NANOMATERIALS FOR BIO-MEDICINE

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The National Institute of Nuclear Physics (INFN - Istituto Nazionale di Fisica Nucleare) is an organization for research in nuclear physics. There are different divisions in Italy. The Frascati National Laboratories (LNF) is the largest and one of the most important ones. The research here is primarily concentrated on particle physics.

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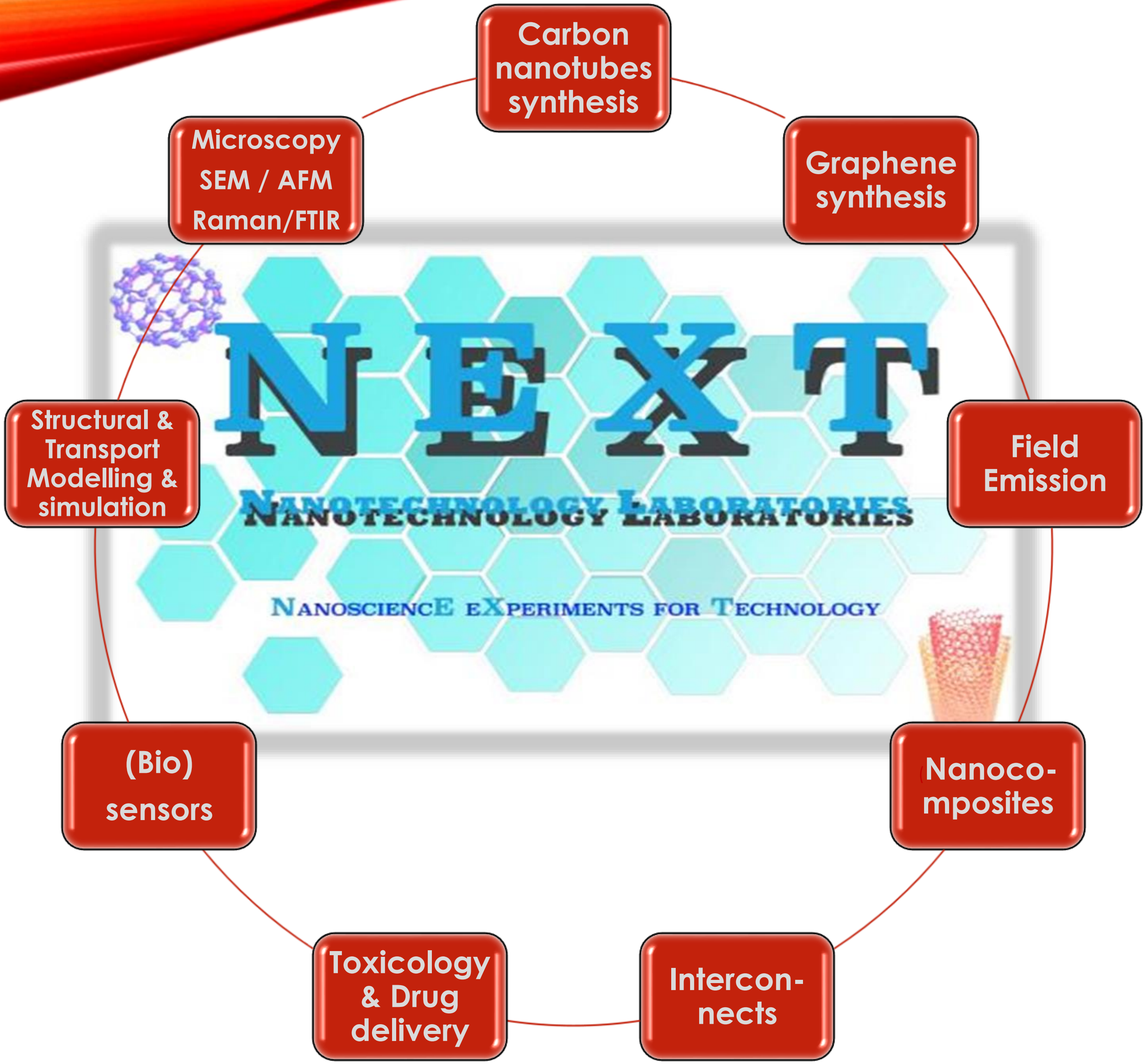
Laboratori Nazionali di Frascati

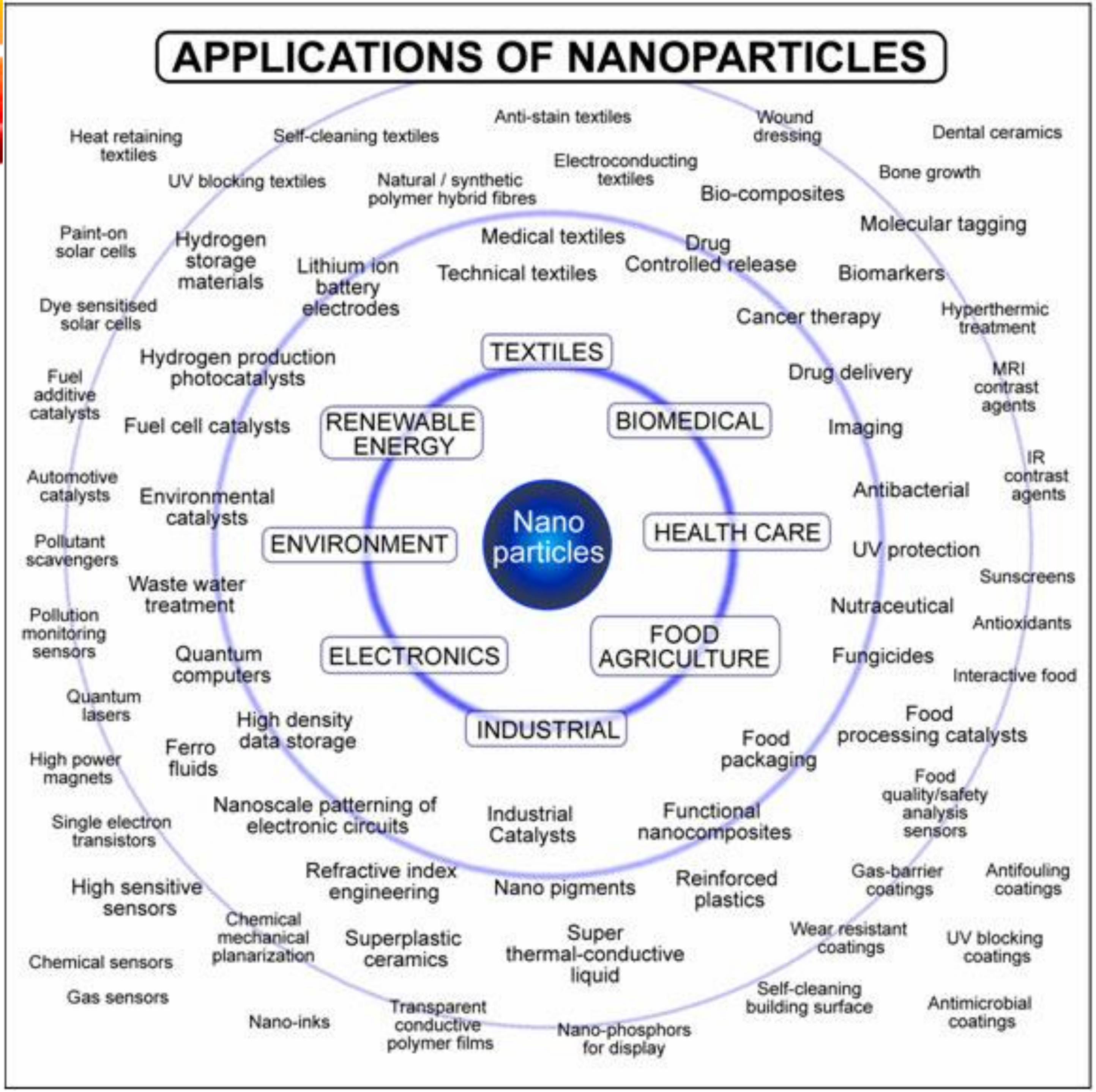
ACTIVITY 360° ON NANOTECHNOLOGY



INTRODUCTION TO NANOPARTICLES AND THEIR USES

OUTLINE

Introduction
Impact on health and environment
Safe uses of nanotechnology
Drug delivery nanosystems

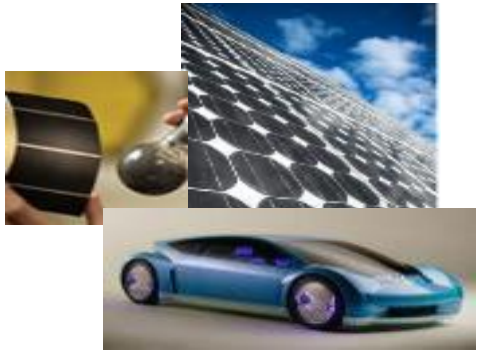

APPLICATIONS OF NANOPARTICLES
Nano particles
TEXTILES
BIOMEDICAL
HEALTH CARE
FOOD AGRICULTURE
INDUSTRIAL
ELECTRONICS
ENVIRONMENT
RENEWABLE ENERGY
Heat retaining textiles
Self-cleaning textiles
Anti-stain textiles
Wound dressing
Dental ceramics
UV blocking textiles
Natural / synthetic polymer hybrid fibres
Electroconducting textiles
Bio-composites
Bone growth
Molecular tagging
Medical textiles
Technical textiles
Drug Controlled release
Biomarkers
Paint-on solar cells
Hydrogen storage materials
Lithium ion battery electrodes
Cancer therapy
Hyperthermic treatment
Dye sensitised solar cells
Hydrogen production photocatalysts
Drug delivery
MRI contrast agents
Fuel additive catalysts
Fuel cell catalysts
Imaging
IR contrast agents
Automotive catalysts
Environmental catalysts
Antibacterial
UV protection
Sunscreens
Pollutant scavengers
Waste water treatment
Nutraceutical
Antioxidants
Pollution monitoring sensors
Quantum computers
Fungicides
Interactive food
Quantum lasers
High density data storage
Food packaging
Food processing catalysts
High power magnets
Ferro fluids
Food quality/safety analysis sensors
Single electron transistors
Nanoscale patterning of electronic circuits
Industrial Catalysts
Functional nanocomposites
High sensitive sensors
Refractive index engineering
Nano pigments
Reinforced plastics
Gas-barrier coatings
Antifouling coatings
Chemical mechanical planarization
Superplastic ceramics
Super thermal-conductive liquid
Wear resistant coatings
UV blocking coatings
Chemical sensors
Gas sensors
Nano-inks
Transparent conductive polymer films
Nano-phosphors for display
Self-cleaning building surface
Antimicrobial coatings

Nanotechnology

The science of manipulating matter at the atomic and molecular level to obtain materials with specifically enhanced chemical and physical properties.

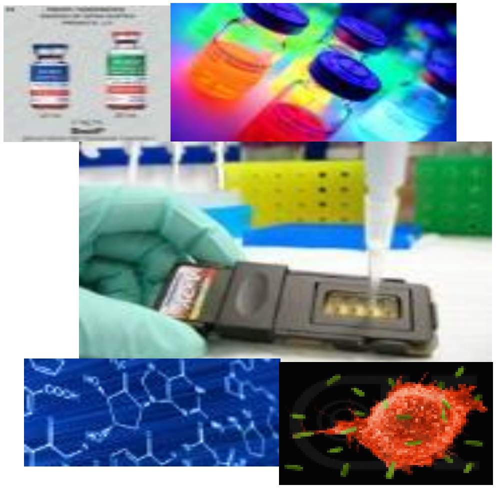
Information Technology

- Smaller, faster, more energy efficient and powerful computing and other IT-based systems



Energy

- More efficient and cost effective technologies for energy production
  - Solar cells
  - Fuel cells
  - Batteries
  - Bio fuels



Medicine

- Cancer treatment
- Bone treatment
- Drug delivery
- Appetite control
- Drug development
- Medical tools
- Diagnostic tests
- Imaging

Consumer Goods

- Foods and beverages
  - Advanced packaging materials, sensors, and lab-on-chips for food quality testing
- Appliances and textiles
  - Stain proof, water proof and wrinkle free textiles
- Household and cosmetics
  - Self-cleaning and scratch free products, paints, and better cosmetics

THE BASICS OF NANOTECHNOLOGIES

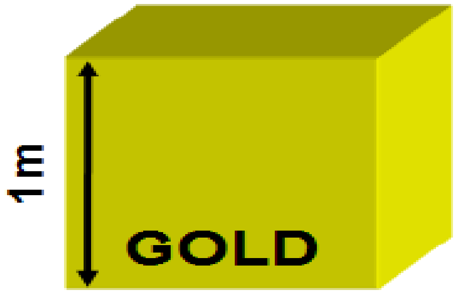
- You work at the atomic, molecular, and supramolecular levels...
- The scale of lengths involved is approximately between 1 and 100 nm
- The aim is the creation and use of materials, devices, systems with fundamentally innovative properties and functions, due to their very small (nanoscopic) structure.

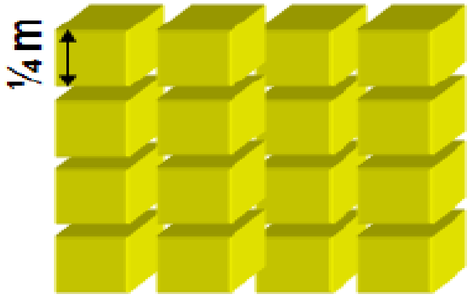
Physical-chemical properties

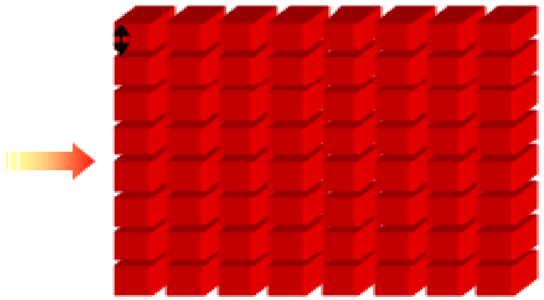
1. Surface to volume ratio: extremely large surface area;

2. High number of surface atoms (a particle of 300 nm has 5% of the surface atoms, one of 30 nm has got 50%).

New Properties of Matter Based on Size <u>and</u> Surface Area







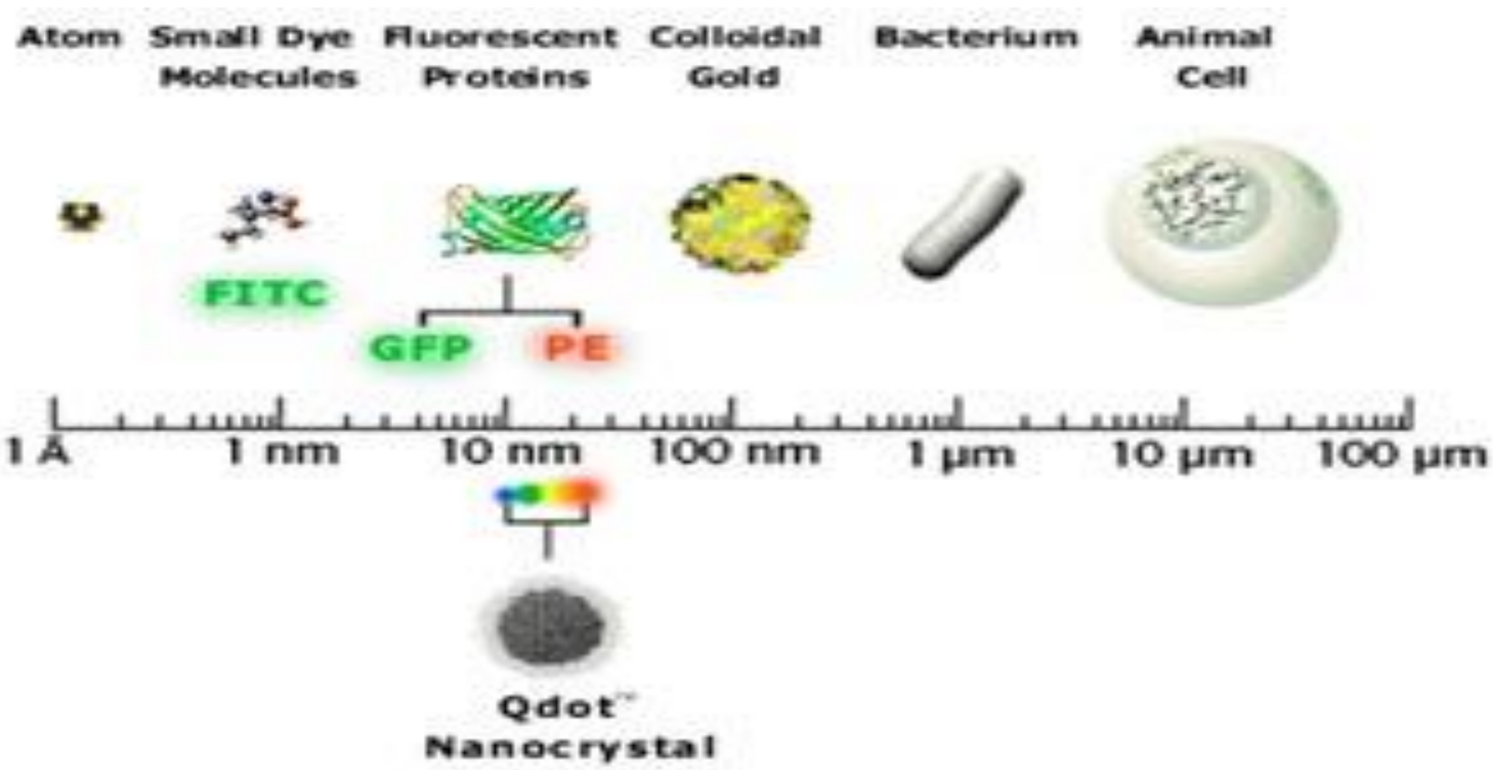
Each side=1 M
Mass≈43,000 lb
Surface Area (SA)=6 m^2
≈ 8 ft x 8 ft room

Each side=1/4 M
Mass≈43,000 lb
SA=24 m^2

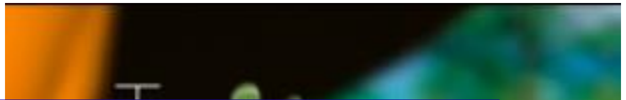
Each side=1 nM
Mass≈43,000 lb
SA=6 billion m^2 ≈ 2500 $miles^2$
State of Delaware= 2490 $miles^2$

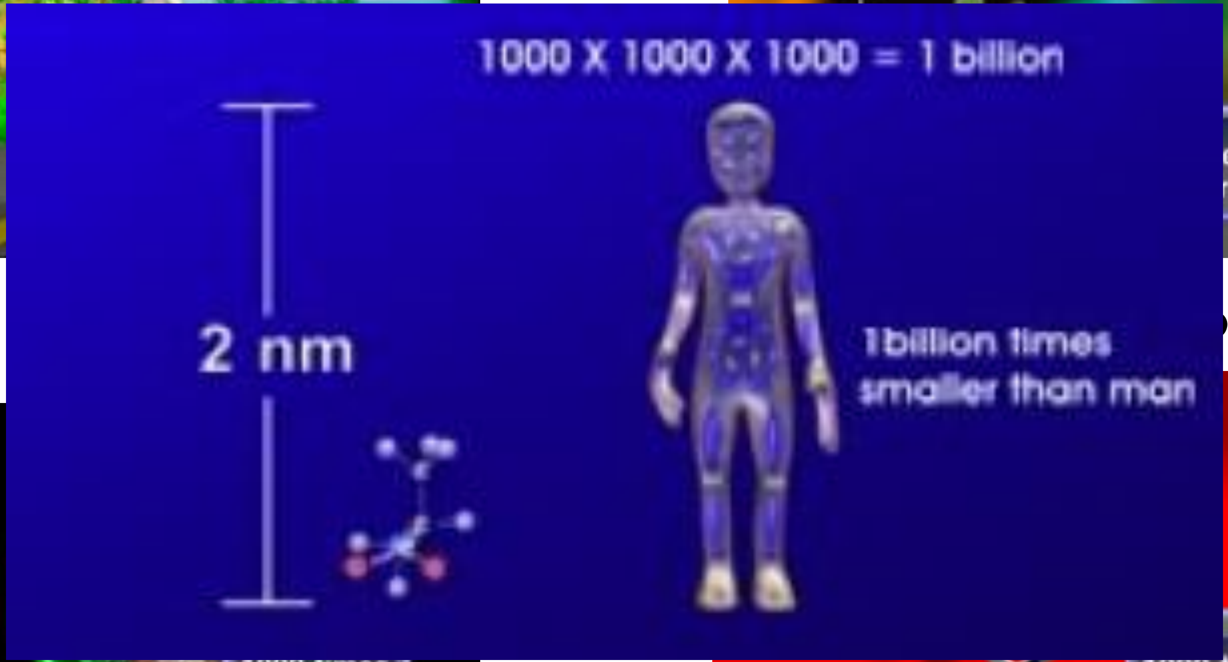
NANOSCOPIC SCALE

- Nanometer = 1 million-th of millimeter
- One Nanometer is as big as a layer of 3-5 atoms



Nano? Let's look at dimensions



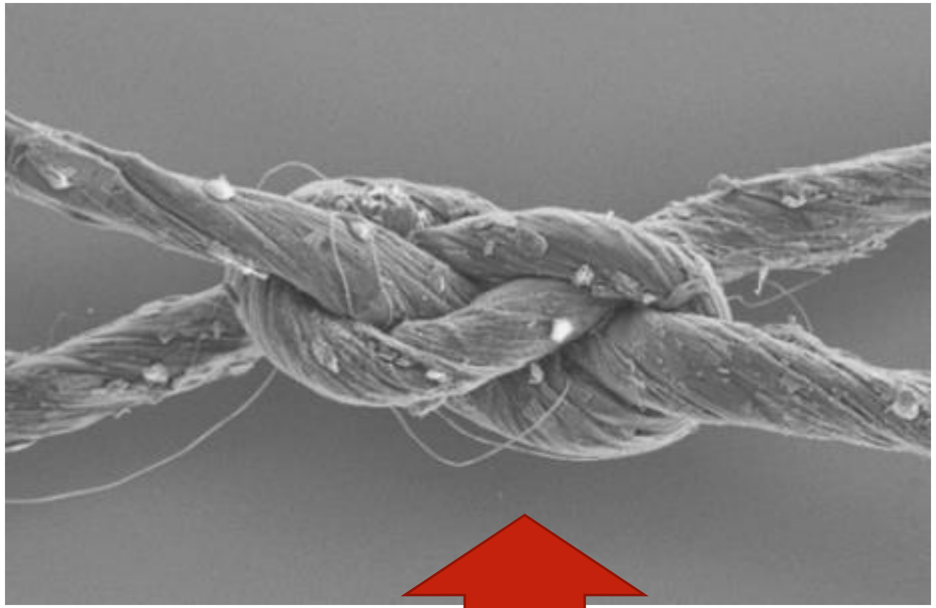


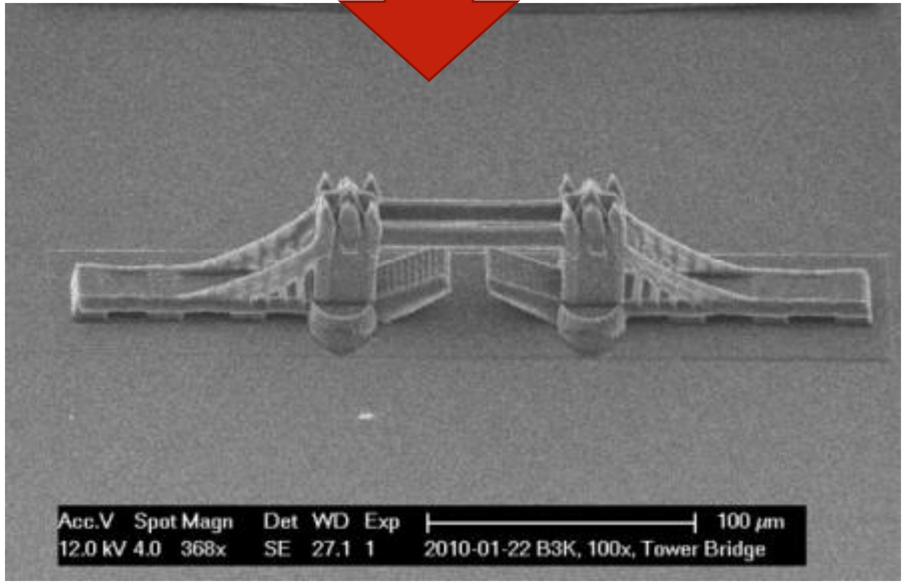
Let's …

…we come to his eyes…

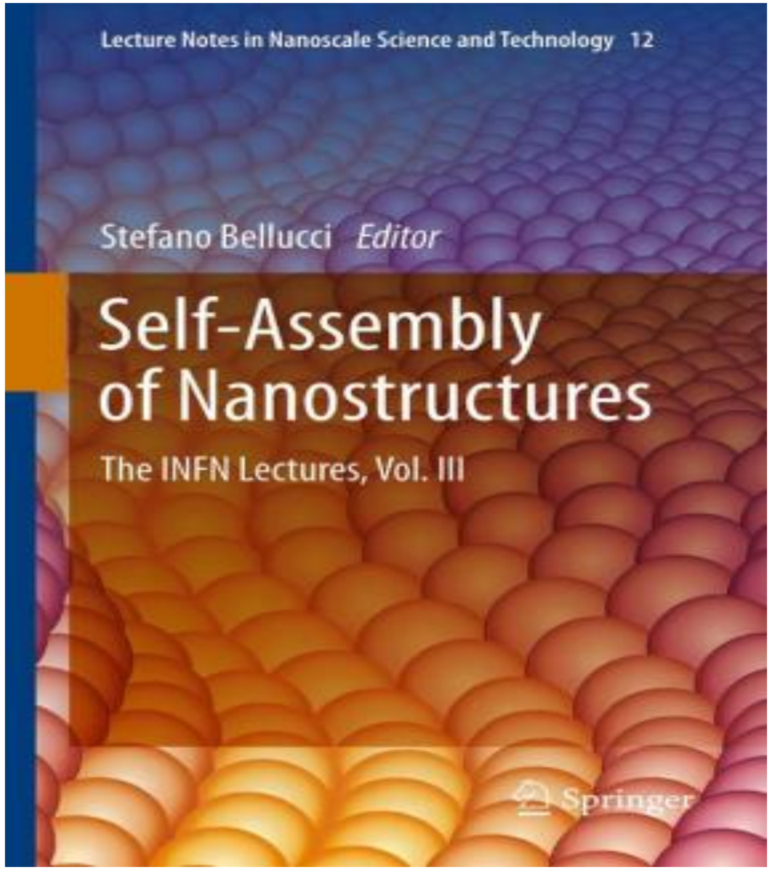
…and we finally get to the nanometer!!!

"Top – Down Bottom- Up"

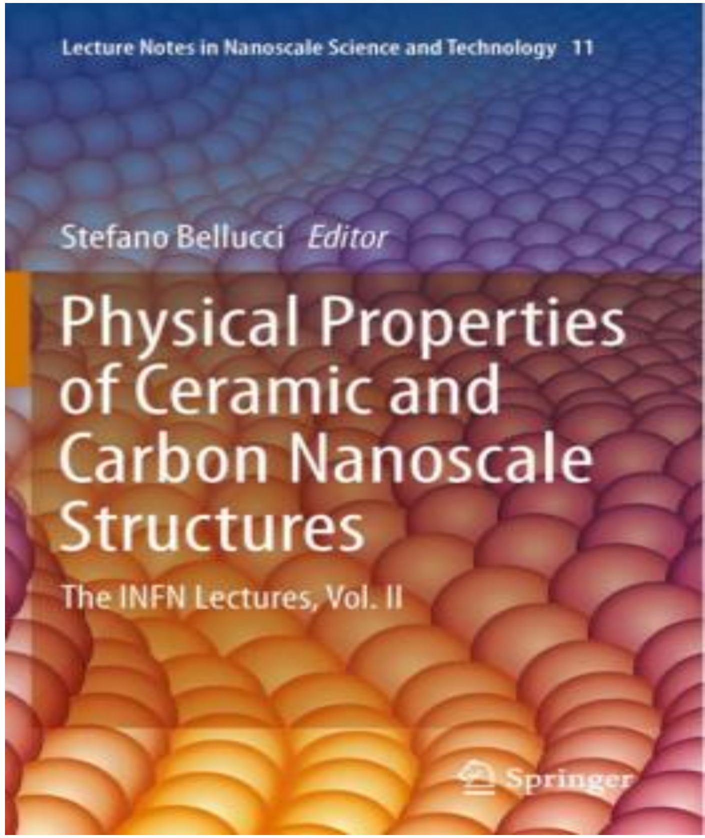




"BOTTOM-UP" APPROACH



- A concept introduced by Eric Drexler
- Process of costructing systems atom by atom, to the aim of
  - minimizing waste
  - increasing reactivity



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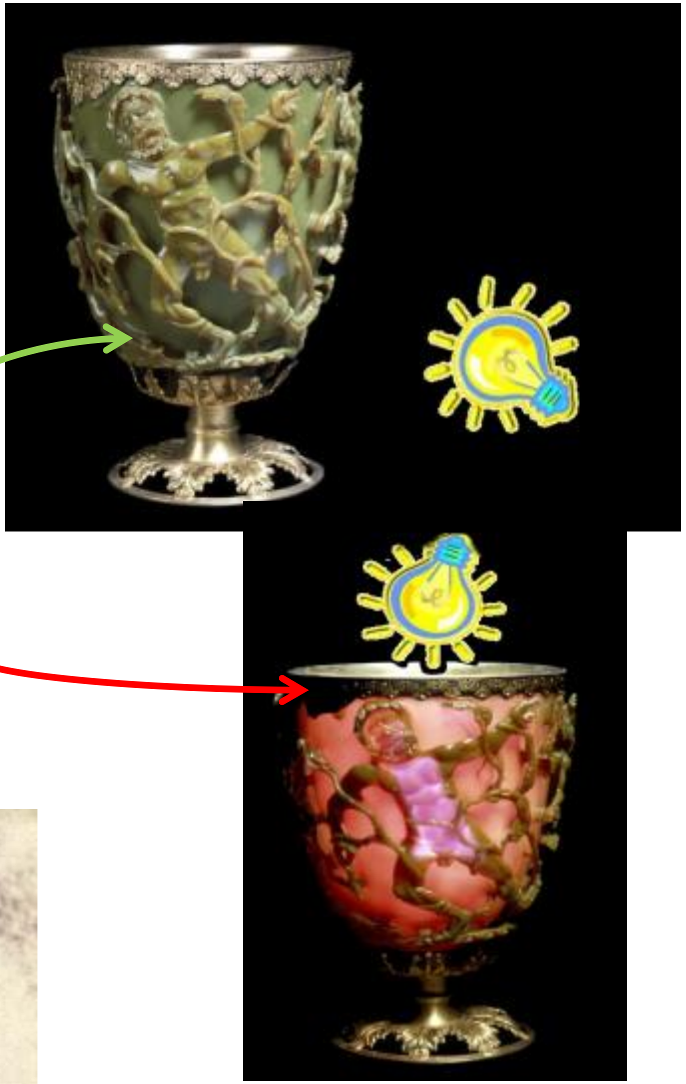
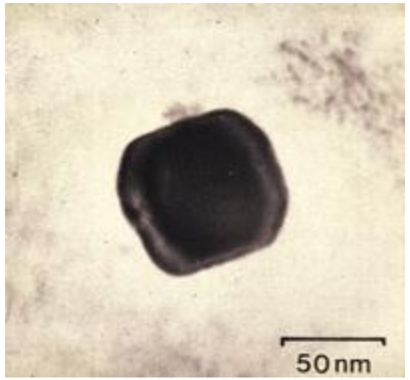
First example of nanotechnology!

Lycurgus Cup
(IV sec. CE,
British Museum)



It has a different coloration when observed in **reflection**, or in **transmission**, owing to the presence of nanoparticles of gold and silver.



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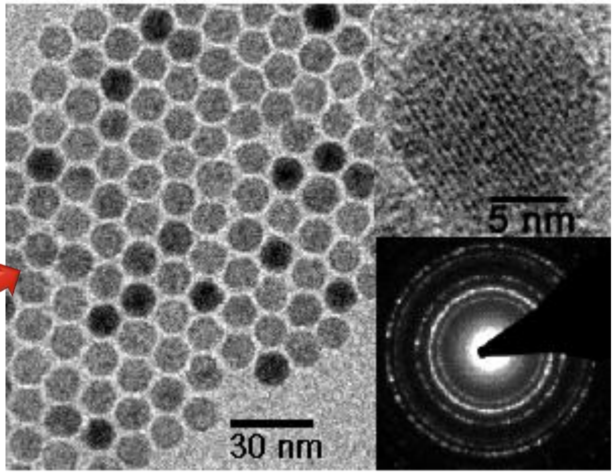
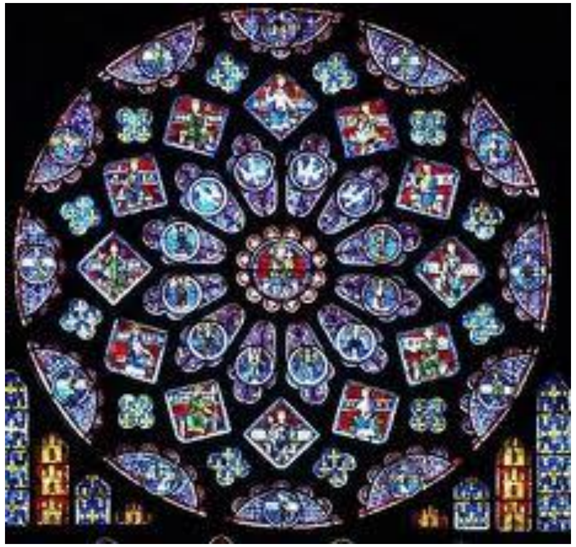
Another example of nanotechnology

Metal nanoparticles of different species
In the stained glass windows of medieval churches.





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Microscopy characterization

In **1931**, Max Knoll and Ernst Ruska invented the ***transmission electron microscope (TEM)***,
nearly 34 years after the discovery of the electron by J. J. Thomson.
M. Von Ardenna built ***the first protopy of Scanning Electron Microscope in 1938***, followed soon by the first commercial TEM, built by Siemens in 1939. The first commercial SEM was commercialized by Cambridge Instrument Company Inc. in 1965.

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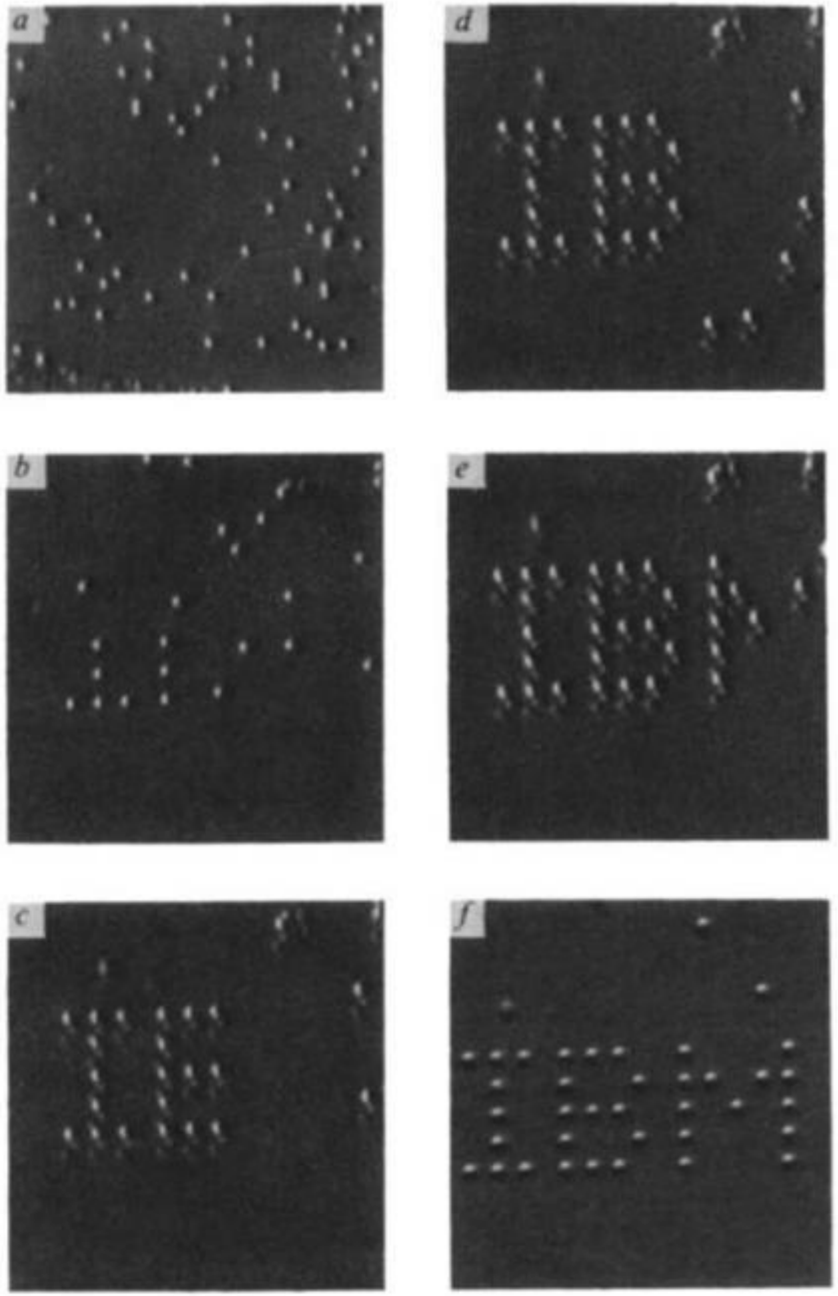
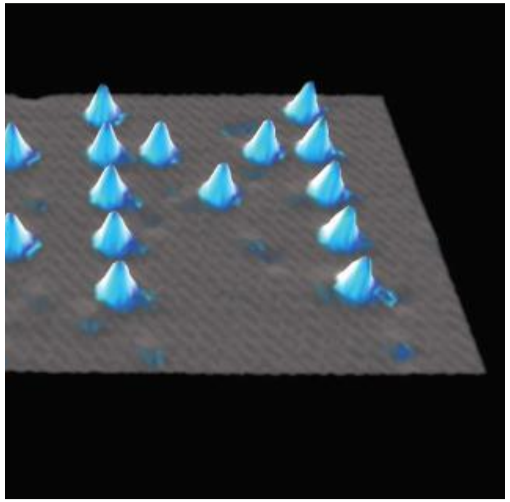
aracterization

Gerd Binnig and Heinrich Rohrer a introduced a new l scope that is not wavelength : Scanr Microscope (STM),



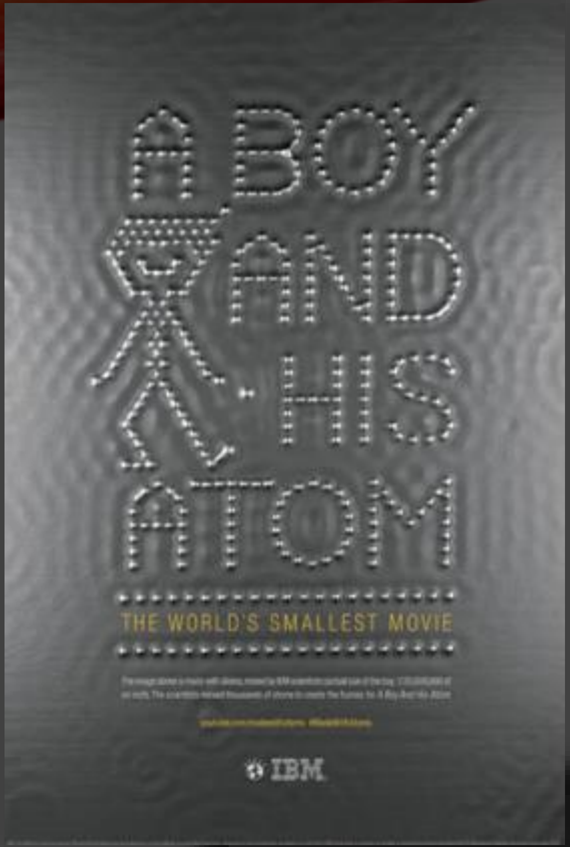
Eigler, Schweizer. *Nature* 1990

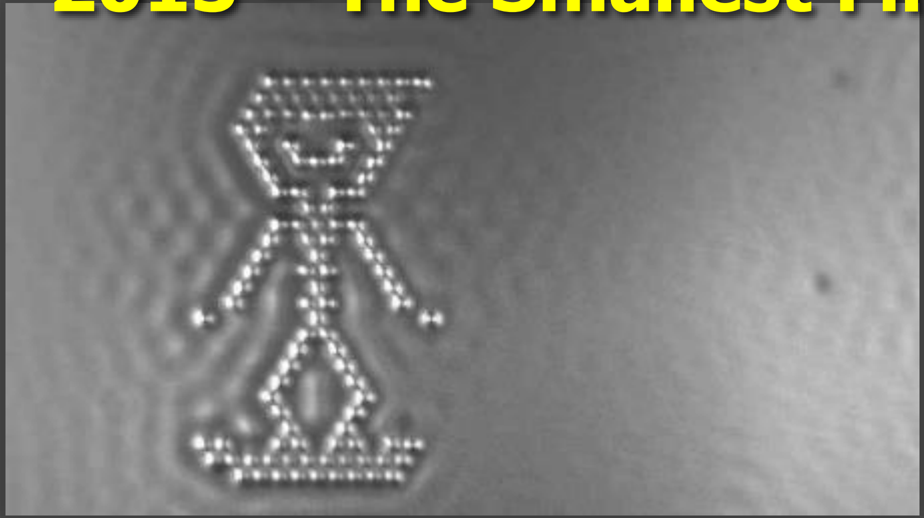
ı nickel (110) surface at ultralow bell "IBM" with the aid of an STM up at the IBM Almaden Research ok 22 hours to complete. The image zine in 1990 and formally ushered

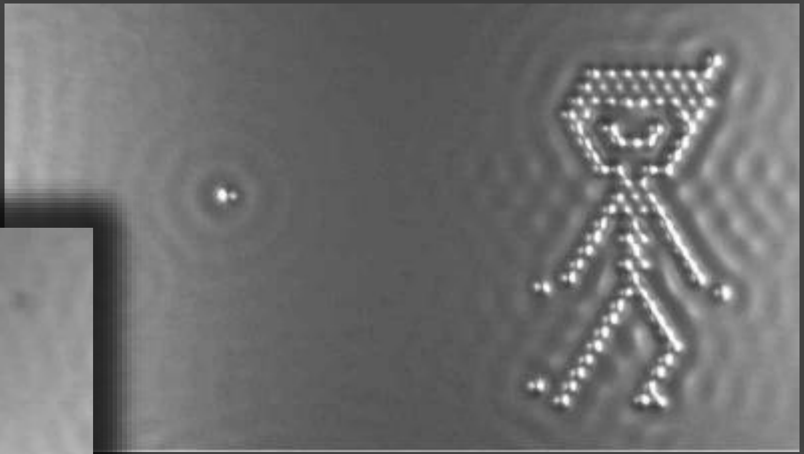


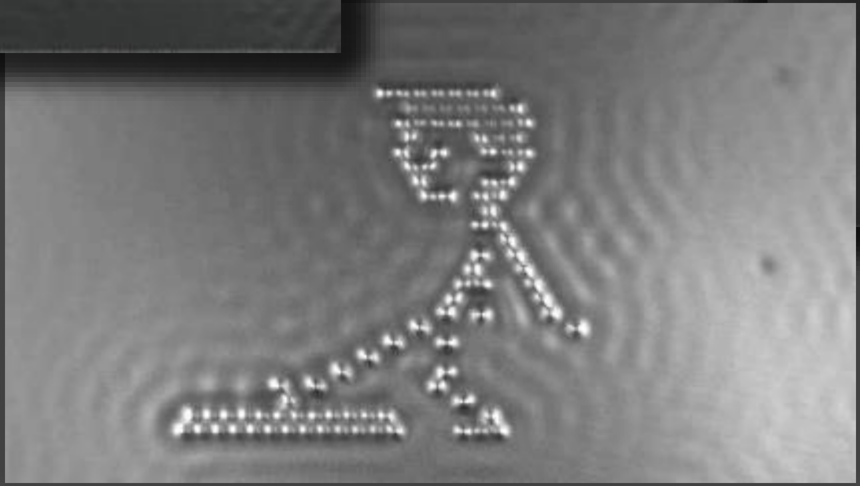
Binnig, Quate, and Gerber tomic force microscope e specific purpose of rfaces on the atomic scale lucting, 1985.

2013 – The Smallest Film in the World

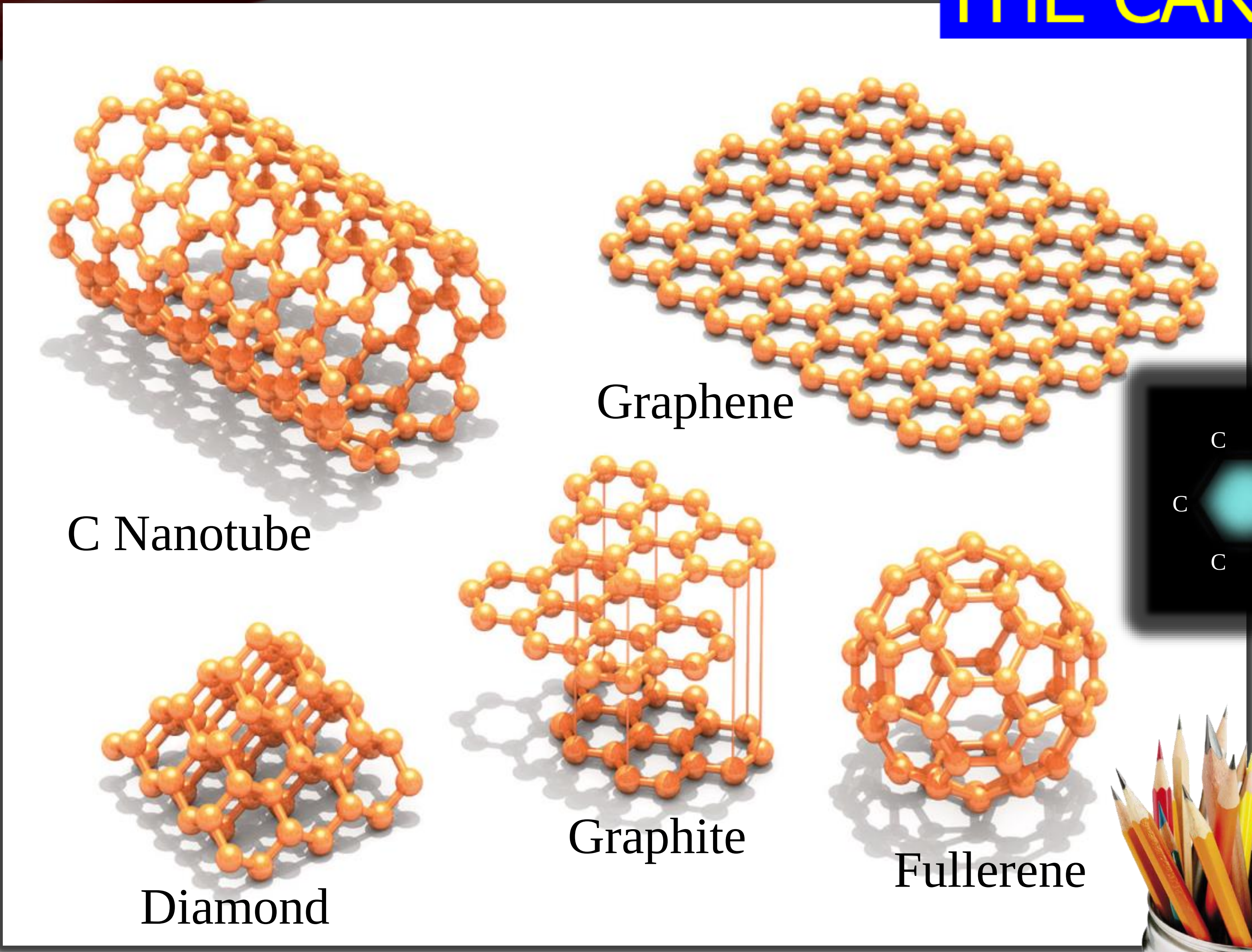


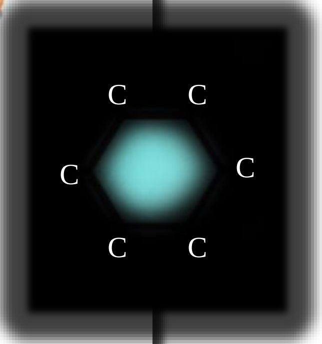






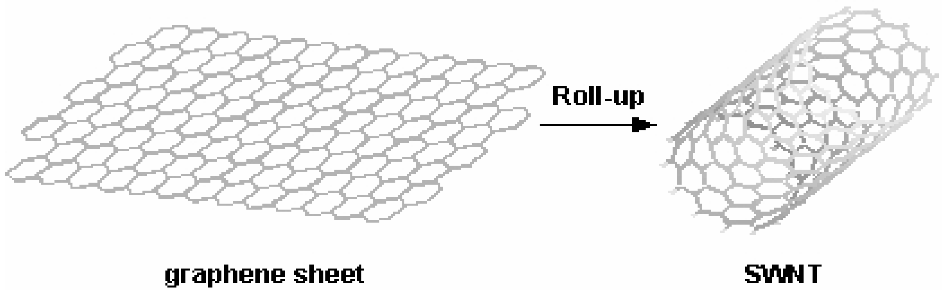
THE CARBON FAMILY

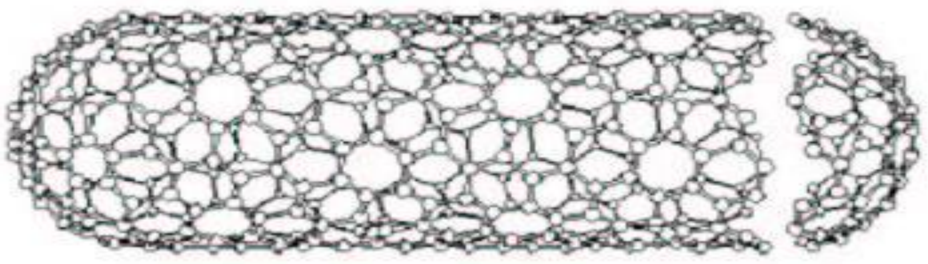


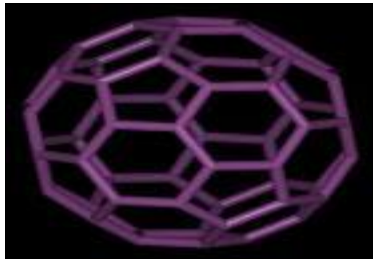


CARBON NANOTUBES

- Discovered in 1991 by **Sumio Iijima**, a researcher at Nec Labs in Tsukuba, Japan.
- Hollow cylinders, long and thin; they can be thought of a sheet of graphite (a hexagonal lattice of carbon atoms) rolled up into a cylinder, closed by two fullerene emispheres

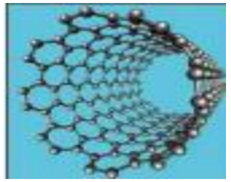






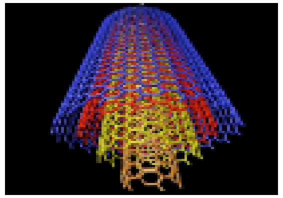
We can distinguish:

SWNT
(Single wall Nanotubes)



$\Phi = 1 \div 3$ nm
$L = 0.5 \div 10^4$ μm

MWNT
(Multi wall Nanotubes)



$\Phi = 5 \div 200$ nm
$L = 0.5 \div 200$ μm

WHAT'S SO SPECIAL IN A C NANOTUBE?

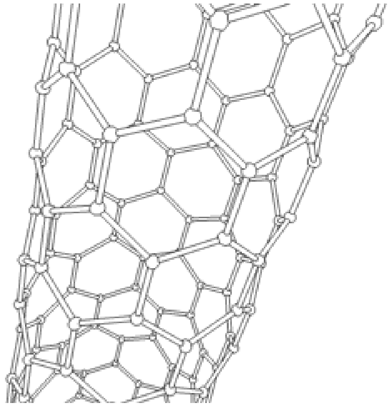
High aspect ratio (L/Φ) ⇒ one-dimensional structure

Ability to carry high currents, without overheating (current density 10^9 A/cm^2).

High thermal conductivity both at high and at room temperature (1800-6000W/m*K).

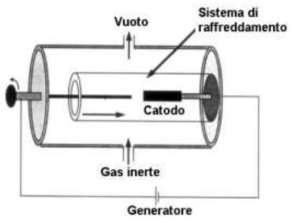
50000 times thinner than a human hair

High elastic modulus (up to 1 Tpa) and high tensile strength (150 Gpa).



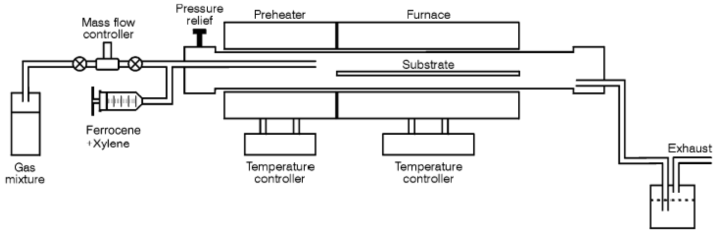
METHODS FOR CNTS SYNTHESIS

✓ *Arc discharge:*



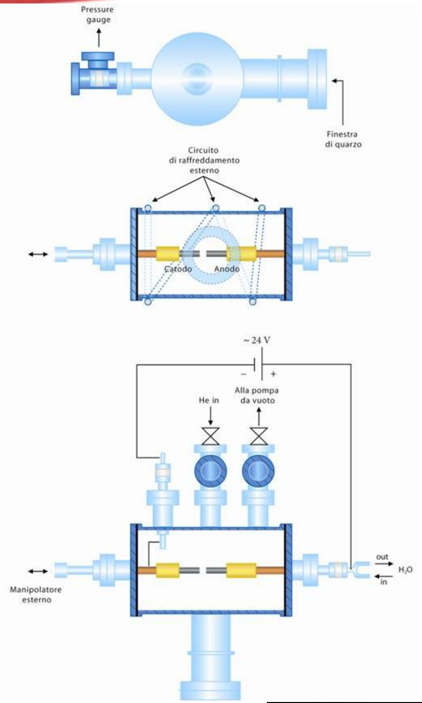
✓ *Laser ablation:*

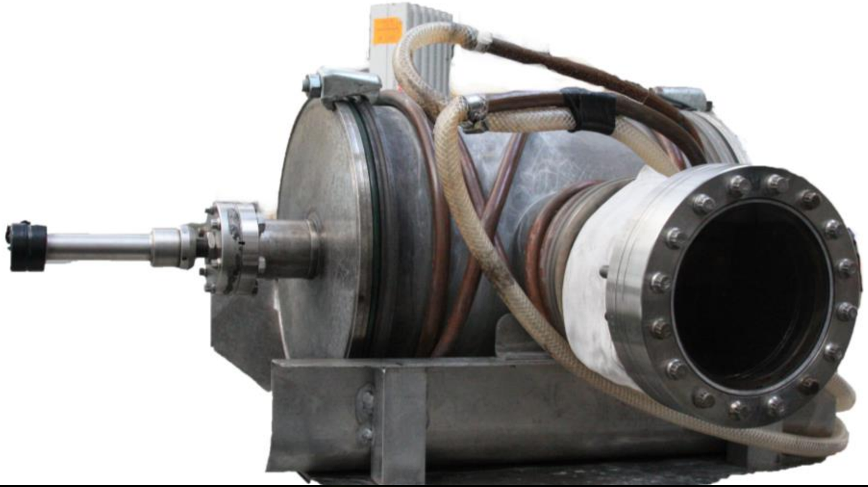
✓ *Chemical vapour deposition:*

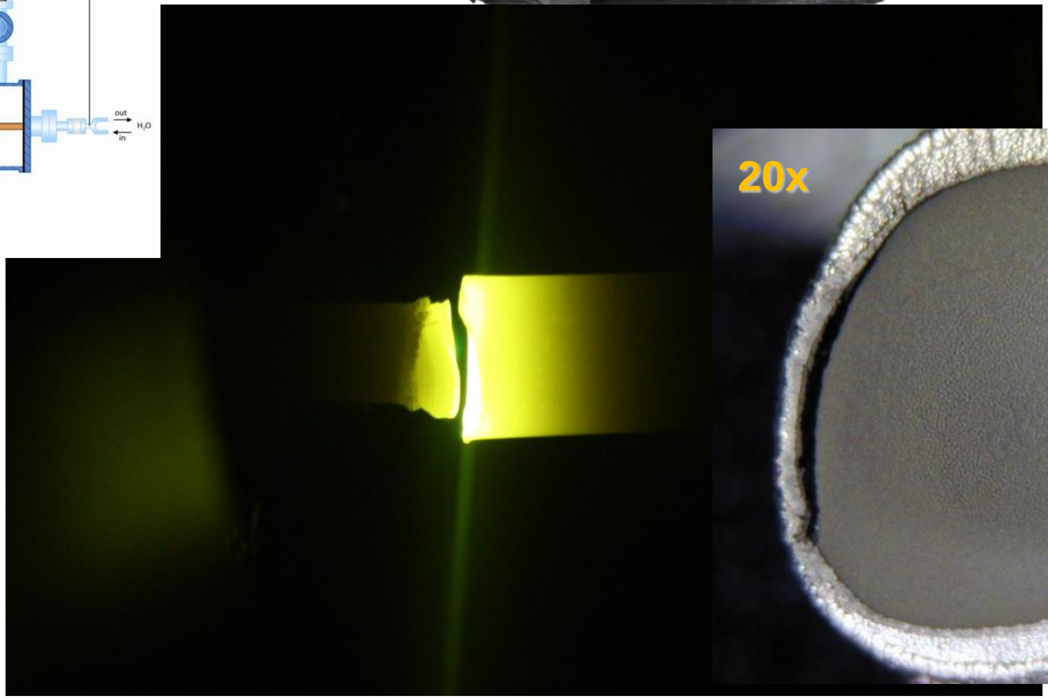


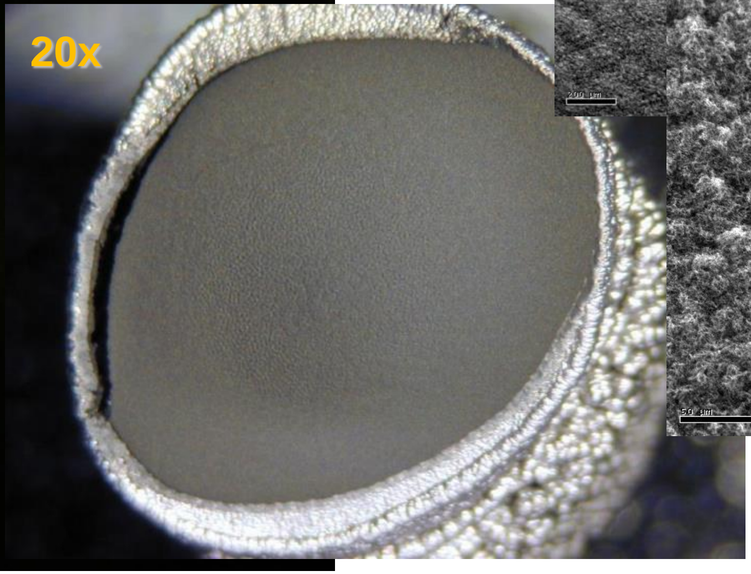
Pros	Cons
Very simple process. **CNTs of high quality and purity, with few defects.**	**Dispersion in CNTs size.** **Low amount of CNTs achievable** **Need for purification from unwanted forms of C (onions, amorphous).**
Long CNTs. **Controllable pipe diameters.**	**Low amount of CNTs achievable.**
Possibility to grow CNTs oriented and according to predefined geometries. **High amount of CNTs.**	**Need for a catalyst for decomposition of hydrocarbons.** **High density of both local and topological defects.**

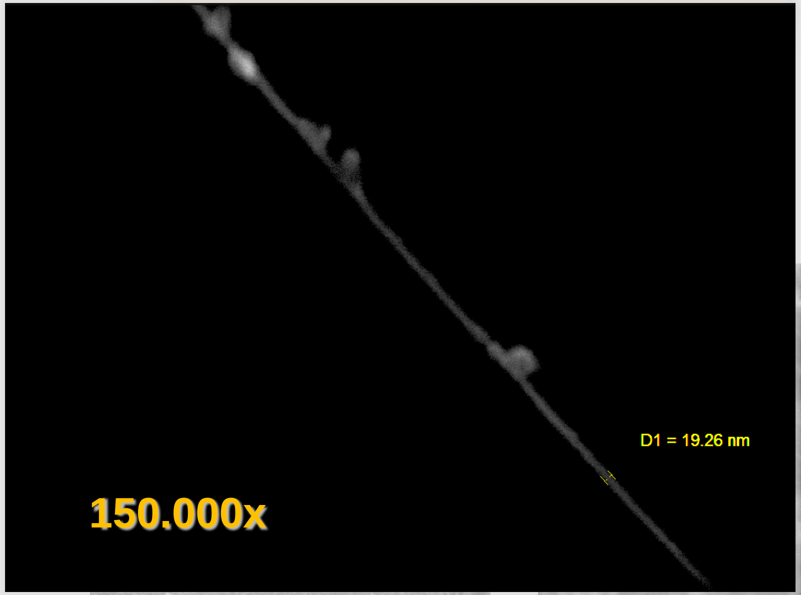
Synthesis

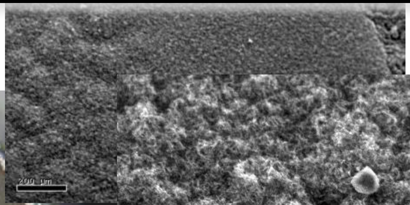

Pressure gauge
Finestra di quarzo
Circuito di raffreddamento esterno
Catodo
Anodo
~ 24 V
He in
Alla pompa da vuoto
out
H_2O
in
Manipolatore esterno

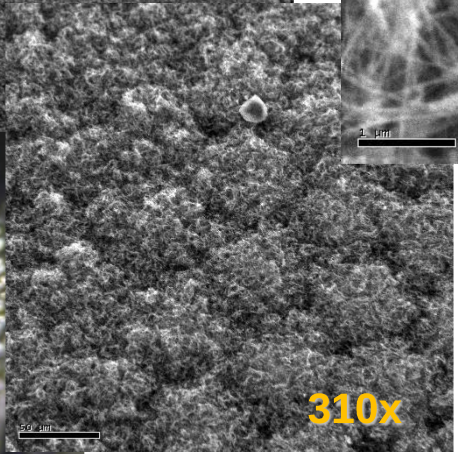


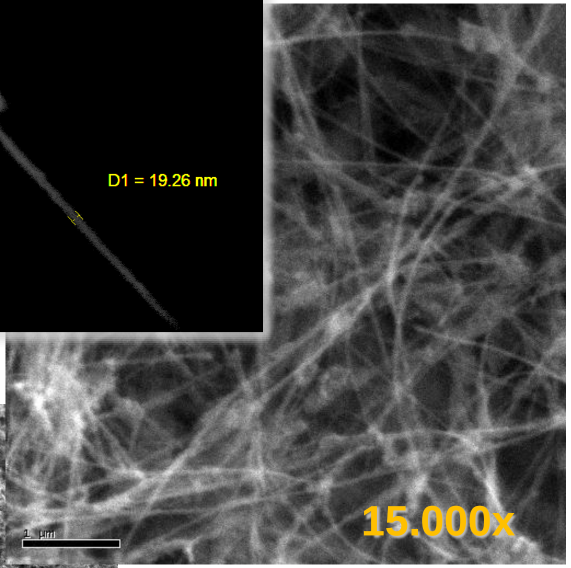



20x


D1 = 19.26 nm
150.000x




310x


15.000x

FERRARI F2007

- La Ferrari F2007 was a concentrate of nanotechnology:
- Carbon nanotube brakes
- Car body made of ultra-light material obtained using carbon nanotubes
- Special tyre compound using C nanotubes composites

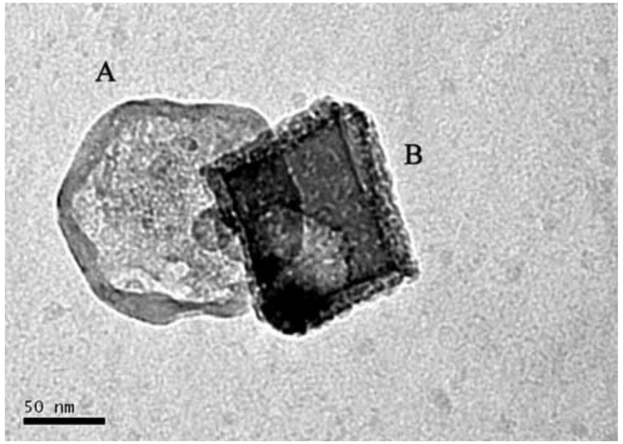
Nano for Future Transportation & Mobile

Symbiosis Car: Symbiosis Vehicle Runs on Solar Piezoelectric Energy

Samsung Flexible Mobile: display technology known as an OLED (organic light emitting diode) (active matrix light emitting diode) screen. As the OLED pixels create their own light source, they don't need a back light like LCD screen technology, but the circuitry to control the pixels is fused into glass.

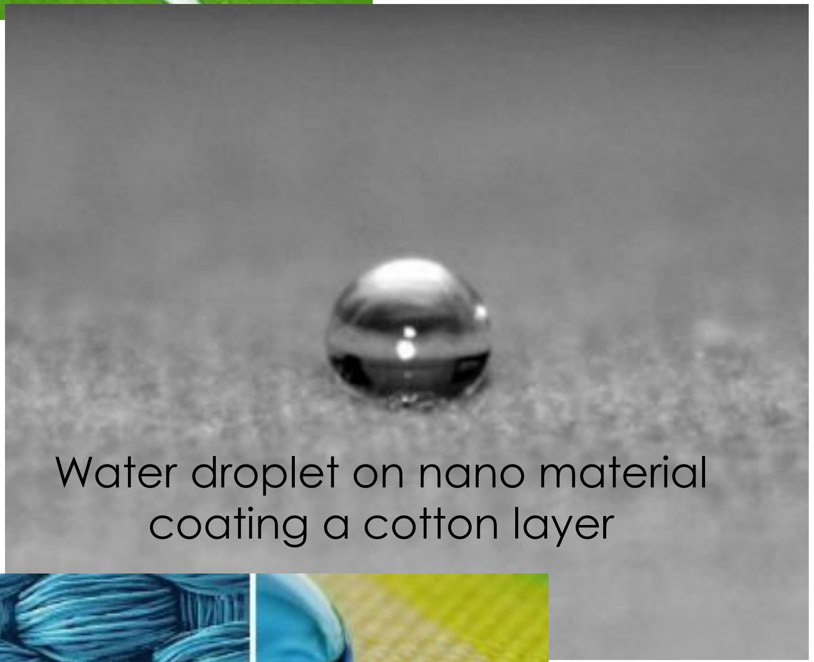
Nanotechnology in Restoration!

Calcium hydroxide nanodispersions used for nanocleaning; TEM Images of two nano-sized particles in suspension:
$Ca(OH)_2$ hexagonal (A),
$CaCO_3$ prismatic (B)



Beato Angelico's fresco at San Marco's Abbey in Florence

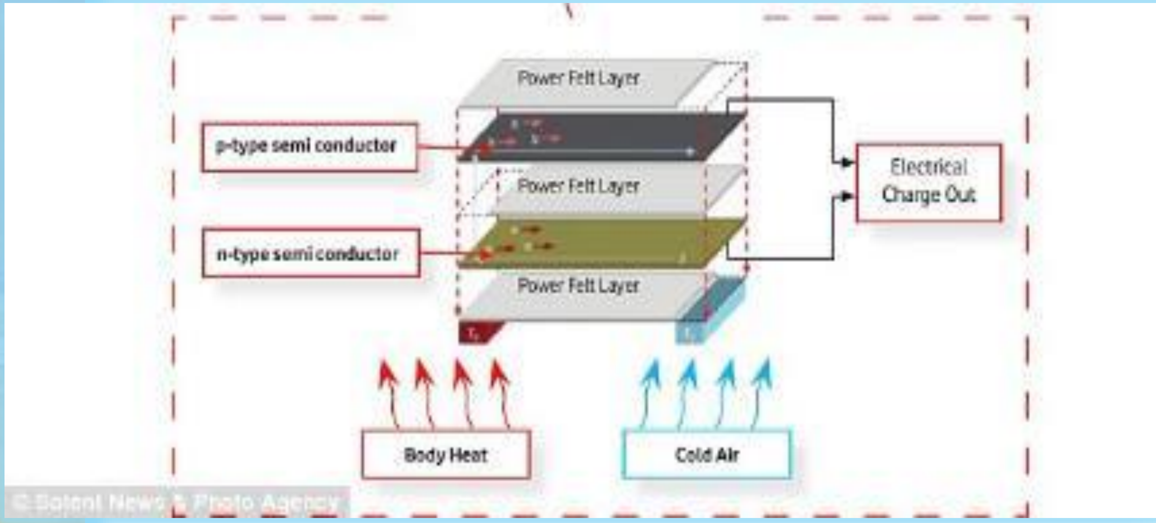
Biomimetic & Cleaning



Water droplet on nano material coating a cotton layer

Nanoparticeles having diameter smaller than 100 nm are coating the matrix

Nano – ENERGY!

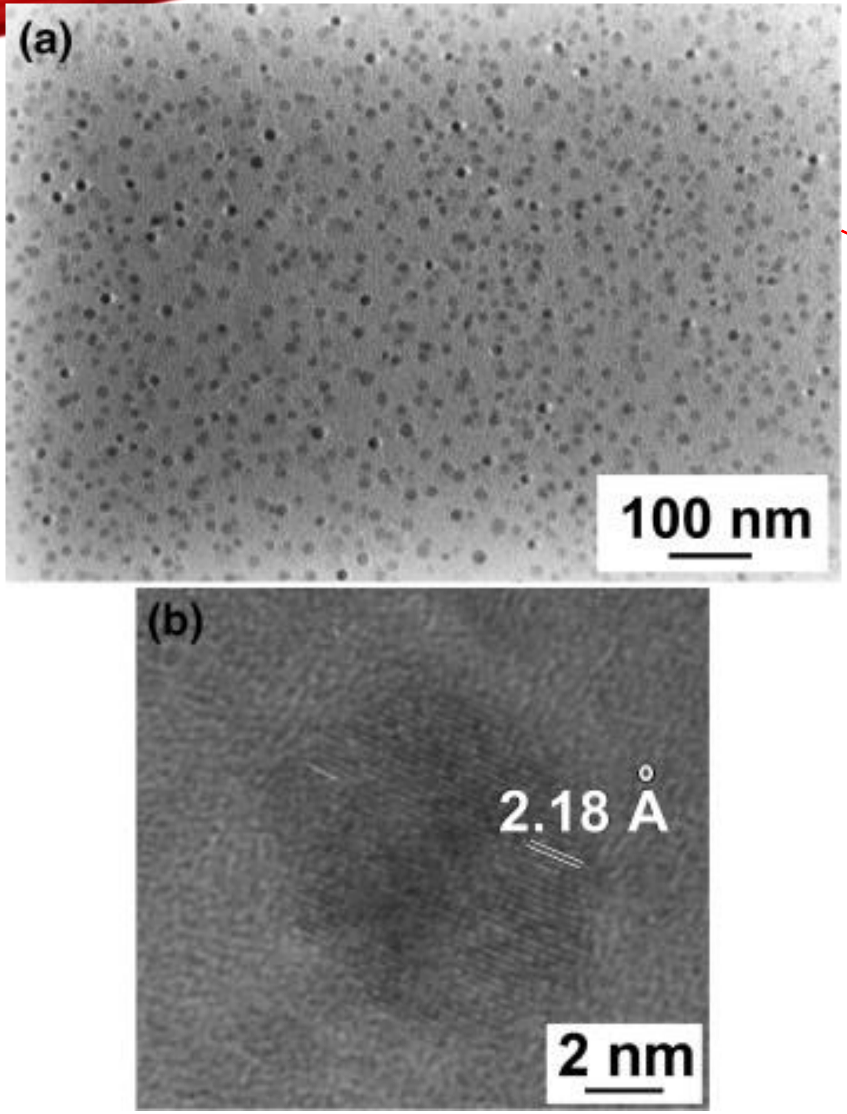


Il Power Felt è in grado di produrre 0,1 v/mq in presenza di un Δt di 17°C.
Incrementando il Δt, la superficie (o la dimensione dei nanotubi di carbonio, o gli strati) del "tessuto" è possibile incrementare l'energia prodotta.

Wake Forest University's Center for Nanotechnology and Molecular Materials

1. IL POWER FELT

Nano – Cosmetic !



High UV protection through nanoparticles' dispersion

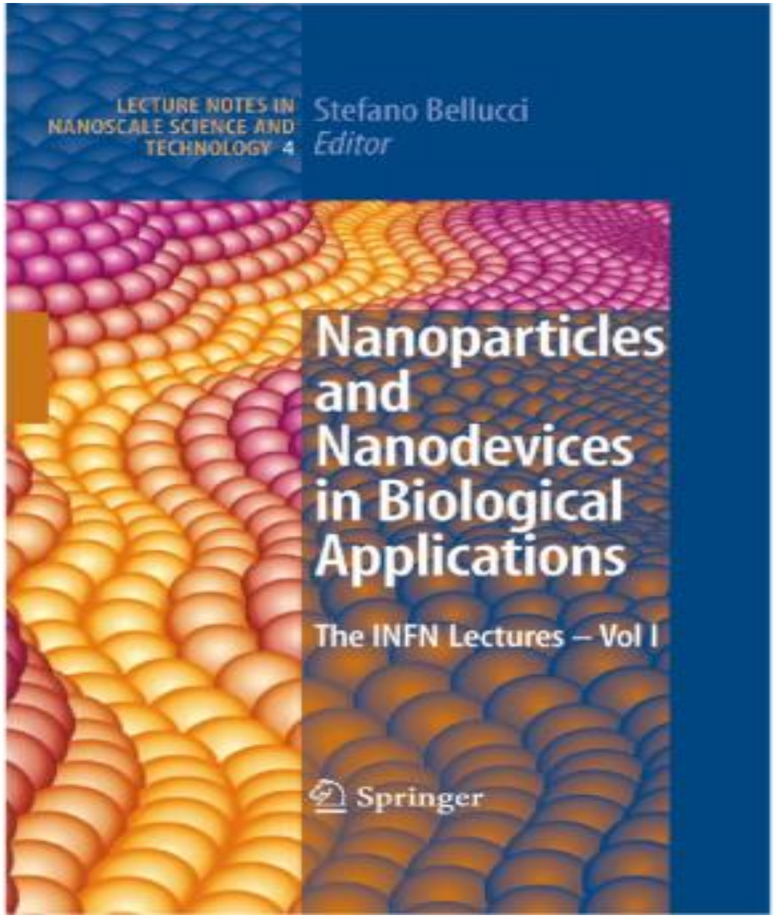
USES OF NANOTECHNOLOGIES

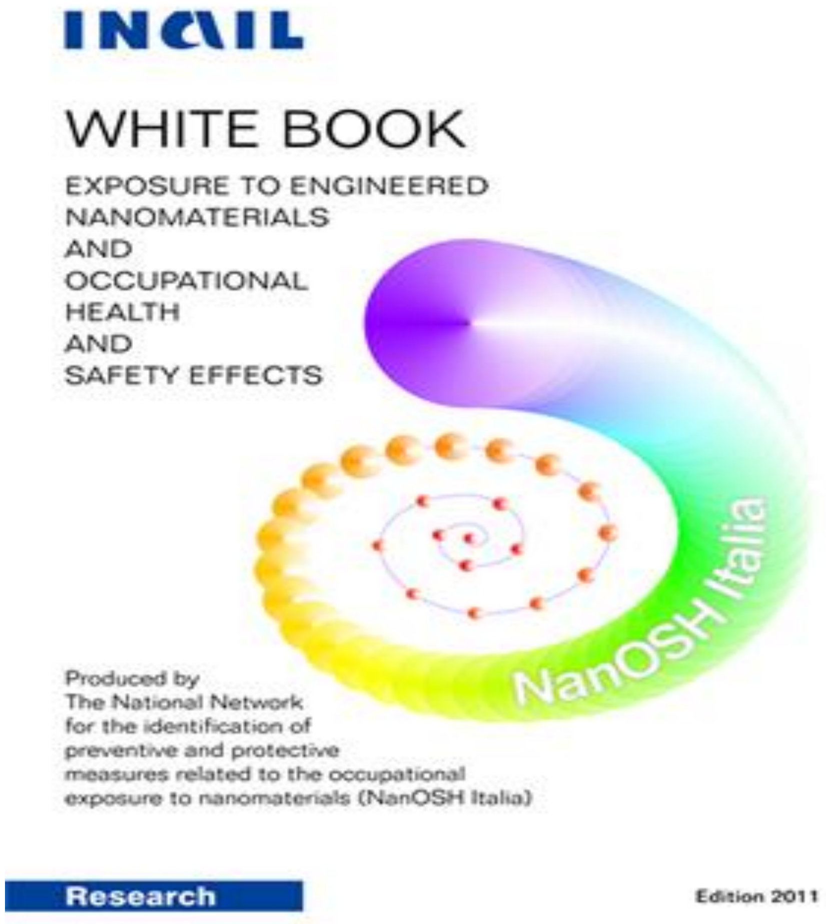
- **Pervasive** and **enabling** technology
- Utilization of Nanotechnology is found everywhere (**ubiquitous** technology)
- Solar energy, batteries, weapons, instrumentation design and manufacture... in any application area, nano-technologies could play a role in the future.
- Given the multiplicity of their uses, we must necessarily be concerned about their **impact on the environment and human health**, in particular on professionally exposed workers.

IMPACT OF NANO ON HEALTH AND ENVIRONMENT

IMPACT ON ENVIRONMENT AND HEALTH

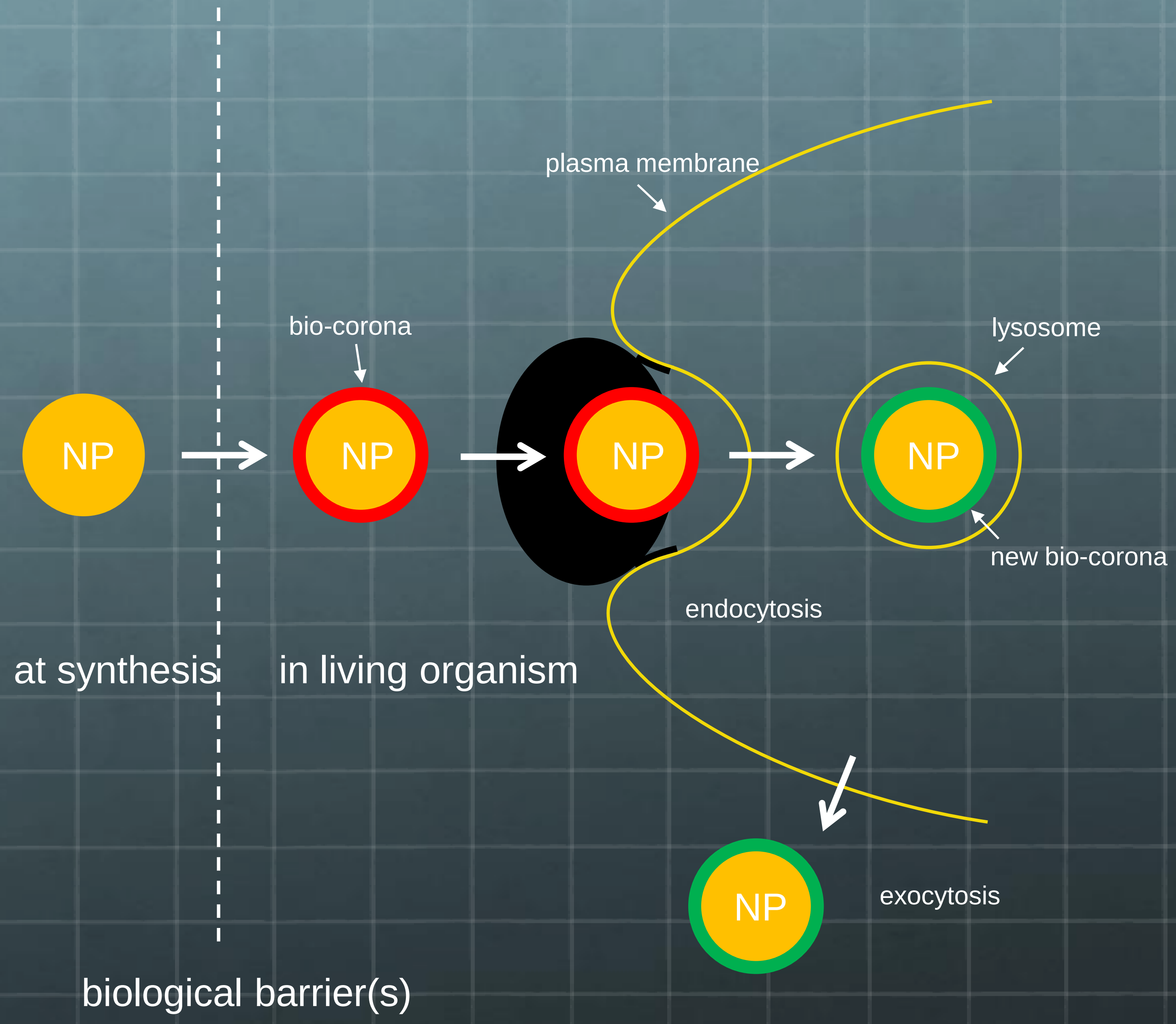
- Possible instability of certain nanostructures
  - E.g. potential problem from “fullerene” dissolved in water which can bind to DNA, hence affecting structure, stability and biological functions of DNA molecules





GRAND CHALLENGES OF NANOTECHNOLOGY

- The materials are difficult to handle and it is difficult to keep them stable.
- Understanding the characteristics of nano materials
  - A single particle of silicon does **not** behave like bulk silicon
  - Dependence on size, shape, and surroundings of the particle (e.g. ***bio corona***)



plasma membrane
bio-corona
lysosome
NP
NP
NP
NP
new bio-corona
endocytosis
at synthesis
in living organism
NP
exocytosis
biological barrier(s)

NANOPARTICLES PRODUCED DURING COMBUSTION PROCESSES

- **Epidemiology**
- **Toxicology**

Nanoparticles in use in **industry**

Nanotechnology

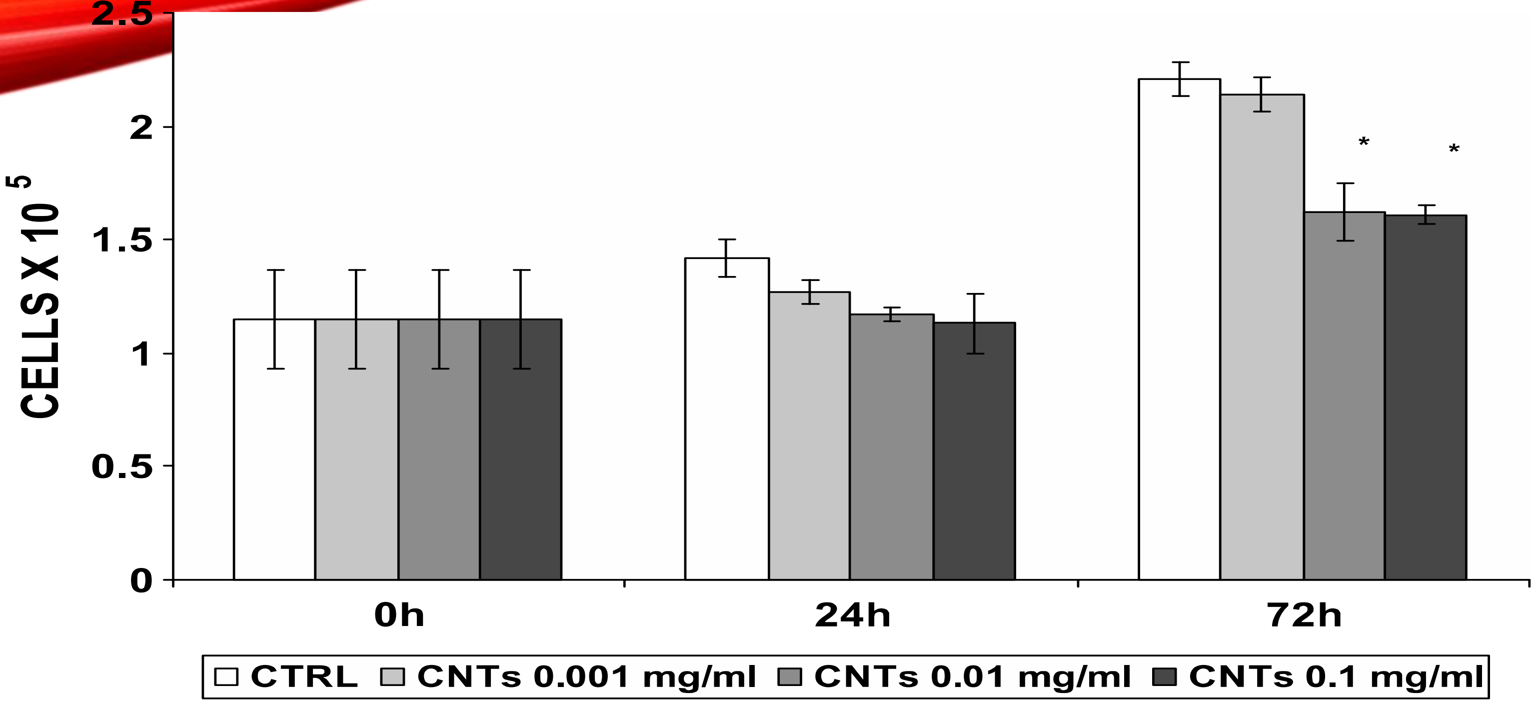
FOR NANOTECHNOLOGIES CURRENTLY .....

Application

Toxicology and industrial hygiene

Norms and regulations

Toxicity



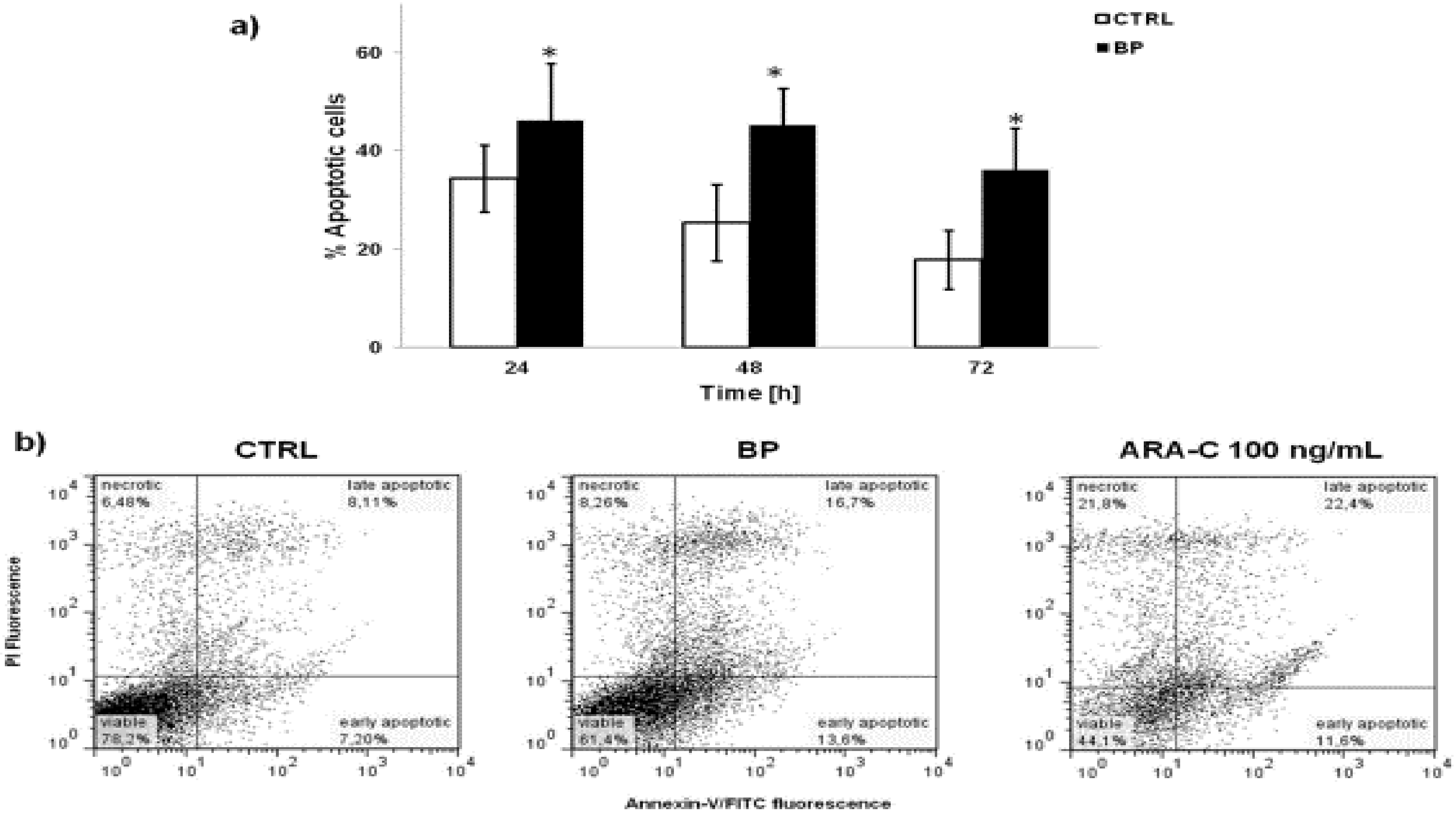
Effects of MWCNTs on the proliferation of the human arterial smooth muscle cells (hSMCs). The cells were treated with MWCNTs at concentrations from 0.001 to 0.1 mg ml−1 for 24 and 72 h. Cell proliferation was determined by a count performed by a particle count and size analyzer. Each column represents the mean value ± SD of three separate experiments performed in duplicate. $* \, p < 0.01$ versus CTRL.

Carbon nanotubes toxicology and effects on metabolism and immunological modification in vitro and in vivo

M Chiaretti, G Mazzanti, S Bosco, S Bellucci, A Cucina, F Le Foche, GA Carru, S Mastrangelo, A Di Sotto, R Masciangelo, AM Chiaretti, C Balasubramanian, G De Bellis, F Micciulla, N Porta, G Deriu, A Tiberia - *Journal of Physics: Condensed Matter Volume 20 Number 47 , 26Nov. 2008*

Toxicity

The cytoxicity evaluation of MWCNT buckypaper treatment on human and cancer cells was carried out on **human colorectal, breast and leukemic cancer cell lines in vitro**, while having no effect on proliferation and viability of normal human arterial smooth muscle cells and human dermal fibroblasts in vitro.



Growth inhibition, cell-cycle alteration and apoptosis in stimulated human peripheral blood lymphocytes by multiwalled carbon nanotube buckypaper, O Zeni, A Sannino, S Romeo, F Micciulla, S Bellucci, MR Scarfi Nanomedicine, 1-10 (2014)

Cytotoxicity of Multiwalled Carbon Nanotube Buckypaper in Human LymphocytesO Zeni, A Sannino, S Romeo, MR Scarfì, L Coderoni, F Micciulla, I Sacco, ...

Sensors and Microsystems, 489-493 (2011)

Toxicological and biological in vitro and in vivo effects of carbon nanotubes buckypaper S Bellucci

Semiconductor Conference, 2009. CAS 2009. International 1, 107-116

Nanomedicine & Cytotoxicity

Nanomedicine is the preservation and improvement of human health using molecular tools and molecular knowledge of the human body

Since over two decades the potential environmental and occupational impact is studied of carbon nanotubes, which exist in many different forms and can be chemically modified and/or functionalized with biomolecules.

«ACCIDENTAL» ARTIFICIAL NANOPARTICLES

«Traffic jams, LA California»

«Gulf of Mexico, off-shore oil well burning»

«Bari, Italy, 2006: implosion of Punta Perotti residential complex »

THE UNIVERSE OF EXPOSURE TO NANOMATERIALS

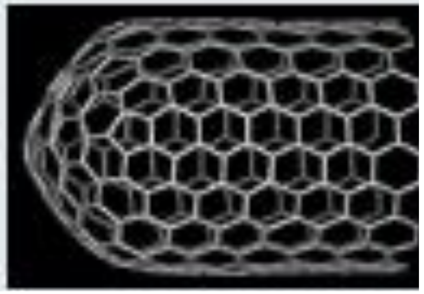
Accidental Exposure to NP originating in combustion processes

NP diesel, soldering fume, termodegradation of plastics

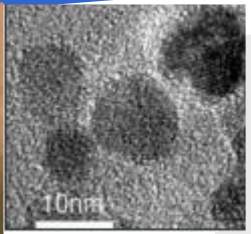
Accidental Exposure to newly synthetized materials

Carbon black, TiO_2

Accidental Exposure to newly synthetized and modified/ functionalized NP



Carbon nanotubes

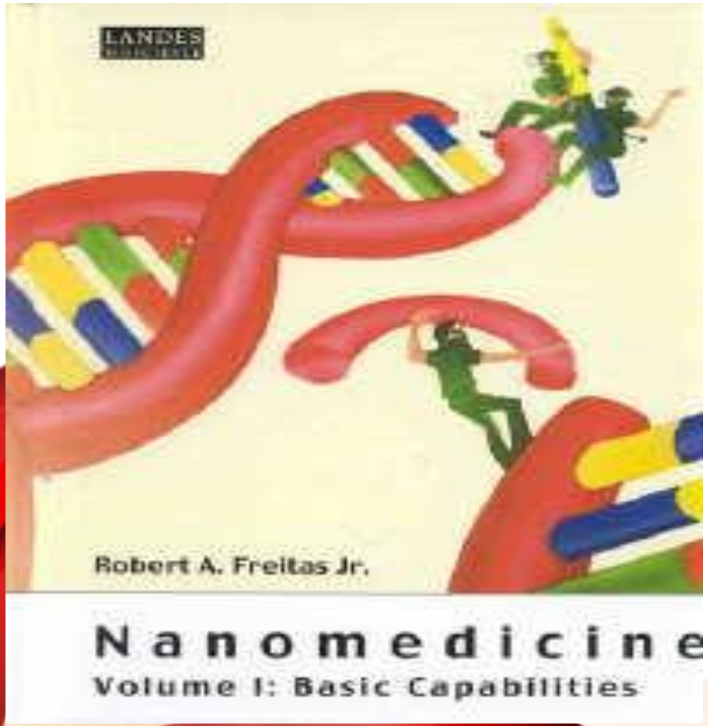


Deliberate Esposure deliberata to NM in biomedicine

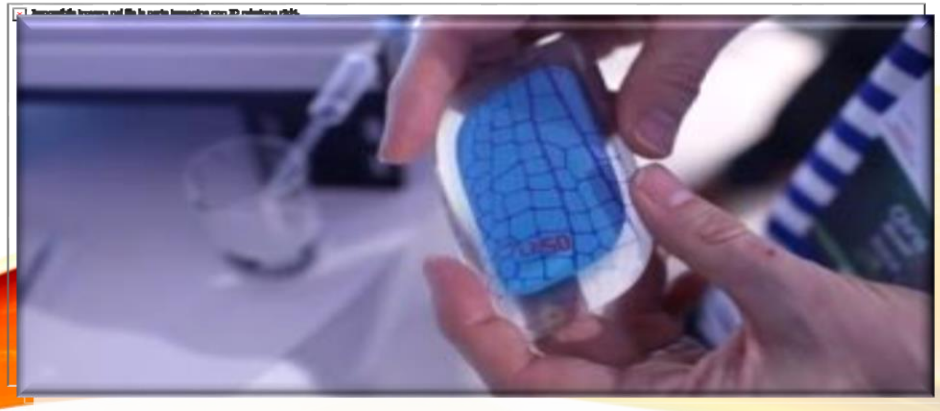
Dendrimers, fullerenes, *quantum dots*

ENGINEERED NANOPARTICLES (ENMs)

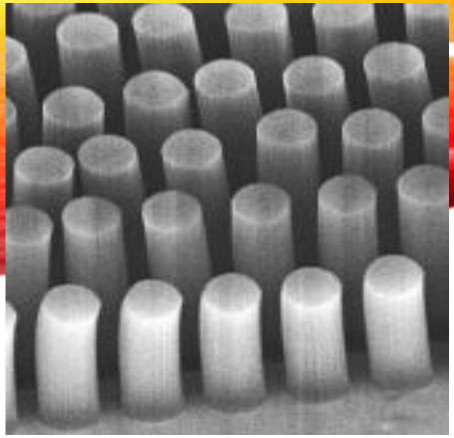
Nanomedicine as a single cell medicine

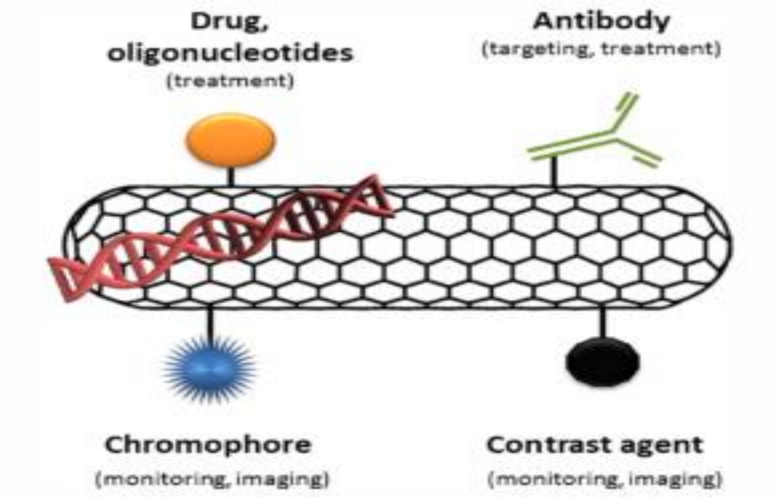


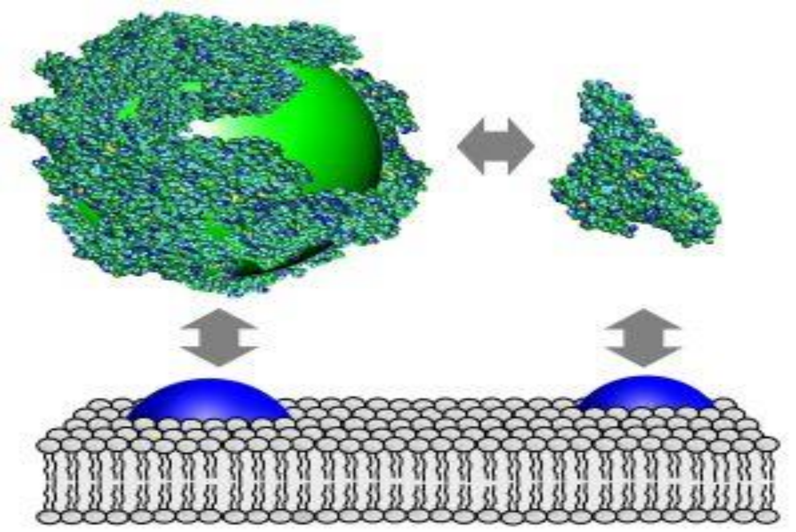
...no more windshield wipers…

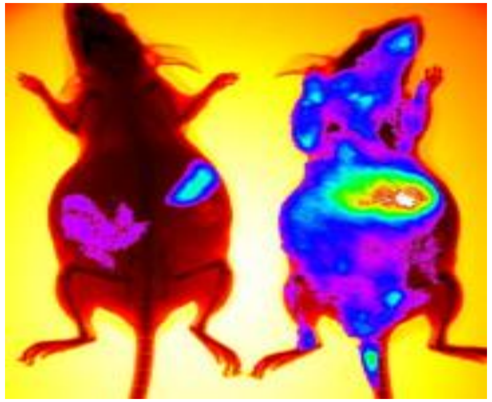


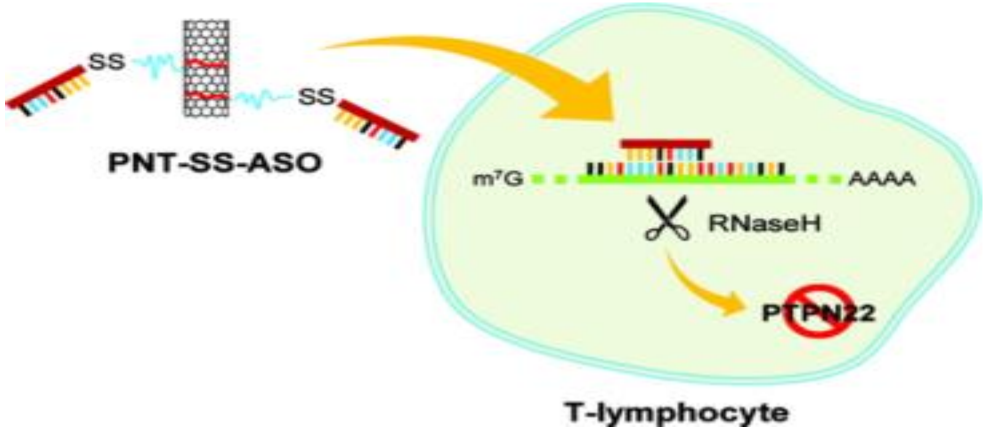
…or «fingerprints» on displays











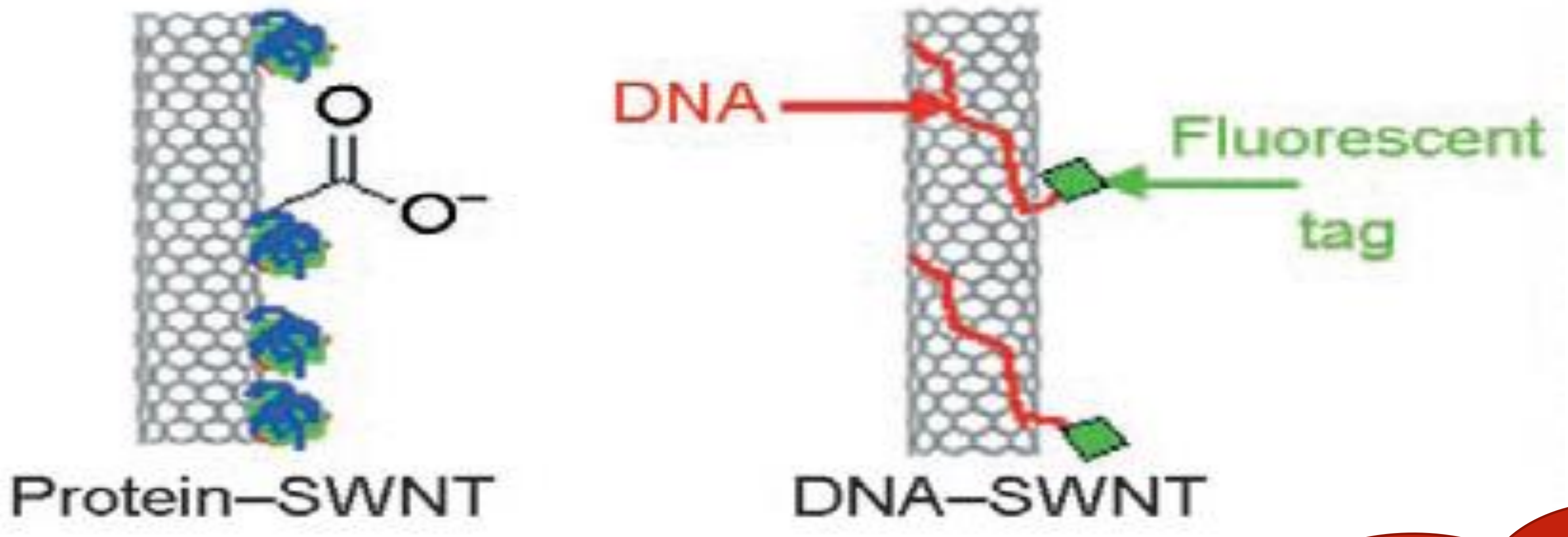
Nanotubes as seen by a physicist/chemist

Modified by a pharmacologist

Studied by a biologist

Seen by a physician

NANOMATERIALS CAN BE ALSO MADE BY ORGANIC AND INORGANIC PARTS ….



Possibilities become infinitely many

……

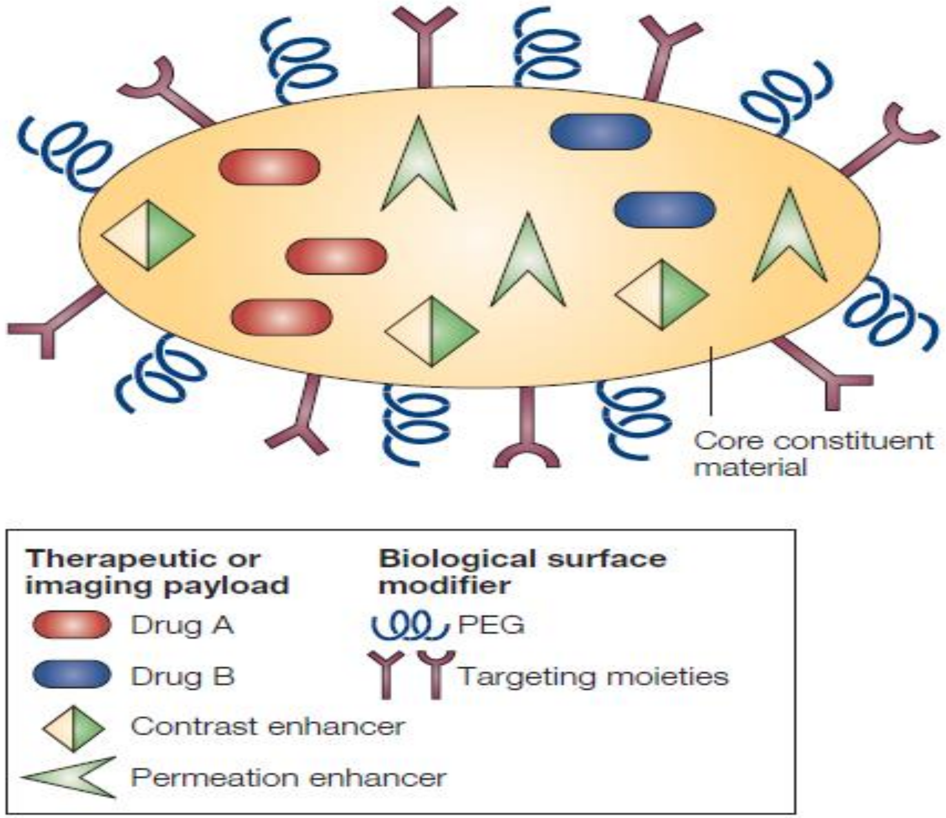
MULTIFUNCTIONAL NANOPARTICLES.

- CAPABILITY TO CARRY ONE OR MORE THERAPEUTIC AGENTS;

- MOLECULES FOR TARGETING (CONJUGATED ANTIBODIES OR OTHER AGENTS FOR RECOGNITION);

- ELEMENTS FOR SIGNAL AMPLIFYING AND FOR RECOGNITION;

- ELEMENTS FOR STABILIZATION (CONSERVATION IN CIRCLE) AND FOR ENHANCING CAPABILITY TO PENETRATE



Synthesis and characterization

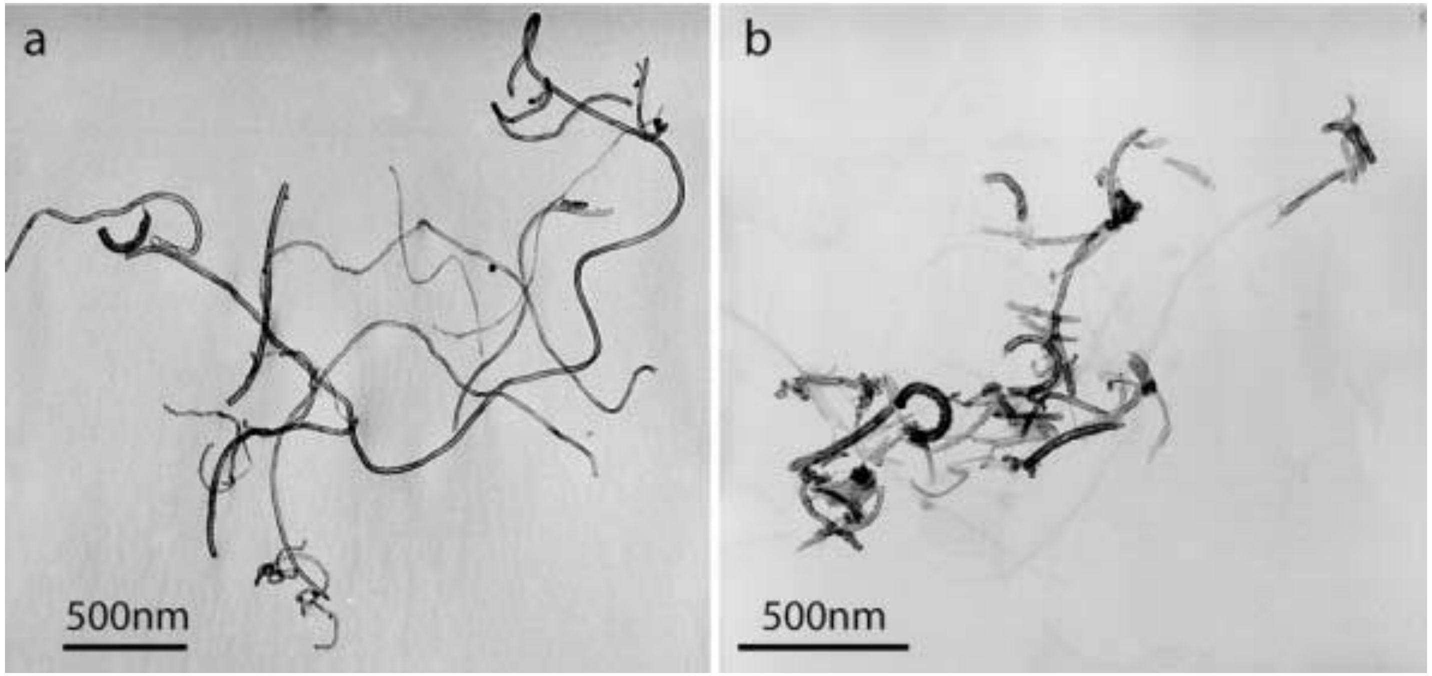


Fig 1: Multi-walled carbon nanotubes before (a) and after (b) oxidation in nitric acid.

The oxidized CNT (CNT-COOH) were shorter and straighter (Fig. 1b).

Synthesis and characterization

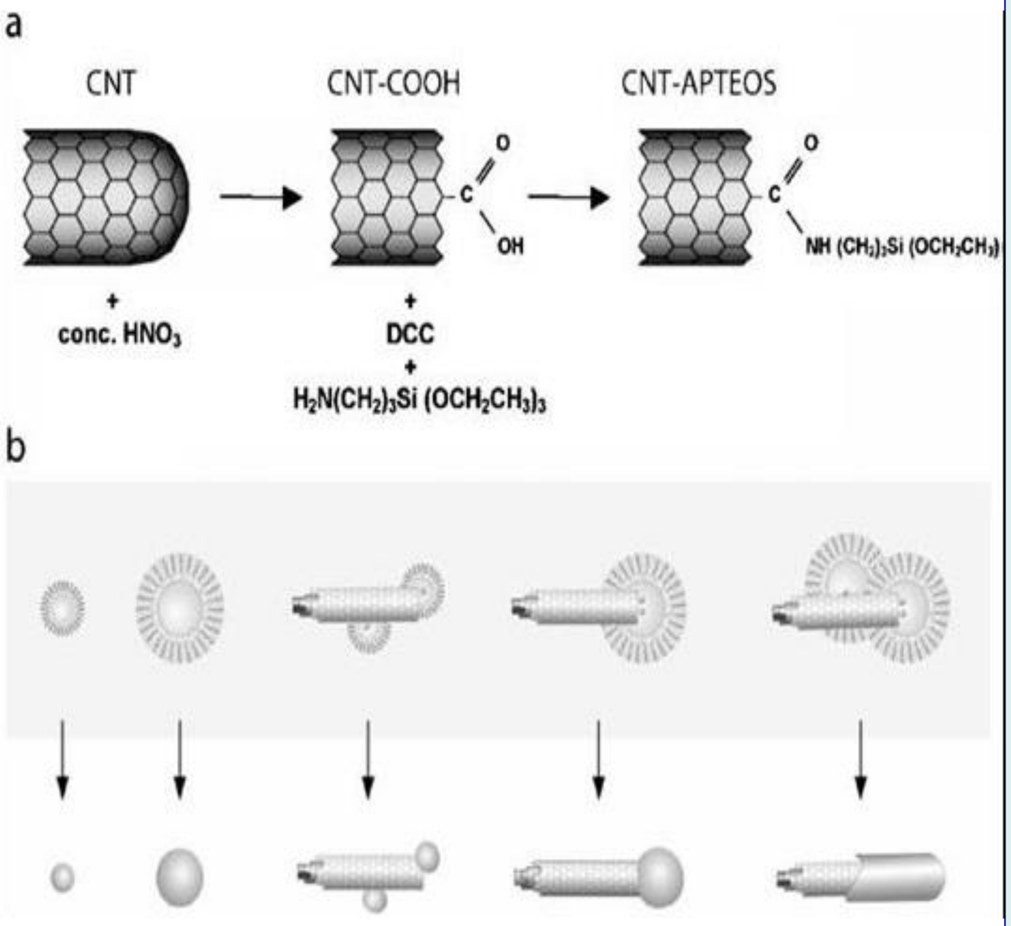


Fig. 2: Scheme for preparing the CNT–nanoparticle composite.

(a) Oxidation and preparation of the CNT-APTEOS precursor.

(b) Formation of silica nanobeads in reverse micelles in a water-in-oil microemulsion. Nanobeads are covalently linked to the CNT only at locations functionalized with triethoxy-silane groups (dots inside the micelles), while the bare graphitic wall of the pristine CNT did not associate with reverse micelles.

Their carboxylic acid groups greatly facilitated their dispersion in aqueous solutions, as well as their further functionalization (Fig. 2a).

Synthesis and characterization

Using these procedures, we obtained new CNT–nanocomposites with covalently attached silica nano-beads. Non-oxidized CNT (with negligible COOH content) do not support any composite formation.

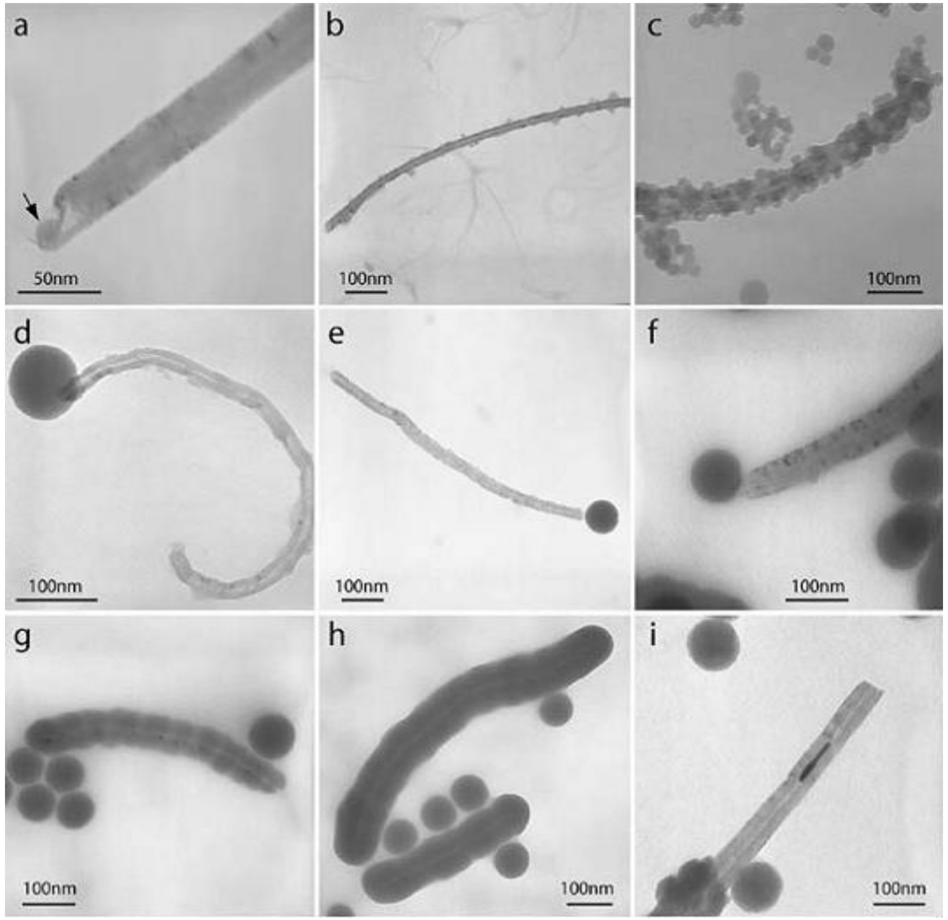
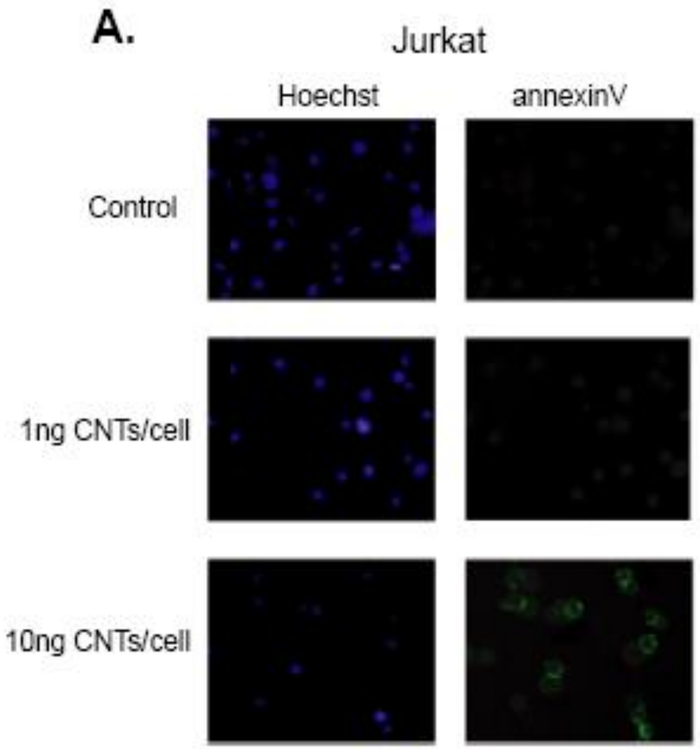


Fig. 3: Transmission electron microscopic images of the CNT–nanocomposites prepared using conditions for small (a–c) or large (d–i) silica nanobeads.

The arrow in panel (a) indicates a nanobead at the tip of the CNT.

The arrow in panel (i) indicates a polymerized silica inside a CNT.

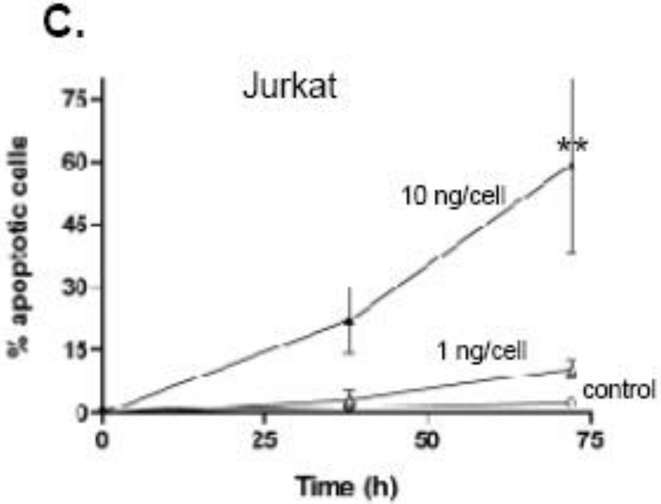
Cytotoxicity of MWNT: apoptosis on PBL

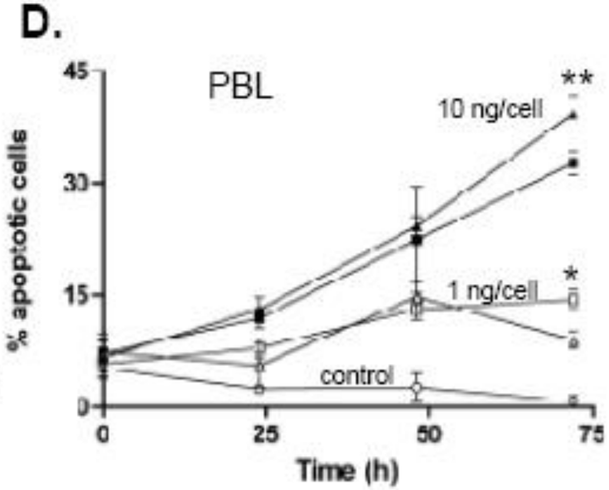


CNTs induce apoptosis of human T cells.

B. At higher magnification annexin V positive Jurkat cells show pyknotic nuclear DNA condensation and membrane blebbing, two typical features of apoptotic cell death.

A. Immunofluorescence images of untreated Jurkat cells (upper panels) and cells treated 24 h with oxidized MWNT.





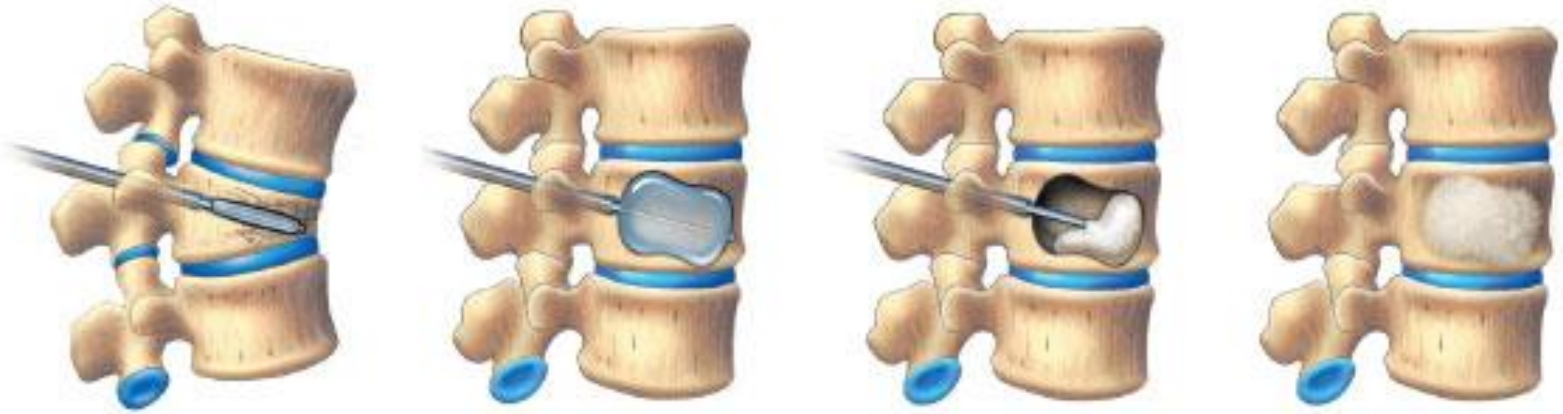
C. Time course of Jurkat cell apoptosis after treatment with 1ng/cell (open triangles) or 10 ng/cell (filled triangles) of oxidized MWNT.

D. Time course of human peripheral blood lymphocytes (PBL) apoptosis after treatment with 1ng/cell (open) or 10 ng/cell (filled) of pristine (squares) or oxidized (triangles) MWNT.

SAFE USE OF NANOTECH IN HEALTH

EXAMPLE BIOCEMENT 4 BONES

Microfractures: skull, vertebrae

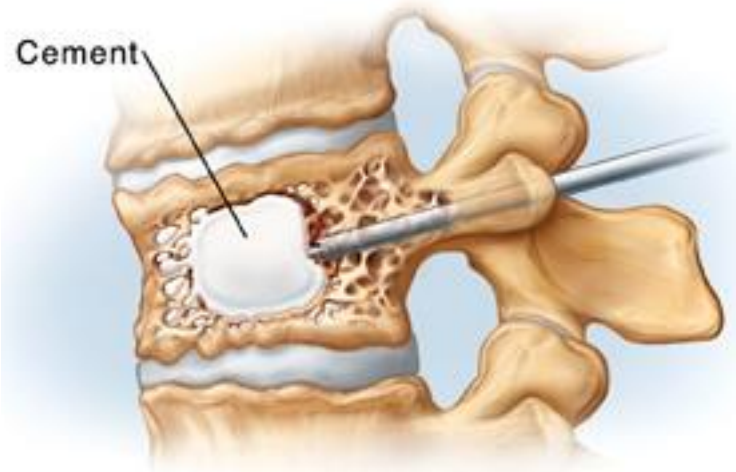


Balloon inserted into fractured vertebra

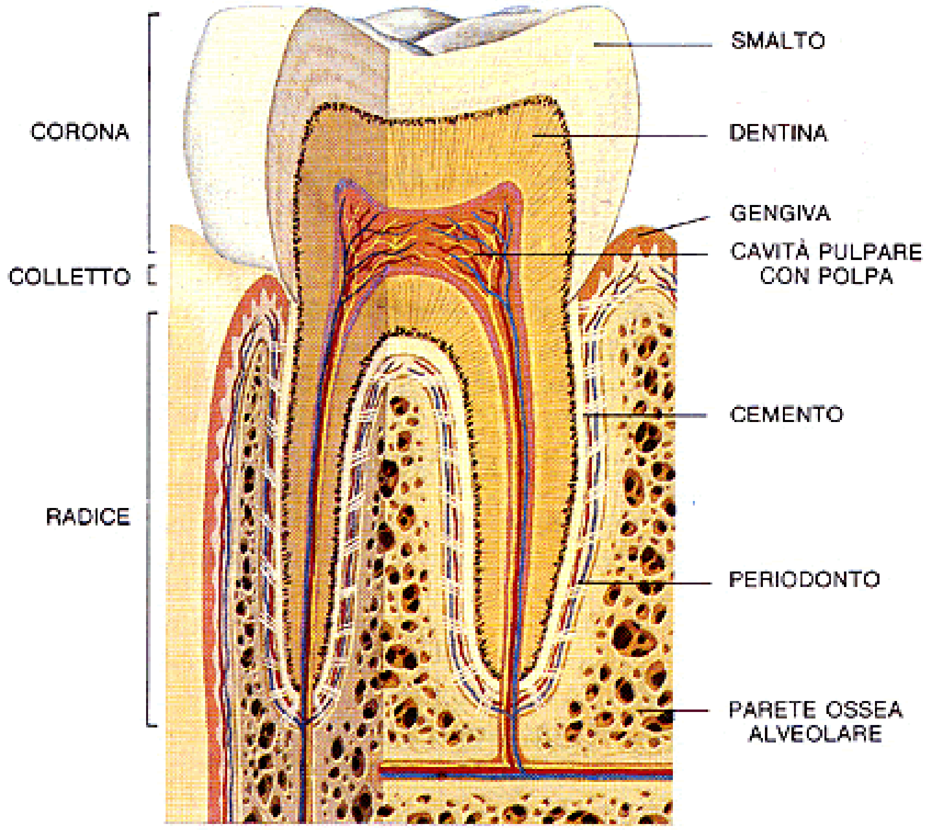
Balloon inflated inside damaged vertebra

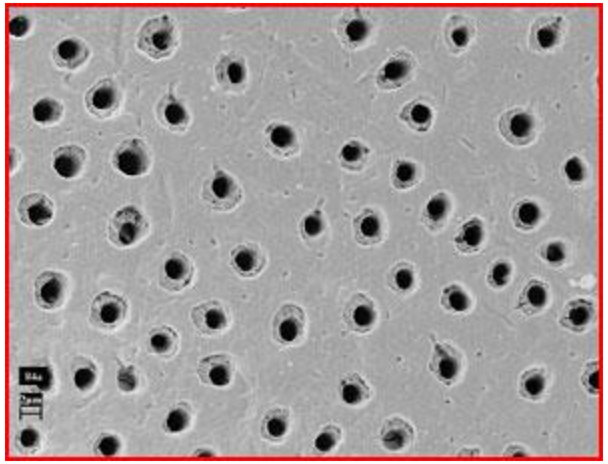
Special material injected into fractured vertebra

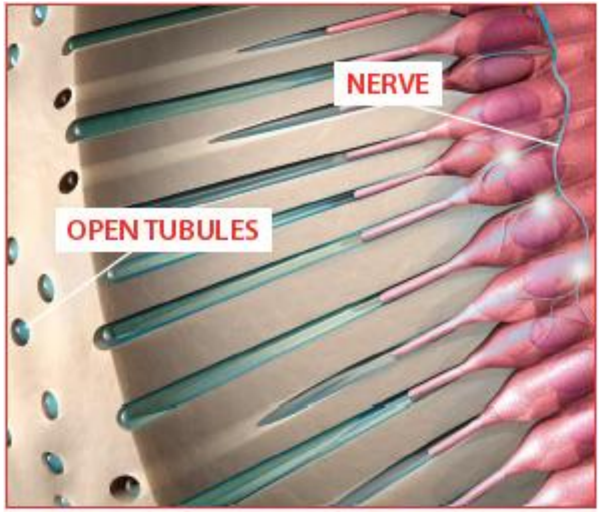
Special material hardens, stabilizing vertebra



BIOCEMENT: DENTAL APPLICATIONS



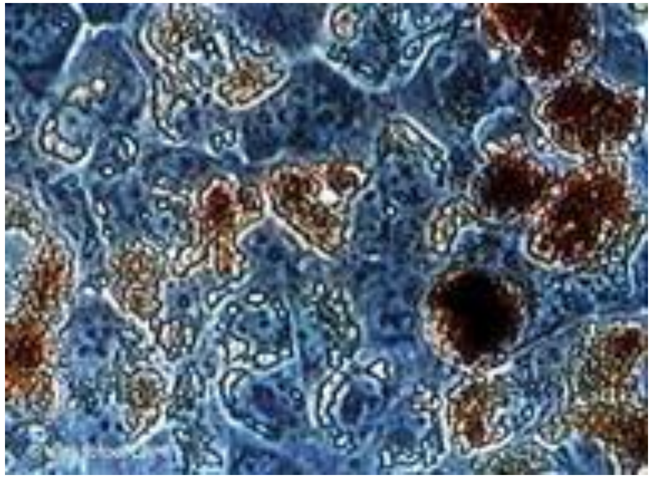




Graphical representation; for illustration purposes only.

NANOTECH FOR TUMOR THERAPY

Iron oxide nanoparticles, with diameters 10,000 times smaller than that of a human hair, can easily penetrate cancer cells and wreak significant damage once inside, to fight a particularly aggressive form of brain cancer called glioblastoma, but which can be used to treat other forms of the disease.



The image shows nanoparticles surrounding cancer cells.

The procedure involves coating the tiny iron oxide particles with an organic substance, such as the sugar glucose, and injecting them into a malignant tumor. The tumor, which has a fast metabolism and correspondingly high energy needs, greedily sucks up the little particles masquerading as sugar pellets of a sort. Healthy cells, instead, show little interest.

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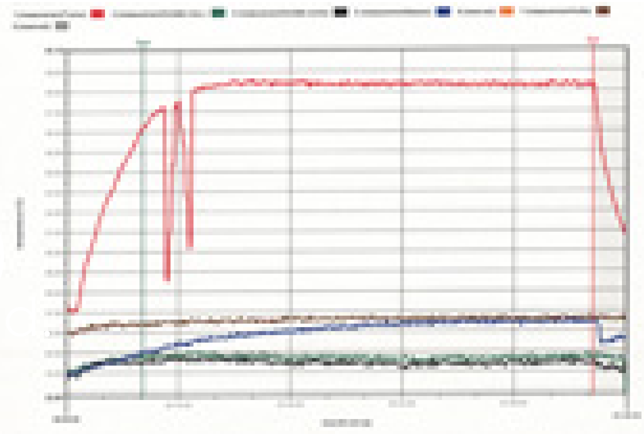
NANOTECH FOR TUMOR THERAPY

- The magnetic field heats up nanoparticles in the malignant tissue to temperatures up to 45 degrees Celsius. Heat destroys many of the cancer cells in and around the tumor or weakens them to a point that they are more effectively treated with radiation or chemotherapy.

The treatment is automatically recordec
Herein the temperature of the tumor (rec
and other body-temperatures are register



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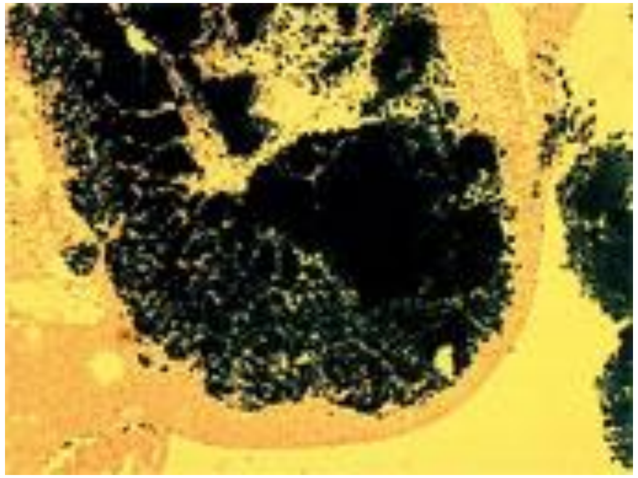
NANOTECH FOR TUMOR THERAPY

In many pre-clinical tests the characteristics of nano-particles were optimized. Here: Accumulation of nano-particles in tumor tissue (RG-2 glioblastoma of the rat).



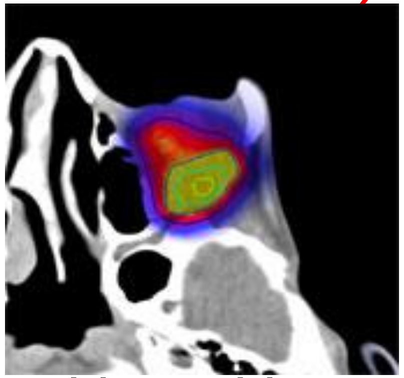
- The treatment, known as magnetic fluid hyperthermia, was successfully used in 2003 for extending the lives of laboratory rats which were implanted with malignant brain tumors. The rats receiving the nanotherapy lived four times as long as rats receiving no treatment.

Images source: MFH Hyperthermiesysteme GmbH and MagForce Applications GmbH, Berlin, Germany

NANOTECH FOR TUMOR THERAPY

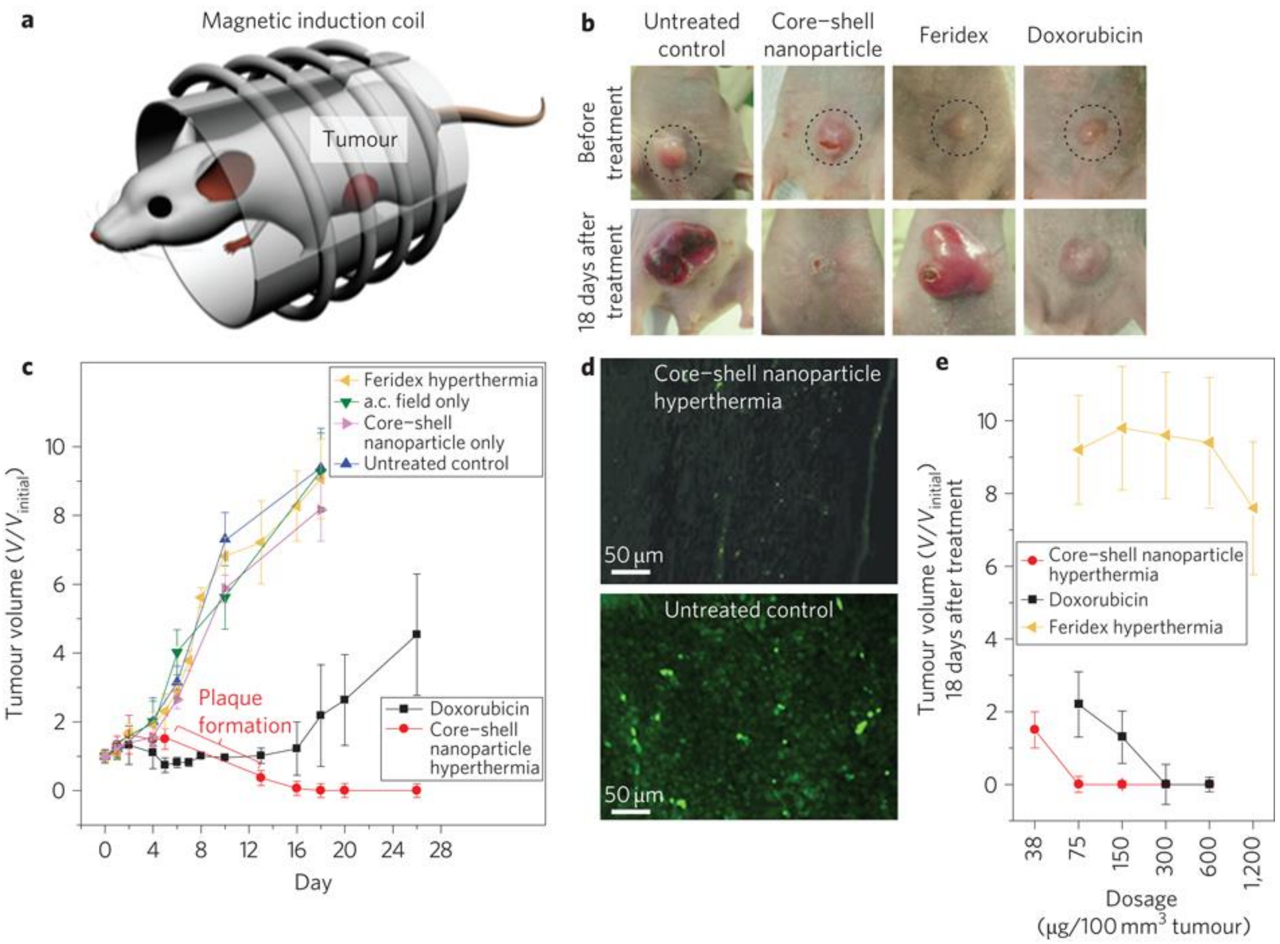
- Subsequently the new technique was applied on 15 patients suffering from *Glioblastoma multiforme,* the most common primary brain tumor and the most aggressive form of brain cancer (life expectancy prognosis in humans: 6-12 months).

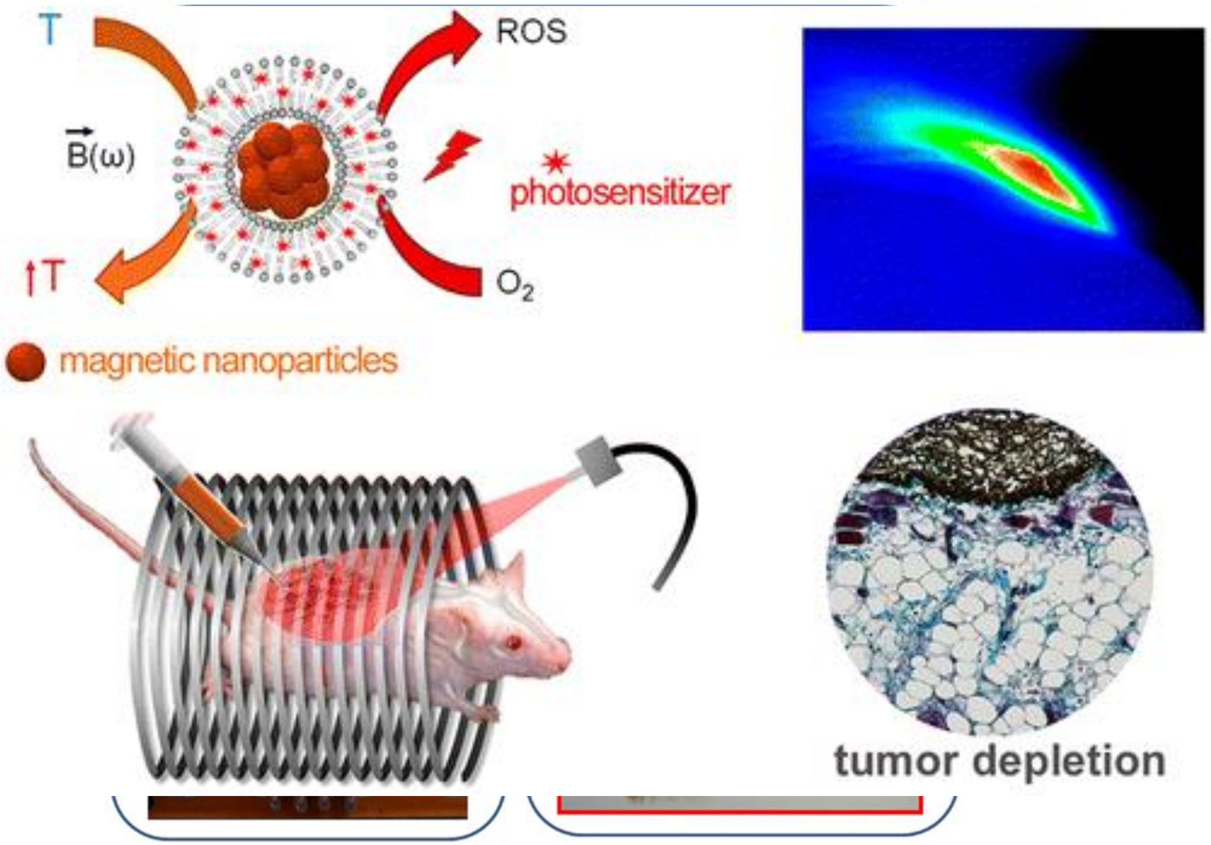
precise thermotherapy of target areas in almost eve
egion of the body is possible (here: Thermotherapy c
the orbita up to a maximum temperature of 49°C).



- The treatment is particularly attractive to doctors working with tumors in the brain since the nanoparticles are placed in the malignant tissue by means of an extremely precise electronic navigation system. So they can reach tumors that lie outside the reach of conventional surgical treatment, such as those situated deep in the brain or in regions that are responsible for essential tasks like speech or motor functions.

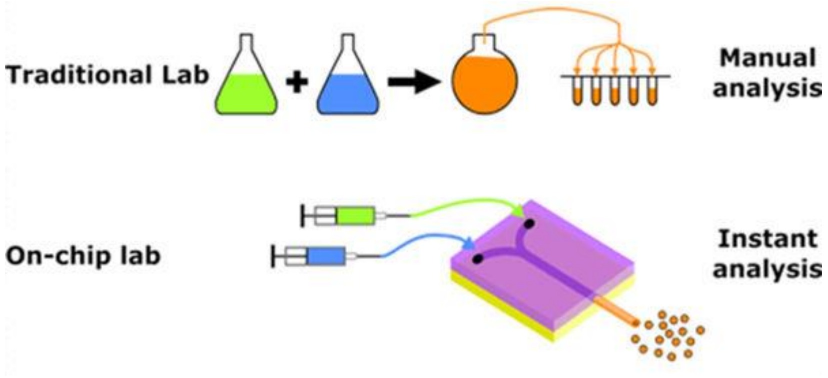
TERANOSTICS

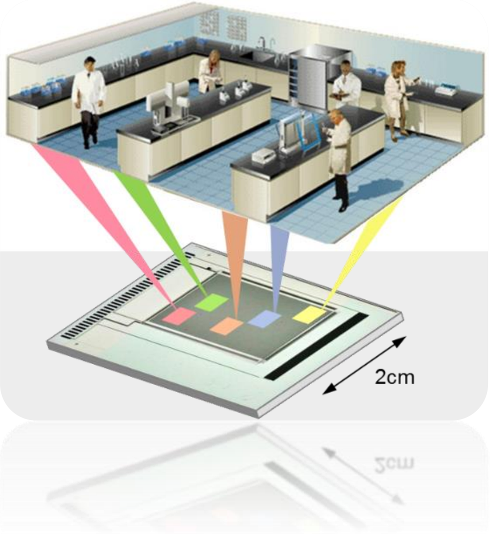


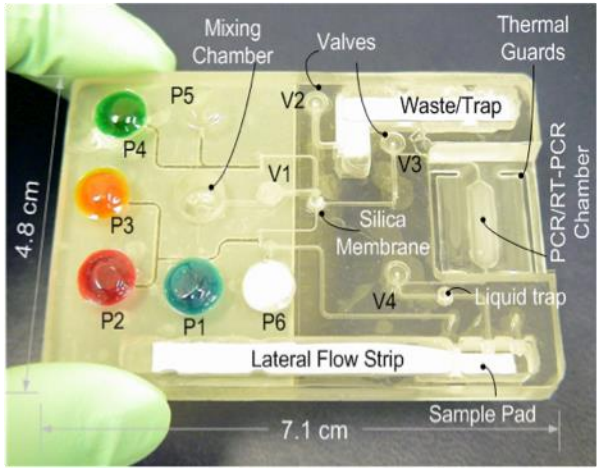


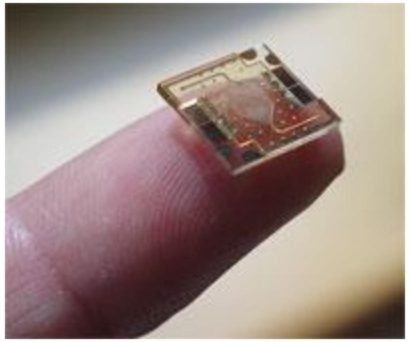
DIAGNOSTICS: LAB ON CHIP

LAB ON CHIP

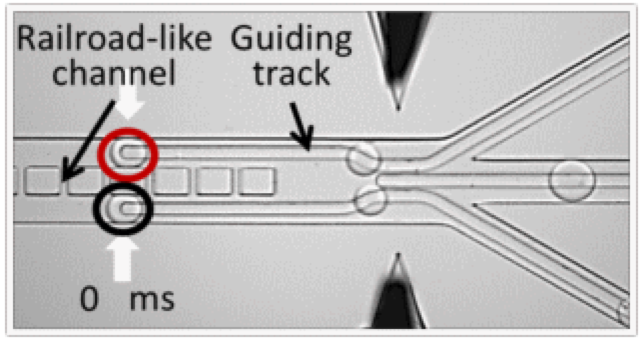






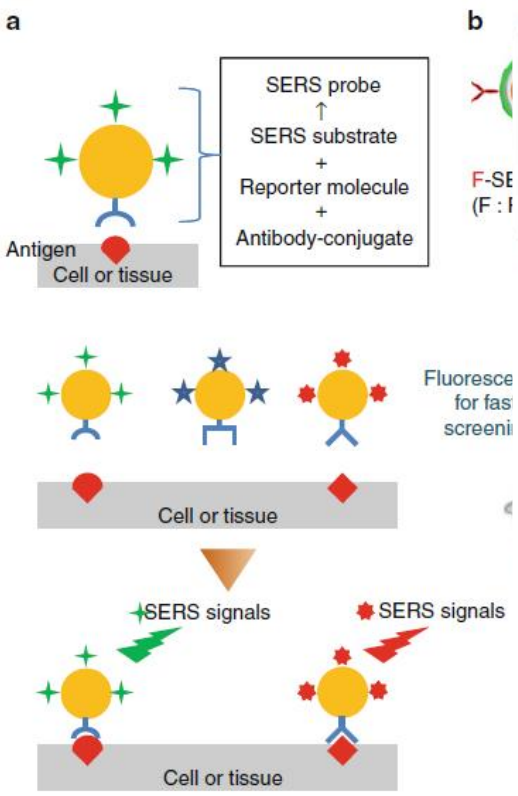


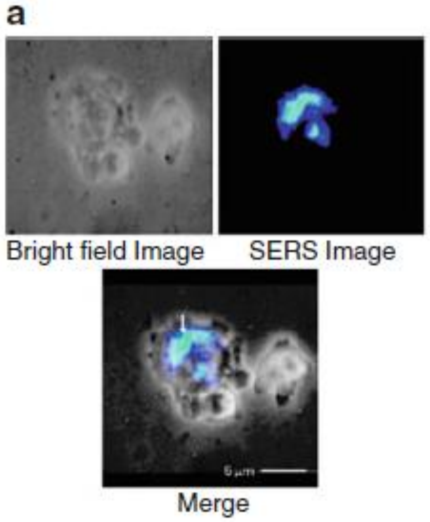
Fusion and sorting of two trains of droplets

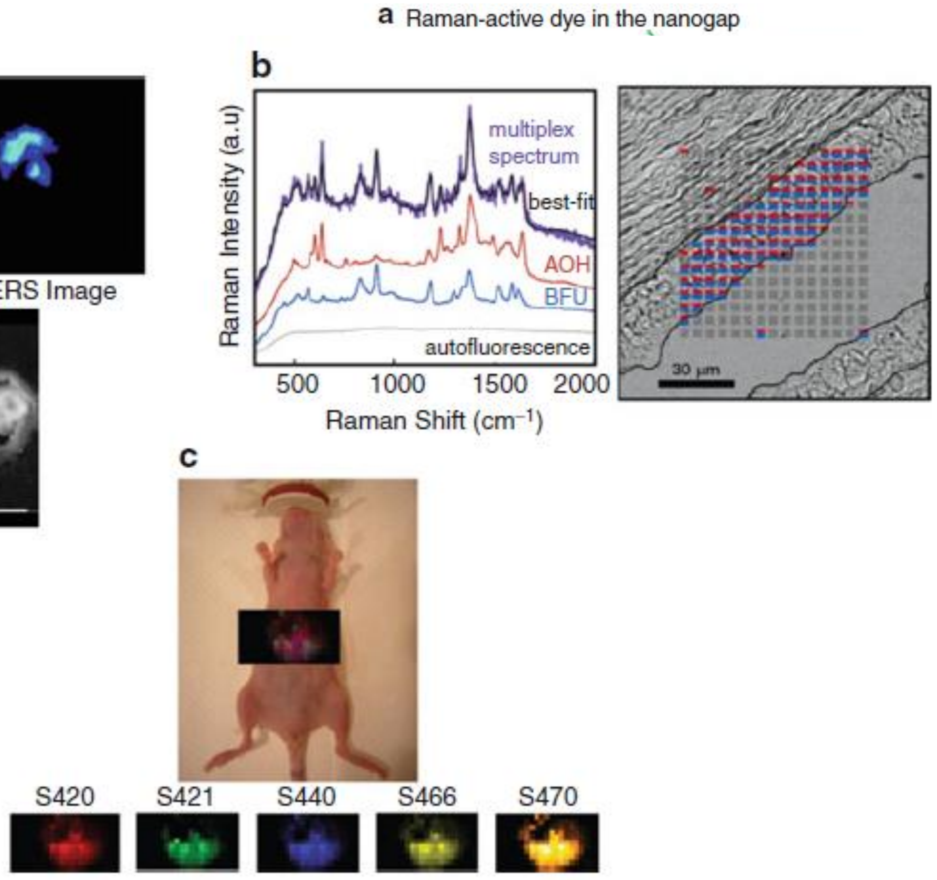


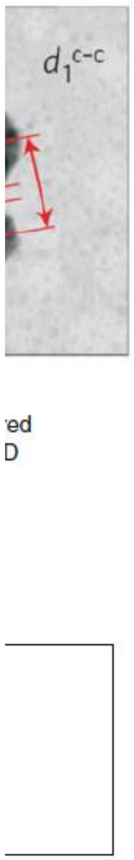
WiFi
Free Zone

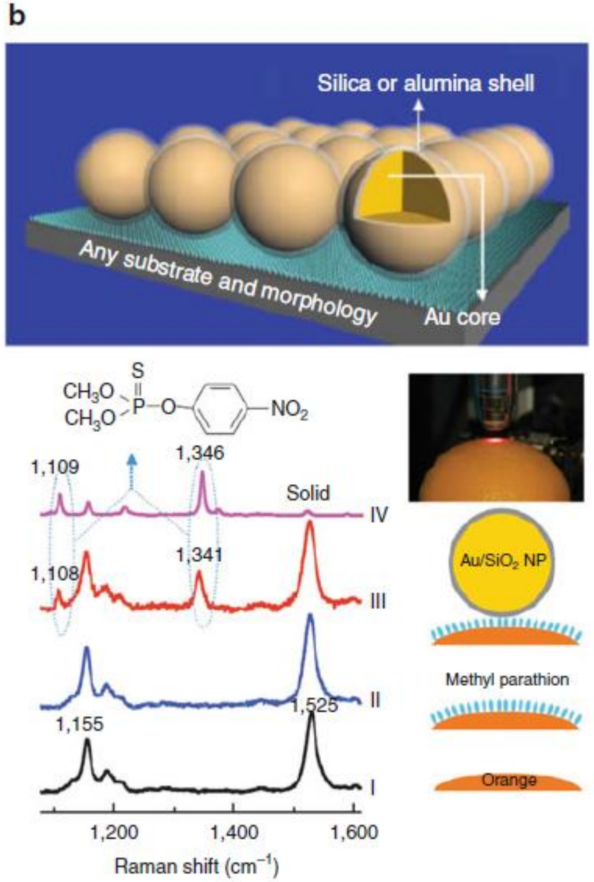
SENSORS BASED ON RAMAN SPECTROSCOPY



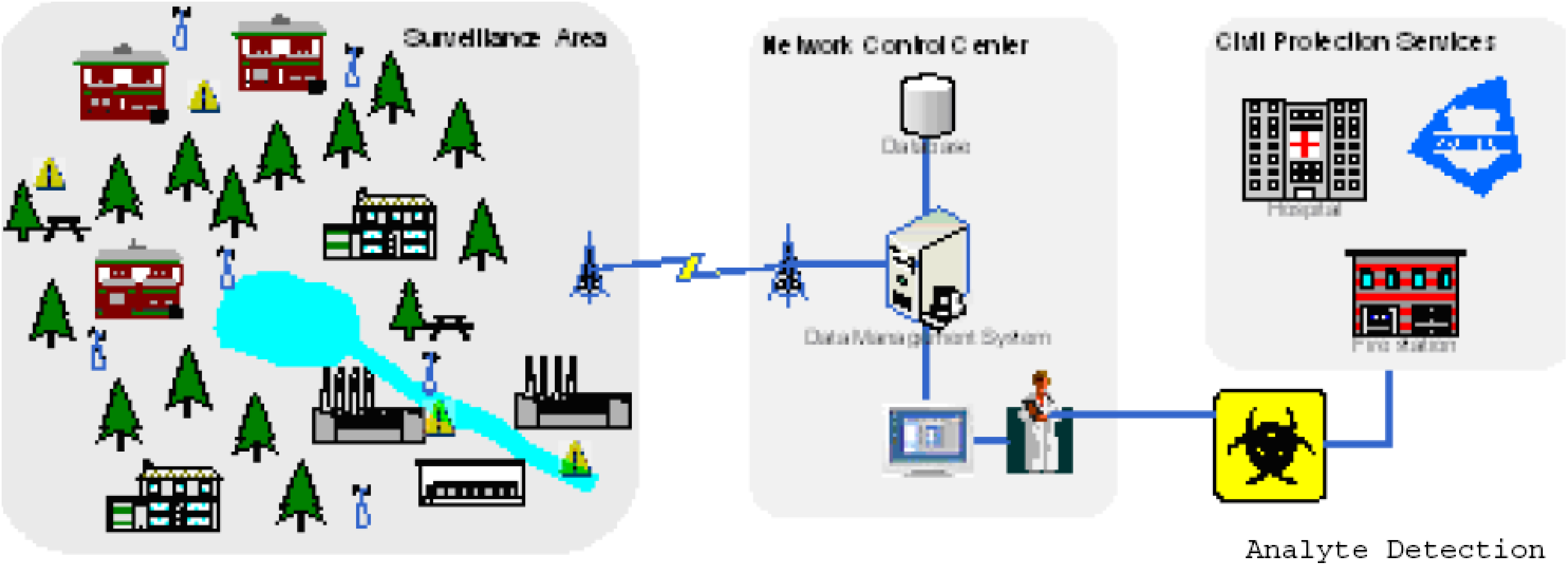






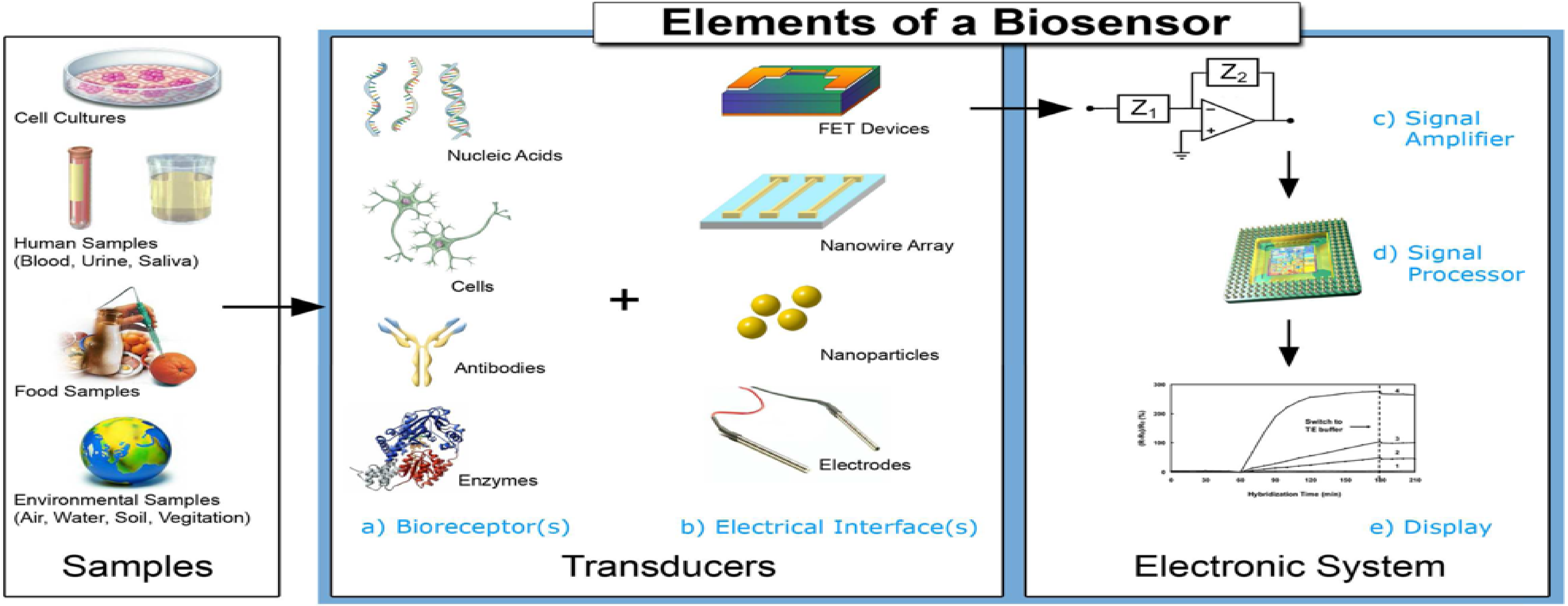


Wireless biosensors for homeland security



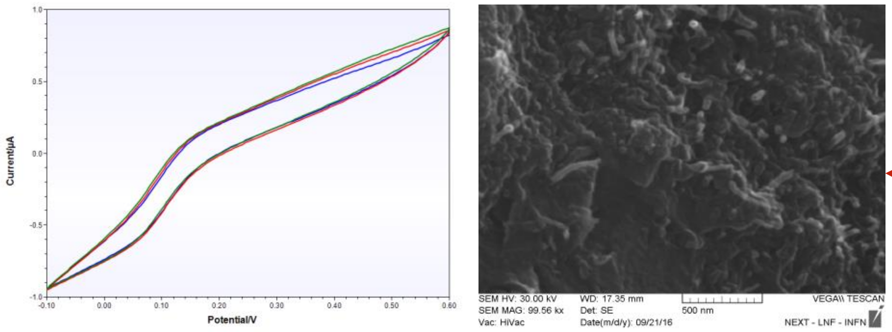
e-mail: bellucci@lnf.infn.it

BIOSENSORS: DNA CHIP

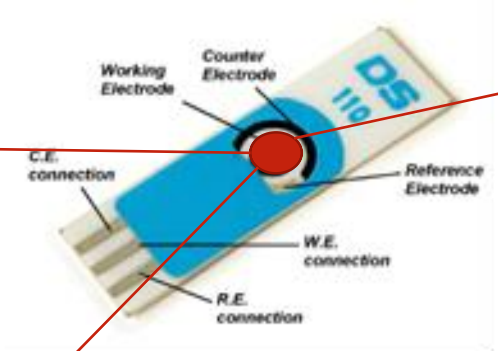


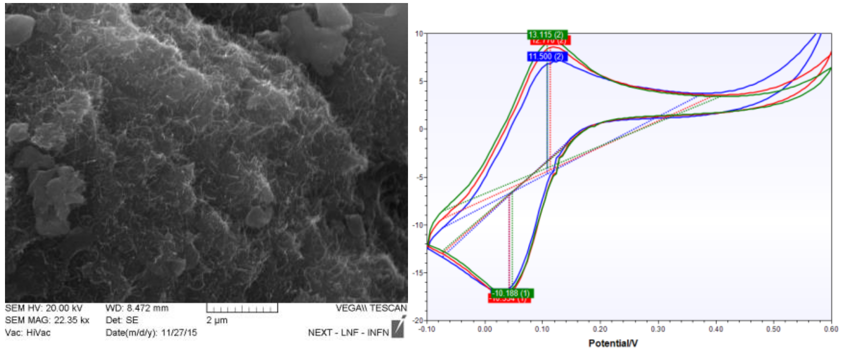
Sensing

Electrochemical sensing using composite coatings based on carbon nanostructures

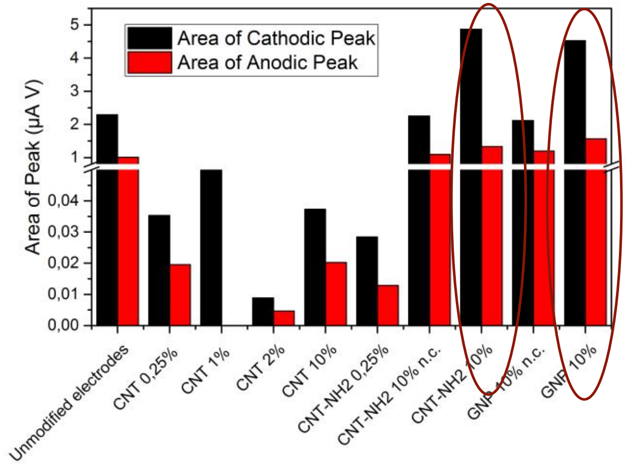


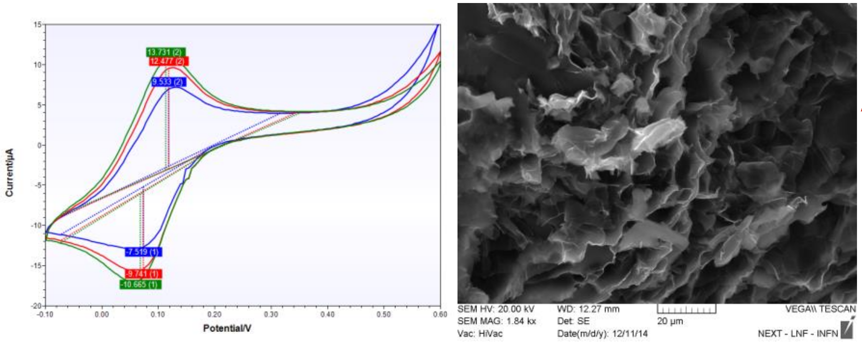
Ciclic Voltammetry and SEM images of nanocomposite Epoxy-CNT 10%





CV and –SEM images of nanocomposite Epoxy-CNT-NH$_2$ 10%





CV and SEM images of nanocomposite Epoxy-GNP 10%

Modification of screen printed electrodes (SPE) with nanocomposite materials

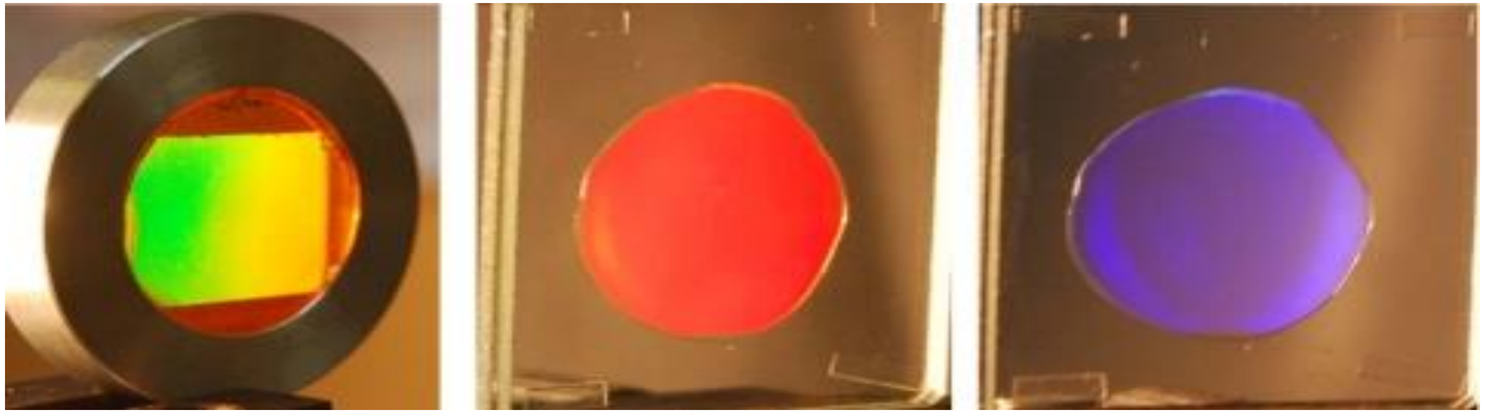
SPE modified with Epoxy-CNT-NH$_2$ 10% and Epoxy-CNT-NH$_2$ 10% most sensitive than SPE unmodified

Nanocomposite based photonic crystal sensors of biological and chemical agents

NEXT group @INFN Frascati, in collaboration with the National Academy of Science of Kiev and the Lviv Polytechnic in Ukraine and with the Fraunhofer Institute of Potsdam-Golm in Germany, proposed developing cheap, yet effective photonic crystal (PC) structures, formed by a periodic distribution of nanoparticles (NP) in polymer matrix for PC powered sensor applications and fluorescent and Raman spectroscopy, for highly sensitive detection of chemical and biological agents. The volume PC structures will be fabricated using holographic method in original photopolymer nanocomposites

NATO OTAN

2018-2021



(a) (b) (c)

Figure 1– White light diffraction by polymer gratings–Ag NP (a), $LaPO_4$ NP (b), TiO_2 NP (c)

NANOVECTORS

FOR

DRUG DELIVERY

Review

Journal of Nanoscience and Nanotechnology
Vol. 14, 1–17, 2014
www.aspbs.com/jnn

Targeted Nanodrugs for Cancer Therapy: Prospects and Challenges

Massimo Bottini[1,2,3,*], Cristiano Sacchetti[1,4], Antonio Pietroiusti[5], Stefano Bellucci[3], Andrea Magrini[5], Nicola Rosato[2], and Nunzio Bottini[4,*]

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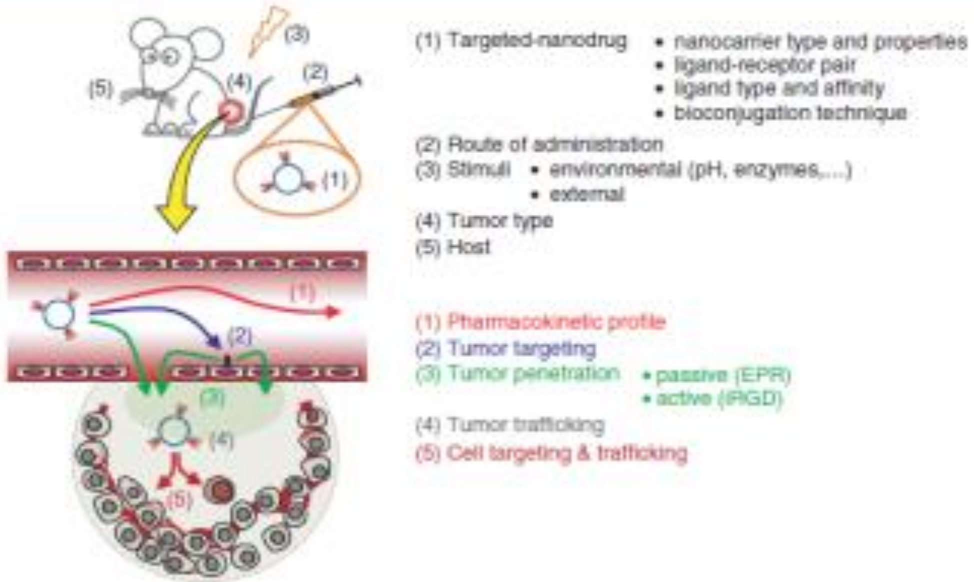
[2] Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Via Montpellier 1, 00133 Rome, Italy
[3] INFN, National Laboratory of Frascati, Via Enrico Fermi 40, 00044 Frascati, Rome, Italy
[4] Division of Cellular Biology, La Jolla Institute for Allergy and Immunology, 9420 Athena Circle, La Jolla, CA 92037, USA
[5] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Via Montpellier 1, 00133 Rome, Italy



Targeted Nanodrugs for Cancer Therapy: Prospects and Challenges Bottini et al.

Massimo Bottini holds a degree in Electronic Engineering and a Ph.D. in Sensorial Systems. He received postdoctoral research training at the Sanford-Burnham Medical Research Institute in La Jolla, California, and he was appointed as an Assistant Professor at the University of Rome Tor Vergata (Rome, Italy) in 2009 and as an Adjunct Assistant Professor at the Sanford-Burnham Medical Research Institute (La Jolla, CA) in 2012. He was awarded a John Vaughan Scholar by the Arthritis National Research Foundation in 2011 and 2012. His research is focused on the investigation of the biological performance of carbon nanotube-based nanoparticles and their use as targeted drug delivery systems for the therapy of cancer and autoimmune diseases.

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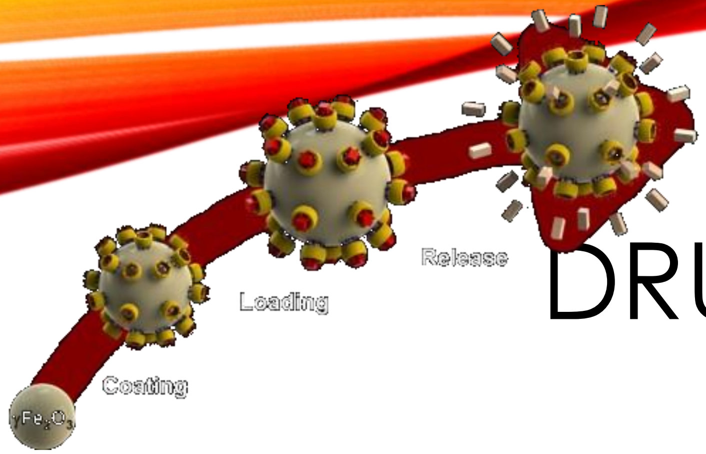
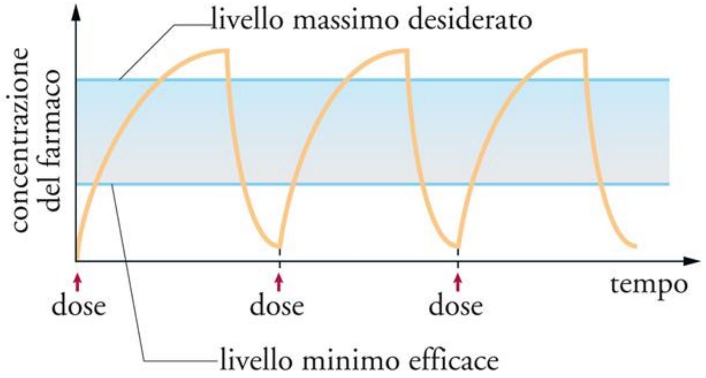
Antonio Pietroiusti is an Assistant Professor of Occupational Medicine at the University of Rome Tor Vergata (Rome, Italy). He is a partner in the FP7-MARINA, a project focusing on reference methods for risk management of nanomaterials, in the COST action MODENA, aimed at quantitative nanostructure-toxicity-relationship modeling to facilitate risk assessment of novel nanomaterials, and in the NanoReg, focused on delineating regulatory measure for the use of nanomaterials.

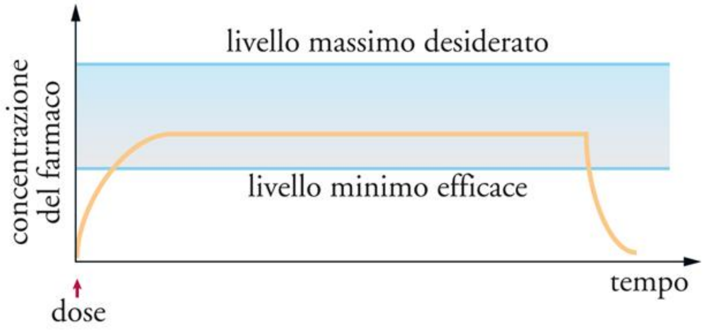
Stefano Bellucci obtained his Ph.D. in the physics of elementary particles at SISSA (Trieste, Italy) in 1986. He worked in the USA (1983–1988) as a Research Associate at Brandeis University and as visiting researcher at M.I.T., University of Maryland, and University of California at Davis. He returned to Italy as a Tenured Researcher (Research Staff) at INFN (Istituto Nazionale di Fisica Nucleare) Laboratori Nazionali di Frascati (LNF) in 1987. He was appointed as INFN First Researcher (Senior Research Staff) in 2005. His research interests include theoretical physics, condensed matter, nanocarbon-based composites and biomedical applications. He is INFN scientist in charge of EU projects "BY-NanoERA—Institutional Development of Applied Nanoelectromagnetics: Belarus in ERA Widening," "NAmiceMC—Nano-thin and micro-sized carbons: Toward electromagnetic compatibility application," and "FAEMCAR—Fundamental and Applied Electromagnetics of Nano-Carbons."

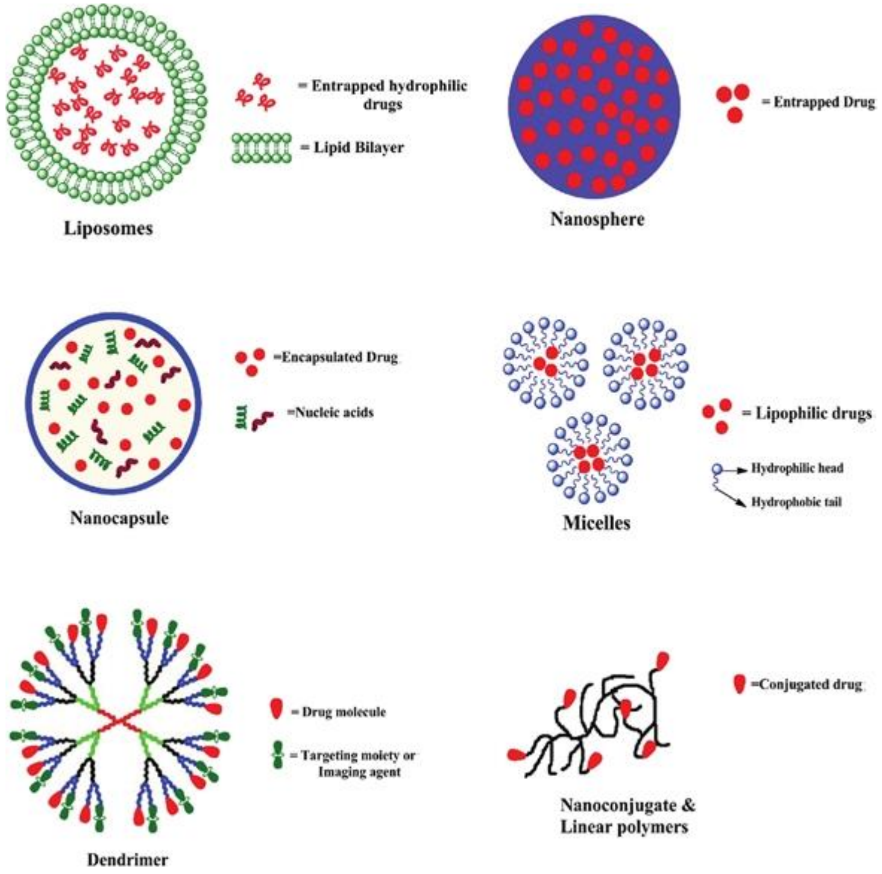
Andrea Magrini is an Associate Professor at the University of Rome Tor Vergata (Rome, Italy). He is head of the Unit of Occupational Medicine, Director of the School of Occupational Medicine and Vice-President of the Ph.D. in Prevention Techniques in the Environment and at Worksites at the University of Rome Tor Vergata. He is also chief of the Division of Occupational Medicine at the Tor Vergata University Hospital and Secretary of the Italian Society of Occupational Medicine and Industrial Hygiene. His primary scientific interest is the health effects of nanoparticles.

DRUG DELIVERY SYSTEMS



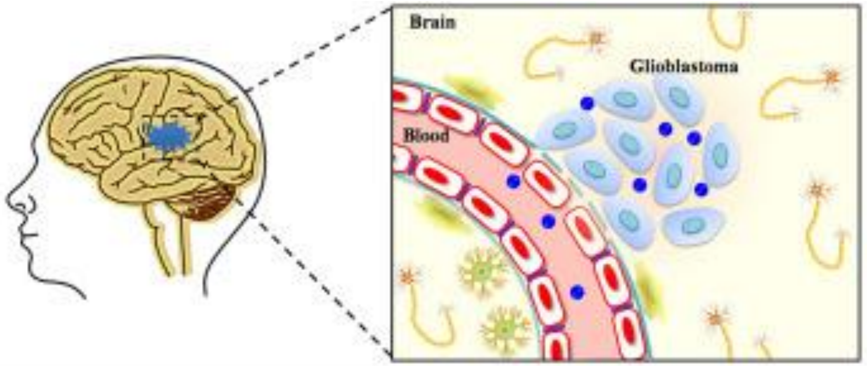


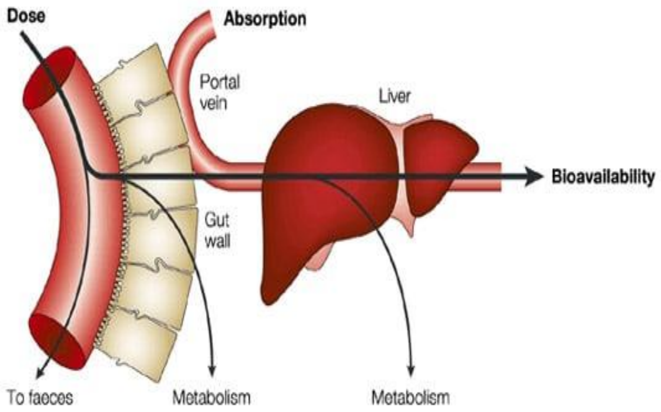




NOSE 2 BRAIN DELIVERY

WHEN A DRUG IS SWALLOWED THIS IS ABSORBED BY THE DIGESTIVE APPARATUS AND REVERSED INSIDE THE SYSTEMIC CIRCULATION (BLOOD) THAT CARRIES IT FOR THE ENTIRE BODY. THIS CANNOT REACH THE BRAIN, OWING TO THE SCREENING EFFECT OF THE BLOOD BRAIN BARRIER (BBB) THAT ALLOWS THE PASSAGE OF VERY FEW MOLECULES.





WHAT IF THE DRUG IS FOR CURING NEUROLOGICAL DISEASES?

THE DRUG CROSSES THE MEMBRANE AND REACHES THE BRAIN

IT TAKES CARE OF THE PATHOLOGY INDIRECTLY BY NOT USING THE APPROPRIATE DRUG

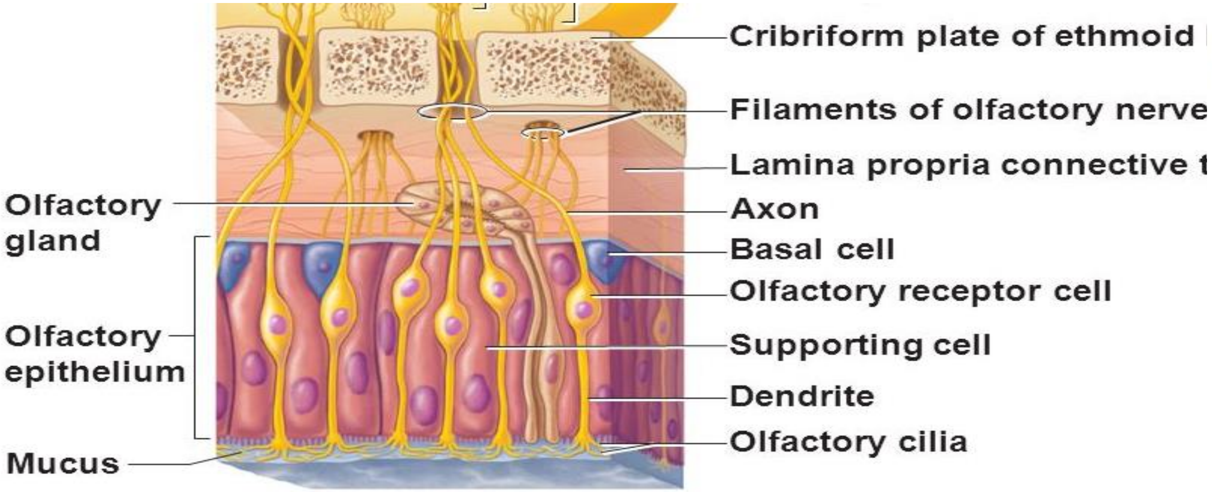
COLLATERAL EFFECTS

INVASIVE CARE:

- LUMBAR INJECTION
- OPEN THE HEAD

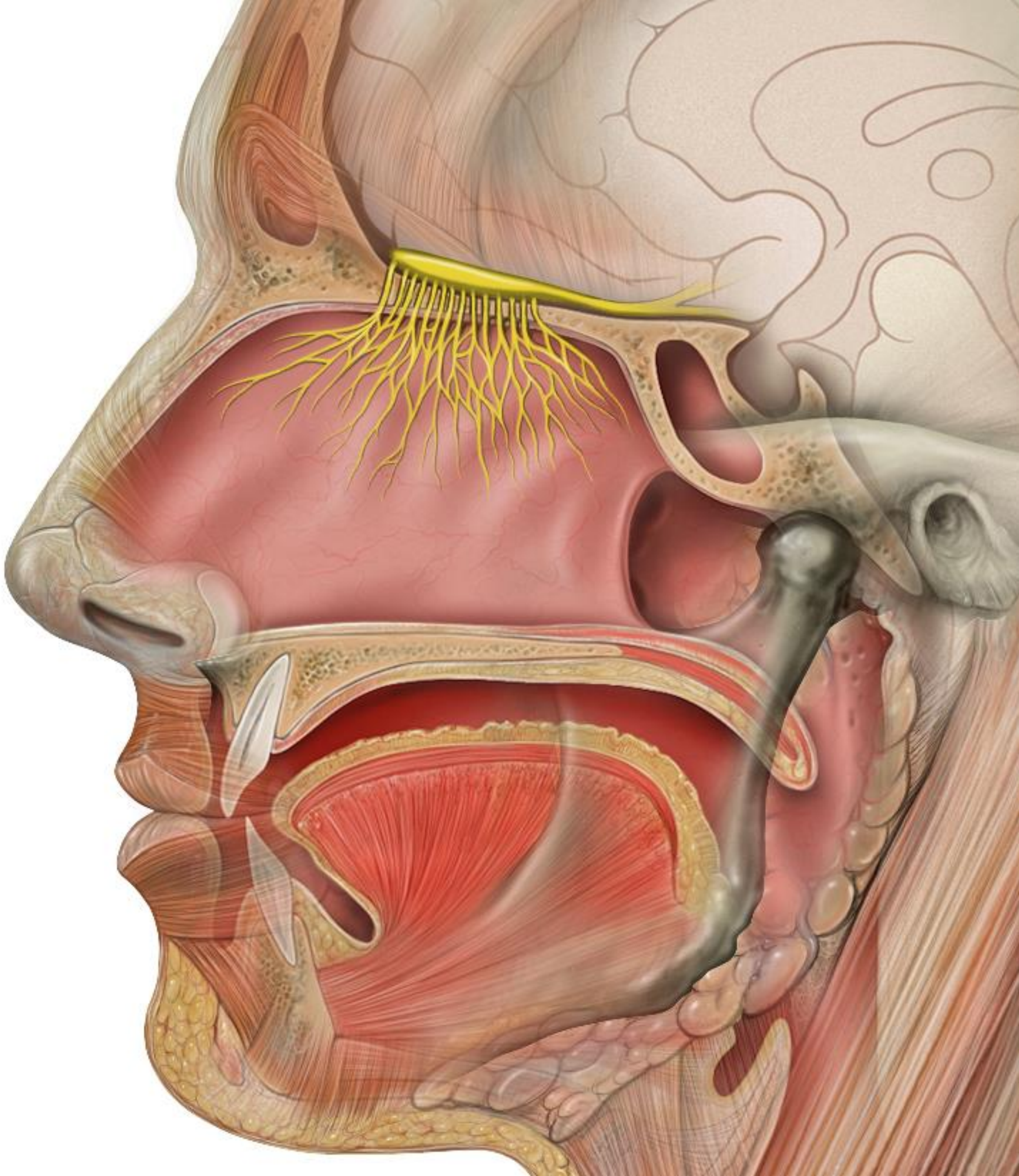
OUCH!!

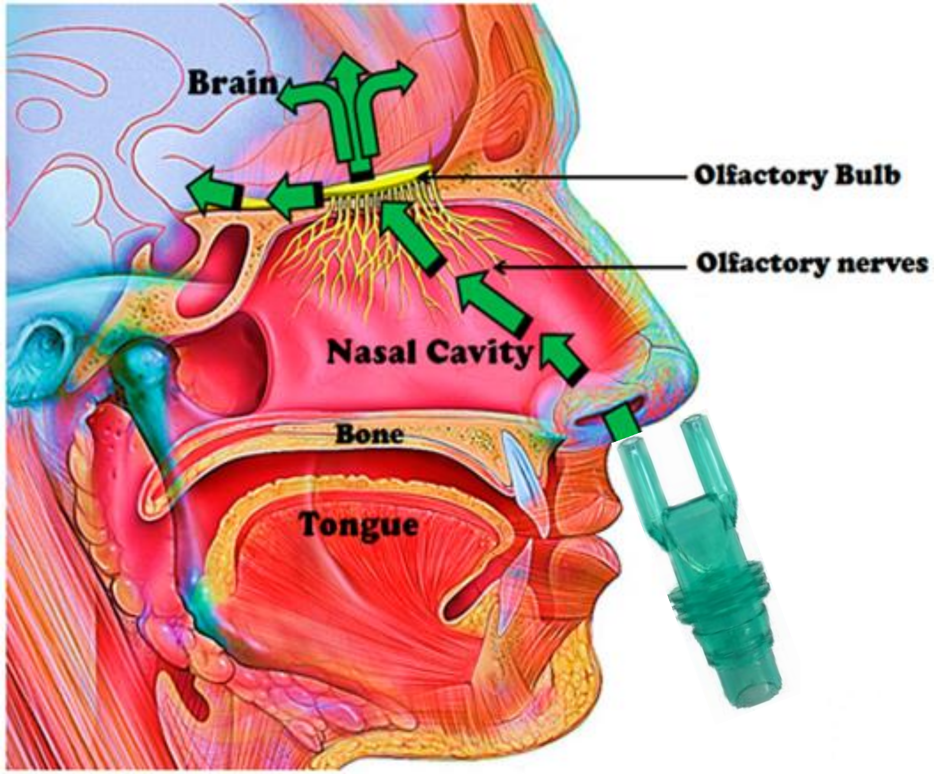
AN ALTERNATIVE WAY THAT WOULD ALLOW TO DELIVER ANY TYPE OF DRUG TO THE BRAIN EXISTS. PASSING THROUGH THE NOSE, EXPLOITING THE AXONIC TERMINATIONS OF THE OLFACTORY BULB.



USING 2 TRASPORT ROUTES:

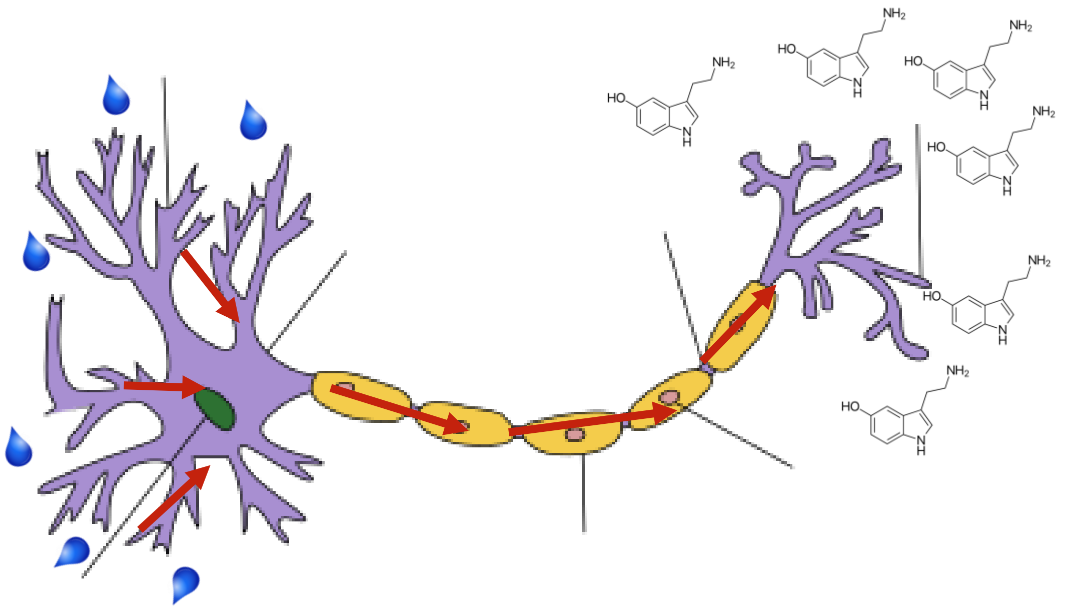
- AXONAL TRANSPORT
- TRANSPORT BETWEEN SUPPORT CELLS





USING AEROSOL IT IS POSSIBLE TO OBTAIN A SELF-ADMINISTRATION

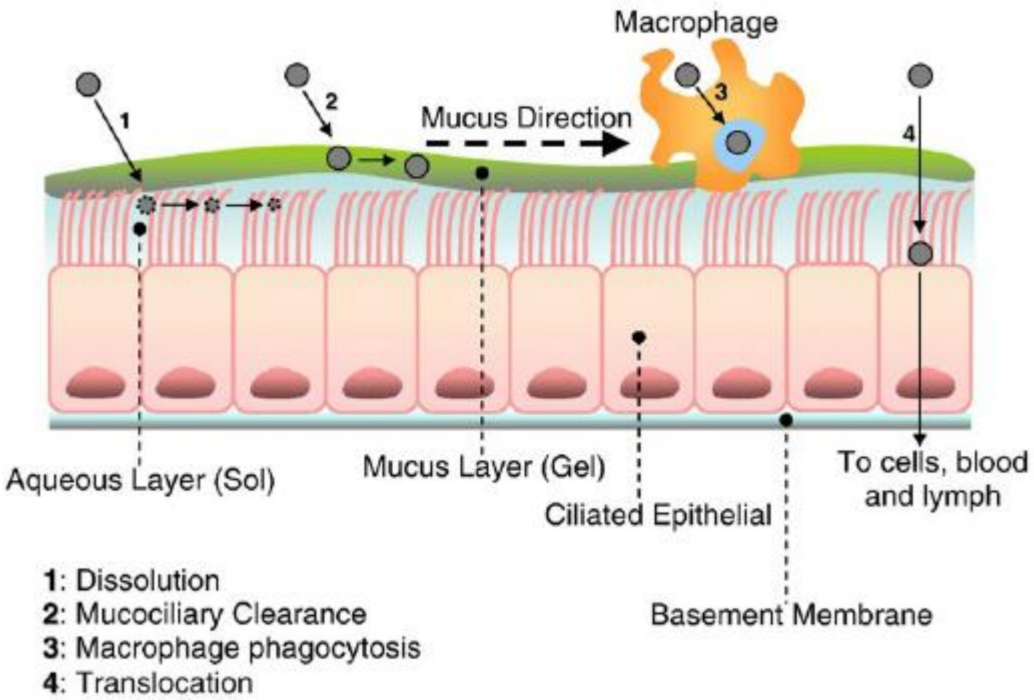
GRAPHICAL REPRESENTATION OF AXONALLY-MEDIATED TRANSPORT

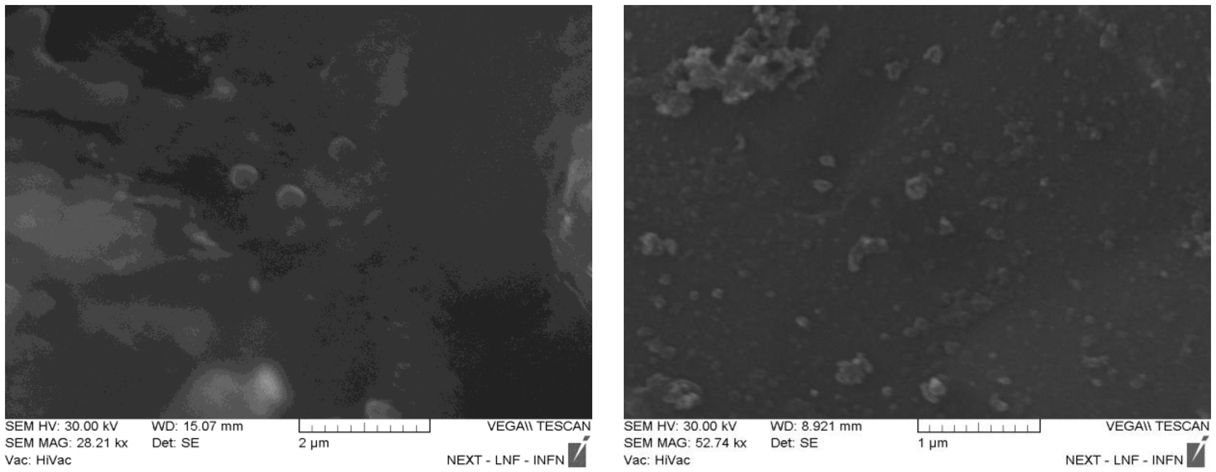


STEP 1 : DENDRITES ABSORPTION
STEP 2 : AXONALLY PASS
STEP 3 : STREAM INTO THE BRAIN

PROBLEM:

SOLUTION:





THE MOLECULES IN THE NOSE ARE **QUICKLY ELIMINATED BY MUCOCILIAR CLEARENCE**. THE CELLS OF THE NOSE ARE COVERED BY CILIA THAT MOVE IN A SYNCHRONOUS WAY, TO ELIMINATE THE DRUG TOWARDS THE RHINOPHARYNX.

MUCOADHESIVE NANOVECTORS CAN BE USED TO ENCAPSULE THE DRUG. THIS PERMITS **TO INCREASE THE RETENTION TIME IN THE NASAL CAVITY**, THUS ALLOWING THE DRUG TO REACH THE TARGET.

Delivery and imaging of miRNAs by multifunctional carbon nanotubes and circulating miRNAs as innovative therapeutic and diagnostic tools for pediatric pulmonary hypertension

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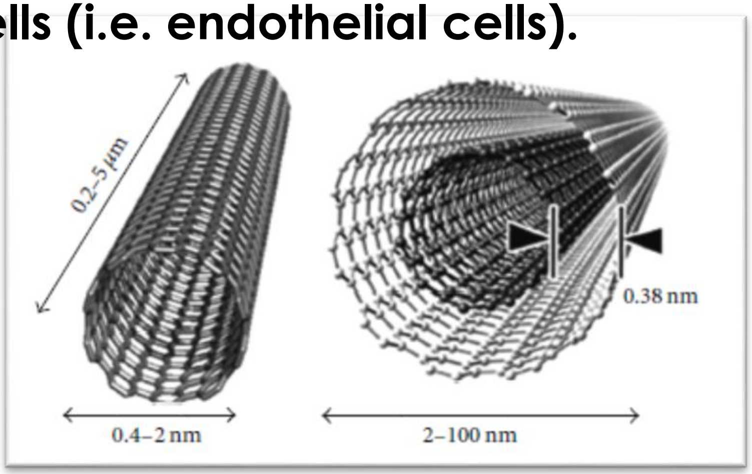
Polyamine-coated carbon nanotubes allow for an efficient release of microRNAs in endothelial cells

Current applications (use of bulk nanotubes):
- As <u>composite fibers</u> embedded in polymers to improve the mechanical, thermal and electrical properties of the bulk product.
- As <u>tips</u> for atomic force microscope probes.
- As <u>scaffold for bone growth</u> in tissue engineering (Zanello LP et al., Bone cell proliferation on carbon nanotubes. Nano Lett. 2006;6(3):562-7).

In the biomedical field the use of CNTs is further limited by their **insolubility** in aqueous solutions, by their intrinsic **toxicity** and in some cases by safety regulations.

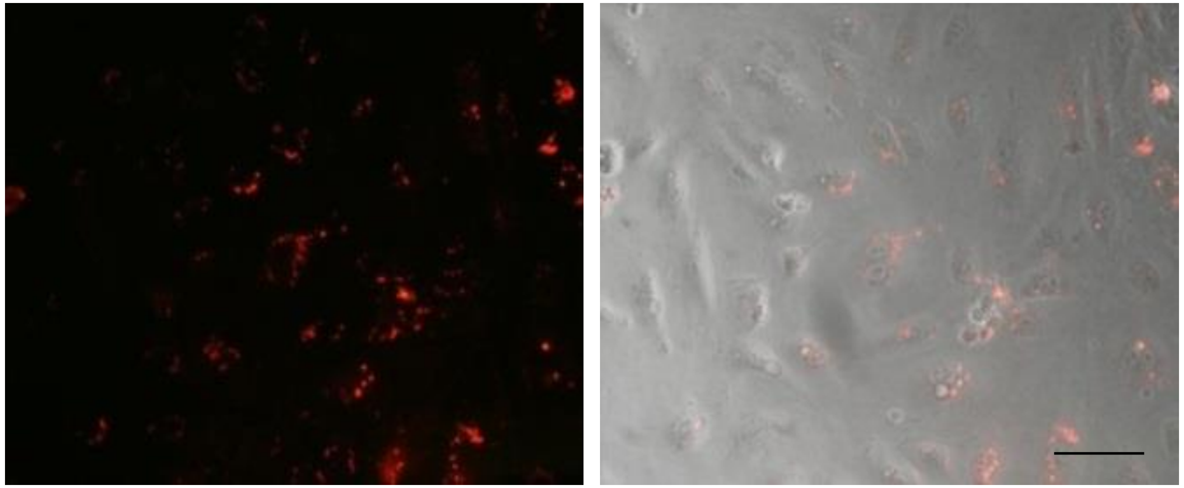
AIM: Develop novel non-toxic CNT-based vectors for nucleic acid delivery in human cells (i.e. endothelial cells).



Delivery of miRNAs in endothelial cells

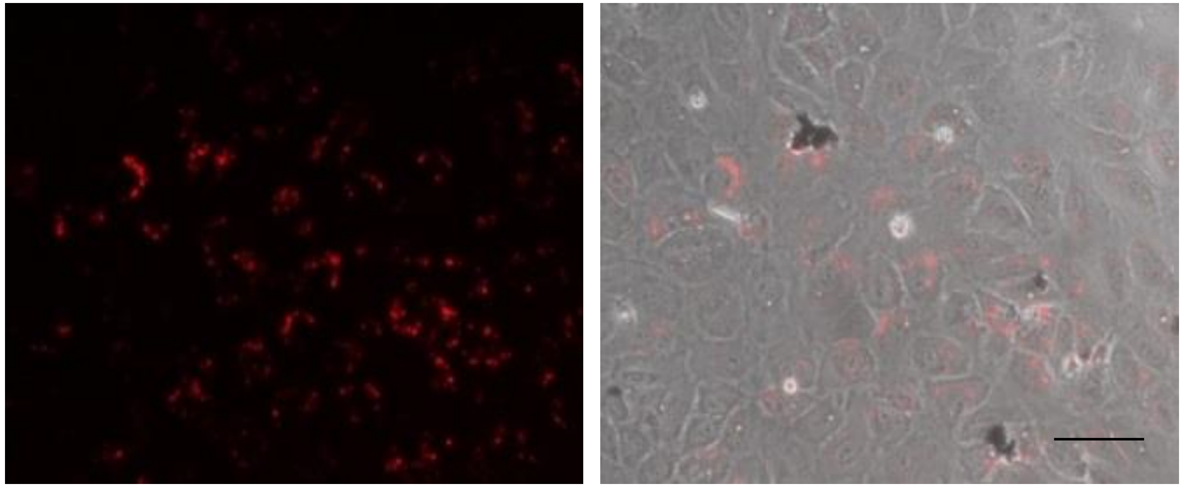
PEI-CNT-pre-miR-Cy3

HUVEC

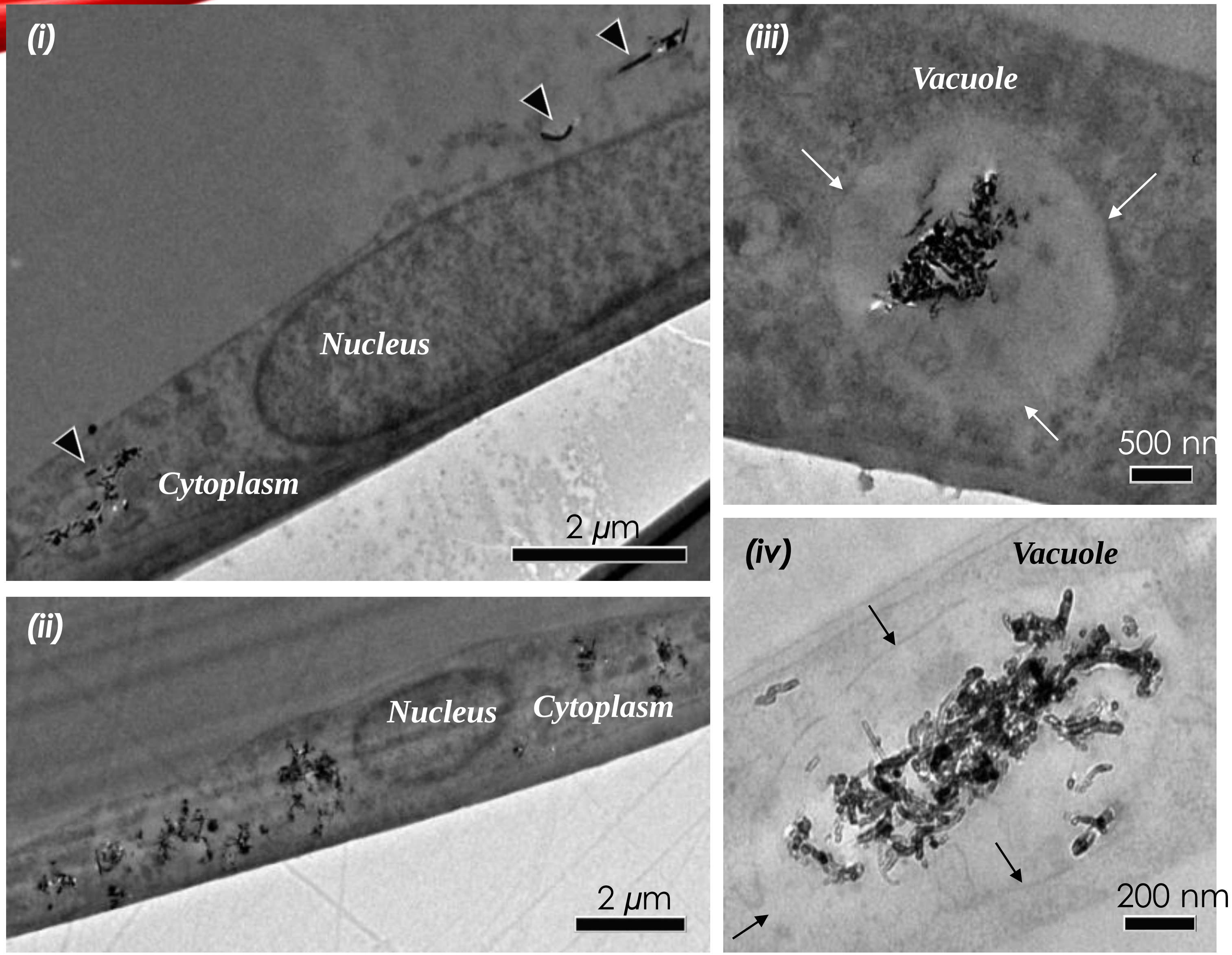


PAMAM-CNT-pre-miR-Cy3

HUVEC



Intracellular localization

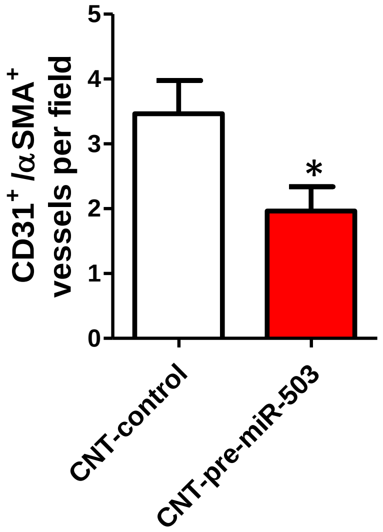


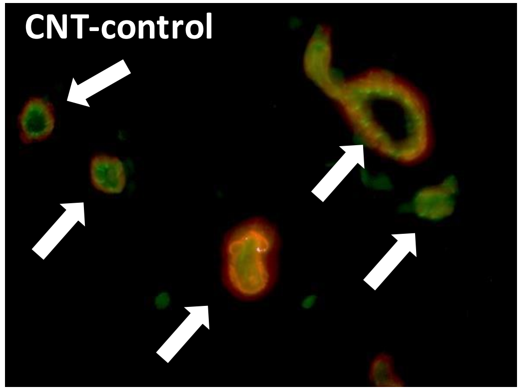
In vivo Delivery

Sponge implant model. The sponge-induced inflammatory angiogenesis consists of the implantation (in mice) of a synthetic polymer in subcutaneous sites. This model can be used as controlled sustained-release delivery system of therapeutic agents.

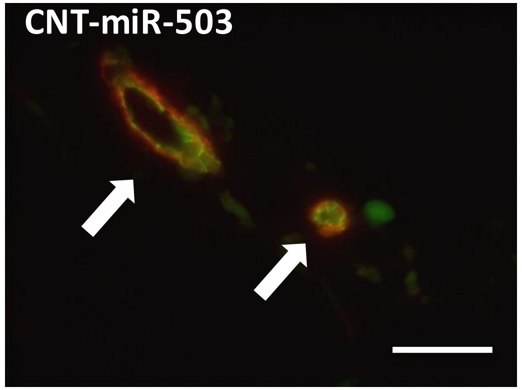
PERSPECTIVES

- **Therapeutic angiogenesis**
- **Vascular Remodeling**





CD31 α-SMA



CD31 α-SMA

QUESTIONS ?

NEXT

LABORATORY OF NANOTECHNOLOGY

Thanks for your attention

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