



Nanotechnology Advances in Controlled Drug Delivery Systems

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**Nanobio Europe
9-13 June, 2008, Barcelona, Spain**

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Outline

- Nanomedicine
- Controlled Drug Delivery Systems
- Nanocarriers
- Crossing Biological Barriers
- Drug Delivery Devices
- Diagnostics and Imaging
- Future Challenges

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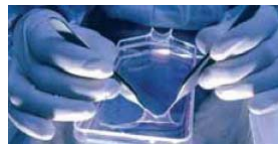


Nanomedicine



The term **Nanomedicine** refers to the application of nanotechnologies to **diagnosis and treatment** of diseases.

- ✓ It deals with the interactions of **nanomaterials** (surfaces, particles, etc.) or analytical **nanodevices** with “living” **human material** (cells, tissue, body fluids).
- ✓ It is an extremely large field ranging from in vivo and in vitro **diagnostics** to **therapy** including **targeted delivery** and **regenerative medicine**.



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Functionalized Drug Delivery Systems

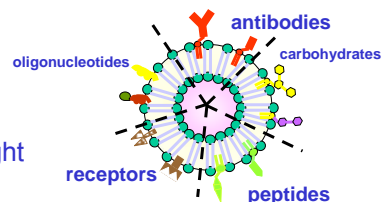


The concept of “Clever” drug targeting system includes the coordinating behavior of three components: **the targeting moiety**, **the carrier** and **the therapeutic drug**.

- The first one recognizes and binds the target.
- The second one carries the drug
- The third one provides a therapeutic action to the specific site

Targeting moieties:

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



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Advantages of Carrier-based Systems



- Decreasing the **non-specific delivery** of the drug to non-target tissues.
- Increasing the **drug concentration at its site of action** (be it intracellular or extracellular).
- Prolonging the **residence time** of the drug at its site of action by reducing clearance.
- Decreasing **toxicity** due to high initial doses of the drug.
- Improving the **stability** of the drug in vivo.
- Decreasing **irritation** caused by the drug.
- Improving **taste** of the product.
- Improving **shelf life** of the product.

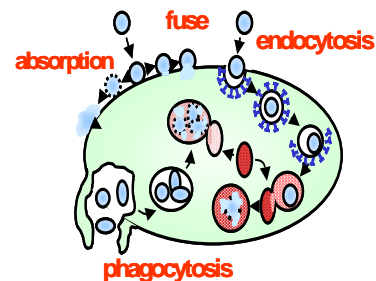


Interactions Between Biological Systems and Nanostructures



The potential of targeted delivery will only be realized with a much better understanding of **how such structures interact with the body and its components – in vitro and in vivo.**

- ✓ **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




➤ The potential of nanocarriers as Drug Delivery Systems

- ✓ 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**.



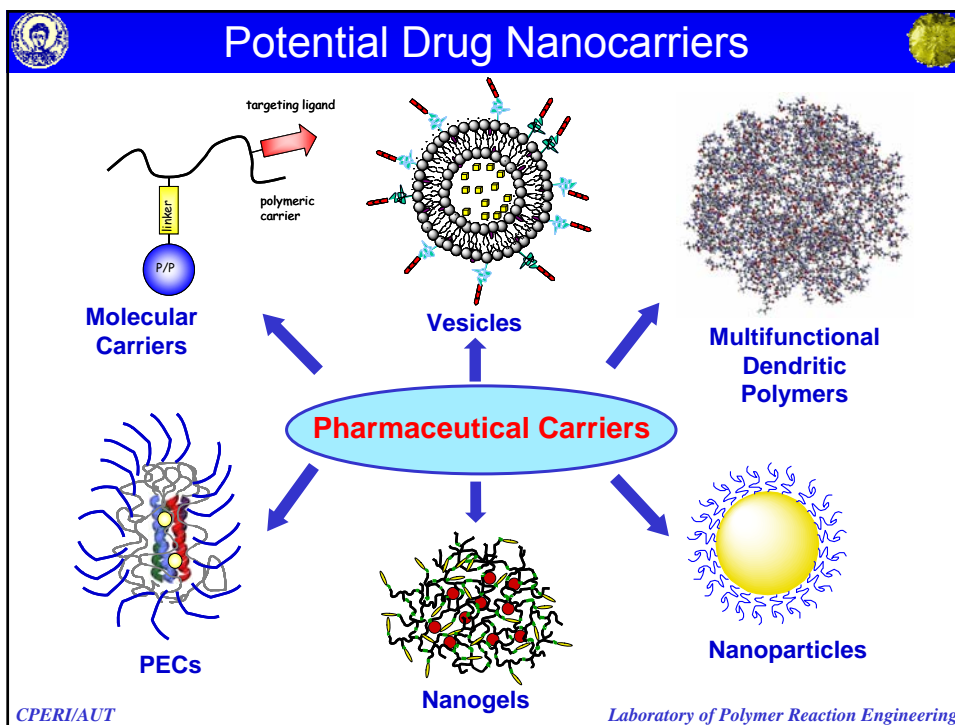


Carrier Types



- **Molecular Carriers**
 - ✓ Polymer- P/P Drug Complexes
 - ✓ Polyelectrolyte Complexes (PECs)
 - ✓ Copolymer-Metal Ion Complexes
- **Dendritic Polymers**
- **Micelles**
- **Nanoemulsions**
- **Lipid based Vesicles**
 - ✓ Liposomes
 - ✓ Solid Lipid Nanoparticles (SLNs)
 - ✓ ISCOMs
- **Nanogels**
- **Nanoparticles**
 - ✓ Polymeric
 - ✓ Inorganic
 - ✓ Hybrid

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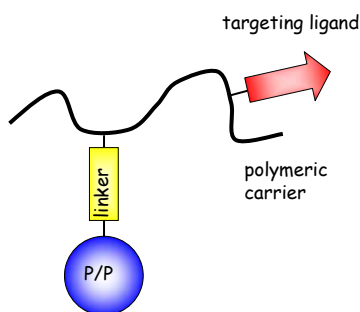




Polymer- P/P Drug Complexes



- Covalent attachment of P/P Drugs to polymer chains via specific linkers.



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

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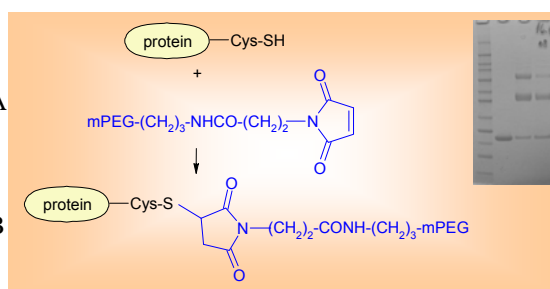
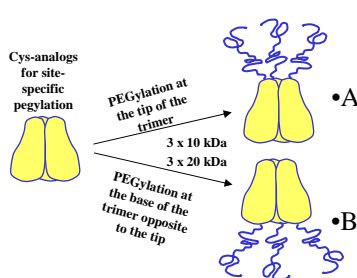
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PEGylated TNF- α (PEG-TNF)



PEG-TNF for Cancer Therapy



Goals:

- ✓ Prolonged half-life (30 min \rightarrow 5 – 10 hrs)
- ✓ Reduced toxicity
- ✓ Better protection to degradation
- ✓ Improved antitumor activity

Problem:

Non-specific pegylation of naturally present disulfide bond

Solution:

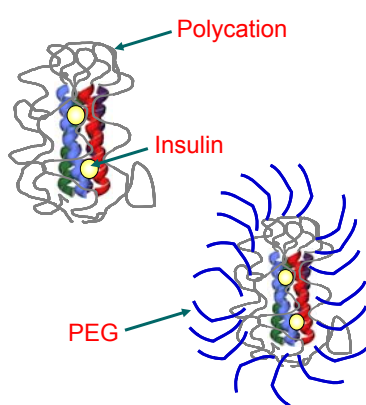
Preparation of a new cysteine analogues without SS-bond

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Polyelectrolyte Complexes (PECs)


➤ Formation of polyelectrolyte complexes (PECs) loaded with insulin via ionic complexation



The polymer family

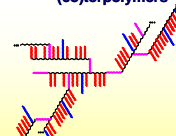
From a macroinitiator PEO

Homopolymerisation of MADAM



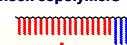
From a macromonomer

Hyperbranched (co)terpolymers




From Poly(MADAM)

Block copolymers



Block terpolymers



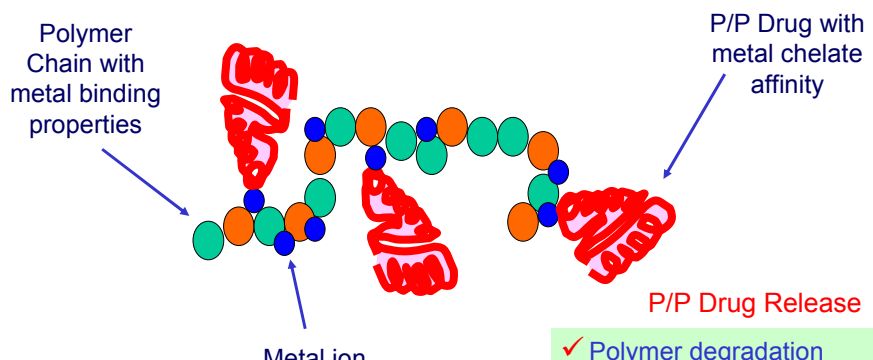
- ✓ Drug loading: > 80%
- ✓ DLS size of the PEC: 500 nm
- ✓ Insulin: the formulation remained stable in a saline for several weeks at 4°C.

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Copolymer-Metal Ion Complexes

➤ Biodegradable, biocompatible copolymer-metal ion complexes and P/P drug attachments through the metal ions.

Self assembled nano-structure: *polymer-Zn-P/P drug*



- ✓ Polymer degradation
- ✓ Removal of metal ion by higher affinity chelator

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Dendritic Polymers

- Multifunctional **dendrimers** and **hyperbranched polymers** as DDS.
 - ✓ Cell specificity via attachment of targeting ligands.
 - ✓ Decreased toxicity, biocompatibility, stability, and protection in the biological milieu via functionalization with PEG.

FITC-labeled PEGylated biodegradable hyperbranched polyester as a carrier for ADNF peptide

BH40-PEG-FITC

Confocal microscopy on A549 cells revealed preferential uptake of BH40-PEG in cells nuclei

PEGylated BOLTORN H40

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Multifunctional Micelles

- **Targeting ligands:** folic acid, RGD peptide, antibodies, RNA aptamer, glucose & lactose.

PCL-PEG-Mal

- ✓ Micelles with **sensitivity to external stimuli** can also be prepared in order to trigger drug release at the target site.

D. Sutton, N. Nasongkla, E. Blanco and J. Gao, *Pharmaceutical Research* 24, 1029 (2007)

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Second Generation Liposomes

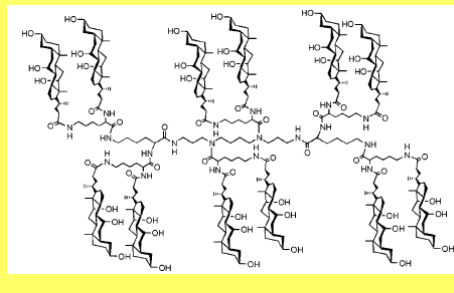
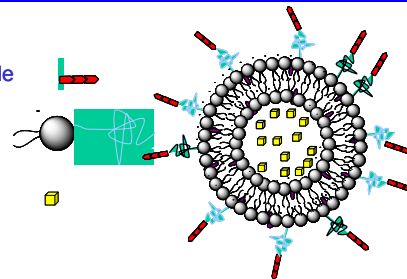


- Surface functionalized liposomes exhibiting both **targeting specificity** and **circulation longevity**.

Targeting peptide

Pegylated phospholipid

Drug



Pore-forming amphiphile

- Combination of a pore-forming amphiphile and thermally sensitive liposomes.

- ✓ At temperatures above the **gel to liquid-crystalline phase transition temperature** of the lipid, the amphiphile creates pores within the membrane through which entrapped aqueous solutes can readily pass.

W.-H. Chen and S. L. Regen, *J. Am. Chem. Soc.* 127, 6538 (2005)

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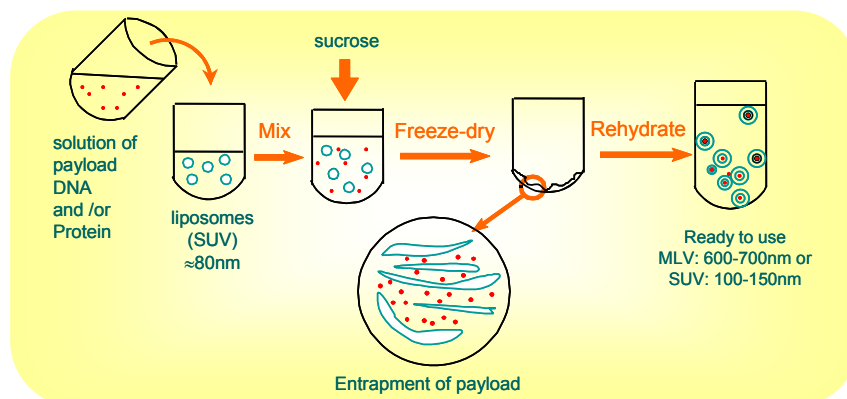
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Liposomes for Vaccination



- Liposomes containing P/P vaccines composed of a variety of lipids by the dehydration-rehydration method.



- ✓ Entrapment: 85-100% for plasmid DNA and 60-85% for co-entrapped protein.
- ✓ Vesicle diameter: 600-700 nm
- ✓ Liposomes relatively stable in simulated gastric media

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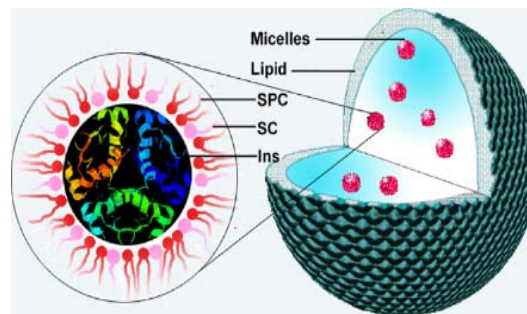


Solid Lipid Nanoparticles (SLNs)



- **SLNs** are made from solid lipids (e.g., triglycerides, fatty acids, etc.) and can be produced to incorporate either lipophilic or hydrophilic drugs.

- ✓ Their colloidal dimensions and the controlled release behavior enable drug protection and administration by various routes thus emphasizing their versatility.



SLNs containing insulin-loaded inverse micelles

J. Liu, T. Gong, C. Wang, Z. Zhong, Z. Zhang, Int. J. Pharm. 340, 153 (2007)

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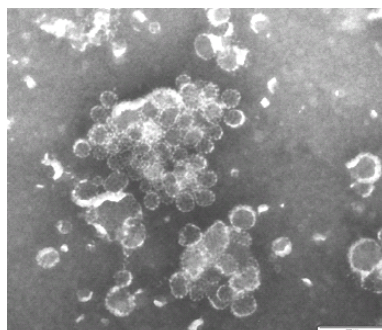


Immunostimulating Complexes (ISCOMs)



- Colloidal, cage-like structures comprising of a protein antigen, the saponin adjuvant Quil A, cholesterol and phospholipids.

- ✓ The protein antigen is trapped in the formed matrix.



ISCOMs prepared by hydration of freeze-dried lipid matrix

M. Liang, I. Toth, N.M. Davies, European J. Pharm. Biopharm. 68, 840 (2008)

Clinical studies have shown a good safety and tolerability profile in humans as well as induction of both humoral and cellular immune responses.

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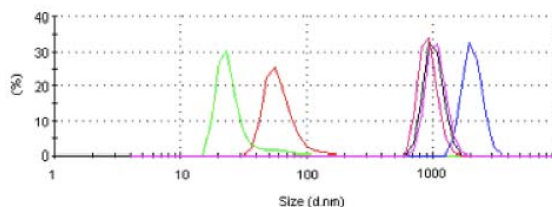
Nanogels



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

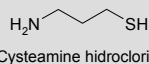
- ✓ Thermosensitive: NIPAAm-Aam, NIPAAm-DMAM, DEAM-DMAM

- ✓ pH sensitive: 2-hydroxyethyl methacrylate, acrylic acid

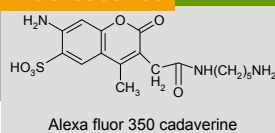


Surface
modification

Adhesion



Fluorescence



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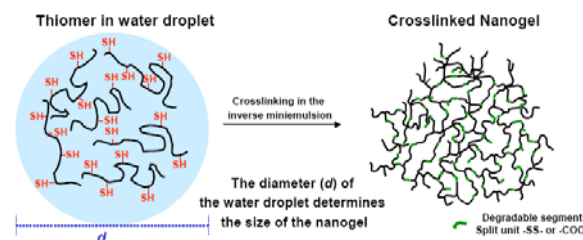
Thiomer Nanogels



- Biodegradable nanogels by crosslinking thiol functionalized starPEG or poly(glycidols) in the inverse miniemulsion via oxidation or Michael addition with diacrylates.

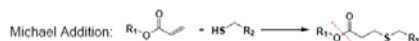
- ✓ Synthesis of hydrophilic oligomers via radical polymerization with cysteamine-modified N-acrylosuccinimide.

- ✓ Crosslinking of hydrophilic polymers possessing hydroxyl groups with disulfide crosslinker.

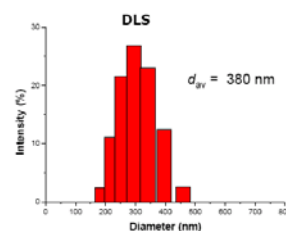


Crosslinking of -SH groups:

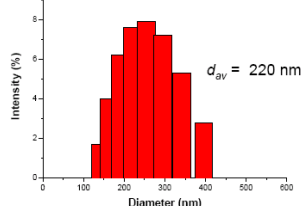
Oxidation: $-\text{SH} + \text{HS}- \rightleftharpoons -\text{SS}-$



starPEG nanogels



Poly(glycidols) nanogels



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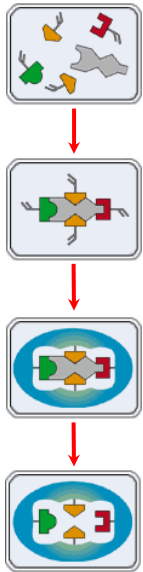
Molecularly Imprinted Polymers

➤ Molecularly Imprinted Polymers for drug delivery should:

- ✓ Compromise between rigidity and flexibility
- ✓ Exhibit high chemical stability to resist enzymatic and chemical attack and mechanical stress
- ✓ Ensure biocompatibility

Three main drug delivery approaches:

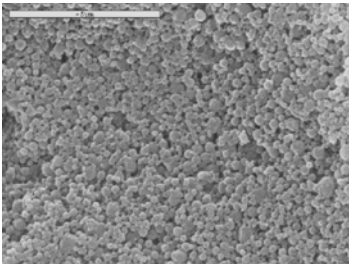
1. Rate-programmed drug delivery: where the drug diffusion from the system has to follow a specific rate profile.
2. Activation-modulated drug delivery: where the release is activated by some physical, chemical or biochemical processes.
3. Feedback-regulated drug delivery: where the rate of drug release is regulated by the concentration of a triggering agent, the concentration of which is dependent on the drug concentration in the body.



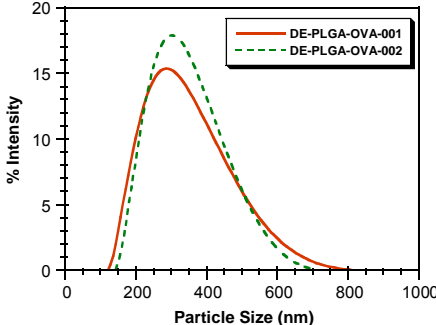
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PLGA & Derivatives

OVA-loaded PLGA NPS



✓ OVA loading: 17.4%wt



Particle Size (nm)	% Intensity (DE-PLGA-OVA-001)	% Intensity (DE-PLGA-OVA-002)
200	5	10
300	15	18
400	10	12
500	5	5
600	2	2
800	0	0

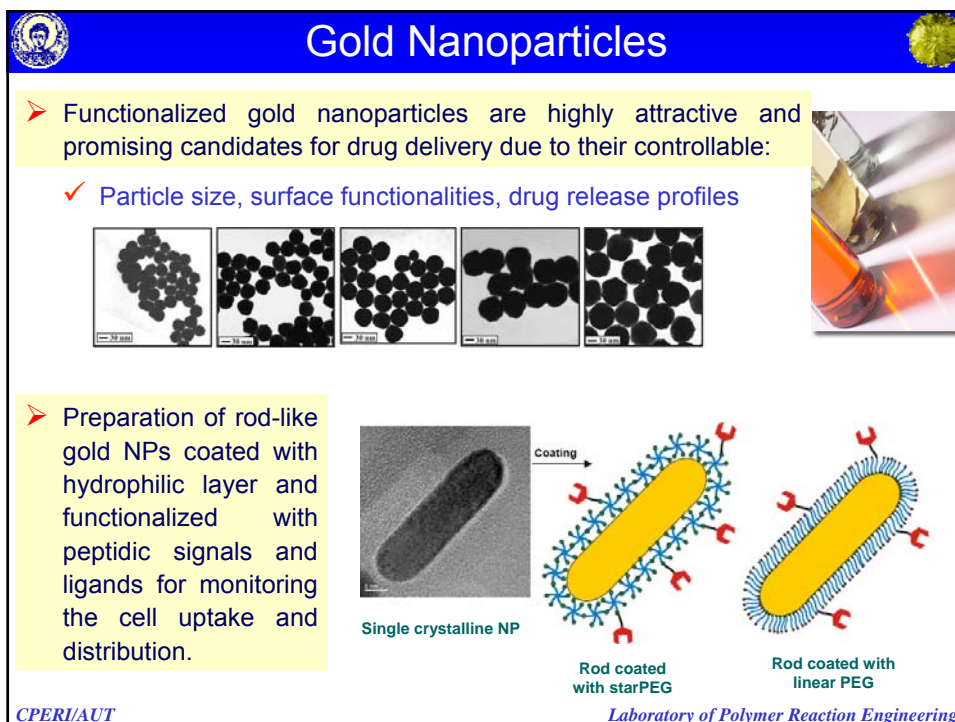
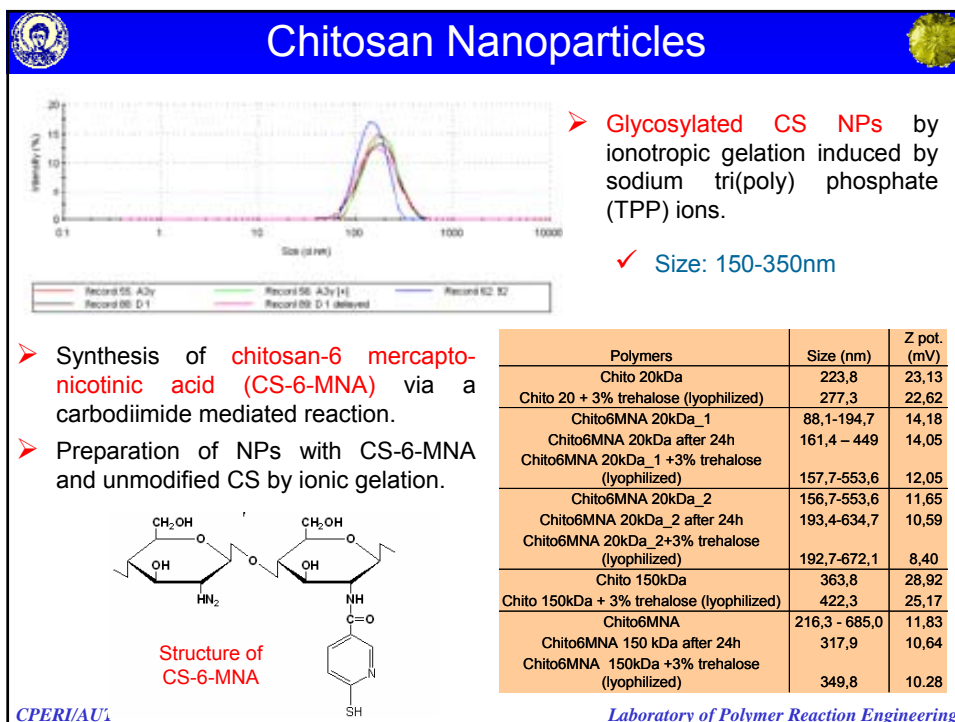
PVA-based branched polyesters bearing PLGA side chains

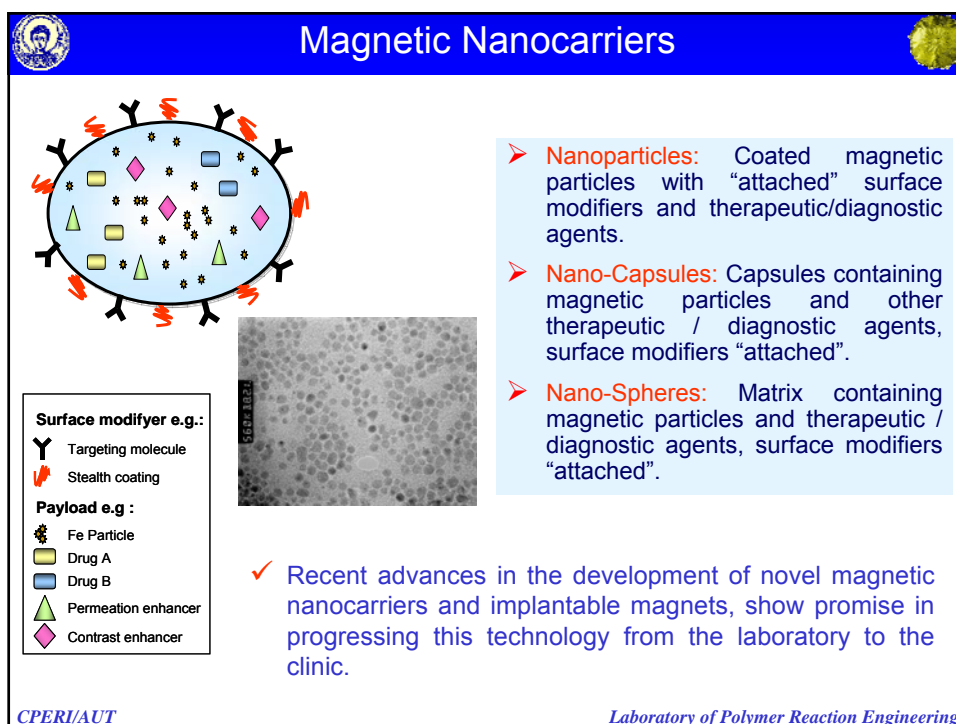
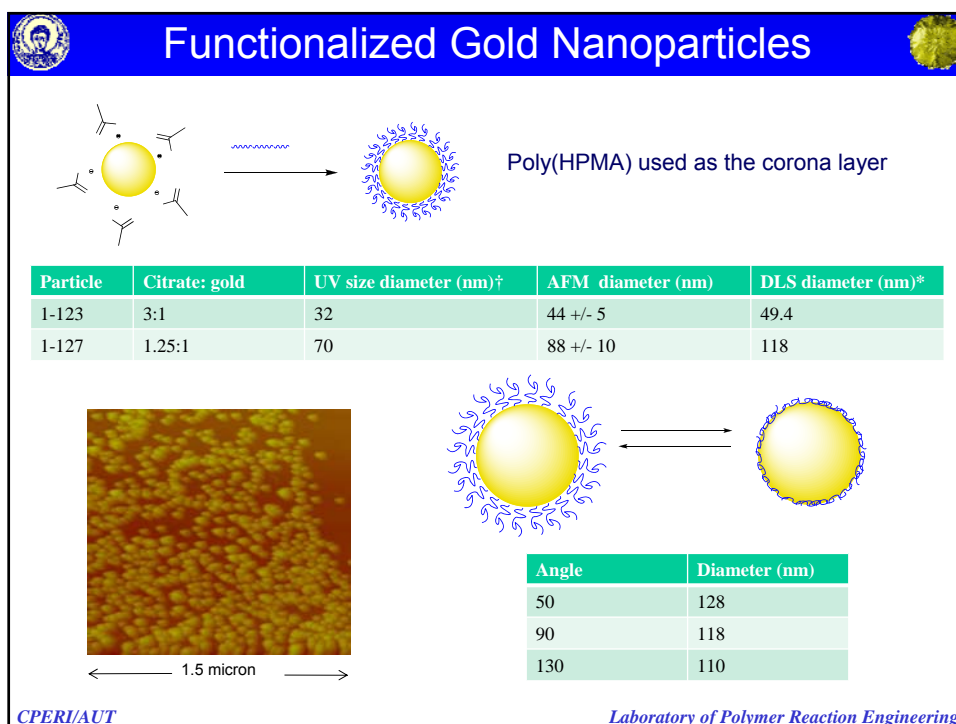
First Generation:
PVA-g-PLGA for parenteral protein delivery

Second Generation:
Negatively charged Sulfobutyl-PVA-g-PLGA as nanoparticulate adjuvants for tetanus toxoid vaccines

Third Generation: Positively charged Amine-PVA-g-PLGA as nanoparticulate adjuvants for DNA vaccination, and protein carriers.

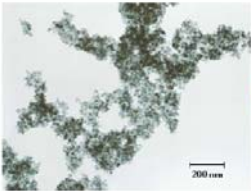

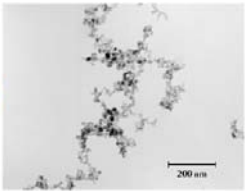
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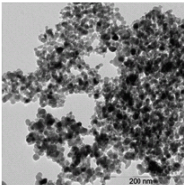

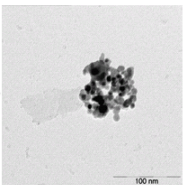

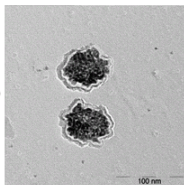
Functionalized Magnetic NPs

➤ Precipitation of Iron-salts in NaOH, then aminofunctionalization and NCO-sPEG coating:

✓ No proper control over aggregation

➤ Addition of NCO-sPEG to either the Iron-salt solution or the NaOH prior to precipitation:

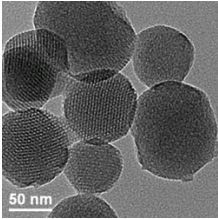
✓ Better control over aggregation

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Mesoporous Silica-based DDS

- ✓ High surface area ($> 900 \text{ m}^2/\text{g}$).
- ✓ Controllable pore diameter (2-20nm)
- ✓ Uniform mesoporous structure (e.g., hexagonal, cubic, lamellar)
- ✓ Encapsulation of guest biomolecules inside the porous matrix

Mesoporous Silica Structure



Development of **stimuli-responsive controlled release systems** via surface functionalization of silicas with photo- or redox-responsive organic groups, inorganic nanoparticles, dendrimers and polymers.

Recent breakthroughs in controlling the size and shape of these materials have greatly **improved their biocompatibility and cellular uptake efficiency**.

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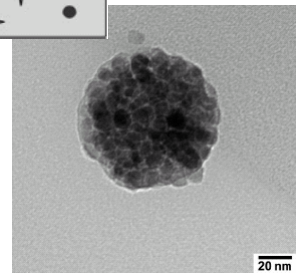
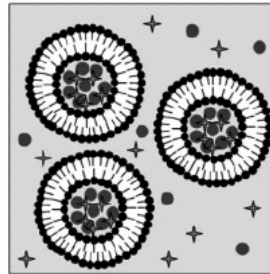


Liposome / Nanoparticle Hybrids



- Promising candidates as nanoscale delivery systems for **combinatory therapeutic-imaging modalities**.

- ✓ Encapsulation of various types of **nanoparticles** (e.g., iron oxide, quantum dots, silica, etc.) in liposomes to enhance their **compatibility** with the biological milieu *in vitro* and *in vivo* as well as their **pharmacological efficacy**



Lipid vesicle containing Fe_3O_4 NPs

W. T. Al-Jamal and K. Kostarelos, *Nanomed.* 2, 85 (2007)
A. Wijaya and K. Hamad-Schifferli, *Langmuir*, 23, 9546 (2007)

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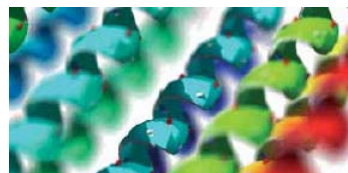


Crossing Biological Barriers



- Most nanomedicines are currently administered parenterally, but both the market and patients would prefer other routes such as oral, pulmonary and nasal.

- ✓ Oral delivery – Gastrointestinal Tract (GIT) Epithelium
- ✓ Respiratory delivery
- ✓ Crossing the blood brain barrier (BBB)



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Oral Delivery



➤ Advantages of Oral Delivery:

- ✓ Ease of administration
- ✓ Patient acceptability and compliance
- ✓ Large surface area for systemic absorption

➤ Barriers to Oral Delivery of P/P drugs:

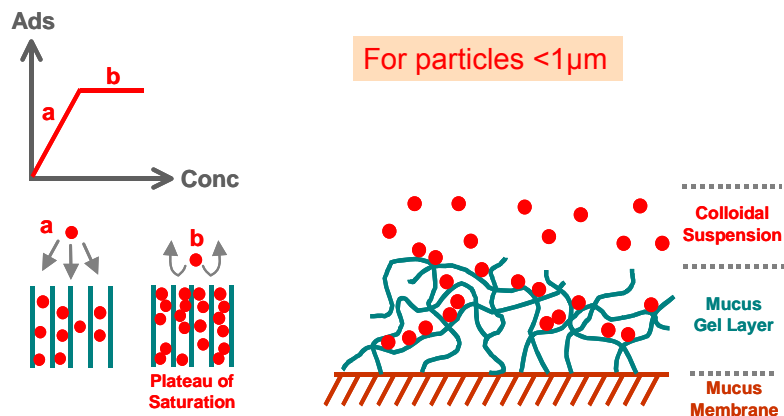
- ✓ Acid-induced **hydrolysis** in the stomach.
- ✓ **Enzymatic degradation** through the gastrointestinal track (GIT) by several proteolytic enzymes.
- ✓ **Bacterial fermentation** in the colon.
- ✓ Viscous mucus layer covering the surface of the **GI epithelium**.
- ✓ **Intercellular spaces** gated by closely fitting tight junctions.

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Oral Delivery



- ✓ The linear increase in the isotherm corresponds to the creation of new adsorption sites when the bulk particle concentration is increased.
- ✓ These sites are available for further adsorption up to the isotherm plateau which corresponds to a saturation of the available sites.

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Oral Administration for Systemic Delivery



➤ Transcellular passive transport

- ✓ Drug lipophilicity is the most important parameter for the drug crossing through this route.

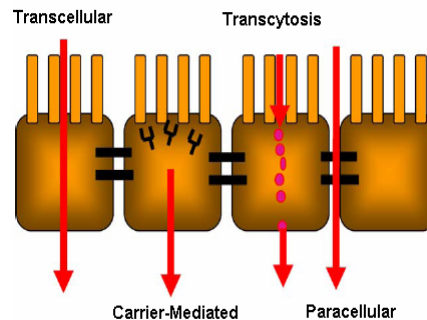
➤ Transcellular carrier - mediated active or facilitated transport

- ✓ Carrier size and its surface functionalization are crucial parameters.

➤ Paracellular passive transport

- ✓ Drug hydrophilicity and molecular size are the most important parameters for the paracellular drug crossing. This route takes advantage of the leakiness of cell to cell junction.

Transepithelial pathways available for transport from intestinal lumen to the bloodstream:



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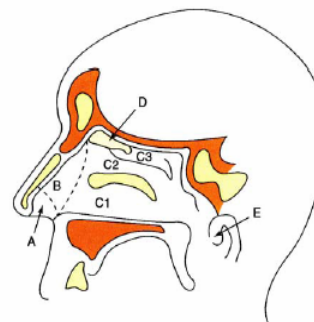
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Nasal Vaccination



- Viral infections can be acquired through the nasal associated lymphoid tissue (NALT).
- Both mucosal and systemic immune responses can be induced, in contrast to injected vaccines, which only induce a systemic immune response.
- Intranasal immunization is straightforward (i.e., administration via drops or sprays) and in general lower doses are required to elicit comparable antibody titers than those elicited by other mucosal routes of immunization.



Sagittal section of human nasal cavity

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Nasal Vaccination Requirements



Three major parts should constitute the nanostructure-based vaccines: the carrier, the antigen and danger signals (e.g., lipopolysaccharides or their derivatives, ssRNA, etc.)

Carrier Properties

- Size in the range of 100 nm would be ideal for both sterile filtration and optimal in vivo efficacy.
- NPs should preferentially be mucoadhesive with negative zeta potential.
- Positively charged NPs may aggregate due to the presence of negatively charged substances in the mucus.
- A minimum 3-4 weeks stability (at least with respect to size and antigen integrity) is required.
- Injectable, isotonic excipient/buffer solutions can be used.

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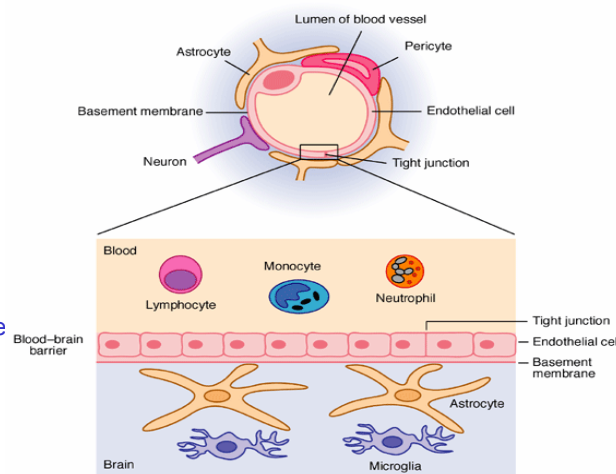


Delivery to the Brain



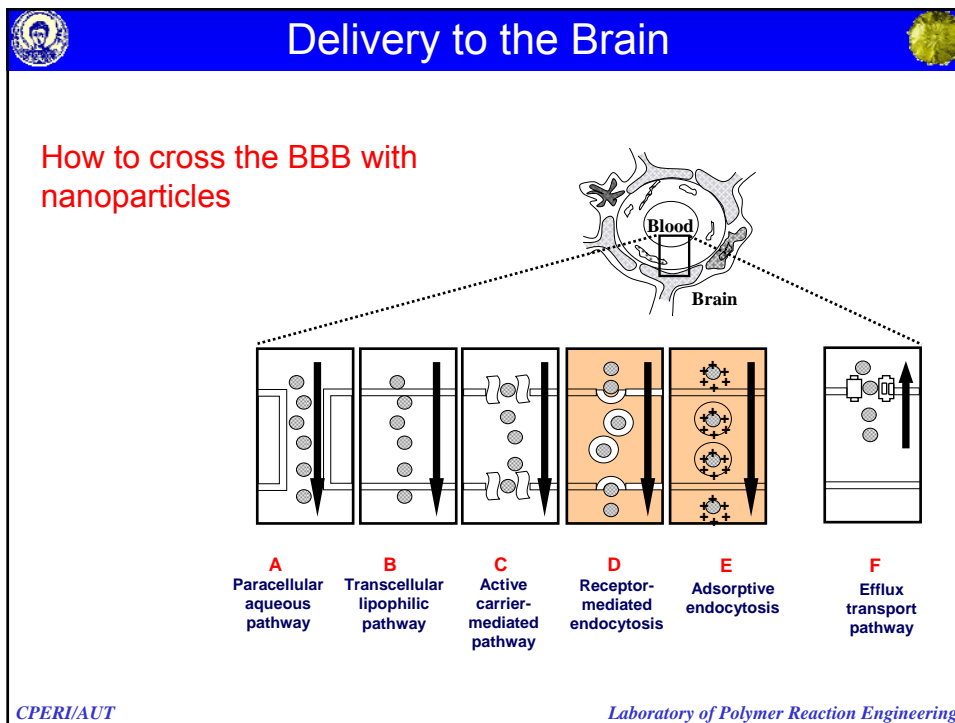
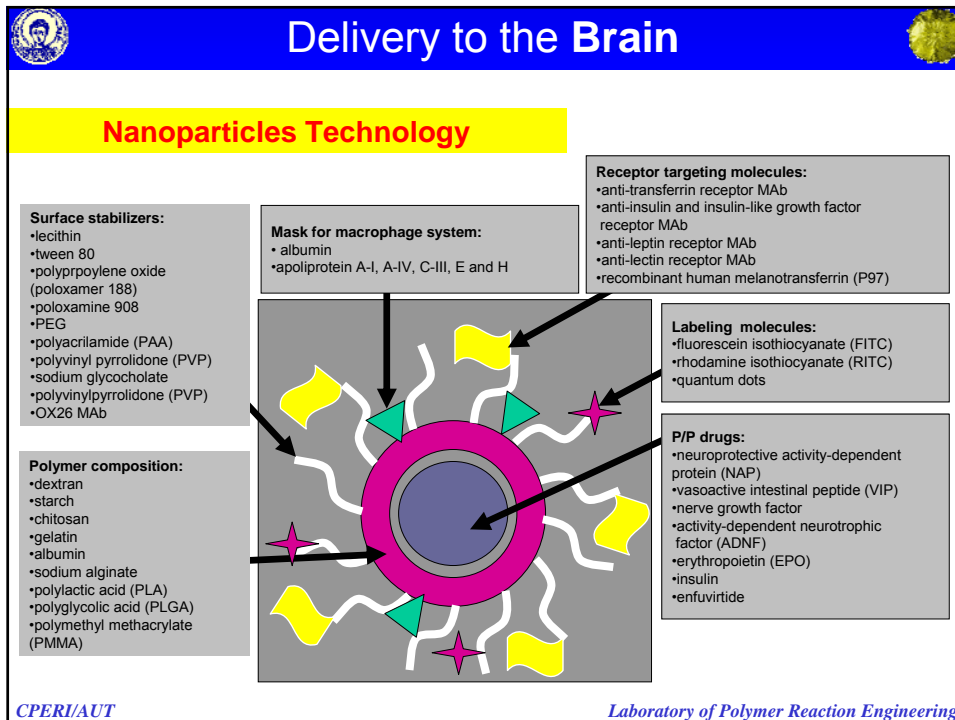
➤ Ideal Properties of Polymeric-Based Nanoparticles for Drug Delivery to the Brain:

- ✓ Stable in blood
- ✓ Non-toxic
- ✓ Non-thrombogenic
- ✓ Non-immunogenic
- ✓ Non-inflammatory
- ✓ Biodegradable
- ✓ Avoidance of the reticuloendothelial system



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Drug Delivery Devices



- The ultimate goal in controlled release is the highly reproducible mass-fabrication of **injectable, implantable, transdermal, mucoadhesive devices** with the ability to store and release **multiple chemical substances** on demand.
- Miniaturized targeted devices are characterized of high spatial and temporal control over drug release kinetics.
 - ✓ **Spatial control** allows for high anatomic specificity, lower dosage, and decreased side effects.
 - ✓ **Temporal control** allows for sustained dosing and minimized fluctuations from the therapeutic window.

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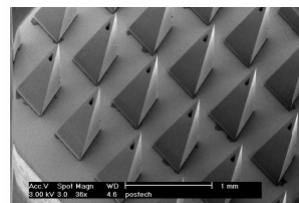
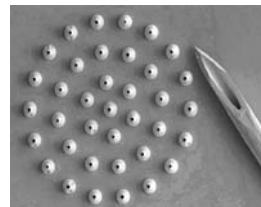
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Drug Delivery Devices



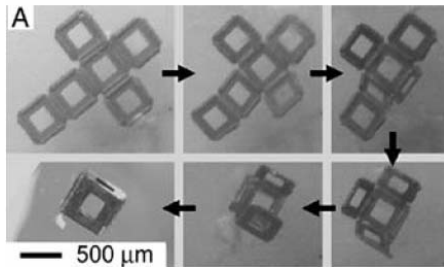
- Recent advances in **micro-, nano-fabrication techniques** (e.g., photolithography, etching, etc.) and **micro-electro-mechanical systems (MEMS) technology** have provided a unique opportunity to fabricate **miniature biomedical devices** for a variety of applications.
 - ✓ **Nearly pain free microneedles**, extending the capabilities of patches to large molecules (e.g., proteins) that cannot diffuse through intact skin, can be manufactured by reactive etching or polymer casting onto a plate.
 - ✓ **Modern stents** are equipped with small micromachined reservoirs which release antineoplastic drugs directly into the tissue rather than the bloodstream.



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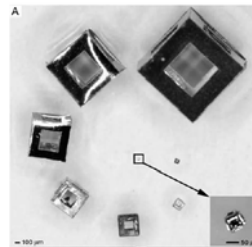
3D Containers based on Lithography / Self Assembly



- The 3D structure is first laid out and patterned as a 2D precursor template interconnected by a set of hinges.
- Upon activation by a thermal trigger, the hinges cause the 2D template to fold into a 3D structure.

Ch. L. Randall, T. G. Leong, N. Bassik and D. H. Gracias, *Adv. Drug Delivery Rev.* 59, 1547 (2007)

- ✓ The devices are **loaded with gels** either after self-assembly (by microinjection) or during the folding process.
- ✓ **Drug encapsulation** is achieved in polymers/gels loaded into the container.
- ✓ The gels either **dissolve spontaneously** in the release medium or are collapsed by **remote heating** to release the drugs on-demand.



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Biochips

- **MEMS-based micro-dosing drug delivery devices (i.e., biochips)** consist of micro pumps, micro sensors, micro fluid channels and necessary related circuits and are mainly aimed at **serious chronic diseases** such as diabetes, or **abrupt life threats** such as heart attack, stroke, etc.

- ✓ Based on a real-time measurement from micro sensors, the appropriate and effective amount of dose is precisely calculated by a controller and released by micro actuators/mechanisms in time.
- ✓ These devices can be either implanted or simply placed under the skin.
- ✓ A key issue to be seriously taken into account is **biocompatibility**.

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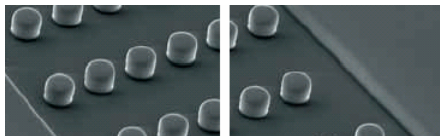
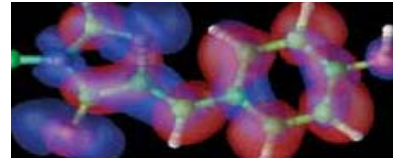
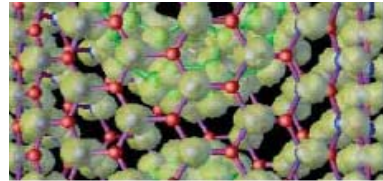


Diagnostics and Imaging



- The application of micro- and nanobiotechnology in medical diagnostics can be subdivided into three areas:

- ✓ In-vitro diagnostics
- ✓ In vivo diagnostics
- ✓ Medical devices



- The development of these applications relies on a common ground of enabling technologies.

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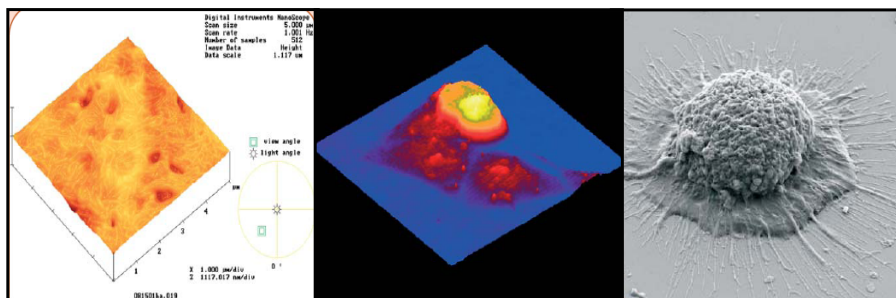


Nanotechnology-based Diagnostics



In-vitro Diagnostics

Goal: fast, reliable, specific and cost-effective detection of a few molecules (or even a single molecule) in a complex, non amplified and unlabelled biological sample.



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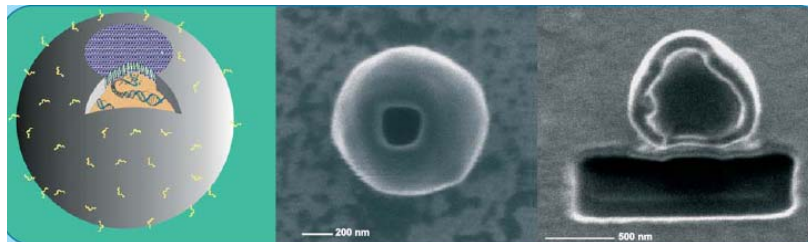
Nanotechnology-based Diagnostics



In-vivo Nano-imaging

Goal: to create highly sensitive, highly reliable detection agents that can also deliver and monitor therapy.

- ✓ The tissue of interest can be imaged, using target-specific contrast nanostructures
- ✓ The pharmacologically active agent can be directly enclosed to nanostructures for applying therapy
- ✓ Monitoring of treatment effects is possible by sequential imaging



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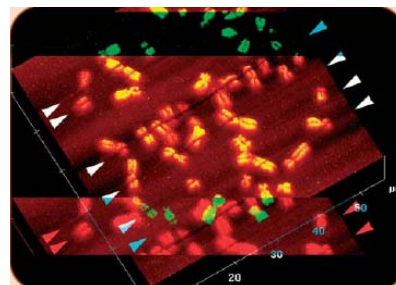
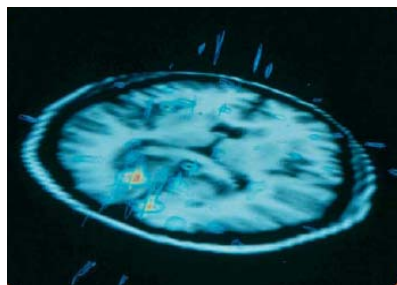
Nanotechnology-based Diagnostics



Improved Detection

Goal: A major objective is to develop efficient, reasonably priced clinical cameras capable of acquiring whole-body images in one step and undertaking multi-isotope studies, using imaging modalities:

- Positron emission tomography with magnetic resonance imaging,
- Magnetic resonance imaging with ultrasound or with electroencephalogram-based brain mapping,
- Ultrasound with optical technologies.



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Nanotechnology-based Diagnostics



Nano Probes

- In the development of nanoprobes, the major issues are **specificity** and the **ability to penetrate the cell**.
- Further research is required into the creation of an '**all-purpose nanoparticle**' that can be imaged by the variety of existing instruments (e.g. optical, acoustic, magnetic). Apart from identifying disease and delivering therapy, the **non-toxic labeling of specific cell types** is important for the **imaging of intracellular trafficking**.



Future Challenges



- Development of synthetic nanometer sized delivery systems for therapeutic agents of increased complexity, able to tackle challenging diseases:
 - ✓ Targeted delivery schemes that accumulate the therapeutic agent specifically on the diseased cells for **cancer** treatment.
 - ✓ Targeted agents able to deliver a drug that stabilizes the **atheromatic plaque** and prevents rupturing.
 - ✓ Delivery of NPs that selectively attach to stem cell niches and release local stimulating factors for the treatment of **musculoskeletal disorders**.
 - ✓ Nanocarriers with special surface properties able to cross the blood-brain-barrier (BBB) for the treatment of **neurodegenerative diseases**.
 - ✓ Non-parenteral formulations of NPs containing insulin.



Future Challenges



- Development of “smart” drug delivery systems enabling therapy that is responsive to the patient's needs.
 - ✓ These DDS should be manufactured inexpensively, loaded easily with drugs, delivered with minimal trauma, be easily tracked, programmed or controlled and allow for precise spatial positioning of drug release.
 - ✓ Advanced functional modules such as sensors, memory and logic devices, should be incorporated directly onto the drug delivery device.
 - ✓ On-demand release should be enabled by remote communication or autonomous logic.