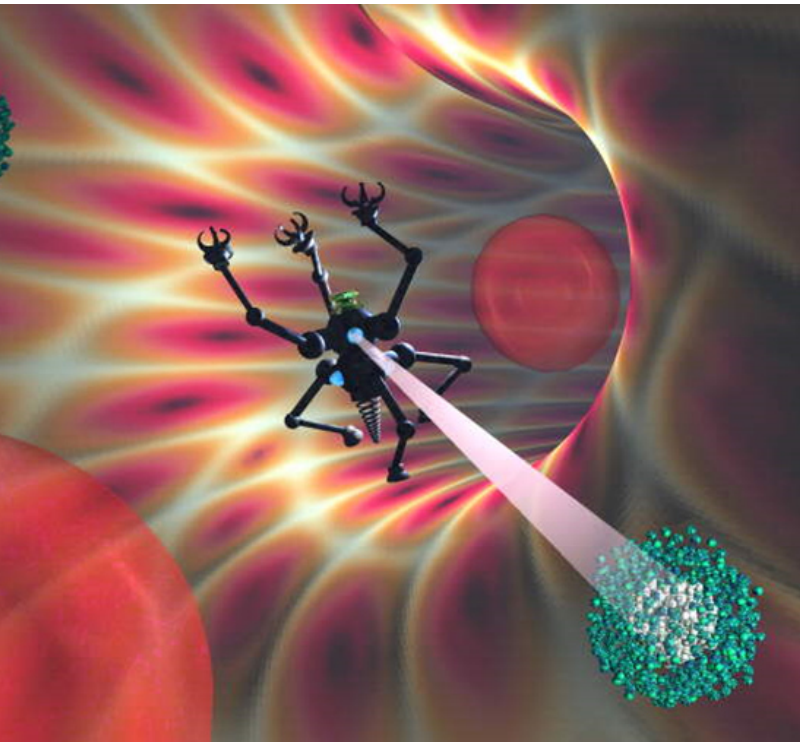




APLLICATIONS OF NANOMATERIALS IN MEDICINE

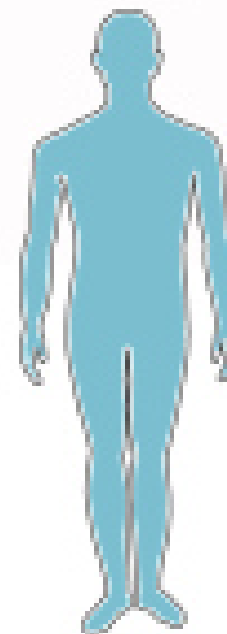
By

Dr B. DIVBAND

Key Benefits of nano based drug delivery systems

- Provides multi-functionality: targeting, delivery, reporting
- Provides **improved** therapeutic index
- Provides **lowered** toxic side effects
- Delivers multiple drugs directly to tumor site
- Enables nucleic acid delivery
- Enables non-drug therapies (photothermal, photodynamic)

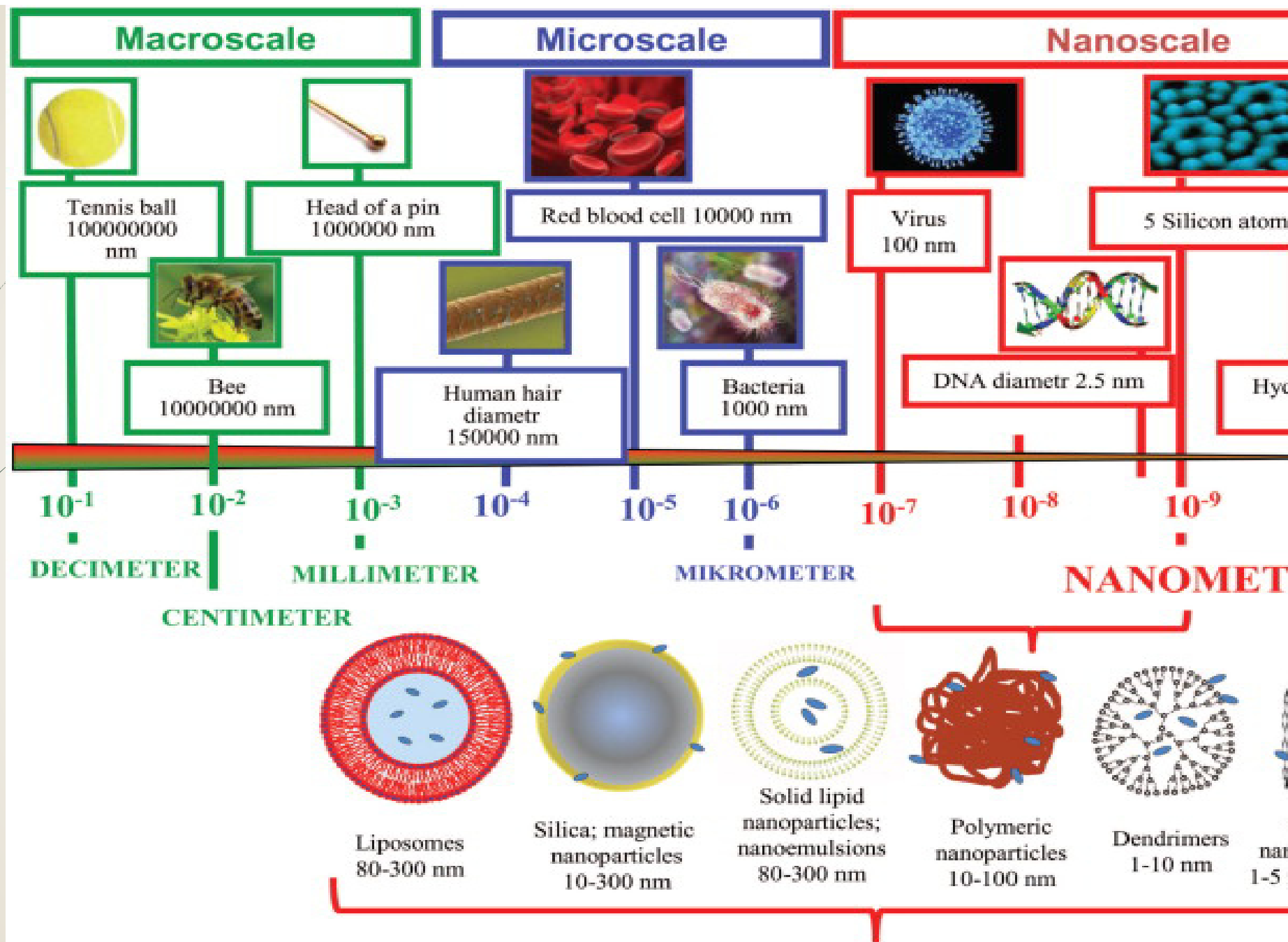
Traditional
Drugs



Nano-
particles



Nanomaterial characterization: Responsible, Systematic, Standardized



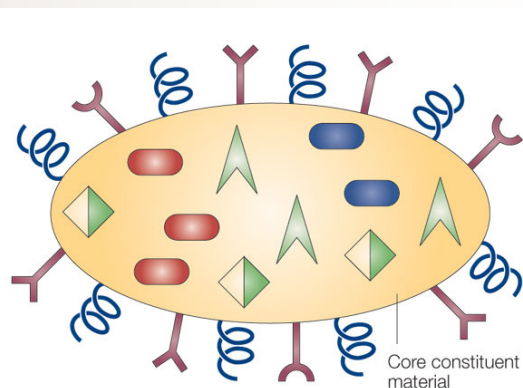
Nanoparticles as a drug delivery systems

The concept of “Clever” drug targeting system includes the coordinating behavior of three components:

- Multi-functional platforms:
 - Targeting
 - Delivery
 - Reporting, biosensing

→ **In one package**

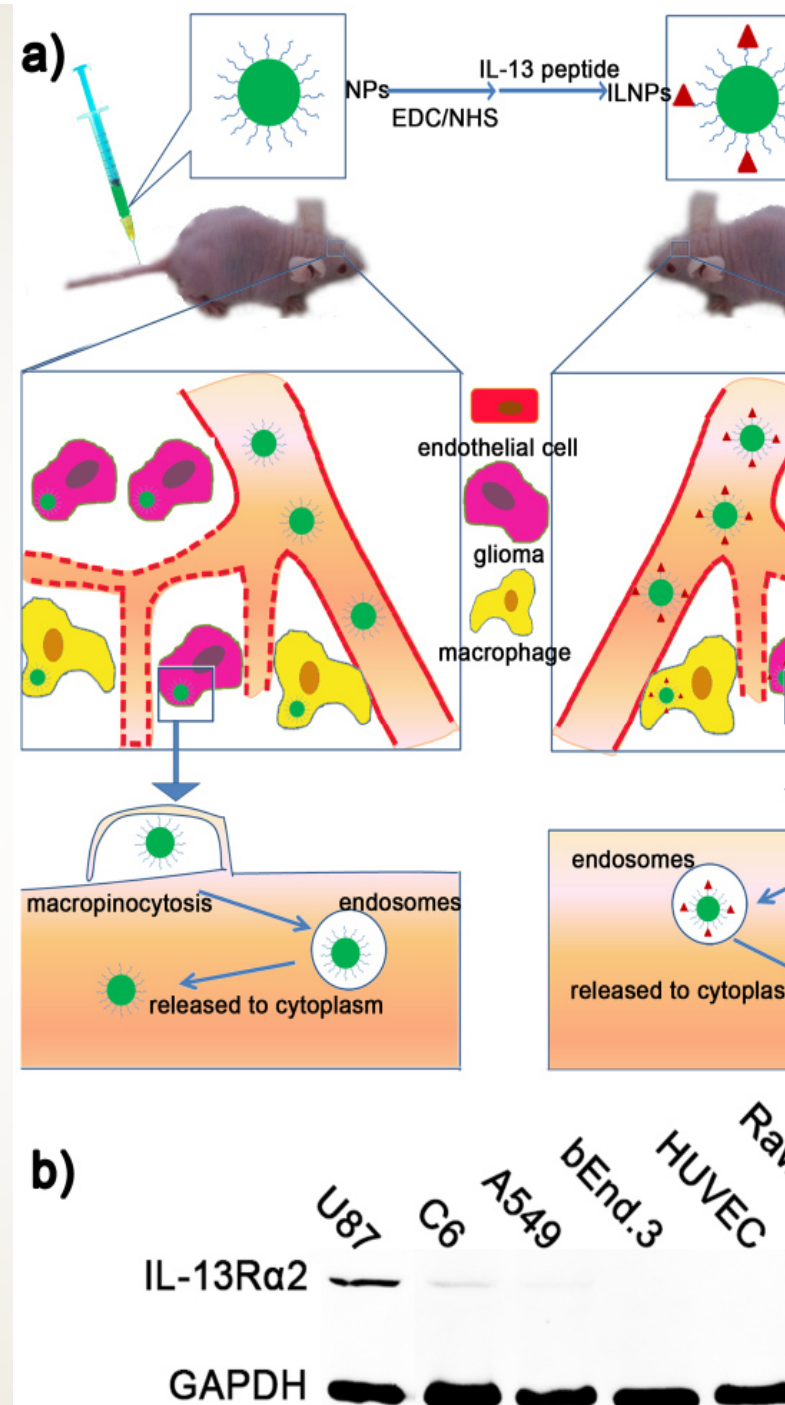
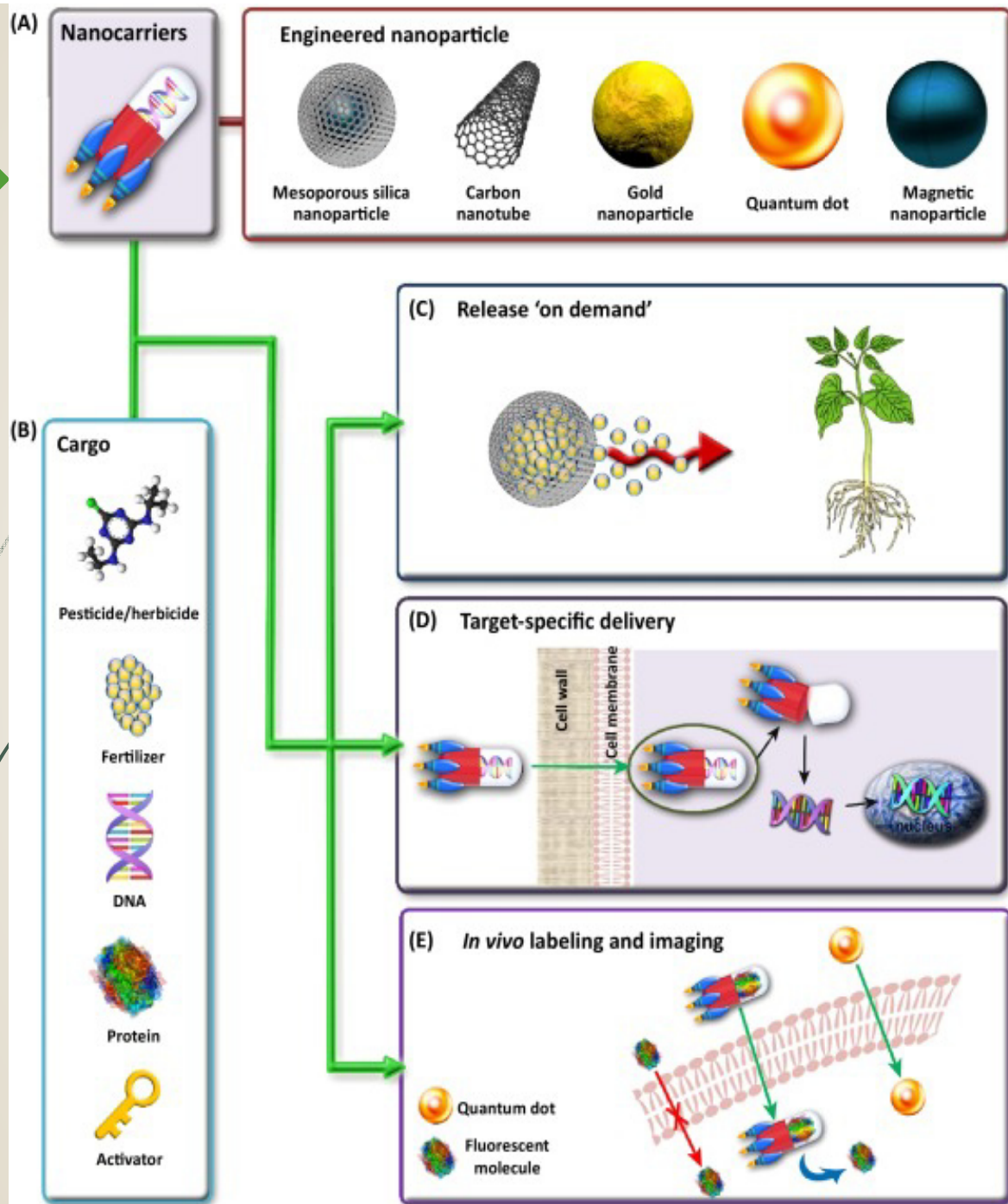
Free drug formulations do not possess multi-functional characteristics

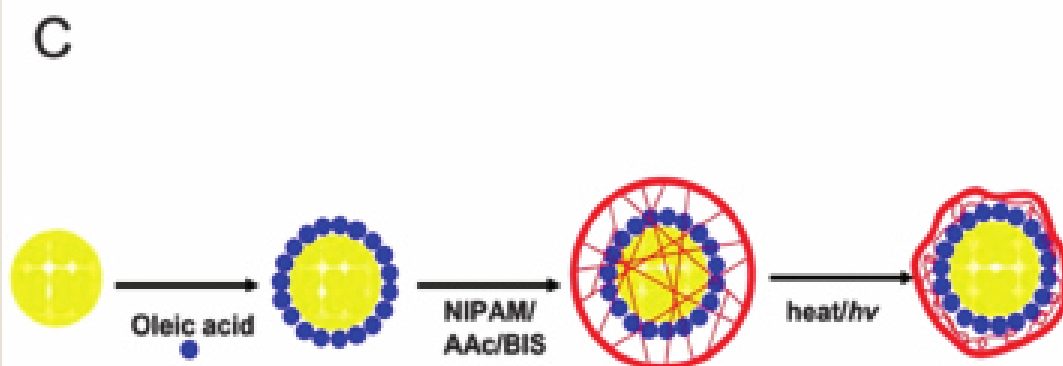
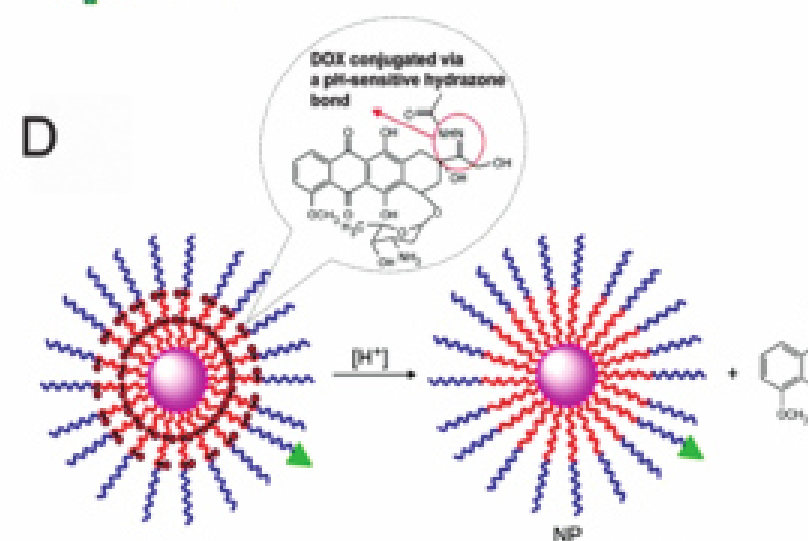
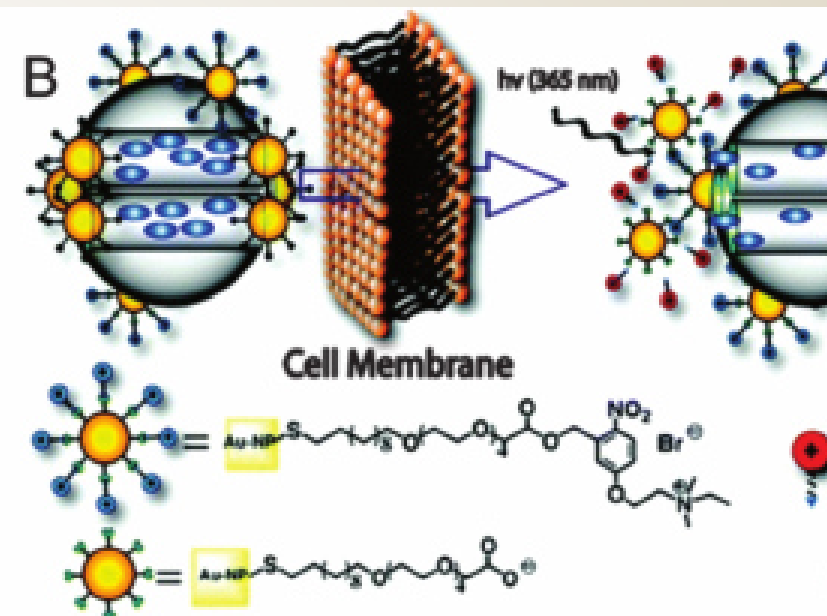
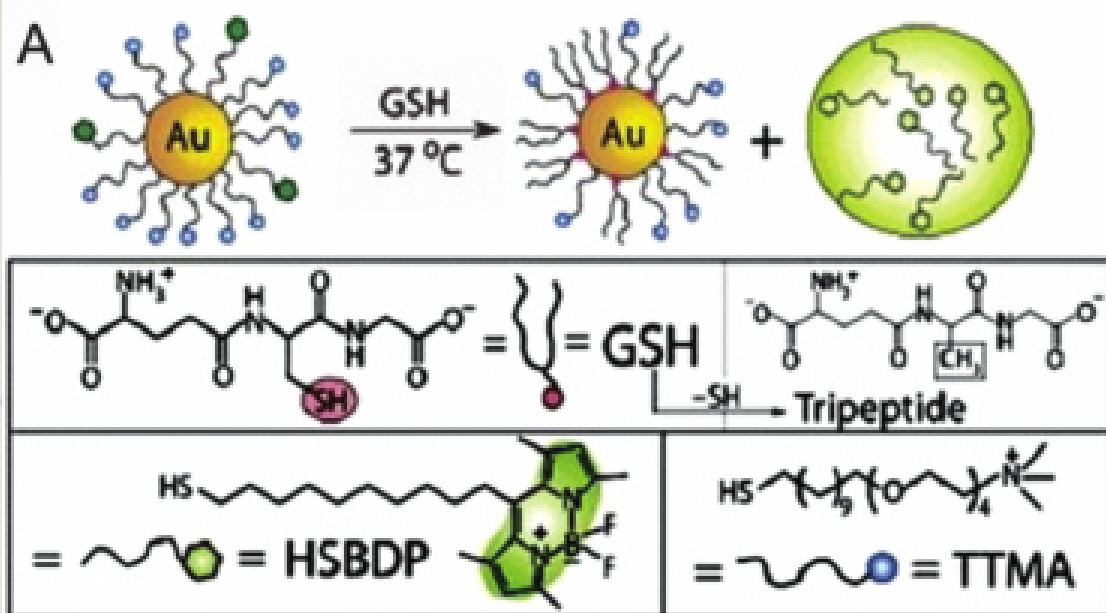


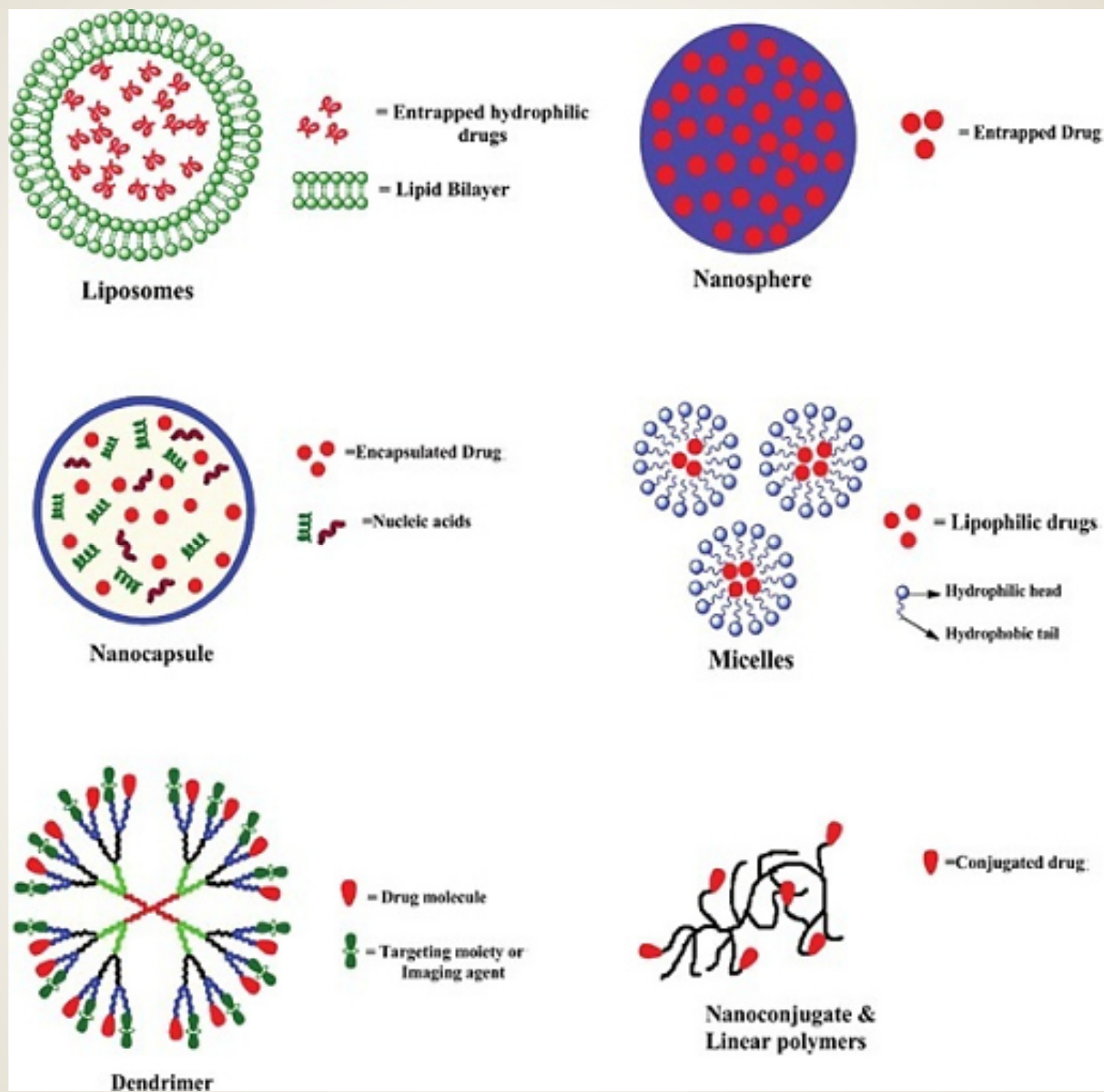
Therapeutic or imaging payload	Biological surface modifier
 Drug A	 PEG
 Drug B	 Targeting moieties
 Contrast enhancer	
 Permeation enhancer	

recognizes and binds the target
carries the drug
provides a therapeutic action to the specific

M. Ferrari, Nature Reviews 5, 161 (2005)

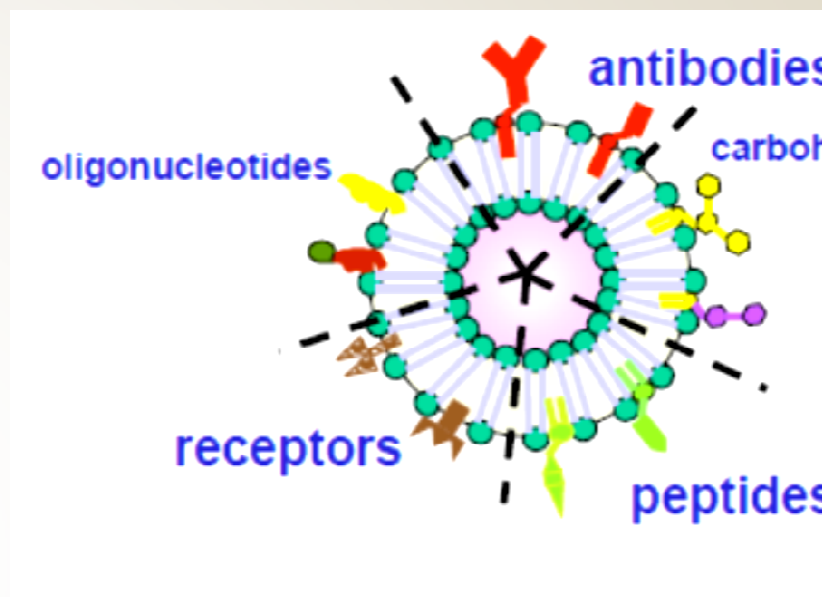






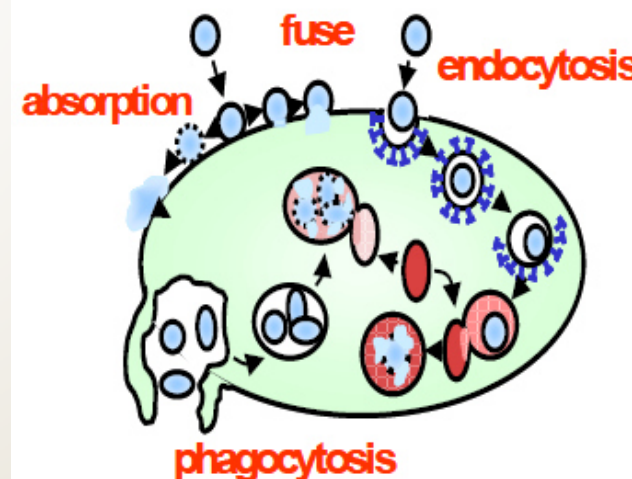
Targeting moieties:

- Antibodies
- Proteins
- Lipoproteins
- Hormones
- Charged molecules
- Polysaccharides
- Low-molecular-weight ligands



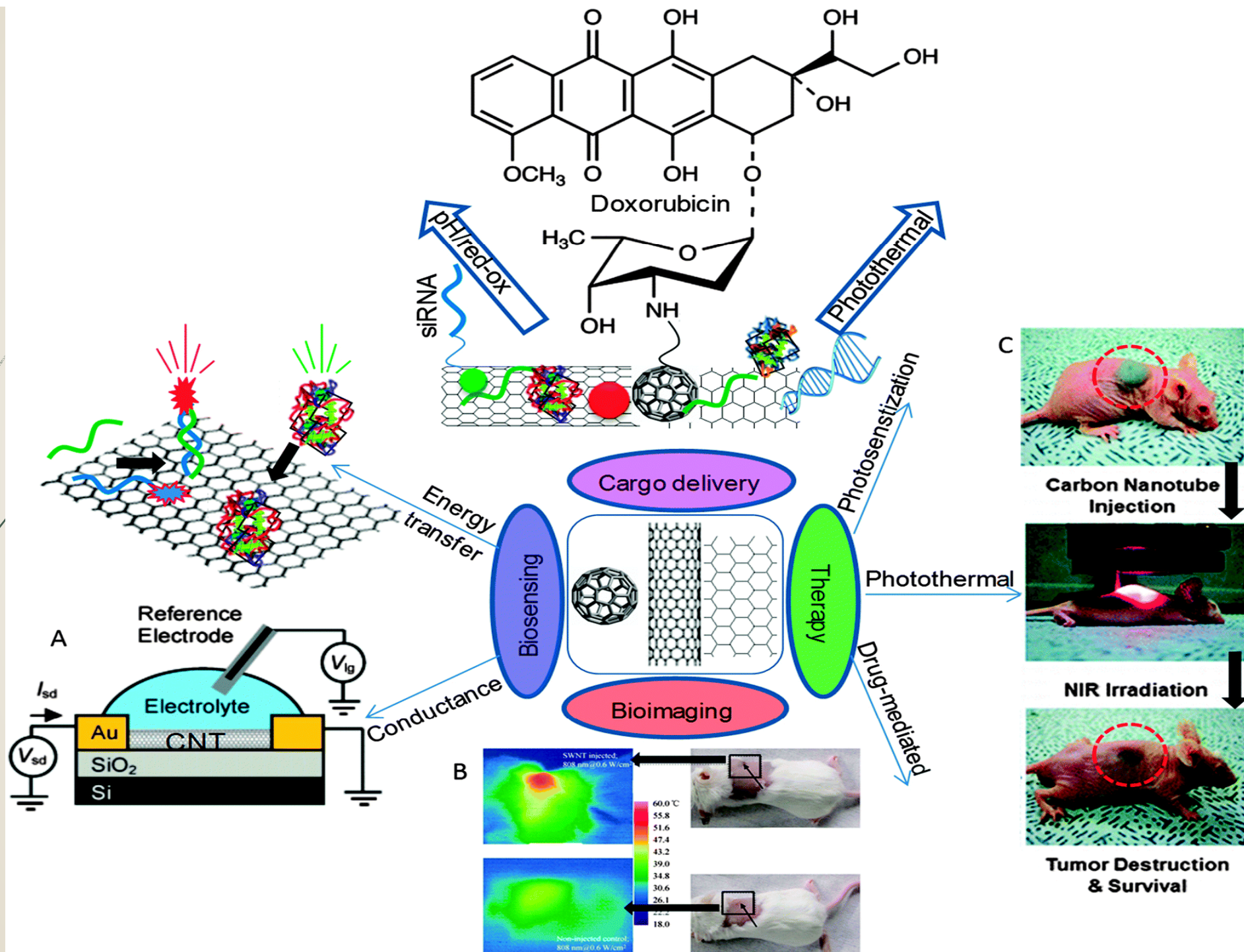
Interactions Between Biological Systems and Nanostructure

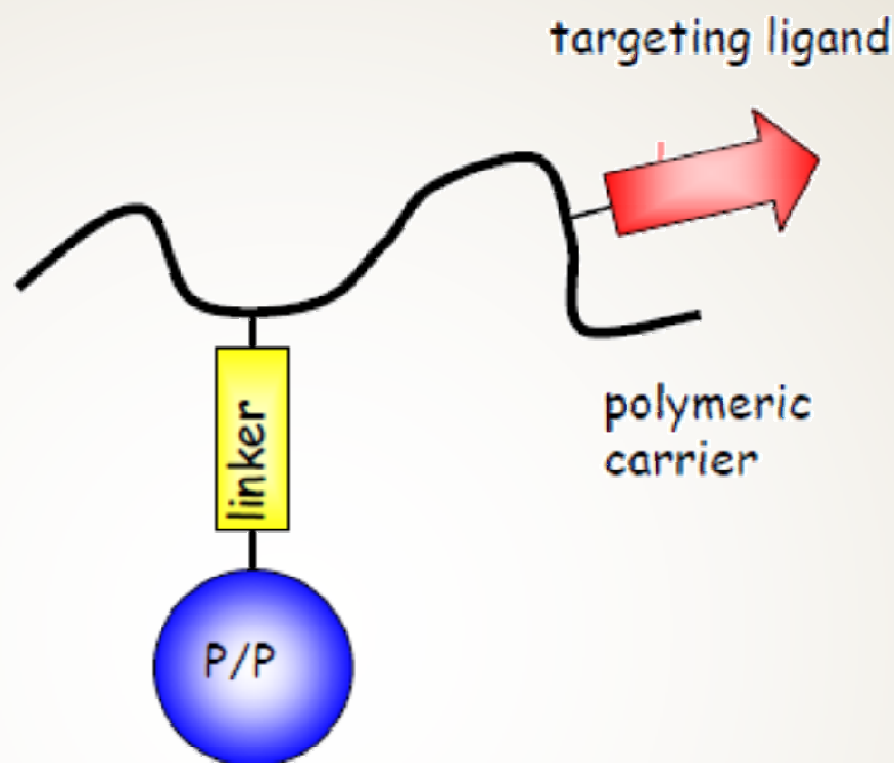
- Interaction of nanostructures with plasma proteins and relation between protein adsorption and removal of nanostructures from the circulation by the reticulo-endothelial system.
- Adsorption of nanostructures to cells
(in relation to the surface chemical characteristics, size and shape of the nanostructures).
- Uptake and recycling, trans-endocytosis and endosomal escape of nanostructures.
- Safety evaluation:
In vitro/in vivo cytotoxicity, haemocompatibility, immunogenicity and genotoxicity testing.
- In vivo carrier biodistribution and degradation.



Nanocarriers as DDS

- ❖ Exhibit higher intracellular uptake
- ❖ Can penetrate the submucosal layers while the microcarriers are predominantly localized on the epithelial lining.
- ❖ Can be administered into systemic circulation without the problems of particle aggregation or blockage of fine blood capillaries
- ❖ The development of targeted delivery is firmly built on extensive experience in pharmacology, chemistry, pharmacology, toxicology, and nowadays is being pursued as a multi- and interdisciplinary effort.





- | | |
|---------------------------|--|
| • P/P | : peptide / protein |
| • Linker | : enzymatically or pH sensitive |
| • Targeting ligand | : peptide / saccharide |
| • Polymer carrier | : Hydrophilic polymers, polyelectrolytes |

PEGylated for Cancer Therapy



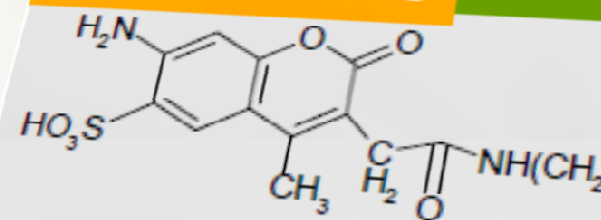
Surface
modification

Adhesion



Cysteamine hydrochloride

Fluorescence



Alexa fluor 350 cadaverine

Nanogels

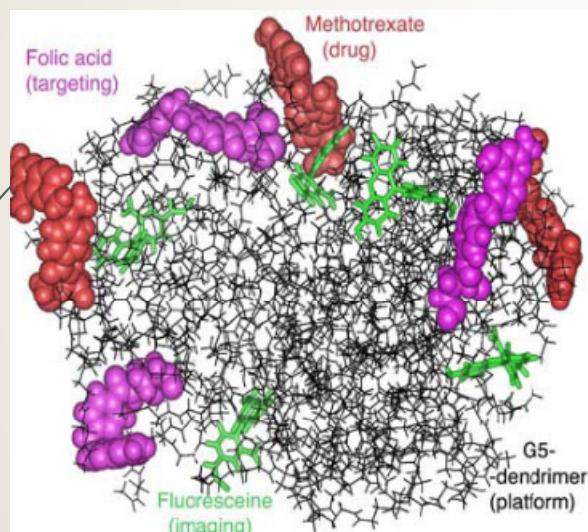
Three-dimensional, hydrophilic, stimuli-responsive polymeric networks:
exhibit dramatic changes in network structure or swelling behavior in response to various external stimuli.

- ✓ **Thermosensitive:** NIPAAm, NIPAAm-DMAM, DEAM-DMAM
- ✓ **pH sensitive:** 2-hydroxyethyl methacrylate, acrylic acid

Nanoparticle-based Therapies: Different Approaches

Dendrimers:

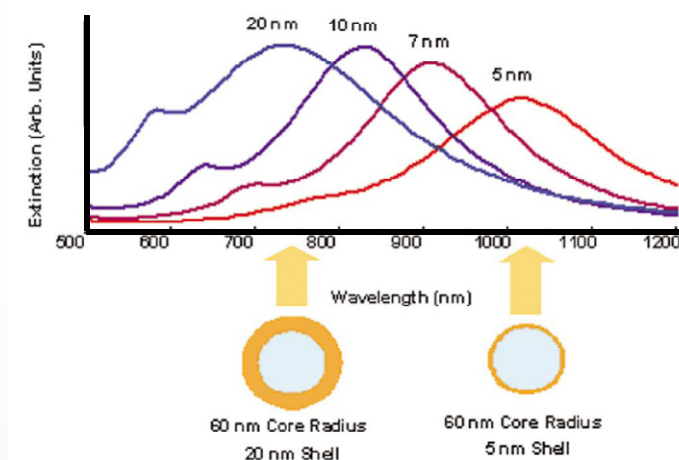
Targeted delivery of methotrexate



J. Baker, et al., Cancer Res. 65, 5317 (2005)

Nanoshells:

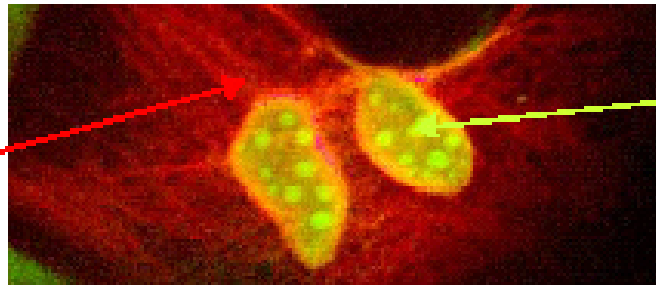
Photothermal therapy



N. Halas, J. West et al,
Ann Biomed Eng. 34, 15 (2006)

Nanocrystals as Fluorescent Biological Labels

5 nm
crystals
bound to
actin fibers



3.5 nm
crystals
bound to
cell nucleus

- ▶ Significant advantages over conventional dyes:
- ▶ Reduced photobleaching
- ▶ Multi-color labeling, parallel screening
- ▶ Infrared labels, blood diagnostics
- ▶ Molecular size nanocrystals are bio-compatible, with many other possible applications

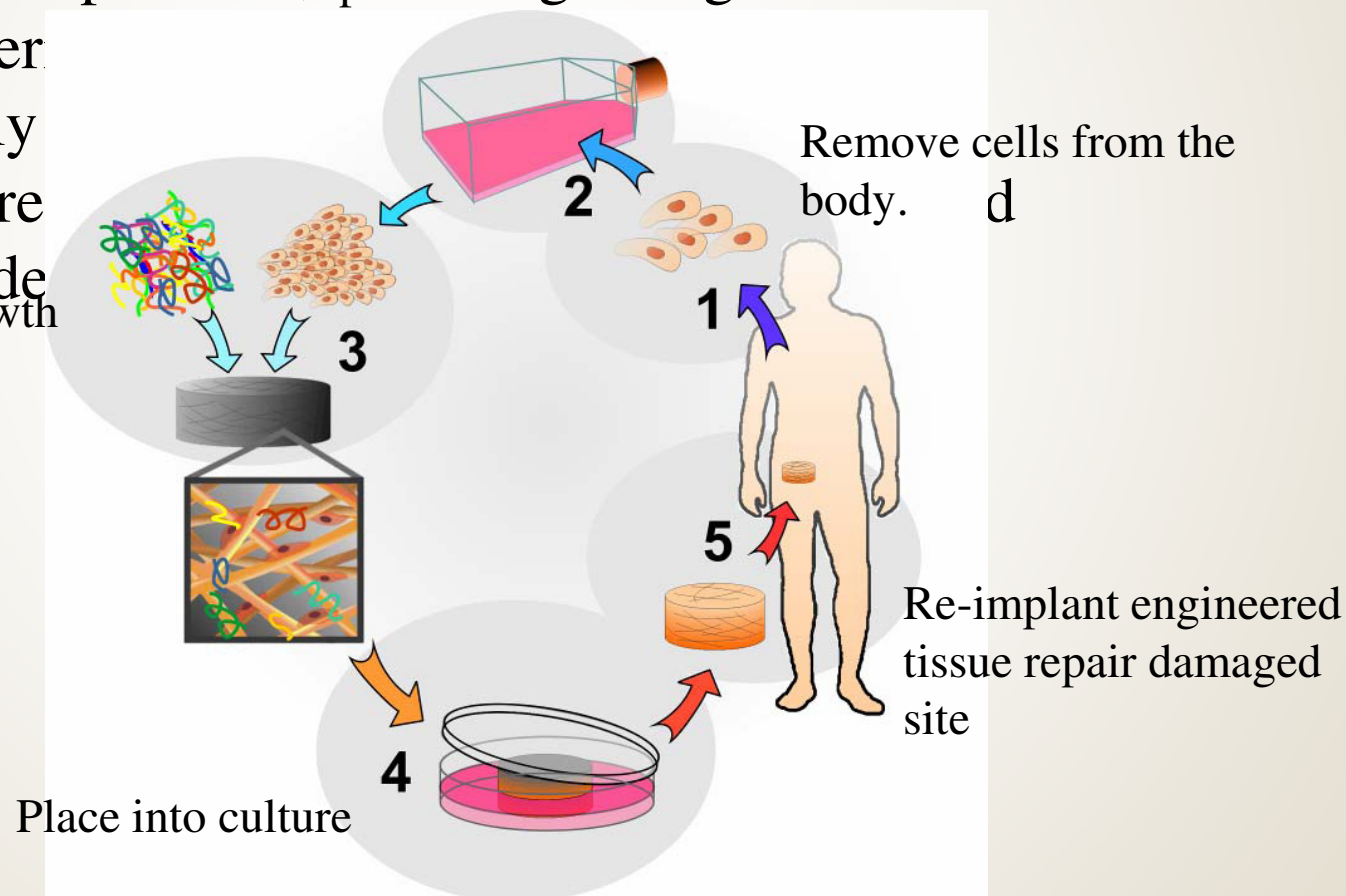
ANY?

Tissue Engineering

- Nano/micro particles, including living animal cells, bacteria

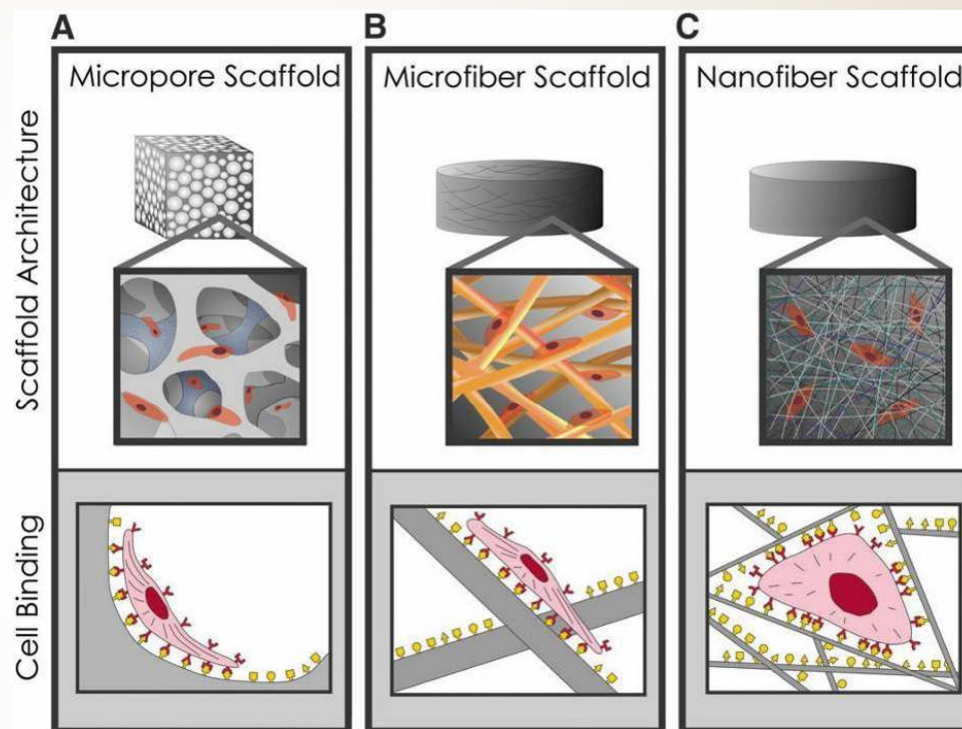
be optically defined through laser-guided

Seed onto an appropriate scaffold with suitable growth factors and cytokines



Why we apply Nanotech in TE?

Tissue Engineering is a methodology
+
Nanotechnology is a tool



Cells on microfibrinous scaffolds have a polarized relationship, with one side of the cell attached to the scaffold, the other exposed to physiological media. **In comparison, it is likely that cells are more naturally constrained by nanofibrous scaffolds.**

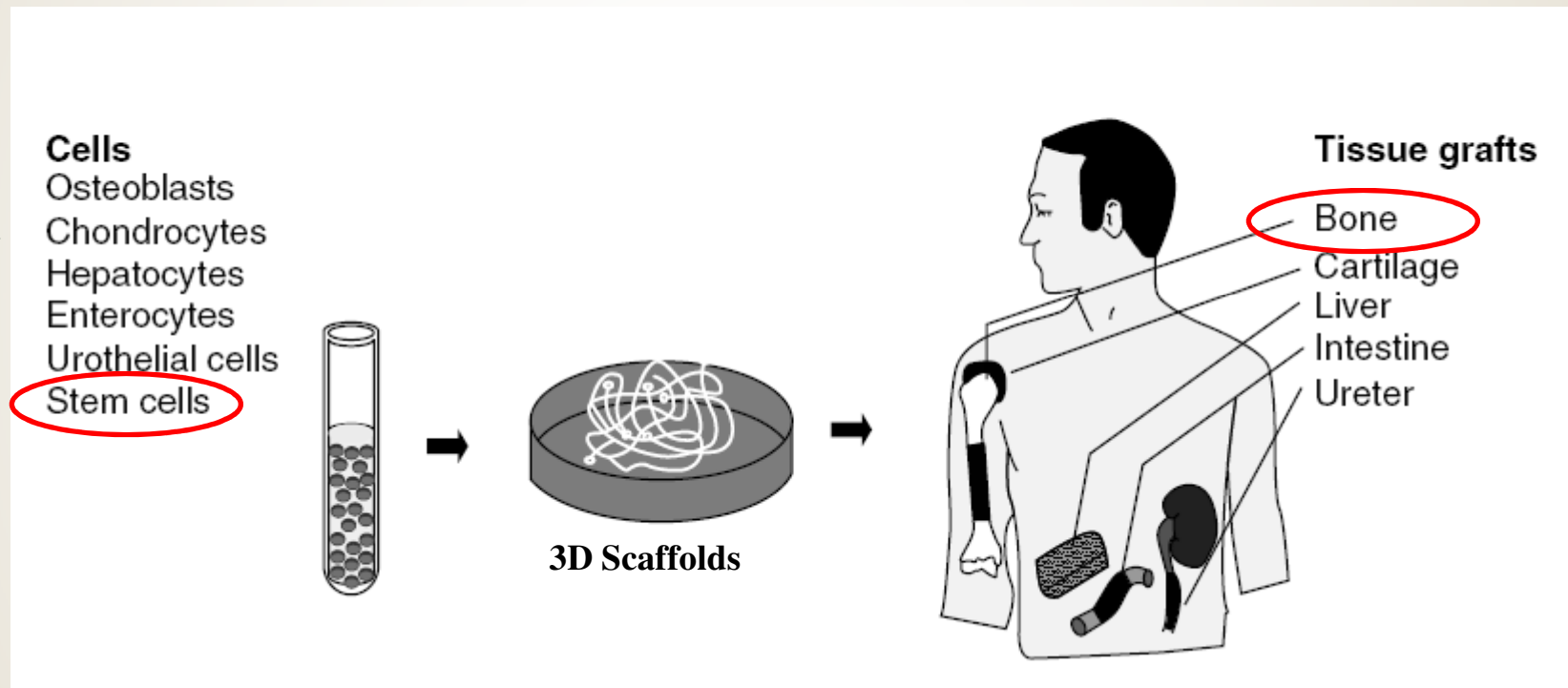
Synthetic polymers

- Polyglycolic acid (PGA)
 - Highly crystalline, hydrophilic, byproduct is glycolic acid
- Polylactic acid (PLA)
 - Hydrophobic, lower melting temperature, byproduct is lactic acid
- Polydioxanone (PDO)
 - Highly crystalline
- Polycaprolactone (PCL)
 - Semi-crystalline properties, easily co-polymerized, byproduct caproic acid
- Blends
 - PGA-PLA
 - PGA-PCL
 - PLA-PCL
 - PDO-PCL

Natural

- Elastin
- Gelatin collagen
- Fibrillar collagen
- Collagen blends
- Fibrinogen

Overview



DIABETIC DELAYED WOUND HEALING

Manish Mishra, Her
Department of Med
Varanasi, INDIA-22

Diabetes mellitus is r
have impaired wound
abnormal apoptosis o
diabetes. Silver has b
Nowadays, silver-bas
infections in burns,
nanosized and highly
exchanging. This revi
involved in delayed w

Keywords: Diabetes m

(Received March 25, 2

Int. J. Mol. Sci. **2013**,

Article

Active Silver Nanoparticles

Chiara Rigo ¹, Letizi
Chiara Gardin ², Wan
Carlo Barbante ⁴ and

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Santa Marta, Dorso

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Italy; E-Mails: letizi

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Received: 23 Decemb

Published: 1 March 2

Influence of Gold Nanoparticles on Wound Healing Treatment in Rat Model: Photobiomodulation Therapy

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Wan Norsyuhada Binti Wan Mohd Shukri, MSc,¹ Nurlaili Zakaria, Dip,¹
Nurfatin Musa, BSc,² and Ganesan Krishnan, PhD¹

¹Laser Center, Ibnu Sina Institute for Scientific and Industrial Research (ISI-SIR), Universiti Teknologi
Johor Bahru, Johor 81310, Malaysia

²Faculty of Science, Universiti Tun Hussein Onn Malaysia, Parit Raja, Johor 86400, Malaysia

Background and Objective: The aim of this study is to investigate the effect of gold nanoparticles (AuNPs) in photobiomodulation therapy (PBMT) on wound healing process.

Materials and Methods: AuNPs are synthesized by Q-switched Nd:YAG laser ablation technique. Cutaneous wound are induced on 45 Sprague Dawley rats on its dorsal part and then randomly divided into three groups. One group serves as non-treatment group (GC) and another two groups are subjected to AuNPs with and without PBMT. About 808 nm diode laser with output power of 100 mW is used as a light source for PBMT. The treatment was carried out daily with exposure duration of 50 seconds and total fluence of 5 J/cm². Wound area is monitored for 9 consecutive days using a digital camera, and histological examination is performed at 3rd, 6th, and 9th day through hematoxylin and eosin stain as well as Masson's trichrome stain.

Results: The group of rats subjected to AuNPs with PBMT shows significantly accelerated wound closure compared to other groups. Histological results indicate that AuNPs and PBMT group is more effective in stimulating angiogenesis and triggers inflammatory response at early stage.

Conclusion: The application of AuNPs in PBMT has potential to accelerate wound healing due to enhanced epithelialization, collagen deposition and fast vascularization. *Lasers Surg. Med.* 49:380–386, 2017.

© 2016 Wiley Periodicals, Inc.

Key words: gold nanoparticles (AuNPs); photobiomodulation therapy (PBMT); wound healing; Q-switched Nd:YAG laser; 808 nm diode laser; laser ablation synthesis

researchers. Number of wound treatment proposed, that is, pharmacotherapy [1], apy [2–4], extracorporeal shock wave therapy, pressure wound therapy (NPWT) [6], electric therapy [7] as well as light therapy [8–10]. known as photobiomodulation therapy (PB level light to stimulate cellular function cellular respiratory chain to increase the process [11]. A large number of positive res on wound healing have been reported *in v studies* [12–14]. PBMT has capability to inc migration, reduce cellular apoptosis, stimula sis, restore microcirculation, and enhanc wound [15–16]. Typically, during healing immune system releases molecular media inflammatory cytokines, neutrophils, and p amount of reactive oxygen species (ROS) lesion [17–18]. ROS is generated as an acti from cellular metabolism, which function signalling pathways [19]. Yet, the excess an interacting with biological molecules would RNA, protein, cellular function, and inhibi High level of ROS leads to oxidative stress, v healing process. Therefore, antioxidants are lower the level of oxidative stress and a damaging effects of ROS [21].

Institution at where the work was performed Ibnu Sina Institute for Scientific and Industrial (ISI-SIR), Universiti Teknologi Malaysia, 81310 Joho Malaysia.

Conflict of Interest Disclosures: All authors

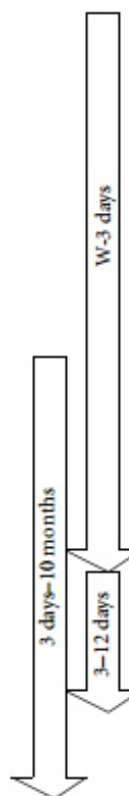


FIGURE 1: The main biological phases of wound healing are well defined. Although pre-healing and healing phases overlap to a certain extent, the

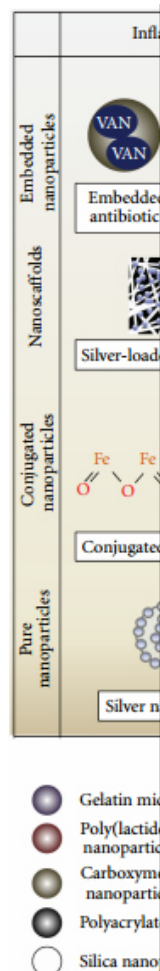


FIGURE 2: Nanostrategies currently employed in wound healing are illustrated. The time course of the healing phase to which each strategy is applied is listed. Two- and three-dimensional scaffolds, PLACL, polyurethane, and PLGA

ACS Central Science

Outlook

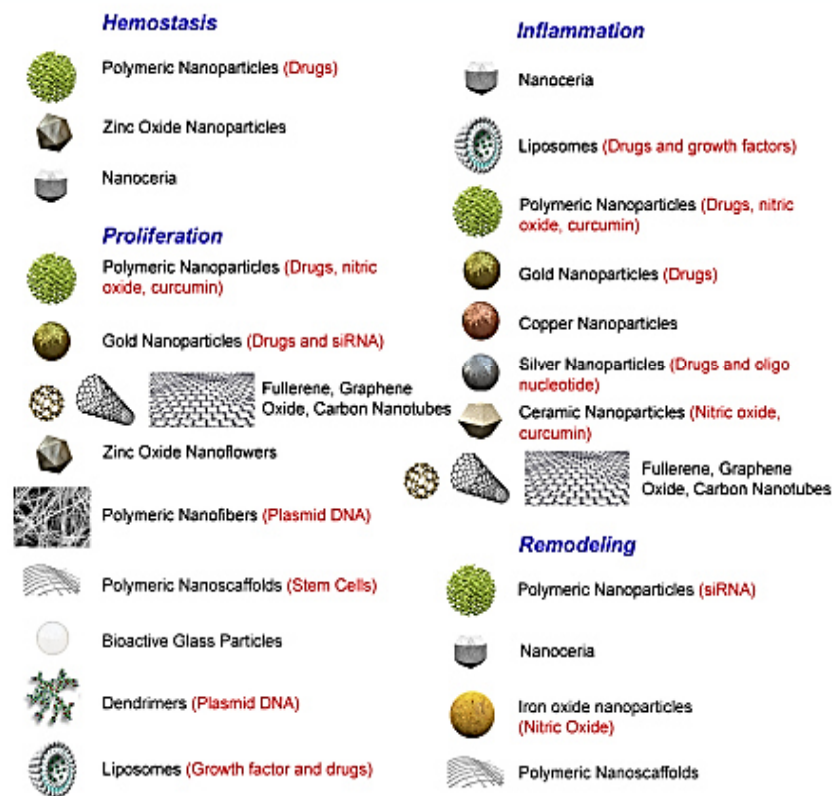


Figure 2. Schematic representation of the nanotechnology-based therapies employed in wound healing.

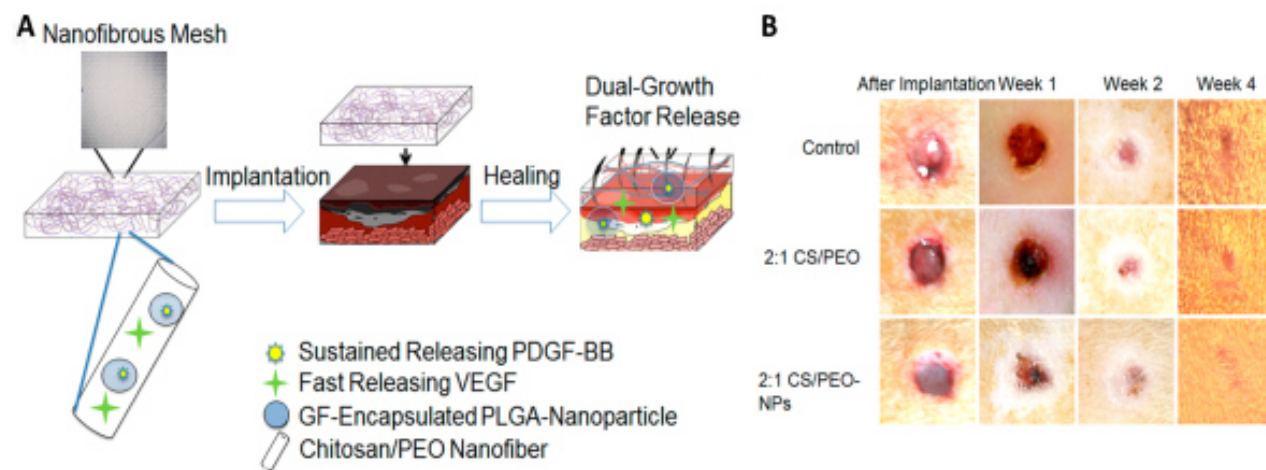


Figure 4. (A) Schematic illustration of the nanoparticle-embedded electrospun nanofibers loaded with two growth factors VEGF and PDGF-BB for the wound healing and (B) representative macroscopic appearance of wound closure after treatment of rat wounds with control, 2:1 chitosan/PEO (CS/PEO) without growth factor, and 2:1 CS/PEO-NPs with nanoparticles and growth factors. Adapted with permission from ref 114. Copyright 2013 Acta Materialia Inc. Published by Elsevier Ltd.

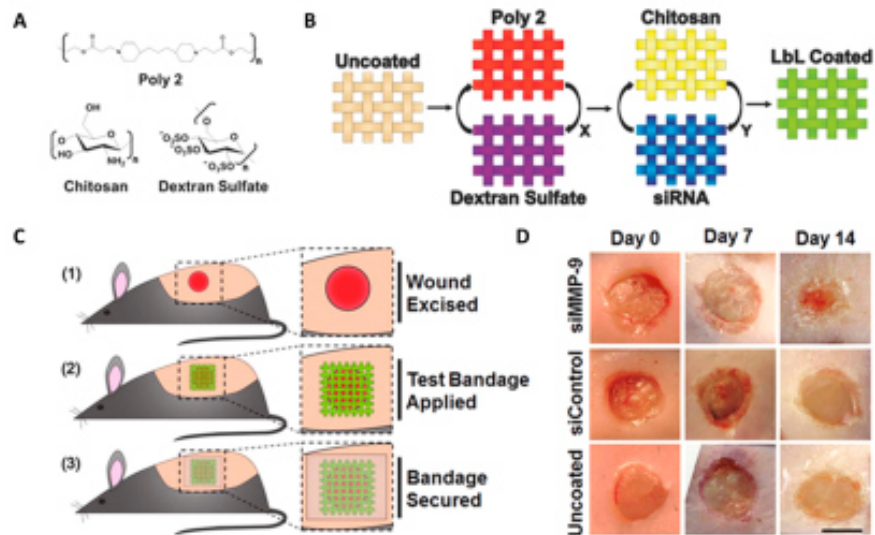
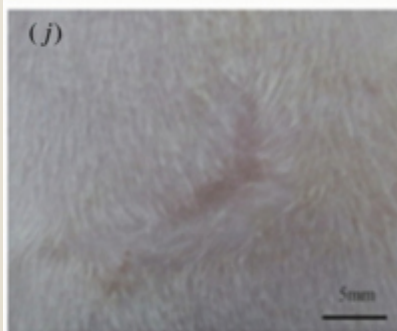
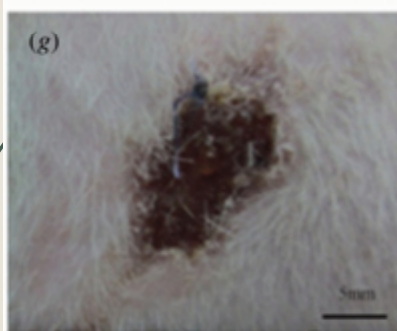
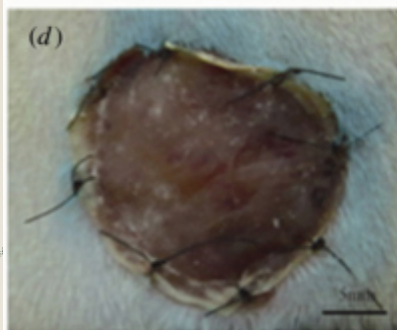
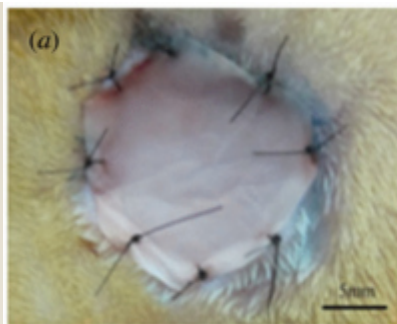


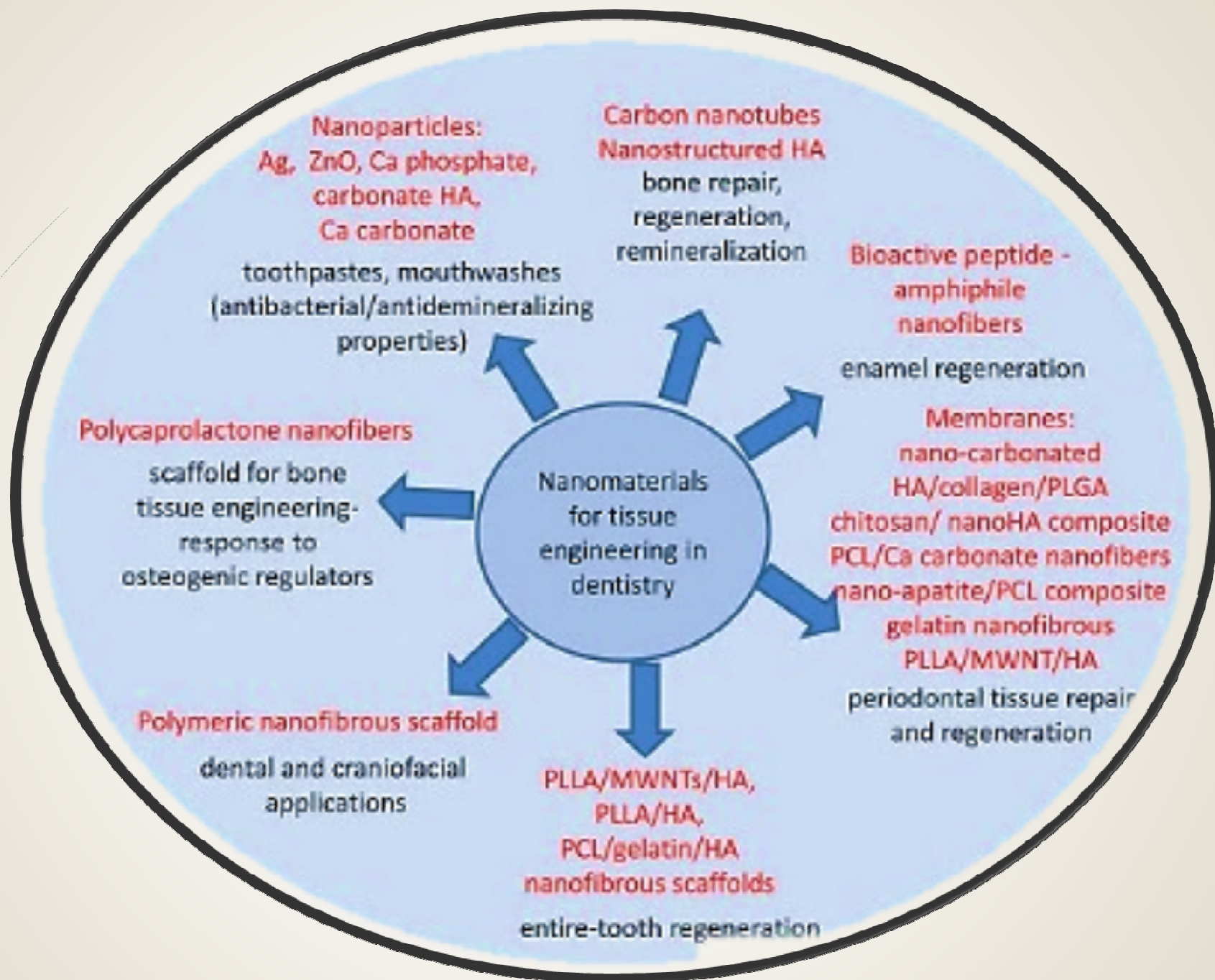
Figure 5. Layer-by-layer (LbL) coating for sustained release of siRNA and reduction of MMP-9 expression. (A) Chemical structures of polymers used for the preparation of LbL coating. (B) Hierarchical structure of LbL films into a single coating. (C) Application of bandages on full-thickness excisional wounds on the backs of mice. (D) Digital imaging of wounds immediately following surgery (day 0) and after 7 or 14 d of treatment. Adapted with permission from ref 118. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.



Group A

ANY?





Nanomaterials

Therapeutic

PolyGA-
PEG-
cisplatin



Solid
lipids



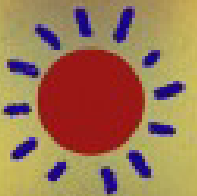
Hydrogels



Gold
nanoparticles



Quantum
dots

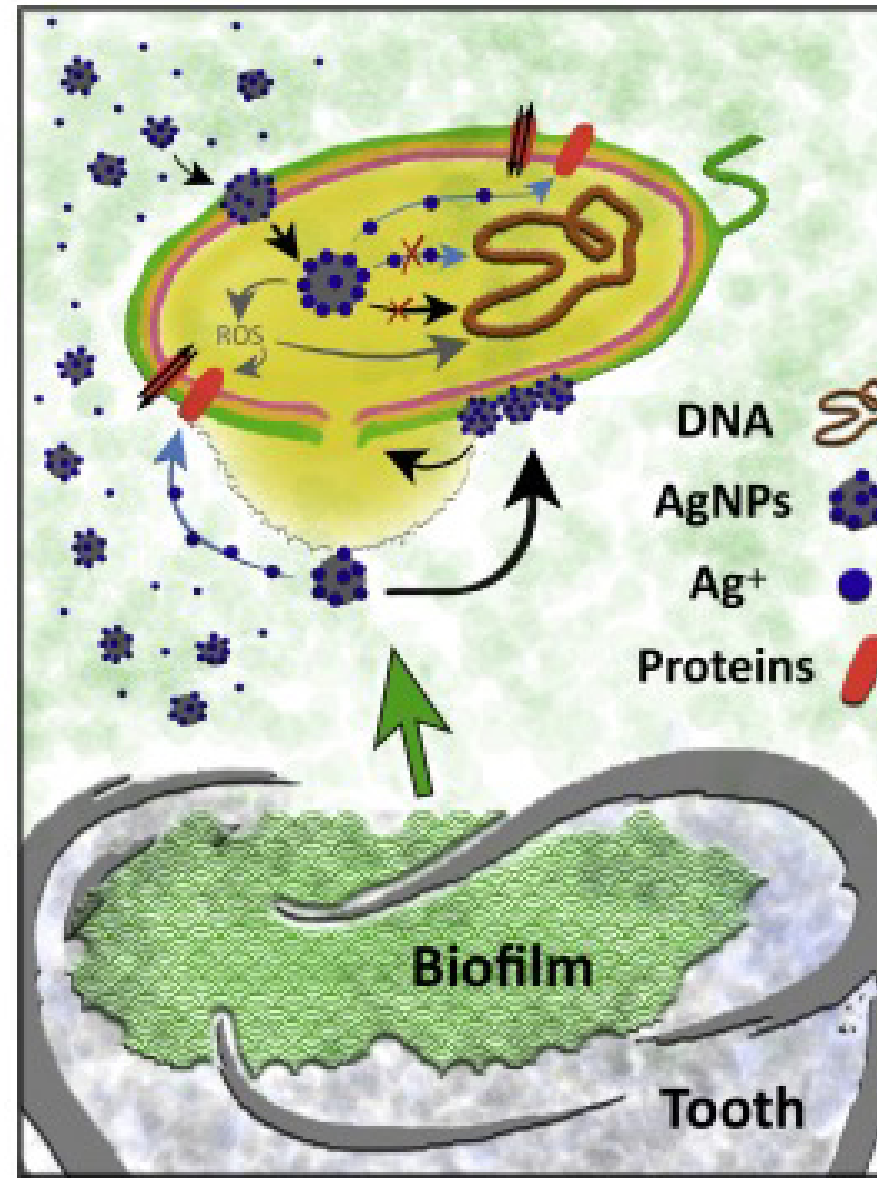
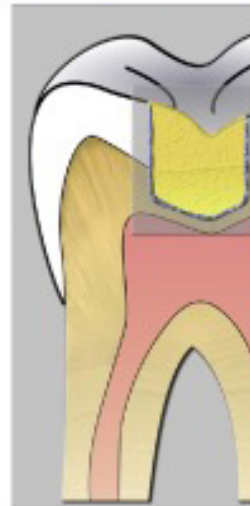
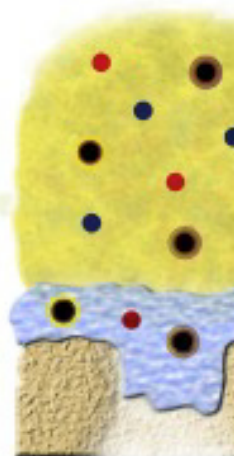


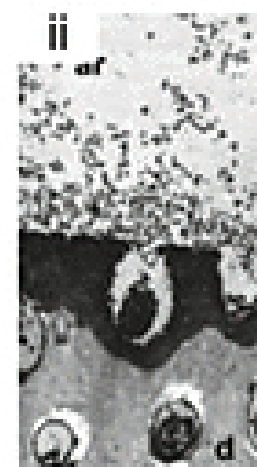
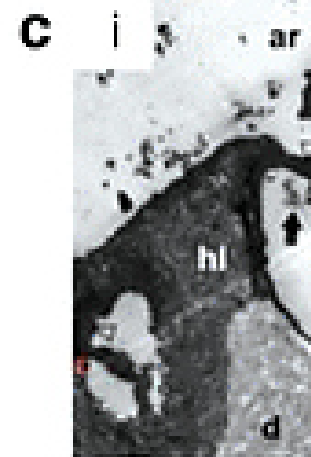
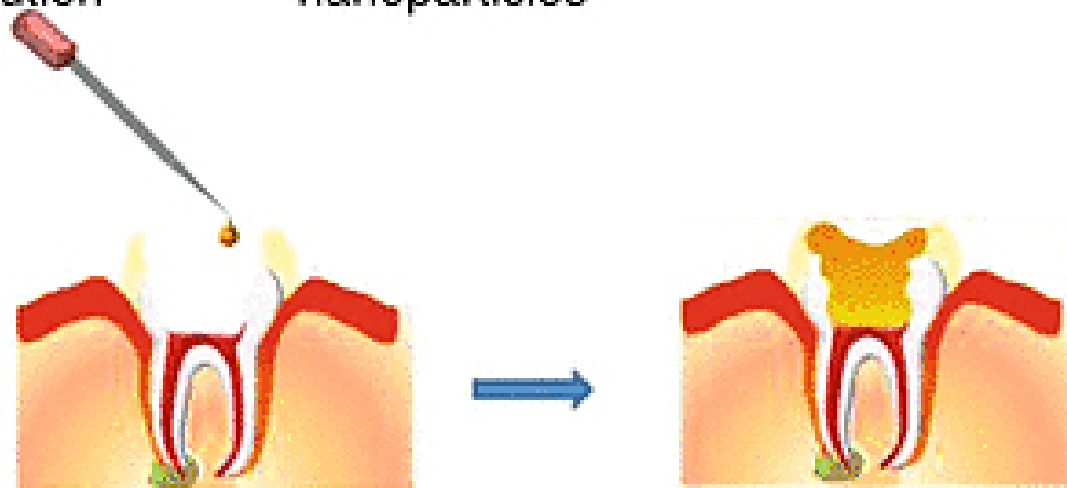
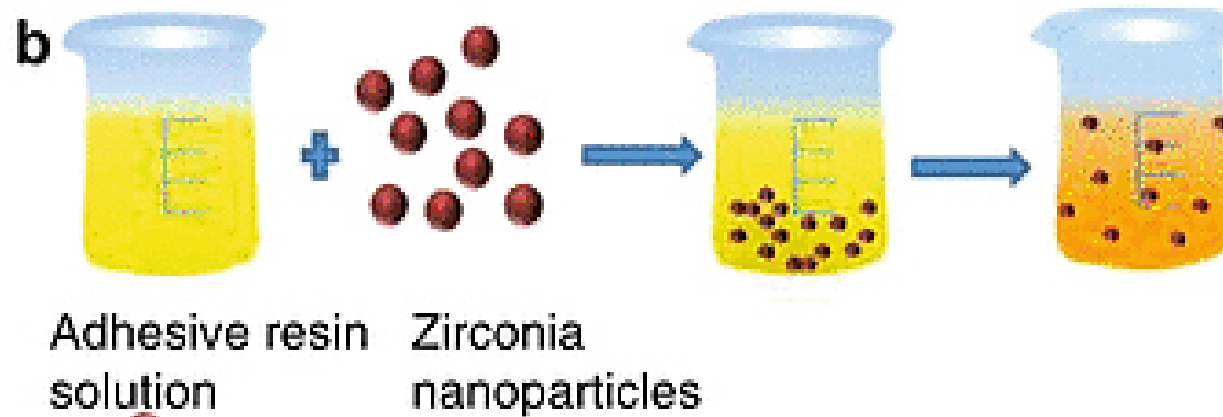
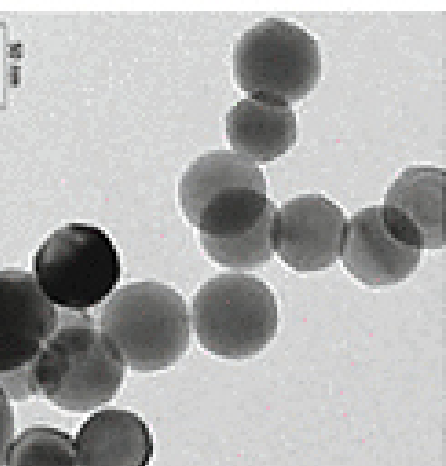
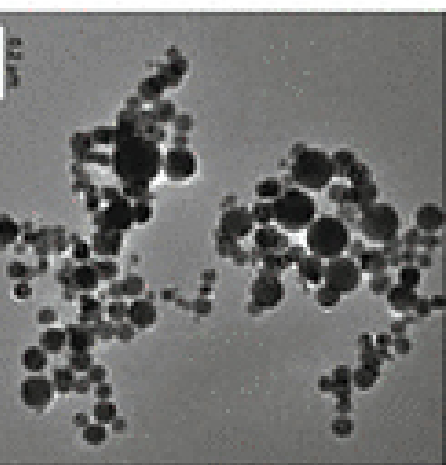
Dendrimers

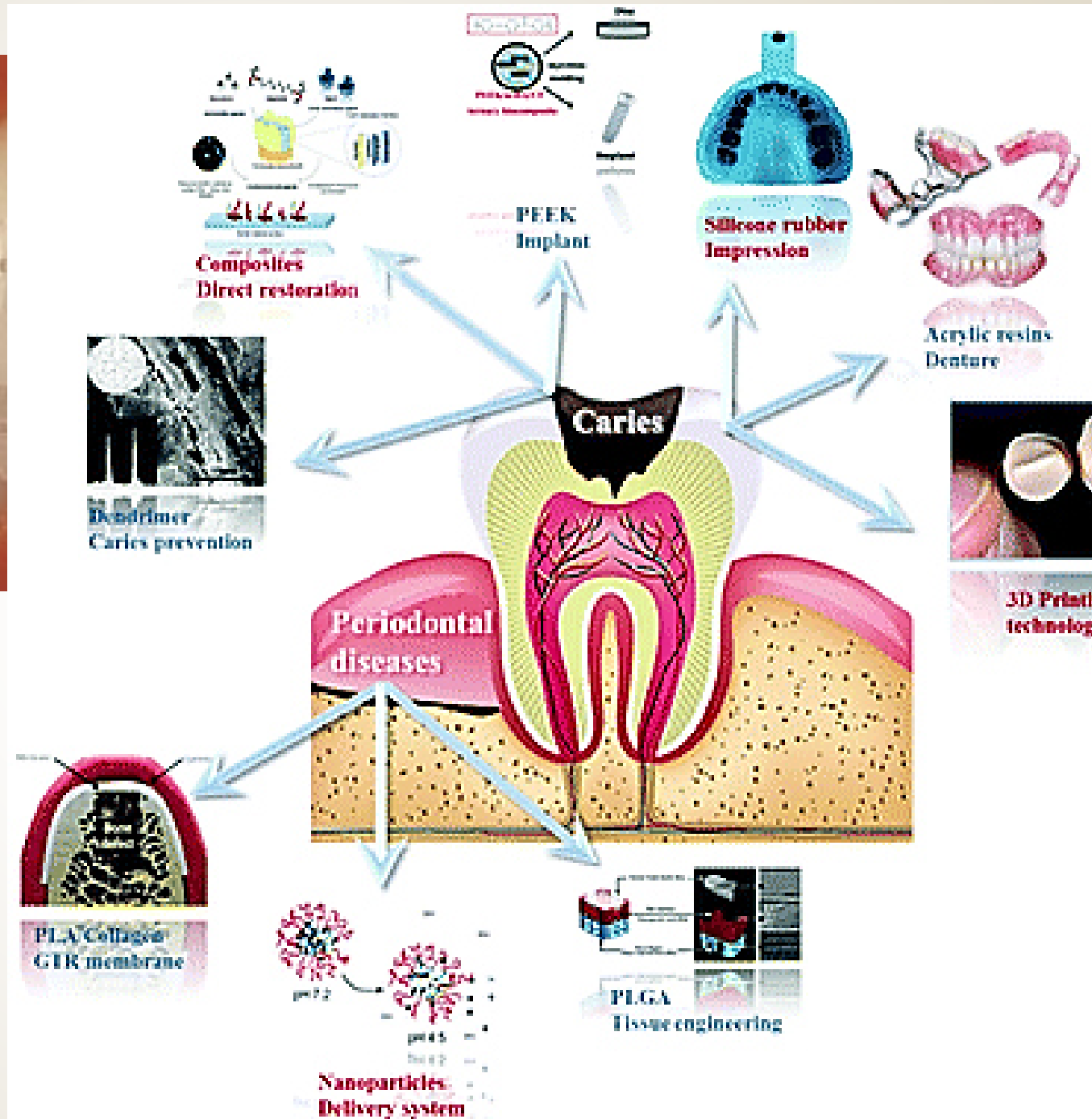


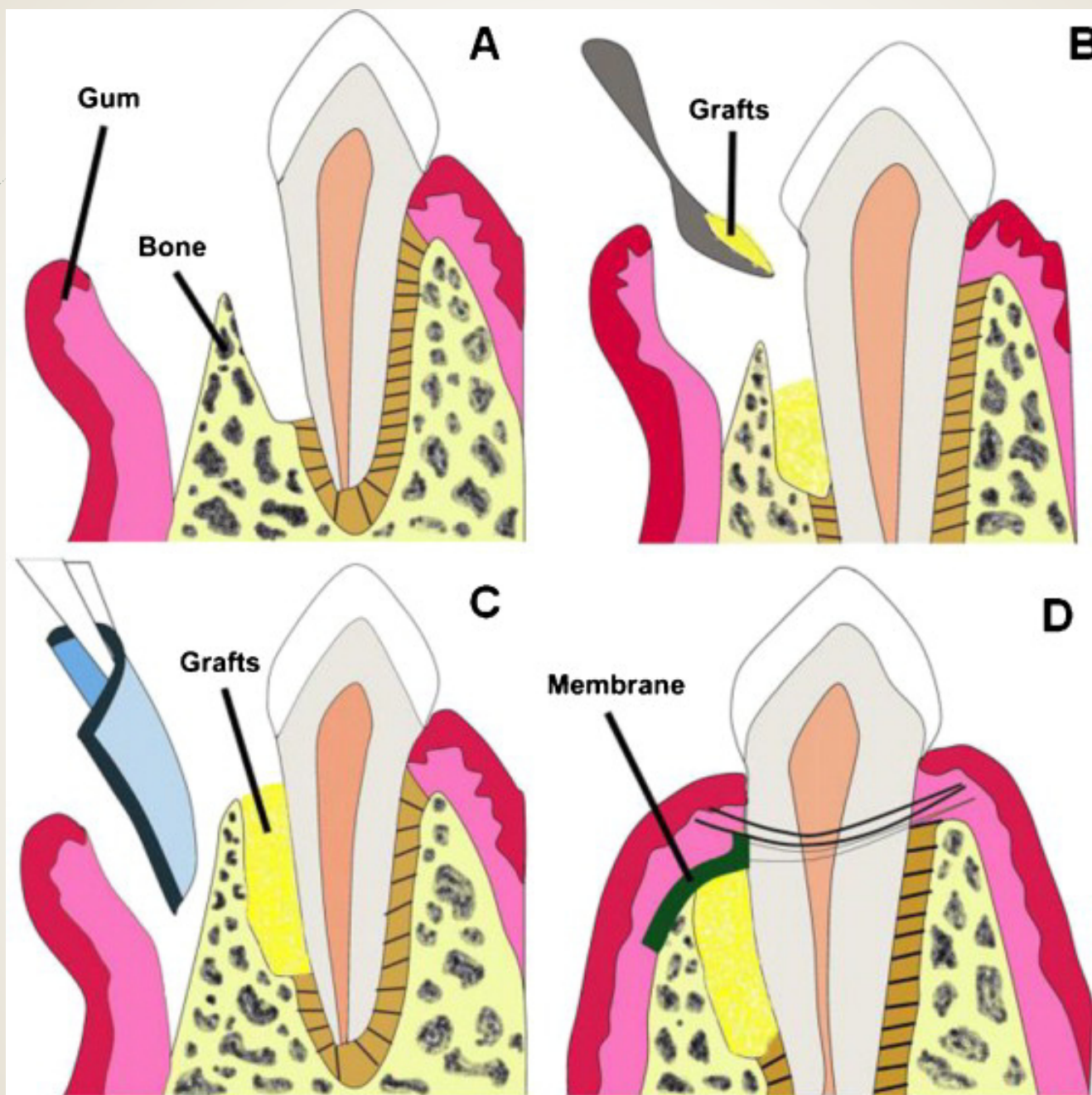
Key:

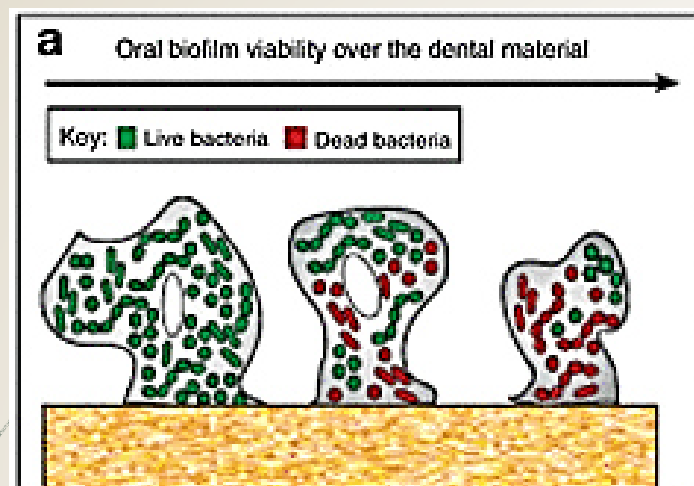
- Bioactive molecules: antimicrobial, antibiotics,...
- Organic monomers
- Nanoparticle
- Nanoparticle



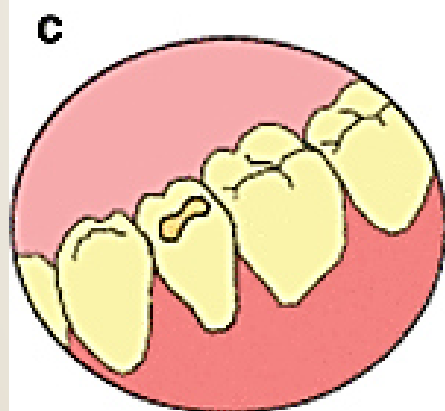




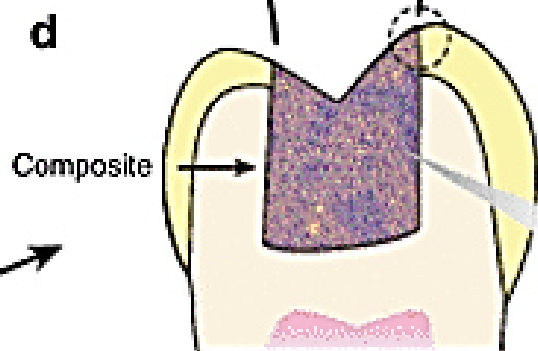




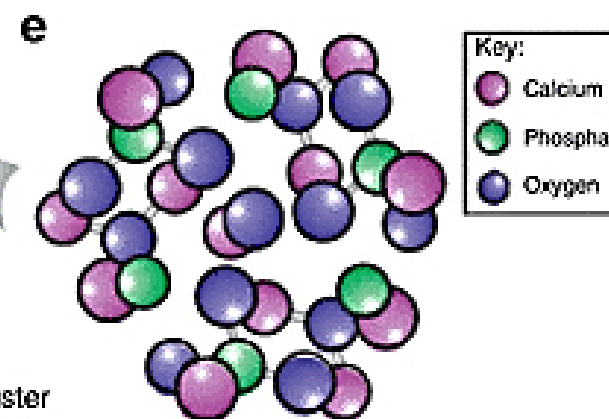
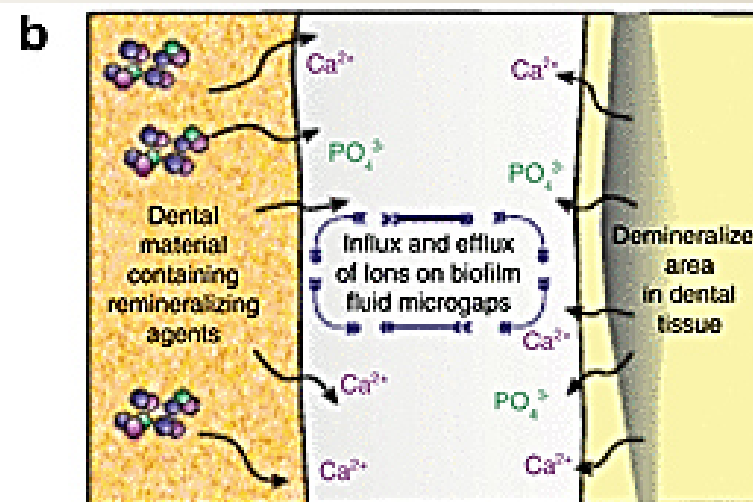
Contact with dental material containing antibacterial agents



Restored tooth with anticaries materials

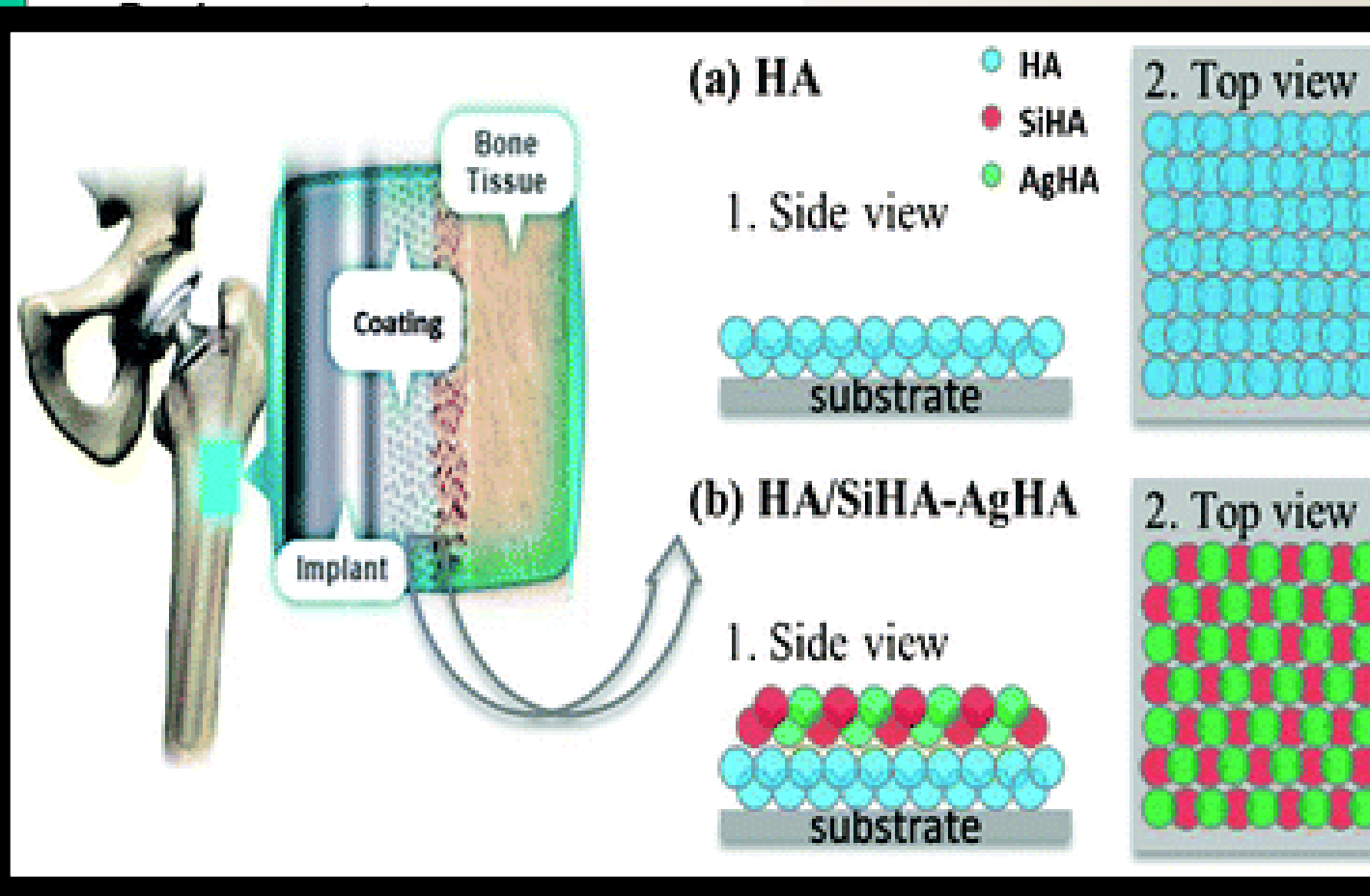
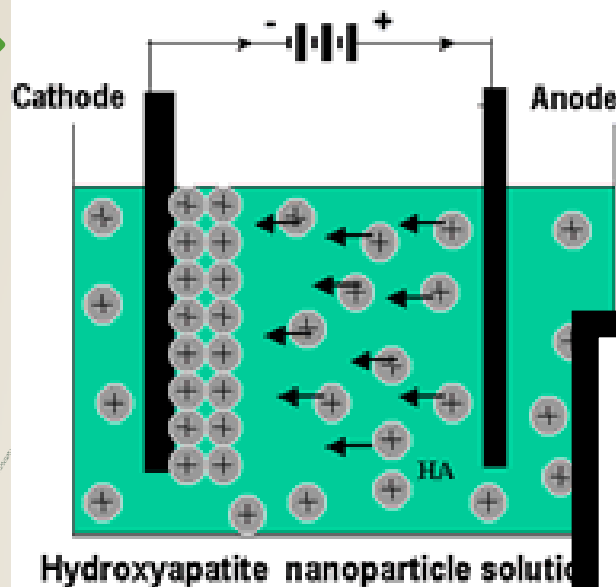


Representative cluster to form nano ACP particles



Nano-Hydroxyapatite

Orthopedics & Drug Delivery -
NanoCoatings for
Artificial Hip, Knee, & Dental



ANY?

ANY?

Nanotechnology: Environmental and Safety Considerations

- Hazard identification
 - *In vitro* toxicity
 - Acute *in vivo* toxicity
 - Subchronic/chronic toxicity
 - Route of exposure
- Dose response
 - External dose
 - Internal dose
 - Biologically effective dose
- Exposure assessment
 - Human exposure

Nanomaterials
production



Chronic exposure
of the worker

Nanomaterials
use for
biomedical
applications

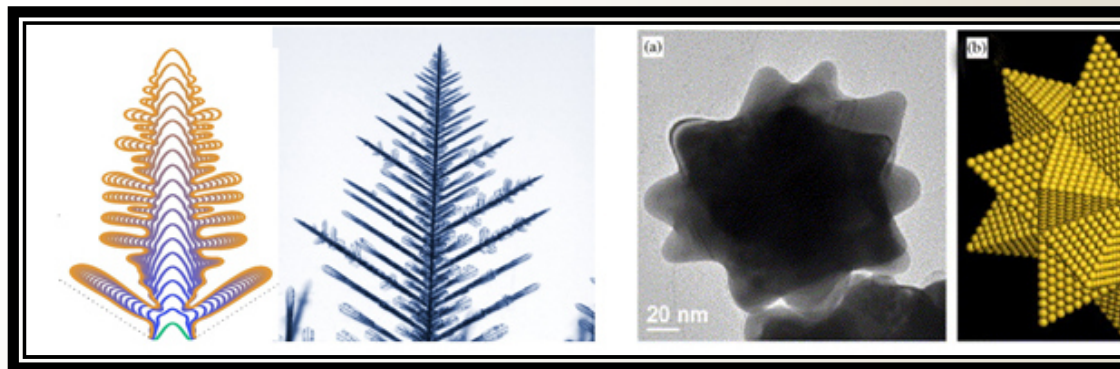


Preclinical studies

ANY?

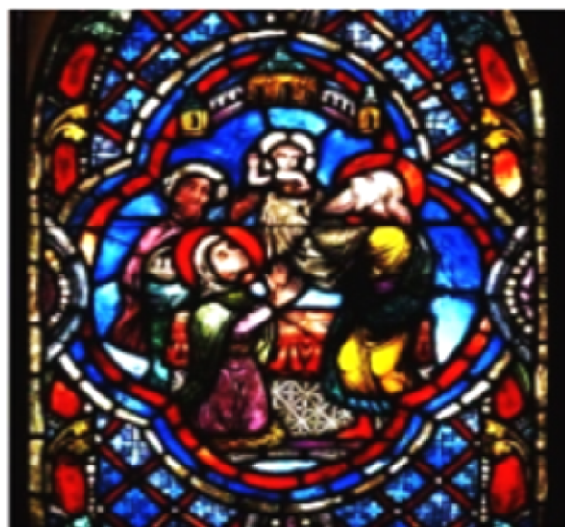
Synthesis methods

- **Precipitation, Coprecipitation**
- **Wet Synthesis Methods**
- **Solution Phase Synthesis**
- **Bottom Up Method**
- **Thermal Decomposition**
- **Solvothermal**
- **Sol-Gel**
- **Hydrothermal**
- **Microemulsion**
- **Reverse Micelle**
- **Chemical Precipitation**
- **Polymer pyrolysis**
- ...

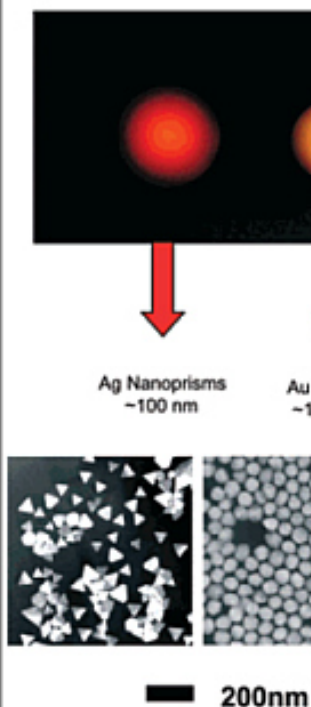


Examples: Gold and silver

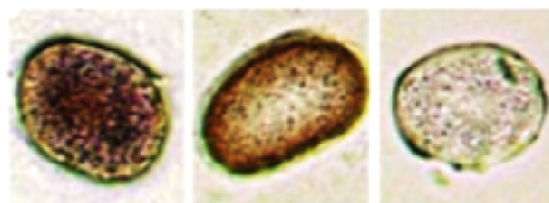
Some Ancient Nano Material

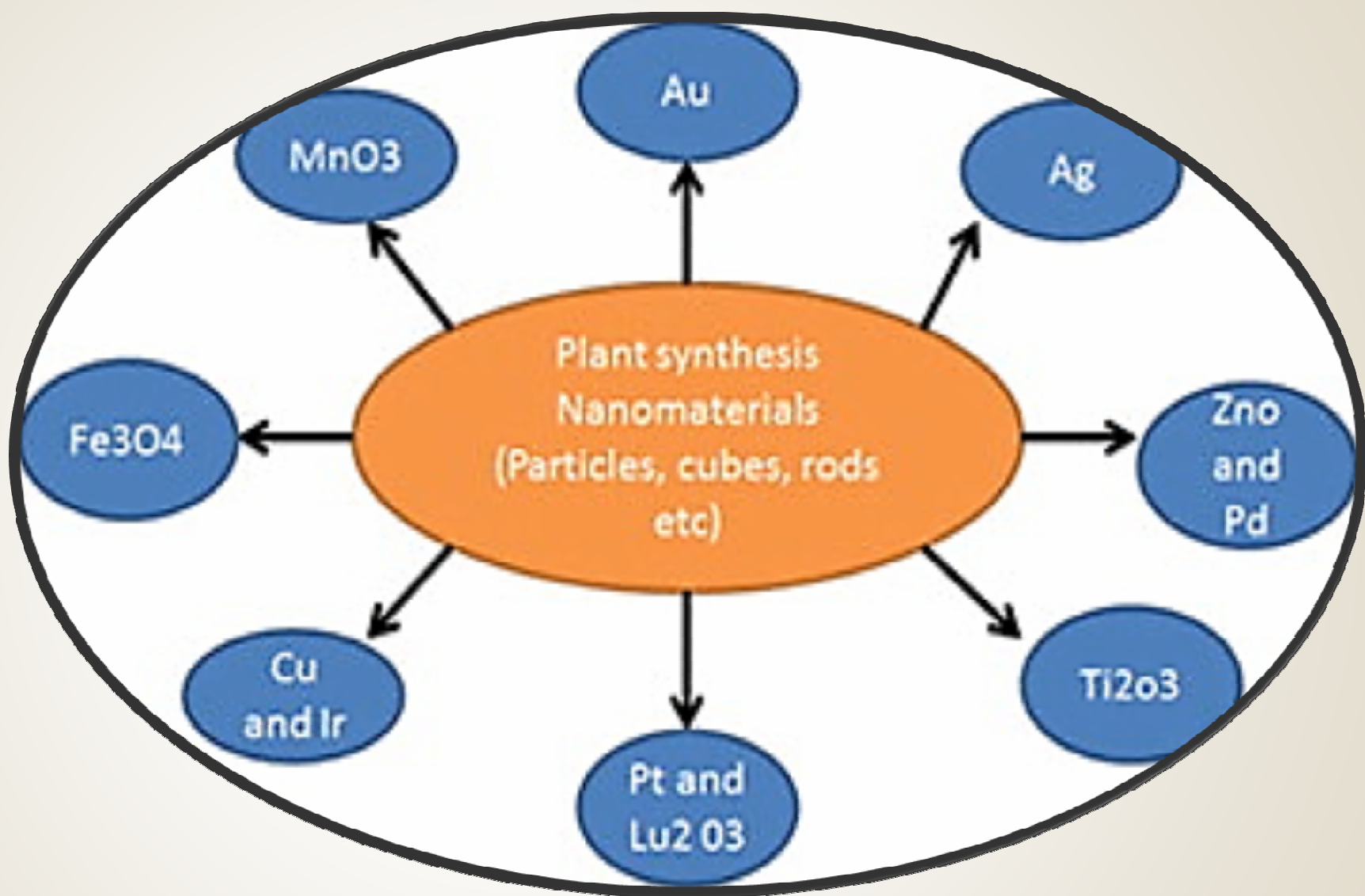


1000 year's ago different size "Gold Nanoparticles" are used for produces stained glass windows.



2000 year's ago "Sulphide Nano crystals" used by the Greek and Roman for dye of the hair.



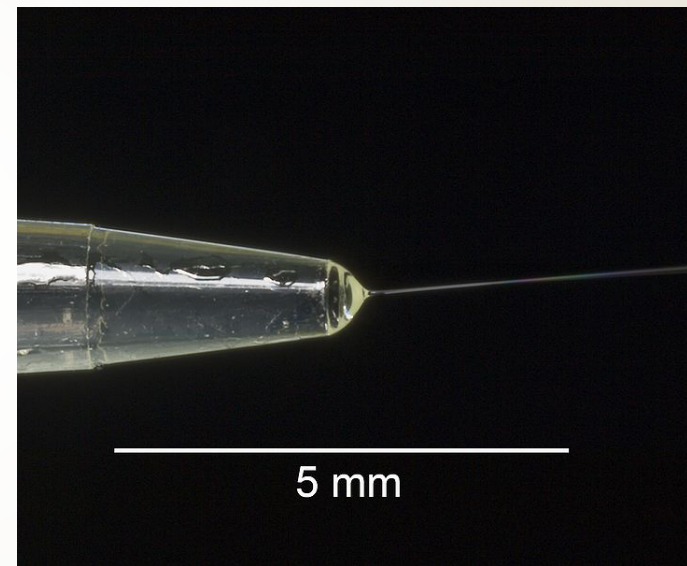
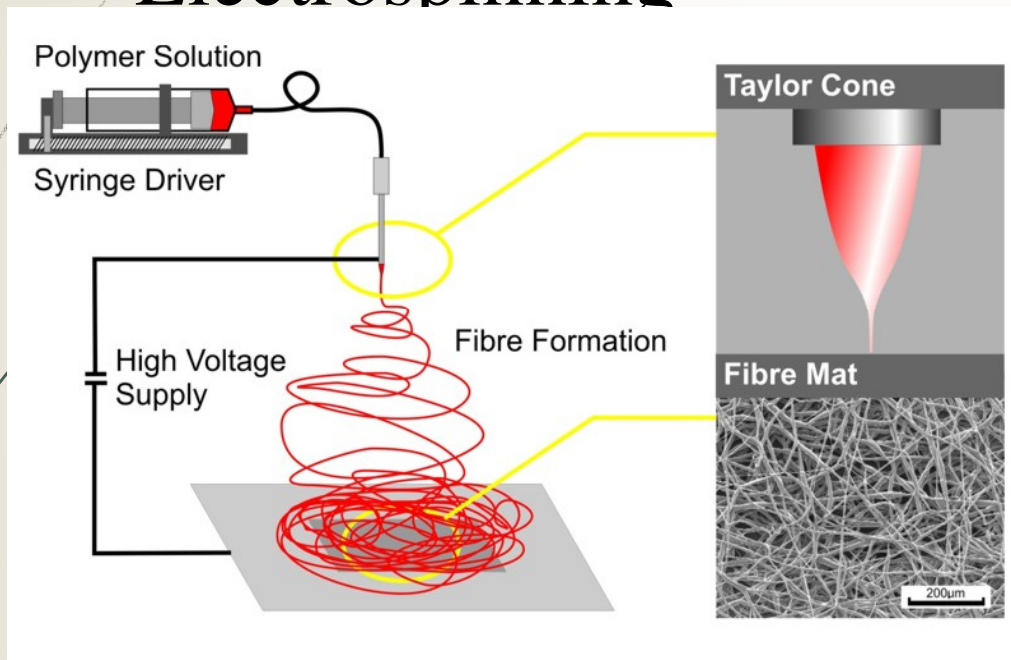


Nanofibrous Scaffold

0

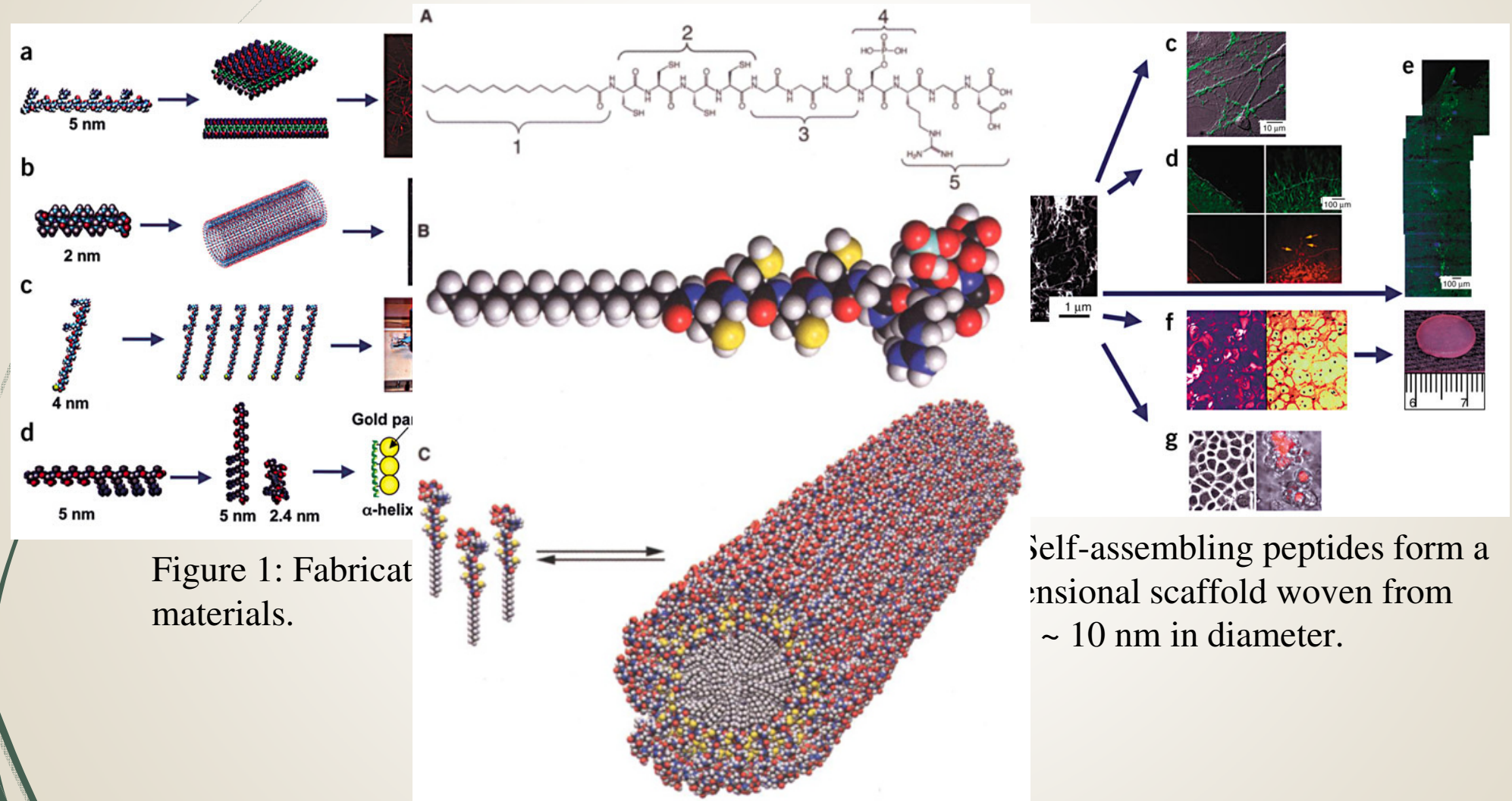
Electrospinning

- Electrospinning



- This process involves the ejection of a charged polymer fluid onto an oppositely charged surface.
- Multiple polymers can be combined
- Control over fiber diameter and scaffold architecture

Self Assembly



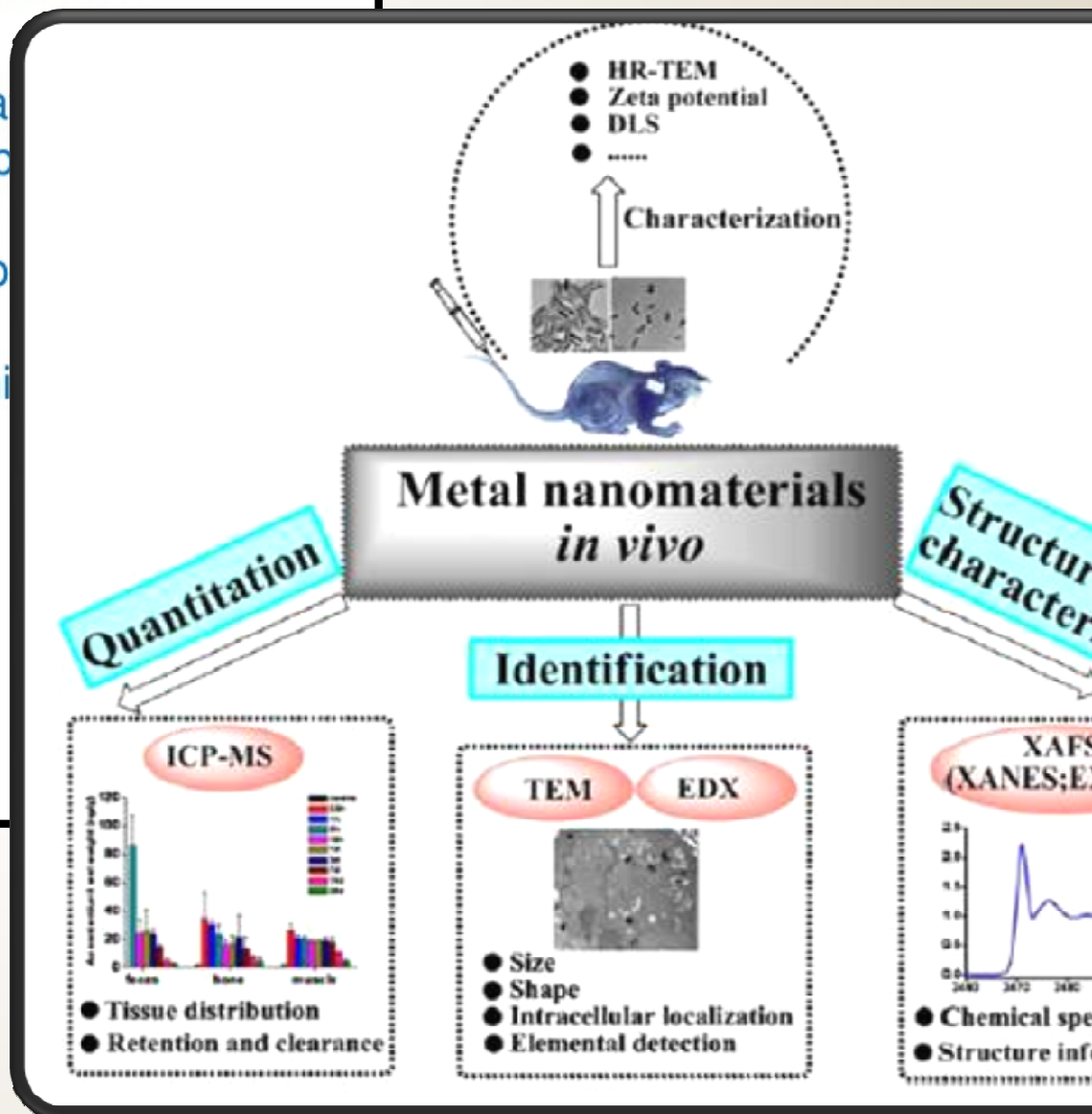
ANY?

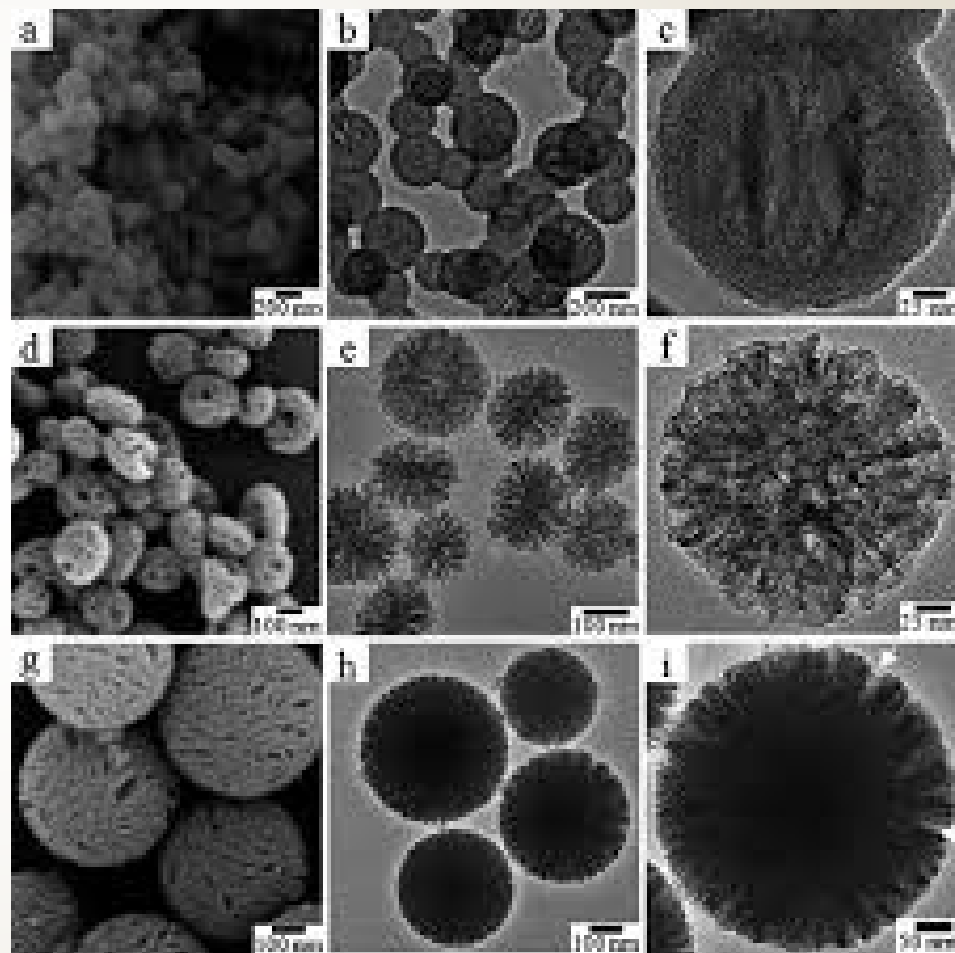
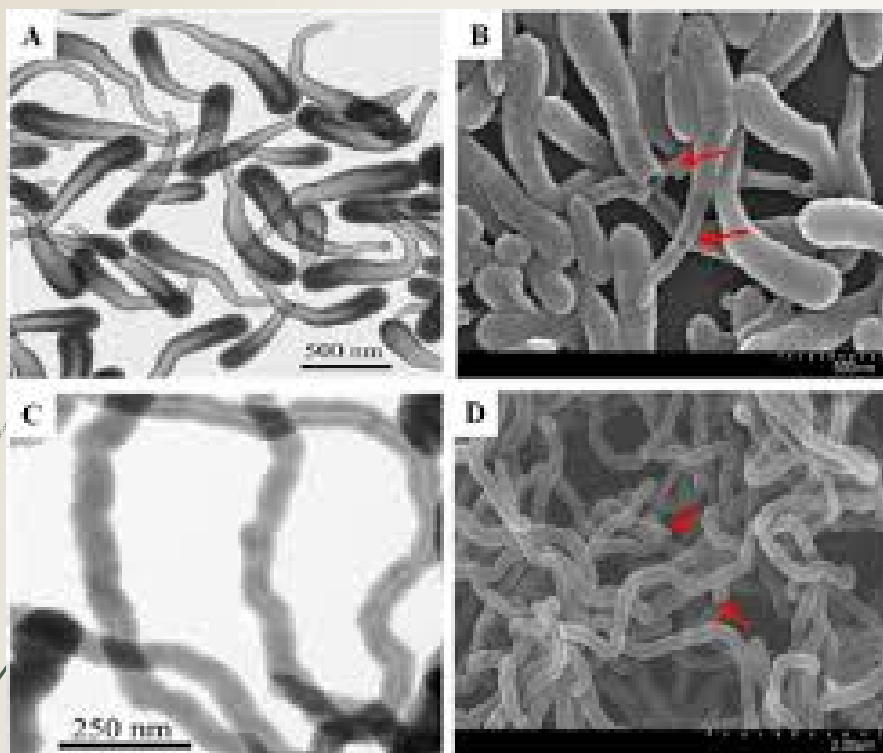
Structural Characterization

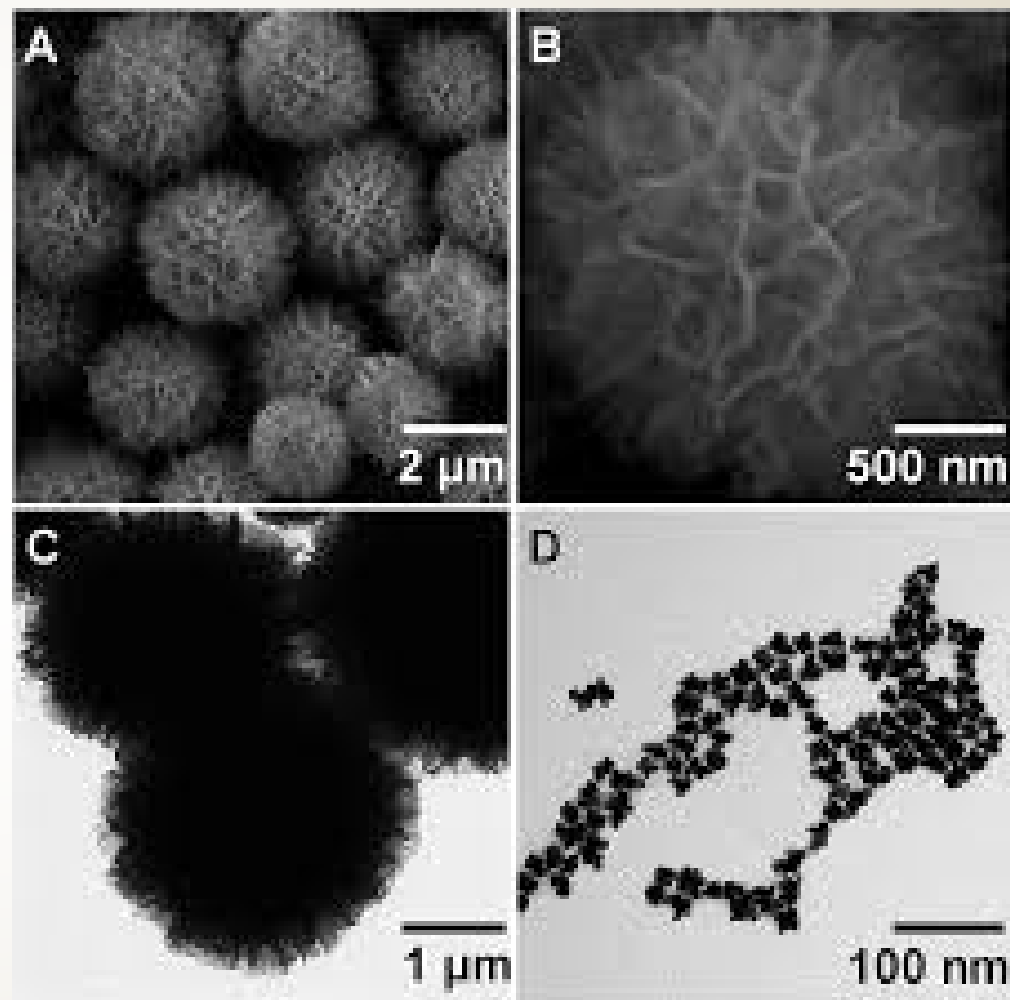
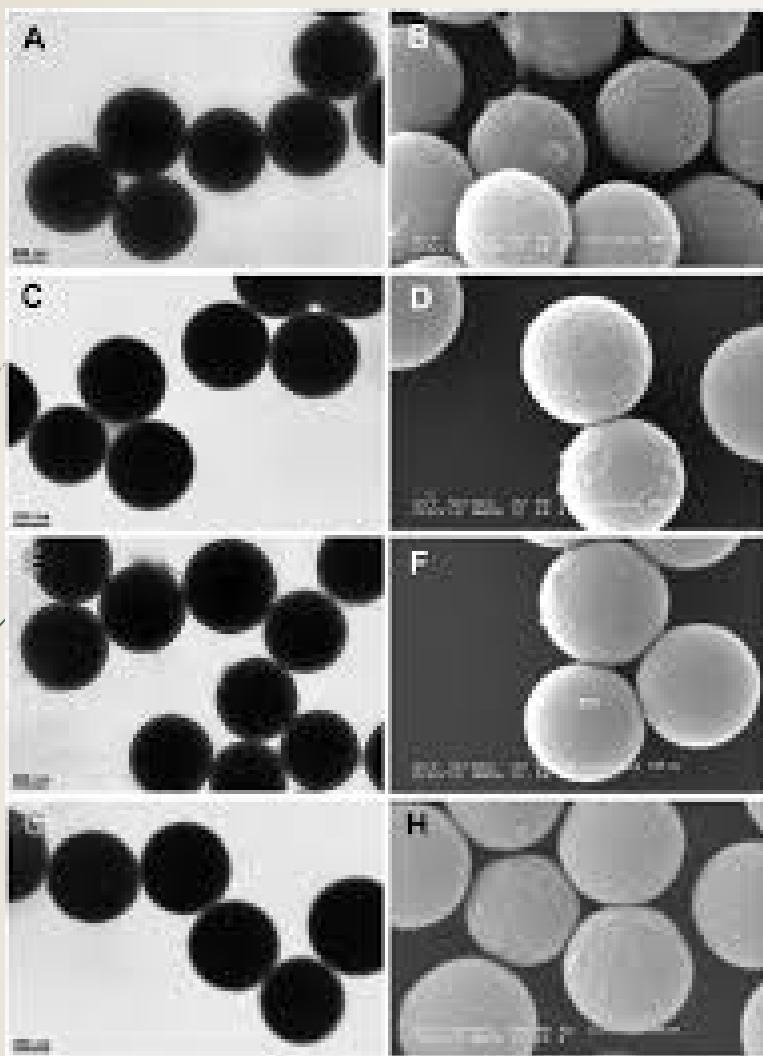
Characterization of nanomaterials has been largely based on surface analysis techniques and characterization methods developed for materials.

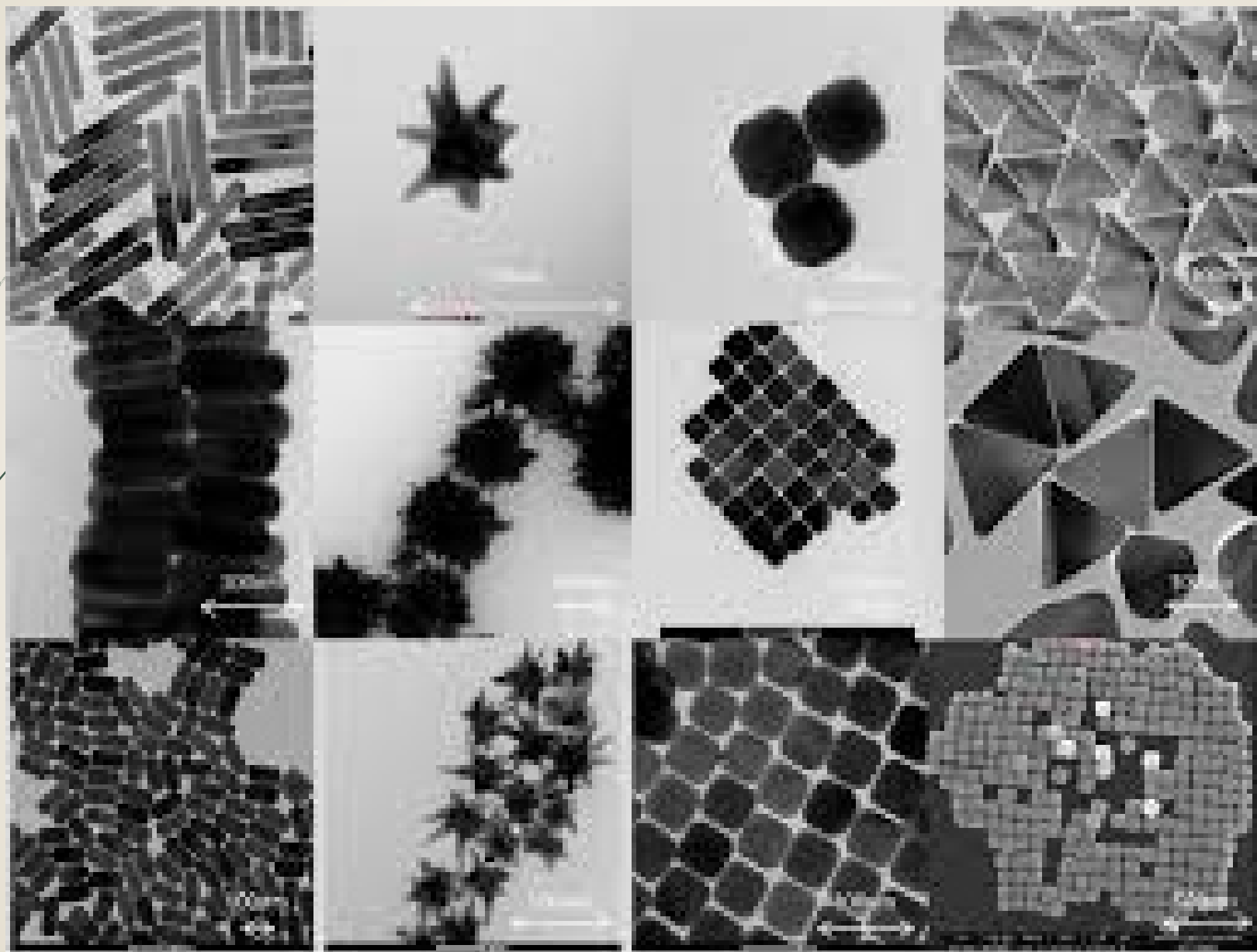
The structural characterization techniques include:

- ❑ X-ray diffraction (XRD)
- ❑ Small angle X-ray scattering (SAXS)
- ❑ Scanning electron microscopy (SEM)
- ❑ Transmission electron microscopy (TEM)
- ❑ Scanning probe microscopy (SPM)









SEM and AFM images

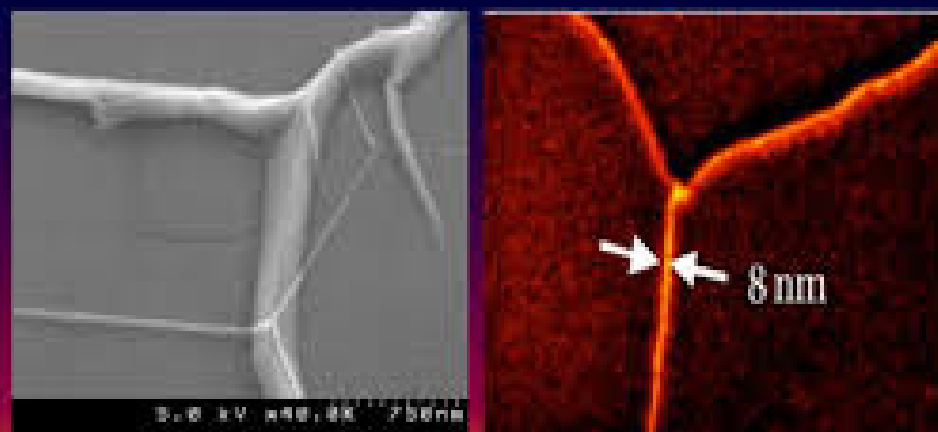
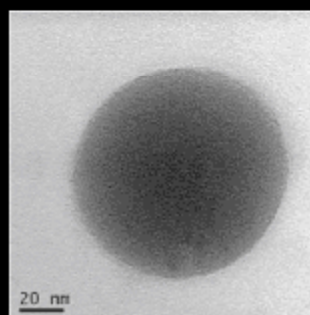
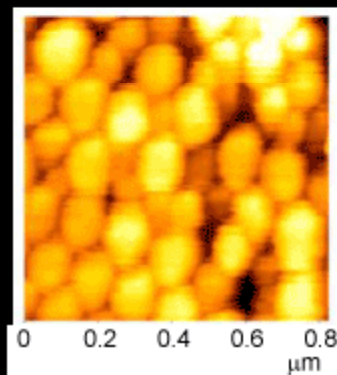


Fig. SEM & AFM images of Cu Nanowires

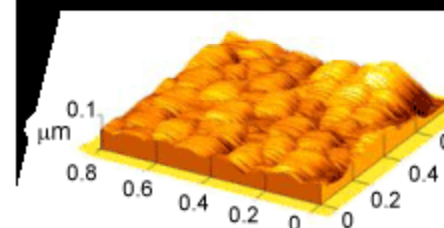
TEM microphotograph



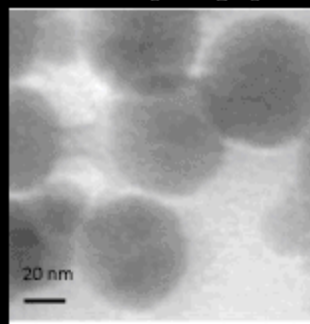
"Height" AFM image



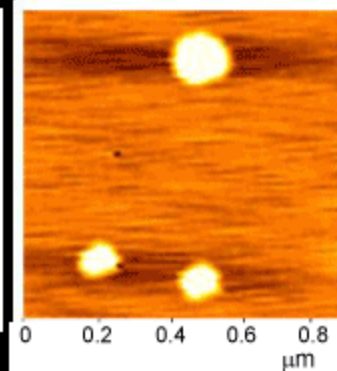
"3D reconstruction"



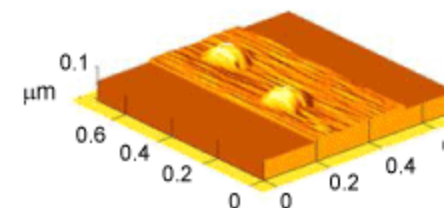
TEM microphotograph

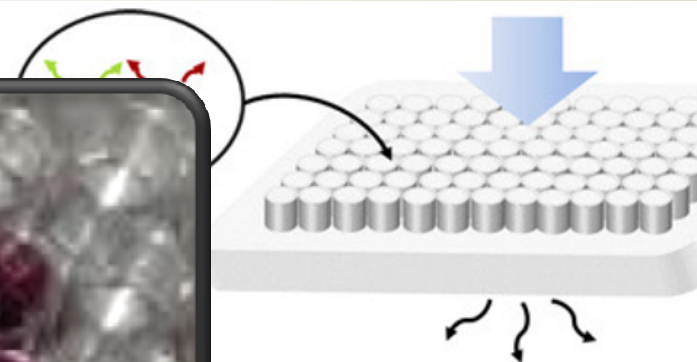
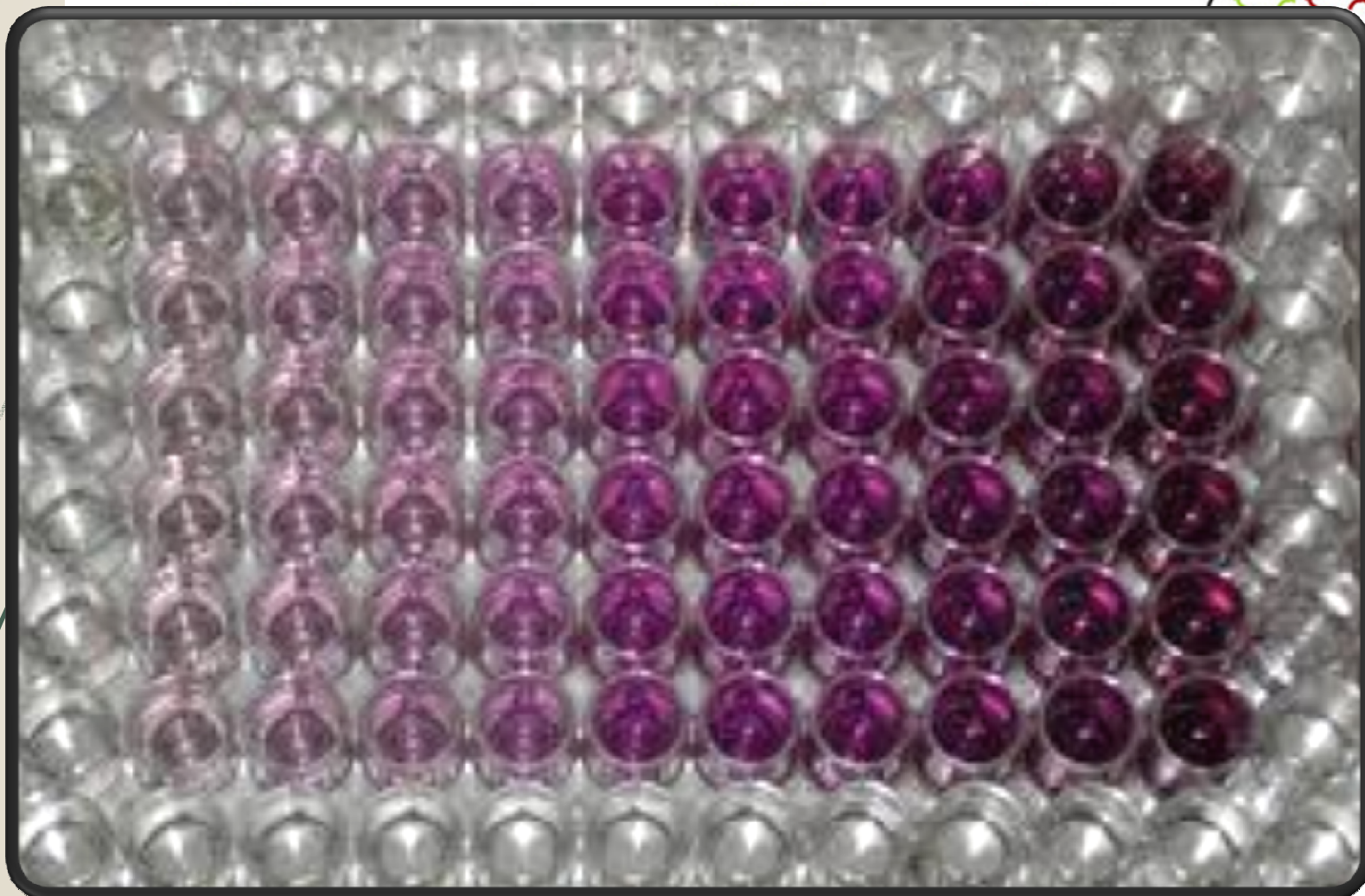


"Height" AFM image

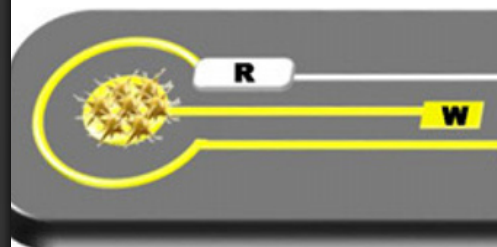


"3D reconstruction"

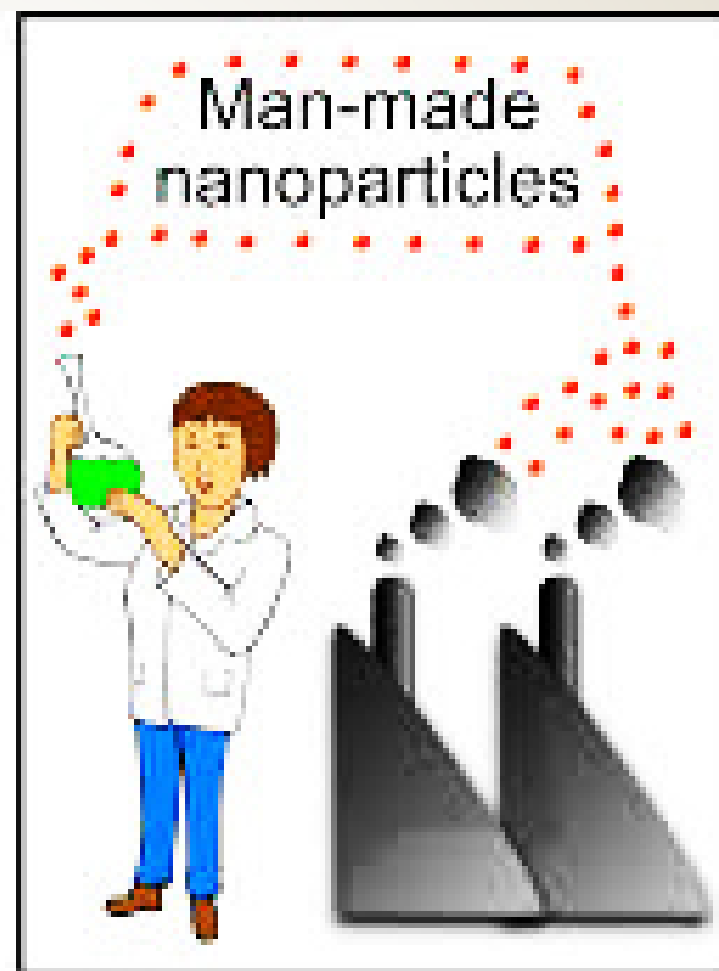
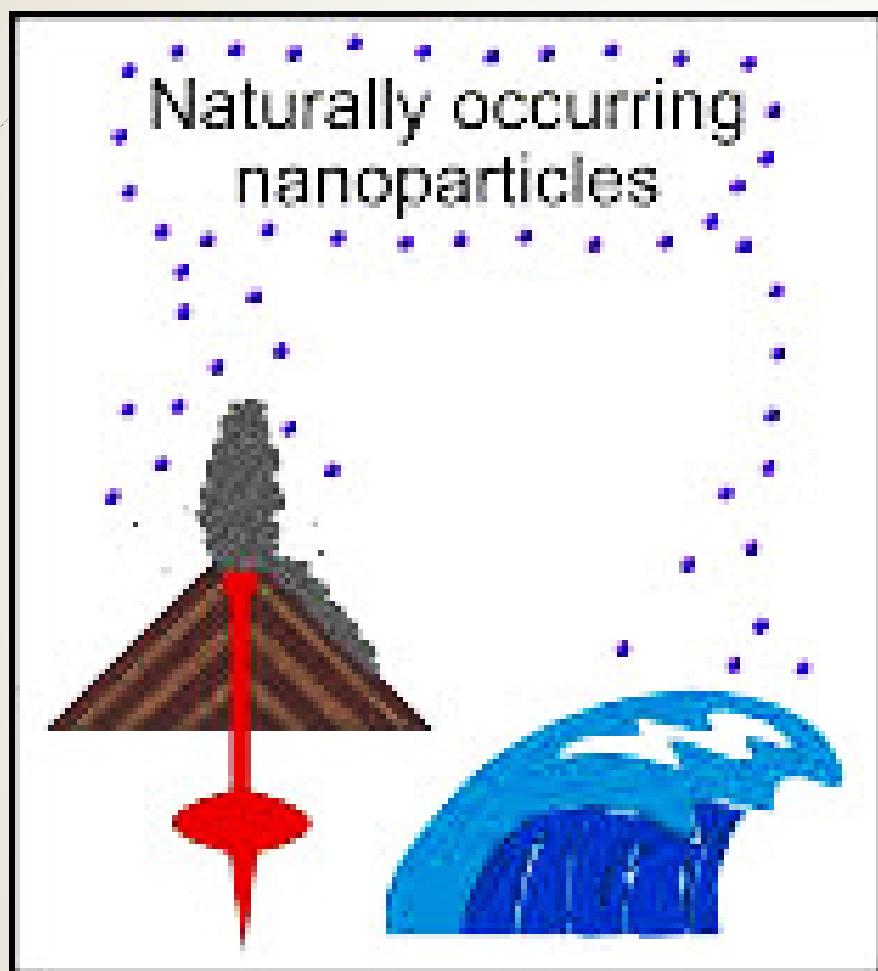




Optical detection
(Mitochondrial activity)



Electrochemical detection
(Cellular redox environment)



ANY?