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'Cinderella' story for former Genzyme execs at X4 Pharma

By Marie Powers, News Editor

The glass slipper fit. In short, that's how the founders of X4 Pharmaceuticals Inc. managed to in-license a platform, corral a $37.5 million series A round and secure FDA clearance of an investigational new drug (IND) application to move lead candidate, X4P-001, into a phase Ib/IIa study in patients with refractory clear cell renal cell carcinoma (ccRCC), expected to begin enrolling in the first quarter of 2016.

Paula Ragan, X4's president and CEO, and fellow Genzyme alumni pulled the pieces together, more or less under the radar, in about 18 months.

"There's been a convergence of clinical information and clinical successes – albeit imperfect successes, demonstrating there need to be more – along with the science around this particular mechanism," Ragan told *BioWorld Today*. "We're sitting right in the middle of that at a very exciting time. It's a phenomenal Cinderella story."

The platform of the Cambridge, Mass.-based company encompasses intellectual property and a portfolio of issued patents and pending applications for a family of small molecules targeting C-X-C receptor type 4 (CXCR4). The chemokine receptor belongs to the superfamily of G protein-coupled receptors that plays a crucial role in white blood cell trafficking. Inhibition of CXCR4, which is overexpressed in many cancers, is designed to block noncancerous immunosuppressive and pro-angiogenic cells from populating the tumor, thereby disrupting the cancer microenvironment and restoring normal immune surveillance functions. The mechanism of CXCR4 inhibition increases the ability of T cells to track and destroy cancer.

Ragan and others on the X4 team were still at Genzyme when they identified a portfolio of oral CXCR4 inhibitors "that were not getting the priority they deserved," Ragan recalled. "That's a very natural thing in these large companies that have their own priorities and constraints."

Henri Termeer, former Genzyme chairman and a founding advisor and investor in X4, was among those who initiated the conversation with Genzyme's parent company, Paris-based Sanofi SA, about out-licensing the assets into a start-up.

"Both parties recognized the potential of these drugs and believed they should have a continued life in a smaller company," Ragan said.

Those efforts led to a quiet licensing deal in July 2014, followed by a seed round in January – $1.2 million, according to an SEC document filed at the time – led by Termeer. The funds were used to file the IND as the X4 team began to meet with potential investors. The company officially completed the series A in late August, according to a second SEC filing. Maxim Merchant Capital, a wholly owned division of Maxim Group LLC, served as the sole placement agent for the financing, with Cormorant Asset Management serving as lead investor.

'WE'RE VERY OPEN TO CONVERSATIONS'

In addition to Ragan and Termeer, other X4 execs with Genzyme ties include scientific co-founder Renato Skerlj, who headed Genzyme's small-molecule discovery, and co-founder Richard Peters, current senior vice president and head of rare diseases at Sanofi Genzyme. Interim chairman Alan Walts, another co-founder, previously served as president of Genzyme Pharmaceuticals, senior vice president of corporate development of the big biotech and managing director of Sanofi-Genzyme Bioventures.

Keith Flaherty, director of the Henri and Belinda Termeer Center for Targeted Therapies at the Cancer Center at Massachusetts General Hospital and associate professor of medicine at Harvard Medical School, also is a co-founder, while others on X4's board include serial biotech entrepreneurs Isaac Blech and Michael Gilman.

Alison Lawton, who is serving on a consulting basis as chief operating officer of X4, was a senior vice president and general manager of Genzyme's biosurgery business and senior vice president of global market access. Lawton led the regulatory team for the 2008 FDA approval of Mozobil (plerixafor), a CXCR4 inhibitor used in combination with granulocyte-colony stimulating factor to mobilize hematopoietic stem cells from the bone marrow into the bloodstream for collection in preparation of a transplant. (See *BioWorld Today*, Dec. 17, 2008.)

The first portion of X4's U.S., multicenter phase Ib/IIa study of X4P-001 will assess the safety and tolerability of escalating doses of the study drug in combination with the multikinase inhibitor, Inlyta (axitinib, Pfizer Inc.), approved

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to treat patients with ccRCC, with the goal of establishing either a maximum tolerated or recommended dose for the combination. The phase IIa portion will be a randomized study exploring two dose levels of X4P-001, both in combination with axitinib.

In addition to safety and tolerability, the phase IIa will evaluate early signs of biological activity using biomarkers and clinical efficacy measured by overall response rate and progression-free survival over 18 months. The company has set an ambitious target of launching a phase III study at the end of next year.

"Within our financing horizon, we feel we're going to get a sense for activity, both in terms of surrogate markers and clinical activity in renal cells," Ragan said.

It's a propitious time to take the asset into the clinic, she added, based on published findings over the past two years that showed "the profound impact of CXCR4 antagonism – the mechanism of our drug – in increasing the rate that key immune cells traffic into the tumor microenvironment and attack and kill the cancer."

At a macro level, the field of immuno-oncology is quickly learning "that the best prediction of patient improvement in the context of these agents is the presence of these cell types in the tumor microenvironment," Ragan observed.

In addition to the ccRCC program, X4 is evaluating X4P-001 in other solid tumor indications. The company hasn't disclosed other targets, but "they are in a field where we can discern whether the molecules will have an impact on the immune surveillance or anti-angiogenesis, which is where our drugs best play," Ragan said.

X4 – the name is lab shorthand for the CXCR4 receptor – has a second disclosed asset, X4P-002, in preclinical development. That agent, which penetrates the blood-brain barrier, is being optimized to treat brain cancers and is expected to enter the clinic in 2017.

Initially, the company's regulatory strategy is focused on the U.S., "but we certainly have our eye on the global market," Ragan acknowledged. She predicted that X4 will begin to engage with ex-U.S. regulators in about a year, as the team builds out from its current roster of 10 full-time employees.

As for its long-term business strategy, "we're very open to conversations," Ragan said. "We have a number of folks that are seeking to build relationships with us so it's a very exciting time. But we're just getting off the ground. We want to make sure we're focused and achieving our milestones by demonstrating that mechanistic proof of concept in the next 12 to 18 months."

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