Surface chemistry: attaching nanomedical structures to the core

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Introduction – Basic attachment Strategies

A. attachment strategies typically depend on core composition

B. but the attachment strategy should not drive the core choice

C. the choice of core should still depend on the desired overall “multifunctional” nanomedical device
“Surface chemistry” strategies for attachment of biomolecules to the core material for biocompatibility

A. hydrophobic versus hydrophilic core materials

B. addition of biomolecules for biocompatibility

C. monofunctional versus bifunctional surface chemistry strategies – begin with the end in mind!

D. pay attention to overall zeta potential during the surface chemistry process
Stabilizing, Biocompatible Coatings of Core Materials

A: Adsorption of amphiphilic diblock polymers
B: Chemical coupling of hydrophilic polymeric molecules
C: Linkage of spacer molecules with hydrophilic surface groups

Source: Kumar, C. 2005
Two main attachment strategies

A. Covalent bonding
B. Non-covalent bonding
Covalent bonding strategies

1. Advantages
   a. Very stable
   b. Can control process of bond disruption for multilayering

2. Disadvantages
   a. Can be too stable and difficult to disassemble
   b. Must be careful to avoid or minimize use of strong organic solvents that can be cytotoxic even at trace concentrations
Non-covalent (primarily electrostatic) Bonding Strategies

1. Advantages
   a. Can use very gentle chemistries for biocompatibility
   b. Chemistry can be very simple layer-by-layer assemblies
   c. Easier to disassemble multilayered structures

2. Disadvantages
   a. Instability - different pH and ionic strength environments can cause layers to spontaneously disassemble at undesired times
   b. Zeta potential can suddenly change as layers spontaneously strip off
Four Common Approaches to Hydrophilic Surface Modification of TOPO stabilized Quantum dots

1. Thiol + carboxyl hydrophilic end
2. 2 Thiol + carboxyl hydrophilic ends
3. Stable silane shell with crosslinking
4. Stabilization of TOPO layer with PEG or other polymers

Source: Kumar, C. 2005
Example: More complicated strategies: Coupling PEG and folate to an iron oxide nanoparticle

Source: Kumar, C. 2005
I. Introduction

A. Preparing the nanoparticle for addition of targeting and therapeutic molecules

B. What are the special requirements, if any, for these molecules?

C. Testing for targeting an efficacy at the single cell level
Aqueous dispersion of monodisperse magnetic iron oxide nanocrystals

Cryo-TEM photograph of water dispersible iron oxide nanocrystals.

Structure of water dispersible iron oxide nanocrystals (R stands for a functional group, e.g. –COOH).

Direct capping of QDs with thiolated DNA oligonucleotides

Figure 1. a) One-step in situ DNA functionalization of CdSe@ZnS core–shell QDs. b) photoluminescence (PL) spectra of CdSe core QDs and the DNA-capped CdSe@ZnS core–shell QDs. Both the green and red QDs show a significant increase of the QY after growth of the ZnS shell and DNA capping, simultaneously. The intensities were normalized by green CdSe@ZnS core–shell QDs. c, d) TEM images of green and red core–shell QDs, respectively. Higher-magnification images of individual dots are shown in the insets.

Formation of pPEGMA-coated MNPs with biotin

The procedure for formation of pPEGMA-coated MNPs and subsequent conjugation of biotin.
Attaching different types of targeting molecules (some types and examples)

A. antibodies
B. peptides
C. aptamers
D. small molecule ligands (e.g. folate)
Superparamagnetic Iron Oxide Nanoparticle–Aptamer Bioconjugation

Figure 1. a) Schematic illustration of the TCL-SPION–Apt bioconjugate system; b) confirmation of TCL-SPION–Apt bioconjugate formation by gel electrophoresis (1. 100-bp ladder; 2. A10 aptamer; 3. TCL-SPION–Apt bioconjugate; 4. TCL-SPION).

Attaching antibodies and peptides to Nanoparticles

- Usually done with “soft aqueous chemistry” involving bonding to carboxyl (COO\textsuperscript{-}) or amine (NH\textsubscript{2}) groups on surface of nanoparticles.

- May need molecular spacer arms of 8-12 carbons to give good access (reduce steric hindrance problems) of antibodies and peptides.
Testing the nanoparticle-targeting complex

A. Ways of detecting this complex

B. Ways of assessing targeting/mistargeting efficiency and costs of mistargeting

C. Is the nanoparticle still attached to the targeting molecule?
Attaching/tethering different types of therapeutic molecules

A. antibody therapeutics - need to interact with the immune system to activate
B. peptides (e.g. apoptosis-inducing peptides)
C. therapeutic aptamers
D. transcribable sequences
E. small drugs
Figure 1. Design of a multifunctional nanoparticle for siRNA delivery. Because of their photostable fluorescence and multivalency, QDs are suitable vehicles for ferrying siRNA into live cells in vitro and in vivo. Conjugation of homing peptides (along with the siRNA cargo) to the QD surface allows targeted internalization in tumor cells. Once internalized, these particles must escape the endolysosomal pathway and reach the cytoplasm to interact with the RNA-induced silencing complex (RISC), which leads to degradation of mRNA homologous to the siRNA sequence. Source: Derfus et al. Bioconjugate Chem., Vol. 18, No. 5, 2007
Testing the nanoparticle-therapeutic molecule complex

A. direct and indirect ways of detecting the therapeutic molecules

B. ways of assessing the therapeutic efficacy at single cell level

C. Is the nanoparticle still attached to the therapeutic molecule? Is that important?
Nanomedical pharmacodynamics –
the great unknown!

A. Little is known about complex nanoparticle pharmacodynamics
B. Obtaining quantitative biodistribution data is extremely difficult!
C. Some possible new approaches
Lecture 8 References


