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# Lean and Mean: Nanoparticle-Based Delivery Improves Performance of Cancer Drugs

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Very few drugs are potent enough to fight tumors yet gentle enough on the body. To this eternal dilemma of cancer therapy, nanotechnology offers a solution: hide the drug inside tiny packages that break open only when they reach the tumor. The drug will then attack only the tumor, not healthy cells, making it both safer and more effective. Although this idea of nanoparticle-based drug delivery is in an early stage, it has already spawned a vast range of new formulations. A handful of them are in clinical use and dozens of others are in various stages of development. "Nanotechnology is opening up a whole series of new platforms for cancer therapeutics," says Anthony Tolcher, MD, of South Texas Accelerated Research Therapeutics, a group in San Antonio that specializes in phase I clinical trials of cancer drugs. "This is clearly the most exciting time in oncology drug development."

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Nanoparticle-based delivery exploits the so-called enhanced permeability and retention (EPR) effect associated with tumors. The idea is to infuse the nanoparticles into the bloodstream, and allow them to seep out of the leaky blood vessels in tumors and release their drug inside the tumor tissue. For this "passive targeting" to work, the particle has to meet several criteria. It has to circulate in the blood for a sufficient period, which implies a long plasma half-life and low clearance rate. It should be stable—but not too stable—for it to remain intact in the blood but break open inside the tumor. Thus, the particle's size becomes critical: if it's too small, it will quickly pass into the kidneys and be eliminated before it can get to the tumor, whereas if it is too large, it can't get into the tumor. Nanoparticles with a diameter in the 10–100 nm range work best, says Mark Davis, PhD, of the California Institute of Technology, who has designed several nanoparticles including two that are now in clinical trials.

The earliest attempt at building such a particle happened back in the 1960s, when a team of researchers led by Alec Bangham published a landmark paper on unilamellar vesicles of phospholipids, now called liposomes (Bangham et al., 1965). These forerunners of modern nanoparticles self-assemble from a lipid bilayer into microscopic bubbles that are hydrophilic outside and hydrophobic inside. Bangham described them in a later essay as "pharmacological punching bags" that could perform miracles (Bangham, 1989). Their potential for drug delivery was obvious: the water soluble bubbles can encapsulate and deliver a wide range of molecules, including highly insoluble ones. (According to one estimate, poor solubility causes the rejection of nearly one in two trial pharmaceutical compounds, especially those of natural origin.) Although early liposomes disintegrated easily, scientists soon developed methods to stabilize them. "That was the true beginning of the nanoparticle era," says Davis.

Thanks to their early start, liposomes are used for making three of the four nanoparticle formulations currently approved by the FDA. Among the best known is Ortho Biotech's Doxil, first approved in 1999 for refractory ovarian cancer. The formulation contains the chemotherapy drug doxorubicin encapsulated in a liposome stabilized with a coating of polyethylene glycol. It is reported to have a plasma half-life about 100× higher and clearance rate almost 300× lower than free doxorubicin. Thanks to these attributes, administering the nanoparticle formulation instead of the free drug increases the drug concentration in tumor 10-fold. Another liposome-encapsulated therapeutic that achieves similar pharmacokinetic improvements is NeXstar Pharmaceuticals's DaunoXome, approved in 1996 for Kaposi's sarcoma. Abraxis Bioscience's Abraxane, approved in 1995 for metastatic breast cancer, is a special case: a nanoscale albumin-bound form of the chemotherapy agent paclitaxel, it is not considered a true nanoparticle by some experts, but achieves the same effect of solubilizing its base drug.

Liposomes have several desirable traits. Made from harmless natural materials, they enjoy a long in vivo lifetime and have been successfully used in many pharmaceutical applications. However, as delivery vehicles for cancer drugs, they have performed only modestly, despite encouraging preclinical data. Few have been shown to significantly improve response rate or overall survival compared to the corresponding free drugs. While they do seem to reduce overall toxicity, they appear to introduce new ones in some cases. For instance, in one trial for breast cancer, Doxil reduced cardiac toxicity but increased skin toxicity. Part of the problem with liposomes may be lack of stability, according to Glen Kwon, PhD, an expert on polymeric micelle nanoparticles at the University of Wisconsin at Madison. "Poorly soluble chemotherapy drugs tend to leak out of them before they reach their target," he says. "This makes it hard to achieve the EPR effect." Liposomes also don't offer much scope for precise control over the location and rate of drug release, he adds.

Now a "second generation" of nanoparticle methodologies has emerged, promising better stability, lower toxicity, and greater efficacy. Some deliver multiple drugs, some carry ligands to

actively target tumor cells, some incorporate multiple functionalities, and some incorporate mechanisms to control drug release. The majority of these are based either on polymer-drug conjugates or polymeric micelles, both highly versatile and flexible design strategies. Notable among the former is Cell Therapeutics's Opaxio, a polymer-paclitaxel conjugate featured in more than 20 clinical trials for lung, breast, ovarian, and other cancers. A notable example of polymeric micelle is Samyang's Genexol-PM, another paclitaxel formulation, now in a clinical trial for pancreatic cancer; the drug has already been approved in South Korea. Nearly two dozen other formulations are also in clinical trials.

"We're learning that there's a tremendous amount of subtlety in how you develop these miniaturized delivery systems," says Alan Crane, chief executive of Cerulean Pharma, a startup that is commercializing a second generation nanoscale delivery technology developed by MIT researchers. Crane says it is crucial to be able to control the rate of drug release; some agents work best when released in a sudden burst, while others prefer sustained release. Cerulean's product, Nanocell, incorporates both these release modes. On reaching the tumor, it first discharges a burst of an antiangiogenic agent to destroy the tumor vasculature. It then slowly releases an anticancer compound to destroy the now-isolated tumor. "Nanotechnology allows you to fine tune the release of your drug to whatever profile you are trying to achieve," says Crane. "It allows you to go beyond chemistry and add more functionalities to your drug."

Tumors often develop drug resistance by exploiting natural cellular mechanisms such as efflux pumps to eject drugs before they can act. One way to combat this is active targeting. "The idea is not just to localize the therapeutic in the tumor, but to actively take it into the cell," says Davis. Equipped with the right ligand, a nanoparticle can use the endocytic pathway to enter a tumor cell and can thus bypass the cell surface pump mechanisms of drug resistance. This is particularly beneficial for therapeutics such as siRNAs that have to be delivered and released within the cell. Davis has designed a nanoparticle formulation called CALAA-01 that employs both targeting as well as controlled release mechanisms. Targeting is achieved by transferrin molecules on the particle's surface that bind to the corresponding receptor on cancer cells. Once inside an endocytic vesicle, a chemical sensor in the particle reacts to the ambient acidity to release the payload of about 2,000 siRNA molecules. A phase I trial with this nanoparticle began in May 2008 and is ongoing, says Davis.

Despite these advances, cancer nanoparticles face significant obstacles before they make it to the clinic. Like any new medical entity, they pose safety concerns: for instance, they may provoke an immune response or breach the blood-brain barrier. Evidence for such concerns has so far been minimal, but may emerge as more trials are conducted. And like any new medical entity, nanoparticle-based formulations are likely to be expensive, particularly the more advanced ones. "But by far the biggest challenge is complexity," says Laird Forrest, PhD, an expert in nanoparticle design at the University of Kansas. He fears that many formulations being developed incorporate so many functions and components that they may prove unstable and hard to manufacture on a commercial scale. "The simple truth is most of them are never going to be clinically feasible," he says. "That may be why big pharma hasn't embraced nanotechnology."

Investors, however, have shown more interest. "The field has great potential, although the majority of technologies out there are just incremental," says Nick Wachtel of Lux Capital Management, an early stage venture capital firm that includes Cerulean in its portfolio. Wachtel says that biotechnology groups that simply see nanoparticles as a carrier for their drugs may miss the full potential of the idea. As investors, "we're not interested in something that will address one specific issue for a cancer drug," he says. "We're looking for new ideas, new architectures, clever engineering approaches, technologies that will dramatically impact the whole of drug delivery."

Also on the hunt for breakthrough technologies is the Nanotechnology Institute, a nonprofit based in Philadelphia that assists drug commercialization by promoting industry–university partnerships. "Cancer therapy is still very unfocused, both literally and figuratively," says Anthony Green, PhD, who directs the institute. "By going nano, you can get much more bang for the buck." The institute has invested in several nanotechnology companies including Keystone Nano, a startup that makes a drug-carrying nanoparticle built from a calcium phosphate matrix. Green is not surprised at nanoparticles' modest clinical track record; he likens the present state of the field with the early, setback-plagued days of monoclonal antibodies. "Monoclonals took almost 15 years before the first product was approved," notes Green. "We are maybe only 10 years into nano."

Once nanoparticle-based delivery has matured into a safe, reliable, and practical scheme, it could play a pivotal role in cancer therapy, says Neal Davies, PhD, a pharmacologist at the Washington State University in Pullman who evaluates the safety of nanoparticle-based drugs. "We can dramatically improve the treatment of some cancers, such as pancreatic and primary liver, for which there are not many other options," says Davies. "Looking into my crystal ball, I see the potential for major breakthroughs with this technology."

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