How does Nanoparticle Design Affect Targeting Selectivity: Computer Modeling

S. Wang* and E. E. Dormidontova**

*Department of Chemical Engineering, University of Michigan,
Ann Arbor, MI, USA, wshihu@umich.edu
**Institute of Materials Science and Physics Department, University of Connecticut, Storrs, CT, USA,
eed@ims.uconn.edu

ABSTRACT

One of the active areas in the development of modern nanomedicine is the application of polymer tethered nanoparticles for drug/gene delivery and imaging. The optimal nanoparticle design for targeting one type of cell may be quite different from that for another cell and will depend on the density, distribution and mobility of receptors. Computer modeling allows a systematic investigation of multiple nanoparticle design factors and provides a unified platform for the comparison of the efficiency of different nanoparticles. We investigate the dominant factors influencing selectivity of nanoparticle-cell surface interactions and make predictions regarding the favorable nanoparticle design for achieving nanoparticle attachment to cells with high receptor density while sparing healthy cells with low density of receptors. Based on the obtained data, we make experimentally testable predictions regarding enhancement of selectivity of nanoparticle-cell surface interactions by optimization of the nanoparticle design.

Keywords: nanoparticle, targeting, selectivity, ligand-receptor interactions, computer modeling

1 INTRODUCTION

One of the areas of active development of modern nanomedicine is application of polymer tethered nanoparticles for drug/gene delivery and imaging. [1] To achieve recognition of specific cells nanoparticles are functionalized by ligands, aptamers or antibodies capable of specific interactions with cell surface receptors. The optimal nanoparticle design for targeting one type of cell may be quite different from that for another cell and will depend on the density, distribution and mobility of receptors. Computer and theoretical modeling allows a systematic investigation of the influence of multiple factors and provides a unified platform for the comparison of the efficiency of different nanoparticles. [2-4] Ideally, for the best therapeutic/imaging results one wants to achieve the situation when there is no (or very small) nanoparticle adsorption to benign cells (with low receptor densities) and there is a significant nanoparticle accumulation at targeted cells with high receptor density, which corresponds to an abrupt increase in affinity in excess of some critical onset value of receptor density, ρ_{onset} (Figure 1). So far the search for improved nanoparticle selectivity has been directed toward better matching of targeting groups to specific receptors. Considerably less attention has been paid to the nanoparticle design, which is much easier to control and understanding how the design can influence the selectivity of targeting becomes increasingly important as development of nanoparticulate formulations progresses from the laboratory stage to clinical testing.

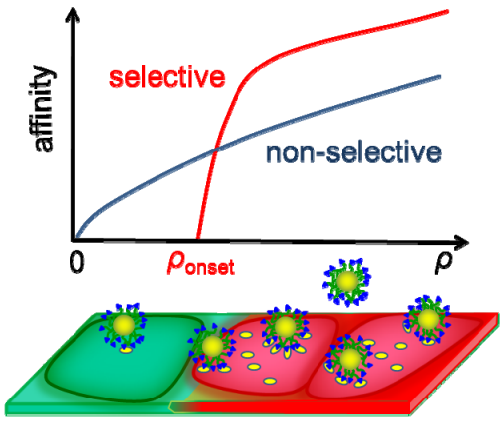

Figure 1: Schematic presentation of nanoparticle affinity to cell surfaces with different receptor densities ρ. The onset of adsorption is indicated.

2 SIMULATION DETAILS

We use Monte Carlo simulations to investigate the interactions between (solid-core) spherical nanoparticles grafted with flexible tethers carrying targeting groups at their distal end and receptor surfaces containing different densities of mobile receptors. The simulation methodology, as described in ref. 3, accounts for both the enthalpic gains from ligand-receptor interactions and the entropic loss for a nanoparticle (including conformational changes for ligand-bearing and free tethers) in the vicinity of a cell surface and the translational entropy loss for receptors gathering on the cell surface in the vicinity of a nanoparticle. The minimum of the free energy of nanoparticle-cell surface interactions ΔF_{min} obtained as a function of separation distance between the nanoparticle and cell surface is related to the equilibrium nanoparticle binding constant $K_{bind}=\exp(-\Delta F_{min}/kT)$, (with k being the Boltzmann constant and T the

temperature), which can be taken as a measure of the nanoparticle affinity to a cell surface. By comparing nanoparticle affinities for cell surfaces with different receptor densities, we can investigate the influence of nanoparticle design (e.g. size, tether length, density, ligand type, etc) on its targeting selectivity.

3 RESULTS

Using computer modeling we investigate the influence of the nanoparticle properties (nanoparticle size, polymer tether length and density, ligand density and valence) on selectivity of nanoparticle-cell surface interactions and make predictions regarding favorable nanoparticle design for achieving nanoparticle attachment to cells with high receptor density while sparing healthy cells with low density of receptors. In particular, our results demonstrate that the energy of ligand-receptor interactions affect ρ_{onset} (see Figure 1 above) in an exponential manner:

$$\rho_{onset} \sim \exp\left(-\frac{E_{bind}}{kT}\right) \qquad (1)$$

confirming that strong ligand receptor interactions can be counter-productive in achieving selectivity [1,2] (Figure 2).

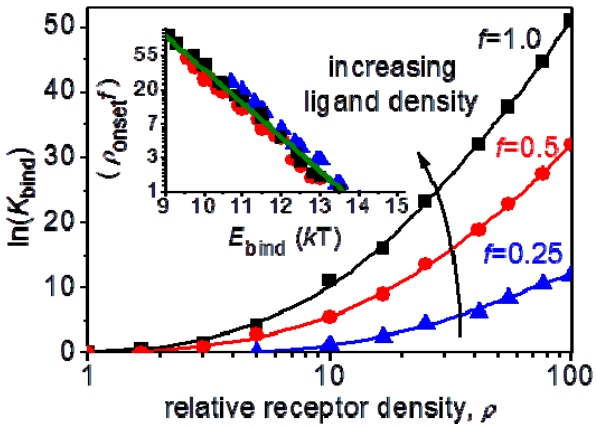

Figure 2: Results of computer simulations for the relative density of cell receptors ρ (normalized by the smallest receptor density considered) for spherical nanoparticles with core radius of 10nm with 128 flexible tethers (with free tether end-to-end distance R_{end}=10nm) for different fractions of ligated tethers, f: f=1.0 (squares), f=0.5 (circles) and f=0.25 (up triangles) at ligand-receptor binding energy E_{bind}=14kT. Inset: The relative receptor density at the onset of nanoparticle binding, ρ_{onset}, multiplied by the fraction of ligated tethers, f, as a function of ligand-receptor binding energy E_{bind}.

We show that an increase in ligand density (n_{lig}), which can be achieved by varying different nanoparticle design parameters, such as nanoparticle size, number of ligands or tethers, decreases ρ_{onset} in an inverse manner

$$\rho_{onset} \sim \frac{1}{n_{lig}} \qquad (2)$$

Taking into account these two dependences, the onset of binding for a range of nanoparticles can be merged into a single curve (Figure 2, inset). These results demonstrate that by employing a large density of ligands with high binding energy E_{bind} one ensures high nanoparticle affinity, but can compromise targeting selectivity and lead to undesirable interactions with benign cells, as the critical receptor density at the onset of nanoparticle binding ρ_{onset}, becomes quite low.

Thus the question is how to achieve targeting selectivity while maintaining sufficient affinity? One solution which is actively employed in nature is to use a large number of weakly-interacting ligands, such as carbohydrates. Indeed, an increase in ligand density results in an inversly proportional decrease of ρ_{onset} (eq.2) while a decrease of the interactions energy exponentially increases ρ_{onset} (eq.1) and hence dominates the effect. One can further improve the result by specifically designing nanoparticles to carry a sufficiently large number of weakly interacting ligands and at the same time maintaining a relativly low ligand density, as the ligand density n_{lig} affects the onset of binding (eq. 2) and hence the selectivity [4], while number of (available) ligands influences the number of bound ligand-receptor pairs and hence determines the nanoparticle affinity to cell surfaces with a large density of receptors. To this end one can employ nanoparticles with a larger core size or longer tethers or use multivalent ligands.

While currently available experimental data for the binding onset or even for the nanoparticle affinity are too limited to construct the corresponding dependences as a function of nanoparticle design or receptor density dependences to directly compare with our results, experimental development will likely produce such data during the next decade and our results can serve as guidance in this process.

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