Going stromal with docetaxel

By Chris Cain, Senior Writer

Abraxane nab-paclitaxel is the model example of how an old microtubule-stabilizing chemotherapy can be revitalized through a new nanoparticle formulation. Now, **Ontario Institute for Cancer Research** scientists have developed glycopolymer-conjugated docetaxel nanoparticles that outperform Abraxane in mouse models of breast cancer.¹

The Ontario Institute for Cancer Research (OICR) is backing the program with \$1.5 million to take it to the clinic. The expectation is that the product's ability to target the tumor stroma rather than the tumor itself will differentiate it from Abraxane and other chemotherapeutic formulations.

The toxicity of the tubulin-stabilizing cancer chemotherapeutics paclitaxel and docetaxel has led numerous companies to attempt to develop new versions with better safety profiles that enable their use at higher and thus more efficacious doses.

The poster child for these efforts is **Celgene Corp.**'s Abraxane, which is marketed to treat metastatic breast cancer and non-small cell lung cancer (NSCLC) and is under review in the U.S. to treat metastatic pancreatic cancer.

Abraxane consists of albumin-bound paclitaxel that is assembled into nanoparticles. This permits its delivery at higher doses without the use of toxic solvents, and its nanoparticle formulation leads to higher accumulation in tumor tissue.

Other next-generation paclitaxel formulations in clinical development include **NanoCarrier Co. Ltd.**'s NK-105, a liposomal formulation that is in Phase III testing to treat breast cancer, and **Cell Therapeutics Inc.**'s Opaxio paclitaxel poliglumex, a formulation of paclitaxel covalently linked to a polyglutamate polymer that is in Phase III trials to treat ovarian cancer.

In 2005, Opaxio, then known as Xyotax, failed to show superiority to paclitaxel in Phase III NSCLC trials.

Bind Therapeutics Inc. is pursuing an improved version of docetaxel. The company's BIND-014, a polymeric nanoparticle containing docetaxel that is targeted to prostate-specific membrane antigen (PSMA; FOLH1; GCPII), is in Phase II testing to treat prostate cancer.

Nanoparticle formulations of docetaxel in preclinical development include **Cerulean Pharma Inc.**'s CRLX301, which consists of docetaxel covalently linked to a cyclodextrin polymer.

In 2011, Shyh-Dar Li, a principal investigator of drug delivery and formulation at OICR and an assistant professor at the **University of Toronto**, threw his hat into the ring with Cellax, a nanoparticle formulation of docetaxel and polyethylene glycol (PEG) that is covalently linked to a cellulose derivative called acetylated carboxymethylcellulose.

Li chose to link docetaxel to the cellulose derivative because it is relatively stable in blood, is biologically inactive and has many available sites for drug or PEG linkage. His team showed that Cellax increased the half-life of docetaxel in the blood more than fivefold compared with unmodified Taxotere docetaxel.² **Sanofi** markets Taxotere, which went off patent in 2010.

Last year, Li's group published a detailed preclinical comparison of Cellax with Abraxane. In multiple xenograft mouse models of cancer, Cellax had a higher maximum tolerated dose and lower tumor growth and metastasis than Abraxane.³

Now, Li's team has shown that a key reason for Cellax's increased efficacy could be its pronounced effect on the tumor stroma.¹

In two orthotopic mouse models of breast cancer, Cellax reduced the number of actin $\alpha 2$ smooth aorta muscle (ACTA2; α -SMA)-expressing tumor cells by 70%–80%, whereas Abraxane or Taxotere had no significant effect on α -SMA-expressing cells. Cellax also significantly increased vascular permeability of the tumors and decreased metastases compared with Abraxane or Taxotere.

α -SMA is a marker of the tumor stroma.

In line with earlier studies, mice receiving Cellax did not have neutropenia or elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels and did not lose body weight. Side effects included mild inflammation in the liver and lungs.

Results were published in *Cancer Research*.

Stromal breakdown

Li said that the effect on the tumor stroma could be a key differentiator between Cellax and other nanoparticle formulations in development.

"The majority of cancer patients succumb to metastases and/or tumor drug resistance. Both these problems have been linked to tumor stroma," he said. "Stroma is a noncancerous component of the tumor that supports cancer cell growth and invasion. Stroma also makes tumors denser, reducing blood flow and making it harder for drugs to reach and kill cancer cells. Cellax acts directly on stromal cells, increases blood perfusion in tumors and inhibits the spread of cancer in mouse models of metastatic disease."

"The key aspect and finding of Cellax is that unlike existing clinically available taxane drug delivery systems, it targets and depletes tumor-associated stromal cells that play an important role in tumor growth and metastasis," said Sangyong Jon, head of the global research lab in the Department of Biological Sciences at the **Korea Advanced Institute of Science and Technology**.

Although one proposed reason for Abraxane's efficacy, particularly in pancreatic cancer, has been that the drug could disrupt tumor stroma, recent preclinical results have cast doubt on the mechanism.⁴

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—Sangyong Jon,
**Korea Advanced Institute of
Science and Technology**

Jon added that a key unanswered question is precisely how Cellax preferentially affects the tumor stroma.

Triantafyllos Stylianopoulos, lecturer at the **University of Cyprus**, was impressed by the functional effect of stromal depletion in the mouse models.

“It is interesting that stromal depletion results in improved tumor perfusion and a lower interstitial fluid pressure,” he said. “Hypoperfusion and the uniform elevation of interstitial fluid pressure in many breast cancers are major barriers to the effective delivery of chemotherapy and nanomedicine. Overcoming these barriers can improve drug delivery and treatment outcomes not only for breast cancers but also for other desmoplastic tumors, such as pancreatic cancers.”

Cristianne Rijcken, cofounder and CEO of **Cristal Therapeutics**, said the covalent linkage of docetaxel to the carboxymethylcellulose polymer could provide advantages over formulations such as Abraxane, in which the drug is not covalently conjugated, because covalent linkage “provides more control over docetaxel release and distribution compared with current taxane formulations.”

She added that “the substantial increase in tolerability, combined with increased accumulation of drug in tumors, provides an opportunity to achieve improved therapeutic outcome in patients as compared to conventional taxane therapy.” Rijcken did say that she wants to see more characterization of safety in models including rats and additional studies to show that Cellax does not trigger an immune response.

In 2014, Cristal plans to start Phase I testing of its CriPec polymeric, covalently linked nanoparticle formulation of docetaxel to treat solid tumors.

Last November, Li received a \$1.5 million grant to develop Cellax from the OICR IP development and commercialization program, which funds early stage applied research and development at the institution.

Li said that he is using the funds to scale up Cellax production and to run additional preclinical studies in preparation for Phase I testing. He said that he is in discussions with potential partners.

OICR has filed for two patents covering Cellax's composition of matter, nanoparticle structure and method of use. The work is available for licensing from **MaRS Innovation**, the technology transfer organization for a consortium of 16 Toronto institutions including OICR.

Celgene did not respond to requests for an interview.

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COMPANIES AND INSTITUTIONS MENTIONED

Bind Therapeutics Inc., Cambridge, Mass.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Cell Therapeutics Inc. (NASDAQ:CTIC; Milan:CTIC), Seattle, Wash.
Cerulean Pharma Inc., Cambridge, Mass.
Cristal Therapeutics, Maastricht, the Netherlands
Korea Advanced Institute of Science and Technology, Daejeon, South Korea
MaRS Innovation, Toronto, Ontario, Canada
NanoCarrier Co. Ltd. (Tokyo:4571), Chiba, Japan
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