ZymoGenetics' moves recall young Genentech

In a move reminiscent of Genentech's early days, Seattle-based ZymoGenetics signed an agreement with Leverkusen, Germany–based Bayer Healthcare in June to share marketing rights to Zymo's recombinant thrombin, a coagulation protein that potentially has wide application in controlling bleeding during surgical procedures.

The deal calls for Bayer Healthcare to coordinate with ZymoGenetics to market recombinant thrombin in the US for three years after its expected approval in January. ZymoGenetics will pay a commission to Bayer for its commercialization efforts, whereas Bayer will make milestone payments and pay tiered royalties to ZymoGenetics. (Bayer will develop and commercialize the product outside the US.) ZymoGenetics received $30 million up front and will receive an additional $40 million upon FDA approval.

ZymoGenetics' steam plant headquarters on Lake Union in Seattle.

The current thrombin market is dominated by bovine thrombin, sold by Bristol, Tennessee–based King Pharmaceuticals, with sales of $246 million in 2006. That market is ripe for penetration, however, because bovine thrombin is associated with development of antibodies that may cross-react with human blood antibodies—a phenomenon that has been linked to serious bleeding complications.

ZymoGenetics is betting that its deal with Bayer will take over that market and propel it forward on the path to becoming a fully integrated biotech company. Its stock has subsequently underperformed, partly because expectations are too high for recombinant thrombin, notes analyst Kevin DeGeeter at New York–based Oppenheimer & Co. Investors will come around eventually, he believes, but it may take time because recombinant thrombin is no more effective than bovine thrombin—and although it has a better safety profile, it isn't clear what clinical significance that better profile will have. Another issue is competition from Tel Aviv, Israel–based Omrix Biopharmaceuticals, which has a deal with New Brunswick, New Jersey–based Johnson & Johnson to commercialize a thrombin product derived from human plasma. "There's a place in the market for both types of products," says DeGeeter.

ZymoGenetics president and CEO Bruce Carter points out that no recombinant replacement proteins have failed in the clinic—nor have they failed in the market. "That's the basic model for ZymoGenetics," adds DeGeeter. "With something like thrombin, which isn't extraordinary, you can get cash that can be invested in mid-stage programs that are really pretty intriguing." He points to Atacicept, a soluble fusion protein that links part of the cytokine receptor TACI to the Fc portion of immunoglobulin, which ZymoGenetics is developing for rheumatoid arthritis and lupus, among other indications.

In that sense, ZymoGenetics' deal with Bayer evokes S. San Francisco–based Genentech's development of human growth hormone, which it used to fund its earlier pipeline candidates that had greater economical potential but higher development risk. Recombinant thrombin is a safe bet that could pave the way for ZymoGenetics' riskier pipeline products, which are being developed for indications including autoimmune diseases, cancer and hepatitis C.

And ZymoGenetics and Genentech have more in common than a portfolio management strategy, as both are affiliated with large pharmaceutical companies that hold significant equity stakes, giving them some shelter from the vagaries of stock movements.

Basel-based Roche acquired a majority interest in Genentech in 1990, then exercised an option in 1999 to acquire the rest of the shares it didn't already own. But the pharma company sold 42% of Genentech's common stock in three offerings on the open market, keeping a controlling interest and pledging to allow Genentech to operate as an independent company. So far, Roche has kept its promise and Genentech has grown into a preeminent, research-driven biotech. Genentech's 1999 deal gave Roche an option to license non-US rights to products, eliminating Genentech's sales and marketing forces outside the US and allowing the company to focus more of its resources on R&D.

ZymoGenetics' partner is Bagsværd, Denmark–based Novo Nordisk, which bought ZymoGenetics in 1988. ZymoGenetics remained a subsidiary of Novo Nordisk before being spun out in 2000. Since then, the companies have maintained a close partnership, and Novo owns about 31% of the company. Novo Nordisk also possesses a licensing arrangement with ZymoGenetics similar to Roche's with Genentech. Until November 2006, for example, Novo maintained rights outside North America to a number of proteins in ZymoGenetics' pipeline, and it continues to collaborate on development of certain others, including Factor XIII, IL-20 and IL-21.

In September, 2004, ZymoGenetics made another arrangement with Geneva-based Merck Serono (formerly Serono Labs), in which Serono gained access to a large portfolio of ZymoGenetics' genes and proteins for in-house evaluation. The deal also gave Serono the option to license up to 12 products from ZymoGenetics' pipeline over the next five years. In an unusual twist, Serono's rights to license proteins outside the US were subordinate to certain options maintained by Novo, until its claim expired in November 2006. "I would say that ZymoGenetics has served as the protein discovery engine now for two companies," says Edward Tenthoff, a senior research analyst at Minneapolis-based Piper Jaffray.

Nevertheless, the shape of ZymoGenetics' future may depend on recombinant thrombin's performance.

If the launch is as successful as Zymo's management believes it will be, "the stock price should react accordingly," says DeGeeter. If not, Novo Nordisk could swoop in and acquire the firm. DeGeeter points out that it has an option coming in autumn to increase its equity stake in the firm. "Their first window to make a bid opens up this fall. On the one hand, it may make sense—the stock is cheap and the pipeline has matured a bit. On the other hand, if you have to pay one-and-a-half billion for a company, you want to have an idea of what product you're betting on. It will be much more clear 12 to 18 months from now where the rheumatoid arthritis program [atacicept] is. It's tough for me to see anyone coming in and making a serious bid until we have a sense for what that data looks like."

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