Lecture 14: Designing and Testing Integrated Nanomedical Systems

14.1 Introduction to integrated designs
   14.1.1 “Total design” but there is some order in the design process
   14.1.2 A brief outline of the total design process

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
   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)

14.4 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 microscopy is unavailable
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 signs of 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 being rapidly filtered by the kidneys in-vivo?

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 target the diseased cells in-vivo?

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
   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, etc.)
   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 molecular measure attached cells

14.8 A few final words on design of integrated nanomedical systems
   14.8.1 We are still in the early days of designing nanomedical systems. 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!
References


