Nanoparticles offer ‘infinite’ possibilities for cancer treatment

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When researchers at the University of Missouri combined an active ingredient in tea called epigallocatechin-gallate (EGCg) with radioactive gold particles, the EGCg directed the nanoparticles to selectively localize around the tumor site. As a result, doses of this treatment could be significantly smaller than traditional chemotherapy.

EGCg offers a huge benefit to the body: It halts DNA damage.

“I used this property of EGCg to synthesize my nanoparticle,” Kattesh V. Katti, MScED, PhD, DSc, FRSC, director of the University of Missouri’s Cancer Center Nanotechnology Platform, told HemOnc Today. “Once I
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The encapsulated particles were associated with less toxicity, and once the nanoparticles arrived at the tumor site, they stayed there.

“If I took my gold nanoparticles encapsulated with EGCg and injected them directly into the tumor, these particles would not migrate to other organs,” Katti said. "They stuck to the tumor because EGCg has this very strong affinity for the tumor receptors."

This formulation is an eco-conscious option. Because of their instability, nanoparticles must be encapsulated in a protein or organic chemical. Usually, researchers use toxic chemicals to stabilize the particles.

Globally recognized as the “Father of Green Nanotechnology,” Katti has pioneered the utility of phytochemicals from soy, cinnamon, cumin, and a host of herbs and plants for the creation of tumor-specific gold nanoparticles, without the intervention of any chemicals.

“My approach uses green nanotechnology,” Katti said “I’m not using any chemicals. All I’m doing is mixing gold salt with tea.”

In related research, Katti and colleagues showed that this gold nanoparticle was safe and had fewer adverse effects than traditional cancer treatment when tested in dogs. Testing in dogs is an important precursor to human testing, as dogs develop prostate cancer in a similar way as men, researchers said.

Potential breakthrough for bladder cancer
A study in mice showed that nanoparticles could offer tremendous potential as a treatment for advanced bladder cancer.

“In advanced bladder cancer, there have been no new drugs for the last 3 to 4 decades; therefore, survival has not changed over the last 3 decades,” Chong-Xian Pan, MD, PhD, associate professor of hematology and oncology at UC Davis Comprehensive Cancer Center, said in an interview.

In this research, published in 2012 in Nanomedicine, targeted micelles coated with bladder cancer-specific ligands and loaded with paclitaxel delivered three times the maximum tolerated dose to mice carrying patient-derived xenografts, yielding better control with less toxicity.

Further, the targeting micelles were superior in controlling cancer growth ($P=.0002$) and extending OS ($P=.002$).

The researchers also loaded the micelles with imaging agents, Pan said.

“We can load a radioisotope for a PET scan,” he said. “And the isotope can also be used for radiation treatment. We can combine chemotherapy and radiation on the same nanoparticle.”

Pan and colleagues have not studied whether these nanoparticles will induce an immune system response. Although some research has indicated they do, “it is probably not a big issue,” he said.

**Overcoming resistance in multiple myeloma**

Nanoparticles also have shown promise in the treatment of multiple myeloma.

One of the greatest challenges associated with that disease is that it develops drug resistance to doxorubicin, said Basar Bilgicer, PhD, an assistant professor of chemical and biomolecular engineering and chemistry and...
biochemistry at the University of Notre Dame.

“The drugs that you initially start the treatment with may appear to be working well and treating the disease,” Bilgicer said in an interview. “However, after a while they lose their efficacy. The drug resistance develops due to the adhesion of the multiple myeloma cells to the bone stromal cells in the bone marrow. This adhesion activates a mechanism that develops drug resistance.”
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Bilgicer and colleagues targeted one of the receptors responsible for drug resistance, very late antigen-4 (VLA-4).

“By doing so, we prevented these receptors from interacting with their microenvironment and targeted the particles more directly and more efficiently to the tumor,” Bilgicer said.

In addition, they promoted particle uptake, allowing more precise delivery of doxorubicin.

“You will be directing the drug only to the site of the tumor,” he said.
They built in a controlled release mechanism, so the tumor gets the full amount of drug; there is no leaking or migrating to other parts of the body.

“The drug is not released until it is taken up by the tumor itself,” Bilgicer said. “The change in the pH activates the release of the drug only after it is taken up by the tumor cells.”

Bilgicer and colleagues hope to make this nanoparticle available for human use soon.

“Our aim is to actually figure out the best formulation as soon as we can, so we can do the transition from bench to bedside as quickly as possible,” he said.

**Barriers to use**

Despite the promise demonstrated by these studies, there are barriers to the widespread use of nanotechnology in cancer.

As researchers try to create nanotechnology with more function, the complexity increases, Davis said. The increased complexity makes manufacturing more challenging and raises questions about how to regulate the technology.

The FDA already announced it would have no special rules for nanotechnology, Davis said.

“[The FDA feels] they can use the procedures that are currently in place for other cancer drugs,” Davis said. “If you make a nanoparticle for cancer, it will follow the same route.”

Another significant question is clearance.

“Everyone wants to know that nothing of this stays in the body and they’re eliminated,” Labhasetwar said.
Safety also is a concern.

“You have to be very careful here. It depends on which nanoparticles you’re talking about,” Davis said. “I live in Los Angeles. We breathe nanoparticles every day from truck exhaust. There are health issues associated with those.

“But when you talk about trying to create nanoparticle medicine, that’s a well-designed nanoparticle that is going to be tested a lot in animals before it’s tested a lot in humans,” he added. “That’s an entirely different issue than an environmental exposure that you have through an inherent nanoparticle. You have to delineate whether these nanoparticles are being injected into the patient or are being breathed through the environment.”

**From promise to practice**

The benefits of nanoparticles may extend beyond treatment. Research shows they also can aid in cancer diagnosis.

“We can see these nanoparticles being used as contrast agents in imaging to determine the location of the tumor, as well as the tumor behavior after therapy to see if the tumor is shrinking,” Grodzinski said.

Although considerable research must be undertaken and completed before nanotechnology becomes mainstream in oncology, there is reason for optimism, Davis said.

“The field is so new that, over the next several years, it’s going to be very interesting to see how it all plays out,” Davis said. “So far, it is encouraging. What we are seeing from a number of these studies, and from moving things into the clinic, is the opportunity to make highly effective therapeutics with a high quality of life for patients. It is only going to improve. These are sophisticated systems and, as people learn more about how to control them and design their properties, things can only get better.”

Grodzinski agreed.
“The number of possibilities is infinite,” Grodzinski said. “We need to mature this technology, select which ones are most promising and move them to the clinical environment.” – by Colleen Owens

References:


For more information:

Gregory I. Berk, MD, can be reached at BIND Therapeutics, 325 Vassar St., Cambridge, MA 02139; email: gregberk@bindtherapeutics.com.

Basar Bilgicer, PhD, can be reached at College of Engineering, University of Notre Dame, 165 Patrick Hall, Notre Dame, IN 46556-5637; email: bbilgicer@nd.edu.

Mark E. Davis, PhD, can be reached at California Institute of Technology, 215 Spalding, Pasadena, CA 91125; email: mmdavis@cheme.caltech.edu.

Leo I. Gordon, MD, FACP, can be reached at Northwestern Medical Faculty Foundation, Division of Hematology/Oncology, 676 N. St. Clair, Suite 850, Chicago, IL 60611; email: l-gordon@northwestern.edu.
Do the benefits of nanotechnology outweigh potential safety concerns?

**POINT**

The safety of nanomedicines is exhaustively studied during regulatory approval.

Nanomedicines, such as liposomal doxorubicin and taxol-containing albumin nanoparticles, have been in clinical use for many years and have been employed to treat hundreds of thousands of patients. There currently are about a dozen different nanoparticle types in clinical use in oncology, including truly novel agents — such as iron oxide nanoparticles for the thermal ablation of brain malignancies.
— that are currently approved in Europe but not in the United States. An entire new generation of “actively targeted” nanoparticles is in clinical trials, with the objective of adding localization specificity to the therapy. Many new nanomedicines are in preclinical development worldwide.

The fundamental concept behind nanomedicine is to attain an improved therapeutic index — that is, greater localization at the target lesion — with reduced off-target distribution and the resulting side effects. Thus, the whole concept behind the use of nanoparticles for therapy is to increase safety for a given therapeutic regimen.

In addition, before entering clinical use, all nanotherapeutic agents must be tested for safety in phase 1 trials and reconfirmed during successive phases of clinical trials. It is true that, at times, the use of nanoparticles induces biodistributions that give rise to adverse side effects that are not found in conventional regimens; such is the case with the hand-and-foot syndrome in liposomal doxorubicin. However, effects of this type are exactly what clinical trials are designed to ascertain. Thus, the safety of nanomedicines for the patients is the very reason for their existence and is exhaustively studied during regulatory approval, as is the case for all other drugs.

Questions remain about the safety of health care workers, those who are near the patients and the environment. Although speculation on these adverse bystander effects is always possible and should actually be encouraged, it must be kept in mind that the chemotherapeutic agents themselves are very toxic substances (and that is why they are used), and they actually are much more toxic than the nanoparticles themselves. As is the case for all chemotherapeutic and biological cancer therapies, the management and disposition of nanomedicines is tightly controlled, thus reducing or eliminating the risk of adverse effects on health care workers, family members and the environment.
The situation for industrial nanoparticles is entirely different: There are hundreds of nanoparticle-containing commercial products currently in the marketplace, for which the toxicity profiles have not been sufficiently studied and to which no regulatory approval process was applied. Still, after 30 years of nanotechnology, no case has ever been reported of death or serious adverse health effect brought about by nanoparticles.

Mauro Ferrari, PhD, is president and CEO of The Methodist Hospital Research Institute, director of the Institute for Academic Medicine at The Methodist Hospital, executive vice president of The Methodist Hospital System, senior associate dean and professor of medicine at Weill Cornell Medical College in New York, and president of the Alliance for NanoHealth in Houston. He can be reached at The Methodist Hospital Research Institute, 6670 Bertner St., M.S. R2-216, Houston, TX 77030; email: mferrari@tmhs.org.

Disclosure: Ferrari reports no relevant financial disclosures.

There is valid concern over nanoparticles’ long-term toxicity profile.

After years of discussion, research and speculation, nanoparticles are beginning to make an impact in cancer therapy. Two recent studies, using entirely different approaches, have produced results that provide reasons for optimism.

Results presented at the recent AACR Annual Meeting showed that a targeted polymeric nanoparticle formulation of docetaxel, BIND-014, has a favorable toxicity profile compared to that of docetaxel. This nanotherapeutic is being...
evaluated in several solid tumors. Earlier this year at the Gastrointestinal Cancers Symposium, data were presented showing that a protein-bound paclitaxel (Abraxane, Celgene) had clinical effectiveness against pancreatic cancer, which has been resistant to most chemotherapeutics.
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