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Designing high specificity anti-cancer nanocarriers by exploiting non-equilibrium effects KONSTANTINOS TSEKOURAS, Cal Poly, IGOR GONCHARENKO, New Economic School, MICHAEL COLVIN, UC Merced, KERWYN HUANG, Stanford University, AJAY GOPINATHAN, UC Merced — Although targeting of cancer cells using drug-delivering nanocarriers holds promise for improving therapeutic agent specificity, the strategy of maximizing ligand affinity for receptors overexpressed on cancer cells is suboptimal. To determine design principles that maximize nanocarrier specificity for cancer cells, we studied a generalized kinetics-based theoretical model of nanocarriers with one or more ligands that specifically bind these overexpressed receptors. We show that kinetics inherent to the system play an important role in determining specificity and can in fact be exploited to attain orders of magnitude improvement in specificity. In contrast to the current trend of therapeutic design, we show that these specificity increases can generally be achieved by a combination of low rates of endocytosis and nanocarriers with multiple low-affinity ligands. These results are broadly robust across endocytosis mechanisms and drug-delivery protocols, suggesting the need for a paradigm shift in receptor- targeted drug-delivery design.

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