BIOTECHNOLOGY

GamaMabs Pharma SA

Sugar-free antibodies against gynecologic cancers

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Contact: Stéphane Degove, CEO & CFO
Business: Targeted cancer immunotherapeutics
Founded: June 2013
Founders: Stéphane Degove; Jean-François Prost, MD, VP R&D & Strategy
Employees: 5
Financing To Date: €4.2 million
Investors: Alto Invest; Bpifrance; InnoBio; IRDINov; iXO Private Equity
Board Of Directors: Gérard Tiraby (Invivogen); Philippe Boucheron (Innobio); Jean-Michel Petit (Irdinov); Benjamin Mery (LFB); François Thomas (Independent); Stéphane Degove; Jean-François Prost

Around the globe, companies large and small are investing in technologies they believe can help the body's own immune system effectively battle cancers. One of the approaches considered highly promising these days entails trimming particular sugar groups from therapeutic antibodies. The tailoring causes the antibodies to bind their targets on cancer cells at a unique angle, which apparently spurs T cells and macrophages to vigorously attack tumors. **Roche** and its subsidiary **Genentech Inc.**, together with **Biogen Idec Inc.** and **Chugai Pharmaceutical Inc.** received FDA's approval in 2013 to market one of the first drugs of this type: *Gazyva* (obinutuzumab) for chronic lymphocytic leukemia (CLL) in previously untreated patients. This anti-CD20 antibody binds to the same epitope as the top-selling therapy *Rituxan/MabThera* (rituximab).

Deliberately intended to supercede rituximab, Gazyva is made with technology that was spun out of the **Swiss Federal Institute of Technology** in Zurich in 2000, into a company called **GlycArt Biotechnology AG**. Roche acquired GlycArt and its *GlycoMAb* methodology in 2005 for CHF 235 million ($181.58 million). That acquisition, and the resulting clinical and regulatory success, is encouraging other investors to support start-up companies that have their own means of tailoring sugar groups on antibodies.

GamaMabs Pharma SA is one of the latest contenders aiming to boost the biological activity of antibodies by altering their attached sugar groups, or glycosylation. The company, located in Toulouse, France, was founded in June 2013 to develop therapeutic antibody treatments for gynecologic cancers. Its core technologies were licensed from the **French Laboratories for Biotechnologies**, or Laboratoire Français du Fractionnement et des Biotechnologies (LFB). In 2010, LFB spun out **TG Therapeutics Inc.**, to leverage the same *EMABling* technology in certain cancers and potentially also autoimmune diseases. TG Therapeutics is currently developing an anti-CD20 antibody it calls *Utuxin* (ublituximab), which could compete with Gazyva.

GamaMabs aims to treat ovarian cancer by using an antibody to stimulate a receptor of a very specific hormone typically expressed only during the fetal development of females. Jean-François Prost, the company's VP for R&D and strategy, explains that anti-Müllerian hormone naturally functions in the male fetus to promote apoptosis, or programmed cell death, of the Müllerian duct, which is the precursor of female sexual organs. In recent years, he says, several research groups have shown that a particular receptor for this hormone is expressed in about 65% of gynecologic cancers such as ovary and endometrium. "In adults, there is some local hormone micro-secretion in ovary and in testis co-located with its receptor," Prost declares. He says GamaMabs believes an antibody that binds anti-Müllerian hormone receptor 2 (AMHR2) will prove to be a potent and specific therapeutic for ovarian cancer, "because this receptor is restricted in its distribution to that organ only." The hormone and its receptor are also sometimes found in the testes of males with testicular cancer, Prost adds.

Like other companies developing targeted therapies, GamaMabs anticipates that its lead drug candidate will have minimal side effects because of its specificity. CEO Stéphane Degove says the antibody now known as 3C23K has been shown to bind AMHR2 in mice implanted with human cell lines engineered to express the human hormone receptor. He claims, "In the in vivo models, 3C23K significantly decreases tumor growth and increases survival. It does this alone and in combination with chemotherapy." This efficacy has been documented, Degove adds, as resulting "from the action of immune effector cells triggered by the EMABling-optimized antibody at the level of the tumor."

"We are making the antibody more effective by changing the glycosylation. It is a very exquisite change, limited and precise: just the deletion of a fucose moiety," Prost explains, adding that the deletion occurs at "a critical site that is exactly where the antibody binds its receptor and engages with the cell." The antibody's mechanism of action in cancer has come to be better understood in just the past year, he says, adding, "This is a technology that appears more and more pertinent, because it helps the human body do its job."

GamaMabs will first pursue ovarian cancer, which is the fifth leading cause of cancer death in women worldwide. The disease is often called "the silent killer" because it causes few symptoms in the patient until the point that it has significantly invaded the body. By then, it is often too late for surgery to solve the problem. "There is a bad prognosis for anyone diagnosed with ovarian cancer," Degove says, noting that the average survival rate at five years post-diagnosis is just 50%. Beyond the strong unmet need for better treatments in the marketplace, Prost argues that the scientific rationale is also attractive. He explains that ovarian cancer is often found to be invaded, physiologically, by macrophages. But for some reason these immune cells are able to mount a very robust response in this disease. "The cells

are there, and they try to kill the tumor, but they can't do it on their own. We are finding that if we bring these immune cells in contact with antibodies that bind to the hormone receptor, they then become able to kill the tumor."

Degove says GamaMabs is confident that it will be able to create an effective treatment for ovarian cancer, because the start-up's findings in animal are very much in sync with the clinical data published by Roche and GlycArt for Gazyva in CLL. He notes, "It has been well shown by our colleagues that antibodies with altered sugar groups are able to reverse the lack of sensitivity that macrophages typically display in that pathology."

Researchers, physicians, and regulators are all becoming more accepting of the idea of treating cancer by making the cancer cells more provocative to the immune system, Prost argues. Investors are too, thanks in no small part to **Bristol-Myers Squibb Co.**'s *Yervoy* (ipilimumab) and a growing number of other immunotherapeutics now advancing through clinical trials. Still, GamaMabs and other developers of targeted therapies for cancer face a key challenge, Prost acknowledges: "We have to have a companion test that will allow for quantification of the receptor in tumor samples, so we can stratify patients," separating out those likely to respond to the therapy from others less likely or clearly unable to respond.

While some developers of targeted therapies can utilize existing laboratory tests as companion diagnostics, GamaMabs will have to create from scratch a test for the hormone receptor 3C23K targets. Prost says the start-up has already begun developing one in partnership with a specialized company he declines to name. "This is the price we pay for working on an original target," he says, noting that many clinicians have said they are eager to be involved in development of both the drug and a companion diagnostic.

GamaMabs aims to begin testing 3C23K in humans in 2015, and to use this lead candidate to prove the merits of its technology. Once the start-up has gathered proof-of-concept in humans, Degove says the firm will seek to partner the molecule for further clinical development. The company already has three other targets in its sights, "two of them very innovative," Prost declares. Although it is unusual for a cancer target to be limited to one particular type of tissue, as AMHR2 appears to be, Prost suggests that EMABling technology can be applied to antibodies for a variety of diseases, "provided that stimulating natural killer cells and macrophages is important in a given pathology."

In March 2014, GamaMabs raised financings of €0.5 million from Alto Invest and €0.6 million from Bpifrance, in addition to €3.1 million in seed financing contributed in the summer of 2013 by the investors InnoBio, IRDINov, and iXO Private Equity. **SU**

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– Deborah Erickson