Title: Physiologically Validated Models for Adhesion of Functionalized Nanocarriers to Endothelium in Targeted Drug Delivery

Authors: N. Ramakrishnan, Jin Liu, Portonovo S. Ayyaswamy, David M. Eckmann, Vladimir Muzykantov, Ravi Radhakrishnan

University of Pennsylvania, Philadelphia

PATargeting nanocarriers (NCs) loaded with drugs and probes to precise locations in the body may improve the treatment and detection of many diseases. Generally, to achieve targeting, the surface of the NC is coated with affinity ligands to enhance binding to molecules present on the cells of interest. Optimization of ligand density is a critical parameter in controlling NC binding to target cells [1,2]. Other tunable properties include NC size and shape, surface chemistry (e.g., tethers of various lengths and stiffnesses) and deformability (such as gel-based NCs) [1,2].Our objective is to develop a computational platform for modeling the targeting of functionalized NCs to optimize experimental design protocols for drug delivery. Recently we introduced a computational methodology based on Monte Carlo and the weighted histogram analysis method to calculate the absolute binding free energy between functionalized NC and endothelial cell surfaces [3]. The calculated NC binding free energy landscapes have been validated against measurements performed in vivo as well as in cell-culture experiments. The effect of antibody surface coverage of NC on binding has been studied using the model that accounts for physiological factors such as hydrodynamic forces (e.g., shear stress) and resistance due to glycocalyx layers [4,5]. We validated the simulations against three distinct classes of experiments: in vivo targeting in mice, targeting in cultured cells under flow, and binding assays using Atomic Force Microscopy [3-5].While higher ligand density always leads to higher binding avidity, it is not always the most effective. In a recent study, we investigated how NC avidity affects targeting to the pulmonary vasculature comparing NC binding to quiescent endothelium and inflamed endothelium. Expectedly, NC avidity was controlled by ligand density, with the higher avidity NCs demonstrating greater pulmonary uptake than lower avidity NCs in both naive and pathological mice. However, in comparison with high-avidity NCs, low-avidity NCs exhibited several-fold higher selectivity of targeting to pathological endothelium. This finding was translated into a Positron Emission Tomography imaging platform that was more effective in detecting pulmonary vascular inflammation using low-avidity NCs. Our computational modeling revealed that elevated expression of ICAM-1 on the endothelium is critical for multivalent anchoring of NCs with low avidity, while high-avidity NCs anchor effectively to both quiescent and activated endothelium. These results provide a new paradigm whereby computational model predictions are used to optimize NC targeting in pathological vasculature. In current work, we are developing multiscale computational strategies to incorporate NC adhesion to live cells, where membrane compliance and fluidity play dominant roles. In particular, we investigate the explicit effects of membrane stiffness and deformation on the NC adhesion landscape.

References

1. Dynamic factors controlling carrier anchoring on vascular cells, T. N. Swaminathan, J. Liu, B. Uma, P. S. Ayyaswamy, R. Radhakrishnan, D. M. Eckmann, IUBMB Life, 2011, 63(8):640-647. Pubmed ID: 21721099
2. Dynamic factors controlling targeting nanocarriers to vascular endothelium, D. M. Eckmann, R. Radhakrishnan, V. Muzykantov, R. Radhakrishnan, D. M. Eckmann, Current Drug Metabolism, 2012, 113, 70. Pubmed ID: 22292809.
3. A Computational Model for Nanocarrier Binding to Endothelium Validated Using In Vivo, In Vitro, and Atomic Force Microscopy Experiments, J. Liu, G. E. R. Weller, B. Zern, P. S. Ayyaswamy, D. M. Eckmann, V. Muzykantov, R. Radhakrishnan, Proceedings of the National Academy of Sciences, 107(38), 16530-16535, 2010. Pubmed ID: 20823256.
4. Multiscale Modeling of Functionalized Nanocarriers in Targeted Drug Delivery, J. Liu, R. P. Bradley, D. M. Eckmann, P. S. Ayyaswamy, R. Radhakrishnan, Current Nanoscience, 2011, 7(5): 727-735. Pubmed ID: 22116782.
5. Multivalent binding of nanocarrier to endothelial cells under shear flow, J. Liu, N. J. Agrawal, A. Calderon, P. S. Ayyaswamy, D. M. Eckmann, R. Radhakrishnan, Biophysical J., 2011, 101(2):319-326. Pubmed ID: 21767483
6. Reduction of nanoparticle avidity enhances the selectivity of vascular targeting and PET detection of pulmonary inflammation, B. J. Zern, A.-M. Chacko, J. Liu, C. F. Greineder, E. R. Blankemeyer, R. Radhakrishnan, V. Muzykantov, ACS Nano, 7(3), 2461-2469, 2013."