BIOWORLD™ TODAY
THE DAILY BIOPHARMACEUTICAL NEWS SOURCE
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OCTOBER 1, 2015
VOLUME 26, NO. 187
SPECIAL REPRINT

FLX Bio takes up Flexus mantle, marches on in immuno-oncology

By Marie Powers, News Editor

Both the name and mission at FLX Bio Inc. are clear throwbacks to predecessor Flexus Biosciences Inc., which was picked up in February by New York-based Bristol-Myers Squibb Co. (BMS) in a potential $1.25 billion takeover that included $800 million up front. (See *BioWorld Today*, Feb. 24, 2015.)

Top management at FLX is new, including CEO Brian Wong, recruited from Five Prime Therapeutics Inc., of South San Francisco, where he served as senior vice president of research and head of immuno-oncology (IO). Wong previously held leadership roles at Roche AG and Rigel Pharmaceuticals Inc.

Even though it's early days, "I think FLX Bio is positioned to become a leading IO company," Wong said. "And the way we're going to do that is to leverage our drug discovery expertise and immunology expertise. We have an incredible team here that works extremely well together and has a track record of success."

Bill Ho, also new to FLX as chief medical officer, previously served as vice president of clinical development at Igenica Biotherapeutics Inc., of Burlingame, Calif., where he led the development of antibody-based therapeutics. Prior to Igenica, Ho was a senior medical director in the exploratory clinical development group at Roche unit Genentech Inc.

The rest of the FLX management team is outfitted with Flexus veterans. They include Jordan Fridman as chief scientific officer, Jay Powers as vice president of drug discovery and Steve Young as vice president of technology. In all, the South San Francisco-based company has about three dozen employees – mostly chemists, biologists and immunologists. Their work generated the indoleamine 2,3-dioxygenase 1 (IDO1)/tryptophan 2,3-dioxygenase (TDO) discovery program that included IDO-selective, IDO/TDO dual and TDO-selective compound libraries to which BMS gained full rights, including the lead preclinical small molecule IDO1 F001287.

The remainder of the Flexus assets stayed with the FLX reboot, which continued operations more or less seamlessly. At the head of the FLX pipeline is FLX925 (previously AMG 925), a dual inhibitor of FMS-like tyrosine kinase 3, or FLT3, and cyclin-dependent kinase 4/6, or CDK4/6, in-licensed from Amgen Inc., of Thousand Oaks, Calif., in what Tim Lin, the company's controller, called "a strategic opportunity."

At the beginning of September, FLX moved the compound into a phase I study in patients with relapsed or refractory acute myeloid leukemia (AML). The trial is expected to recruit approximately 123 patients to evaluate safety, to determine the maximum tolerated and recommended phase II doses and to assess anti-tumor activity at the recommended dose, according to Cortellis Clinical Trials Intelligence. The study will take several years to complete, Wong estimated.

FLX also inherited two earlier stage small-molecule Treg cancer immunotherapy agents that were developed at Flexus, and Wong said the company's future efforts will focus on internal development. He cited the expertise of FLX scientific advisory board members, including Memorial Sloan Kettering Cancer Center's Alexander Rudensky, who chairs the board, University of California San Francisco's Jeff Bluestone, Stanford Cancer Institute's Holbrook Kohrt and University of California Los Angeles tumor immunology researcher Antoni Ribas.

"These folks are steeped in the tumor microenvironment, regulatory T cells and other areas that we're very interested in," Wong said. "Our plan is to build on the success of Flexus by moving the existing programs forward. But also, frankly, we're going to take the company into areas that were not originally envisioned. We're going to expand and build on the success of the original founders."

'CLEARLY A GAP IN TERMS OF UNMET MEDICAL NEED'

Wong well understands that IO could hardly be a hotter – or more competitive – space that will inevitably leave some companies behind. The differentiator for FLX, he said, is a focus on small molecules rather than biologics, "which allows us to go after targets that are not accessible to biologics. This opens up a relatively untapped and less appreciated area for IO drug discovery."

Key to that strategy is the company's emphasis on combating cancer by reversing tumor immunosuppression. Its drug discovery efforts are designed to target pathways relevant to multiple tumor types, to enhance the immune system's inherent ability to destroy tumor cells and to

reduce the escape options for tumors. Achieving those goals, in tandem, could enable broad response to treatment across larger patient populations.

"Most of the industry is focused on checkpoint inhibitors," Wong said, ticking off the usual suspects: PD-1s, PD-L1s and CTLA-4s. "Those are showing great promise, but most patients actually don't respond to those therapies and, of the patients who do, many don't achieve long-term benefit. There's clearly a gap in terms of unmet medical need."

Indeed, checkpoint inhibitors Opdivo (nivolumab, Bristol Myers Squibb Co.), Keytruda (pembrolizumab, Merck & Co. Inc.) and Yervoy (ipilimumab, BMS) appear to cure a small minority of patients, but half or more of those treated have no response, and the rest respond only temporarily. (See *BioWorld Today*, April 17, 2015.)

Although the exact targets of the FLX Treg programs are undisclosed, Wong maintained that modulating tumor-infiltrating regulatory T cells is an untapped mechanism for therapeutic innovation.

"Even beyond regulatory T cells, we believe there are many key pathways and cell types that contribute to immunosuppression in the tumor microenvironment that might not be accessible to biologics," he told *BioWorld Today*. "Using our approach, we believe we can control those cell types to help relieve that immunosuppression."

FLX is blessed with patient investors, Wong added. They include Kleiner Perkins Caufield & Byers, The Column Group and Celgene Corp. "This is a group that thinks long term about doing a great scientific story and building a great portfolio," he said.

The company hasn't disclosed its full funding, but the amount exceeds $29 million, according to Lin. For future financings, FLX will keep its options open.

"We like the idea of equity financing and bringing in new partners to help advance our technology," the controller said. "But at the same time, that's dilutive, so we're open to debt, as well."

The funding won't underwrite a lab operation. On average, FLX aims to file one investigational new drug application per year and keep moving assets through the clinic.

"Our long-term plan is to create a robust and comprehensive portfolio of highly effective IO drugs and hope to see those extend the lives of patients with cancer," Wong said. "That's our mission."