BIOTECHNOLOGY

X4 Pharmaceuticals Inc.

Restoring immune system surveillance against cancer

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Business: Oncology therapeutics
Founded: July 2014
Founders: Henri Termeer (formerly Genzyme); Renato Skerlj, PhD (formerly Genzyme); Alan Walts, PhD (formerly Genzyme); Keith Flaherty, MD (Massachusetts General Hospital); Michael Gilman, PhD (Padlock Therapeutics)
Employees: 9
Financing To Date: $39.2 million
Investors: Cormorant; Other undisclosed investors
Board Of Directors: Alan Walts; Michael Gilman; Isaac Blech (formely Celgene); Paula Ragan

Much of the buzz surrounding cancer immunotherapy has focused on checkpoint inhibitors, which act as brakes on the immune system. Some tumors exploit them to remain hidden from the body's defenses. Drugs like **Bristol-Myers Squibb Co.**'s nivolumab (*Opdivo*) and **Merck & Co. Inc.**'s pembrolizuma (*Keytruda*) have generated well-earned excitement.

But these drugs are no panacea. They work in just 20% to 25% of patients, and that has companies and researchers scrambling for other immune-dodging mechanisms that could offer similar or better benefits to checkpoint inhibitors, or find synergy in combination with them. (*See "IO Combos By The Numbers"* — IN VIVO, *February 2016.*)

In 2014, **X4 Pharmaceuticals Inc.** was spun out from a promising program at **Sanofi**, which targeted the CXCR4/CXCL12 system. This ligand-receptor pair acts as a sort of traffic director for blood cells, moving them toward a specific tissue, or shunting them away. It points immune cells toward infections, but also sends stem cells to a location to build new blood vessels. In pregnant mice, the cells help populate fetal bone marrow.

Some tumors have hijacked this system by overproducing CXCL12, and this has two important effects. It bars cancer-killing T cells, while recruiting the cells that build new blood vessels, which feed the growing mass.

Sanofi had a portfolio of orally available compounds that could block CXCL12, the most advanced of which had completed Phase IIa studies in HIV. But the company ultimately decided that the program wasn't a good fit for its portfolio. "They felt these assets could be better advanced by placing them externally," says Paula Ragan, president and CEO of X4. She had been at Genzyme Corp. when she first heard of the program, and after the two companies merged in 2011 she joined Sanofi, where she helped shepherd the out-licensing deal.

> Using a drug combination to switch cytotoxic T-lymphocyte production back on and eliminate the traffic conductor "could have a dramatic effect on response rate and durability," says Ragan.

X4 projects to pour $30 million into development of the pipeline in the next two to three years, something Sanofi was not prepared to do.

The company's lead candidate is X4P-001, which has been tested in over 70 subjects, and 2016 should be a big year for it. A Phase Ib/IIa trial will assess the activity of X4P-001 on its own and in combination with the tyrosine kinase inhibitor axitinib, in renal cell carcinoma.

About 80% of renal cell carcinomas bear a mutation in a tumor suppressor gene that ultimately leads to the overexpression of CXCR4, and overexpression correlates with higher mortality. Renal cell carcinoma has also been historically more sensitive to immunotherapies and angiogenesis inhibitors – the two primary effects of inhibiting CXCR4/CXCL12. "It's the right test cancer to explore both of those mechanisms," says Ragan.

She expects the drugs to work well in combination with nivolumab, as the two could complement one another. Tumors use the PD-1/PDL-1 system to inhibit production of cytotoxic T lymphocytes. Inhibition turns production back on again, so the immune system has its tanks ready to bring the fight to the enemy. But an overactive CXCR4/CXCL12 system directs them away from the tumor. With PD-1/PD-L1 inhibitors, "Clinical studies are not getting the response rates one would hope for, and we believe it's because of a trafficking problem," says Ragan.

Using a drug combination to switch cytotoxic T-lymphocyte production back on and eliminate the traffic conductor "could have a dramatic effect on response rate and durability," says Ragan. The company has been in discussions with potential partners, though Ragan isn't prepared to disclose them. "We've had some early conservations in the immune oncology

space, large pharmas and large biotechs," she says.

Aside from renal cell carcinoma, other potential targets include ovarian cancer and melanoma, which have proven vulnerable to other immune-oncology approaches. Hepatocellular cancer could be a target also because it has responded well to anti-angiogenic therapies, such as tyrosine kinase inhibitors.

The company may also explore XP-001 for certain rare immune system diseases.

Another study, to be initiated this year, will look at how XP-001 behaves in the tumor micro-environment. "We're hoping to define what piece of the immunosuppressive milieu we're affecting, what pieces of pro-angiogenesis we are affecting, and that can direct us to the next layer of clinical trials. As a little company, we need to ensure that we understand mechanistically how our drug is working, and then optimize it to make sure we're rightly aligned for further development in additional cancers," says Ragan.

Next in line is XP-002, a preclinical candidate targeted to brain cancers, including glioblastoma multiforme (GBM), which should enter the clinic in the second half of 2017. These cancers are aggressive, with an average survival of 14 months. As in renal cancer, heightened CXCR4 expression has been linked to higher mortality.

These tumors tend to grow as finger-like projections that invade other parts of the brain, making surgery difficult or impossible. Preclinical studies demonstrated that CXCR4 and CXCL12 increase along the growth of the projections, peaking at the tips. That suggests that a drug that could block CXCR4/CXCL12 could stop tumor growth by blocking these pro-tumor growth signals.

The market potential of X4's drugs isn't simple to pin down. "It's always very dependent on how you think your drug will do versus the standard of care. Hopefully it will be better. In renal cancer alone, **Pfizer Inc.**'s *Sutent* [sunitinib] is a $750 million dollar drug. That's a benchmark for its potential value in a single indication," says Ragan.

X4's Sanofi and Genzyme roots have ensured a strong management team. At Genzyme, Ragan led the strategic partnership program in rare diseases. Alison Lawton, the company's consulting COO, headed up Genzyme's regulatory affairs group and held vice president roles in biosurgery and global marketing. Robert Arbeit, MD, X4's senior vice president of clinical development and translational science, ran the infectious disease unit at the VA Medical Center in Boston, then went on clinical development roles at Cubist, Paratek, and Idera.

To date, X4 has raised $1.7 million in seed money and $37.5 in a Series A round, which was led by Cormorant Asset Management. **SU**

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-Jim Kling