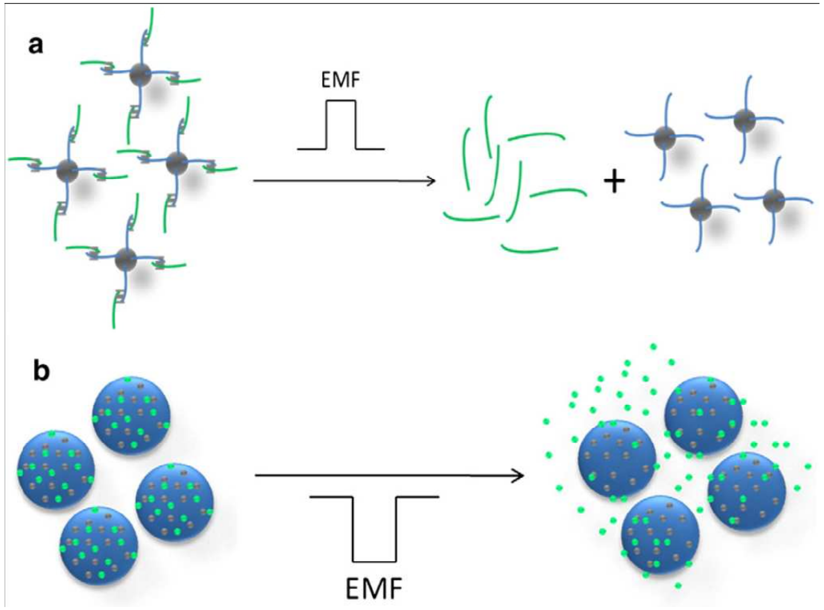
Magnetic nanoparticles



Schematic representation of the use of magnetic nanoparticles in medicine (Kumar and Mohammad, 2011)

Magnetic nanoparticles :

Temperature-controlled transport of drugs



Temperature-controlled transport of drugs by using heating of magnetic nanoparticles by action of external magnetic field (hysteresis during heating).

a) mobilization of substances (drugs) bound to the nanoparticle through thermolabile bond (by changing the temperature of nanoparticles due to applications of magnetic field

b) mobilisation of substances (drugs) from the polymer envelope which also contains magnetic nanoparticles. The release of substances is enabled by the presence of micro-cracks that occur during heating of the nanoparticles present in the polymer by exposure to changing magnetic field

Kumar, Mohammad, Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery, Adv. Drug Deliv. Rev. (2011)

MUNI

Magnetic nanoparticles

Table 1
List of magnetic nanoparticles reported for application in hyperthermia-based therapy and controlled drug delivery.

S. no	Type of magnetic nanoparticle	Application
1.	Fe doped Au NPs	Hyperthermia-based therapy
2.	γ-Fe_2O_3	Hyperthermia-based therapy
	Cobalt ferrite	
3.	Fe_3O_4	Hyperthermia-based therapy
	Fe_3O_4-poly vinyl alcohol	
4.	$NiFe_2O_4$	Hyperthermia-based therapy
5.	γ-Fe_2O_3	Hyperthermia-based therapy
7.	Fe_3O_4@chitosan	Hyperthermia-based therapy
8.	Fe_3O_4@block copolymers	Hyperthermia-based therapy
9.	Fe_3O_4-dextran stabilized	Hyperthermia-based therapy
	Fe_3O_4@Aminosilan	
10.	Ferrite-Dextran stabilized	Hyperthermia-based therapy
11.	Fe_3O_4-dextran (mono and bilayer) stabilized	Hyperthermia-based therapy
12.	Fe_3O_4-lauric acid stabilized	Hyperthermia-based therapy
13.	Fe_3O_4-lauric acid stabilized	Hyperthermia-based therapy
	$MnFe_2O_4$-lauric acid stabilized	
	$CoFe_2O_4$-lauric acid stabilized	
14.	Fe@biscarboxyl-terminated poly(ethylene glycol) (cPEG)	Hyperthermia-based therapy
15	γ-$Mn_xFe_{2-x}O_3$ coated Acrypol 934 polymer	Hyperthermia-based therapy
16.	FeCo@Au	Hyperthermia-based therapy
17.	Fe@MgO	Hyperthermia-based therapy
18.	Fe_3O_4@Si	Hyperthermia-based therapy
19.	Fe_2O_3@SiO_2	Hyperthermia-based therapy
20.	FeNi@Au microdiscs	Hyperthermia-based therapy
21.	Fe@Fe_3O_4	Hyperthermia-based therapy
22.	$La_{0.56}(CaSr)_{0.22}MnO_3$@$SiO_2$	Hyperthermia-based therapy
23.	Fe_3O_4@Au	Hyperthermia-based therapy
24.	Magnetite cationic liposomes (MCL)	Hyperthermia-based therapy
25.	Fe_3O_4-lauric acid stabilized	Hyperthermia-based therapy
26.	Fe_2O_3@SiO_2 bound LHRH	Hyperthermia-based therapy
27.	SPIONs bound fluorophore bimane	Hyperthermia-based Controlled drug delivery
28.	Porous Fe_3O_4/Fe/SiO_2	Hyperthermia-based Controlled drug delivery
29.	Fe@SiO_2	Hyperthermia-based Controlled drug delivery
30.	poly-(*N*-vinyl-2-pyrrolidone) (PVP)-modified silica core@iron oxide shell	Hyperthermia-based Controlled drug delivery
31.	Mg-Al layered double hydroxides (LDH) coated magnesium ferrite NPs	Hyperthermia-based Controlled drug delivery
32.	Yolk-shell type nanospheres with movable cores of Au, SiO_2, Fe_3O_4	Hyperthermia-based Controlled drug delivery
33.	γ-$Mn_xFe_{2-x}O_3$ coated Acrypol 934 polymer	Hyperthermia-based therapy and controlled drug delivery
34.	Fe_3O_4@lipid membrane (MCL, magnetite cationic liposome)	Hyperthermia-based therapy and controlled drug delivery
35.	Fe@carbon nanoparticles bound polymer	Hyperthermia-based therapy and controlled drug delivery
36.	Co@Au@ poly(sodium styrene sulfonate)/poly(allylamine hydrochloride)	Hyperthermia-based therapy and controlled drug delivery
37.	SPIONs@ sensitive poly (*N*-isopropylacrylamide) hydrogels	Hyperthermia-based therapy and controlled drug delivery
38.	Fe@Fe_3O_4 loaded 4-tetracarboxy phenyl porphyrin	Hyperthermia-based therapy and controlled drug delivery
39.	Carboplatin-Fe@C-loaded chitosan	Hyperthermia-based therapy and controlled drug delivery
40.	Zinc doped iron oxide nanocrystals encapsulated mesoporous silica	Hyperthermia-based therapy and controlled drug delivery
41.	MCL loaded 4-*S*-Cysteaminylphenol	Hyperthermia-based therapy and controlled drug delivery

Overview of magnetic nanoparticles and their possible use

Kumar, Mohammad, Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery, Adv. Drug Deliv. Rev. (2011)

Nanocrystal: Medical applications: Contrast Media for MRI Imaging

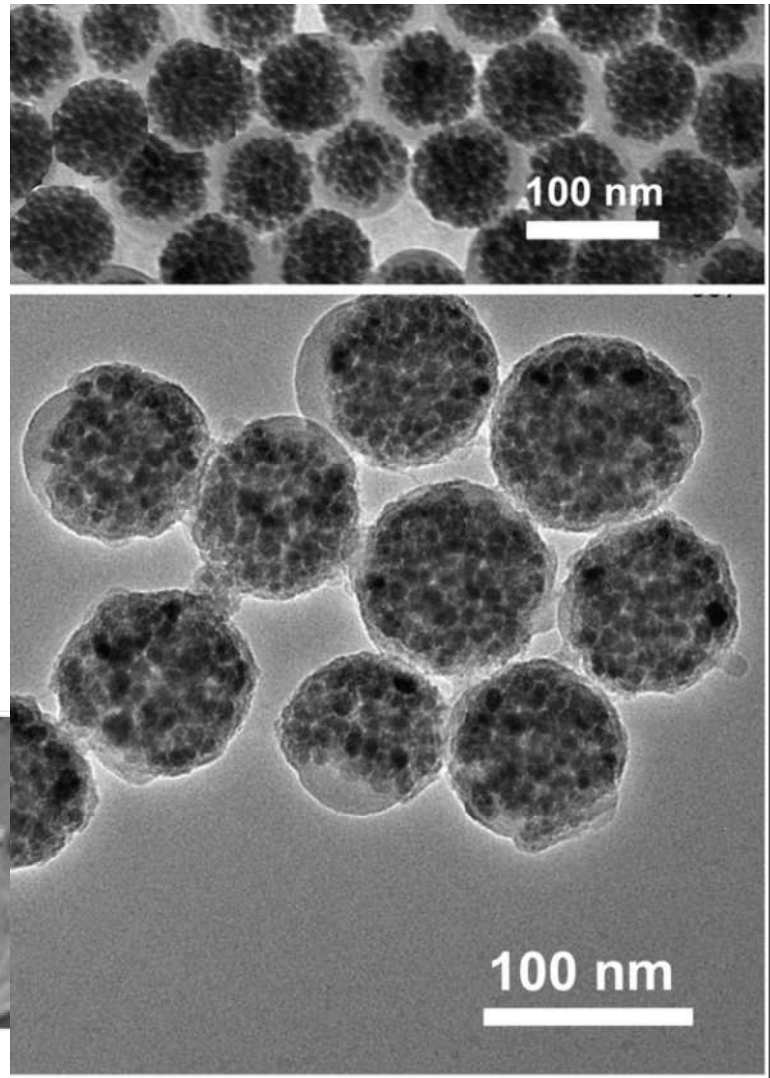
Magnetic resonance imaging

- Superparamagnetic nanocrystalls (**dark** contrast effect in images)
  - Superparamagnetic iron oxide (SPIO) nanoparticles (50-500 nm) – *on the market*
    - Lumirem® and Endorem™, Advanced Magnetics Inc, USA
  - Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles (<50nm) – *clin. investigation*
    - Supravist™, Schering AG, Germany
    - Sinerem®, Guerbet SA, France

Roszek et al. Medical nanotechnology

Magnetic nanoparticle: Contrast Media for MRI Imaging

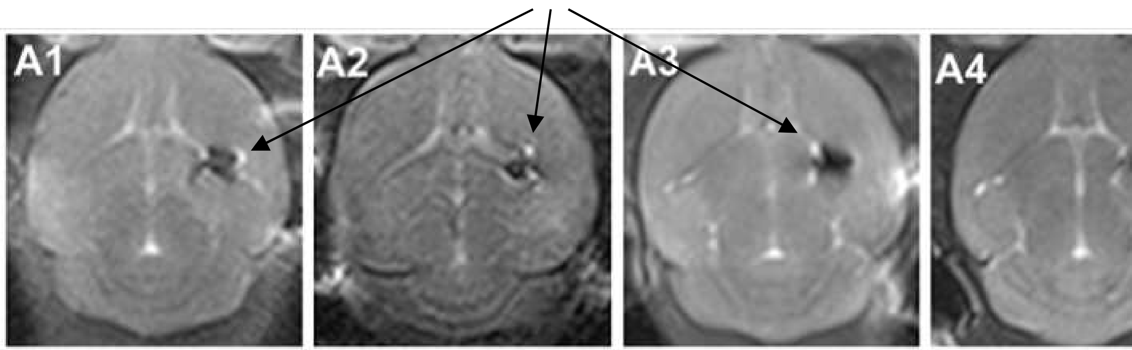
TEM microscopy - magnetite nanoclusters consisting of magnetite nanoparticles



The use of magnetic nanoparticles as contrast agents for MRI views, in this case, monitoring the distribution of stem cells (containing these nanoclusters) in mouse brain.

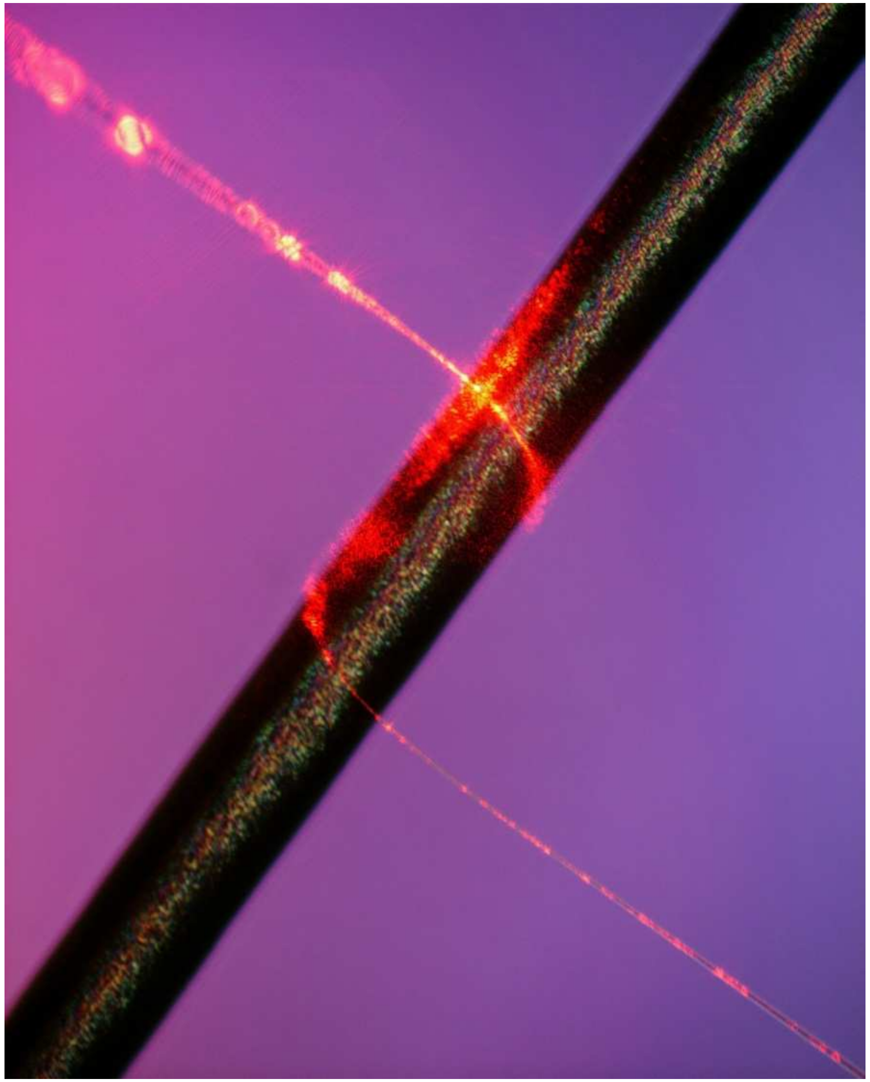
Chunfu Zhang et al., High MR sensitive fluorescent magnetite nanocluster for stem cell tracking in ischemic mouse brain, *Nanomedicine: Nanotechnology, Biology and Medicine*, *Available online 8 April 2011*

MRI signal of magnetic nanoparticle



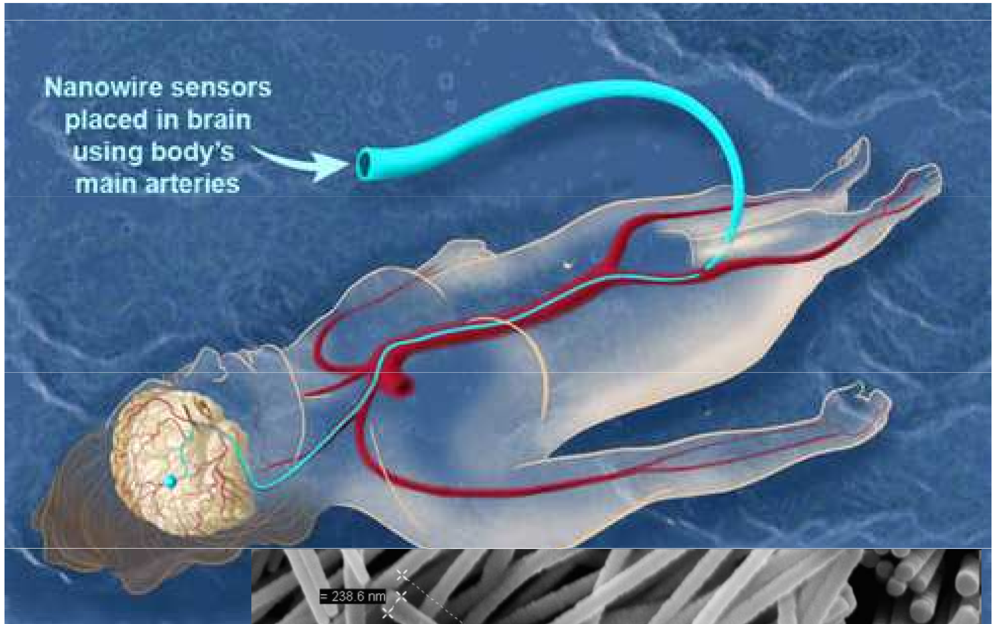
Nanowires

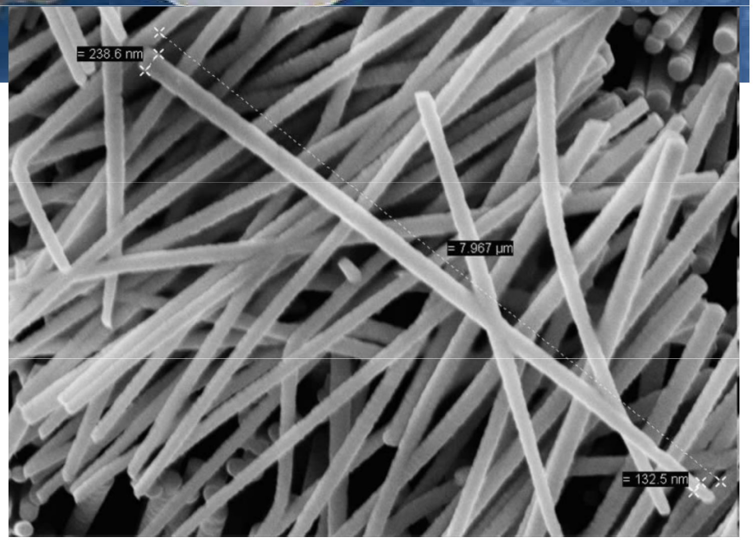
- A nanowire is a wire of diameter of the order of nm.
- Photo: A light-conducting silica nanowire wraps a beam of light around a strand of human hair. The nanowires are flexible and can be as slender as 50 nanometers in width, about one-thousandth the width of a hair.
- This is far smaller than the smallest capillary in the body! That means nanowires could, in principle, be threaded through the circulatory system to any point in the body without blocking the normal flow of blood or interfering with the exchange of gases and nutrients through the blood-vessel walls



Nanowires: Medical Applications – Brain studies and therapy - fantasy

- Bunch of nanowires being guided through the circulatory system to the brain. Once there, the nanowires would spread out branching into tinier and tinier blood vessels. Each nanowire would then be used to record the electrical activity of a single nerve cell, or small groups of nerve cells (better than PET or fMRI!) giving the ability to pinpoint damage from injury and stroke, localize the cause of seizures, and other brain abnormalities. It's long been known that people with Parkinson's disease can experience significant improvement from direct stimulation of the affected area of the brain with electrical pulses. Indeed, that is now a common treatment for patients who do not respond to medication. But the stimulation is currently carried out by inserting wires through the skull and into the brain, a process that causes scarring of brain tissue. The hope is, by stimulating the brain with nanowires threaded through pre-existing blood vessels, doctors could give patients the benefits of the treatment without the damaging side effects.

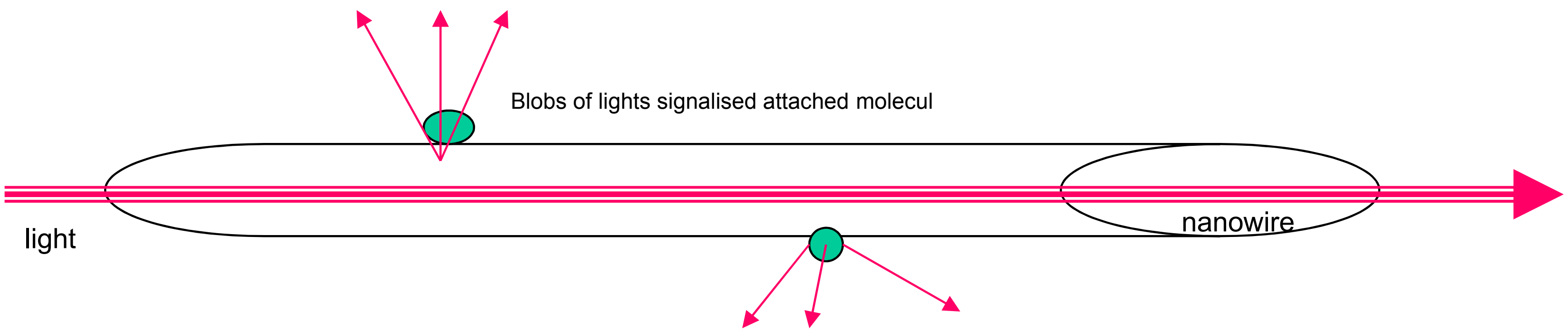




Prof. Bernard NYSTEN , Université catholique de Louvain

Nanowires: Medical Applications – Environmental Molecular Sensors

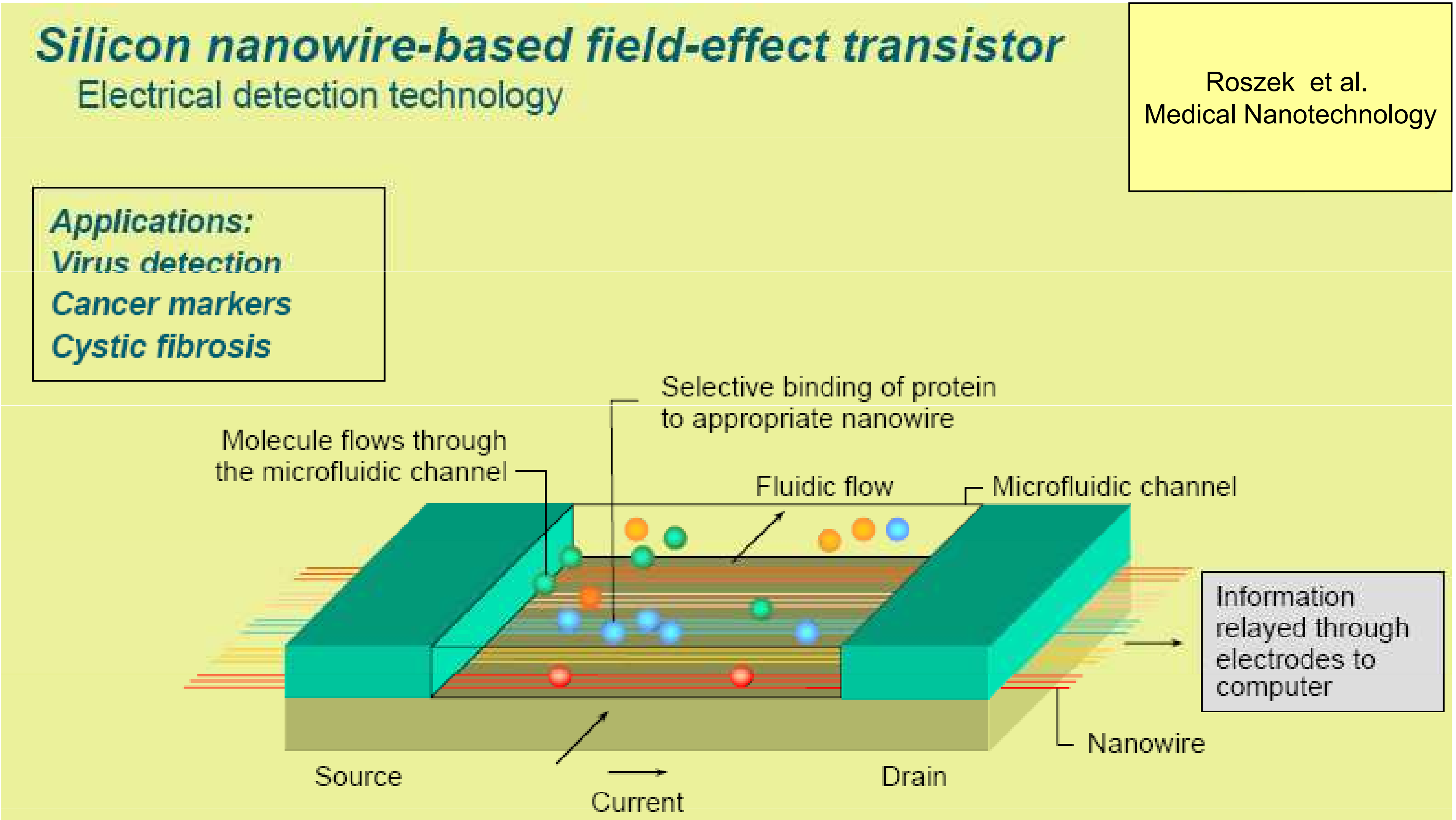
- Compared to ordinary fiber optic cable, which appears to the naked eye as a uniform glowing line, nanowires have a beaded appearance when viewed under magnification. That's because unlike a normal fiber, which confines light within its walls, minuscule particles of dust along the nanowires' surface can scatter the light beam. This sensitivity to surface contaminants could lead to use of the nanowires as molecular sensors.
- One could fit the surface of the wire with receptors for environmental molecules. If those target molecules are present, they'll attach to the receptors and blobs of tiny lights will be seen when the wires are illuminated.



Carmel J Caruana, BioMedical Physics, Institute of Health Care, University of Malta

Vladan Bernard Deparment of Biophysics Lf MU

Nanowires: Medical Applications: Biomolecular Sensors



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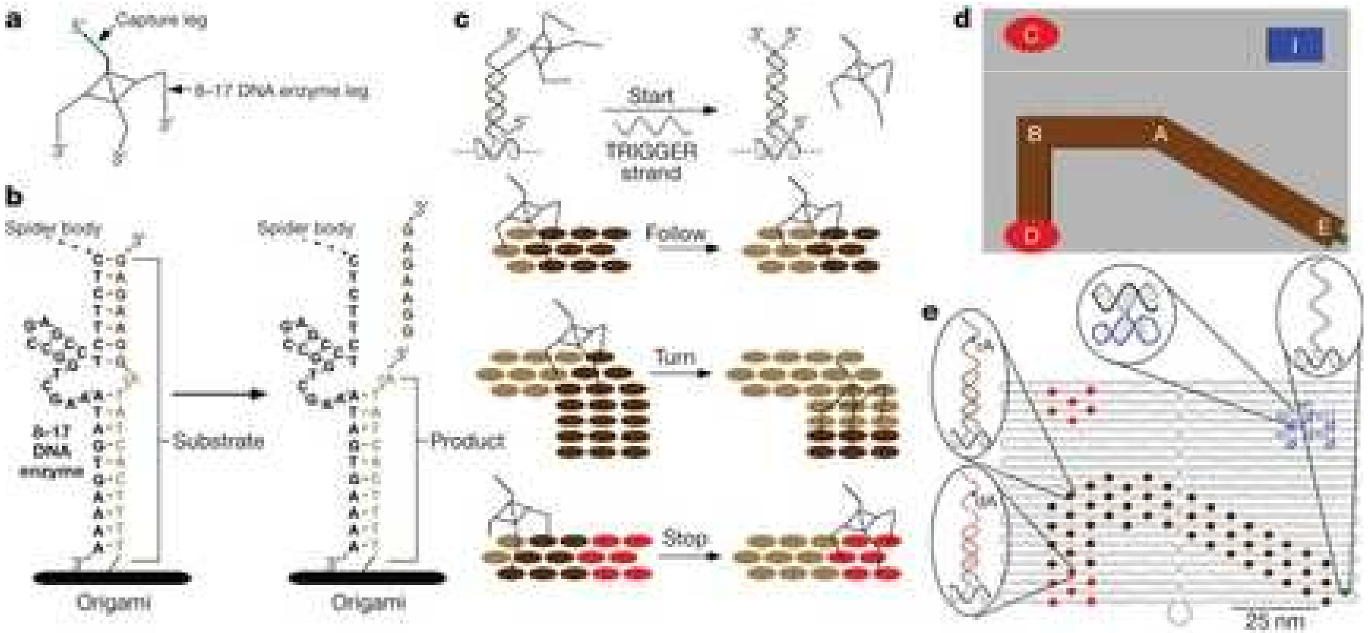
Robotic nanoworld

DNA-based nanorobotics

Nature 2010 - Molecular robots guided by prescriptive landscapes – Lund et al.

Nature 2010 - Molecular robots guided by prescriptive landscapes - Lund et al.

The authors of this paper presented "nano-spider" which is consist of protein and DNA and that can move along the trajectory by using pre-programmed short ss DNA chains. Nano-spider has the body formed by the protein streptavidin. Despite biotin (vitamin H) are linked to him four short stretches of single-stranded DNA / enzyme. The total size of nano-spider is 4 nm. The trajectory is given by compatibility ss DNA chains that are on pads and ss DNA chains forming the "legs". It is controlled by the commands "start", "change the direction" and "stop„.

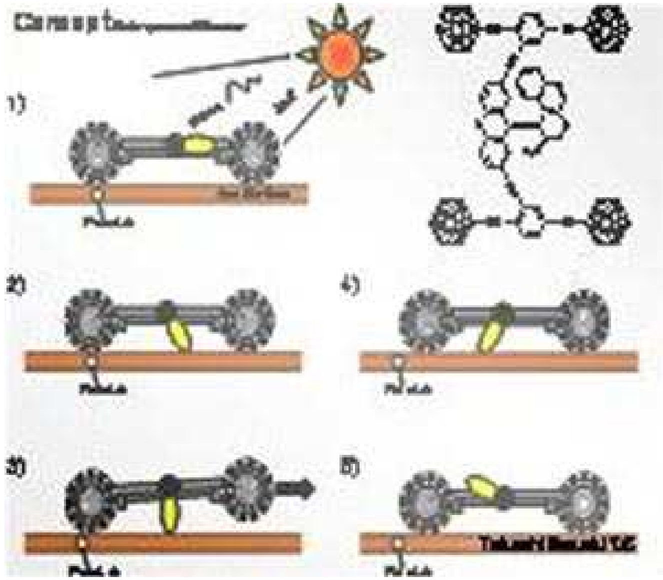


Robotic nanoworld

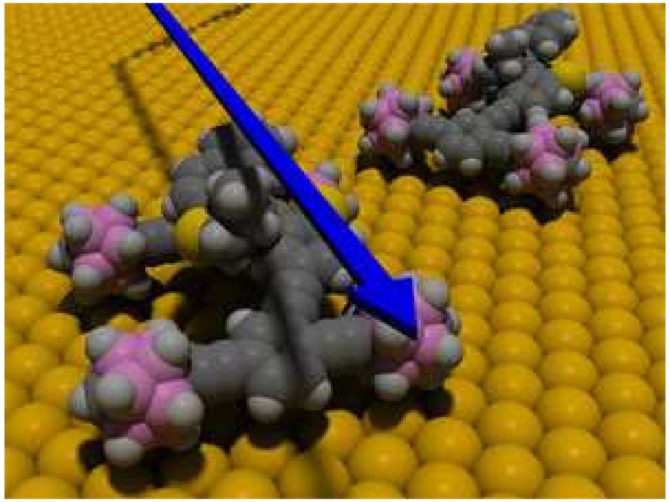
nano-robotics based on organic molecules

The size of molecules of „nanocar" are less than 4 nm, "wheels" are formed by molecules of p-carborane, "engine" of combination of aromatic rings. After iradiation by electromagnetic wave , it is absorbed by central molecule, and this begins to rotate on the gold surface and move the whole "nanocar". The highest speed is 2 nm per minute.

www.newscientist.com



Princip of moving of „nanocar“ (Rice University)



http://www.youtube.com/watch?v=lASdcW-BtiU

http://www.youtube.com/watch?NR=1&v=57GYz69GFbI

Health Risks

- Nanoparticles are able to cross biological membranes and access cells, tissues and organs that larger-sized particles normally cannot. They can gain access to the blood stream after inhalation or ingestion. At least some can penetrate the skin. Once in the blood stream, they can be transported around the body and are taken up by organs and tissues including the brain, heart, liver, kidneys, spleen, bone marrow and nervous system. Unlike larger particles, they may be taken up by cell mitochondria and the cell nucleus. Studies demonstrate the potential for DNA mutation and induce major structural damage to mitochondria, even resulting in cell death.
- Hundreds of consumer products incorporating nanoparticles are now on the market, including cosmetics, sunscreens, sporting goods, clothing, electronics, baby and infant products, and food and food packaging.

Current status and future prospects of nanotechnology in cosmetics

Albert Mihranyan *, Natalia Ferraz, Maria Strømme *

Nanotechnology and Functional Materials, Department of Engineering Sciences, Uppsala University, Box 534, 75121 Uppsala, Sweden

Progress in Materials Science 57 (2012) 875–910

Table 2
Examples of nanomaterials currently marketed as cosmetic products.

Class	Material	Action	Product example
Active	Arbutin	Whitening	Nano Bright™
Metals and metal oxides	ZnO	Suncreen	ZinClear-IM™
	Ag	Antibacterial	GNS Nanogist; Susie-K Nano Beauty Soap
	Fe_xO_y	Concealer	Mineral foundation
	Au	Conjugated silk microfiber	Chantecaille Nano Gold Energizing Cream; Nanorama
	Pt/Ag	Absorptive NP	*Platinum Silver Nanocolloid Milky Essence*
	ZnO/Ti_xO_y	Concealer	*Face Brushes™ After Glow Brush and Brush Colores; Sunforgettable™*
	Ti_xO_y	Sunscreen	Soltan®
	Al/Al_2O_3	Concealer	Alusion™
	$Ag/Ti/Ti_xO_y$	Hair care	*Nano Weight Pro 1800*
Carbon	Fullerenes	Free radical inhibition	*Zelens®; Radical Sponge®*
	Fullerosomes	Free radical inhibition	*Sircuit®*
Nanoclays and silica	SiO_2	Tightens skin, delivery of active ingredients	LEOREX®; Rénergie®
	SiO_2/Me_xO_y	Sunscreen	*Eusolex® UV Pearls*
	$Mica/ZnO/\ Ti_xO_y$		*Dual Finish Pressed Compacts*
Vesicular lipid nanocarriers	Liposomes, ceramides, nanoemulsions	Delivery of active ingredients	Revitalift®; Lyphazome®; Celazome®; Psorinel Lotion;Hydra Zen®
		Ethosomes	anti-cellulite
Solid lipid nanopartciles	Solid lipids	Delivery of active ingredients	Lipopearl™; Nanopearl™
	Wax	Hair styling	Pureology®
	Solid lipids	Delivery of active ingredients	Swiss Cellular™ White Illuminating Eye Essence; Olivenöl™ Anti Falten Pflege; IOPE™ Super Vital Cream; SURMER™ Creme Legere
Native and modified polymers	Modified polyaminoacids	Skincare	Collamin_G™
	Hyaluronic acid	Moisturiser	PowerMoist™ Nano Hyaluronic acid
	Collagene	Skincare	*bīm·ə·nē* ®
Synthetic polymers	Nanocapsules	Delivery of active ingredients	Primordiale Intense; Hydra Flash® Bronzer

Titanium dioxide nanoparticles in food and personal care products, Weir A et al, Environ Sci Technol. 2012, 46

Average day quantity per adult (in USA) - 1 mg nano TiO_2 per 1 Kg of human weight

Approx 5000 tonne (5 000 000 kg) of nano TiO_2 was used in products of daily care.

---

titanium white or E 171, average man 80 kg * 365 day * 1 mg = 29 200 mg = 29,2 g TiO2 (one sugar cube cca 10 g, teaspoon of flour cca 7 g)

TITANOVÁ BĚLOBA KA-100

Oxid titaničitý (Anatas) typ KA 100 (výrobce Scheruhn Industrie Mineralien)

Klasifikace: ISO 5911:1977

Titanová běloba je bílý jemný prášek bez zápachu.Titanová běloba A 01 je nemikronizovaný, nemodifikovaný, povrchově neupravený anatasový pigment. Titanová běloba je nejedovatá.

Použiti:

- Pro výrobu vnitřnich, na vzduchu schnoucich nátěrových hmot, vodných i nevodných systémů.
- Pro výrobu základnich i podlahových barev.
- K přímému plnění papiroviny a stavebních materiálů.
- Při výrobě plastových hmot, pro výrobu podlahových krytin.

Kvalitativni a fyzikálni parametry:

Obsah TiO_2	min.	98,5%
Vlhkost při 105 °C	max.	0,4%
Zbytek na sítě(0,045 mm)	max.	0,05%
Spotřeba oleje	max.	22g/100g
pH vodného výluhu	--	6,5-8,0
Jasnost	min.	98%

Baleni:

papirové pytle 25 kg netto, na paletě 1000kg

Země původu suroviny:

Čína

Carmel J Caruana, BioMedical Physics, Institute of Health Care, University of Malta

Vladan Bernard Deparment of Biophysics Lf MU

nanomaterials are everywhere around us

Carmel J Caruana, BioMedical Physics, Institute of Health Care, University of Malta

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Content collaboration:

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