Engineering Nanomedical Systems

Lecture 5

Nanomaterials for core design

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5.1 Introduction

A. core building blocks

B. functional cores for theranostics

C. “functionalizing” the core surface chemistry to attach other molecules
# Types of Core Materials and their detection

<table>
<thead>
<tr>
<th>Core material</th>
<th>Detection</th>
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<tbody>
<tr>
<td>Iron oxide</td>
<td>x-ray, MRI, add fluorescent probe</td>
</tr>
<tr>
<td>C60 and carbon nanotubes</td>
<td>add fluorescent probe</td>
</tr>
<tr>
<td>Gold</td>
<td>surface plasmon resonance</td>
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<tr>
<td>Silver</td>
<td>surface plasmon resonance</td>
</tr>
<tr>
<td>Silica</td>
<td>add fluorescent probe</td>
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<tr>
<td>Quantum dots</td>
<td>intrinsic long-lifetime fluorescence</td>
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<tr>
<td>“Next generation” quantum dots</td>
<td>intrinsic fluorescence</td>
</tr>
<tr>
<td>Hybrid materials</td>
<td>mixture of detectable properties</td>
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</table>
5.2 Ferric oxide cores

A. paramagnetic cores
B. superparamagnetic cores
C. ferric nanorods
D. advantages and disadvantages
Figure 1. Transmission electron micrographs (TEM) of (a) spherical iron nanoparticles with diameters of 2 nm, and (b), rod-shaped iron nanoparticles with dimensions of 2 nm 11 nm, (Inset: High-resolution electron micrograph of a single nanorod) The images were obtained with a JEOL JEM-2000EX II instrument. From: Park et al., J. Am Chem. Soc. 2000
5.3 C60 and carbon nanotubes

A. size and structure of C60
B. elongation of C60 into carbon nanotubes
C. advantages and disadvantages
C60 “Buckyballs” and Carbon nanotubues as drug carriers

http://www.ydaei.edu
http://www.udel.edu
5.4 Gold cores

A. gold nanoparticles
B. gold nanorods
C. other shapes (e.g. "stars")
D. gold nanoshells
E. advantages and disadvantages
Gold and silver nanoparticles

From: Rosi and Mirkin, 2005.
Gold nanorods, which fluoresce red, were photographed inside the blood vessels of a live mouse by researchers in Purdue's Weldon School of Biomedical Engineering and Department of Chemistry. The researchers have taken a step toward developing a new type of ultra-sensitive medical imaging technique that works by shining a laser through the skin to detect the tiny rods injected into the bloodstream. In tests with mice, the nanorods yielded images nearly 60 times brighter than conventional fluorescent dyes, including rhodamine, commonly used for a wide range of biological imaging to study the workings of cells and molecules. (Purdue University photo courtesy of Weldon School of Biomedical Engineering and Department of Chemistry)
5.5 Silica cores

A. Silica nanoparticles
B. Embedding fluorophores to prevent photobleaching
C. Other advantages and disadvantages
Possibility of low toxicity silicon nanoparticles for in-vivo use? (Allison Hubel group and collaborators at Univ. Minnesota)

Achievements:
- Scaleable high-yield synthesis approach for silicon quantum dots
  Mangolini et al., NanoLett 5, 655, 2005
- Organic surface passivation
- Photoluminescence quantum yield > 60%

Fundamental issues:
- Crystal formation in low-temperature plasmas
- Surface properties of quantum dots

Source: Research Highlights, Univ. Minnesota 2006
Silica nanoparticles can be easily made in different sizes and can embed conventional fluorescent molecules and prevent photobleaching.

FIGURE 1. Transmission electron micrographs of different sizes of silica nanoparticles prepared in various microemulsion systems.

(a) 15-nm nanoparticles; (b) 40-nm nanoparticles; (c) 120-nm nanoparticles; scale bars are 200 nm, 200 nm, and 1 µm, respectively.

From Wang et al., 2006.
Use of fluorescent dye embedded silica nanoparticles

FIGURE 3. (a) SEM image of an E. coli O157:H7 cell incubated with nanoparticle–antibody conjugates, showing nanoparticle binding to the target bacterium. Scale bar is 2.73 µm. (b) SEM image of an E. coli DH5a cell (negative control) incubated with nanoparticle–antibody conjugates, showing no nanoparticle binding. Scale bar is 1.5 µm. The black small dots in (a) and (b) are the pores on the surface of the filter membrane, and the white spots are unbound nanoparticles. (c) Fluorescence image of an E. coli O157:H7 cell after incubation with nanoparticle–antibody conjugates. Scale bar is 4 µm. The fluorescence intensity is strong, enabling identification of a single bacterial cell in aqueous solution.

From: Wang et al., 2006
Mesoporous Silica NPs (MSNs) for drug release

Transmission electron microscopy images of three spherical MSNs with different particle and pore sizes: a) Particle size ca. 250 nm; pore diameter ca. 2.3 nm. b) Particle size ca. 200 nm; pore diameter ca. 6.0 nm. c) Particle size ca. 50 nm; pore diameter ca. 2.7 nm.

5.6 Quantum Dots

Increasing size

4 nm → 7 nm

* Not including coatings
Quantum Dot Nanoparticles

- Excitation/emission spectra
- Photostability
- Size tunable
- Bioconjugation

Comparison of quantum dot excitation and emission spectra to Rhodamine fluorescent dye.
Quantum Dot Nanoparticles

Biocoating to make hydrophilic and biocompatible (e.g. poly(ethylene glycol) or PEG)

ZnS cap

Semi-conductor core material (e.g. CdSe)

Surface group (e.g. -NH$_2$ or -COOH)

Transmission electron microscopy (TEM) image of amino-functionalized Qdots. Size was determined to be ~10 nm.
Biomolecular Targeting: Peptide

- Use of biomolecules offers advantages toward other uptake mechanisms: Cell receptor is targeted and functions normally.
- Peptide offers ease of synthesis and well understood chemistry. These are also on the size order of the nanoparticles.
  - QTracker® Cell Labeling Kit (Invitrogen Corporation, Carlsbad, CA) offers Qdot nanoparticles conjugated to a universal peptide. This will enter all cell lines.
  - Specific peptides will enter only certain cell types; the focus of nanomedical approach to disease.

![Diagram showing universal peptide entering all cell types and specific peptide entering SKBR3 cells only.](image-url)
**UNIVERSAL PEPTIDE**

**ALL CELL TYPES**

**MCF-7**
CONTROL

**SkBr3**
EXPERIMENTAL

<table>
<thead>
<tr>
<th>Positive Control Sample - QTracker</th>
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<tbody>
<tr>
<td>CELL (BLUE)</td>
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<tr>
<td>![Image a]</td>
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<td>![Image d]</td>
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**QDOT**

**UNIVERSAL PEPTIDE**

**ALL CELL TYPES**
**In vitro SkBr3 Study:**
Confocal Images

SkBr3 cells with application of Qdot-LTVSPWY complex
Quantum Dot Nanoparticles

- Agglomeration properties based on:
  - Chemistry of the Qdot; its properties, surface charge/molecules, elemental makeup, etc.
  - Chemical environment; for instance pH

Qdots imaged in biological environments. (a) *In vitro* Qdots in cell (Red, scale bar 5µm). (b) *In vivo* Qdots within tissue (White, scale bar 100µm).
In vivo SkBr3 Tumor Study: Results

Fluorescent microscopy images of *in vivo* tumor tissue. 
(a) Image of control kidney tissue, this sample did not receive any Qdots. 
(b) Image of tumor tissue from a peritumoral injection. 
(c) Image of tumor tissue from a tail vein injection.
Qdot Agglomeration

(a) *In vivo* tumor image. (b) Graphic representation of agglomerated Qdots.

**NANOPARTICLE AGGLOMERATION:**

~1000 - 2000 nm IN DIAMETER

APPROXIMATE: 50 – 100 NANOPARTICLES PER CLUSTER IN DIAMETER

CONSIDERING THREE DIMENSIONS, THE NUMBER OF NANOPARTICLES PRESENT COULD BE BETWEEN 125,000 AND $10^6$
Cytotoxicity: Some DNA damage!

- Confocal imaging
  - ROS are present normally in cells. Heightened presence indicates a state of cellular stress.
  - Detection of ROS was observed in the positive control sample and the QTracker® sample.

Dihydroethidium is shown in red QTracker® is shown in green.
(a) Control (b) $\text{H}_2\text{O}_2$ (c) QTracker®
5.5 Next generation quantum dots

A. Water-Soluble Doped ZnSe Nanocrystal Emitters

B. Organic quantum dots
Future of Quantum Dots is Still being written…

• Concerns are arising over potential in-vivo toxicity of Cd based quantum dots

• But new less toxic “d-dots” are being developed

Efficient, Stable, Small, and Water-Soluble Doped ZnSe Nanocrystal Emitters as Non-Cadmium Biomedical Labels
Narayan Pradhan, David M. Battaglia, Yongcheng Liu, and Xiaogang Peng
Nano Lett.; 2007; 7(2) pp 312 - 317; (Letter)
5.8 Hybrid material cores

A. Gold-ferric oxide nanoparticles and nanorods

B. NIR fluorescent-chitosan polymer-iron oxide core hybrids
Polymers as vehicles for SPIO NPs

- Glycol Chitosan
- Pluronic
- PEG-oleic acid

Dual Modality NPs
- High stability
- Low toxicity

Previous studies

work of graduate student Jaehong Key
In-vivo fluorescent imaging (eXplore Optix) of NIR (Cy5.5) fluorescent chitosan-SPIONPs

work of graduate student Jaehong Key
Ex-Vivo imaging of NIR (Cy5.5) fluorescent chitosan-SPIO NP labeled isolated mouse organs

work of graduate student Jaehong Key
Lecture 5 References


