Lecture 8

Surface chemistry: attaching targeting and therapeutic molecules to the nanoparticle core

8.1 Introduction
- 8.1.1 attachment strategies typically depend on core composition
- 8.1.2 but the attachment strategy should not drive the core choice
- 8.1.3 the choice of core should still depend on the desired overall "multifunctional" nanomedical device

8.2 "Surface chemistry" strategies for attachment of biomolecules to the core material
- 8.2.1 hydrophobic versus hydrophilic core materials
- 8.2.2 addition of biomolecules for biocompatibility
- 8.2.3 monofunctional versus bifunctional surface chemistry strategies
- 8.2.4 PEGylation as "stealth strategy" to minimize opsonification and increase circulation time
- 8.2.5 pay attention to overall zeta potential during the surface chemistry process!

8.3 Two main attachment strategies
- 8.3.1 covalent bonding strategies
  - 8.3.1.1 advantages
    - 8.3.1.1.2 very stable
    - 8.3.1.1.3 can control process of bond disruption for multilayering
  - 8.3.1.2 Disadvantages
    - 8.3.1.2.1 can be too stable and difficult to disassemble
    - 8.3.1.2.2 must be careful to avoid or minimize use of strong organic solvents that can be cytotoxic even at trace concentrations
- 8.3.2 non-covalent (primarily electrostatic) Bonding Strategies
  - 8.3.2.1 advantages
    - 8.3.2.1.1 can use very gentle chemistries for biocompatibility
    - 8.3.2.1.2 chemistry can be very simple layer-by-layer assemblies
    - 8.3.2.1.3 easier to disassemble multilayered structures
  - 8.3.2.2 disadvantages
    - 8.3.2.2.1 instability - different pH and ionic strength environments can cause layers to spontaneously disassemble at undesired times
    - 8.3.2.2.2 zeta potential can suddenly change as layers spontaneously strip off

8.4 Special considerations for the final attachment design
- 8.4.1 preparing the nanoparticle for addition of targeting and therapeutic molecules
- 8.4.2 what are the special requirements, if any, for these molecules?
  - 8.4.2.1 how to attach without changing function of molecule
  - 8.4.2.2 does this molecule need to stay attached, or not, to the nanoparticle in order to function
- 8.4.3 testing for targeting and therapeutic efficacy at the single cell level

8.5 Attaching different types of targeting molecules (some types and examples)
- 8.5.1 antibodies – which end to attach?
- 8.5.2 peptides – which end to attach, steric hindrance? Spacer arm needed?
- 8.5.3 aptamers - which end to attach, steric hindrance? Spacer arm needed?

8.5.4 small molecule ligands - which end to attach, steric hindrance? Spacer arm needed?

8.6 Testing the nanoparticle-targeting complex
- 8.6.1 ways of detecting this complex
- 8.6.2 ways of assessing targeting/mistargeting efficiency and costs of mistargeting
- 8.6.3 is the nanoparticle still attached to the targeting molecule?

8.7 Attaching/tethering different types of therapeutic molecules
- 8.7.1 antibody therapeutics - need to interact with the immune system to activate
- 8.7.2 peptides (e.g. apoptosis-inducing peptides)
- 8.7.3 therapeutic aptamers
- 8.7.4 transcribable sequences
- 8.7.5 small drugs

8.8. Testing the nanoparticle-therapeutic molecule complex
- 8.8.1 direct and indirect ways of detecting the therapeutic molecules
- 8.8.2 ways of assessing the therapeutic efficacy at single cell level
- 8.8.3 is the nanoparticle still attached to the therapeutic molecule? Is that important?

8.9. Nanomedical pharmacodynamics – the great unknown
- 8.9.1 little is known about complex nanoparticle pharmacodynamics
- 8.9.2 obtaining quantitative biodistribution data is extremely difficult!
- 8.9.3 some possible new approaches

Lecture 8 References

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