PURDUE UNIVERSITY

Weldon School of Biomedical Engineering

The Convergence of Differences, The Future of Excellence

BME 695

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Engineering Nanomedical Systems

Lecture 14

Designing and testng integrated nanomedical systems

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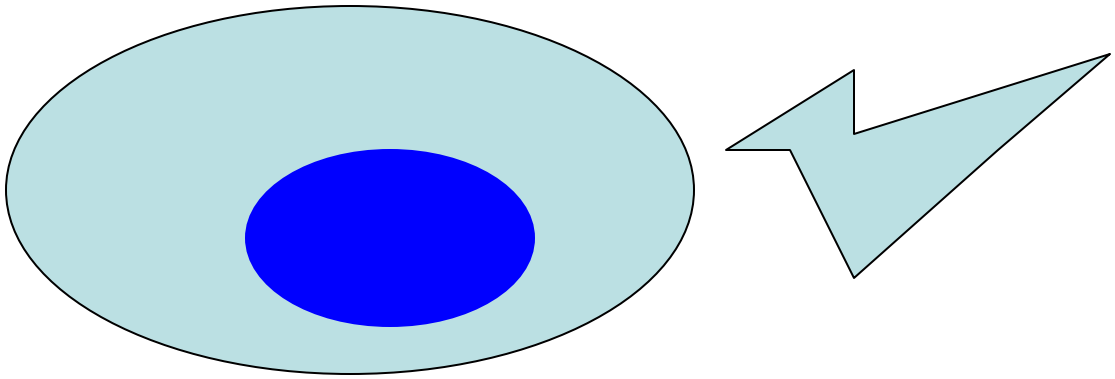
14.1 Steps in designing a nanomedical system

1. Choose autonomous or non-autonomous system
2. Choose type of external intervention
3. Choose core material, size and shape
4. Choose type and intracellular target of therapy
5. Choose therapeutic molecules
6. Choose diseased cell biomarker
7. Choose zeta potential
8. Choose stealth molecule

14.2 Choose autonomous or non-autonomous system

A. If autonomous, will there be error-checking to correct mistargeting?

B. If non-autonomous, what form of external modulation of the in-vivo nanomedical system will be used?



Choose autonomous or non-autonomous design

14.2 Choose autonomous or non-autonomous design

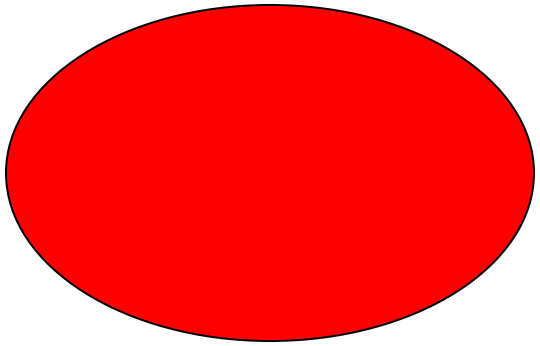
- 14.2.1 If autonomous, will there be error-checking to correct mistargeting?
- 14.2.2 If autonomous, does the NMS perform all of the multi-step process sufficiently to accomplish the objective?
- 14.2.3 If non-autonomous, what form of external modulation of the in-vivo nanomedical system will be used?
- 14.2.4 If non-autonomous, are the external interactions able to adequately control the actions of the NMS?
- 14.2.5 Evaluate reaction of NMS to external intervention
- 14.2.6 Compare actions of NMS with and without external intervention.
- 14.2.7 How do the actions of the NMS scale (linear? nonlinear? resonance?) with the size or extent of the external intervention?

14.3 Choose core material, size and shape

A. How will the core be used for diagnosis? Therapeutics?

B. Does this dictate the core material? Size?

C. Does shape alter circulation time or target cell penetration?



Commonly used core materials include: gold, ferric oxide, silica, Qdots,

Choose core material, size and shape

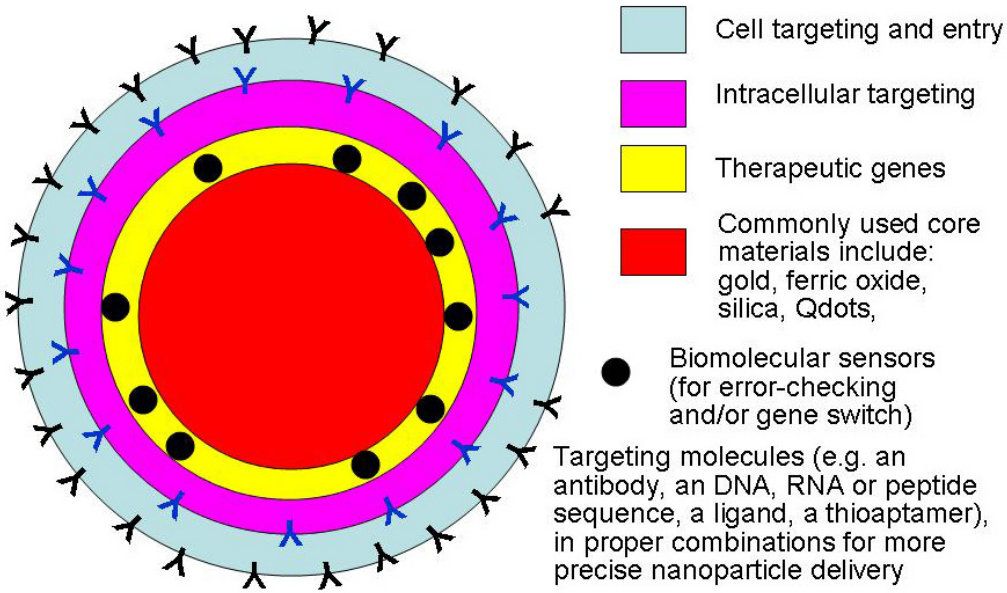
14.3 Choose core material, size and shape

- 14.3.1 How will the core be used for diagnosis?therapeutics?
- 14.3.2 Does this dictate the core material? Size?
- 14.3.3 Does shape alter circulation time or target cell penetration?
- 14.3.4. Evaluate size and shape of nanosized core by transmission (TEM) or scanning electron microscopy (SEM), or by atomic force microscopy (AFM)
- 14.3.5 Evaluate size of complete NMS (other parts may not be electron dense) by dynamic light scattering (DLS)
- 14.3.6 Evaluate materials present at each layer of construction by x-ray photoelectron spectroscopy (XPS)

14.3 Choose diseased cell biomarker

A. Choose cell surface biomarker on diseased cell

B. Choose targeting molecule type (antibody, peptide, aptamer…)



Design NMS targeting and evaluate its effectiveness

14.4 Design NMS targeting and evaluate its effectiveness

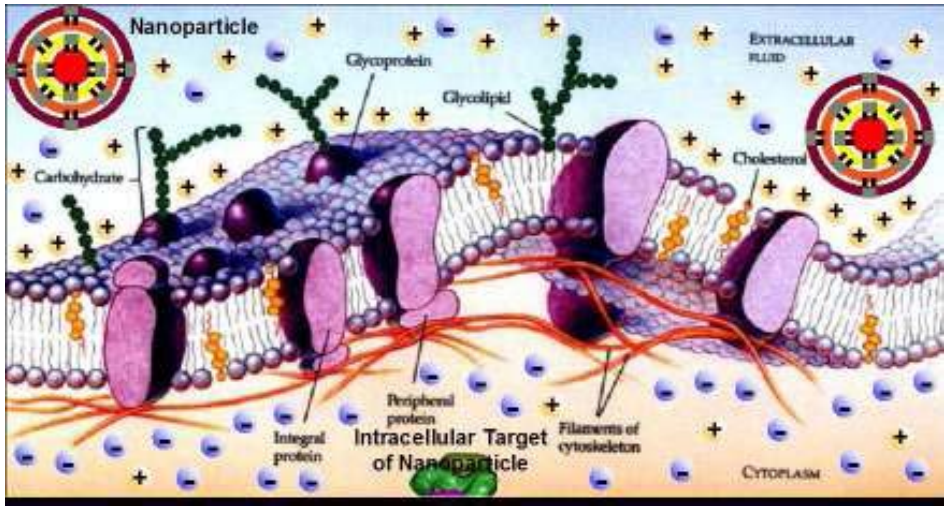
- 14.4.1 Choose cell surface biomarker on diseased cell. Is it unique or just elevated in expression (e.g. folate receptors)
- 14.4.2 Choose targeting molecule type (antibody, peptide, aptamer…)
- 14.4.3 Use flow or image cytometry to evaluate correctness of targeting to diseased cell using that biomarker system
- 14.4.4 How much mis-targeting is anticipated?What are the consequences of mistargeting?
- 14.4.5 Determine degree of mistargeting and consider the costs of misclassification (e.g. how many normal cells are mis-targeted for each diseased cell successfully targeted)
- 14.4.6 Based on the costs of misclassification, reconsider additional or alternative diseased cell biomarkers?
- 14.4.7 Evaluate intracellular targeting by TEM if NMS is not fluorescent)
- 14.4.8 Evaluate intracellular targeting by 3D confocal fluorescence microscopy (if NMS is fluorescent)
- 14.4.9 Evaluate intracellular targeting by 2D fluorescence microscopy if confocal microcopy is unavailable

14.5 Choose zeta potential

A. Determine required zeta potential for outer/inner layers

B. Determine pH of encountered microenvironments

C. Determine ionic strength of encountered microenvironments



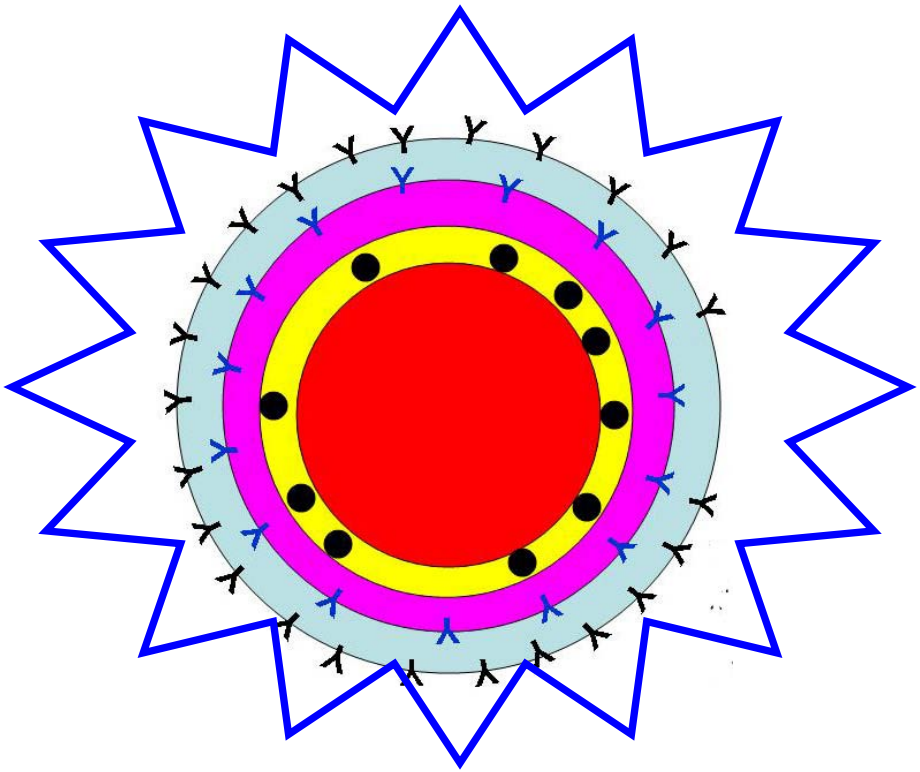
Choose zeta potential

14.5 Choose zeta potential

- 14.5.1 Determine required zeta potential for outer/inner layers
- 14.5.2 Determine pH of encountered microenvironments
- 14.5.3 Determine ionic strength of encountered microenvironments
- 14.5.4 Evaluate suitability of zeta potential
- 14.5.5 If agglomeration, modify zeta potential of NMS.
- 14.5.6 Are the NMS sticking to any surfaces or cell types?
- 14.5.7 Are the NMS rapidly filtered by the kidneys in-vivo?

14.6 Choose stealth molecule

A. Determine required time of circulation



Choose stealth molecule

14.6 Choose stealth molecule

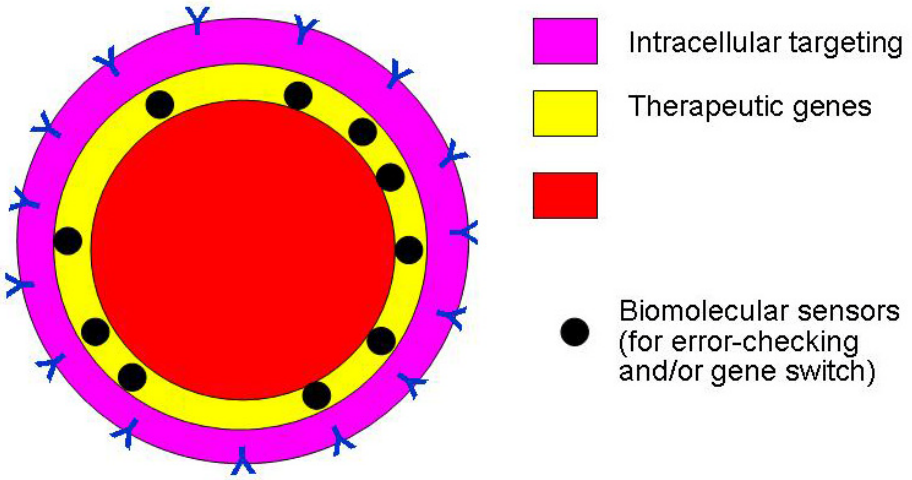
- 14.6.1 Determine required time of circulation
- 14.6.2 Circulation time will determine dose needed
- 14.6.3 Evaluate effectiveness of stealth molecule
  - 14.6.3.1 Do the NMS show signs of protein deposition in-vitro or in-vivo?
  - 14.6.3.2 Are the circulation times of the NMS adequate to sufficiently target the diseased cells in-vivo?

14.7 Choose type and intracellular target of therapy

A. Eliminate or fix the diseased cells?

B. If choice is elimination, choose appropriate therapeutic molecule that will accomplish this action

C. If choice is to fix the diseased cells, what therapeutic molecule can accomplish this action



Choose type and intracellular target of therapy

14.7 Choose type and intracellular target of therapy

14.7.1 Eliminate or fix the diseased cells?

14.7.2 If choice is elimination, choose appropriate therapeutic molecule that will accomplish this action

14.7.3 If choice is to fix the diseased cells, what therapeutic molecule can accomplish this action and how will it be controlled?

14.7.4 Choose molecular measure of effectiveness of therapy (induced apoptosis, restoration of normal phenotype…)

14.7.5 Use single cell analysis by flow cytometry to measure that molecular measure, if cells are in suspension.

14.7.6 Use scanning image cytometry to measure that measure, if cells are attached

A few final words on NMS design

14.8 A few final words on design of integrated nanomedical systems

14.8.1 We are still in the early days of designing NMS. Some of the necessary feedback we need for better designs awaits early clinical trials on human patients and volunteers

14.8.2 We do not understand some of the processes well enough to fully control their design. Still it is important to know what is important even if can not yet control it!