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On Your Radar

In Biopharma, Tiny Carbon Dots Mean Big Opportunities

By Gail Dutton

C-Dots Nanotec is developing nanoparticles that can penetrate biological barriers and set imaging and drug delivery applications aglow

VITAL SIGNS

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Focus
C-Dots Nanotec is developing high-purity carbon nanodots for diverse applications in biomedicine, imaging, sensing, catalysis, engineering, and environmental science.

Crossing the blood-brain barrier is a familiar challenge in therapeutic applications. And it is increasingly recognized as a challenge for imaging applications, too. In the not-too-distant future, therapeutic and imaging applications may be better able to overcome this challenge—provided new, enabling technologies perform as hoped. One such technology is carbon nanoparticle technology.

Carbon nanoparticles, which have a core-shell structure and a diameter of less than 10 nm, exhibit several useful properties. They include ultra-small size, tunable photoluminescence, various surface functionalities, high water dispersibility, and biocompatibility. By exploiting these properties, a small company named C-Dots Nanotech is working to improve drug delivery and bioimaging.

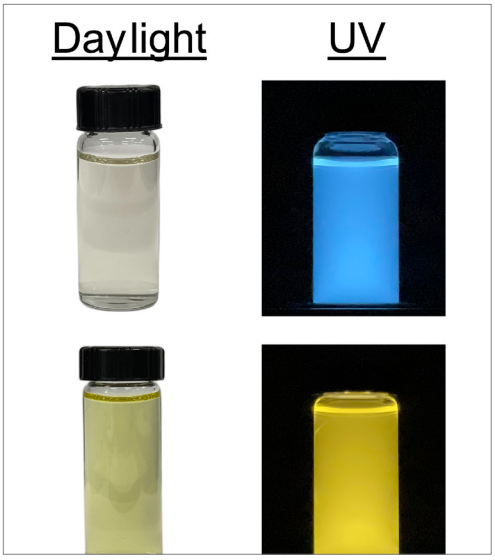
Neuron targeting for imaging

"We have specific types of carbon nanoparticles, called C-Dots, that target neurons," says Elif S. Seven, PhD, senior scientist and production manager, C-Dots Nanotec. "The C-Dots cross the blood-brain barrier and accumulate in the neurons," enabling imaging applications. The alternative is to use dyes; however, relatively few dyes are suitable for in vivo or in vitro imaging.

Seven also suggests how C-Dots may facilitate drug delivery. "We can deliver small molecules to neurons in a nonviral way," she tells *GEN*. According to Seven, the immune response stimulated by the technique is minimal or undetectable.

C-Dots may prove especially useful in the delivery of cancer drugs. "We can customize the drug delivery platform by attaching targeting ligands to the C-Dots along with chemotherapy drugs (singly or in combination) for precise targeting," Seven explains. "We have shown that when two different chemotherapy drugs are conjugated to C-Dots along with transferrin, there is a synergistic anticancer effect on glioblastoma cell lines." C-Dots Nanotec has been working in-house with glioblastomas and neuroblastomas, and it has identified the types of C-Dots that work best for certain scenarios. The company also works with external researchers to develop carbon dots for other cancers.

Seven notes that in a recent study for neuroblastoma, a specific type of C-Dot was iden-



Carbon nanodots developed by C-Dots Nanotec are highly photoluminescent. In addition, they can be tuned for blue, red, green, and yellow photoluminescence, as well as for intermediate colors. In these images, water dispersions of the company's carbon nanodots are shown under room light (*left*) and under ultraviolet light (*right*).

tified that showed a "significant, intrinsic anticancer property while being minimally toxic to healthy cell lines." When C-Dots Nanotec tested the C-Dots against seven or eight cancer cell lines, the company found that the C-Dots killed one cell line that had a specific mutation. Additional studies to explore that capability are being planned.

Nanodots aren't quantum dots

While C-Dots Nanotec's technology looks promising, the company's work is still in the preclinical stage. That's par for the industry. Despite being discovered some two decades ago as a product of carbon nanotube synthesis, carbon nanodots generally are underrecognized in the biopharmaceutical world.

"Carbon nanodots are often confused with quantum dots," Seven points out. "Carbon nanodots are spherical nanoparticles with a diameter of less than 10 nanometers. Even in the nanoparticle world, that's very small. And unlike quantum dots, carbon nanodots don't have toxic metals such as cadmium."

Carbon nanodots exhibit stability and low toxicity. Also, as mentioned earlier, they are both highly biocompatible and highly photoluminescent. They can be tuned for blue, red, green, or yellow photoluminescence—or "anything in between," Seven remarks. Typically, citric acid and urea are the precursors, and adding nitrogen enhances the carbon nanodots' luminescence.

"There are two general types of synthesis: top-down and bottom-up," Seven continues. "We can use small molecules to build the dots from the bottom-up. For top-down, we use larger carbon-based particles to cut down to make the dots."

She also explains how C-Dots can be given different targeting properties that can enhance drug delivery: "Especially for the small molecules, the composition of the surface functional groups may be different based on their precursors. For example, C-Dots made from folic acid target the folic acid receptor, and C-Dots made from glucose enter cells using glucose transporter proteins. So, they sometimes take on the properties of their precursors. That's why they can target specific cells."

High levels of biocompatibility and the ability of these carbon dots to go places other modalities cannot reach easily are expanding their potential applications. Besides having the potential to target brain cancers and neurodegenerative diseases, C-Dots may be able to target pancreatic cancer and dermatology conditions. And C-Dots Nanotec may pursue additional applications by participating in collaborations.

C-Dots Nanotec is one of only a few companies developing these carbon nanodots. This observation, Seven reports, has been confirmed by C-Dots Nanotec's competitive research. She adds that some competitors' products more closely resemble dyes than carbon dots, based upon spectra and other product characteristics.

She declares that C-Dots Nanotec can offer high purity levels and "guarantee batch-to-batch reproducibility." Accordingly, researchers can run experiments with one batch of C-Dots and then reproduce their results by running experiments with C-Dots from other batches.

Focusing on carbon nanodots

C-Dots Nanotec was founded in 2019 as a sister company to C-Dots, which was founded in 2017. Both companies were co-founded by Roger M. LeBlanc, PhD, a professor of chemistry at the University of Miami. He has developed multiple companies around carbon nanodots, including those for neuro-oncology and neurodegenerative diseases, and others for dermatology, fuel additives, and R&D. The dots also have agricultural applications.

"When we started C-Dots Nanotec a few years ago, there were not many companies offering carbon dots, so we are probably first in the market," Seven says. "We really believe carbon dots are unique."

Now, C-Dots Nanotec is working with academic partners at the University of Florida, the University of Miami, and the University of Iowa, and it is also interested in working with corporate partners.

Incorporating carbon nanodots into a research program is as straightforward as chemically conjugating them with a program's small-molecule drugs and/or peptides and then measuring their effects on delivery efficiency. "Carbon dots are like catalysts," Seven says. "As additives, they have been shown to increase efficiency."

Seven looks forward to pursuing applications in two exciting fields: "One, of course, is neurology, with neurodegenerative diseases and oncology as part of that. The second is jet fuel." Applications that improve fuel efficiency could have an impact and generate revenue relatively quickly.

Thriving in a new niche

The carbon nanodot industry is still in its infancy. "If you're not in the field," Seven admits, "there's a high chance you have never heard of carbon nanodots." They may be overlooked by researchers in need of delivery technologies. Indeed, researchers typically opt for more familiar technologies, such as those based on polymers or liposomes.

Seven recognizes that creating a new market will be challenging. Nonetheless, she emphasizes that "more suppliers and more companies are adding carbon dots to their product lines."

Being located in Florida, away from the conventional biopharmaceutical hubs, is an additional challenge. The location issue was evident when C-Dots Nanotec participated in a startup workshop at the Massachusetts Institute of Technology. "The vibe was so high and energetic," Seven recalls. "We did a lot [with researchers], but we may have done a lot more if we had been a Boston-based company." Worse, travel has been limited by the pandemic, she says. This year, C-Dots Nanotec is renewing its efforts to form collaborations that may help the company transition from laboratory work to clinical trials. GEN