

BIOTECHNOLOGY

Intensity Therapeutics Inc.

Delivering improved immunotherapy

Checkpoint inhibitors have garnered much attention in oncology of late. These drugs interfere with a key self-defense mechanism of tumors that helps them hide from the immune system. Treatments like Bristol-Meyer Squibb Co.'s *Opdivo* (nivolumab) and Merck & Co. Inc.'s *Keytruda* (pembrolizumab) have led to dramatic improvements in difficult to treat solid tumors such as advanced melanoma and renal cell carcinoma.

As exciting as these drugs are, they are ineffective in a lot of patients. They tend to be most active in cancers with high levels of mutations, which give them a distinct look that an immune system can swiftly recognize. Rescued by a checkpoint inhibitor, a re-invigorated system can wage war on tumors.

But only if it knows what it's looking for. If the immune system can't distinguish cancer from healthy tissue, the increased activity isn't helpful, and can potentially harm.

Intensity Therapeutics Inc. got its start when Lewis H. Bender, then the CEO of Interleukin Genetics Inc., pondered the treatment failures in checkpoint inhibitors. "I thought, 'There's a steering wheel missing,'" he recalls. The key would be to kill tumor cells, but in a way that left them and their cell surface proteins more or less intact.

Other techniques, such as radiation, also kill tumor cells, but they mangle them. While immune cells may swarm to the site of dying cells, the debris usually is too distorted or too small in quantity, and the adaptive immune cells are not able to recognize the residual tumor cells as being similar to live cancer cells. "Cell-penetrating enhancers may permit potent anticancer drugs to go preferentially into cancer cells and kill them without changing how they appear in three dimensions, and more specifically you could create a significant amount of high-quality antigen to give the adaptive immune system a chance to understand what it needs to go after," Bender says.

Bender knew of a number of technologies that could increase a drug compound's

cell permeation. Those technologies had been applied to transport agents through tissues like the gut wall, the lungs, and the skin to achieve more convenient systemic drug delivery – mostly for injectable drugs such as proteins and peptides. Bender wondered if improved delivery into tumor cells by dosing potent agents with cell-penetration enhancers locally could be more effective at killing tumors than conventional drug approaches.

Anticancer drugs are dosed to achieve systemic exposure because cancer is a systemic disease. Local or intratumoral delivery has largely been abandoned because past attempts to dose a tumor did not address the systemic nature of cancer. But injecting tumors carries its own challenges. Drugs need to be water-soluble to be administered, but a water-soluble drug will not permeate through a cell's fatty membranes. In fact, Lewis describes a tumor as a honeycomb of fat and water compartments. Instead of percolating throughout the tumor, a water-soluble drug injected into a tumor will just be trapped in isolated pockets between cells, sequestered away from the internal cell components the drug needs to reach to inflict damage.

Using excipients, Intensity researchers formulated a combination of cisplatin and vinblastine, which they favored because the compounds are extremely toxic and have a long regulatory and therapeutic history.

Animal models didn't disappoint. By itself, Intensity's product outperformed expectations by activating the immune system, which went on to kill cancer systemically. Then, as the plan had been all along, the company combined it with checkpoint inhibitors, and the results were even better: "More than half of animals treated on a single cycle were cured with permanent T-cell mediated immune protection that lasts the animal's entire life," says Bender.

When researchers implanted large numbers of the same cancer cells under the animal's skin or dosed the cells intra-

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Business: Delivery platform for immunotherapies

Founded: August 2012

Founder: Lewis H. Bender

Employees: 3

Financing To Date: \$4 million

Investors: James Mellon; Kuala Innovations Ltd.

Scientific Advisory Board:

Douglas Hanahan, PhD (Swiss Institute for Experimental Cancer Research); Riccardo Lencioni, MD (University of Miami Miller School of Medicine); Mario Sznoł, MD (Yale University School of Medicine); Jay Berzofsky, MD, PhD, Masaki Terabe, PhD (National Cancer Institute)

venously, their immune systems fended them off.

FDA has agreed to an abbreviated pre-clinical safety program because cisplatin and vinblastine are so well known, and because the drug delivery enhancer is generally considered safe, according to Bender. That agreement should allow a quick jump to the clinic, set to begin in 2016 with Phase I clinical trials of the monotherapy. If those studies go as expected, Bender anticipates combining the drug with checkpoint inhibitors.

Bender is hopeful that the drug can treat solid tumors by directly killing cells in masses, and priming the immune system to seek out metastases, which could lead to effective therapies for metastatic solid tumors.

But there's another market with plenty of potential. Many patients present with localized tumors that are not metastatic, yet are too large or awkwardly placed to be surgically removed. Radiation and chemotherapy often don't work in such cases, leaving few options for a patient. Bender is convinced that the technology's tumor-infiltrating prowess could shrink such masses. "That's a large opportunity. If we can regress or eliminate those tumors in a way that's safe, that's a big potential market

– with likely tens of thousands of people each year,” he says.

Intensity is seeking out partners for its platform technology, which it calls *DfuseRx*, and it could benefit companies that are jockeying for position with third- or fourth-generation checkpoint inhibitors. “The company that can control a technology like ours could leapfrog the current market leaders,” Bender asserts. “If our technology permits the checkpoint drugs to achieve significantly better efficacy results in tumor types where these drugs are currently approved, such as melanoma, renal cell, and

lung cancer, or the cancers where these immune-oncology agents have not yet demonstrated efficacy, I think we would have quite a valuable franchise.”

Bender has over 22 years of biotech and pharmaceutical experience. His background in chemical engineering led him to the drug delivery business, where he held CEO, chief scientific officer, VP of business development, and VP of manufacturing positions, among others, before he landed at Interleukin. Ian Walters, MD, vice president and chief medical officer at Intensity Therapeutics, has over 15 years of drug

development experience in the oncology and immunology space from positions at Bristol-Myers Squibb and Millennium Pharmaceuticals Ltd. The company’s scientific advisory board includes researchers from the National Cancer Institute.

The company has raised about \$4 million and is in the process of a Series A round that has netted cash or commitments totaling \$8 million to date. Investors include Kuala Innovations and a variety of private individuals and small funds. **SU** [A#2015900189]

– Jim Kling

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