When It Comes to Drug Delivery, Size Matters

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(PhysOrg.com) -- One of the great promises of nanotechnologies lies in its ability to create drug-containing nanoparticles decorated with targeting molecules that recognize and bind to cancer cells, providing drug delivery only at the site of the targeted cells. Such site-specific drug delivery would not only boost the cancer-killing activity of a drug payload but also reduce potential side effects by greatly restricting or even eliminating the amount of drug reaching healthy tissue.

It turns out, though, that not all targeting agent-nanoparticle combinations are able to reach and enter their targets with equal effectiveness. To help bring some rationality to the process of designing targeted drug delivery agents, K. Dane Wittrup, Ph.D., and graduate student Micheal Schmidt of the Massachusetts Institute of Technology have developed a mathematical model that predicts the magnitude and specificity of tumor uptake of drug delivery vehicles ranging in size from small peptides to large liposomes. This work was published in the journal *Molecular* Cancer Therapeutics.

The model developed by the Schmidt and Wittrup, who is a member of the MIT-Harvard Center of Cancer Nanotechnology Excellence, accounts for the size of a particular drug delivery agent and a variety of easily measured properties, including how readily it crosses biological barriers and how tightly it binds to a target in test tube experiments. The researchers note that despite the simplicity of their model, it accurately predicts the behavior of HER2-targeted constructs in a mouse model of cancer and of CEA-targeted constructs in humans. In fact, it appears that

size and target affinity account for most of the variability in tumor uptake.

One interesting prediction that the model makes is that large constructs, such as nanoparticles, and small ones, including targeting peptides, will deliver more drug into a tumor than will medium constructs, such as engineered antibody fragments. However, the model also predicts that delivery to tumors by nanoparticles over 50 nanometers in diameter will not improve much when targeting agents are aded to the nanoparticles.

This work, which is detailed in a paper titled, "A modeling analysis of the effects of molecular size and binding affinity on tumor targeting," was supported by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. An abstract of this paper is available at the journal's Web site.

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