Genomics pioneer gets its first drug

The US Food and Drug Administration's February 28 approval of Xermelo (telotristat) marks the first drug successfully commercialized by Lexicon Pharmaceuticals. Founded in 1995 to pursue new target discovery, Lexicon, based in The Woodlands, Texas, built an extensive library of novel targets using a functional genomics approach and mouse knockout technology.

Despite its pioneering approach to target discovery and target validation, Lexicon's first approval has been a long time coming. Throughout most of its life, the company struggled to successfully identify and advance candidate compounds, either on its own or through collaborations. Now, with Xermelo, "they can claim credit through the whole process," says Alan Carr, senior biotech analyst with Needham & Company in New York.

The target for Xermelo is tryptophan hydroxylase (TPH), a rate-limiting enzyme involved in serotonin synthesis. Lexicon is also developing a second drug, sotagliflozin, that targets sodium glucose co-transporter (SGLT) subtypes 1 and 2, and is in late-stage trials in both type 1 and type 2 diabetes.

Lonnel Coats, Lexicon president and CEO

The approved drug Xermelo treats carcinoid syndrome, a rare condition caused by serotonin overproduction by neuroendocrine tumors that can result in flushing and severe diarrhea. Currently, carcinoid syndrome is treated with somatostatin analogs. Somatostatin is a peptide hormone, which inhibits serotonin release as well as growth hormone, glucagon and insulin production. Approximately 8,000 adults in the US are diagnosed each year with carcinoid tumors in the gastrointestinal (GI) tract, with approximately 10,000–15,000 patients treated with somatostatin analogs, according to a research report by Needham & Company.

Xermelo curbs serotonin secretion by targeting TPH's two subtypes. Lexicon discovered the existence of two TPHs when it knocked out TPH1 in the GI tract and found that TPH—and serotonin—were still operating in the brain. Until that point, drug developers had been reluctant to target serotonin production because they were afraid they would deplete it in the brain, says CEO Lonnel Coats.

When Coats arrived at Lexicon in July 2014, few of Lexicon's stakeholders saw the Xermelo program as credible, he says. The company had just undergone a painful restructuring five months earlier that included a downsizing of 45% of its workforce, largely in R&D. Its clinical focus was primarily on developing sotagliflozin for treating both type 1 and type 2 diabetes.

But Lexicon could not move forward with such a large diabetes program, Coats says. It decided to stop all work on the type 2 program to focus on type 1. "In such a specialized market, a company like Lexicon can advance a compound both through the clinic and to the market on its own," he says. Ultimately, in 2015, Lexicon partnered with Paris-based Sanofi for the large-market type 2 diabetes indication.

Xermelo, for its part, was then early in phase 3. It represented the first new mechanism for treating carcinoid syndrome in decades: Basel, Switzerland–based Novartis's somatostatin analog Sandostatin (octreotide) had been approved in 1988. Xermelo had an orphan drug designation and fast track status. "Both the FDA [US Food and Drug Administration] and the EMA [European Medicines Agency] deemed this drug to be an important drug," Coats says. "We wanted to shift people's attention" to the TPH-based treatment strategy, he says. To support approval, Lexicon's Telestar phase 3 trial generated data that showed a reduction in bowel movement frequency and a drop in 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, in urine, when patients used the drug.

Lexicon

Lexicon headquarters in Texas.

In addition to carcinoid syndrome, early work in pulmonary arterial hypertension (PAH) shows that TPH can be an early mediator in the context of heart disease. Karos Pharmaceuticals in New Haven, Connecticut, is in phase 1 studies of a TPH inhibitor in PAH. Serotonin overproduction also causes heart valve damage—another potential application for Xermelo and TPH-inhibiting drugs, Coats says.

Lexicon's technology platform was originally directed towards finding new genes that could be targets. In 2010, the company published details of its extensive mouse knockout library for secreted and transmembrane proteins (*Nat. Biotechnol.* **28**, 749, 2010). It has more than 100 targets in its library, Coats says.

In addition to its two lead programs, Lexicon has a pure SGLT1 inhibitor, LX2761, in preclinical testing. LX2761 could be used to treat a subset of the type 2 diabetes market: patients who may have renal insufficiency and may not be able to tolerate some of the approved SGLT2s (*Nat. Biotechnol.* **31**, 469, 2013), which rely on strong kidney function.

A research collaboration with Bristol-Myers Squibb uncovered another novel target, adapter protein-2 associated kinase 1 (AAK1), which could ameliorate neuropathic pain without the fuzziness and addictive properties of other pain drugs. An AAK1 inhibitor, now wholly owned by Lexicon, is in the preclinical phase.

Lexicon's journey "gives you a sense of just how long it can take to start from the idea of searching for new targets through thousands of knockout mice, identifying the targets, finding drugs that bind those targets, and [to] bring those new drugs through clinical development," says Carr. No longer focused on drug discovery, Lexicon has morphed into a commercial enterprise. It will market Xermelo on its own in the US and, plans to do the same with sotagliflozin, if approved, in type 1 diabetes.

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