

Nanotechnology Takes a New Look at Old Drugs

By Margie Patlak

When tumor necrosis factor (TNF) appeared on the cover of *Time* magazine in the mid-1980s, there were great hopes for this compound, which had dramatically shrunk tumors in mice. Those hopes evaporated when pre-clinical and phase I trials revealed profound side effects, such as life-threatening drops in blood pressure and liver toxicity.

But now TNF is making a comeback thanks to recent advances in nanotechnology. Steven Libutti, M.D., of Montefiore–Einstein Center for Cancer Care in New York showed in a phase I clinical trial that high doses of TNF linked to gold nanoparticles could be safely given to 30 patients with various advanced solid tumors. In fact, the dose escalation trial never found a dose-limiting toxicity for the reformulated TNF, even at what previously was considered a lethal dose.

“We have mitigated the toxicity of a promising agent that for a long time was dismissed because it was too dangerous to give to patients,” Libutti said. Plans are now under way for a phase II study of the gold-bound TNF in combination with a standard cytotoxic drug.

TNF is just one of several older toxic anticancer compounds, long ago shelved or little used, that researchers are now giving a second look. Driving this trend are second-generation nanotechnology products designed to deliver more potent but less toxic drugs to tumors.

“Big pharma produces tens of thousands of new chemical entities by medicinal chemistry, but the majority of those have to be disqualified due to insolubility, toxicity, or so forth,” said Scott McNeil, Ph.D., director of the National Cancer Institute’s Nanotechnology Characterization Laboratory, speaking at a recent Institute of Medicine (IOM) workshop on nanotechnology and cancer. “Nanotechnology might be able to resurrect some of those

drugs, because we can truly engineer properties into and out of those formulations.”

Others, however, question whether cancer nanodrugs will truly be safer. The long-term effects of most new nanodrugs are not known, and with their unique features, the current battery of toxicology tests may not be sufficient to fully assess their safety, these experts say.

Shielding the Body

Cancer nanodrugs made their debut with liposome-encased doxorubicin (Doxil), which was easier on the heart than its naked predecessor and has been on the market for about 15 years. The second-generation nanodrugs tend to be smaller, have added targeting agents, combine multiple drugs, or use encapsulation or carrier materials that are more fine-tuned to better deliver the drugs only to their targets. All these features make the next generation of nanodrugs especially likely to concentrate in tumor tissues, thus enabling larger doses of the drugs to be safely given to patients or allowing smaller doses to be more potent.

For *nab*-paclitaxel—paclitaxel attached to the protein carrier albumin—clinical trials show not only that the maximum tolerated dose is about twice that for paclitaxel alone but also that it is substantially more effective. And it does not require preadministration with a steroid and antihistamines to prevent severe reactions.

The U.S. Food and Drug Administration approved *nab*-paclitaxel for breast cancer treatment in 2005, and a phase III trial recently showed that the drug given with carboplatin was statistically significantly more effective than standard paclitaxel and carboplatin in non-small-cell lung cancer. Patients given *Nab*-paclitaxel had a 33% overall response rate by independent radiologic review, whereas those given standard paclitaxel had a 25% overall response rate. Mark Socinski, M.D., oncologist and associate professor at the University of North Carolina

at Chapel Hill, presented the results last June at the annual meeting of the American Society of Clinical Oncology. *Nab*-paclitaxel is also in a phase II trial in patients with pancreatic cancer or melanoma, according to Neil Desai, Ph.D., vice president of research and development at Abraxis Bioscience.

Several drug companies have also developed various types of liposomal or polymer packaging for standard cytotoxic drugs, including cisplatin, oxaliplatin, and methotrexate. Some of these nanocarriers are designed to evade the immune system and factors that foster their rapid elimination from the body, thereby increasing their circulation and possibly their effectiveness. These nanoversions of standard chemotherapeutic drugs are in clinical trials for solid tumors, such as stomach, lung, and pancreatic cancer, according to the websites of the companies that produce them. These companies include NanoCarrier, based in Japan, and Regulon, incorporated in both California and Europe.

Better concentration in tumors is the aim of cancer drugs whose nanocarriers are decorated with targeting agents. BIND Bioscience, for example, has a version of docetaxel that is ferried to tumors by a polymer nanoparticle dotted with homing molecules that target prostate-specific membrane antigen. Both prostate tumors and the blood vessels that feed other solid tumors express this antigen. In animal studies, targeting this protein led to as much as a 20-fold increase in the concentration of the drug in prostate or lung cancer tissue. It also fostered a more effective tumor response than that of the standard drug or the polymer carrier version of the drug without the targeting proteins, according to Omid Farokhzad, M.D., associate professor at the Harvard Medical School and one of the founders of BIND Bioscience. The company expects to start clinical trials of the compound shortly.

Other researchers, such as Libutti, are linking metallic nanoparticles to cancer drugs, banking on the specialized features of

Why Nanocarriers?

Nanomaterials have several features that make them especially adept at ferrying anticancer compounds to tumors:

- The “Goldilocks effect”: Nanodrugs are large enough that they aren’t rapidly eliminated through the kidney yet small enough that they are more likely to penetrate leaky blood vessels that feed tumors and then get trapped in tumor tissue.
- Nanoparticles are more likely to enter a cell by endocytosis, which protects the particle’s payload from being ejected by cellular pumps known to confer drug resistance. Because they can enter cells, nanoparticles are useful carriers for drugs that operate intracellularly, such as interference RNA. Researchers have developed a nanocarrier for silencing RNA that recently completed phase I testing for certain cancers.
- The surfaces of nanoparticles have much available room to attach compounds, such as antigens and other proteins, which further target nanodrugs to tumors or the blood vessels that feed them. Nanoparticles can also incorporate multiple drugs, making combination therapy possible on a single platform. Researchers have developed nanoparticles that deliver two or more anticancer drugs simultaneously and completed tests in animal models.

these particles that make them especially suited to deliver cancer medicines (*see* sidebar). In addition to using gold to deliver TNF, researchers are exploring its use as a drug ferry for more established cancer therapeutics, such as oxaliplatin. Some investigators have boosted the effectiveness of these metal-based nanodrugs in animal models by using a magnetic field or infrared laser energy to heat up the metal carriers, thereby combining drug therapy with hyperthermia.

Safer in the Long Run?

Most nanodrugs using standard cytotoxic drugs are specifically designed to be safer than their predecessors and have proven less toxic in clinical trials to date. “We are lowering the toxicity of really nasty drugs. This is something that should be celebrated,” said James Heath, Ph.D., of the California Institute of Technology, at the IOM workshop.

But others sound a more cautious note. Most nanodrugs on the market so far are made of biocompatible materials and are relatively simple constructs. By contrast, many of those in company pipelines have more components, and their biocompatibility is either not known or suspect, according to King Li, M.D., a radiologist and professor at the Weill Cornell

Medical College in New York and Methodist Hospital in Houston.

“Yes, nanotechnology is a very exciting field with a lot of potential, but on the flip side, there are things we need to consider that can make them potentially harmful,” he said. “We need to make those considerations up front before we waste a lot of energy, because you can be causing problems before you even know it, and we don’t want to do more harm than good.”

Among those considerations is the binding of nanomaterials to proteins in the body, which impedes the nanomaterials’ excretion and metabolism. Such protein binding can also elicit immune reactions. Li is concerned, for example, about nanoparticles’



Ruth Duncan, Ph.D.

taking up long-term lodging in the lungs after inhalation. Once in the lungs, they could act as persistent irritants that, like asbestos, go on to cause long-term problems.

The standard battery of toxicology and biodistribution tests—which measure mainly acute and not chronic effects—could miss such problems. At the IOM conference, Yuliang Zhao, Ph.D., founder of the Chinese Academy of Sciences Nanosafety Lab, said that his

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nanotoxicology studies have found that some nanoparticles can stay in the body for longer than 9 months. And studies on mice have shown that carbon nanotubes inserted in their trachea or throats led to lung damage akin to the black lung disease seen in coal miners or was linked to heightened atherosclerosis.

Farokhzad concedes that some nanomaterials that do not biodegrade, such as carbon nanotubes, are likely to be problematic if given repeatedly as a drug. But these nanoparticles may not pose problems if they are administered just a few times as part of a vaccine or imaging platform, he said. Farokhzad stressed that nanomaterials should be considered on a case-by-case basis, according to their composition and how they are administered. Long-term toxicity tests are warranted, he said, if the nanodrug appears to be accumulating in the body. And standard adsorption, distribution, metabolism, and excretion (ADME) tests will reveal that accumulation, he argued.

“There might be some unique testing you might want to do for nanodrugs, but we shouldn’t set the bar for evaluating a nanodrug so that it is different from that for any other drug, whether it be a small molecule, protein based, or biologic,” he said. Ultimately, “you still have to demonstrate safety and efficacy.”

Li agreed that if ADME testing does not show potential problems, the nanodrugs might need no additional testing. But, he added, “if your ADME tests raise some red flags, you need to chase them down. You can’t use acute or intermediate toxicity as the ‘gold standard’ when ADME shows you there are clearly some areas that could be problematic.”

Li also pointed out that ADME tests may show that a nanodrug is in the blood, but not what proteins the nanodrug is binding to, a factor that may be essential to its toxicity. ADME tests also won’t reveal the biodistribution of nanodrugs or their subcomponents within cells. Such cellular distribution may be important, since the small size of nanoparticles lets them easily slip inside cells, where they might persist for a long time. “There’s a lot more extensive documentation that should be required,” Li said.

Ruth Duncan, Ph.D., professor emerita at Cardiff University and a member of the European Medicines Agency Ad Hoc Advisory Committee on Nanomedicine, also takes a more cautious approach to evaluating nanomedicines. “It is important that regulatory agencies continue to evaluate innovative nanosized therapeutics on a case-by-case basis to ensure their safe transfer into early clinical trials,” she said.

Zhao concurred, stressing the need to actively evaluate the risk of nanomaterials to avoid harmful adverse reactions that could turn the public against the field. He suggested verifying the suitability of regulations already in place for nanomaterials and creating new laws and regulations to cover any regulation gaps that might lead to nanotoxicities.

But Libutti countered: “We shouldn’t set the bar so high that it is difficult to cross, especially with respect to cancer therapies. We should be so lucky if the patients live long enough to see long-term toxicities from the therapies.” He added that if high toxicity standards were adhered to 50 years ago, no standard chemotherapeutic would be on the market now.

The final word on nanodrug safety in the U.S. will come from the FDA. According to Nakissa Sadrieh, Ph.D., associate director for research policy and implementation at the agency’s Center for Drug Evaluation and Research, the standard battery of toxicology tests is rigorous and adequate to assess the safety of all drugs, including those containing nanoscale materials. “There are currently no special requirements for sponsors to conduct testing solely because nanoscale materials are included in the product,” she said.

But the unexpected could still occur with nanodrugs, just as with other types of drugs, and safety remains a prominent question. “There is a lot of fear in the unknown,” Libutti said. “One of the biggest challenges for us is to turn the unknown into the known.”

Dr. Heath is the founder and board member of Integrated Diagnostics and Momentum Biosciences. Dr. Farokhzad is a cofounder and board member of BIND Biosciences.