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Nanopharma Cerulean Advances Cancer Particle, Looks Ahead To siRNA

By Shirley Haley

Nanotech platform company Cerulean Pharma Inc. has a high-quality problem. The Cambridge, Mass., start-up is poised to take its lead candidate into Phase IIb cancer trials, but the young company must choose among several cancer types in which the nanoparticle shows go-ahead activity.

If Cerulean were a Big Pharma it might run several Phase IIs in parallel, but for a small company, "from a capital efficiency point of view, it makes sense to spearhead into the first one and show [activity] there," Cerulean CEO Oliver Fetzer said during an interview at the BioPharm America meeting in Boston Sept. 17.

Privately held Cerulean announced positive results from a 24-patient Phase I dose finding study of CRLX101 in August; a Phase IIa study is enrolling 36 patients to test that maximum tolerated dose against solid tumors. And in preclinical studies, the compound compared favorably to marketed camptothecin analogues topotecan (GlaxoSmithKline) and irinotecan (Pfizer). All of it is good news for a company barely four years old.

A conjugate of camptothecin, CRLX101 is engineered to focus the natural chemotherapeutic's firepower directly on tumor cells, sparing patients systemic exposure that brings on the toxic side effects that for decades have thwarted the agent's development.

Some patients from the dose finding study, which enrolled patients with progressive disease, have experienced progression-free survival out more than a year with no new side effects, Fetzer said during a presentation at the BioPharm America meeting.

Ten patients had stable disease for three months or more, while four were progression-free for more than six months, he said. Among them two non-small cell lung cancer patients did not progress for 9 and 14 months, a favorable comparison to 2.9 months median PFS for current second-line NSCLC therapies.

And "they feel great," Fetzer enthused during the post-presentation interview. "Camptothecin was a drug so toxic it couldn't be developed, and [CRLX101] totally changes that."

The patient with the longest experience on the drug has had no adverse events, and the drug has kept his pancreatic cancer under control for 22 months, he said.

The Phase IIb choice, however, may ultimately be non-small cell lung cancer. “NSCLC is clearly one of the indications we’re interested in,” Fetzer said during the presentation. “We have very strong data in animals as well as in patients, and the unmet medical need continues to be enormous.”

A Dual-Target Advantage

CRLX101 is a dual inhibitor of topoisomerase 1 and hypoxia inducible factor 1 alpha (HIF-1α), giving it the ability to both stop cancer cells from replicating and to cut off a growing tumor’s nascent blood supply.

While camptothecin analogues topotecan and irinotecan both work to inhibit topoisomerase activity, HIF-1 α has thus far proved an intractable target. NCI researchers discovered several years ago that camptothecins have the unique ability to lower HIF-1 α protein level, but they also found that unless there is sustained drug exposure, the effect is very readily reversible, Fetzer explained.

Because CRLX101 is built to release camptothecin gradually and consistently over time, compared with the spikes in delivery produced by traditional chemo dosing regimens, it provides the kind of prolonged drug exposure required to quench HIF-1α activity.

HIF-1α Targeting = Utility In Combination

While CRLX101’s ability to target HIF-1α is “exciting in its own right,” pairing it with a vascular endothelial growth factor inhibitor, such as Roche’s Avastin (bevacizumab), could produce even more remarkable results, Fetzer said.

HIF-1α is a compensatory mechanism that goes into action when cells become oxygen-starved in order to save the dying cells. Because VEGF inhibitors work by subverting growth of tumor cell vasculature, their activity actually up-regulates HIF-1α production, perversely leading to release of more VEGF, he explained. “We now have the ability to inhibit HIF-1α, thus potentiating the VEGF inhibitor’s effect.”

“We’re sitting on the cusp of really helping to change the way cancer therapy can evolve by allowing chemo ... to become more efficacious and less toxic - and more combinable,” he said. In the same way HIV has become a manageable chronic disease because of cocktails that combine drugs to hit several different targets, cancer drug combinations will “lead the way to a managed cancer,” Fetzer predicted. “It’s not a cure, but it’s a manageable disease.”

How The Nano-Origami Works

The self-assembling nanoparticles that form CRLX101 are made up of a polymer backbone, cyclodextrin, and an amino acid linker that binds the camptothecin. The particle is engineered to be too large to leak from circulation in mature blood vessels, but the right size to leave the larger fenestrations, or pores, of the immature vasculature being laid down by growing tumors and thus enter the tumor.

All the components employed by Cerulean's platforms are well-known to regulators, Fetzer said. "We don't want to create a new liability" by raising questions about how the technology will behave in man.

In addition, the particles are designed to avoid being filtered out by the kidneys, which will catch anything smaller than 10 or 20 nanometers. So the resulting CRLX101 particle is 20-50 nm in diameter. The outside of the particle also is designed to avoid detection and elimination by the immune system.

Chemically speaking, under the right aqueous conditions, the camptothecins form an inclusion complex with the cyclodextrins, cross-linking the different strands, and that forms the nanoparticles, Fetzer explained. The self-assembly is remarkably stable, almost like magnets clicking together, he said.

Inside the tumor, the bond is broken, the drug is released, and with every molecule that comes off, the linkage gets weaker. Eventually the particles fall apart into the polymer strands, which are small enough to be excreted.

So, ultimately, there is very little drug circulating in the system - particles that remain in circulation and deteriorate there are useful for stopping cancer cells setting out to metastasize - and most of it is in the tumor. "The patient feels good, and the drug is released very, very slowly. By the time the next dose comes, you still have plenty of drug on board."

"We have the process up and running that we can do that reproducibly, so we can dial in the right size for the nanoparticles" as well as the release kinetics depending on the half-life of the drug, Fetzer explained. "It sounds easy, but it was years and years."

Using that same platform, Cerulean plans to help other pharmas improve the safety and efficacy of their drugs. The concept is "starting to become interesting to a lot of Big Pharmas," Fetzer said.

Applying The Platform Elsewhere

Cerulean's second candidate is CRLX288, a novel conjugate that folds Sanofi-Aventis' docetaxel into a polymeric nanoparticle with the goal of improved efficacy and safety for the $3 billion/year cancer drug.

In preclinical and animal studies, the particle resulted in delivery of over 20 times more drug directly to the tumor tissue, leading to greater efficacy, less frequent dosing and reduction of toxicities.

"Bone marrow suppression is toxicity number one for docetaxel," said Fetzer. "We don't see that with nanoparticles; we have virtually eliminated it."

"Not only have we completely changed the efficacy of docetaxel, we have eliminated the primary safety issues" with the drug. The CRLX288 particle is now going into IND-enabling work, he said.

Cerulean is also working "aggressively" on a nanotech solution to the siRNA delivery problem that has stymied research in that field, said Fetzer.

"A few months ago, [nano-delivery] was conceptual with RNA ... but we now have done it with RNA and it works," he asserted.

The company has shown that its nanoparticles can resolve the four issues that plague the siRNA industry, Fetzer said. Delivering siRNA intact has been problematic because it degrades quickly. Getting it into the cells once it's there is a challenge, and if you release it on the outside it is not transported in. The primary entrée is through vesicles called endosomes, which are pretty acidic and likely to degrade the siRNA. And finally, RNA is constantly manufactured by the body, so to keep silencing it the siRNA must be released consistently over time.

"We have shown that our nanoparticles do all of these things," Fetzer said.

A Technological Advantage?

Cerulean's ability to engineer nanopharmaceuticals that primarily release their drug payload only after they enter a tumor may differentiate it from other emerging nanopharmas.

"Our data support that CRLX101 is the first nanopharmaceutical that maintains its integrity and remains as an intact nanoparticle in the bloodstream until it reaches tumor tissues," said Fetzer.

"Published data on other nano-carrier approaches suggest that they do not have such biological properties and typically release the majority of the drug while in circulation," he added.

Cerulean in-licensed the clinical stage candidate from Calando Pharmaceuticals in 2009 along with exclusive worldwide rights to the cyclodextrin-based nanoparticle technology ([1] 'Cerulean licenses Calando's delivery platform, candidate.' Elsevier's Strategic Transactions, June 2009).

The self-assembly technology, invented by California Institute of Technology scientist Mark Davis, is one of two Cerulean is using in its product pipeline.

The other, which Fetzer said employs a similar but not yet fully published concept, originated in the Massachusetts Institute of Technology laboratory of Ram Sasisekharan, a Cerulean founder. Cerulean is developing the MIT technology in-house.

"We have effectively united the best approaches on both sides of the country," Fetzer said.

Cerulean started out in 2006 as Tempo Pharmaceuticals, founded by Sasisekharan and Polaris Ventures General Partner Alan Crane, who turned the helm over to Fetzer in April 2009 but remains on as director. Before joining Cerulean, Fetzer was head of R&D and corporate development at Cubist Pharmaceuticals.

Cerulean currently is in a Series C fundraising round led by Polaris, with Venrock, Bessemer Venture Partners and Lux Capital. In July 2009 the company closed a Series B-1 round, in which it raised $10 million.

Hopefully by the time Cerulean is ready for FDA, FDA will be ready for nanotechnology. Updates to the agency's nanotech capacity are part of ongoing efforts to improve regulatory science ([2] 'FDA Not Ready For The Nanotechnology Surge; Infrastructure - Not Technical Capability - Is The Challenge, Hamburg Says,' 'The Pink Sheet,' March 15, 2010).