Throwing Cancer a One-Two Combo

In Situ Vaccination from Intensity Therapeutics Jabs Primary Tumors, Crosses Metastases

Gail Dutton

Many cancer treatments have achieved cures in mice only to fail in humans. **Intensity Therapeutics** has studied these failed challengers, and it may have learned why they failed to go the distance. True to the "train don't complain" ethic, the company is incorporating what it has learned into its platform therapy, DfuseRx℠. A serious contender, DfuseRx binds potent anticancer agents to cell permeation enhancers noncovalently for an intratumoral injection that destroys tumors and elicits a strong adaptive immune response.

For decades, other companies have tried to develop effective intratumoral injections. "They were never more effective than systemic drug administration," broods Lewis Bender, Intensity Therapeutics' founder and CEO. The problem, he says, was twofold.

One problem was the lack of drug dispersion throughout the tumor, which meant insufficient permeation into the cancer cells. None of the companies behind the failed intratumoral injections had added cell perfusion agents to their formulations. "Drugs must be water soluble to be injected, but water-soluble molecules don't disperse well throughout the tumor or penetrate cell membranes for effective delivery."

The other challenge with intratumoral injection was the systemic nature of cancer. "Killing one tumor," Bender mutters, "won't kill the cancer."

Adaptive Immune Response

Intensity Therapeutics, through in situ vaccination, is trying to convert the tumor itself into a high-quantity, high-quality antigenic site to stimulate the adaptive immune response and thereby eradicate tumors throughout the entire body.

By noncovalently bonding anticancer drugs with cell permeation enhancers, the DfuseRx platform creates molecules that are soluble both in water and in lipids. When these molecules are injected into a tumor, they "can saturate the area inside and outside tumor cells," Bender declares, "even in regions far from blood vessels."

The molecules attenuate the tumor, killing it without damaging its surface proteins. "As the tumor breaks apart, the immune system recognizes the tumor as foreign," Bender explains. "We see activation of both CD-8 and CD-4 T-cells."

In immune-competent mouse models of colon cancer, an Intensity Therapeutics anticancer agent called INT230-6 was given intratumorally. It eradicated the tumors and increased median overall survival to 77 days, compared to 42 days with the leading anticancer drugs alone, and 16 days without any treatment. "A significant fraction of animals had a complete response," Bender notes.

Importantly, 90% of the mice that experienced a complete response were fully protected from developing the same cancer when more than one million cancer cells were reintroduced subcutaneously or intravenously. The immune effect lasted for the remainder of the animals' natural lives. Mice immunized against colon cancer also showed significant resistance to the growth of murine breast cancer.

Intensity Therapeutics formulates drug agents with a specially matched compound that enhances cell penetration. The formulations are designed to increase the intracellular concentrations of the drugs throughout the tumors, thereby killing the tumors more effectively. In this image, mouse tumors are shown totally saturated with the drugs. When the dying tumors disintegrate, they elicit a strong adaptive immune response.

Translation to Humans

Intensity Therapeutics believes that there is a good reason to believe that its anticancer agent's benefits will extend to humans. "We've taken a very different, physics-based approach," Bender emphasizes. "Diffusion through a lipid layer isn't dependent on receptors or transport processes that are unique in humans. Using our system, the process of drug diffusion should be the same in mice and human cells. There's little biological difference in that regard."

The membrane of tumor cells, he points out, are up to 10 times more permeable than normal cells. "They absorb nutrients through diffusion," he says. Intensity Therapeutics uses that process to deliver a potent payload to the tumor (including hypoxic regions), saturating it inside and out.

"The process of stimulating the adaptive immune system should translate to humans if the quality and quantity of tumor antigen created is strong," Bender insists. "Our approach is unlike any being developed."

In investigating the translation of mice studies to humans, Bender found that drugs showing complete response in mice often involved tumors smaller than about 100 cubic millimeters and doses larger than 25 mg/kg. "Often drugs that were given at high doses to mice and effective in small tumors," he observes, "were too toxic for humans."

"Compounds that were tested in larger tumors (greater than 200 cubic millimeters), that were administered in doses less than 15 mg/kg, and that just slowed tumors' growth rates—without even showing regression from baseline—often become commercial successes," Bender adds.

In contrast, he continues, "We work with tumors that, at 325 to 350 cubic millimeters, are at least 50% larger than those used by even the most aggressive researchers. Our drug doses are significantly lower (equivalent to less than 4 mg/kg) and are injected into some, but not all, tumors to stimulate an immune response." Consequently, tumors are killed, and systemic exposure is reduced, but the real benefit is that the immune system is trained to recognize and eradicate tumors.

Clinical trials are being planned to begin the first half of 2016. The FDA is allowing a shortened preclinical program because the drugs and the cell permeation enhancers already are well-known and have been administered individually in humans.

Lean Operations

Intensity Therapeutics is a lean organization, relying on contractors and a few key employees who have developed immune-oncolytics and have taken them through clinical trials.

The company has raised approximately $3 million since its formation in 2012, and it continues to raise more funds. "Because the FDA agreed to abbreviated safety trials, we are able to invest our funds efficiently in the development process," Bender informs. "We have little infrastructure and a very low burn rate."

Partnering

Intensity Therapeutics also was awarded a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute in 2014. Jay A. Berzofsky, M.D., Ph.D., chief of the Vaccine Branch and head of the Molecular Immunogenetics and Vaccine Research Section, has replicated Intensity Therapeutic's chemovaccination results.

Additionally, Bender says, "Big pharma is quite interested in our DfuseRx platform, which has great synergy with checkpoint inhibitors (such as PD1 antibodies). Our drug, dosed in combination with checkpoints, is relatively new. The combination in mouse models shows much better effects than any drug we have identified either on the market or in development.

"Our goal is to get to human studies quickly, so people diagnosed with late-stage metastatic disease may be injected with our drug, experience few (if any) side effects, achieve complete remission, and become immunized against their own cancers, hopefully, for the rest of their long lives." GEN

Vital Signs

Intensity Therapeutics

Location
8 Wright Street, Suite 107
Westport, CT 06880

Phone
(203) 682-2434

Website
www.intensitytherapeutics.com

Principal
Lewis Bender
President & CEO

Number of Employees
3

Focus
Intensity Therapeutics, a product-development-stage biotechnology company, is using its DfuseRx platform to create immune-based therapeutics for an emerging field of cancer treatment known as in situ vaccination.