Prime Time: First Therapeutic Clinical Trial of C'Dots Underway

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Cornell dots, originally developed 16 years ago in the lab of Uli Wiesner, the Spencer T. Olin Professor of Engineering, have just begun their third human clinical trial. The newest iteration, C'dot drug conjugates, is being developed by Elucida Oncology as a treatment for patients with advanced, recurrent or refractory cancers overexpressing folate-receptor alpha (FRα), including ovarian, breast and lung cancers.

From the very beginning around 20 years ago, "Cornell dots" – silica-encased fluorescent nanoparticles, developed in the lab of Ulrich Wiesner, the Spencer T. Olin Professor of Engineering – were seen as having great potential as biological markers. C Dots were also touted as having possible applications in displays, optical computing, sensors and microarrays such as DNA chips.

The technology has been refined and improved since its unveiling in 2005. C Dots have been used to create the world's smallest laser and, in collaboration with researchers at Memorial Sloan Kettering (MSK) in New York City, have shown the diagnostic ability to find tumors; a new version – Cornell Prime Dots, or C'Dots, synthesized in water – was armed with nano-sized antibody fragments, and in separate studies actually induced, without attaching a drug, a form of cell death in tumors.

Now C'Dots, proven safe and effective in three previous diagnostic human clinical trials, have just begun their first therapeutic trial, having been further developed by Elucida Oncology, Inc., a New Jersey-based biotechnology company co-founded by Wiesner.

"The first feeling is that of gratitude," said Wiesner, who along with then-doctoral student Hooisweng Ow, Ph.D. '05, developed the original C Dots. "All these years at Cornell and beyond, I have been able to work with so many talented individuals whose work has led, in a highly interdisciplinary effort, to the development of these particles to the point where they

are now. I am particularly thankful for many years of a very close and excellent collaboration with my colleague, Michelle Bradbury, at MSK Institute and Weill Medical College of Cornell University. It was a long voyage, with lots of setbacks for our team."

"This is a major turning point in the evolution of the technology," says Kai Ma, Ph.D. '15, co-founding scientist and CTO, and one of five key personnel at Elucida with ties to Cornell. "I feel very proud that our team is able to successfully close a series of challenging gaps between academia and the pharmaceutical industry to advance the C'Dot technology from the exciting innovation in the labs to real patient care and market success."

The newest iteration of C'Dots is what the Elucida team refers to as CDCs – C'Dot drug conjugates, the nanoparticle with dozens of drug molecules attached. It is being developed under the product codename ELU001 as a treatment for patients with advanced, recurrent or refractory cancers overexpressing folate-receptor alpha, including ovarian, breast and lung cancers.

The company announced Sept. 17 that it had completed the initial dosing of the first patient in its Phase 1/2 clinical study of ELU001. Geno Germano, president and CEO of Elucida, says the company has "taken a meaningful step closer to a new frontier in precision oncology" with the beginning of the current trial.

Other Cornellians at Elucida:

– Paul Rudick '90, vice president of commercial development and business operations;
– Melik Turker, M.S. '15, Ph.D. '19, head of materials science and production;
– Fei Wu, Ph.D. '16, head of materials technology development; and
– Tom Gardinier, Ph.D. '19, head of materials analysis.

Turker, who has been working on C'Dots for more than eight years, is excited about the technology moving from a diagnostic to a therapeutic realm.

“These trials are an important milestone for our technology,” he says, “both for making it into the clinic to be tested for the treatment of cancers as an inorganic hybrid nanoparticle platform, and for showing the scalability of our nanoparticle chemistry.”

Target or Clear

Wiesner’s mission to improve cancer therapy via Cornell dots is highly personal – his father died of the disease in 1984 – and he’s understandably passionate about Elucida’s CDCs.

One key to C’Dots, said Wiesner, a member of Elucida’s board of directors, is their ability to be efficiently cleared from the body via the kidneys with minimal off-target accumulation.

“With Michelle, we developed this [trademarked] ‘Target or Clear’ paradigm,” he says. “They either target the tumor, or they get out and do not accumulate at off-target sites in your body. Therefore, they are expected to substantially reduce side effects, relative to previous [therapeutic] platforms.”

The reason is C’Dots’ size – approximately 5 to 6 nanometers, about a third the size of antibody drug conjugates (ADCs), a comparable therapeutic delivery vehicle. This allows for both penetration of solid tumors and clearance through the kidneys.

Penetration of the solid tumor means quicker destruction of tumor cells, Wiesner says.

“Because C’Dots are so small, they also diffuse better,” he says. “They can basically get through all of the tumor, not just the periphery, which is important because if you only get to the periphery, then the tumor shrinks from outside in, which takes a long time. But if you can diffuse through the entire tumor tissue, you can basically begin disintegrating the whole tumor from day one.”

Elucida’s technology features a 10-step process in which C’Dots either find their mark or are

eliminated. After injection and circulation in the bloodstream, the CDCs find the tumor, which by nature has a porous surrounding vasculature due to rapid growth, a hallmark of cancerous tissue.

CDCs then diffuse through the tumor microenvironment in order to specifically target tumor cells. This is key: The better CDCs diffuse through the entirety of the tumor, the better they can target cells throughout the tumor, and not just those on the surface layer.

“Target or Clear” leads to efficient biodistribution; accumulation in the tumor is maximized, while off-target accumulation (in the liver, for example) is minimized, reducing the potential for negative side effects such as those often suffered by chemotherapy patients.

Despite their ultra-small size, C’Dots can be armed with a payload of up to 80 molecules of synthetic drugs without compromising the desired targeting and pharmacokinetic properties. In comparison, typical ADCs only carry four drug molecules.

The reason for the superior drug capacity? It’s the hydrophilic polyethylene glycol (PEG) shell, which provides colloidal stability in aqueous solutions, including blood serum. The PEG chains are arranged somewhat perpendicular to the silica core’s surface, in what’s called a “brush” conformation.

The drug payload rests in between the PEG chains – the “bristles” of the brush – meaning the hydrophobic drugs don’t destabilize C’Dots in solution.

“You can really think of it as a forest, where you have the drugs in between the trees,” Wiesner said. “An antibody does not have such a surface brush layer. There are no trees to hide in between, leading to a lower drug loading capacity.”

Two-part clinical trial

The open-label, multi-center clinical study has two parts:

– **Dose Escalation Safety Study**: The maximum tolerated dose and/or the recommended phase 2 dose (RP2D) will be identified; and
– **Tumor Group Expansion Cohort(s)**: Specific cancer types will be evaluated for efficacy and safety at the RP2D.

Part 1 is enrolling patients with advanced cancers known to overexpress folate receptor alpha, including ovarian cancer, endometrial cancer, colorectal cancer, gastric cancer, gastroesophageal junction cancer, triple negative breast cancer, non-small cell lung cancer and cholangiocarcinoma (bile duct cancer).

The most promising tumor types studied in Part 1 will proceed to investigation in Part 2. Ma and the team are hopeful that success in the current trial will “open a new door for us to develop a variety of CDCs” to benefit a wider range of cancer patients.

The technology has come a long way in 20 years, and Elucida – dotted with Cornellians in both the board room and in its Monmouth Junction, New Jersey, labs – is hoping this is just the beginning.

“I am proud to be a part of the team responsible for bringing this material into its first therapeutic clinical trial,” Gardinier says. “There is still a lot of work to be completed, however, before the CDCs become an FDA-approved treatment. So in short, while I feel proud of how far we have come, I am looking to the future and the challenges that await us.”

Wiesner has a feeling of “cautious optimism,” he says, regarding the future of C’Dots.

“Clinical trials are never easy,” he says. “There are so many things that can go wrong and that can never be predicted. Of course, we all in the team would be elated to see this technology reach the full approval stage. Having developed a technology that helps improve

the lives of cancer patients would be incredibly rewarding.”

Read the original article on Cornell University.