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AFTER TWO DECADES OF DISCOVERY

Biothera finds serendipity in immuno-oncology

By Marie Powers, News Editor

Biothera Pharmaceuticals Inc. is hardly a traditional biopharma newco. The company's core beta glucan immunomodulator technology, developed by researchers at the Massachusetts Institute of Technology, was picked up following the 1999 liquidation of Alpha-Beta Technology Inc., which had sought to advance the platform to treat bacterial infections. Biothera, known at the time as Biopolymer Engineering Inc., initially sought to develop an alternative or adjunctive approach to antibiotics or vaccines by using the technology to enhance the innate immune defense system against infections.

That effort plodded along without great success until 2005. With the prospect of immuno-oncology (I-O) still a gleam in the eye of most cancer researchers, a collaborator suggested taking a closer look at applying the immunomodulator technology to cancer therapy. The company conducted initial studies on the use of its asset, Imprime PGG, in various tumor types, re-branded as Biothera to reflect its transition from biomaterial science to drug development and shifted its R&D focus toward developing an immunotherapy designed to work synergistically with monoclonal antibodies (MAbs) and vaccines to treat cancer.

The Eagan, Minn.-based company now calls Merck and Co. Inc., Cancer Research UK and Eli Lilly and Co. strategic partners. But along its journey, Biothera reinvented itself several times, emerging a few years ago with a single focus that may see it uniquely positioned in the evolving I-O landscape.

"We've gone through a lot of restructuring in terms of selling off some side businesses to prepare ourselves to be a successful public company," acknowledged CEO Barry Labinger, who had to conduct some due diligence of his own before joining Biothera in December. Labinger, a veteran of Human Genome Sciences Inc. – where he oversaw the launch of the systemic lupus erythematosus drug, Benlysta (belimumab) – 3M Pharmaceuticals Inc. and Immunex Corp., most recently served as executive vice president and president of the biosciences division at Emergent Biosolutions Inc., where he oversaw product development, manufacturing and commercialization.

"I saw a promising mechanism of action that is highly complementary to leading immunotherapies," Labinger told

BioWorld Today. "We are positioned right in the middle of an exciting next wave in immunotherapy, which is to take the great advances of checkpoint inhibitors over the last couple of years and extend those to many more patients."

Biothera's board of directors includes seasoned investors Mike Grey, venture partner at Pappas Ventures, and Brent Ahrens, general partner at Canaan Partners, along with industry veterans such as Annalisa Jenkins, CEO of Dimension Therapeutics and former executive vice president and head of global R&D for Merck Serono, and serial entrepreneur Walter Ogier, founder and CEO of Acetylon Pharmaceuticals Inc. Prominent cancer researchers such as Roy Herbst of the Yale Comprehensive Cancer Center, Fred Hirsch of the University of Colorado School of Medicine and Steven O'Day at the John Wayne Cancer Institute at Providence St. John's Health Center serve as clinical advisors.

The technology, Imprime PGG (beta 1,3/1,6 glucan), is a yeast-derived beta glucan PAMP, or pathogen-associated molecular patterning molecule. The immune system relies on PAMPs to recognize foreign pathogens and cells so it can initiate a coordinated innate and adaptive immune response. But cancer cells lack PAMPs, enabling them to evade the recognition sequence required for an immune response. Imprime PGG circumvents that omission by serving as an ignition switch to drive a fully functional, coordinated anti-cancer immune response and enhance the efficacy of anti-cancer MAbs and checkpoint inhibitors.

A big differentiator for Biothera is that Imprime can be administered systemically, with the potential to target multiple cancer types, while other PAMPs must be injected directly into tumors due to their safety profile, Labinger explained. Unlike bacterial and viral PAMPs, Imprime does not target toll-like receptors or stimulate interferon genes, so the agent does not induce a cytokine storm.

"Imprime has been administered systemically in more than 400 patients, and the safety profile has been favorable," Labinger said. With systemic dosing, "we're not limited to tumors that

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are accessible by intratumoral administration, and there's more reliability to attack distant metastases or micro-metastases of a primary tumor that are spread throughout the body."

'WE CAN GO FORWARD IN ANY NUMBER OF WAYS'

Since 2013, Biothera has explored the use of Imprime PGG in combination with a variety of MAbs, including Erbitux (cetuximab, Eli Lilly/Merck KGaA), Avastin (bevacizumab, Roche AG) and Rituxan (rituximab, Roche AG/Biogen Inc.).

In the past two years, the company has moved to partner with companies developing checkpoint inhibitors. The addition of Imprime to a checkpoint inhibitor regimen prompts expanded activation of both CD4+ and CD8+ T cells and increased production of anticancer cytokines, such as interferon gamma. Imprime also increases programmed death-ligand 1 (PD-L1) expression on tumor cells and infiltrating innate immune cells, potentially enhancing their efficacy by expanding the responder population.

"Imprime activates the innate immune system, which then drives a coordinated response across both innate and adaptive immunity to attack cancer," Labinger explained. "Checkpoint inhibitors are great advances, but with response rates in the range of 20 to 30 percent, there's lots of room for improvement." Imprime PGG was always envisioned as a combination agent, according to Labinger, "and the science is directing us toward immune checkpoint inhibitors as the most promising combination," he said. "That matches up well with the shift in the treatment landscape, where cancer drugs can be more easily developed and better commercialized in the future."

The goal of Biothera's collaborations is to show proof of concept for Imprime PGG in combination with programmed cell death protein 1 (PD-1) or PD-L1 antibodies in multiple tumor types to develop the asset "to where the market is going rather than where the market has been," Labinger added.

Last week, Biothera expanded a collaboration with Merck, of Kenilworth, N.J., to add a program testing its PD-1 inhibitor, Keytruda (pembrolizumab), in combination with Imprime PGG in patients with melanoma. Biothera will sponsor a phase II trial, expected to begin in the fourth quarter, that will enroll up to 95

patients who have advanced melanoma or no longer respond to treatment with a checkpoint inhibitor or whose disease progressed following treatment with one or more lines of therapy for metastatic disease.

Biothera is driving regulatory discussions and submissions for this and other company-sponsored phase II combo studies in triple-negative breast cancer and head and neck cancer.

Biothera and Merck inked their first agreement in December 2015 calling for Merck to supply Keytruda for a phase Ib/II study testing combination therapy with Imprime PGG in non-small-cell lung cancer (NSCLC) patients. That investigator-sponsored, multicenter trial, expected to begin within the next few months, will be conducted by the Big Ten Cancer Research Consortium, which is overseeing FDA interactions.

Long term, Biothera expects to broaden its development program to include European and other regulatory bodies, but "our next step in trials is going to be more U.S.-focused, basically for the regulatory simplicity," Labinger said.

Biothera already is thinking ahead to registration studies, which it could conduct on its own or with a partner in the lead – whichever makes more sense, according to Labinger. To get to that point, the company is looking to raise a \$40 million to \$50 million financing round, enabling it to complete its slate of phase II studies "and get to the next major inflection point," which would likely lead to an IPO, he said.

The company has been financed by angel investors – mostly Minnesota-based individual investors – since its inception. Although funding has flowed in essentially continuous "small chunks," Labinger said, in 2010 Biothera pulled down \$25 million during a single round.

With 55 employees, the company is "at the right size to move forward," he added.

"Our focus now is on generating the final piece in our clinical proof of concept, which is the combination of Imprime and checkpoint inhibitors, and retaining optionality so we can go forward in any number of ways," Labinger said. "We're positioned right in the middle of a very exciting time in the treatment of cancer, in a pretty differentiated way." //