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Does Nanomedicine Have a Delivery Problem?

Michael Torrice

Experts debate a controversial paper that suggests delivery efficiencies for cancer nanomedicines are low and not improving.

Cancer drugs don't discriminate. They kill all cells, not just the cancerous ones. So drugmakers often look for ways to minimize how much of a chemotherapy drug ends up in healthy tissue while still delivering sustained high levels to tumors.

Nanomedicine offers one possible way to thread this therapeutic needle. Loading nanoparticles with drug molecules can help the compounds stay in the blood longer and accumulate in tumors instead of in healthy tissue.

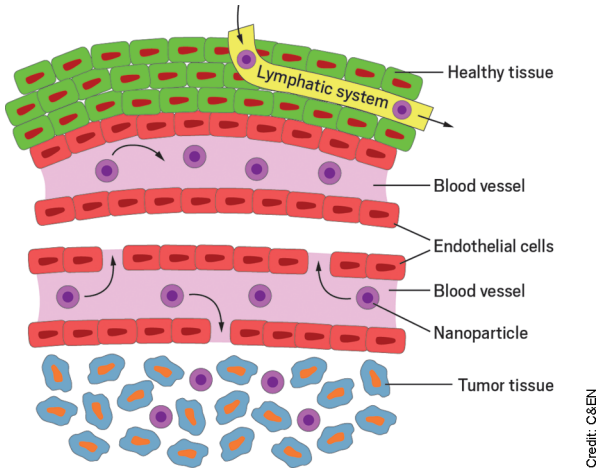
But a recent paper in Nature Reviews Materials questions how effectively current nanoparticles target drugs to tumors.

The authors reviewed the nanoparticle delivery literature from the past decade and estimated that the median delivery efficiency is low—only 0.7% of an injected dose of nanoparticles ends up in a tumor. This low efficiency, the authors argue, is a hurdle for translating nanomedicines into the clinic. They propose a 30-year plan to study the delivery problem in detail to help improve efficiency.

"The paper has caused quite a storm," says Scott E. McNeil, director of the Nanotechnology Characterization Laboratory (NCL) at the U.S. National Cancer Institute.

McNeil and other experts working on nanoparticle cancer therapies say the paper's analysis neglects some critical factors in evaluating nanomedicines and, as a result, doesn't accurately depict the state of the field. These scientists don't see a delivery efficiency crisis thwarting the development of new cancer nanomedicines. Instead, they believe the field has already produced effective therapies and will continue to produce new ones in far fewer than 30 years.

It was more than 20 years ago when the U.S. Food & Drug Administration approved the first nanoparticle drug Doxil. Doxil encapsulates the cancer drug doxorubicin in a lipid sphere called a liposome. Since that decision in 1995, FDA has approved several other nanoparticle formulations.



The enhanced permeability and retention (EPR) effect is supposed to help nanoparticles accumulate in tumors. Because of their size, the particles cannot slip between endothelial cells lining normal blood vessels (top). But tumor tissue often contains leaky vessels that allow nanoparticles to sneak through (bottom), according to EPR theory. Unlike in healthy tissue, tumors lack efficient drainage by the lymphatic system, and this slows the clearance of nanoparticles.

These nanoparticles improve the fate of their drug cargo in several ways. Because of their size—typically in the 10- to 100-nm diameter range—nanoparticles can't easily squeeze between tightly packed cells lining blood vessels and slip out of the bloodstream into surrounding tissue. This property, along with others, allows drug molecules encapsulated in or attached to the particles to hang around longer in the bloodstream, giving them a greater chance of reaching a tumor. Also the drug is less likely to interact with healthy tissue and cause unwanted toxicity.

Many in the field think that the particles accumulate in tumors via a phenomenon called the enhanced permeability and retention (EPR) effect. Blood vessels feeding tumor tissue tend to be leaky. This allows particles to pass into the tumor more easily than into other tissues, the EPR theory says. Once inside the cancerous tissue, the particles clear out slowly because, unlike healthy tissue, tumors typically lack effective drainage by the lymphatic system.

Though some drugmakers develop nanoparticles to passively accumulate in a tumor via this EPR effect, they design others to target tumors actively with small molecules,

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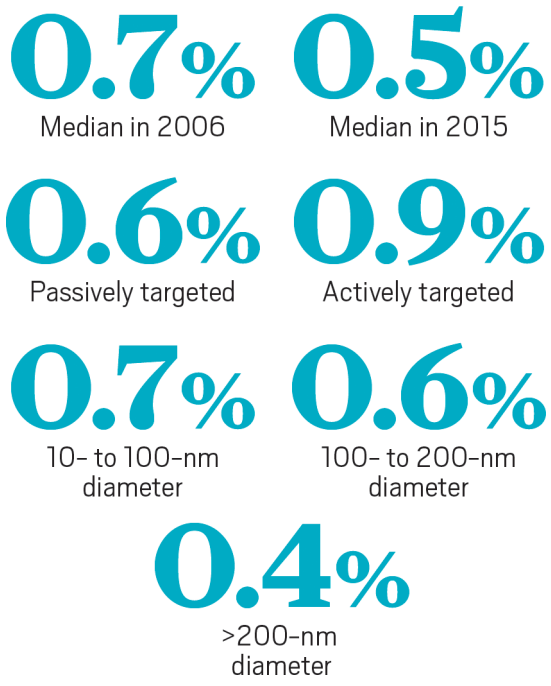

Chan's analysis of the nanomedicine literature reveals small differences in median particle delivery efficiencies over time, by targeting method, and by size. Credit: *Nature Reviews Materials*.

peptides, or antibodies that decorate their surfaces. The decorations are supposed to allow the particles to bind to specific biomolecules on the surfaces of cancer cells.

In his lab, Warren C. W. Chan of the University of Toronto, the new review's senior author, has been studying how changing the design of nanoparticles—such as their size, shape, and surface chemistry—affects how well the tiny therapeutics target tumors. He has found that some of the field's prevailing assumptions about how to improve targeting don't always hold true. These discoveries led Chan and his colleagues to question how targeting actually works and to write the recent review analyzing the state of nanoparticle delivery.

"What this paper did was allow us to provide some perspective on where the field is at," he says. "Because once you know where the field is at, it's easier to try to improve it."

To perform the analysis, Chan and his colleagues used SciFinder and Google Scholar to comb through the scientific literature for the search term "nanoparticle delivery." After winnowing the results, the team was left with 117 papers published between 2005 and 2015 that involved animal studies and had sufficient data on nanoparticle distribution and kinetics.

The scientists looked for data on the concentration of nanoparticles in the animals' tumors over the course of the experiments. More than half of the papers didn't have all the information Chan and his team needed, so they contacted each study's authors to get the missing data. The researchers then calculated the percent of the injected particle dose that ended up in the tumor for each study—the delivery efficiency.

The median efficiency across all 117 studies was 0.7%—meaning out of every 1,000 nanoparticles injected into an animal, only seven accumulate in a tumor.

"It was really surprising," Chan says. He assumed it would be between 5 and 10%, which he thinks is still low, but which would have been in line with what his lab achieves with inorganic particles.

When Chan and his team looked across the 10 years, the median efficiency didn't improve over time. They did see some small differences based on the design of the particles. For example, inorganic particles were slightly more efficient than those made from organic materials—0.8% versus 0.6%. And particles that employed active targeting had a higher efficiency than those that relied on passive targeting—0.9% versus 0.6%. But, Chan says, "if you take a step back and look at it at from a 1,000-foot view, it seems there aren't many differences."

Andre Nel, chief of nanomedicine at the University of California, Los Angeles, wasn't surprised that delivery efficiencies were low. Still, Nel thinks the paper will have a big impact on the field: "It forces us to think through all of the deliberate aspects that need to be addressed to make nanotherapeutics for cancer a reality." For instance, he wonders whether looking more closely at the data might highlight particle designs that have higher efficiencies in certain tumor types.

However, some experts not only question whether the 0.7% figure is an accurate portrayal of the state of the field but also think that, in the proper context, 0.7% isn't actually low.

NCL's McNeil says FDA and nanomedicine developers don't judge delivery systems on the accumulation of nanoparticles in tumors. Instead, they follow the drug itself to calculate standard pharmacokinetic parameters, such as drug half-life in the blood and maximum concentrations in the tumor. "That's how you evaluate drugs, not by number of particles present in the tumor," McNeil explains.

C&EN contacted scientists at a few companies who have developed nanomedicines that have been approved or are currently in clinical trials. For these particles, drug delivery efficiencies are closer to 10% than 0.7%, according to the scientists. For example, Lawrence Mayer, the founder, president, and chief scientific officer at Celator Pharmaceuticals, says in his 20 years working on nanomedicines he hasn't seen a particle smaller than 100 nm that had a drug delivery efficiency below 2%. Above 100 nm, efficiencies begin to drop off.

He points out that nanoparticles can have fairly variable drug delivery efficiencies. So, if the data Chan's team

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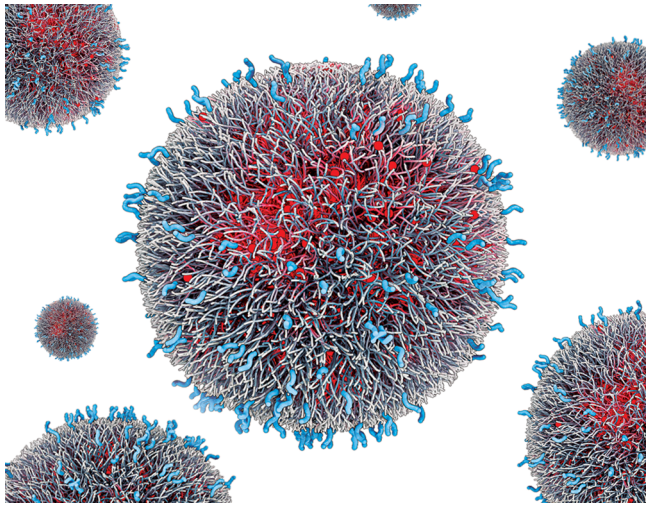

BIND-014 nanoparticles target tumors actively through small molecules (blue) that can bind to proteins on cancer cells or on the blood vessels feeding tumors. The polymer (gray) particles encapsulate anticancer drugs (red) such as docetaxel. Credit: Gaël McGill/Digizyme.

analyzed had similar variability, strong-performing systems may have been lost among the many weaker ones. Mayer compares the paper's analysis to describing vehicle gas mileage over the past decade with a single number—looking at data for all cars, from 2006 4×4 pickup trucks to 2015 hybrids, "and then putting a number in the sand in the middle."

But the bigger issue, Mayer and others say, is that the 0.7% number isn't put in the proper context in the review. Chan's team didn't compare the drug delivery efficiencies with those of the nanoparticle-free drugs, they point out. The whole goal of cancer nanomedicines, the experts say, is to get greater drug accumulation in a tumor with the particles than without them. When drug developers compare their particles with free drugs, they find that the naked drug molecules accumulate with efficiencies that are one-tenth to one one-hundredth the median efficiency reported in the review.

Chan responds that the point of the review wasn't to compare nanoparticles with small molecule drugs. The point was to test assumptions about how nanoparticles work. "The assumption in the nano field is that you can design a particle that can effectively target and deliver a payload to a tumor," he says. "That's what we're testing." By putting a number on that assumption, Chan says, researchers can start to improve it.

Still, in the review, Chan and his coauthors express concern about how the calculated low particle delivery efficiency may impede translation of nanomedicines into the clinic. Through a back-of-the-envelope calculation, the authors demonstrate that a dose of particles with a delivery efficiency of 1% would need to be impractically large to be effective at killing cancer cells. Manufacturing nanoparticles on a scale needed for such doses could be difficult, Chan says. And injecting such a large amount of drug into a patient could lead to toxicity issues. On the basis of these considerations, he says efficiencies should be closer to 10% to achieve therapeutic efficacy.

He and his colleagues start the final paragraph of their review with a pointed assessment of the field based on their findings: "We must admit that our current approach is broken, and that is why we have not observed significant clinical translation of cancer nanomedicines."

Coincidentally, around the time the review came out, Bind Therapeutics, a company developing actively targeted nanomedicines, filed for Chapter 11 bankruptcy. The firm had recently reported mixed results from a Phase II trial of their product BIND-014, a polymer-based particle that targets proteins on prostate cancer cells or the blood vessels feeding tumors via small molecules.

Jonathan Yingling, chief scientific officer at Bind, says that the company's technology already solves many of the delivery issues outlined in Chan's review. "We believe—and we have data that show—that targeting ligands can impact biodistribution," he says. Yingling adds that when the firm's scientists follow the drug molecule itself, they see greater tumor accumulation with their particles than with the naked drug.

Others in the field also point out that there are companies reporting promising clinical trial data. For example, at the American Society of Clinical Oncology annual meeting in June, Celator presented positive results from a Phase III trial of its liposome product Vyxeos in acute myeloid leukemia patients. At the end of May, Jazz Pharmaceuticals displayed its confidence in the nanomedicine platform by buying Celator for $1.5 billion.

McNeil also dismisses the claim that translation of nanoparticles has been limited. His lab works with nanoparticle developers to do preclinical testing of products. Of the 100-some potential drug candidates the lab has worked on over the past eight years, McNeil says, about 10 have gone on to clinical trials. "That's a pretty good ratio," he says. The preclinical success rate for small-molecule drugs is around two in 100, according to some industry estimates. And a search for "liposome" or "nanoparticles" and "cancer" on ClinicalTrials.gov returns more than 700 open or active clinical trials.

Again Chan points out that his team's goal was much more focused in its scope. "It's not to say that this field is dead," Chan says. "The field is working on certain assumptions, and these assumptions drive the development of the nanoparticle design. It is unclear if the real problems of nanoparticle targeting are being looked at."

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To address what they see as the targeting problem, Chan and his coauthors outlined a 30-year research plan that would fill in critical knowledge gaps and then use that information to design more effective nanoparticle systems. They chose 30 years as a time scale because that is the length of time between the first papers on liposomes published in the mid-1960s and the approval of Doxil.

The first 10 years or so of this plan would focus on questions Chan thinks are standing in the way of designing nanoparticles that target tumors effectively.

One area Chan wants to investigate is how nanoparticles leave tumor vessels and how they then interact with tumor tissue. In the review, he and his coauthors write that the field has designed particles mainly with the EPR effect in mind. They'd like to study the transport of nanoparticles in more detail to explore whether alternative routes, in which particles travel through instead of around endothelial cells lining blood vessels, play a bigger role. The researchers also would like to understand how particle design affects how far these particles then penetrate into tumor tissue.

In addition to nanoparticle-tumor interactions, Chan wants to study how the materials behave in healthy tissues—particularly the liver, spleen, and kidney. These tissues have systems in place to seek out foreign materials and eliminate them from the body. That, of course, affects the ability of a nanomedicine to hang around in the bloodstream. Chan says scientists have a general sense of how these tissues interact with nanoparticles, but the details aren't clear. "We need to start testing hypotheses that have been around 20 to 30 years," he says.

To help organize and catalog the large volume of data necessary for this 30-year plan, Chan has set up the Cancer Nanomedicine Repository, an online and open access database for researchers to deposit the results of their own experiments. Catherine J. Murphy, a chemist at the University of Illinois, Urbana-Champaign, applauds this move. She thinks it will help researchers interested in these fundamental questions to determine what has already been done and what still needs to be studied.

But some nanoparticle developers don't agree that the knowledge gaps Chan highlights are the most important ones for nanomedicine. For example, the field has largely found ways to minimize the number of particles landing in nontarget organs, such as the liver, says Daryl Drummond, vice president of discovery at Merrimack Pharmaceuticals. He argues that those questions were more of a concern 20 years ago. The fact that many particles—including Merrimack's Onivyde product, which was approved by FDA in 2015 for pancreatic cancer—have long half-lives in the body is a testament to solutions developed for the problems Chan listed.

As for the EPR effect, the nanoparticle developers C&EN contacted were more interested in developing ways to measure the extent of the effect in patients. Many acknowledge that the field has engaged in some hand-waving about the EPR effect and that it may not be uniform across all tumors—for example, some tumors may have leakier blood vessels than others.

Merrimack is working on imaging agents that could assist in predicting which tumors have greater susceptibility to the EPR effect. The firm has started testing iron oxide particles for magnetic resonance imaging and liposomes loaded with positron emission tomography contrast agents that would allow doctors to determine how much nanoparticle accumulation occurs in a patient's tumor. Such methods could help screen patients for those most likely to benefit from a nanomedicine.

Another big hurdle in developing nanomedicines is scaling up the synthesis of the particles to meet Good Manufacturing Practice standards required for moving the materials to the clinic, McNeil says. That requires characterizing the particles to understand their specific properties and then developing a synthesis that yields particles with those precise properties on a consistent basis. That is still a difficult process, he says.

However, McNeil and others see a lot of hope for progress in the field going forward. One development McNeil sees on the horizon involves a change in the types of drug cargoes that nanomedicines carry. Until now, he says, already-approved small-molecule drugs have been incorporated into nanoparticles. At NCL, his team is working with companies that are developing nanomedicines with small molecules that have not yet been approved on their own. These compounds hit novel cancer targets, which could lead to greater improvements in patient outcomes than those seen with older molecules.

Despite engineering and scientific challenges facing the field, nanomedicine developers think we will not have to wait 30 years to see significant translation of this technology to the clinic. "The field is much more advanced, in our opinion," than Chan's review suggests, says Bind's Yingling, who joined the company at the end of 2015. "Trust me, if I thought it would be 30 years before we could create innovative medicines, then I wouldn't have joined."

Michael Torrice is deputy assistant managing editor at Chemical & Engineering News, the weekly newsmagazine of the American Chemical Society. This story first appeared in C&EN.

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