**Biophysically inspired model for functionalized nanocarrier adhesion to cell surface and the development of next-generation pharmacokinetic models**

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A functionalized nanocarrier (NC) adheres to its target cell through the multivalent interactions of its surface ligands with their corresponding cell surface receptors. The binding efficacy of the NC is governed by a complex set of physico-chemical and physiological parameters, that include its shape, size, and surface chemistry, the receptor expression levels, the chemical composition and the mechanical state of the target cell membrane, and the flow conditions and the thickness of the glycocalyx layer in the vicinity of the target site. Rational design and optimization of functionalized NCs require a fundamental understanding of the interplay between these seemingly disparate factors.

We have developed a mechanistic, thermodynamics based, cellular scale computational framework to study NC adhesion to live cells [1]. This framework significantly improves over existing computational models by also accounting for the mechanical properties of the target cell membrane. We explicitly account for the presence of the cell membrane in order to mimic an *in vivo* like mechanical microenvironment for NC adhesion. Despite being a cellular scale model, we retain the molecular nature of the receptor-ligand interactions which allows us to precisely compute the entropic contributions to binding efficacy. Additionally, in order to compare our model results with *in vivo* experiments, we have also developed a three compartment pharmacokinetic/pharmacodynamic (PK/PD) model that explicitly accounts for the effects of targeting on the biodistribution of NCs.

We have investigated how mechanical parameters, such as the membrane stiffness and the membrane excess area, are key effectors of the binding efficacy of a ICAM-targeted spherical NC. We present comprehensive results for the binding efficacy and demonstrate the interplay between the expression levels of the receptor, the ligand density, and the mechanical properties of the cell membrane. Our studies show that cell membranes with bending rigidity in the range 20-40 KBT and excess areas in the range 15-30% are highly optimal for NC binding. The computational estimates for the biodistribution of ICAM-targeted NCs for five different organs in mouse show excellent agreement with *in vivo* experimental data. Using our computational framework, we developed a mechanism based pharmacokinetic model, using which we present predictions for ICAM biodistributions in humans. We have employed the NC adhesion model, along with pharmacokinetic framework, to delineate the mechanisms that govern enhanced targeting of ICAMs over PECAMs in lungs affected by Acute Respiratory Disorder Syndrome (ARDS) [2].

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**References:**

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