New Nanomedicines May Better Target Tumors

More thoughtful designs could help nanomedicine live up to the hype

Nanotechnology has made a major impact on industry, leading to, for example, batteries that store more energy and solar cell coatings that absorb more light. In theory, scientists can also engineer nanoparticles that carry drug payloads, avoid healthy tissue, and seek out tumors.

“The concept is really beautiful: A drug loaded into a nanoparticle will destroy the tumor with no side effects,” says Warren Chan, PhD, a biomedical engineer at the University of Toronto in Canada. At this point, however, it’s mostly still a concept. “A limited number of nanomedicines have gone through clinical trials,” he says.

Now researchers are trying to apply lessons learned over the past few decades to develop therapies that better target tumors. The key is to go beyond relying on size alone, as in the early days of nanomedicine, and specifically engineer therapies for a particular clinical purpose, says Dean Ho, MS, PhD, a bioengineer at the University of California, Los Angeles.

SIZE ISN’T EVERYTHING

In the late 1990s and early 2000s, scientists reasoned that a drug-carrying nanoparticle of the right size would accumulate in tumors, because tumors are thought to have leaky vessels that let in particles measuring up to about 100 nanometers. Inside the tumor, particles larger than about 4 nanometers tend to get stuck because tumors have poor lymphatic drainage. Researchers have been trying to take advantage of this effect, dubbed enhanced permeability and retention (EPR), to make drug carriers that can’t enter normal tissues but can get into tumors—and accumulate.

Researchers say EPR has been well established in animal models and appears to be a factor in human cancers. The concept has worked for at least one drug: the first-generation nanomedicine Doxil, a lipid nanoparticle loaded with doxorubicin. Its size helps keep it from accumulating in the heart while allowing it to concentrate in tumors.

The reality for most cancers and nanomedicines, however, is far more complex. The immune system detects most of the nanoparticles and carries them to the liver to be cleared from the body. In a 2013 review in ACS Nano, Purdue University (Lafayette, IN) bioengineer Kinam Park, PhD, noted that although experimental nanoparticles tend to stay out of healthy tissue, just 5% of the dose gets to the tumor.

To get higher concentrations of drugs into tumors, researchers are now pursuing more sophisticated nanoparticle designs, says Scott Minick, MBA, president and CEO of BIND Therapeutics in Cambridge, MA. “Making these nanoparticles the right size is necessary, but not sufficient,” he says.

“Successful nanomedicine is also about precise engineering.”

BIND’s nanoparticle technology is based on biodegradable drug-releasing polymers. Like Doxil, the company’s leading candidate, BIND-014, relies on its size and other chemical properties for passive, biophysical targeting. Also, by changing the length, charge, and other qualities of the polymers that make up the carriers, researchers can precisely tune how long the nanoparticle remains in circulation—and control the timing of drug release.

In addition, nanoparticles can be decorated with targeting ligands. BIND-014 incorporates docetaxel and has ligands that bind prostate-specific membrane antigen (PSMA). Minick says they chose docetaxel because it’s a widely used, FDA-approved drug with activity in multiple tumor types, and chose PSMA because it’s on the surface of prostate cancer cells, as well as on the vasculature in other solid tumors.

Researchers are testing BIND-014 in a phase II clinical trial as a first-line therapy for metastatic, castrate-resistant prostate cancer and as a second-line therapy for non–small cell lung cancer.

BEYOND DRUG CARRIERS

Engineered nanomaterials have physical properties that researchers are trying to exploit for cancer therapy. For example, gold nanoparticles have strong interactions with visible and infrared light, effects that can be controlled by changing their size and shape. Researchers can deliver these nanoparticles to the tumor and then illuminate it with a near-infrared laser, an otherwise harmless light source that penetrates tissue well. Light interacts strongly with the surfaces of the nanoparticles, causing them to heat up to temperatures that kill cancer cells.

NanoSpectra Biosciences of Houston, TX, is developing one such photothermal therapy, called AuroLase. It is being tested in primary and metastatic lung cancers, prostate cancer, and certain head and neck tumors.

Cancer imaging also stands to benefit from nanoscale physical properties. For example, Ho wants to make gadolinium-based MRI contrast imaging agents less toxic by combining them with a carbon nanomaterial called nanodiamonds. Gadolinium contrast agents can cause kidney and other problems, limiting how much doctors can use—and the clarity of the images. Nanodiamonds are faceted and their surface charge attracts water molecules. Because the particles interact strongly with water, gadolinium-nanodiamond contrast agents shine more brightly than gadolinium alone.

“We can use potentially 10 to 15 times less gadolinium and it’s still bright—and significantly less toxic,” says Ho, who hopes to test the new agents in the clinic soon.

Admittedly, hype has surrounded nanomedicine, but researchers say the promise is real. Ho says more nanotechnology-enabled therapies and diagnostics should enter the clinic over the next few years. —Katherine Bourzac
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