MEDICAL UPDATE GROUP

9 May 2012

NANOMEDICINE : A REALITY

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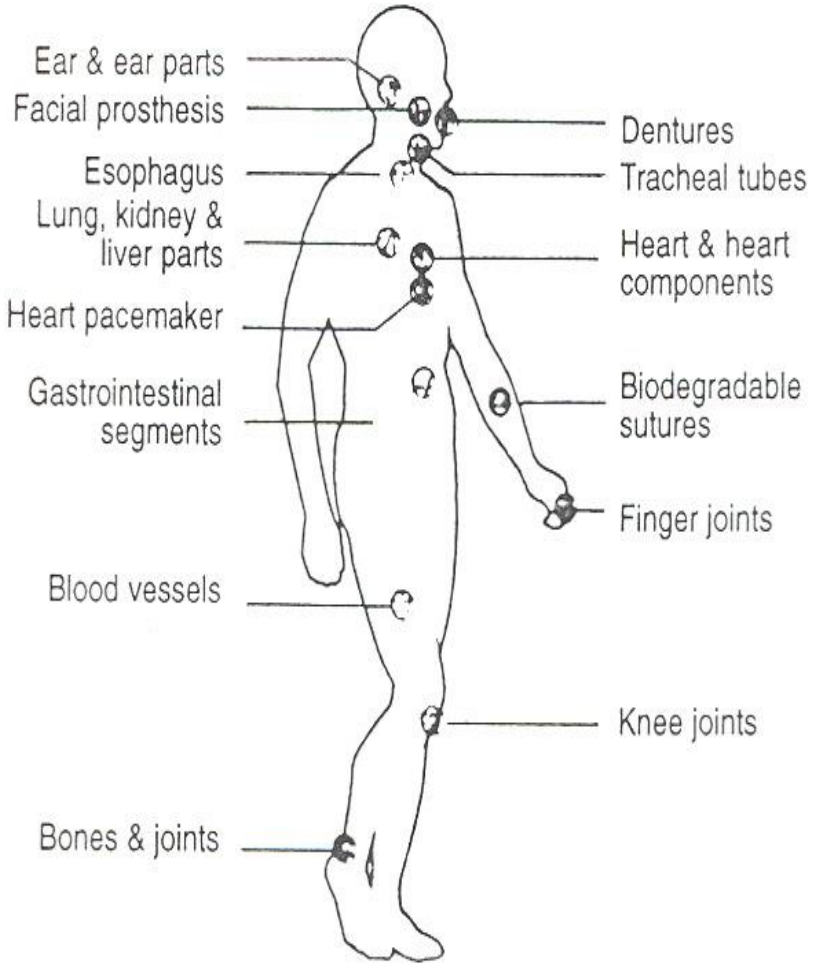
Plan of Presentation

- ✓ **Nanotechnology: definition and properties of nanomaterials**
- ✓ **Nanotechnology in Medicine: Potentials**
  - ➢ **Medical Diagnostics**
  - ➢ **Personalised Medicine: controlled and targeted drug delivery / Nanopharmaceuticals / Nanocarriers**
  - ➢ **Regenerative Medicine: Scaffolds, Biomaterials and Tissue Engineering**
- ✓ **Critical issues**

Polymers in Medicine



Ear and ear parts: acrylic, PE, silicone, PVC

Dentures: acrylic, UHMWPE, epoxy

Facial Prosthesis: acrylic, PVC, PUR

Heart and heart components: polyester, silicone, PVC

Heart pacemaker: PE, polyacetal

Lung, kidney and liver parts: polyester, polyaldehyde, PVC

Esophagus segments: PE, PP, PVC

Blood vessels: PVC, polyester

Biodegradable sutures: PUR, polyester

Gastrointestinal segments: silicone, PVC, nylon

Finger joints: silicone, UHMWPE

Bones and joints: acrylic, nylon, silicone, PUR, PP, UHMWPE

Knee joints: PE

First Revolution

(1780–1840)

Based in United Kingdom

- Steam Engine
- Textile Industry
- Mechanical Engineering

Second Revolution

(1840–1900)

Based in Europe – England, France, Germany

- Railways
- Steel Industry

Third Revolution

(1900–1950)

Based in United States

- Electric Engine
- Heavy Chemicals
- Automobiles
- Consumer Durables

Fourth Revolution

(1950–Present)

Based in Pacific Basin – California, Japan

- Synthetics
- Organic Chemicals (Oil)
- Computers

The Next Big Step

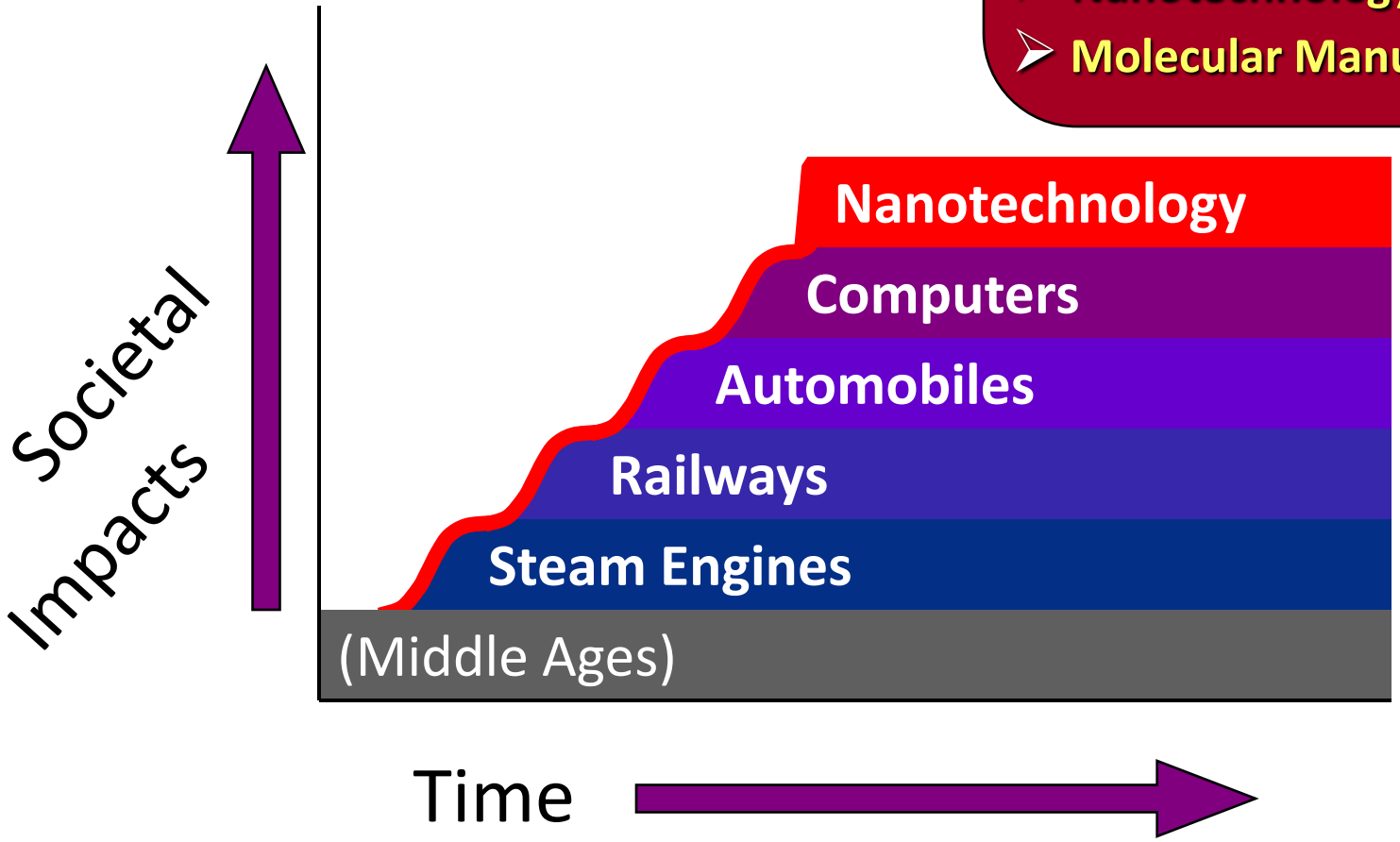
Fifth Revolution

(2010 – ??)

Based in Developing World?

China? India? Brazil?

- **Nanotechnology**
- **Molecular Manufacturing**



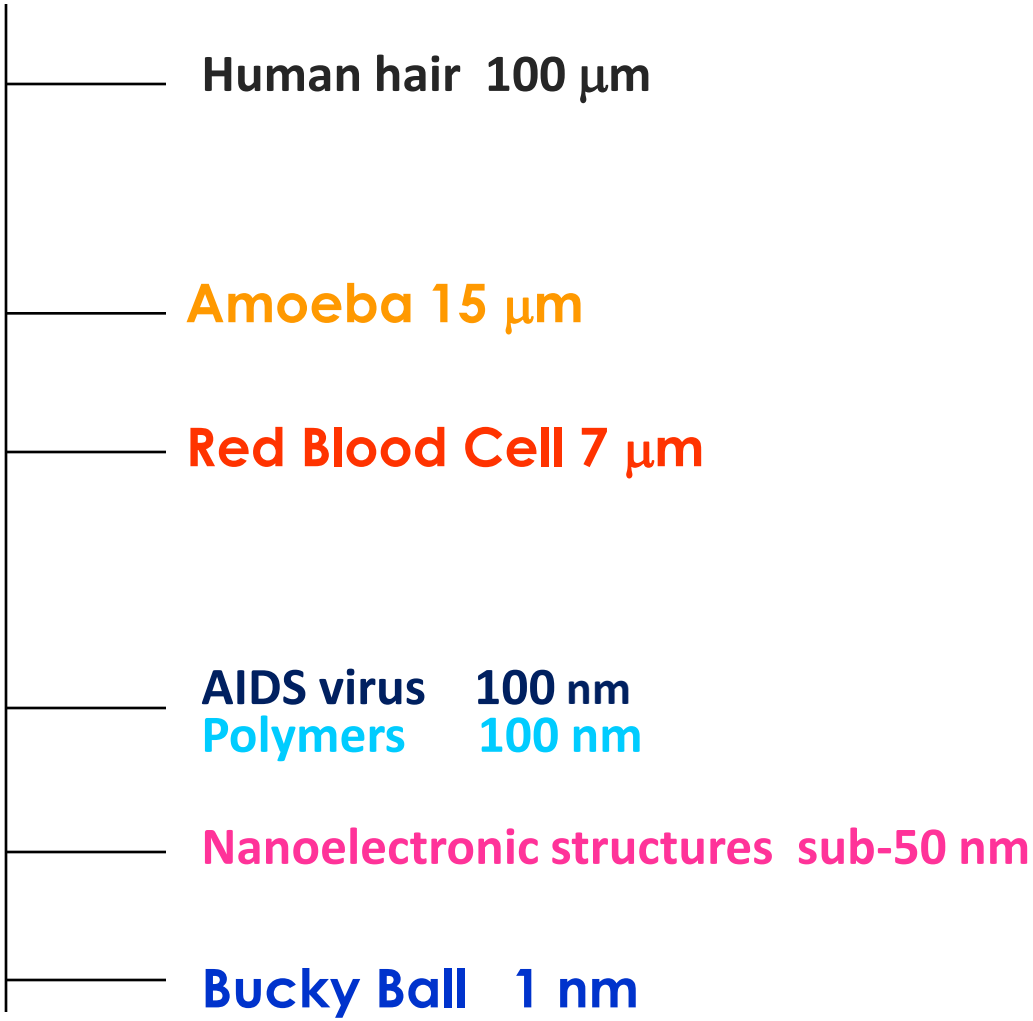
Nanotechnology Definitions

Nano: greek word = dwarf

For comparison, 10 nanometers is 1000 times smaller than the diameter of a human hair.
Approximately 3 to 6 atoms can fit inside of a nanometer, depending on the atom.

Nanoscience is the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties (physical, chemical, biological, mechanical, electrical…) differ significantly from those at larger scale.

Nanotechnology is the design, characterisation, production and applications of structures, devices and systems by controlling shape and size at the nanometre scale.
(bottom-up approach: 1-100 nanometers).


Human hair 100 μm
Amoeba 15 μm
Red Blood Cell 7 μm
AIDS virus 100 nm
Polymers 100 nm
Nanoelectronic structures sub-50 nm
Bucky Ball 1 nm

2 Reasons affecting properties of nanomaterials

Larger surface area

Macroscale surface area to volume ratio: 6×10^{-8}

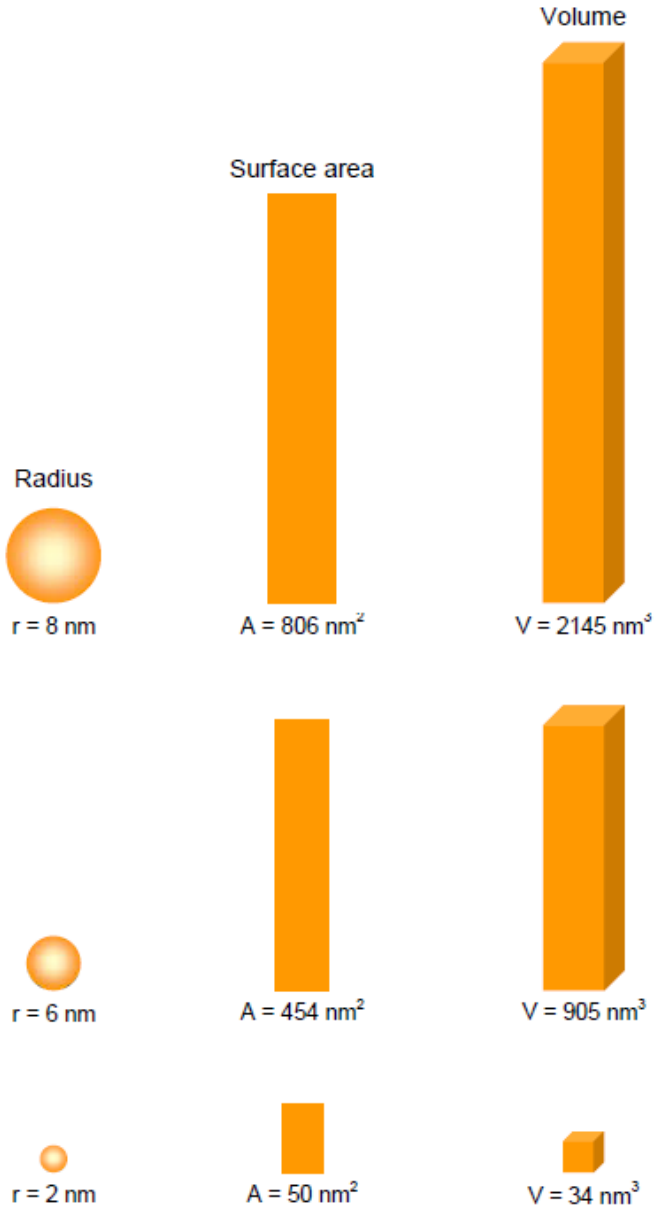
Nanoscale surface area to volume ratio: 0.6

More surface atoms → More energy → Enhanced chemical reactivity

Quantum effects

Quantum effects can begin to dominate the behaviour of matter at the nanoscale – particularly at the lower end - affecting the optical, electrical and magnetic behaviour of materials.

Interrelationships of radius, surface area and volume



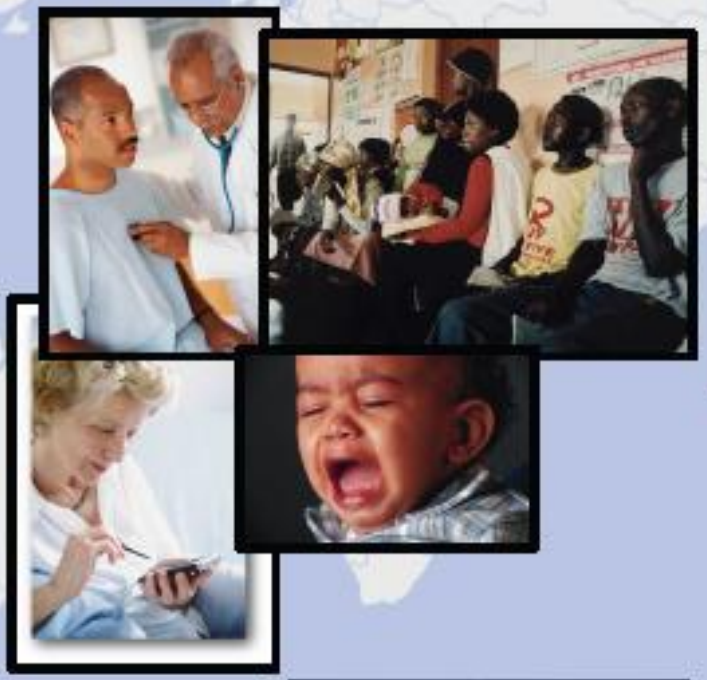
The Field of Nanomedicine

developing nanotechnologies as tools for the Diagnosis, Prevention and Treatment of Diseases

Surgical Tools and Biosensors

different clinical settings/ patient age groups/ethnic background

Diagnostic Tools Used Outside the Patient

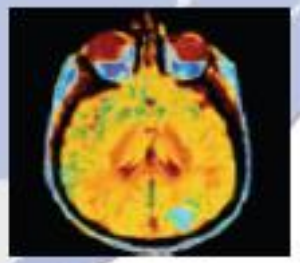


Nanomedicine(s)

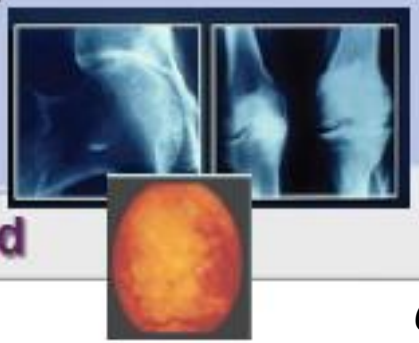
Medicines

Vaccines

Imaging Agents and Theranostics



Biomedical Materials Tissue Engineering and Repair



Courtesy Rogerio Gapsar

Potential of Nanotechnology in Medicine

- Nanoparticles containing labeled antibodies can be injected to detect tumors.
- Drugs can be attached to these nanoparticles to treat diseases with minimal side effects.
- Nanoparticles cross the blood–brain barrier
  - Helpful for the treatment of brain tumors and other CNS diseases
- Incorporation of a very tiny biocomputer chip into the scaffold
    - e.g, transistors and sensors can be used to mimic a brain circuit for the treatment of Alzheimer's disease.

Diagnostics

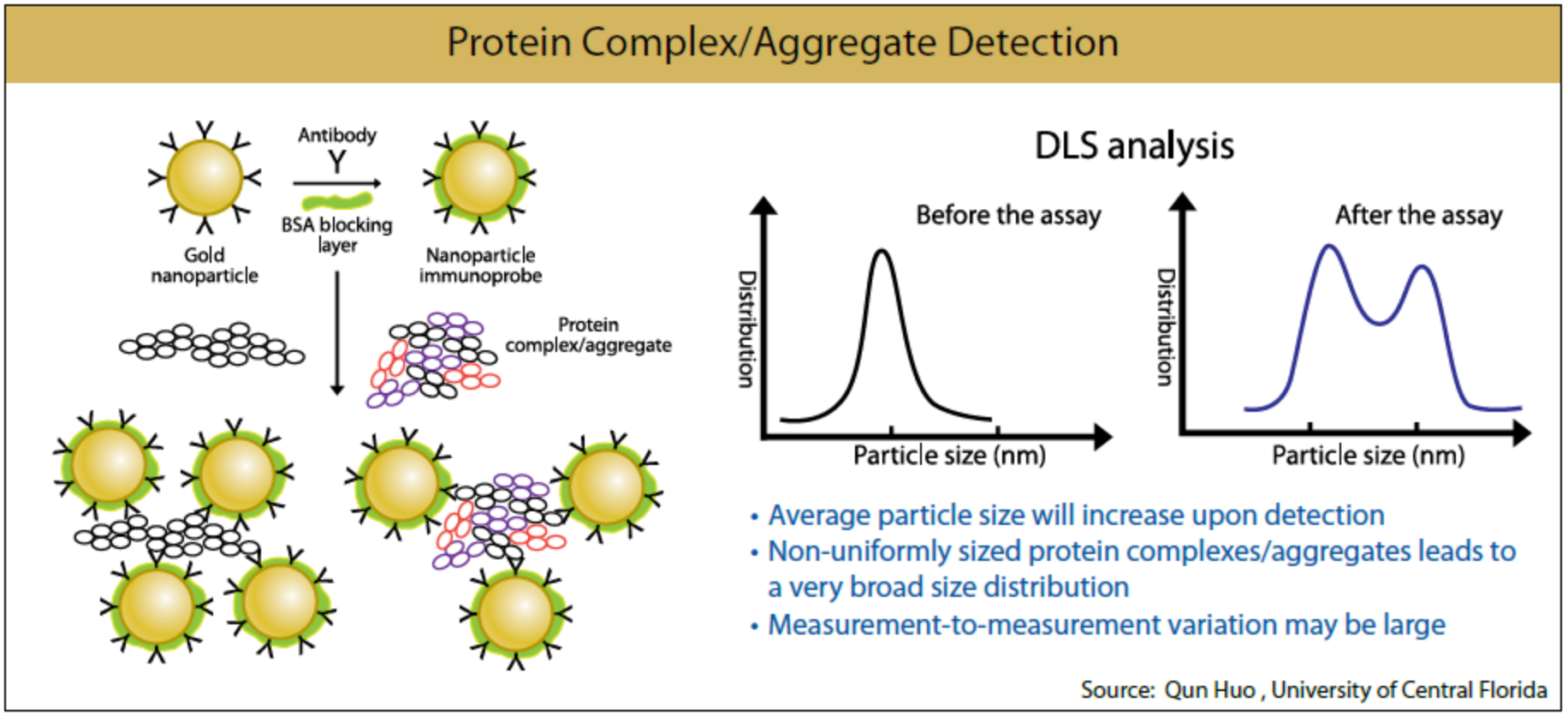
Detection of Prostrate Cancer

- **Today's diagnostic tools use prostate-specific antigen (PSA) tests to detect prostate cancer**

- **One of the challenges with PSA tests is that current tests can't distinguish between markers that signify cancer, and ones that represent a benign prostate hyperplasia.**

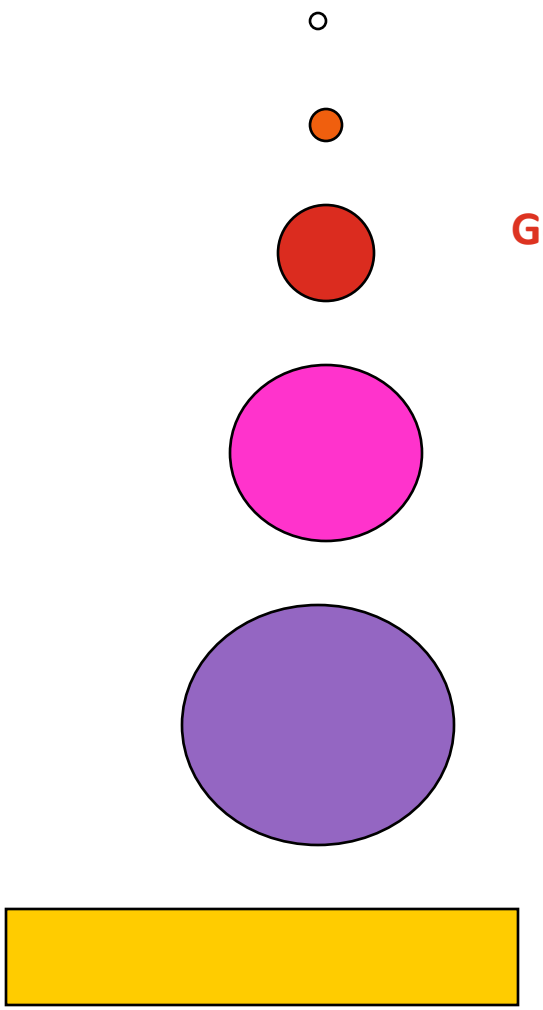
New test for early detection of Prostrate Cancer

Gold nanoparticles coated with antibody molecules.
These recognise and bind with specific target proteins in the blood sample, thus increasing particle size.



Optical absorption

L'or sous toutes les couleurs!



Atoms 1Å, colourless

Gold clusters <1 nm, orange

Gold nanoparticles 3-30 nm, red

Gold particles 30-500 nm
Crimson to blue

Bulk gold film

Aqueous colloidal gold

Photo-Thermal Ablation Therapy with Gold-coated Silica Nanoshells

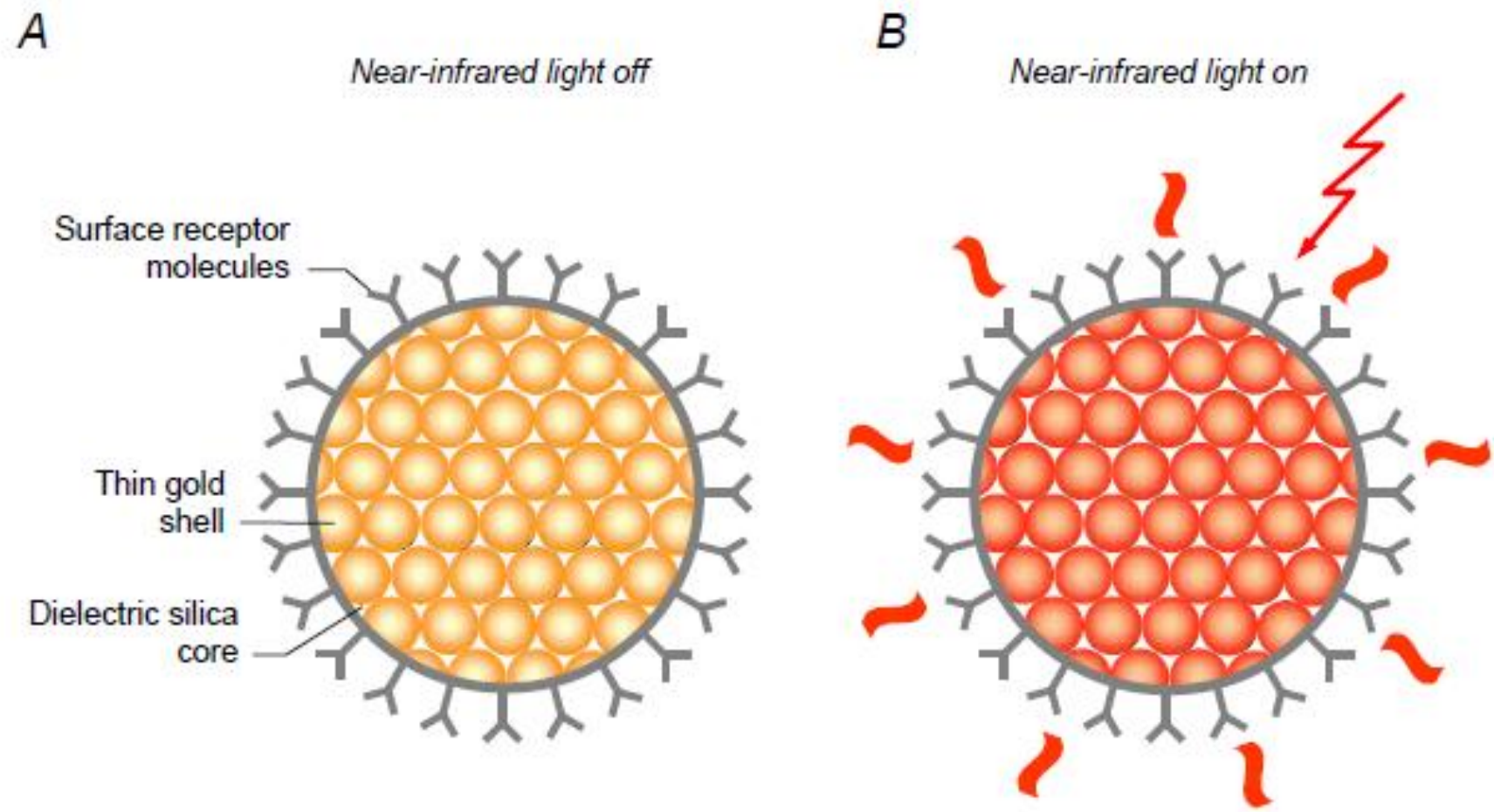


Figure 8. Photo-thermal ablation therapy using gold-coated silica nanoshells. Surface receptor molecules, e.g. antibodies, are used for targeting (A). Once accumulated inside a tumour, near-infrared light is used to activate the gold nanoparticles. The gold nanoparticles absorb near-infrared light turning it into heat which is lethal to cancer cells (B).

Quantum dots (semiconductor nanocrystals) possess remarkable optical and electronic properties that can be precisely tuned by changing their size and composition. Due to their relatively inexpensive and simple synthesis quantum dots have already entered the market for experimental biomedical imaging applications.

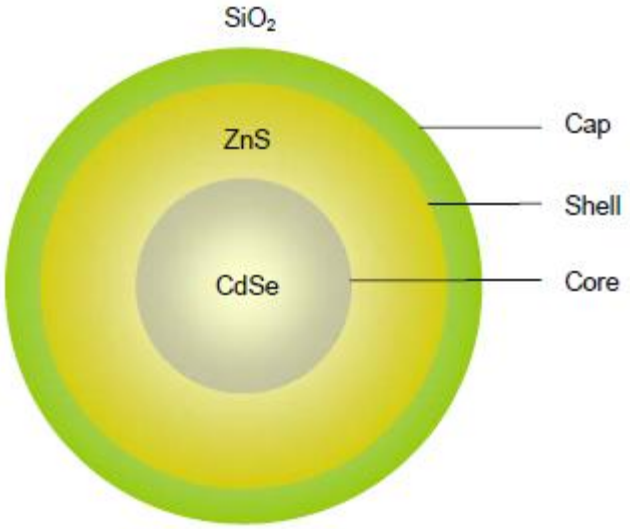
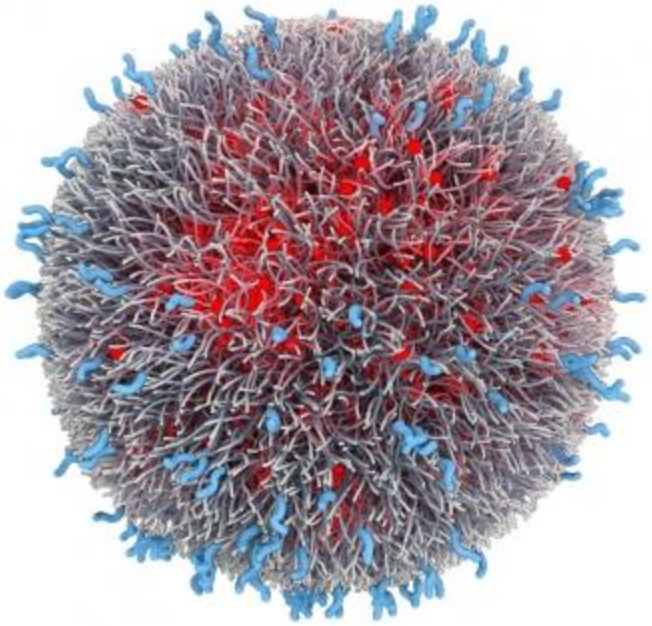


Figure 5. Schematic representation of a quantum dot. The cadmium selenide core is surrounded by a shell of zinc sulphide. Finally, a cap of silica encapsulates the binary quantum dot.The diameter of quantum dots ranges between 2-10 nm.

Quantum dots used in biomedical monitoring for sensitive optical imaging in fixed cells and tissues, living cells and animal models.

CONTROLLED AND TARGETED DRUG DEILVERY



What are limitations of conventional drug delivery systems?

- nonspecific biodistribution and targeting
- lack of water solubility
- poor oral bioavailability
- low therapeutic indices
- toxicity

What is the rationale behind new DDS?

• Need to improve **therapeutic index** of drugs in cancer, inflammatory and infectious diseases.

Therapeutic index = toxic dose / therapeutic dose

How?

- By improving their administration
- By increasing the exposure of diseased tissues to therapeutics

Effectiveness of a drug therapy

Temporal Control

ability to adjust the period of time over which drug is released
or
possibility to trigger the release process at a specific time during treatment

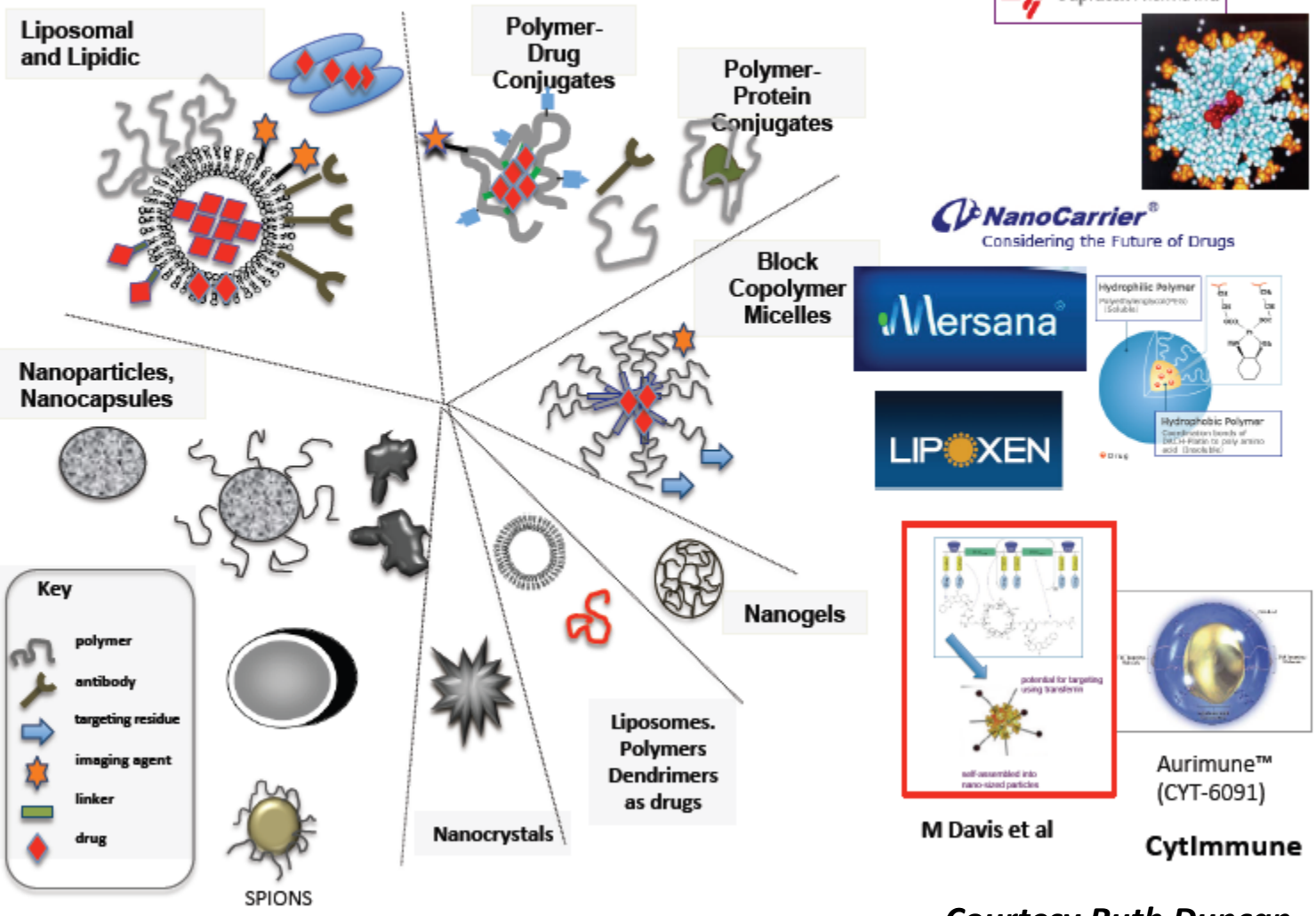
(Thermosensitive micellar drug carriers: PNIPAAm block copolymers)

Distribution Control

To precisely direct the DDS to the desired site of activity.

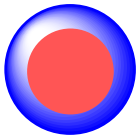
NANOPHARMACEUTICALS

Nanopharmaceuticals and imaging agents in the market/clinical development since ~ 1990 NOT ALL ARE NANOPARTICLES

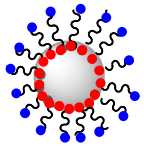


Courtesy Ruth Duncan

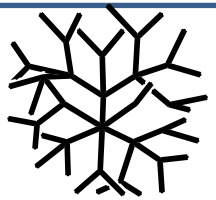
Types of Nanocarriers for drug Delivery



polymeric nanoparticles in which drugs are conjugated to or encapsulated in polymers.



polymeric micelles: amphiphilic block copolymers that form nanosized core/shell structure in aqueous solution.



dendrimers: synthetic polymeric macromolecule of nanometer dimensions

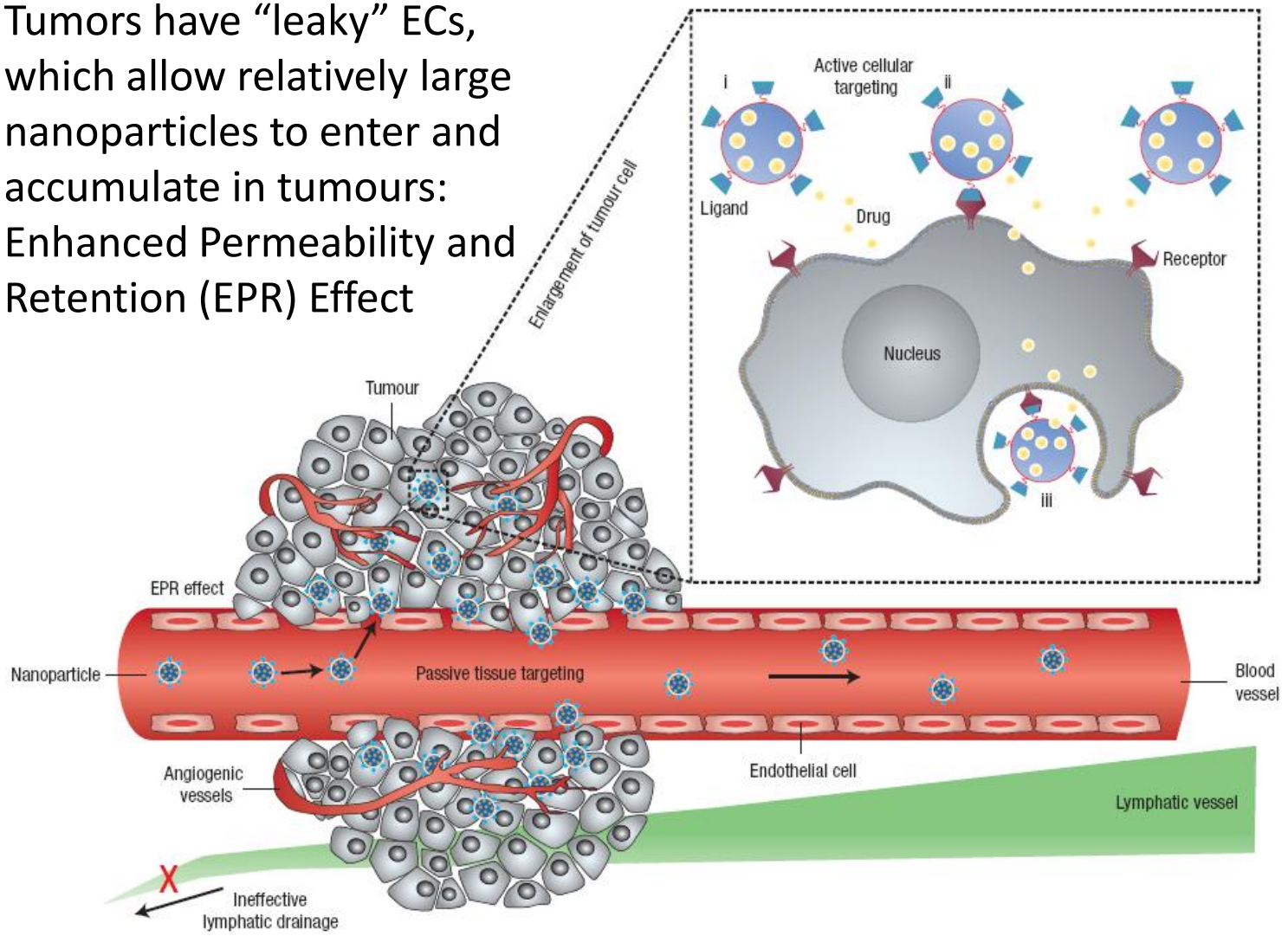
liposomes: self-assembling structures composed of lipid bilayers in which an aqueous volume is entirely enclosed by a membranous lipid bilayer.

viral-based nanoparticles: in general structure are the protein cages, which are multivalent, self-assembled structures.

carbon nanotubes

Tumour targeting of nanoparticles passively by EPR

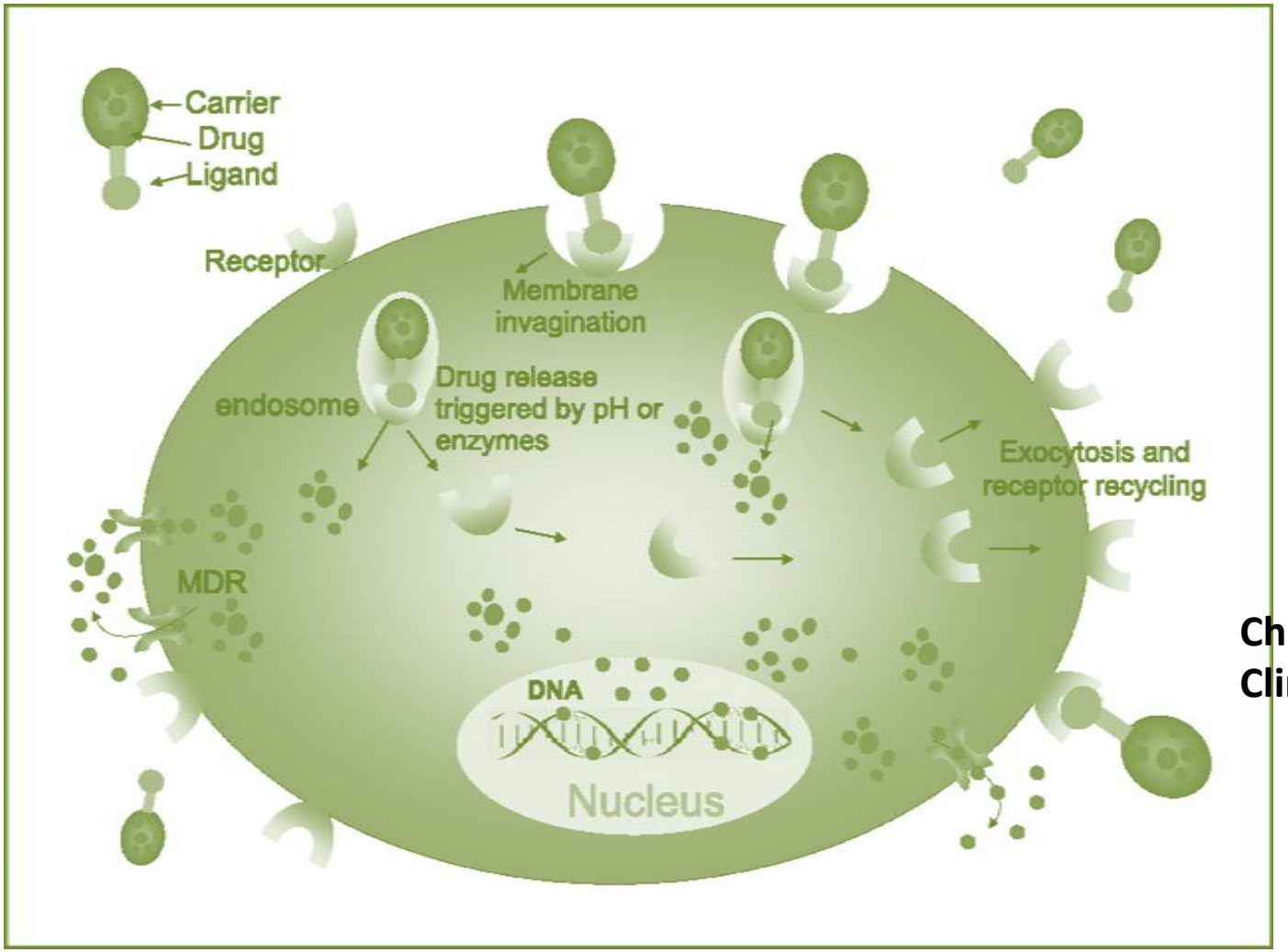
Tumors have “leaky” ECs, which allow relatively large nanoparticles to enter and accumulate in tumours: Enhanced Permeability and Retention (EPR) Effect



Peer, D, et al. *Nature Nanotechnology* **2007**, 2, 751-760

Internalization of nanoparticles via receptor-mediated endocytosis

- Binding of tumor-specific ligands or antibodies on the nanoparticles to cell-surface receptors.
- Internalization of the nanoparticles into the cell through endosome.
- Release of drug from the nanoparticles into the cytoplasm.

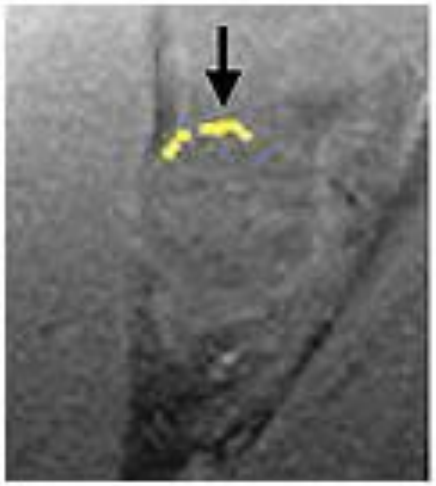


Cho K et al.
Clin Cancer Res 2008

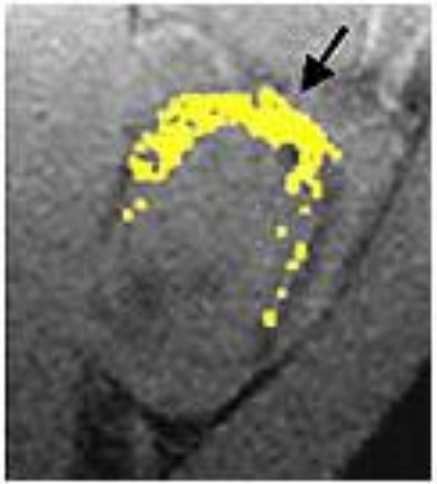
Targeting Tumours

Nanoparticle loaded with cancer-killing drugs can home in on tumors while sparing healthy tissues. A metallic marker added to the nanoparticle makes it visible by MRI.

In each of the MR images above, a rabbit tumor has been infiltrated by the nanoparticles (yellow).



The **nanoparticles carry a chemotherapeutic drug (fumagillin)**; the tumor's growth is dramatically stunted and its network of blood vessels is reduced.



In a control experiment**, the nanoparticles are drug free**; the tumor is flourishing and extensively laced with blood vessels.

Targeted nanoparticles show success in clinical trials

Originally developed by researchers at MIT and Brigham and Women's Hospital in Boston, the particles are designed to carry the chemotherapy drug docetaxel, used to treat lung, prostate and breast cancers, among others.

"The initial clinical results of tumor regression even at low doses of the drug validates our preclinical findings that actively targeted nanoparticles preferentially accumulate in tumors," says Robert Langer, the David H. Koch Institute Professor in MIT's Department of Chemical Engineering.
Science Translational Medicine, April 2012

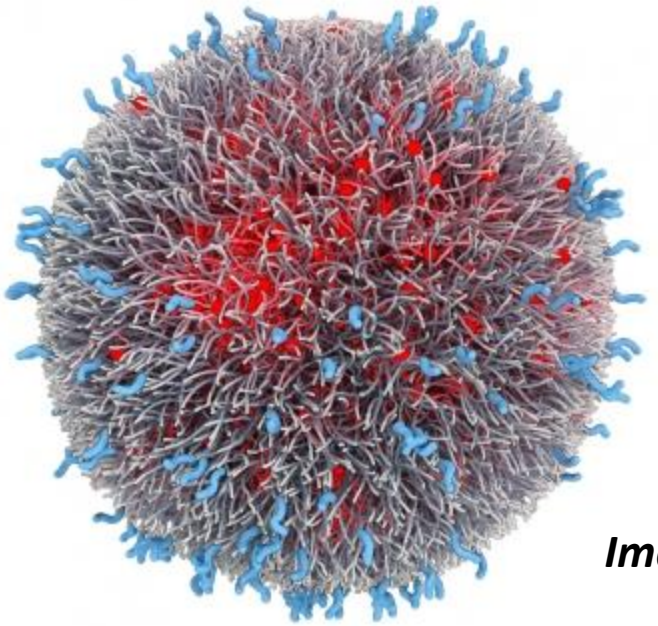
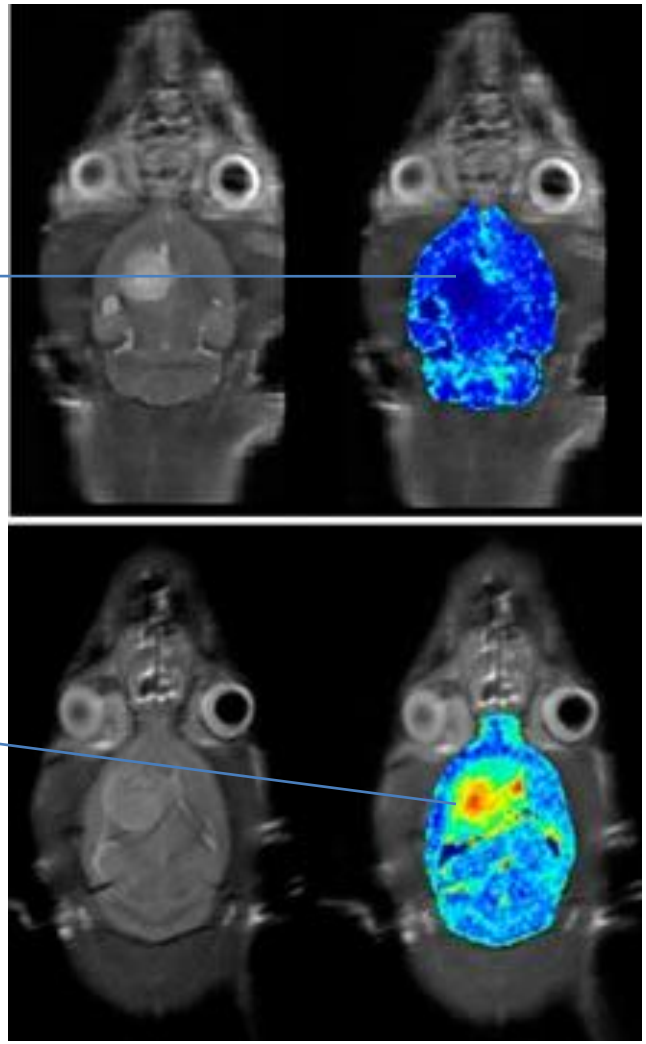


Image: Digizyme, Inc.

Targeting tumors

Two groups of rats were given an infusion of magnetic, drug-coated nanoparticles. Apply ultrasound combined with an active magnetic field

normal blood circulation



More of the anti-tumor drug reaches the brain

Courtesy Chang Gung Memorial Hospital

The Abraxane story

December 2005: *

A number of difficult-to-treat cancers secrete a protein called SPARC (glycoprotein)

SPARC allows the tumor to spread and attracts albumin-bound nutrients to nourish the tumor.

Abraxane

A perfect 'Trojan horse'. It binds to nanometer-sized albumin in which it resides

The tumor itself targets the albumin-bound drug instead of the drug targeting the tumor.

Selected nanomedicine products on the market

Drug	Manufacturer(s)	Indications	Major benefits
Rapamune (Sirolimus)	Wyeth, Elan	Immunosuppressant Kidney transplant	Enhanced bioavailability, Convenient dosage formulation, Extended shelf-life
Abraxane (Taxol)	APP, ABI	Meta breast cancer	Eliminates the use of toxic solvents essential for its microformulated counterpart
Avinza	Elan	Chronic pain	Once-daily dosage Combines immediate and extended-release SO_4 morphine
Naprelan	Wyeth, Elan	Osteoarthritis, Rheumatoid arthritis	Convenient once-daily dosage Combines immediate and extended-release naproxen Na

Anticancer Polymer Therapeutics – Since 1990

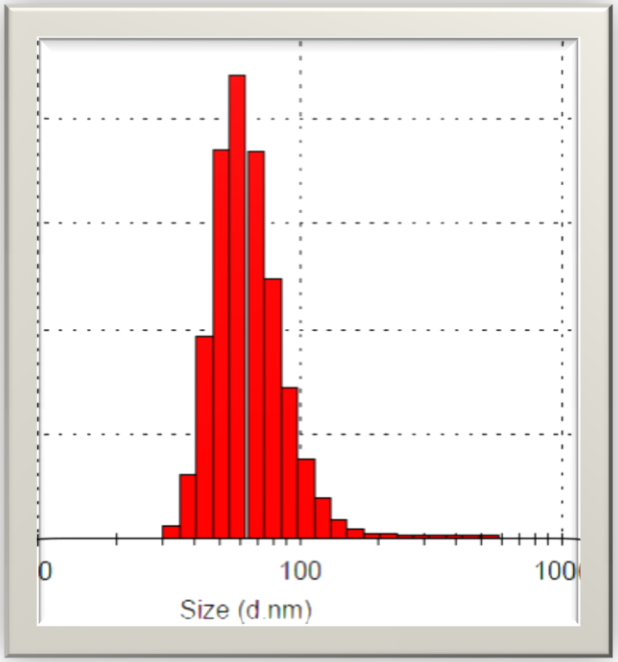
Courtesy Rogerio Gaspar

Product	Description	Application	Stage
Polymer-Protein Conjugates			
Zinostatin Stimalmer®	SMANCS	Hepatocellular carcinoma (local administration via hepatic artery infusion)	Market (Japan)
Oncaspar®	PEG-asparaginase	Acute lymphocytic leukaemia	Market
PEG-Intron®	PEG-Interferon alpha 2b	Hepatitis C	Market
PEG-Asys®	PEG-Interferon alpha 2a	Hepatitis C	Market
Neulasta™	PEG-Human-GCSF	Chemotherapy-induced neutropenia	Market
Polymer-drug Conjugates			
Xyotax™/Opaxio	PGA-paclitaxel	NSCLC and various others	Phase III
Prolindac®	HPMA copolymer-Pt	Melanoma, Ovarian	Phase II
CALLA01	polymer-cyclodextrin-siRNA		Phase I
NKTR-105	PEG-paclitaxel		Phase I

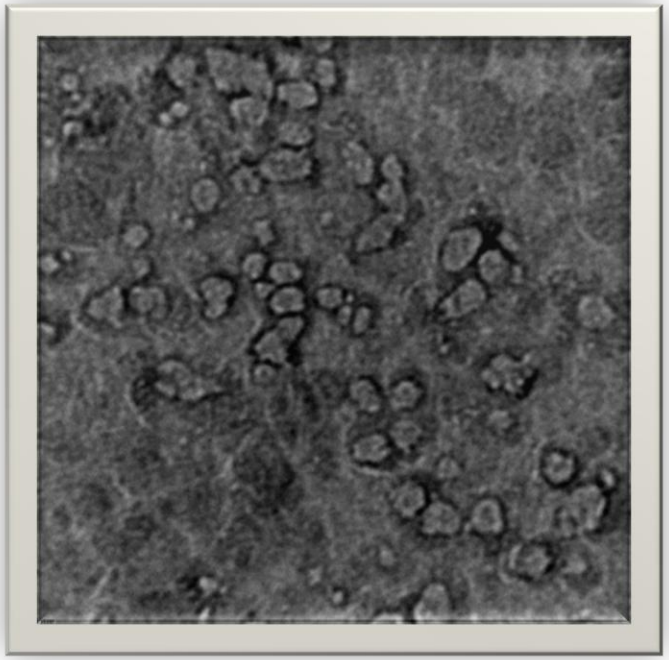
Liposomal and Lipidic Products (Many products in clinical development) *Courtesy Rogerio Gapsar*

TRADENAME	DRUG	INDICATION	COMPANY	STATUS
AmBisome®	Amphotericin B	fungal infections	Astellas Pharma	Marketed
ABELCET®	Amphotericin B	fungal infections	Sigma-Tau Pharmaceutical	Marketed
DOXIL/Caelyx®	Doxorubicin	cancer	Schering-Plough	Marketed
Daunoxome®	Daunorubicin	cancer	Gilead Sciences	Marketed
MEPACT®	MTP	cancer	Takeda	Marketed
Visudyne	Verteporfrin	age related macular degeneration	Novartis	Marketed
Definity®	Octafluoropropane	Ultrasound imaging	Dupont Merck	Marketed
Myocet®	Doxorubicin	cancer	Cephalon	Marketed
Depocyt®	Cytarabine	cancer	Sigma-Tau Pharmaceutials	Marketed
DepoDur®	Morphine	pain relief	Flynn Pharma	Marketed

$(PEG)_{50}$-*b*-[$(PDX)_{35}$-*co*-$(PMeDX)_4$] micelles



DLS particle size distribution
distilled water (c = 0.1 mg/ml)



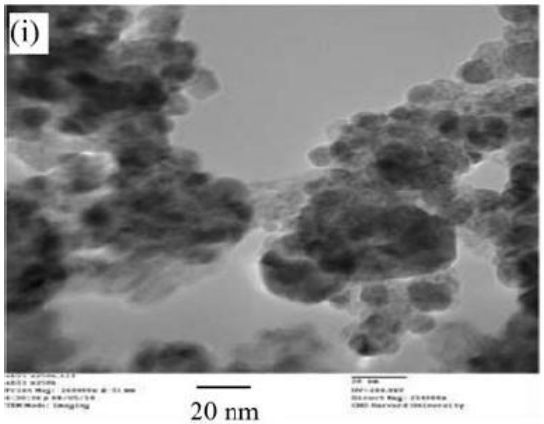
TEM
(c = 5 mg/ml, size range = 25 – 30 nm)

Y. Lochee, A. Bhaw-Luximon, D. Jhurry, A. Kalangos; Macromolecules, Vol 42 (19), 7285-7291 (2009)

R Jeetah, A Bhaw-Luximon, D Jhurry, under review 2012
Amphiphilic (PEG)-b-P(Dioxanone-co-MethylDioxanone) copolymer micelles as drug nanocarriers

Oligoagarose-g-Polycaprolactone nanoparticles for drug delivery applications

Red Seaweeds
Gracilaria



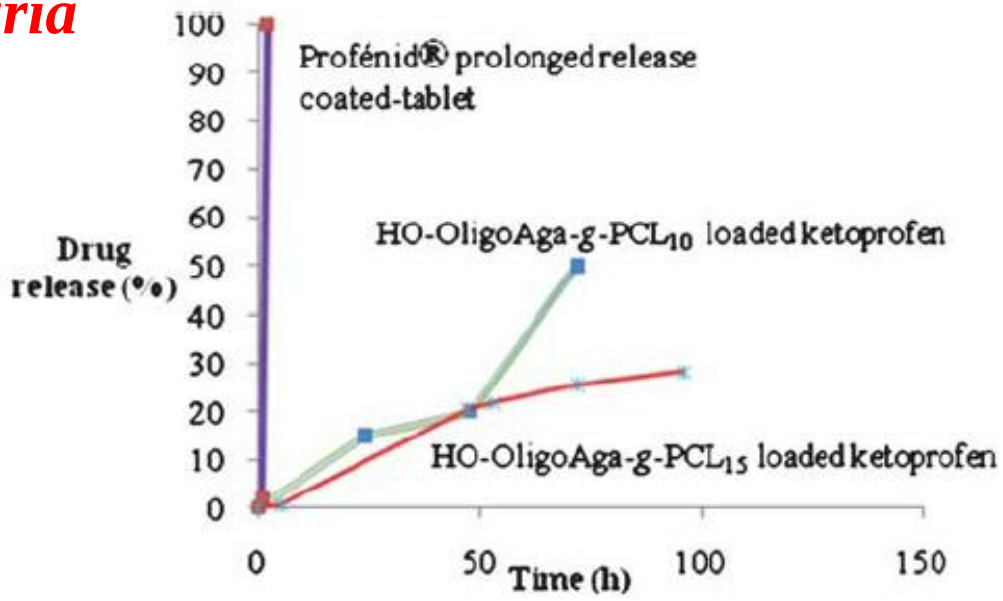


Fig. 5 Comparison of drug release profiles in PBS at 37 °C.

Oligoagarose-g-polycaprolactone loaded nanoparticles for drug delivery applications : **A Bhaw-Luximon, L M Meeram, Y Jugdawa, W Helbert, D Jhurry**
Polym Chem 2, 77, 2011

Biomaterials Module
Lecture 21

Introduction and Fundamentals of Drug Delivery

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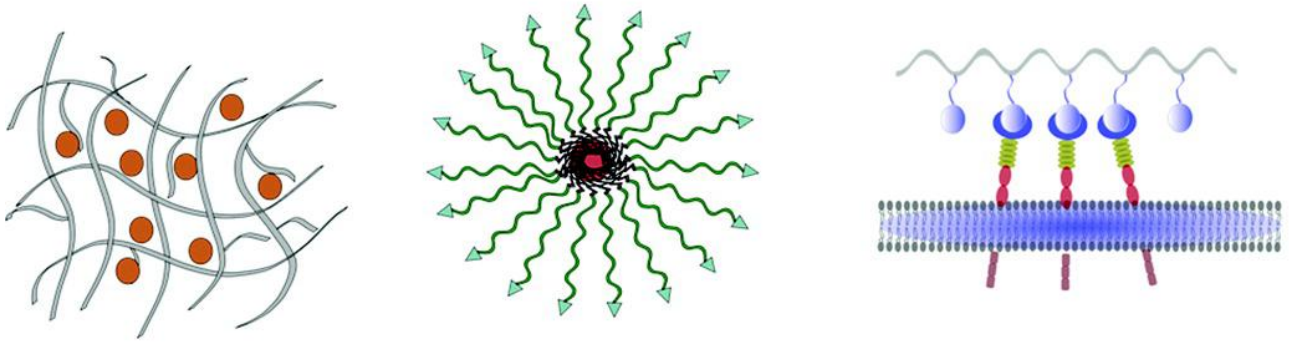
Polymer-Based Therapeutics



Polymer matrix | Polymer assembly | Functionalized polymer

LEARNING OBJECTIVES

Upon completion of this lecture, you will be able to:

- Describe the basic principles of the types, structure and properties of polymers relevant to the delivery of drugs.
- Explain how polymers are used to facilitate oral and parenteral routes of drug delivery.
- Describe responsive polymers for drug delivery with focus on hydrogels.
- List the main types of nano-drug delivery systems including nanoparticle formulations, polymer drug conjugates, nanomicelles based on synthetic polymers and natural polysaccharides
- Explain the functioning of nanomicelles and their advantages over conventional systems.
- Describe drug delivery systems for proteins and nucleic acid.

Module Outline

Part 1

Conventional applications of Polymers in drug delivery
Types of Polymer Drug Delivery Systems
Pharmacological Considerations in Drug Delivery
Physiology of Oral delivery & Parental delivery

Part 2

Nano-based Drug delivery systems
Limitations of Conventional DDS
Non particulate v/s Particuate Delivery System
Types of Nanocarriers for drug Delivery
Exigencies for drug carriers
Nanoparticles as drug carriers
Nanoparticle formulations
Polymer drug conjugates

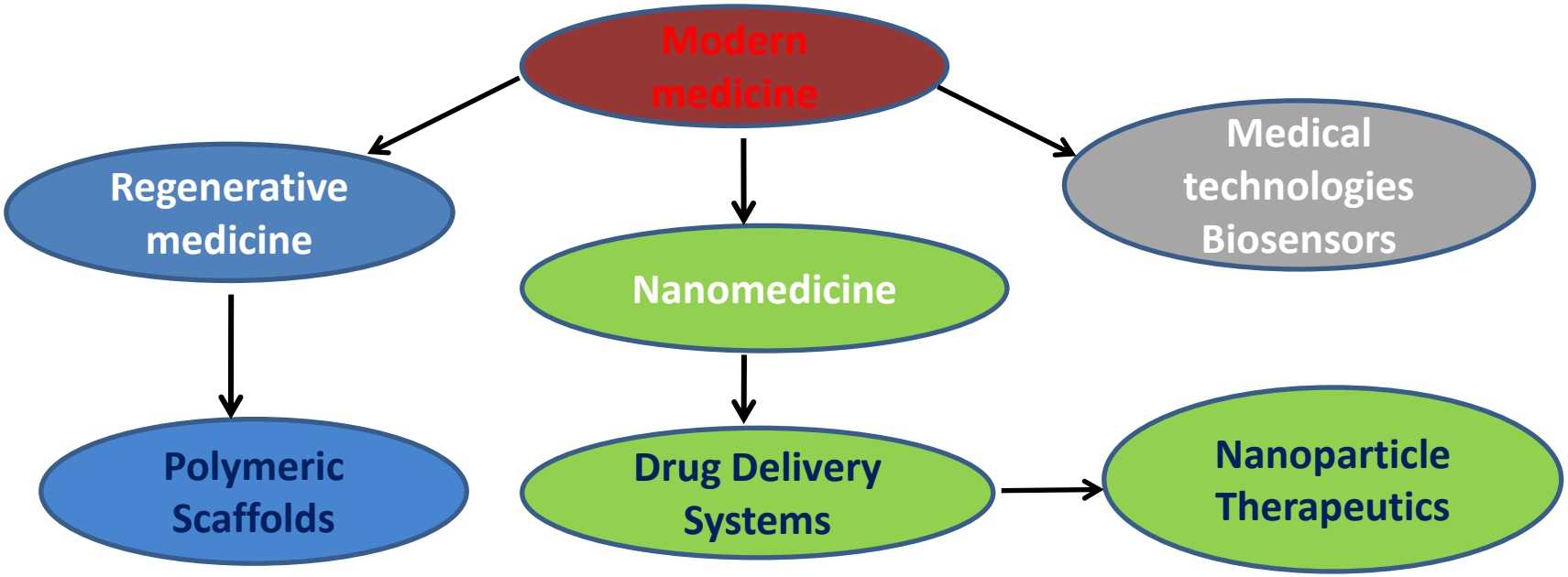
Part 3

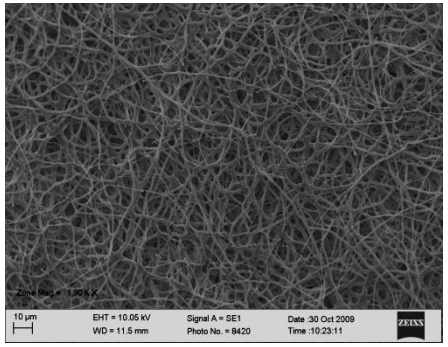
Pegylated Polymers
Amphiphilic block copolymer micelles (ABCs)
Drug Loading in micelles
Factors affecting drug release
1^{st} and 2^{nd} generation polymeric micelles
Polysaccharide-based DDS

Part 4

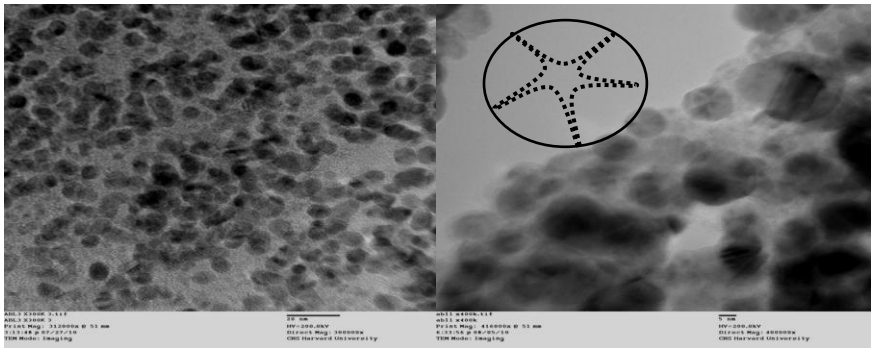
DS for proteins and nucleic acid

BioMaterials & Medicine





Polymeric Nanofibres



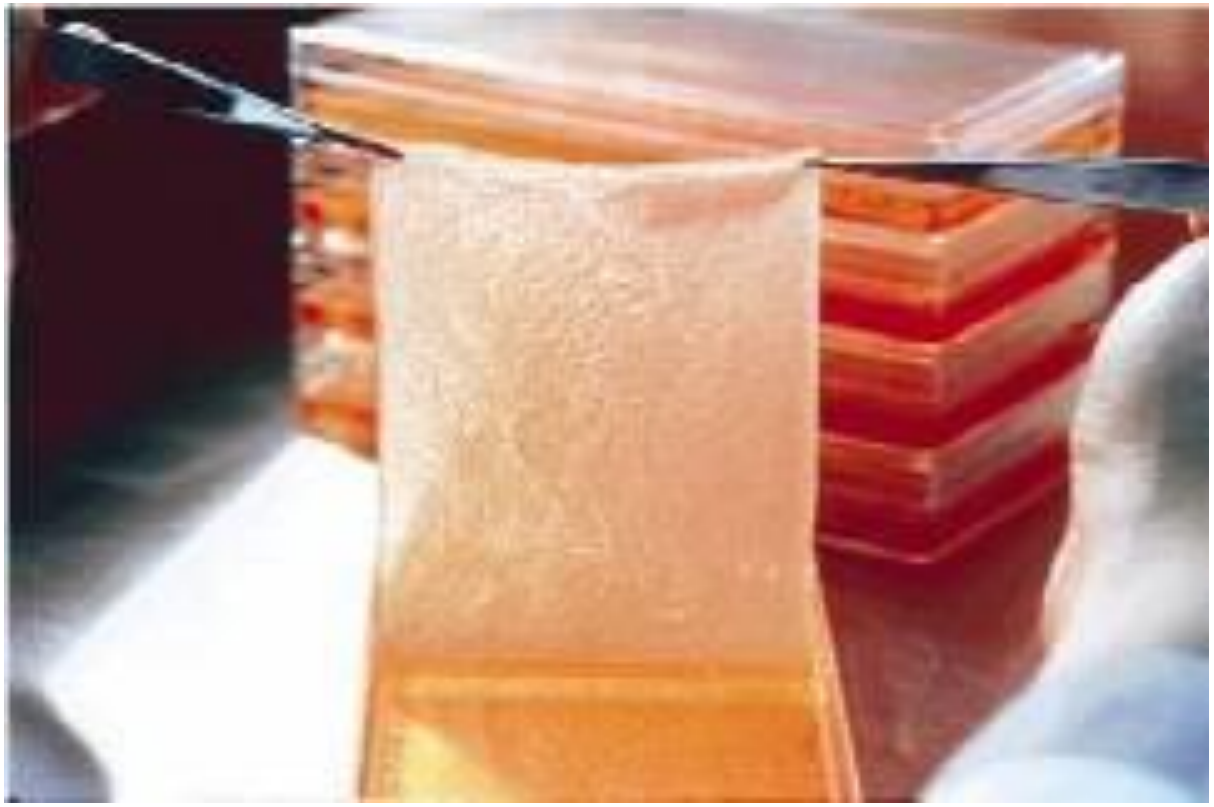
Polymeric Nanomicelles

Scaffolds

- To engineer tissues, mechanical support is necessary
  - For seeding of cells
  - To guide their migration, proliferation, differentiation, maintenance of phenotype, and apoptosis after implantation
    - e.g.To allow formation of blood vessels for nutrient supply and remove waste products
  - To allow the growing cells within to form the extracellular matrix
    - Which in turn confers the physical, mechanical, and functional properties of the tissue or organ.

TE techniques are highly applicable to the treatment of chronic skin damage.

An engineered skin replacement composed of collagen cultured with fibroblasts



Source: JHS George, PhD Thesis Imperial College, London (2009)

BIOMATERIALS

Collaboration with Prof Gary Bowlin
Virginia Commonwealth University, USA

Polymers → Nanofibres → Polymer scaffolds
(PDX, P(DX-MeDX), (PDX-PCL))

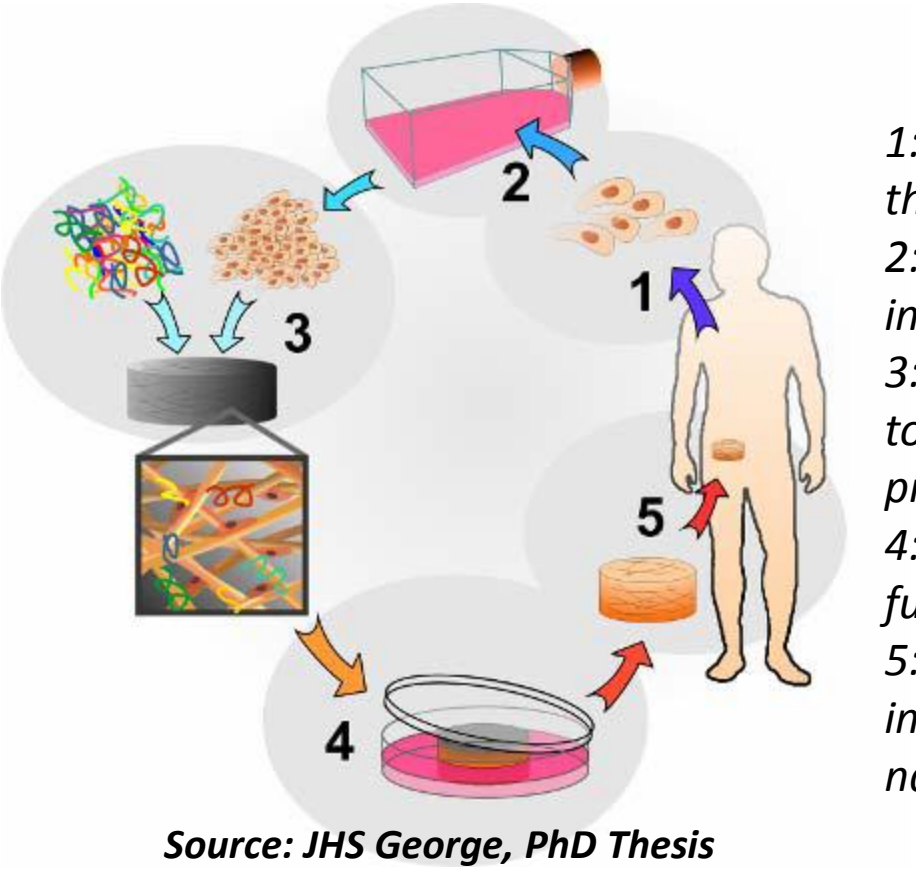
Our Goal

Blood vessel

Vascular grafts

Scaffold Engineering: a complex challenge

The scaffold must provide both the mechanical properties required by the regenerating tissue as well as the cues that cells require.



Source: JHS George, PhD Thesis Imperial College, London (2009)

The tissue engineering cycle, using autologous cells.

1: A small number of cells are removed from the body.

2: They are screened for phenotype and increased in number through proliferation.

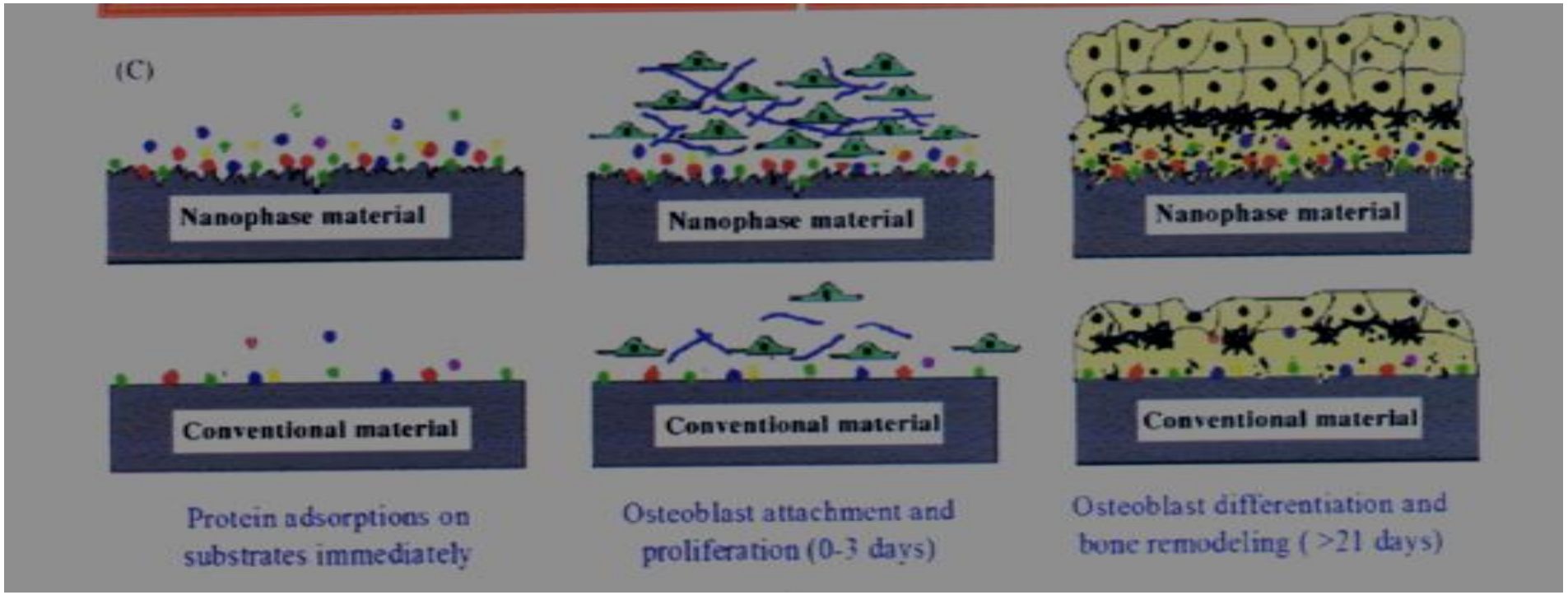
3: These cells are seeded onto porous scaffolds together with growth factors to enhance proliferation.

4: The seeded scaffolds are placed in culture to further increase cell number.

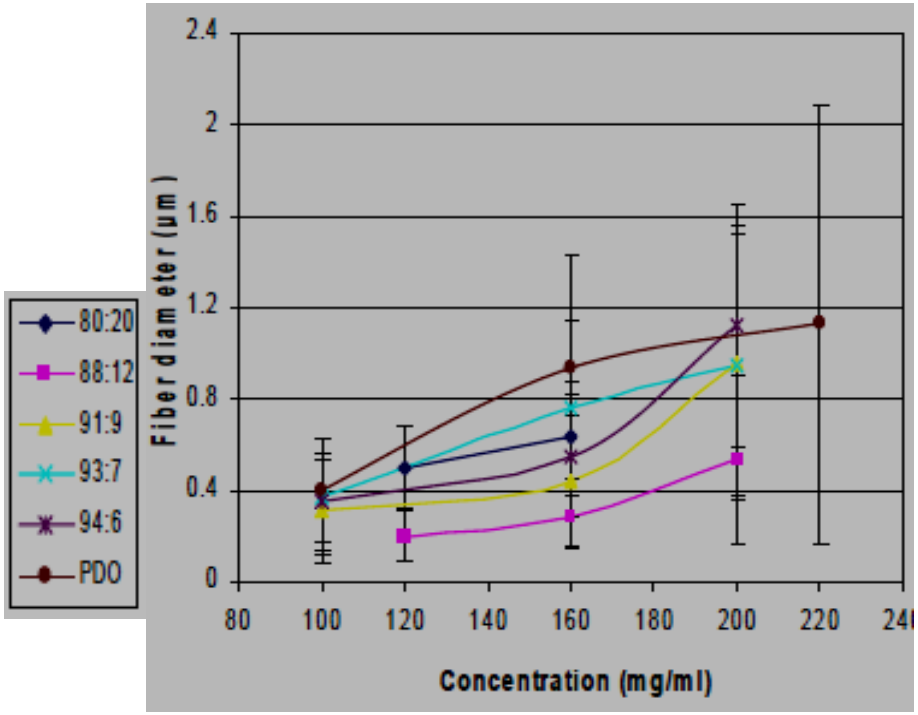
5: Finally, the regenerated tissue is implanted into the site of damage to integrate with the natural tissue.

Why Nanofibre Scaffolds?

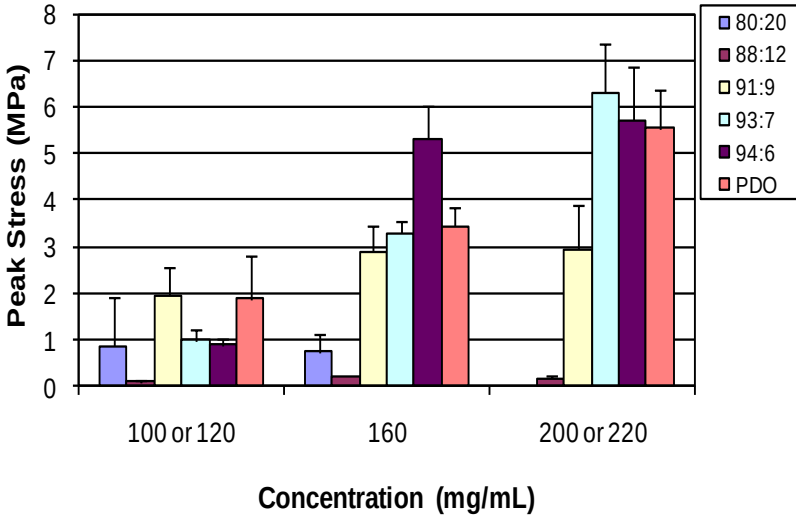
- **For Enhanced Cell proliferation and growth on scaffolds**



Fibre Diameter Optimisation by Electrospinning



Mechanical Performance



Biocompatibility HET-CAM Test

No inflammatory response

P S Wolfe, Y Lochee, A Bhaw-Luximon, D Jhurry and G L Bowlin;

JEFF, Volume 6, Issue 4 – 2011

Issues

- **Materials Science**

– Challenges arising from new materials (inorganic nanoparticles, nonbiodegradable/
non-biocompatible materials, quantum dots, cationic particles
and dendrimeric structures, carbon nanotubes)

- **Formulation / Technologies**

– Adapting existing technologies to new opportunities (e.g. Quality by Design, Process Analytical Technologies)

- **Translational Research**

– Adequacy of non-clinical methodology before first in man use (relevance of, appropriate toxicityfficcacy biomarkers and barriers related to disease phase and different routes of administration)

- **Clinical development**

– Comparability: non-inferiority versus superiority (risk-benefit management)

- **Market Access**

– Comparative pharmacoeconomic assessment