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Has the Time for *In silico* Design of Nanomedicines Finally Arrived?

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Cancer therapy and diagnostics are among the most appealing and well-studied applications of nanomedicine (a recent PubMed query of "nanoparticle delivery+ tumor" returned over 2,400 hits). Targeted drug delivery is based on the notion that nanoparticles (NPs) could be designed to overcome chemotherapy's systemic toxicity by specifically penetrating tumor tissue and delivering drugs directly to the cancer cells. The delivery of medications to a majority of cells at the primaryand metastatic sites is of critical importance to the success of such chemotherapeutics.However, as noted recently by Bae and Park in their excellent recent perspective in the *Journal of Controlled Release* [1], efficient delivery of these drugs to tumors has yet to be achieved. The authors provide multiple reasons for the lack of success of targeted NPs, including:

1. Tumor heterogeneity;
2. Tumor penetration and diffusion problems;
3. An insufficient number of targetable cell receptors;
4. Unfavorable nanoparticle pharmacokinetics, where >95% of the injected dose is wasted due to NP uptake by immune organs.

How are we to solve these apparently challenging problems? One potential approach is that of the Ruoslahti and Tuveson groups, which recently used Hedgehog inhibitors [2] and Neuropilin-1 agonists [3] to improve tumor penetration by exploiting biological mechanisms. These strategies resulted in a remarkable enhancement of tumor penetration by NPs and drugs. Similarly, cancer genomics and proteomics provide enormous amounts of information on tumor markers and receptors, which could be exploited for targeting multiple populations inside the tumor, including tumor macrophages, stromal cells, and stem cells. Significant progress has been made in understanding the interactions of NPs with the biological milieu and the effect of these interactions on the clearance of nanoparticulates.

Next we might ask: How can the nanomedicine field take advantage of this vast pool of knowledge? Usually, the development of NP formulations for in vivo targeting requirestedious and costly empirical optimization studies involving a large number of animals and laborious matrix testing of formulations. We argue that this stage of nanotechnology development can be rightly compared with the small molecule drug development practices of around 20–30 years ago, when the main strategy was the extensive and expensive high- and not-so-high-through put searches of all possible compounds to fit the necessary target. Some simplistic general ideas were frequently used for the selection of specific searches and compounds pools. However, truly dramatic changes in the small molecule drug design arose mostly due to the wide use of bioinformatics and molecular modeling tools. By analogy with a small molecule design strategy called lead optimization, the main goals of nanoparticle design would be to achieve high affinity binding to the target, avoidance of rapid metabolism, and reduction intoxicity.

A number of questions arise when we discuss such possibilities. For example, could nanoparticle affinity to the tumor cell receptors be improved by *in silico* design? NP-receptor binding is a complex interaction, much more complex than a small molecule-receptor interaction. Let's discuss as an example the binding of a vascular endothelial growth factor (VEGF)-coated NP to the VEGF receptor2 (Figure 1). It is apparent that NP parameters including shape, size, ligand density,surface coating and linker type play a critical role in the affinity and avidity to the cell surface receptors. It is thus possible to imagine that a three-dimensional structure of the NP surface with bound ligands could be modeled, with the attendant computational chemistry and biology approaches applied to improve docking of NPs to the receptors. Initial NP screening could be followed by the "lead optimization"*in silico*.

In order to improve NP pharmacokinetics,computer-aided design could be used to optimize the particles' surface parameters. The current paradigm in nanomedicine design is to coat NPs with a bioinert polymer, usually polyethylenoxide (PEG), and on top of it to conjugate a targeting ligand, usually an antibody, peptide, or an aptamer. The function of PEG is to mask the particles and to make them

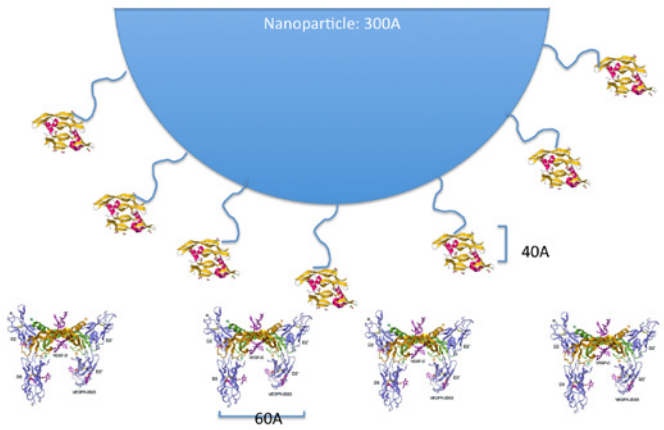

Figure 1: Interaction of NP with tumor-specific membrane receptors. A 30 nm nanoparticle is coated with VEGF molecules (4nm size) . The interaction with VEGFR2 molecules (only one domain of the receptor with the binding pocket is shown) is determined by a variety of nanoparticle parameters including surface charge, size, shape, linker type and ligand density.

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invisible to the body macrophages, which remove the particles from circulation prematurely. Unfortunately, this steric polymer coating often interferes with the NPs' ability to bind to their target. Computer modeling of protein-NP and macrophage receptor-NP interactions could be performed in order to optimize NP surface properties to avoid opsonization and premature clearance. Of course, such an approach needs to be validated in well-controlled *in vitro* and *in vivo* studies.

Some other exciting applications of computational methods in nanomedicine could be design of small targeting ligands instead of bulky antibodies for targeting NPs to tumor epitopes, and virtual screening of NP libraries for tumor targeting.

In summary, numerous resources and efforts are currently wasted on *in vitro* and *in vivo* optimization of NPs. Harnessing the power of supercomputing and drug design will permit faster progress toward achievement of the most importantgoal of nanomedicine: eradication of cancer.

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