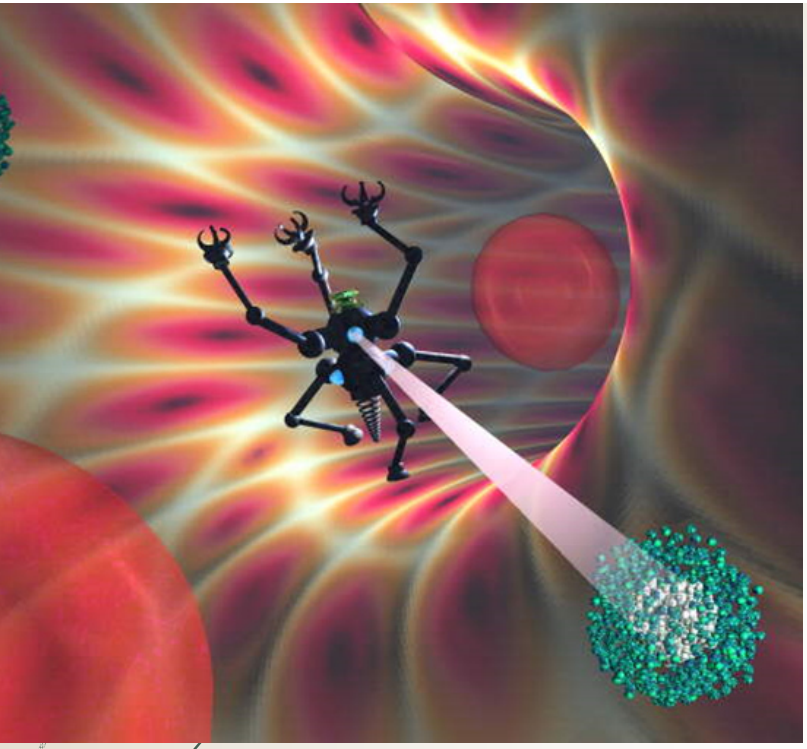


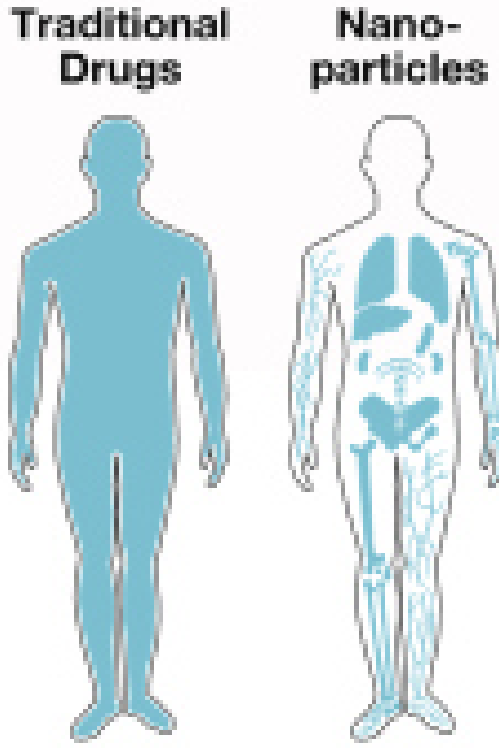
APLLICATIONS OF NANOMATERIALS IN MEDICINE

By

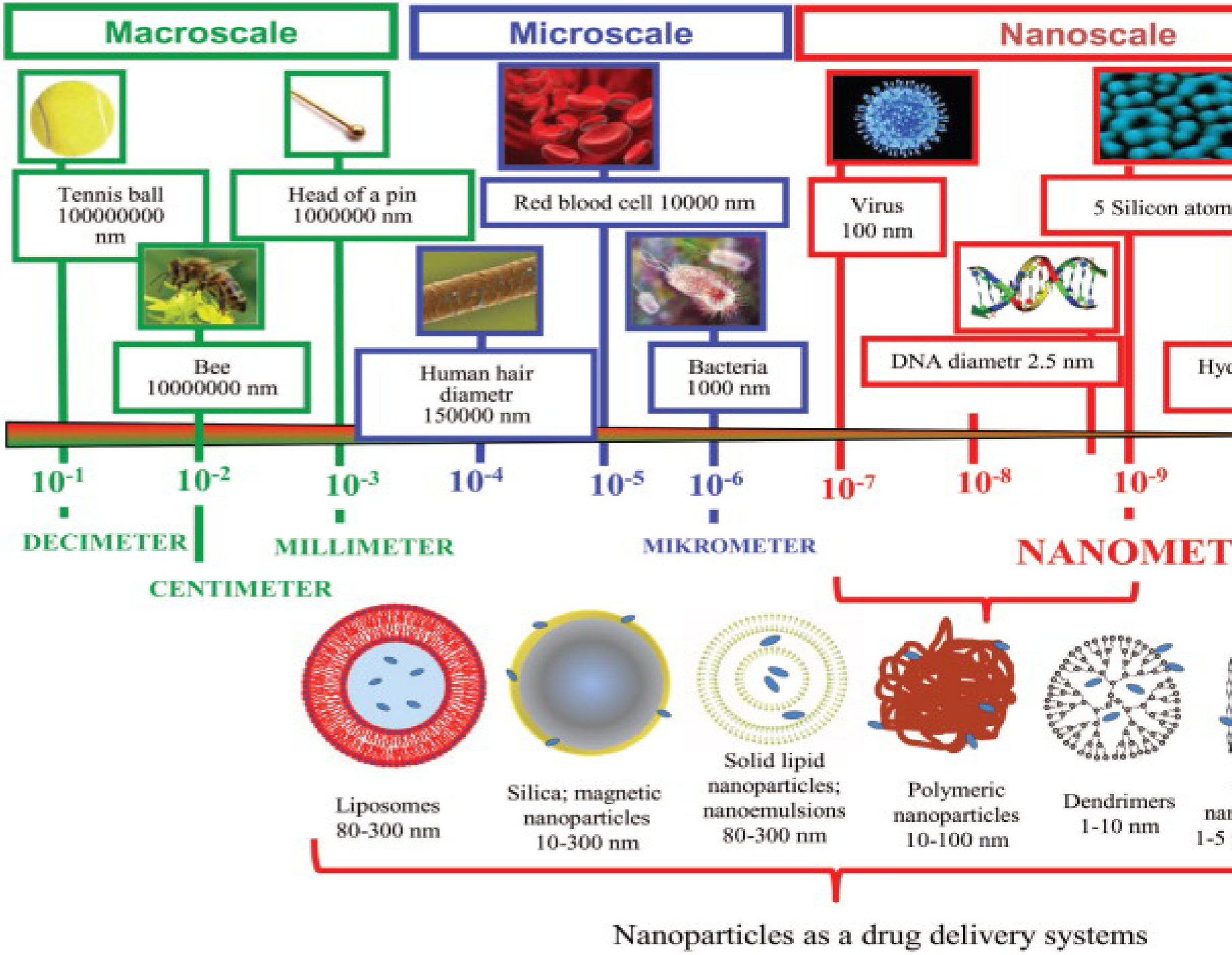
Dr B. DIVBAND

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)



Nanomaterial characterization: Responsible, Systematic, Standardized

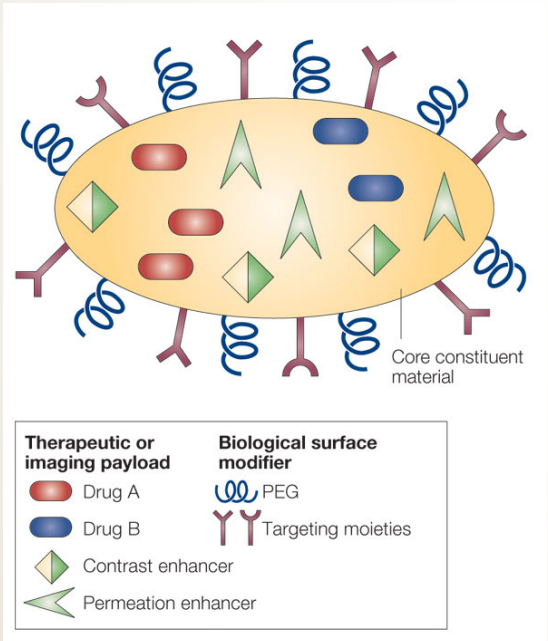

Macroscale
Microscale
Nanoscale
Tennis ball
100000000
nm
Head of a pin
1000000 nm
Red blood cell 10000 nm
Virus
100 nm
5 Silicon atom
Bee
10000000 nm
Human hair
diametr
150000 nm
Bacteria
1000 nm
DNA diametr 2.5 nm
Hyd
10-1
10-2
10-3
10-4
10-5
10-6
10-7
10-8
10-9
DECIMETER
CENTIMETER
MILLIMETER
MIKROMETER
NANOMET
Liposomes
80-300 nm
Silica; magnetic
nanoparticles
10-300 nm
Solid lipid
nanoparticles;
nanoemulsions
80-300 nm
Polymeric
nanoparticles
10-100 nm
Dendrimers
1-10 nm
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

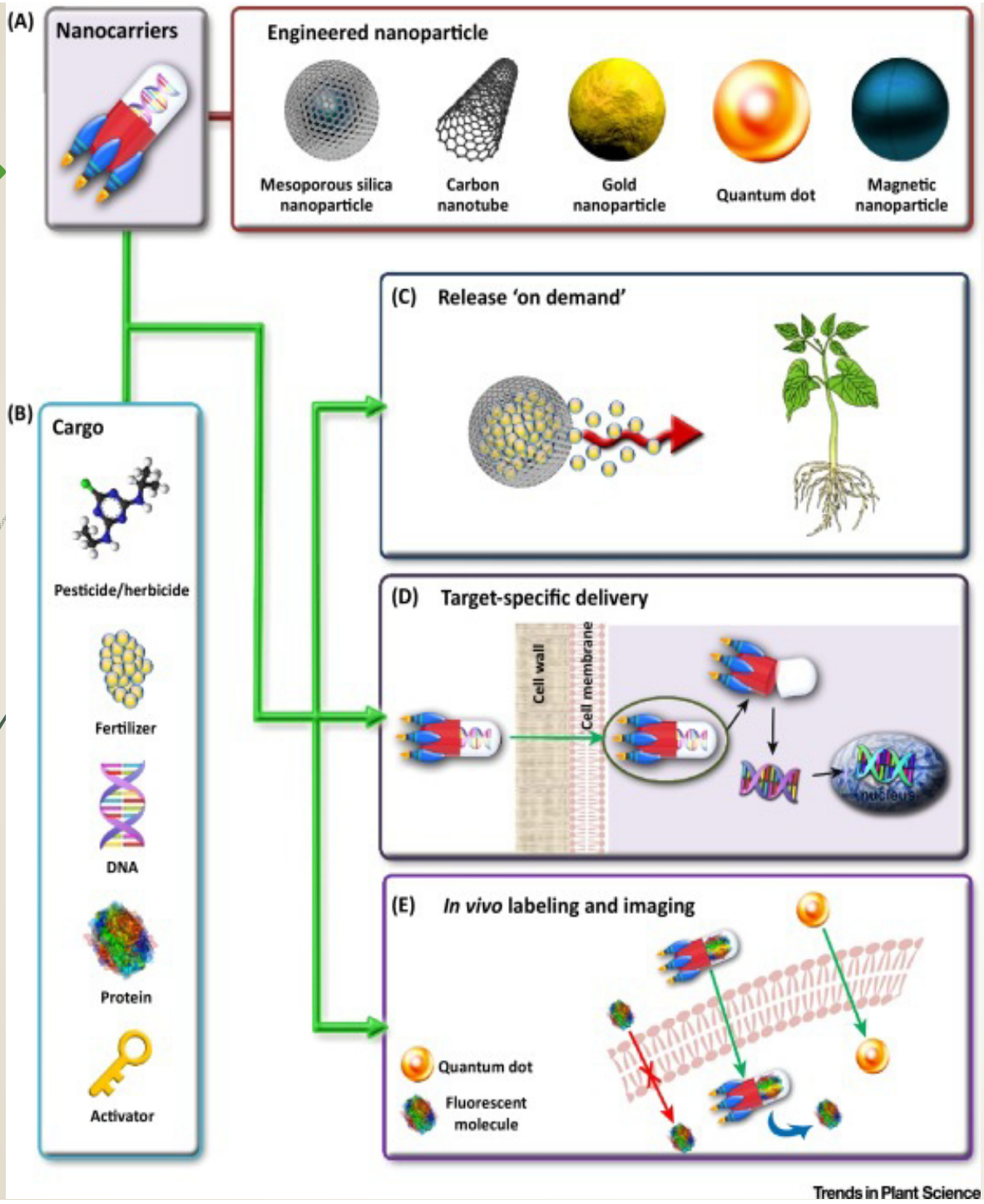
→ **In one package**

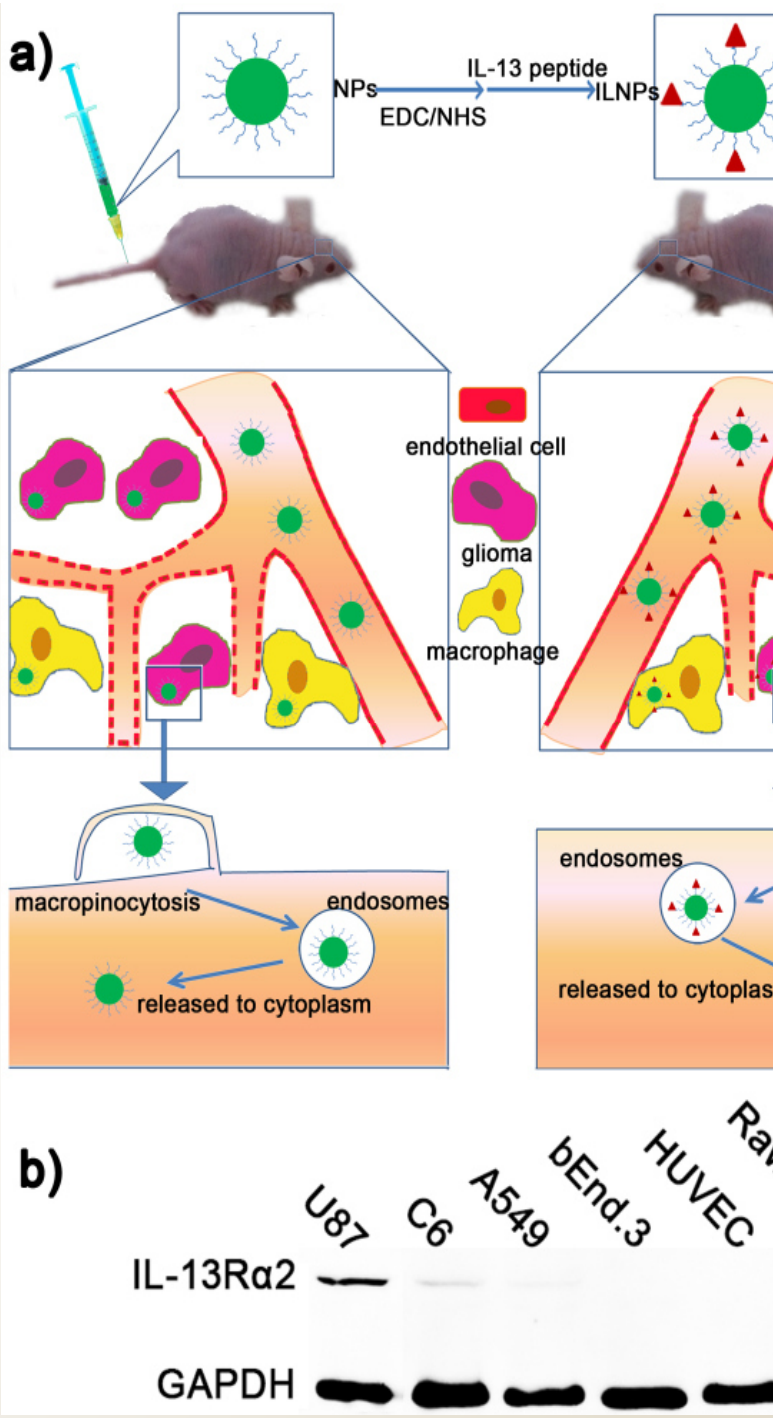
Free drug formulations do not possess multi-functional characteristics

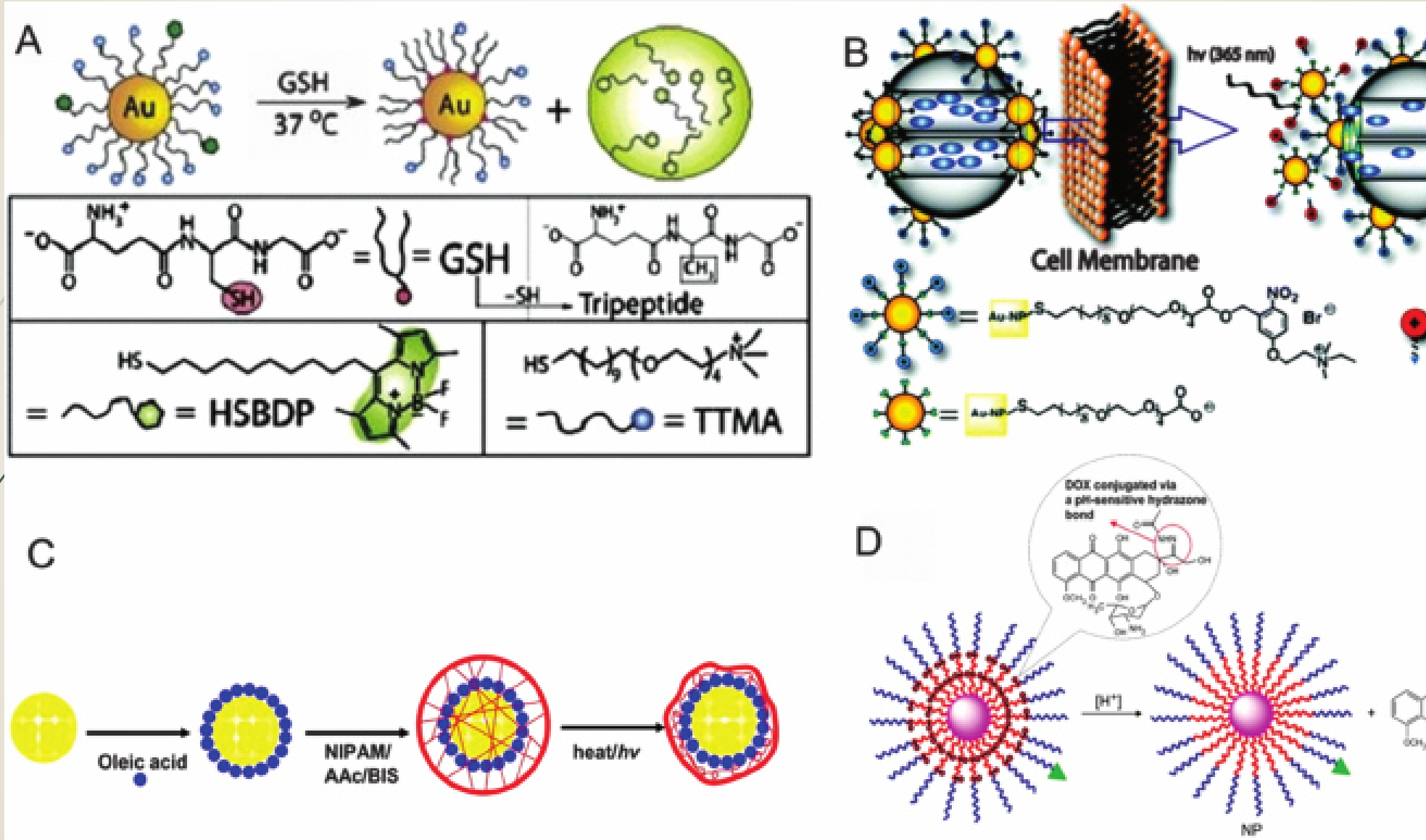


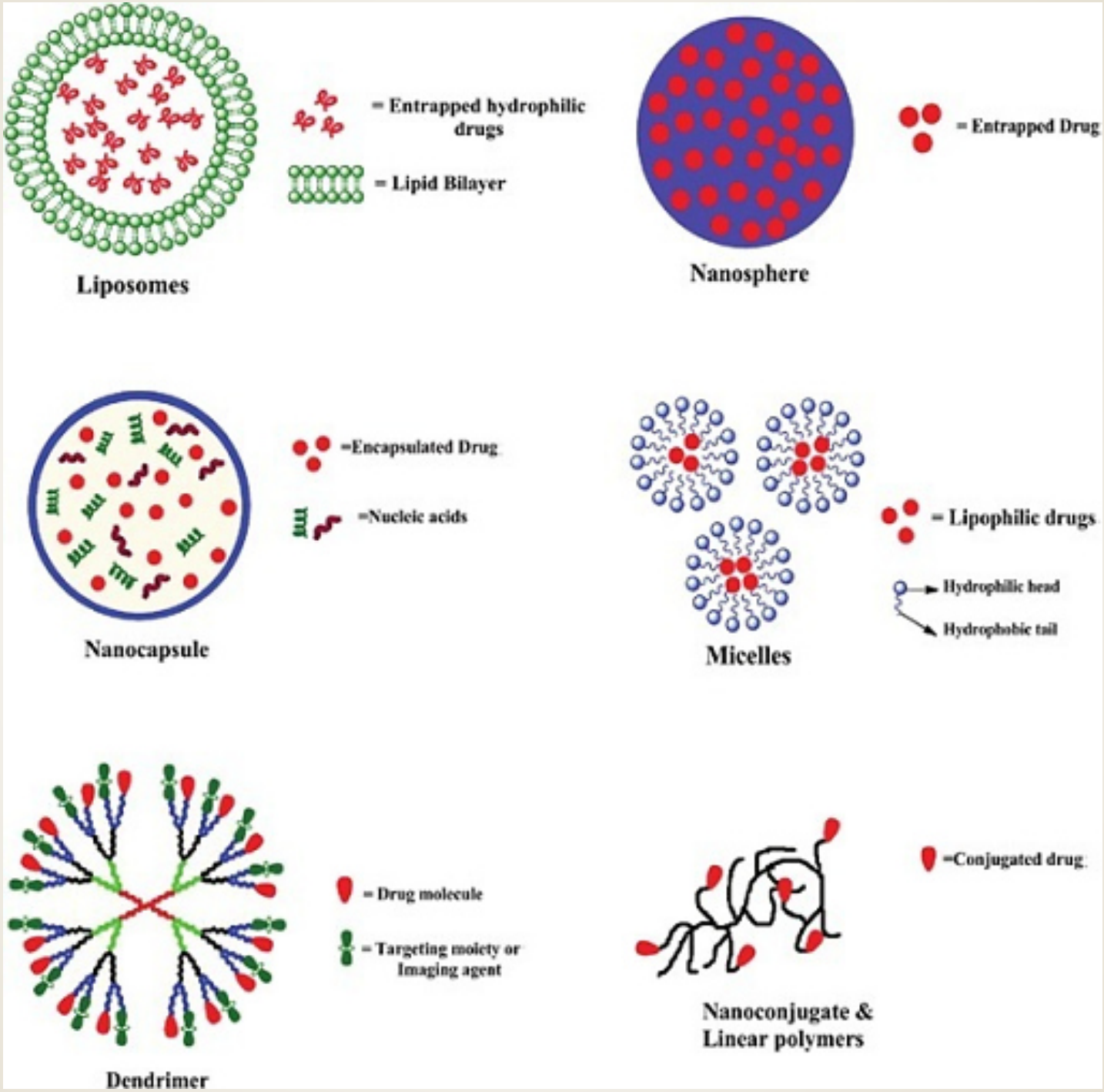
M. Ferrari, Nature Reviews 5, 161 (2005)

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


(A)
Nanocarriers
Engineered nanoparticle
Mesoporous silica nanoparticle
Carbon nanotube
Gold nanoparticle
Quantum dot
Magnetic nanoparticle
(B)
Cargo
Pesticide/herbicide
Fertilizer
DNA
Protein
Activator
(C) Release 'on demand'
(D) Target-specific delivery
Cell wall
Cell membrane
(E) In vivo labeling and imaging
Quantum dot
Fluorescent molecule
Trends in Plant Science

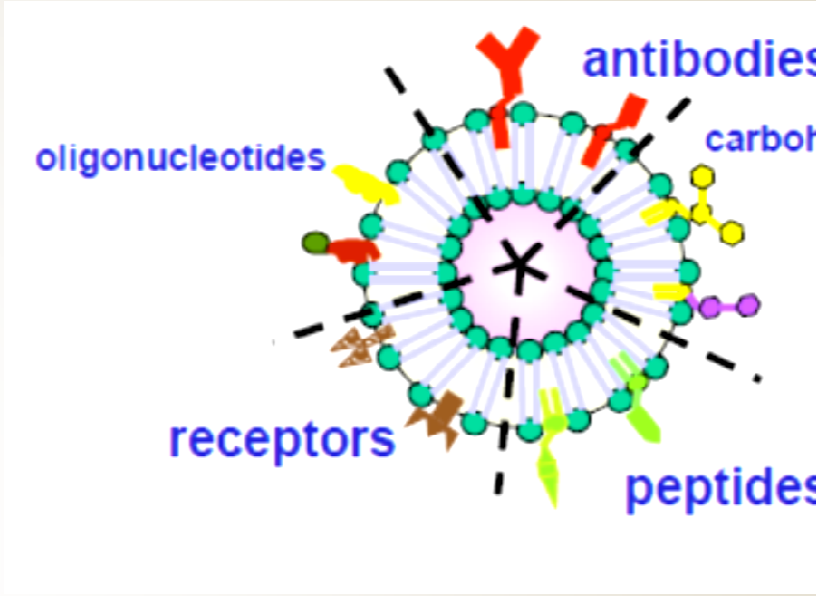

a)
NPs
EDC/NHS
IL-13 peptide
ILNPs
endothelial cell
glioma
macrophage
macropinocytosis
endosomes
released to cytoplasm
endosomes
released to cytoplas
b)
U87
C6
A549
bEnd.3
HUVEC
IL-13Rα2
GAPDH


A
Au
GSH
37 °C
Au
+
= GSH
-SH
Tripeptide
HS
= HSBDP
HS
= TTMA
B
hv (365 nm)
Cell Membrane
C
Oleic acid
NIPAM/
AAc/BIS
heat/hv
D
DOX conjugated via
a pH-sensitive hydrazone
bond
[H+]
NP


= Entrapped hydrophilic drugs
= Lipid Bilayer
Liposomes
= Entrapped Drug
Nanosphere
=Encapsulated Drug
=Nucleic acids
Nanocapsule
= Lipophilic drugs
Hydrophilic head
Hydrophobic tail
Micelles
= Drug molecule
= Targeting moiety or Imaging agent
Dendrimer
=Conjugated drug
Nanoconjugate & Linear polymers

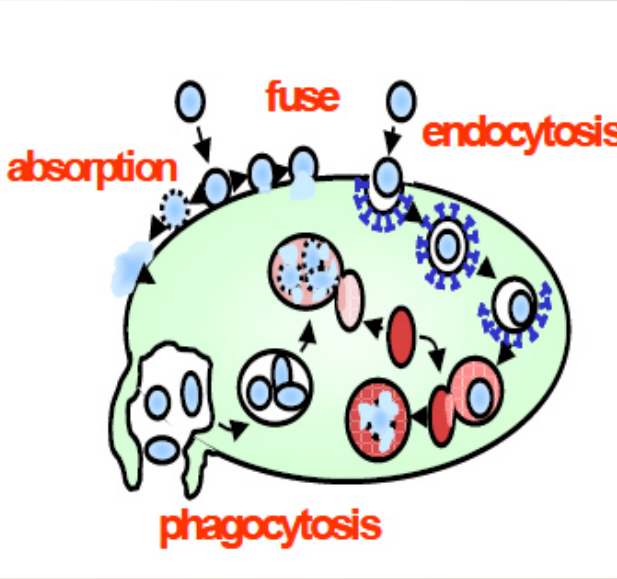
Targeting moieties:

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



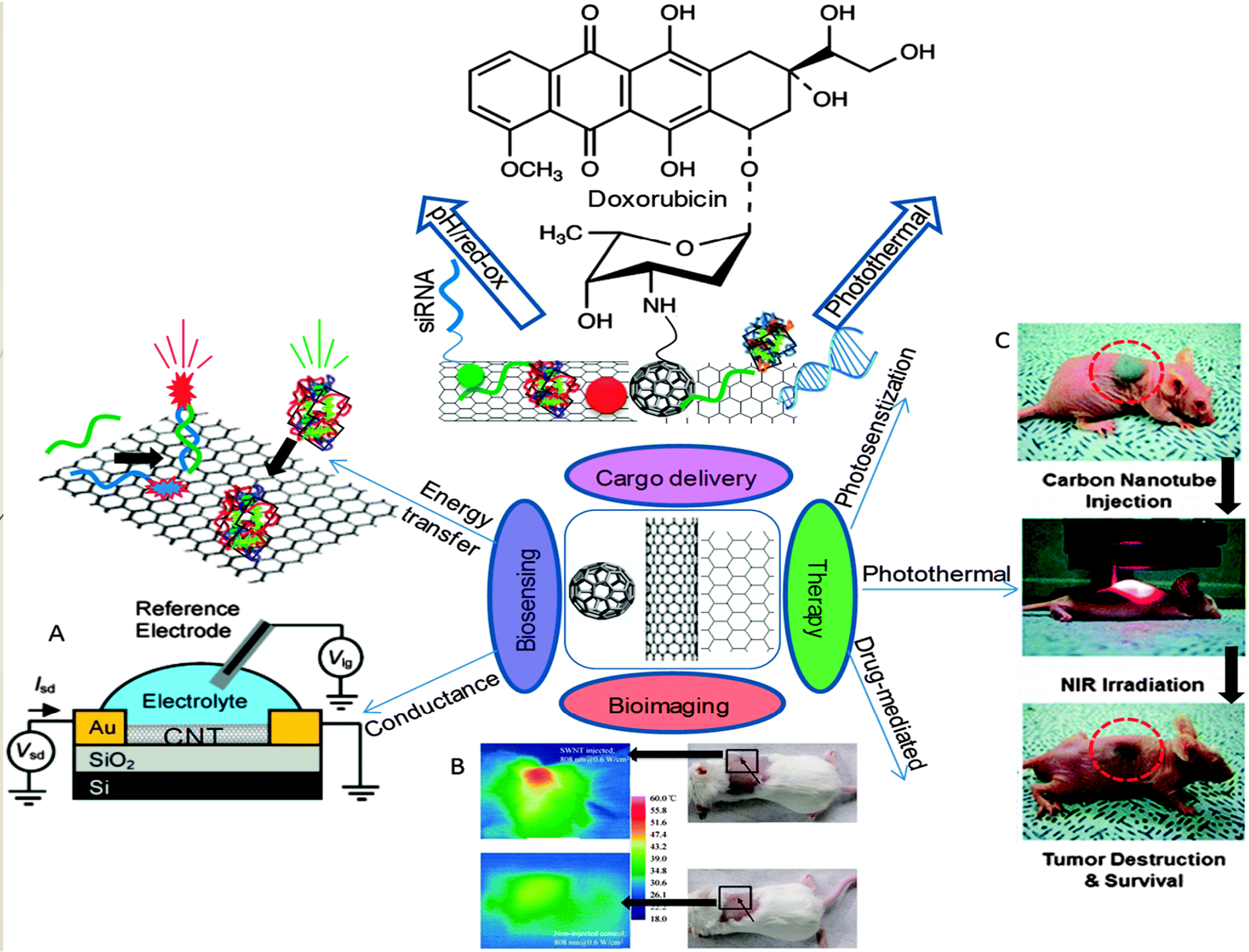
Interactions Between Biological Systems and Nanostructure

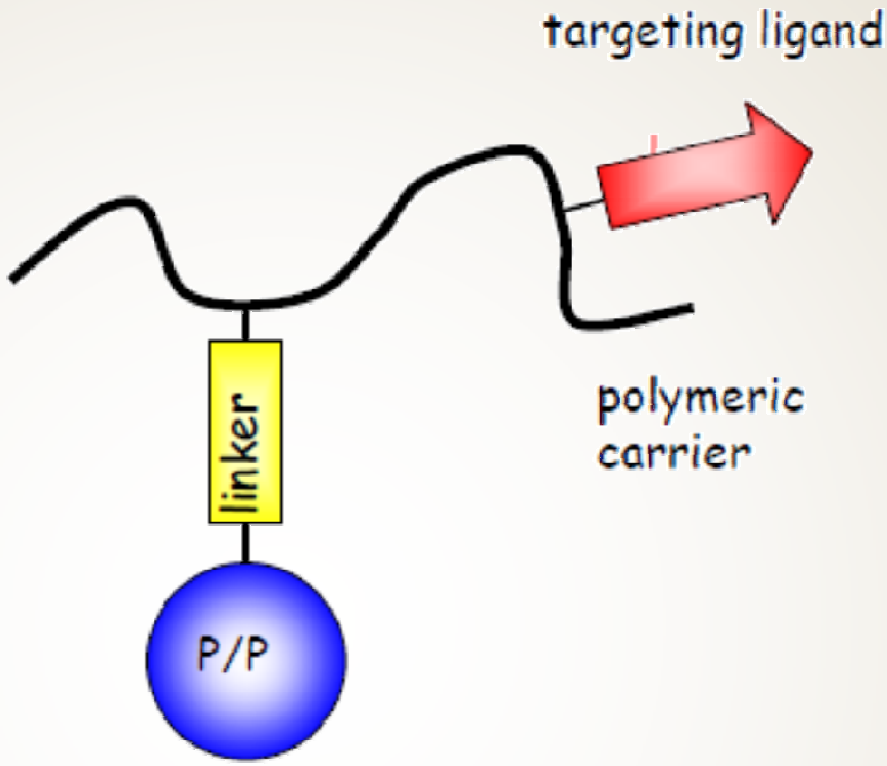
- Interaction of nanostructures with plasma proteins and relation between protein adsorption and removal of nanostructures from the circulation by the reticulo-endothelial system.
- Adsorption of nanostructures to cells (in relation to the surface chemical characteristics, size and shape of the nanostructures).
- 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 pharmaco-chemistry, pharmacology, toxicology, and nowadays is being pursued as a multi- and interdisciplinary effort.


Doxorubicin
pH/red-ox
Photothermal
siRNA
Energy transfer
Cargo delivery
Biosensing
Therapy
Bioimaging
Photosenstization
Photothermal
Drug-mediated
Conductance
A
Reference Electrode
Electrolyte
Au
CNT
SiO2
Si
B
C
Carbon Nanotube Injection
NIR Irradiation
Tumor Destruction & Survival



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

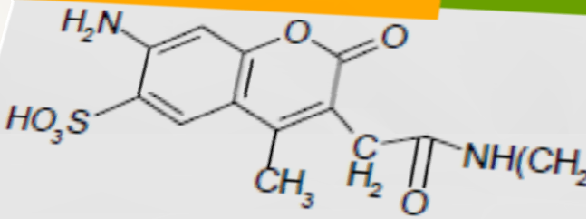
PEGylated for Cancer Therapy

Surface modification

Adhesion

Cysteamine hidrocloride

Fluorescence



Alexa fluor 350 cadaverine

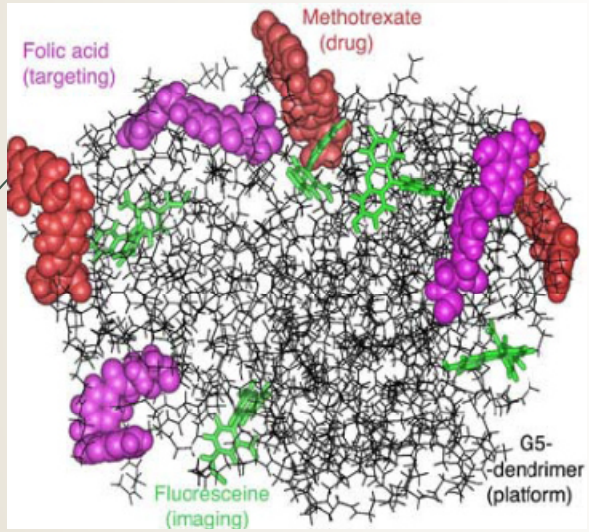
Nanogels

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

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

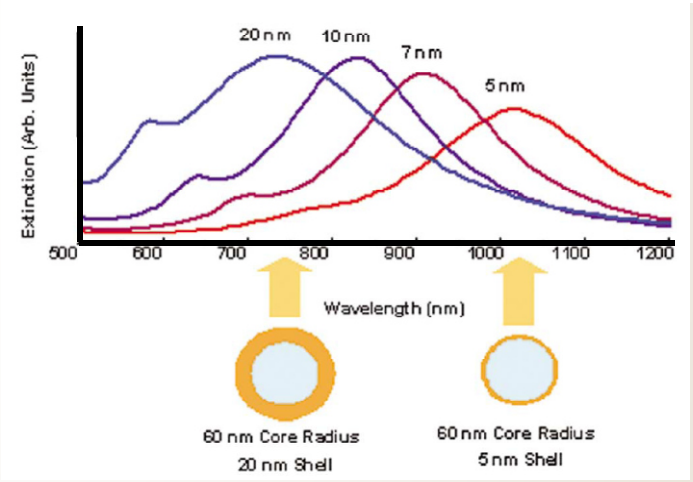
Nanoparticle-based Therapies: Different Approaches

Dendrimers:
Targeted delivery of methotrexate



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

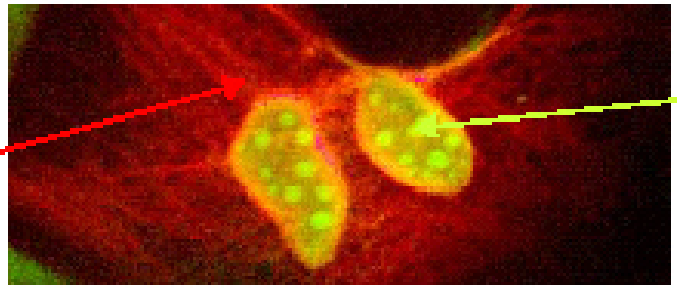
Nanoshells:
Photothermal therapy



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

Nanocrystals as Fluorescent Biological Labels

5 nm crystals bound to actin fibers



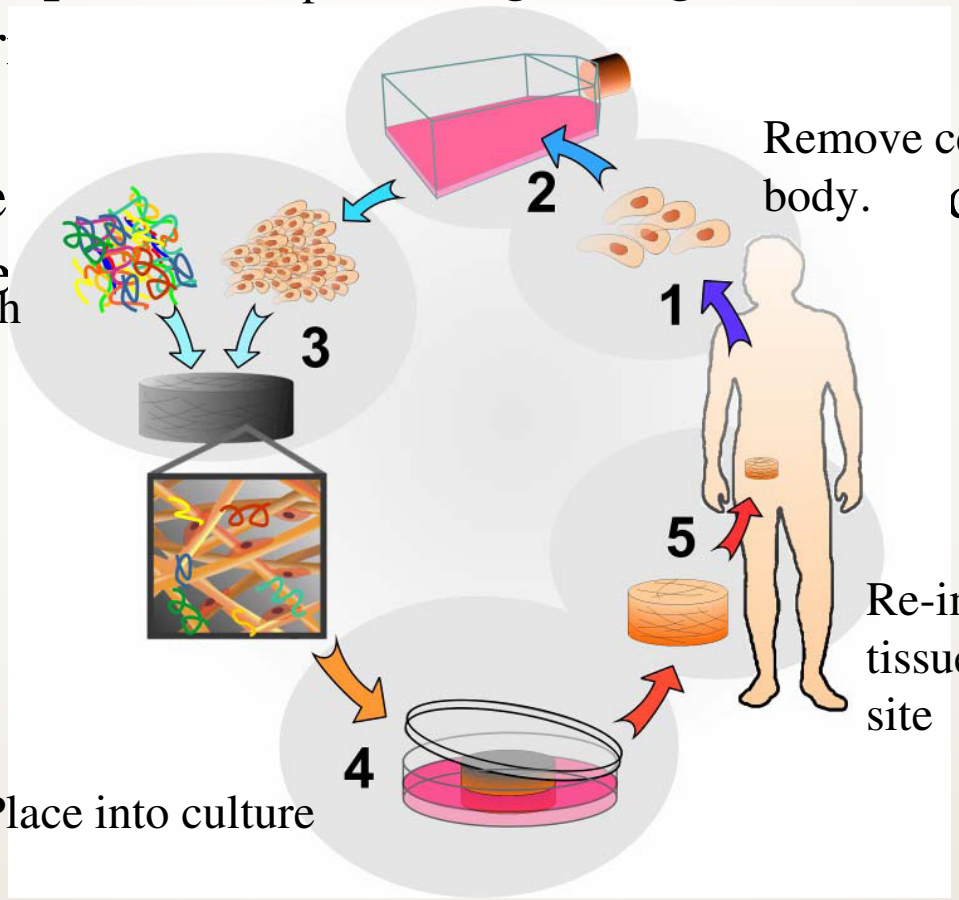
3.5 nm crystals bound to cell nucleus

- 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?

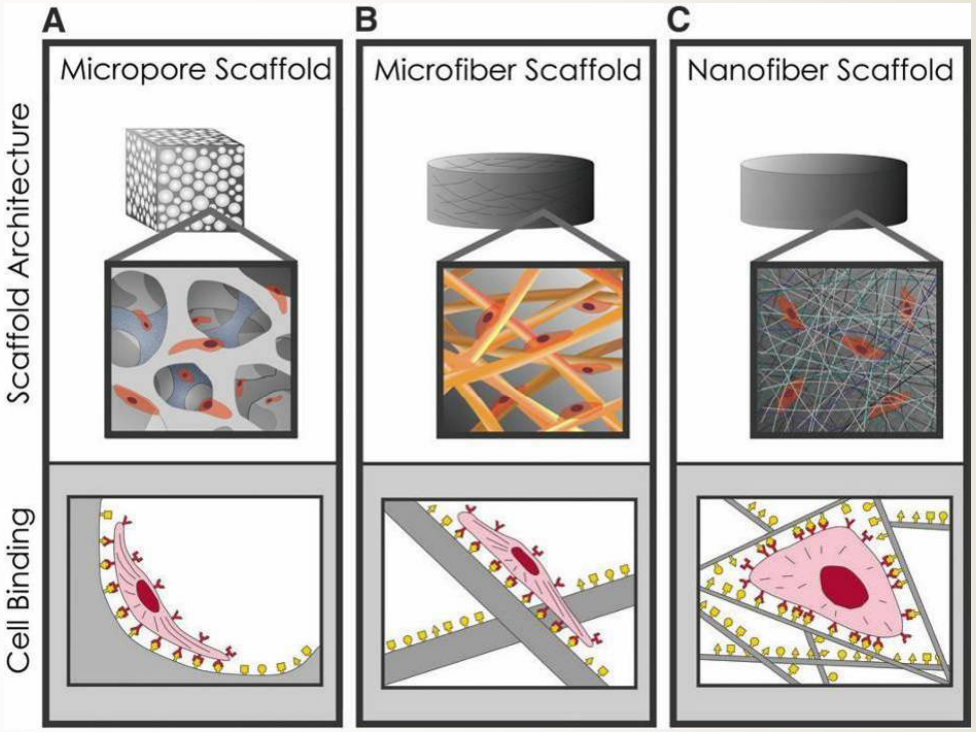
Tissue Engineering

- Nano/micro particles, including living animal cells, bacter
be optically
defined thre
- laser-guide



Why we apply Nanotech in TE?

Tissue Engineering is a methodology
+
Nanotechnology is a tool



Cells on microfibrous 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.

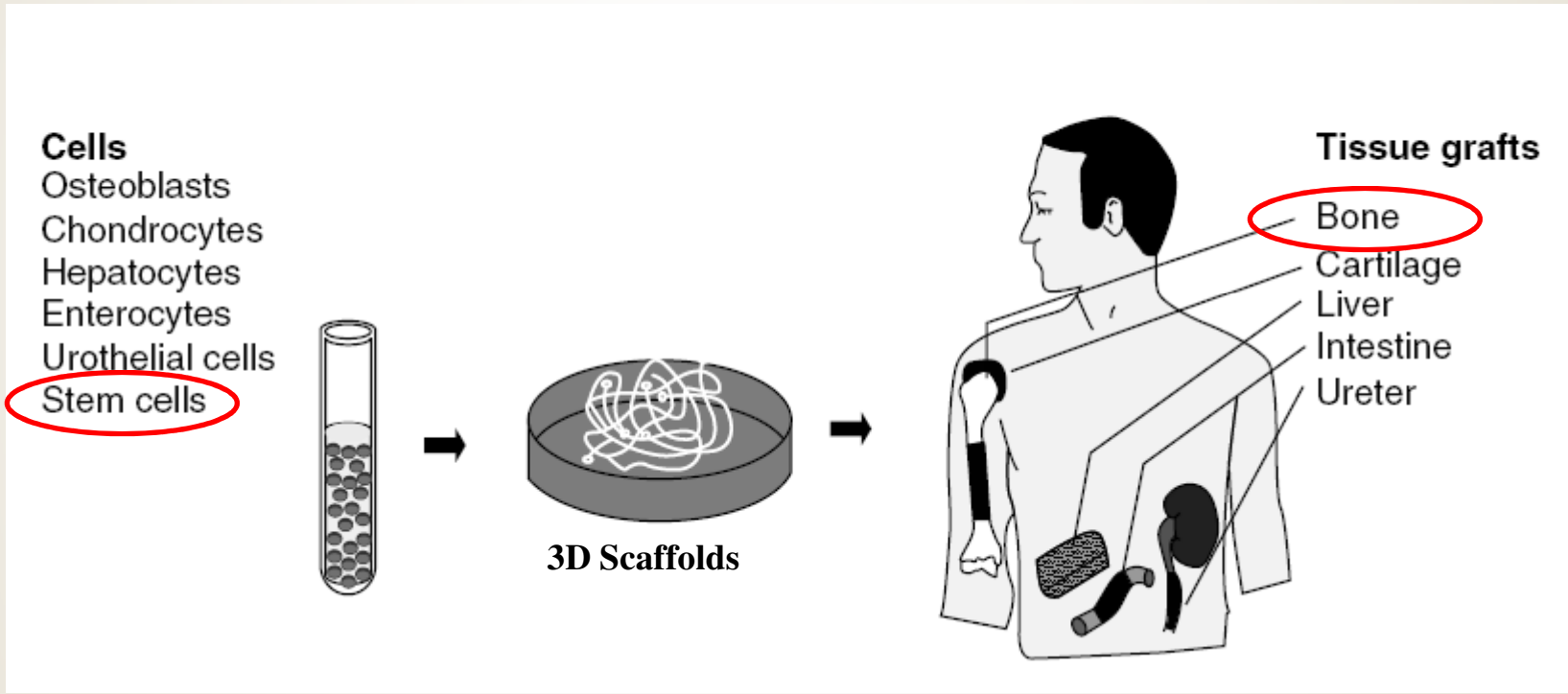
Synthetic polymers

- 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


Cells
Osteoblasts
Chondrocytes
Hepatocytes
Enterocytes
Urothelial cells
Stem cells
3D Scaffolds
Tissue grafts
Bone
Cartilage
Liver
Intestine
Ureter

Digest Journal of Nanomaterials a

DIABETIC DELAY

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

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

Keywords: Diabetes m

(Received March 25,

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

Article

Active Silver

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Chiara Gardin [2], War
Carlo Barbante [4] and

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Santa Marta, Dorso
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Received: 23 Decemb
Published: 1 March 2

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

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Wan Norsyuhada Binti Wan Mohd Shukri, MSc,[1] Nurlaily Zakaria, Dip,[1]
Nurfatin Musa, BSc,[2] and Ganesan Krishnan, PhD[1]
[1]Laser Center, Ibnu Sina Institute for Scientific and Industrial Research (ISI-SIR), Universiti Teknologi Johor Bahru, Johor 81310, Malaysia
[2]Faculty 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/cm^2. 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.

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 therap 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 th 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 enhan 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 a interacting with biological molecules would RNA, protein, cellular function, and inhibi High level of ROS leads to oxidative stress, healing process. Therefore, antioxidants are lower the level of oxidative stress and damaging effects of ROS [21].

Institution at where the work was performed Ibnu Sina Institute for Scientific and Industrial SIR), Universiti Teknologi Malaysia, 81310 Joho Malaysia.
Conflict of Interest Disclosures: All authors

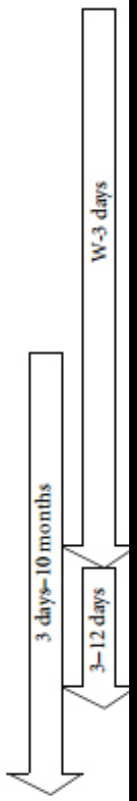


FIGURE 1: The main biolo… well defined. Although pre… phases overlap to a certain …

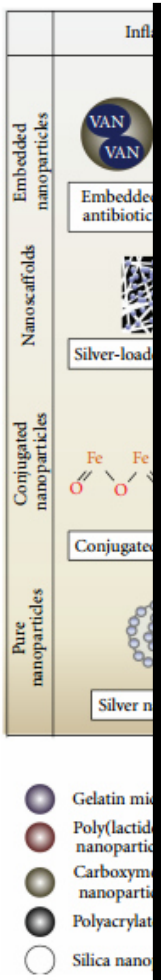


FIGURE 2: Nanostrategies cu… healing are illustrated. The t… the healing phase to which … listed. Two- and three-dime… PLACL, polyurethane, and …

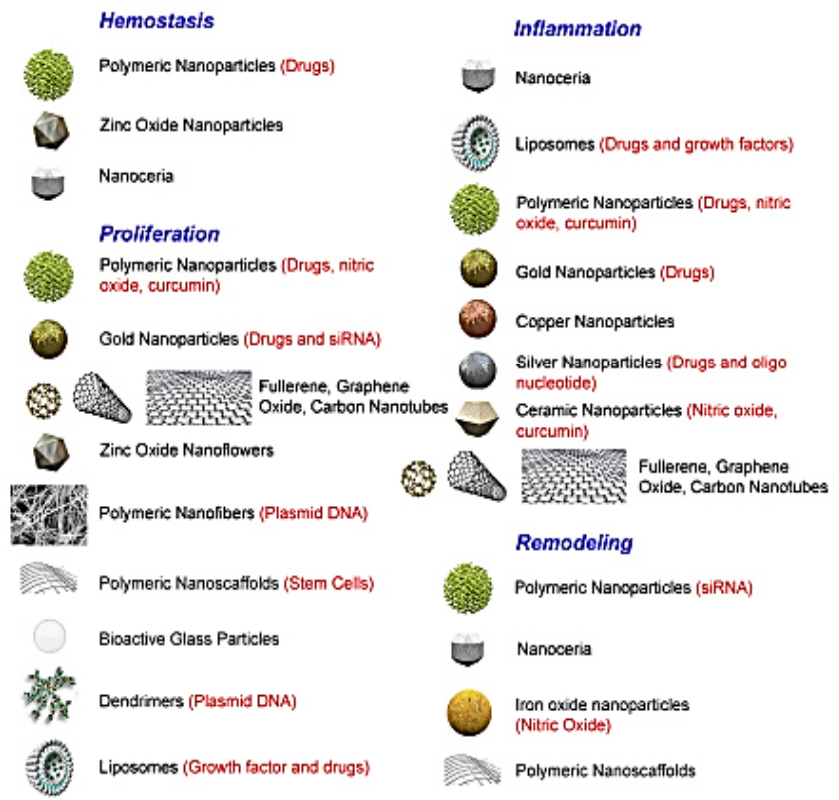
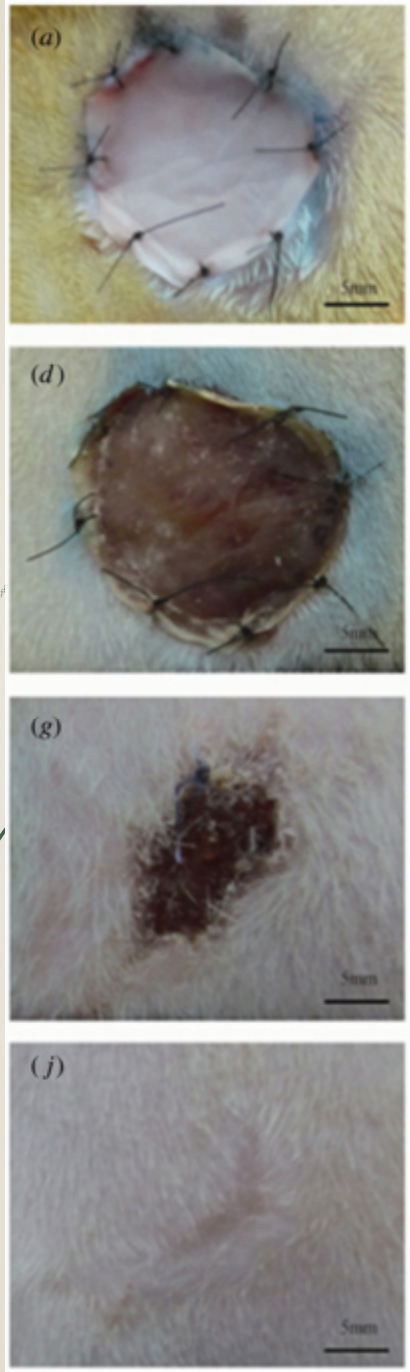


Figure 2. Schematic representation of the nanotechnology-based therapies employed in wound healing.



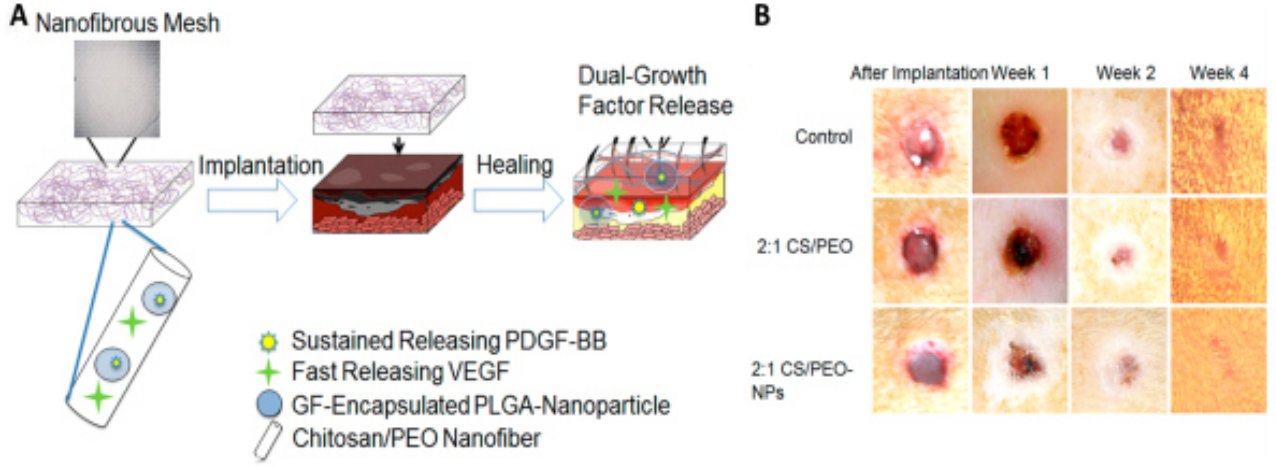


Figure 4. (A) Schematic illustration of the nanoparticle-embedded electrospun nanofibers loaded with two growth factors VEGF and PDGF-BB for the wound healing and (B) representative macroscopic appearance of wound closure after treatment of rat wounds with control, 2:1 chitosan/PEO (CS/PEO) without growth 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.

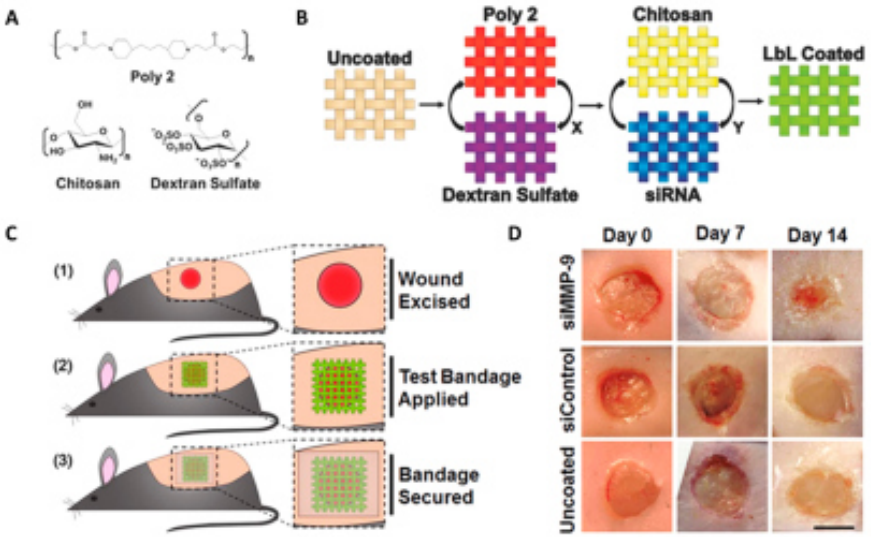
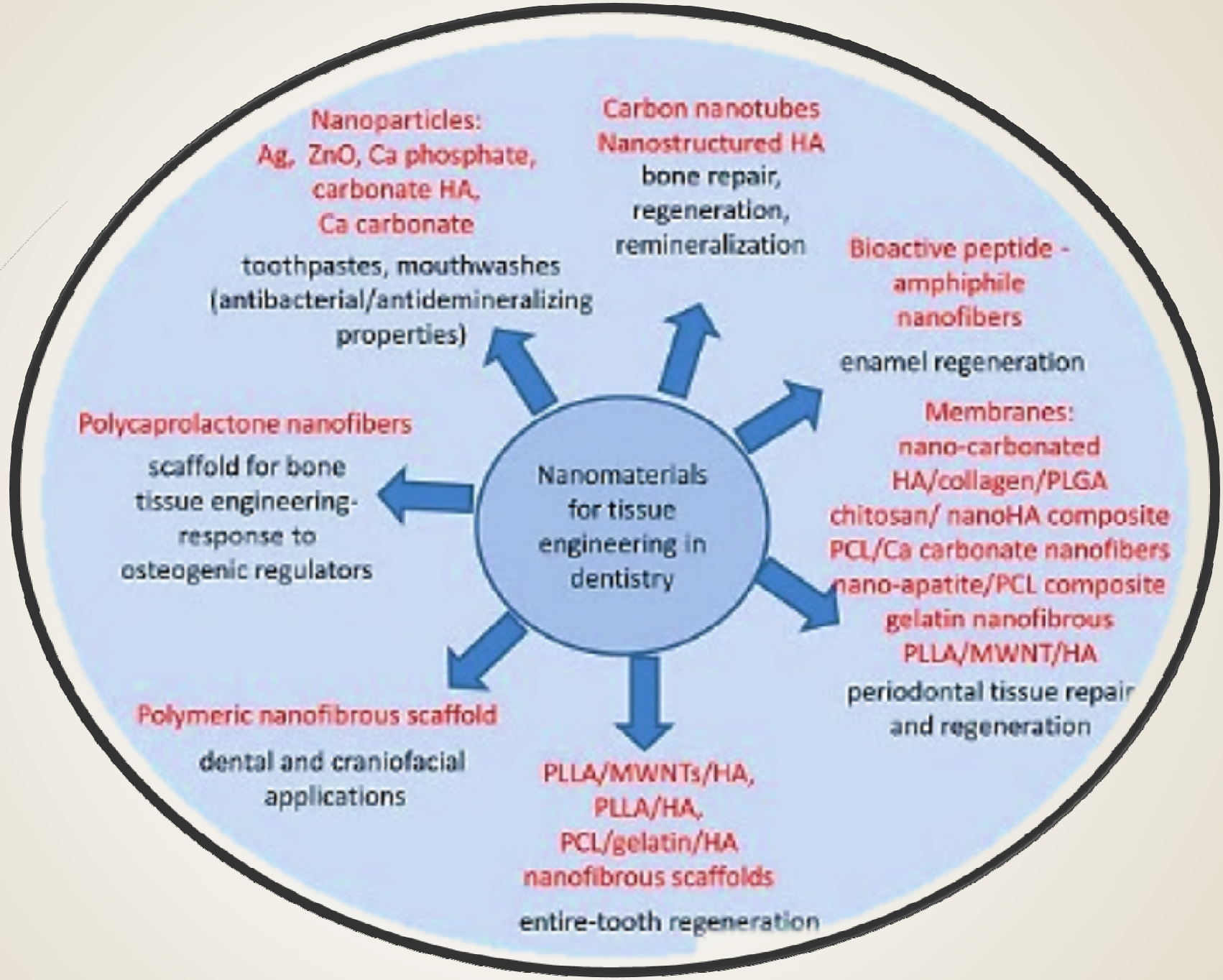
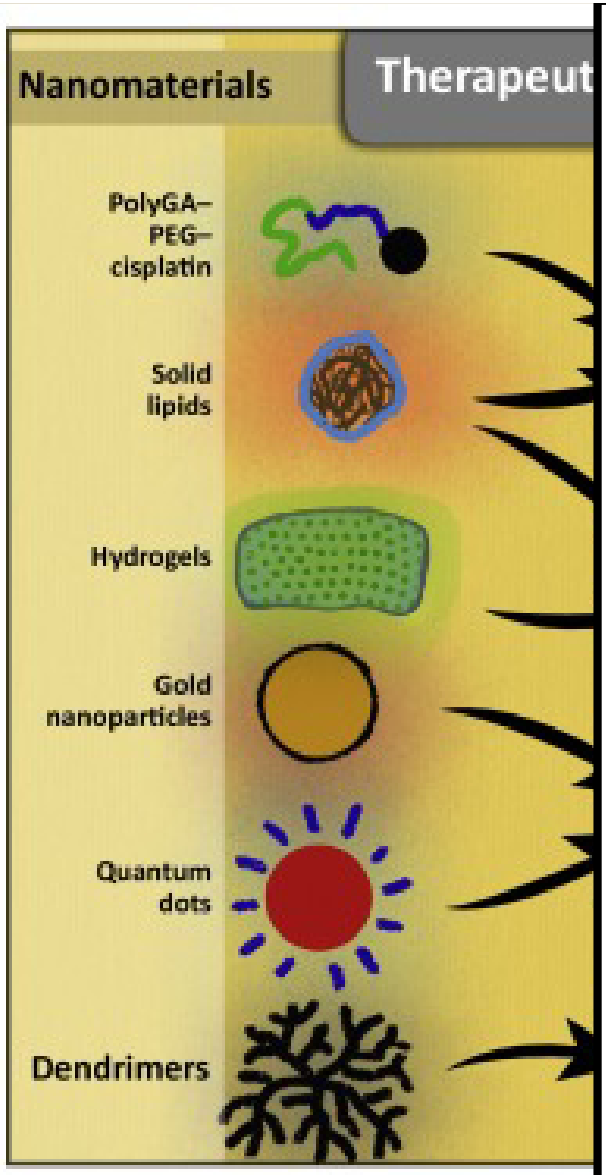


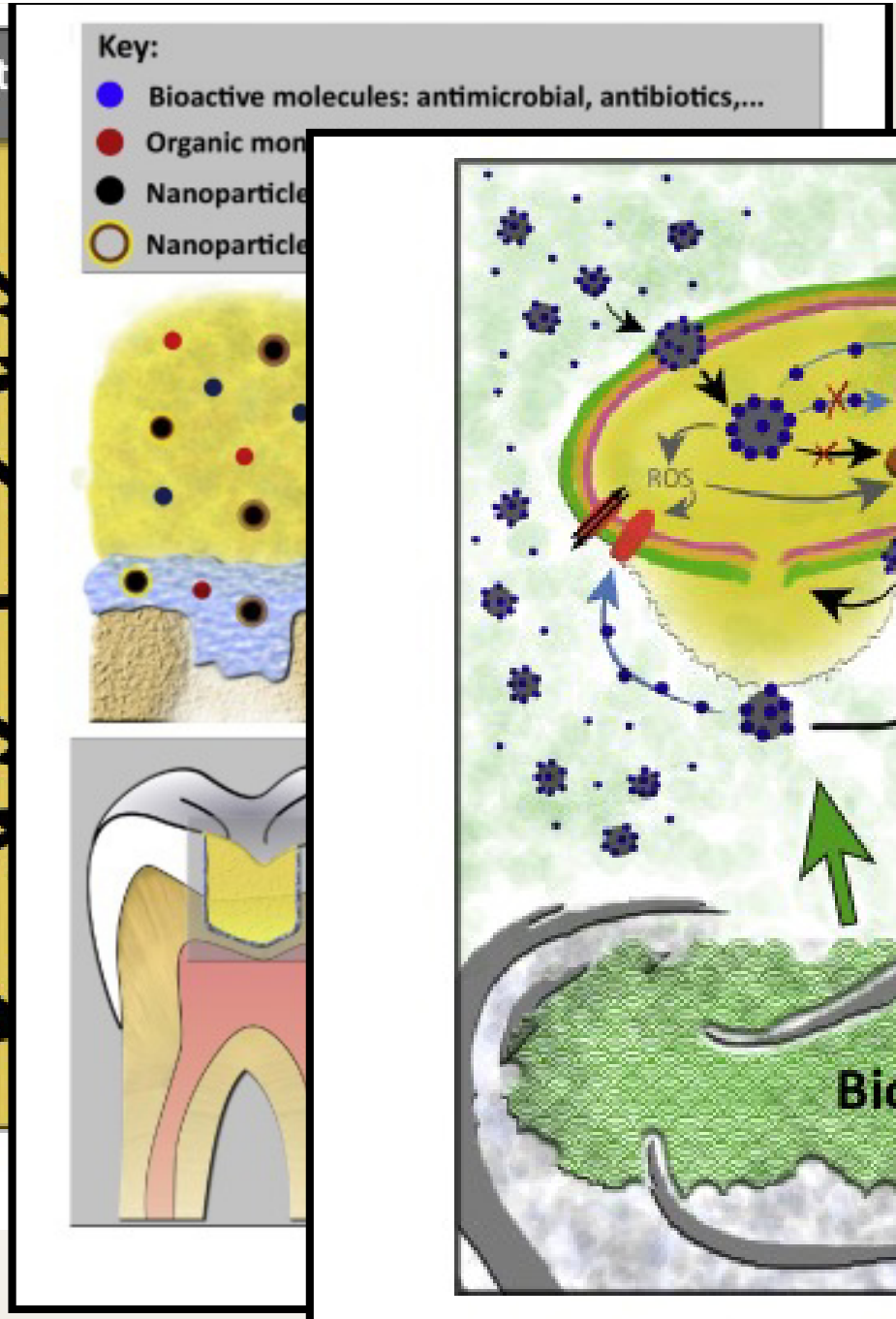
Figure 5. Layer-by-layer (LbL) coating for sustained release of siRNA and reduction of MMP-9 expression. (A) Chemical structures of polymers used for the preparation of LbL coating. (B) Hierarchical structure of LbL films into a single coating. (C) Application of bandages on full-thickness excisional 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.


ANY?

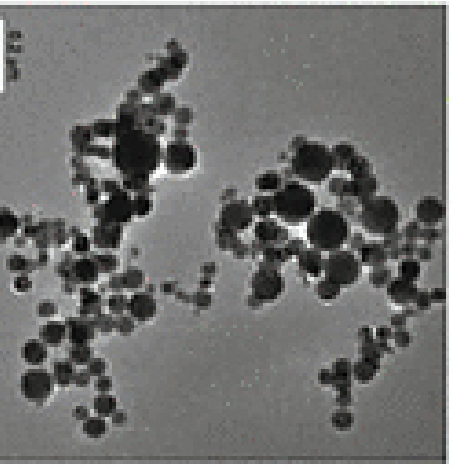

Nanotechnology in dentistry
Therapeutic nanomaterials
cisplatin PEG-PolyGA
• Oral cancer management
solid lipid
• Periodontology
hydrogels
gold nanoparticles
• Oral cancer management
quantum dots
dendrimers
• Biomineralization
• Adhesive dentistry
Antimicrobial nanoparticles
organic
polymeric triclosan
• Periodontology
quaternary ammonium compounds
• Endodontics
chitosan
• Restorative composites
• Adhesive dentistry
• Periodontology
copper-based nanomaterials
• Implant odontology
inorganic
zinc-based nanomaterials
• Temporary materials
• Endodontics
• Adhesive dentistry
ACP
• Periodontology
• Endodontics
titanium dioxide
nanosilver
• Implant odontology
• Restorative composites
• Temporary materials
Mechanical reinforcement nanostructures
nanocarbons
• Prosthodontics (acrylic resins)
• Restorative composites
nanosilica
• Endodontics
• Biomineralization
• Restorative composites
nanozirconia
• Implant odontology
• Bioceramics
nanofibrilar silicates
nanohydroxyapatite
• Restorative composites
• Adhesive dentistry
• Biomineralization
polymeric nanogels
• Restorative composites
• Adhesive dentistry

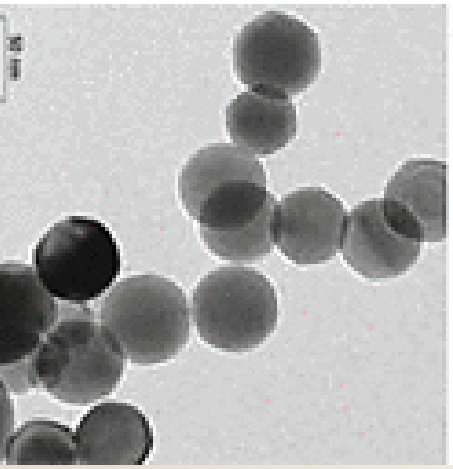

Nanomaterials for tissue engineering in dentistry
Nanoparticles: Ag, ZnO, Ca phosphate, carbonate HA, Ca carbonate
toothpastes, mouthwashes (antibacterial/antidemineralizing properties)
Carbon nanotubes Nanostructured HA
bone repair, regeneration, remineralization
Bioactive peptide - amphiphile nanofibers
enamel regeneration
Membranes: nano-carbonated HA/collagen/PLGA chitosan/ nanoHA composite PCL/Ca carbonate nanofibers nano-apatite/PCL composite gelatin nanofibrous PLLA/MWNT/HA
periodontal tissue repair and regeneration
PLLA/MWNTs/HA, PLLA/HA, PCL/gelatin/HA nanofibrous scaffolds
entire-tooth regeneration
Polymeric nanofibrous scaffold
dental and craniofacial applications
Polycaprolactone nanofibers
scaffold for bone tissue engineering- response to osteogenic regulators



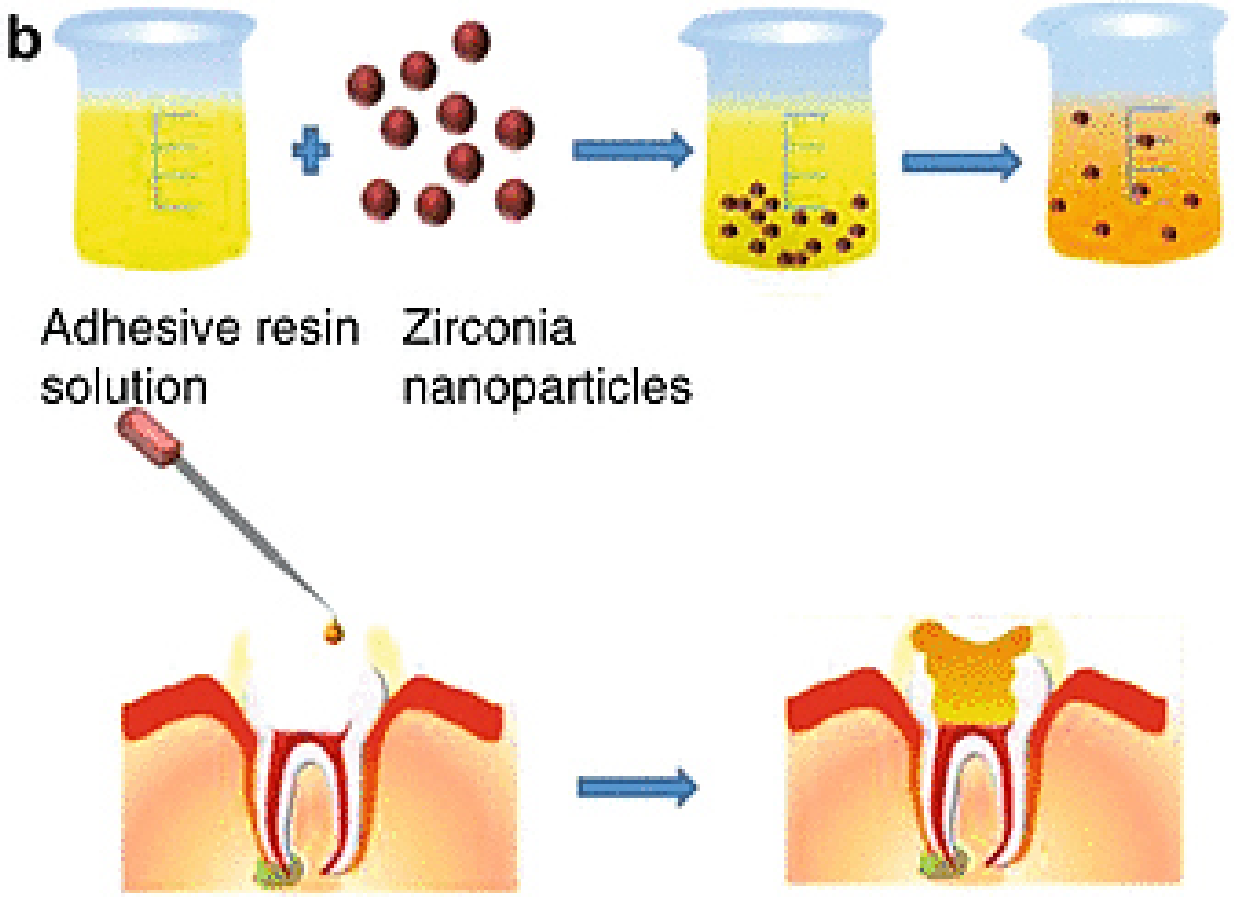


Trends in Biotechnolog



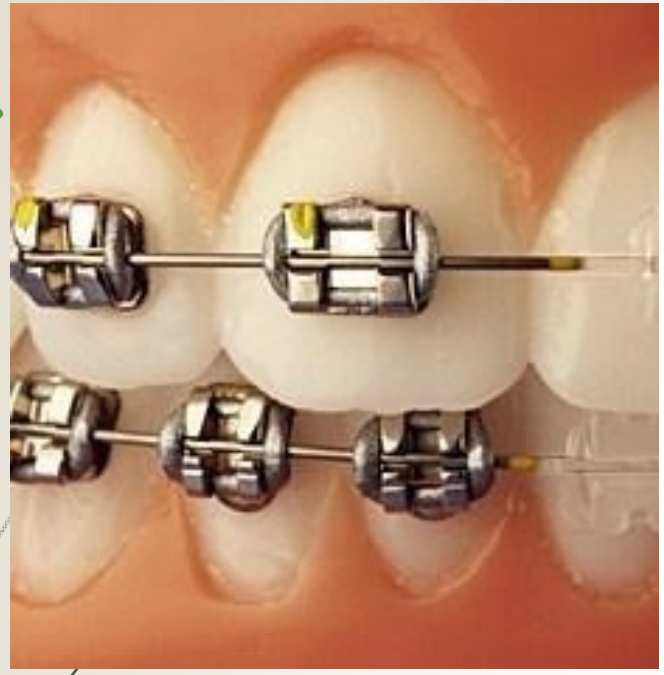


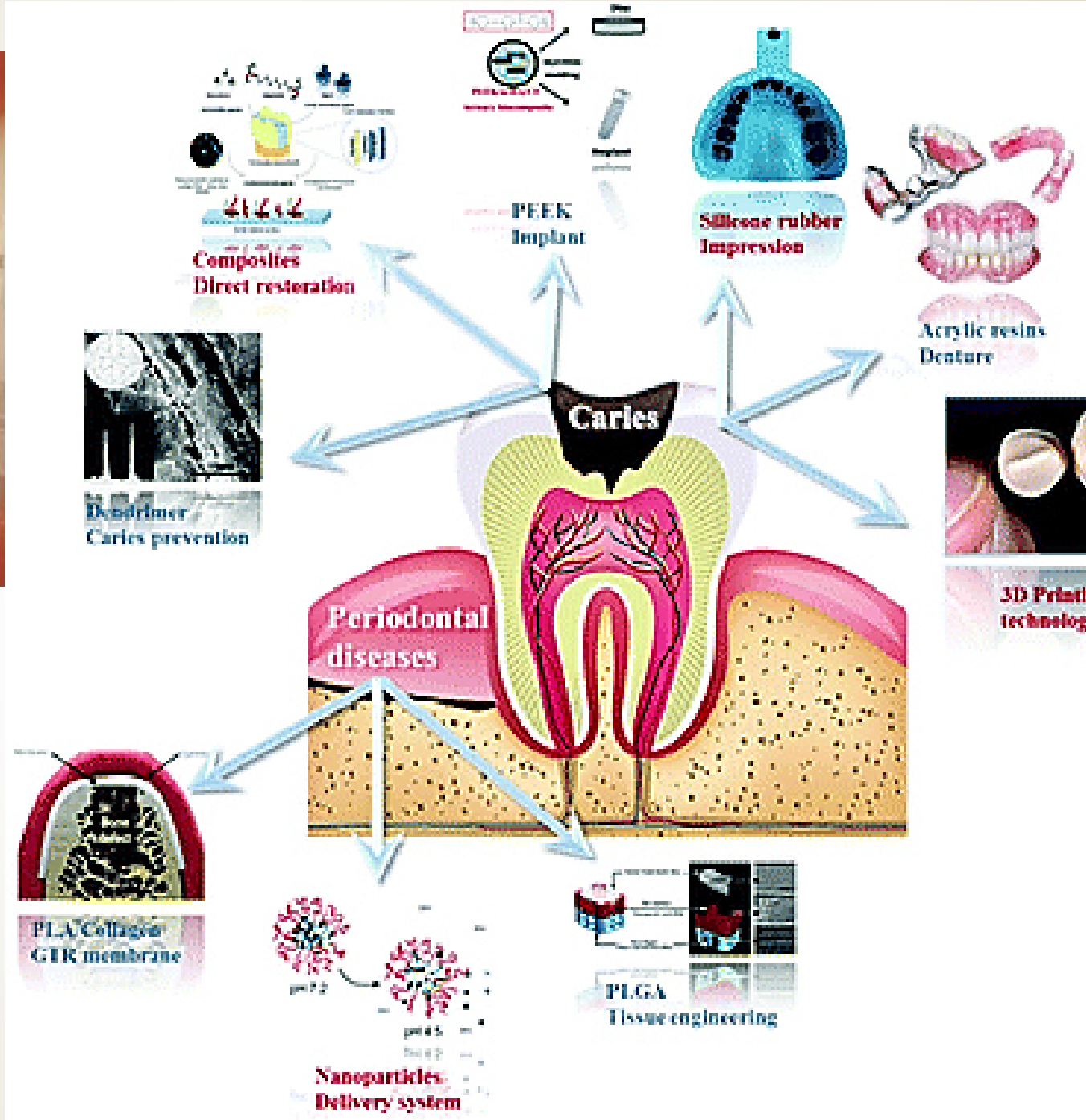
b

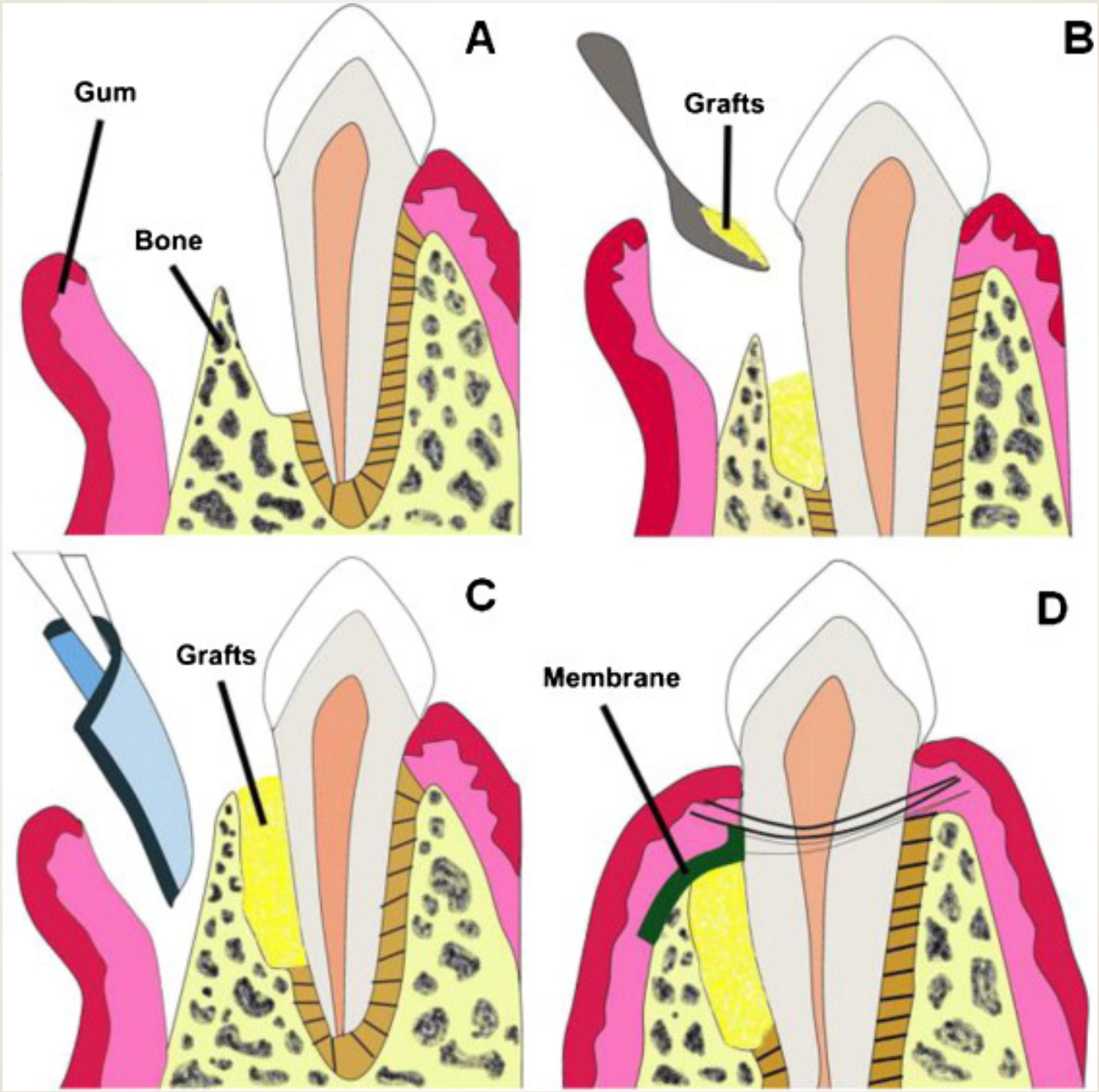


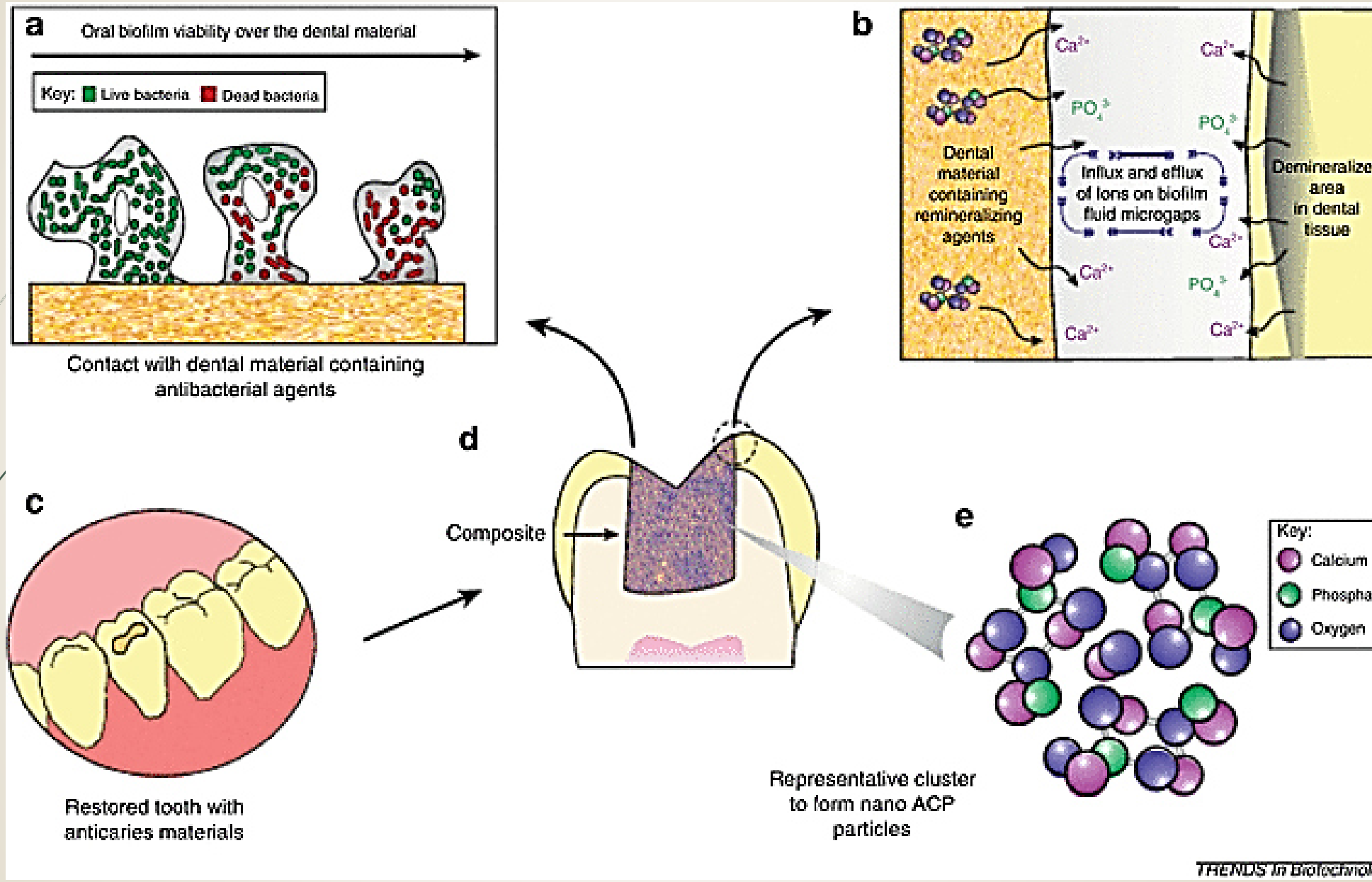
c i

ii

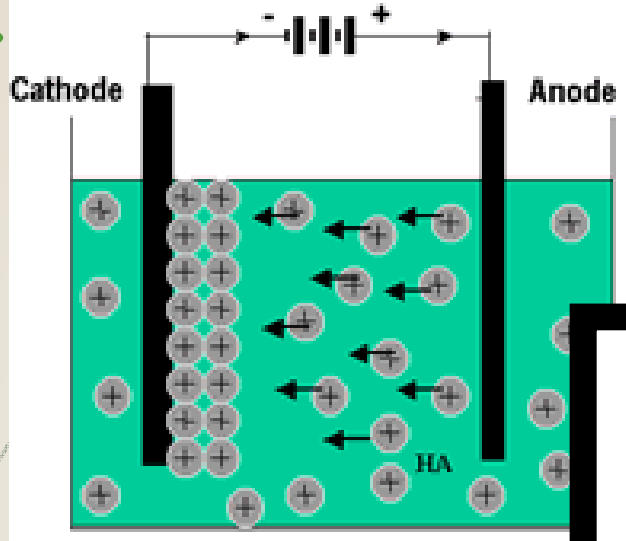



Composites
Direct restoration
PEEK
Implant
Silicone rubber
Impression
Acrylic resins
Denture
Caries
Bonding
Caries prevention
3D Printi
technolog
Periodontal
diseases
PLA/Collagen
GTR membrane
Nanoparticles
Delivery system
PLGA
Tissue engineering


A
Gum
Bone
B
Grafts
C
Grafts
D
Membrane

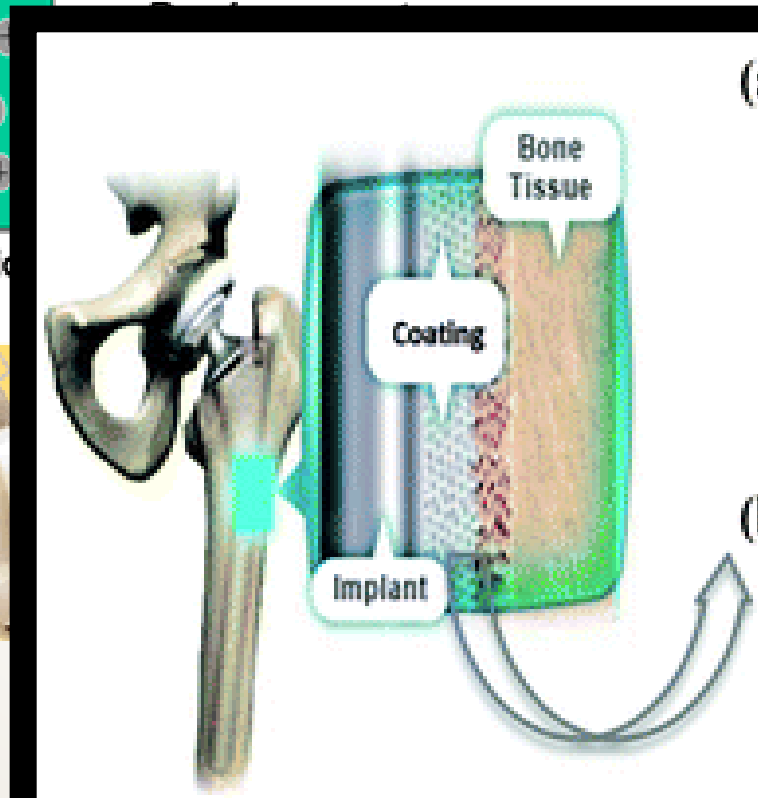

a
Oral biofilm viability over the dental material
Key: Live bacteria Dead bacteria
Contact with dental material containing antibacterial agents
b
Dental material containing remineralizing agents
Influx and efflux of ions on biofilm fluid microgaps
Demineralized area in dental tissue
c
Restored tooth with anticaries materials
d
Composite
e
Key:
Calcium
Phospha
Oxygen
Representative cluster to form nano ACP particles
TRENDS in Biotechnol

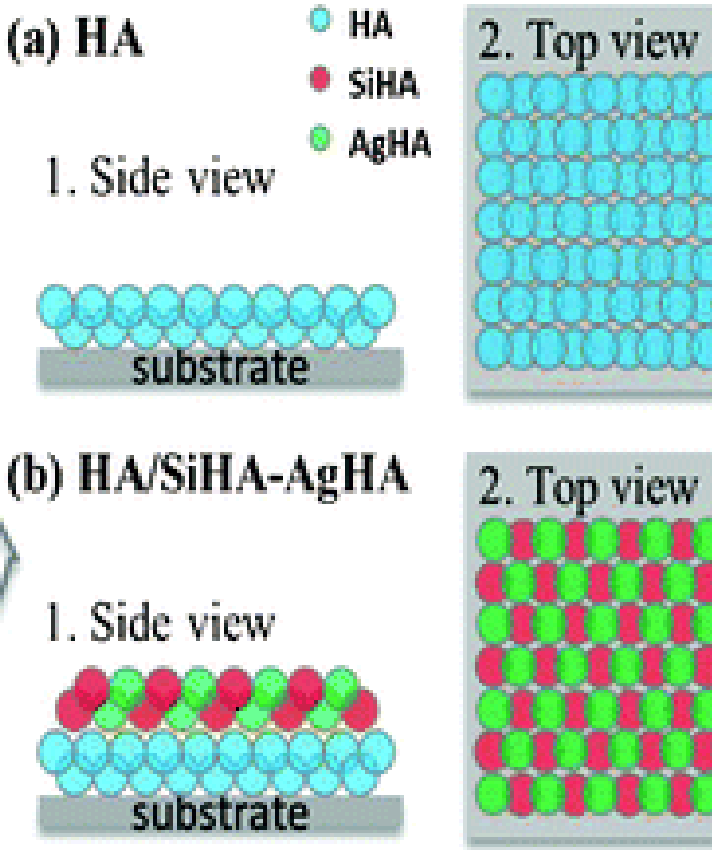
Nano-Hydroxyapatite



Hydroxyapatite nanoparticle solutio

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






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

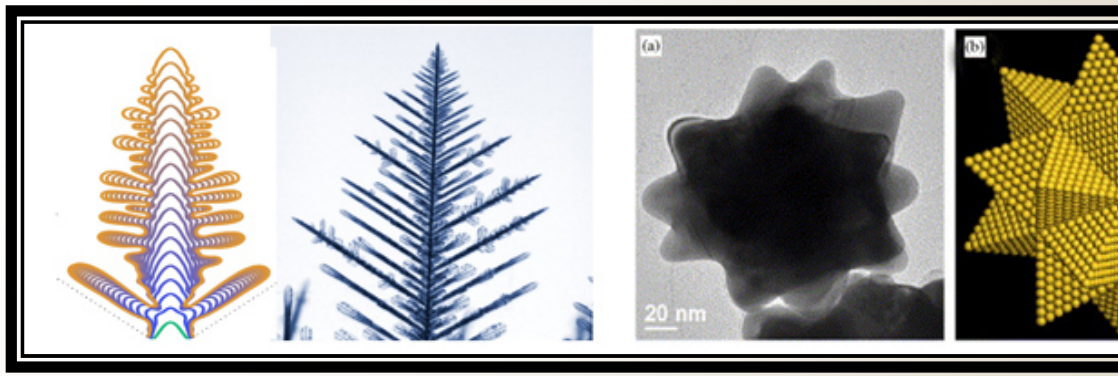
Nanomaterials use for biomedical applications

Preclinical studies

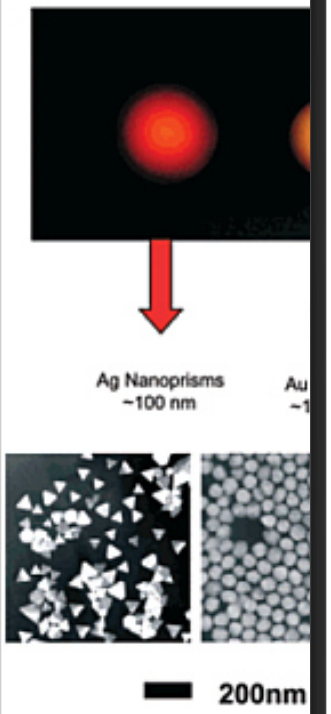

ANY?

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
- ...

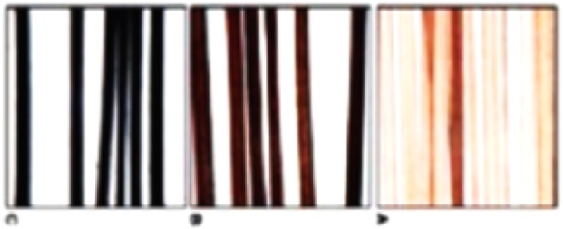


Exam

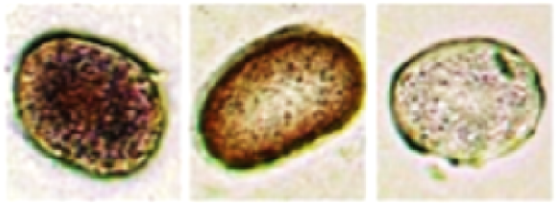


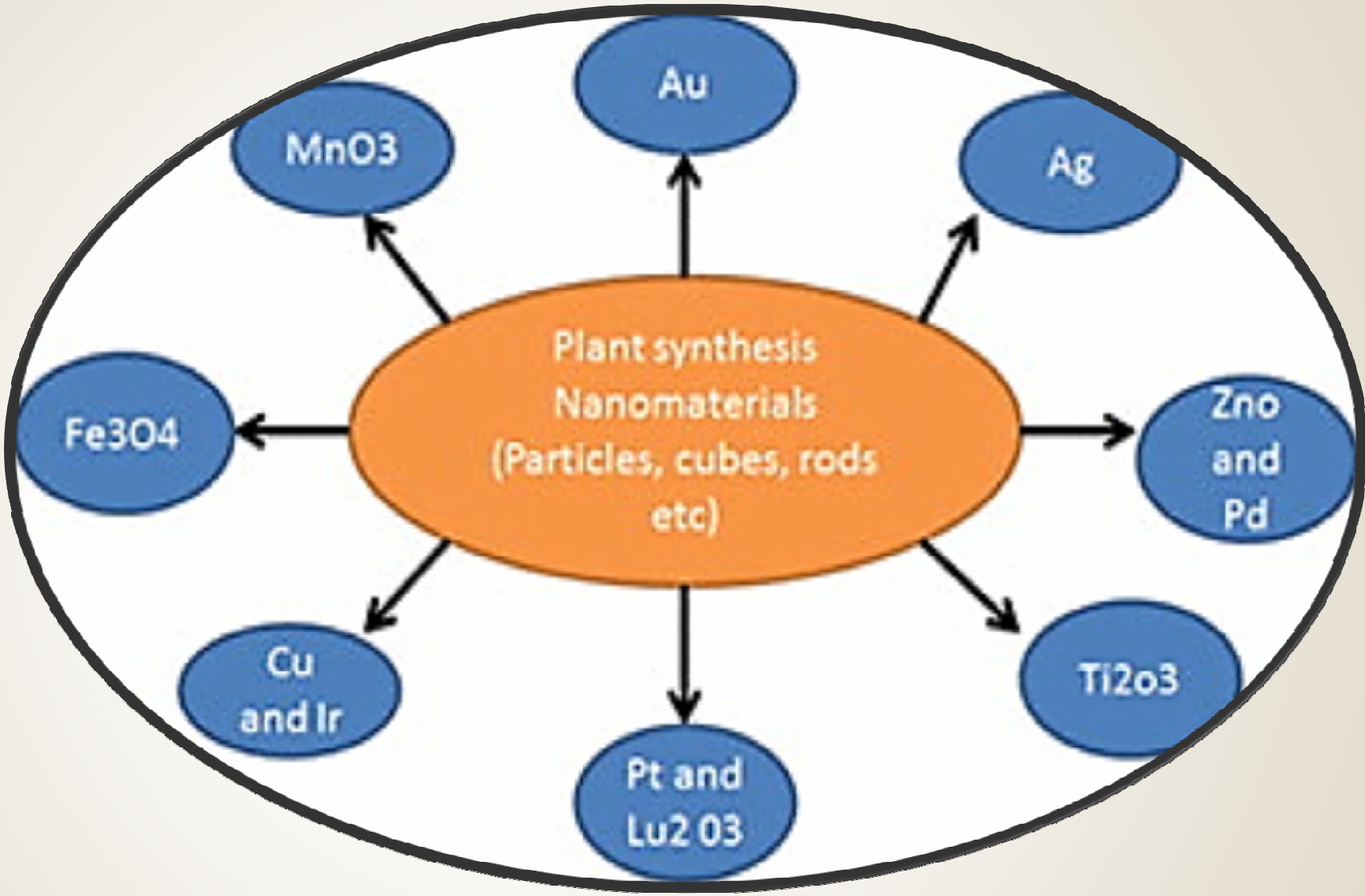
Some Ancient Nano Material

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.

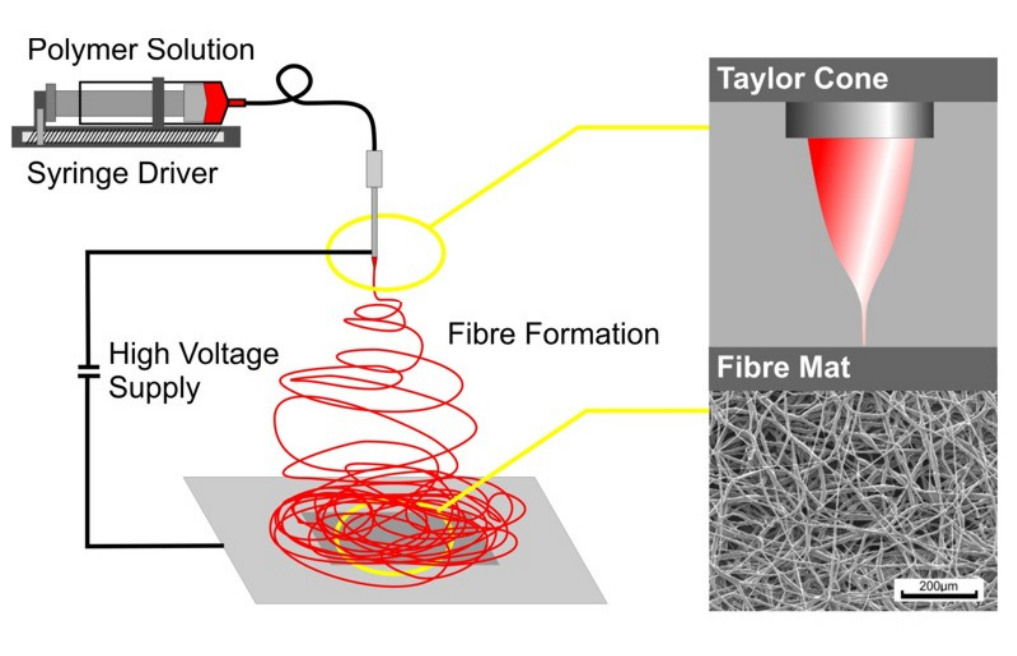


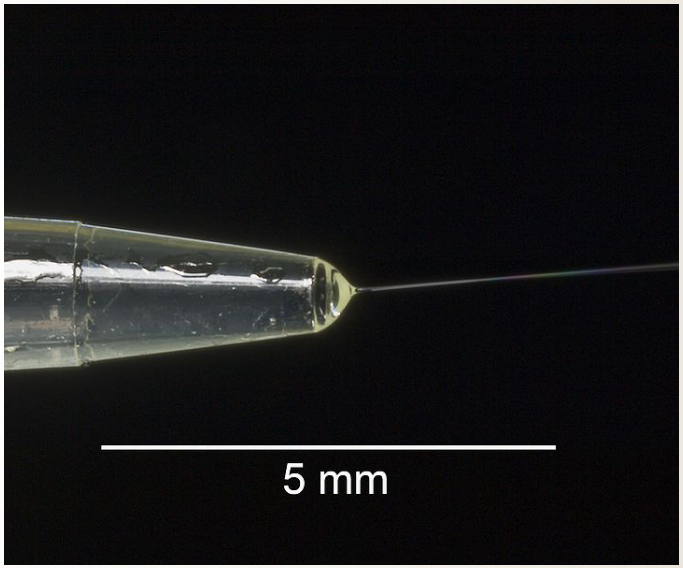

Au
MnO3
Ag
Plant synthesis
Nanomaterials
(Particles, cubes, rods
etc)
Fe3O4
Zno
and
Pd
Cu
and Ir
Ti2o3
Pt and
Lu2 03

Nanofibrous Scaffold

Electrospinning

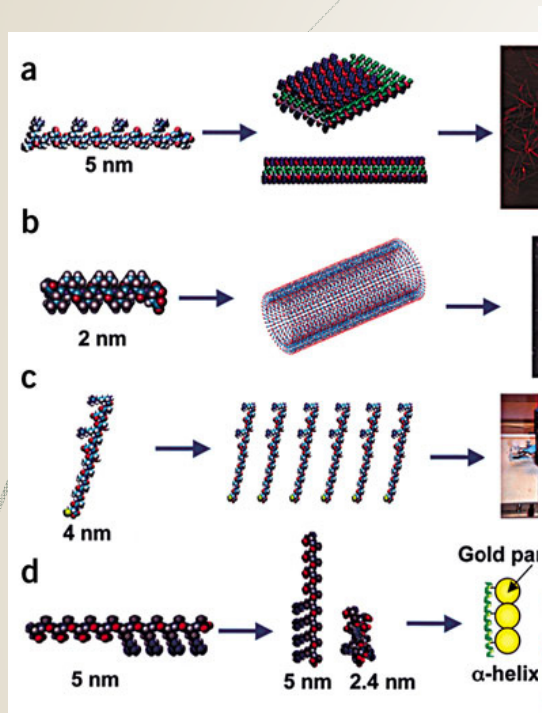
- Electrospinning

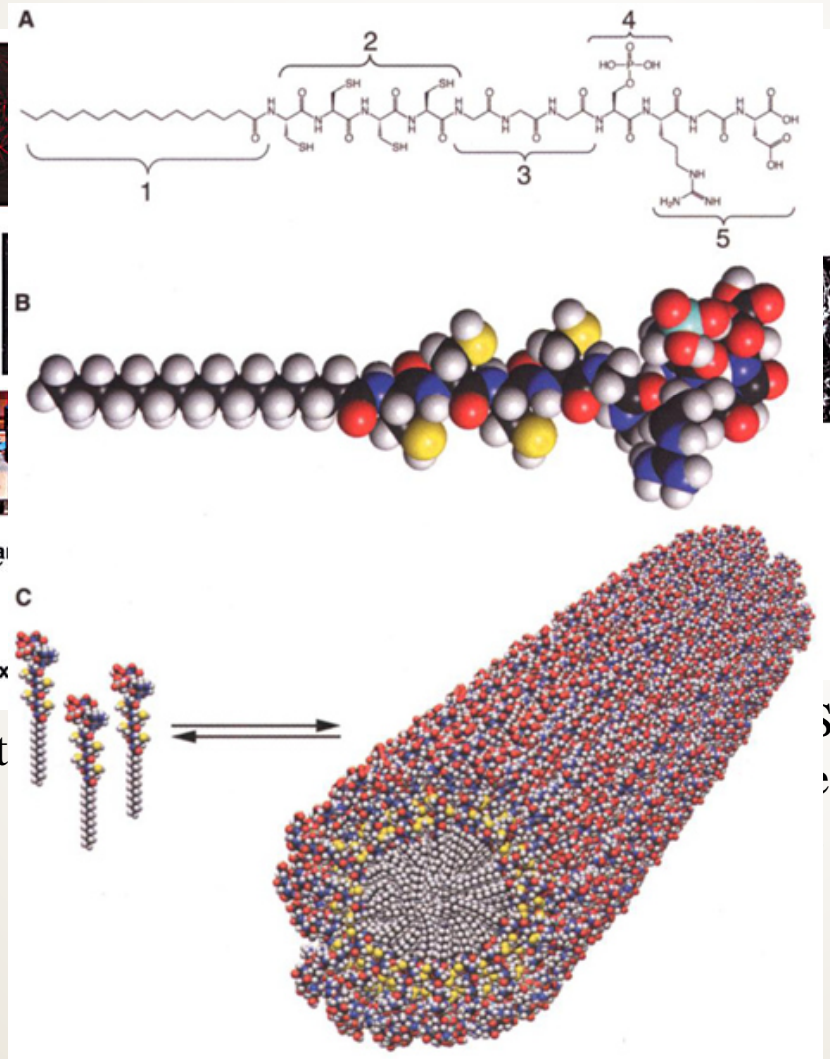




- This process involves the ejection of a charged polymer fluid onto an oppositely charged surface.
- Multiple polymers can be combined
- Control over fiber diameter and scaffold architecture

Self Assembly





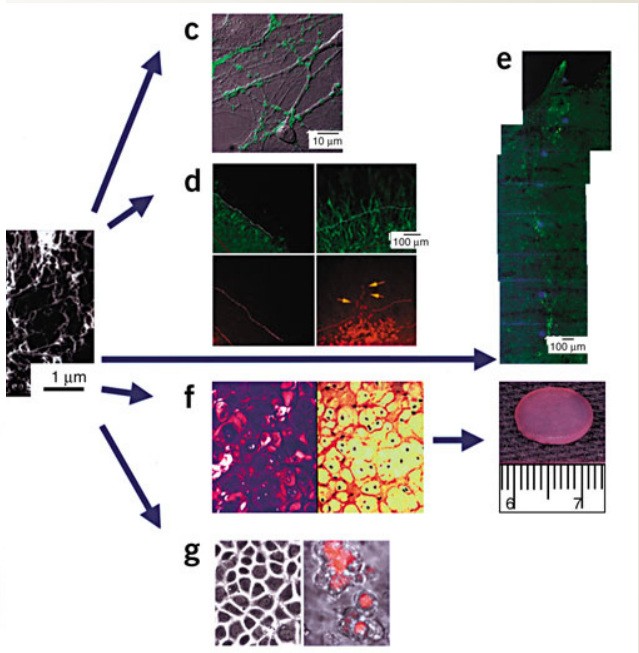


Figure 1: Fabricat
materials.

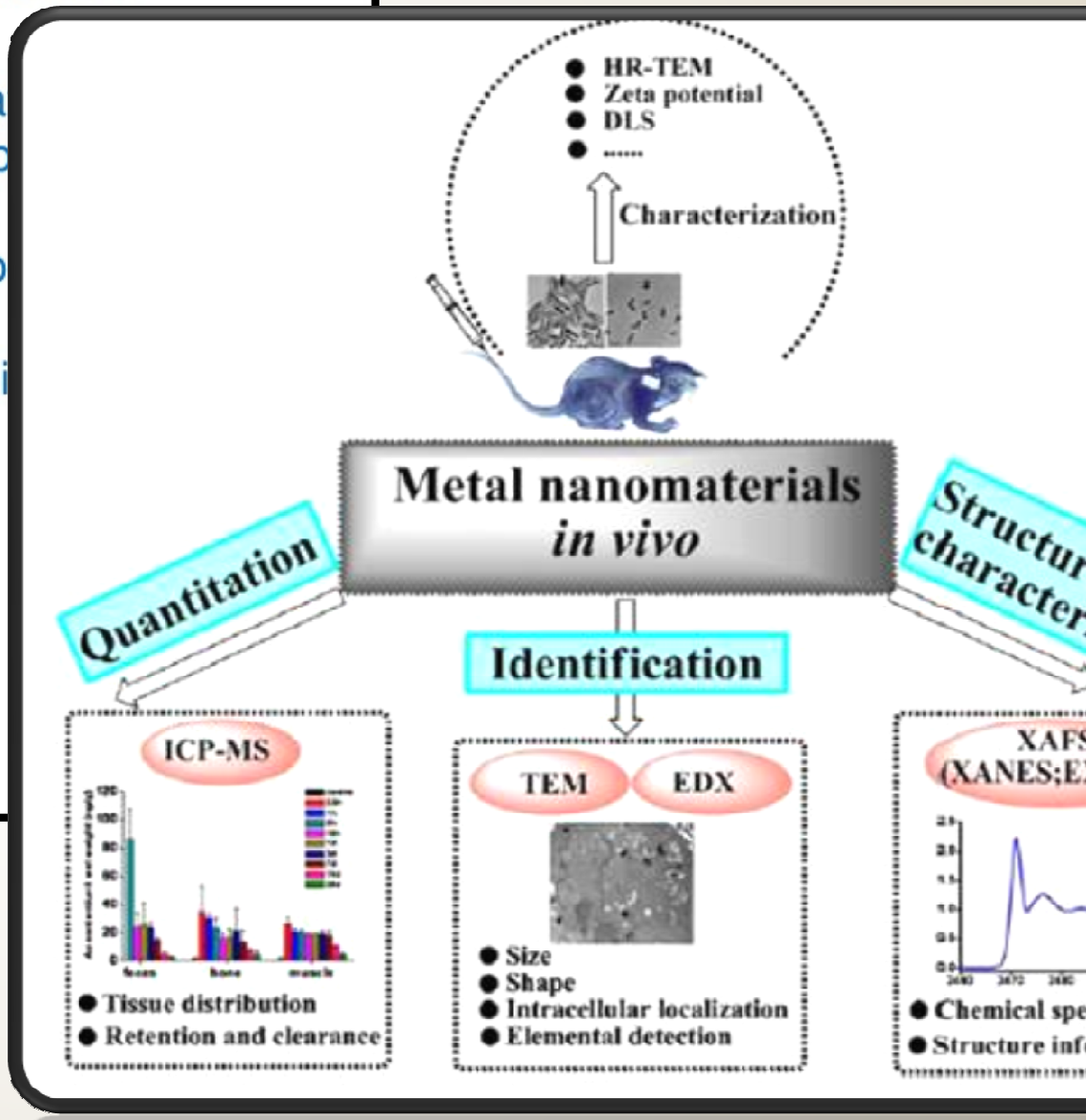
Self-assembling peptides form a
ensional scaffold woven from
~ 10 nm in diameter.

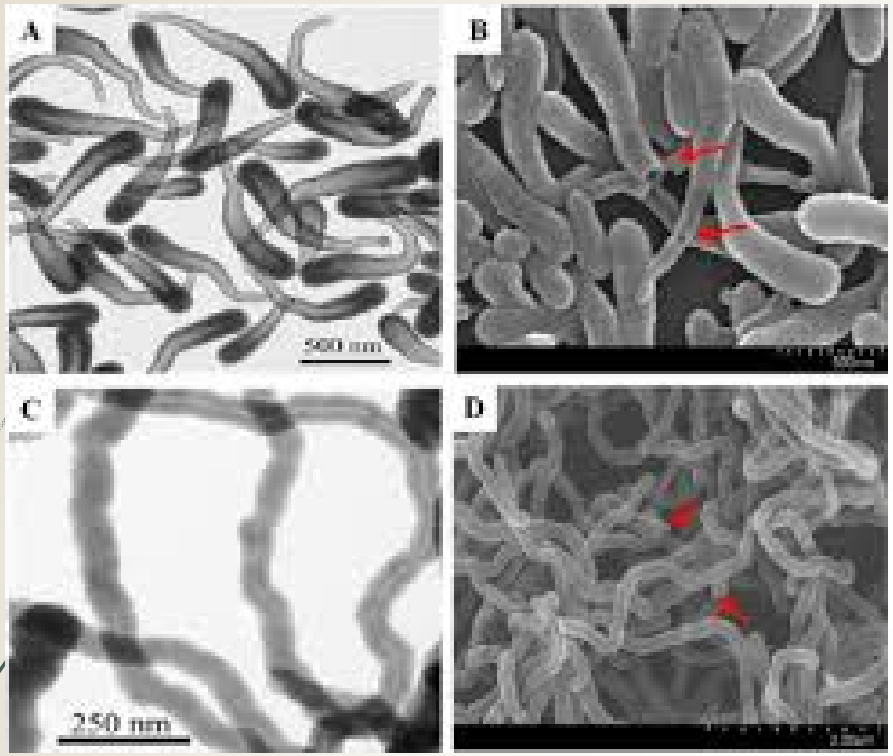

ANY?

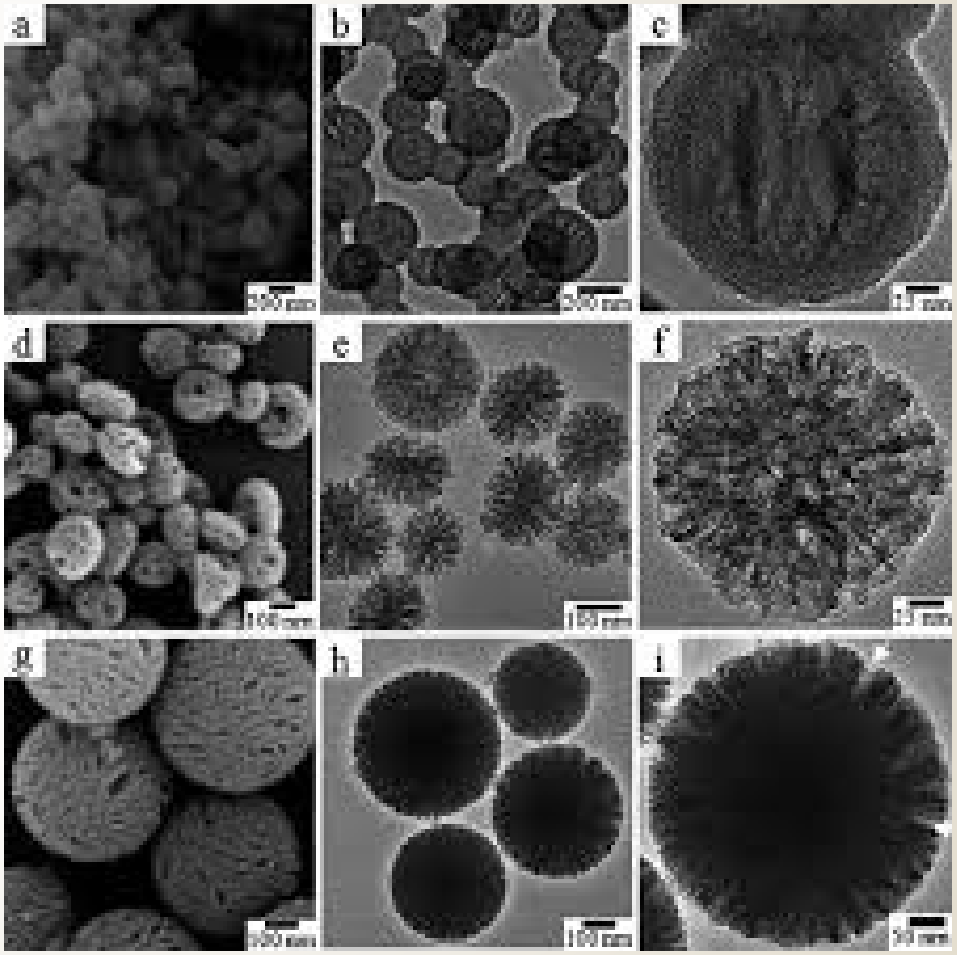
Structural Characterization

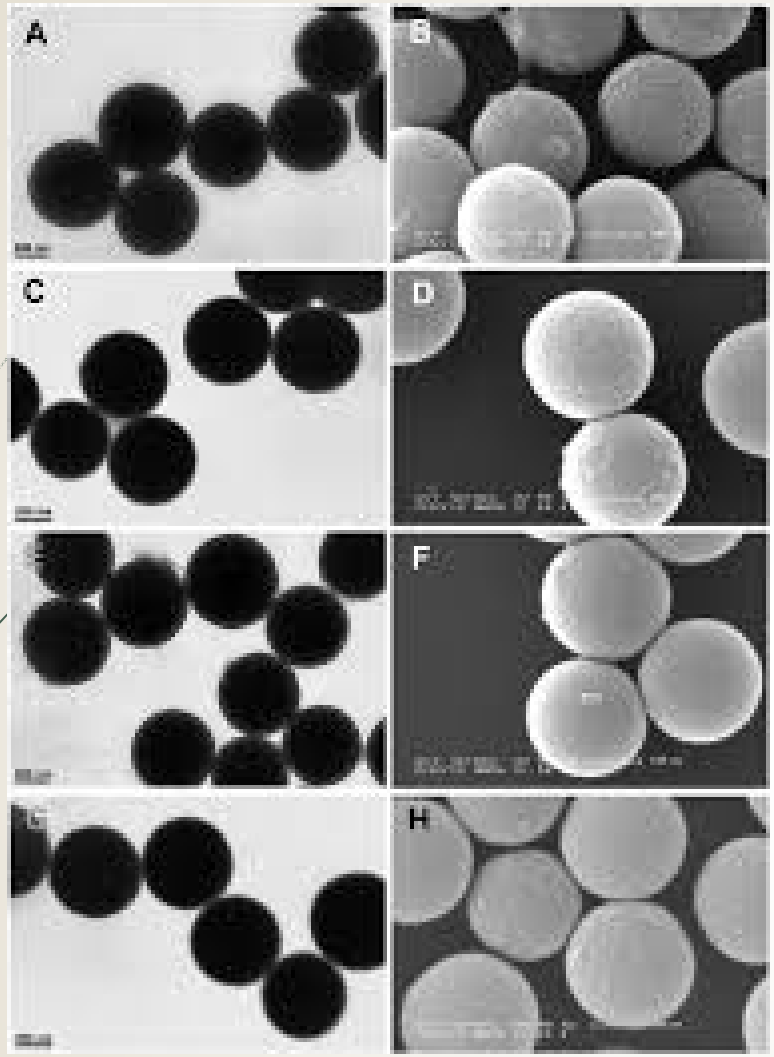
- Characterization of nanoma
nanostructures has been largely b
surface analysis techniques and
characterization methods develop
materials.
The structural characterization techni

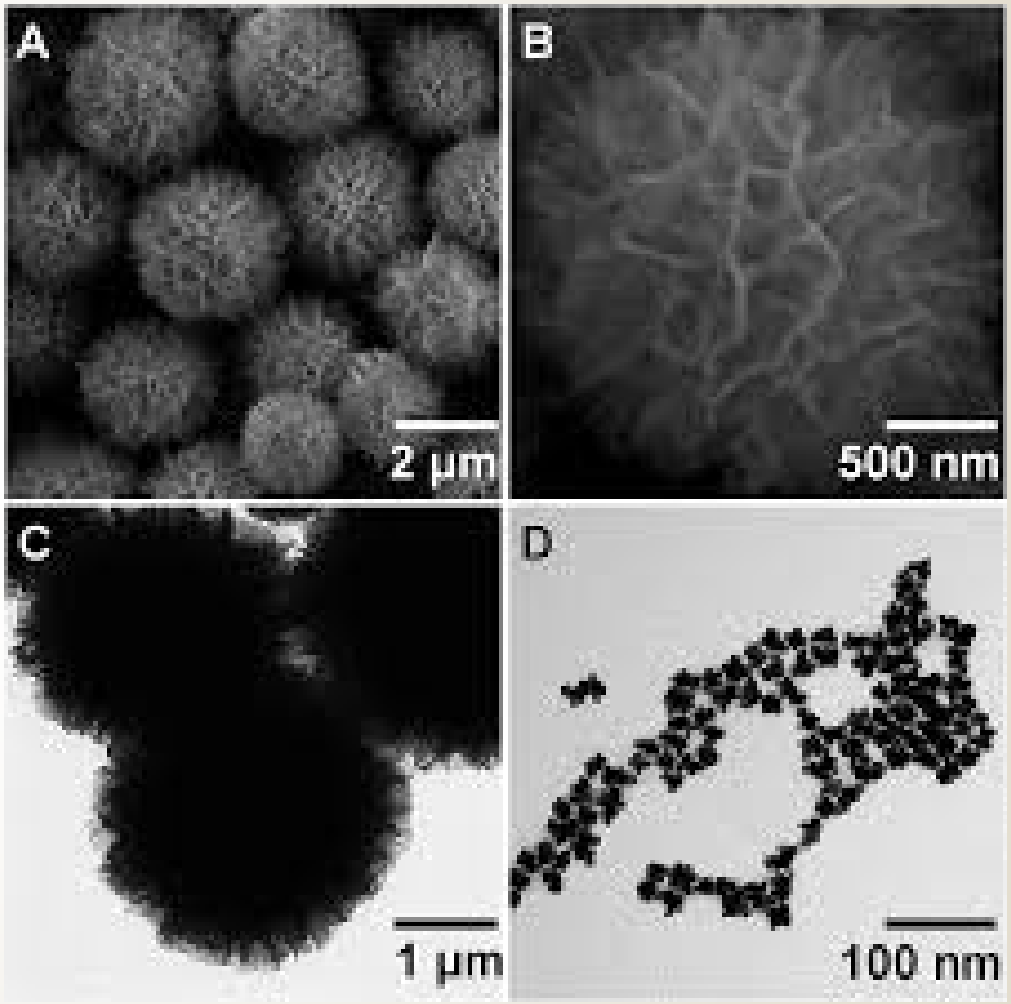
- *X-ray diffraction (XRD)*
- *Small angle X-ray scattering (SAXS)*
- *Scanning electron microscopy (SEM)*
- *Transmission electron microscopy (TEM)*
- *Scanning probe microscopy (SPM)*

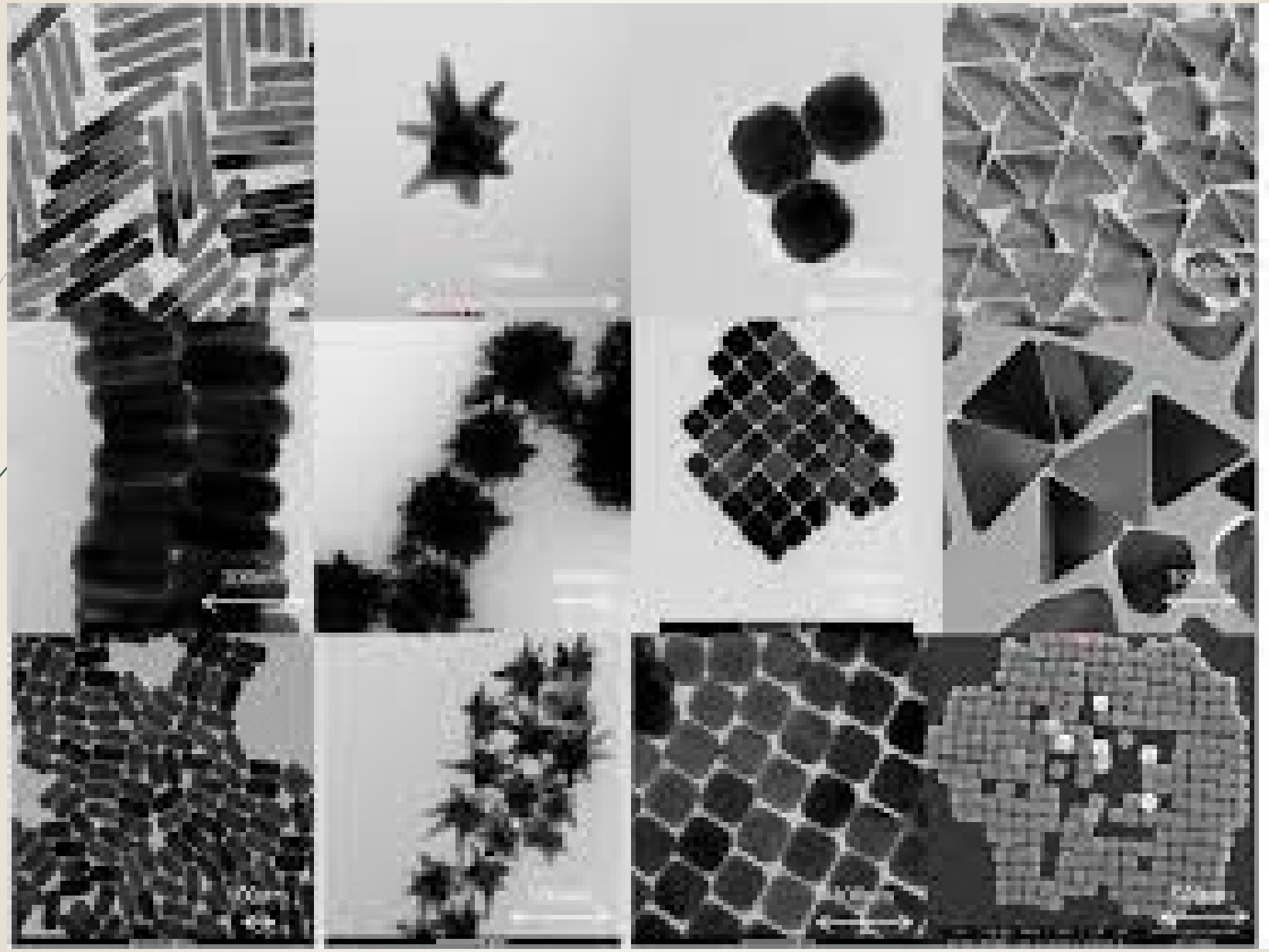



A
B
500 nm
C
D
250 nm


a
b
c
d
e
f
g
h
i


A
B
C
D
F
H


A
2 µm
B
500 nm
C
1 µm
D
100 nm



SEM and AFM images

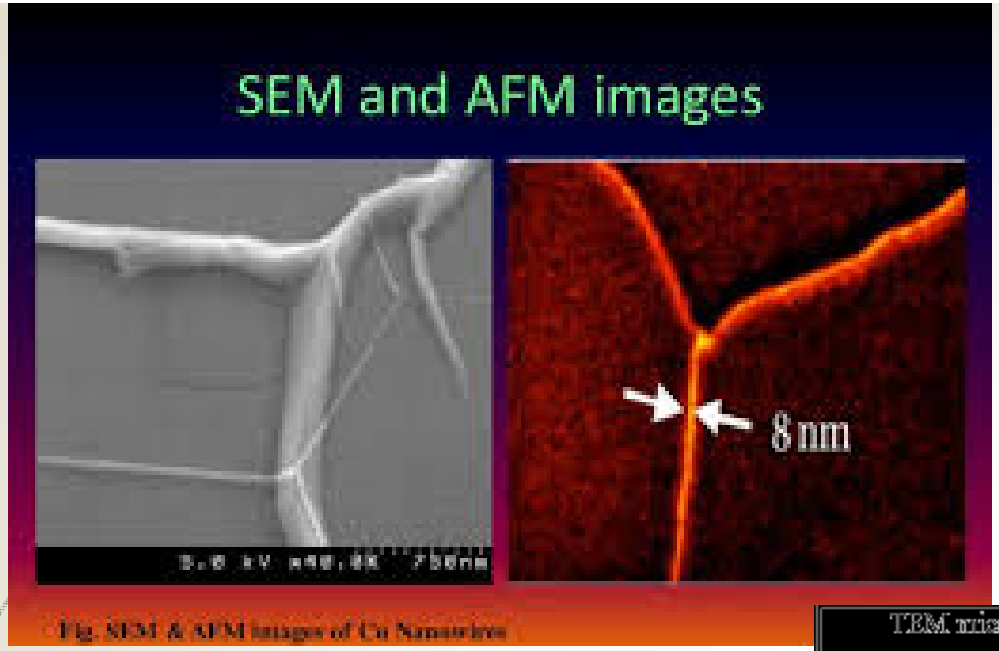
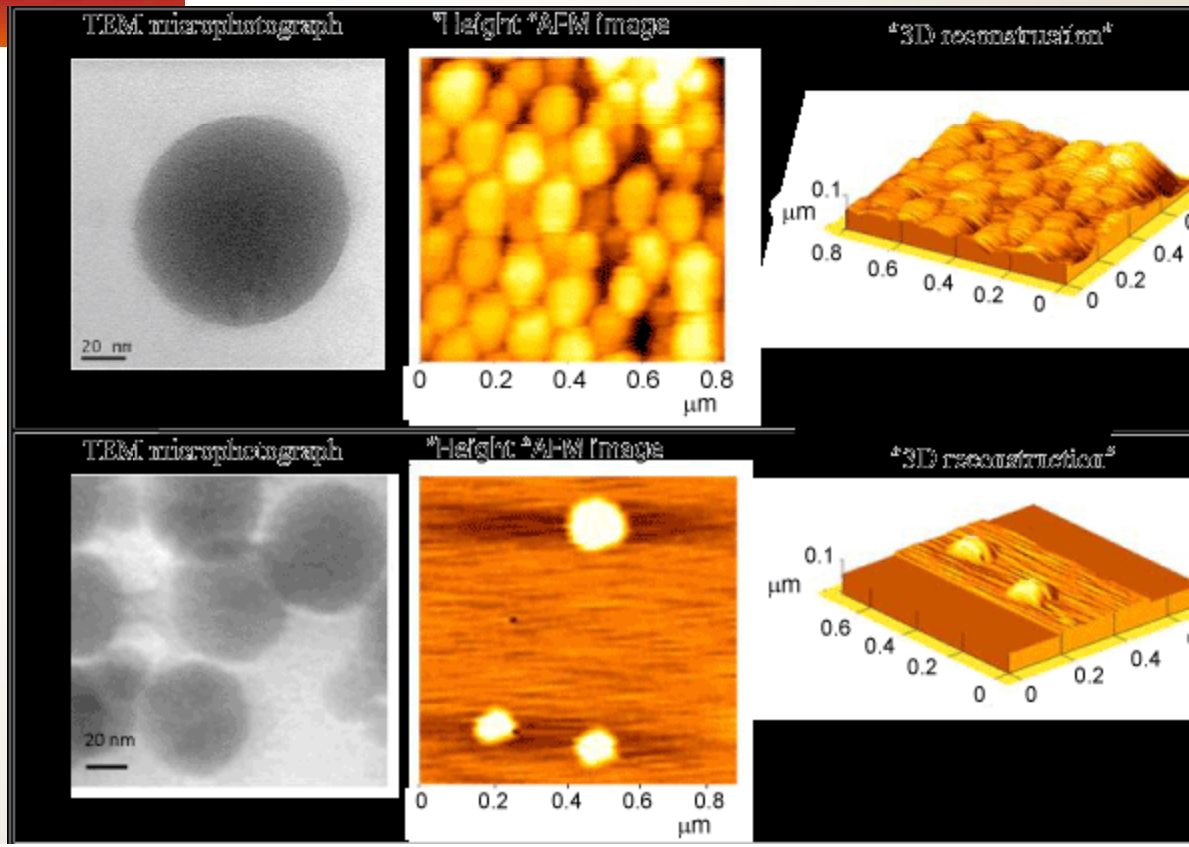
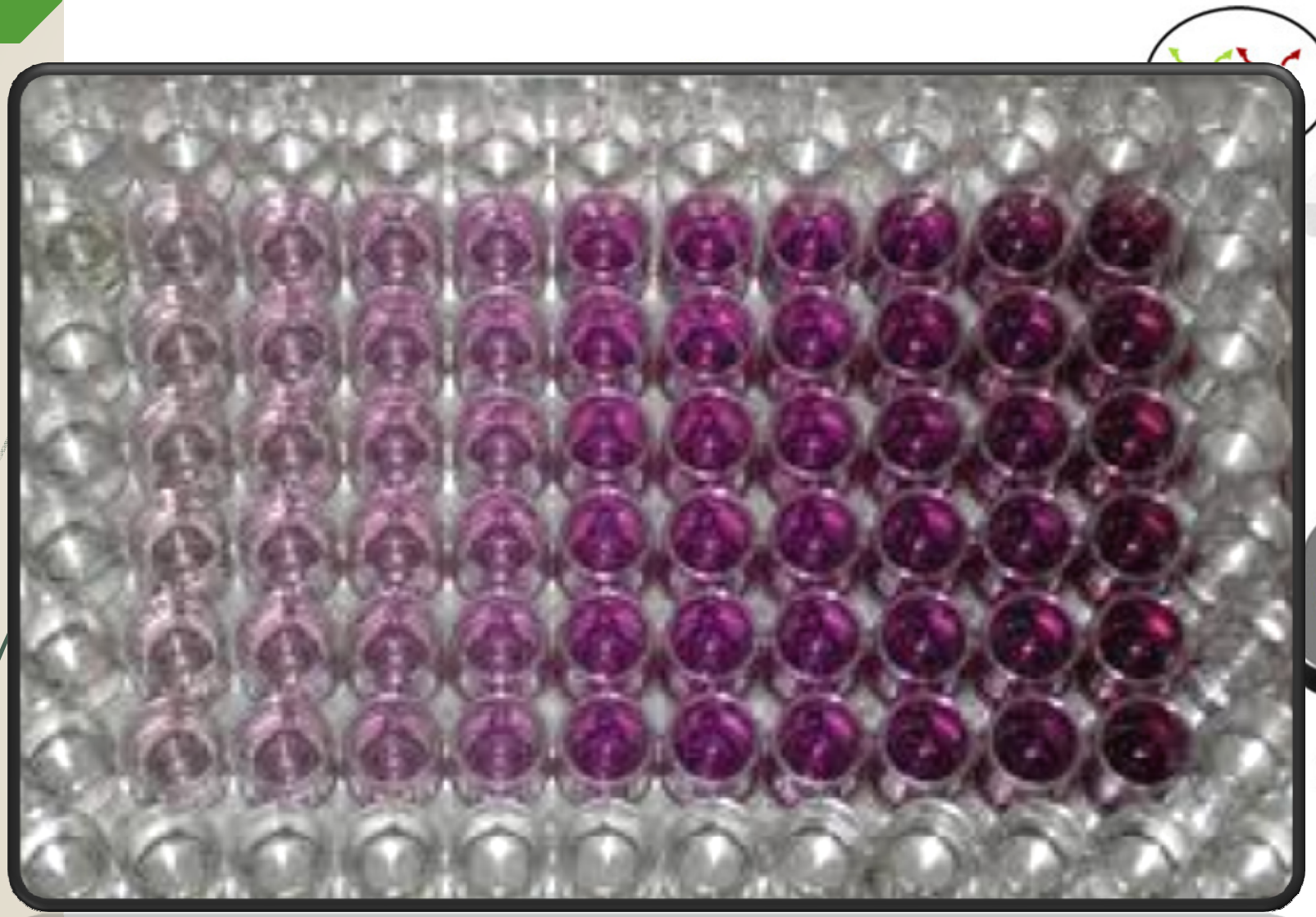
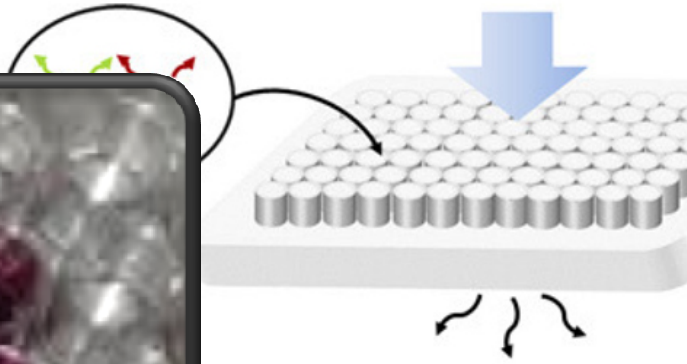


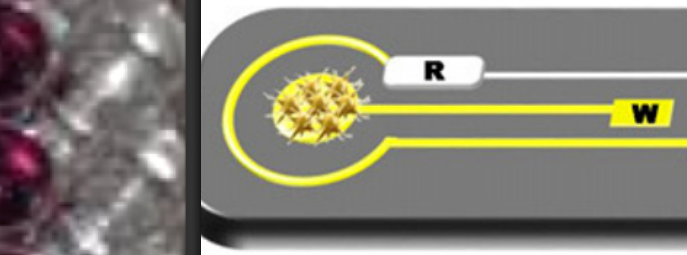
Fig. SEM & AFM images of Cu Nanowires



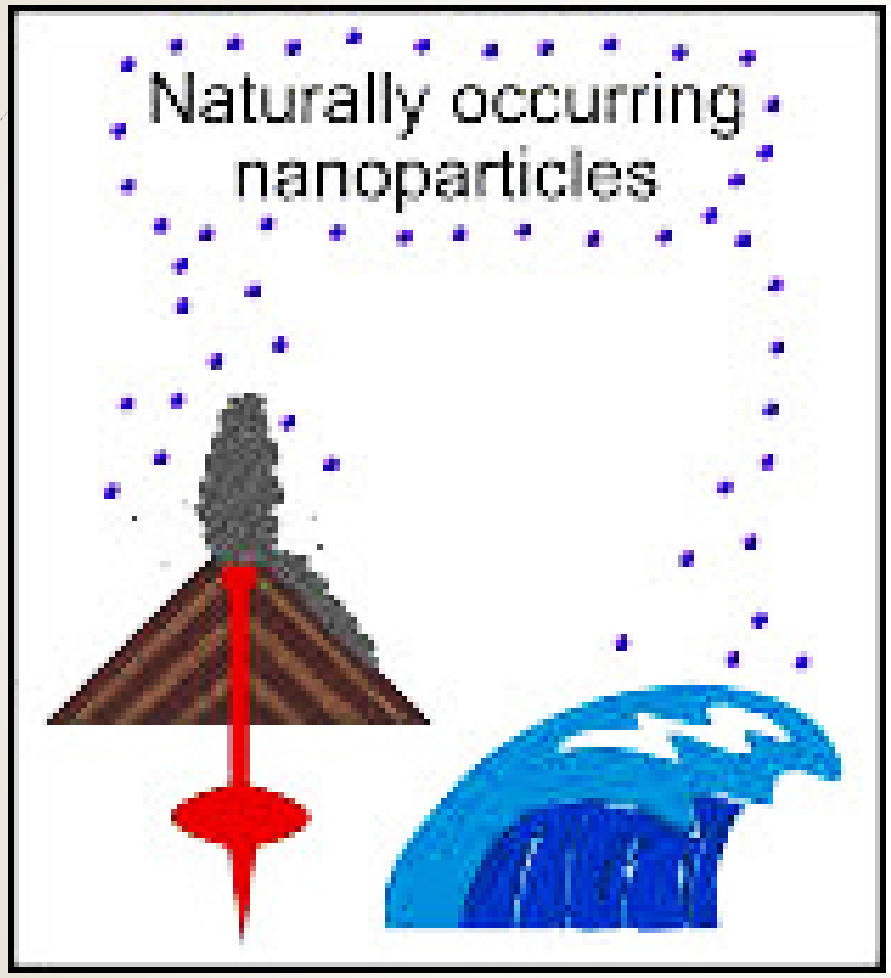


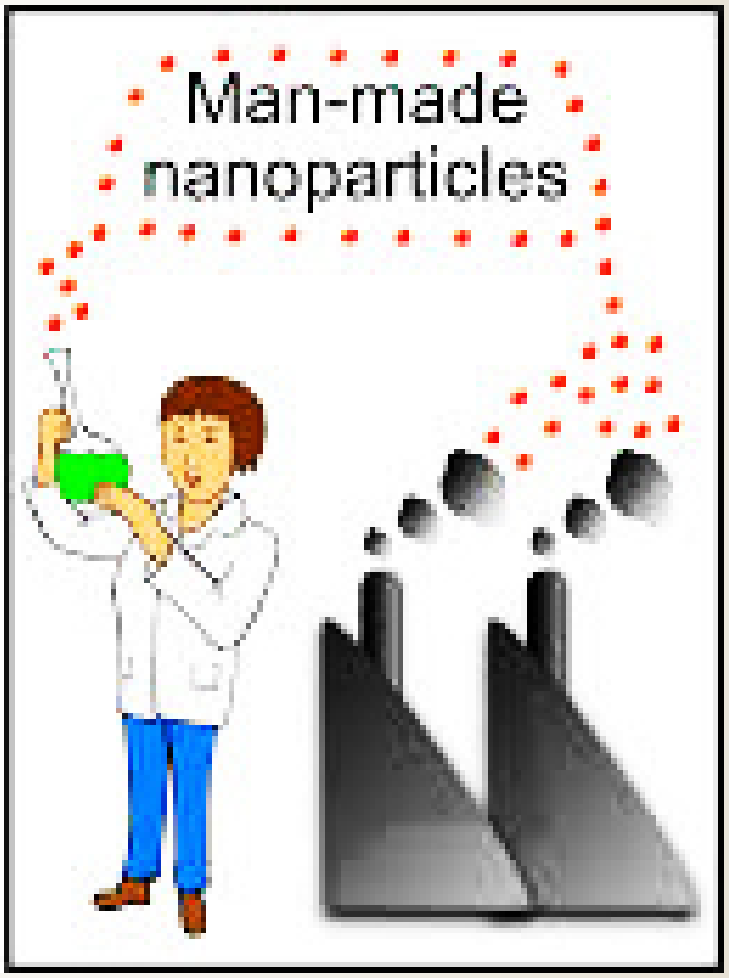


Optical detection
(Mitochondrial activity)



Electrochemical detec
(Cellular redox environme


Naturally occurring
nanoparticles


Man-made
nanoparticles


ANY?