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NOVEMBER 21, 2016 BIOTECH'S MOST RESPECTED NEWS SOURCE FOR MORE THAN 20 YEARS VOLUME 24, NO. 47
SPECIAL REPRINT

NEW DRUG, OLD CLASS, WIDE THERAPEUTIC WINDOW

Novel microtubule-targeting agent largely avoids neuropathy

By Anette Breindl, Senior Science Editor

In cancer therapy, chemotherapy is the workhorse to immuno-oncology's and targeted therapy's show horses.

"There has not been a lot of innovation" in the area of chemotherapy, Gordon Shore told *BioWorld Insight*.

Partly, he said, there are good reasons for the attention lavished on immuno-oncology and targeted therapies. The pathways targeted by those approaches "are where the underlying biology of cancer lies, and where rational intervention makes a lot of sense."

But chemotherapies remain both a market opportunity and an area in need of innovation.

"The vast majority of patients worldwide do receive chemotherapy as part of their standard of care," he said. And that's not about to change. "Until rational therapies can make sufficient inroads so that they are having an impact on all cancers, which is quite a ways in the future, the evidence is that chemotherapies are very widely used and will be used for some time to come," he said.

Even if and when that future comes to pass, targeted agents are often used in combination with chemotherapies. And the development of targeting agents in the form of antibody-drug conjugates that deliver chemotherapies specifically to tumor cells could also benefit from better chemotherapies, such as Kadcyla (trastuzumab emtansine, Roche Holding AG) and Adcetris (brentuximab vedotin, Seattle Genetics Inc.), both of which have microtubule-targeting agents (MTAs) as payloads. Even with improved targeting, there will always be some level of off-target activity, Shore said.

Shore is a professor of chemistry at McGill University chief scientific officer of Diazon Pharmaceuticals Inc., a Montreal-based "semi-virtual" company that is developing DZ-2384, a novel MTA.

CLYDESDALES

If chemotherapy is the workhorse of cancer therapy, MTAs – a class of chemotherapies that includes taxanes and the Vinca alkaloids – are chemotherapy's Clydesdales. MTAs are part of the standard of care for treating more than a dozen different tumor types, making them "probably the most widely prescribed [cancer] therapy on the planet," Shore said.

That status comes despite significant safety liabilities. One of the most troubling side effects of MTAs is neuropathy, the sometimes irreversible damage that MTAs do to neurons.

Anne Roulston, associate director of the Laboratory for Therapeutic Development Center at McGill's Goodman Cancer Research Center, told *BioWorld Insight* that while MTAs have other side effects that stem from targeting rapidly dividing cells in the bone marrow and hair follicles, "there are ways to manage those other effects in the clinic." Neurons, on the other hand, "sometimes don't recover" even after chemotherapy is done.

MTAs target microtubules, a major structural component of the mitotic spindle that pulls chromosomes apart during cell division. Interfering with microtubule assembly or disassembly will throw dividing cells into enough disarray to cause apoptosis.

But microtubules are also part of the cytoskeleton. And like the bones of the macroskeleton, the cytoskeleton is constantly being broken down and rebuilt.

"Even quiescent cells, even differentiated cells . . . are constantly rebuilding their cytoskeleton on a timescale of minutes," Gary Brouhard, associate professor of biology at McGill University, told *BioWorld Insight*.

SEA SPONGE

Neurons are no exception. And because they are the longest cells in the body, there is a lot of cytoskeleton for MTAs to affect.

DZ-2384's story began when researchers working on a precursor compound isolated from a sea sponge noticed that the compound had a very wide therapeutic window.

"The challenge was that the mechanism of action wasn't understood," Shore said. McGill University, together with Sanderling Ventures, provided the initial funding to explore that mechanism, which was detailed by Roulston, Brouhard, Shore and their co-authors in the Nov. 16, 2016, issue of *Science Translational Medicine*.

DZ-2384 binds to tubulin in a new way and increases the so-called rescue frequency.

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When a microtubule is disassembling, Brouhard explained, there is "some possibility that the breakdown is halted and turned around. [The microtubule] is collapsing, ceases to collapse, and regrows. This drug facilitates that rescue process."

The rescue process is affected in dividing cells more than in neurons and other nondividing cells because of differences in the overall landscape of proteins that interact with the microtubules, Brouhard said. "That is where you have the wedge that allows you to differentiate the dividing cell from the terminally differentiated neuron." Current work is focused partly in identifying the specific interaction partners behind DZ-2384's effects.

The team is currently conducting IND-enabling studies and plans to enter the clinic in early to mid-2018, initially in triple-negative breast cancer, an indication that has no targeted therapies approved for treatment.

MTAs date back to the 1970s and many are now off-patent; DZ-2384, therefore, would initially be priced as a branded drug, making it more expensive than its direct competitors. Still, Shore was optimistic about the drug's commercial potential if it makes it to market. "If we are successful, we believe that the value of the agent will become very clear."

He pointed to the last branded MTA to receive market approval, Abraxane (nab-paclitaxel, Celgene Corp.). 2015 annual sales for Abraxane, which has patent protection through 2015, were $967 million, and "the innovation there is simply overcoming formulation problems" by attaching paclitaxel to albumin, Shore said. "It has all of the safety liabilities that paclitaxel has."

Diazon's goal is to take DZ-2384 to phase II studies, and then consider all options with respect to partnering, selling the drug or continuing development alone or with a partner.

"The benefit has to be not just marginal," Shore acknowledged. "It has to be demonstrable. And we believe that that's going to be the case." //

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