

Birth of AIDS drug is 10-year tale

News

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DURHAM -- The Food and Drug Administration's approval Thursday of the AIDS drug Fuzeon marks the end of a 10-year odyssey for Trimeris, the drug's developer, and a coming of age for the Triangle's biotechnology industry.

As the first Triangle biotech company to nurture a drug from the laboratory to the market, Trimeris has benefited from years of research, hundreds of millions of dollars of investment -- and a lot of luck. Fuzeon, a new class of AIDS medication that blocks HIV's entry into healthy white blood cells, is better at reducing patients' virus levels than the Duke University scientists who discovered it ever envisioned.

The drug's approval was unusually fast by FDA standards -- just six months after the marketing application was submitted. It has been eagerly awaited by AIDS patients who have developed resistance to existing AIDS medications, a group that includes some of the sickest and hardest-to-treat patients.

But nothing about bringing the drug to market has been easy, and difficult issues remain unresolved.

Trimeris and its corporate partner, the Swiss pharmaceutical giant Roche, said months ago that it would be hard to meet the initial demand for the drug. More recently, a production bottleneck surfaced at Roche's manufacturing facility in Boulder, Colo.

Even more worrisome, the cost of a year's supply -- set at \$20,000 in Europe with a similar price expected here -- could put it out of reach of some who need it most. Many AIDS drug assistance programs funded with state and federal money are strapped for cash and are unlikely to be able to pay for Fuzeon.

"There is a lot of consternation among the AIDS community about this," said David Gilden, director of treatment information at the American Foundation for AIDS Research in New York. "I think the controversy and outrage are going to build."

But AIDS patients such as Steve M. Kueny of Durham consider Fuzeon a miracle drug -- and one they want access to, its cost notwithstanding.

Before he volunteered to participate in a clinical trial for Fuzeon, Kueny said he was sick every day. He suffered from nausea and diarrhea from the AIDS drugs he was taking. He went on disability because he could barely walk. His weight declined from

a fit 155 pounds to a skeletal 120.

Today, after more than a year of Fuzeon injections, Kueny, 47, feels and looks healthier than he has at any time since he contracted HIV. "It has clearly given me a whole new life," he said.

A company is born

Working in his lab at Duke University in 1992, Tom Matthews wasn't trying to find a drug for people who, like Kueny, already had AIDS. Instead, Matthews, then a scientist at Duke's Center for AIDS Research, was trying to find a vaccine to prevent HIV infections.

First, Matthews identified two sections of the HIV cell exterior that were most sensitive to infection-blocking antibodies. He then mimicked those sections by constructing chains of amino acids called peptides, hoping the insights gained would lead to a breakthrough on the vaccine front. That didn't work. But as a matter of routine, each peptide was sent to the center's virologists to see if it had any effect on the virus.

The 178th peptide the lab synthesized confounded all expectations. "It turned out the dumb thing was quite active," Matthews said. It looked so potent, in fact, that the most logical explanation was that someone had forgotten to add the virus to the petri dish.

So they ran the test again. The peptide proved to be just as potent.

Duke Peptide 178, or DP-178, was the culmination of years of work by Matthews and his boss, Dani Bolognesi, with the help of federal tax dollars. Bolognesi's labs at Duke had received \$27 million in funding for AIDS research from the National Institutes of Health over eight years, according to government records, although only a fraction of that funding went toward Matthews' work.

But neither Matthews nor Bolognesi thought their discovery would ever become a drug. Nor was that the original intent when Trimeris was formed.

The company's creation stemmed from a meeting that Max Wallace, who was in charge of commercializing Duke's technology, arranged with venture capitalists Jesse Treu and Brian Dovey of New Jersey-based Domain Associates.

Wallace had arranged many such meetings between Bolognesi and venture capitalists but had nothing to show for it. He didn't expect this meeting to be any different.

Treu's response stunned them. "Don't go anywhere else," he said. "We'll fund this company."

Bolognesi hadn't contemplated starting a company.

"We were more about the process and the mechanisms [of action] being in the

academic arena," Bolognesi said. "Our head was elsewhere."

But Treu was excited by what he had heard. "It represented a very powerful, totally new approach to AIDS," he said.

In January 1993, Domain committed \$5 million to finance the start-up of Trimeris -- \$2 million up front, with \$3 million more in future payments linked to the company's progress. That enabled Trimeris, headed by Wallace, to hire a small team of scientists to advance the technology.

'It has a half-life!'

DP-178 was renamed T-20 after Trimeris licensed the technology from Duke in exchange for an equity stake in the business. But the company's original plan envisioned T-20 as a means to an end -- a tool for discovering a new AIDS drug, ideally one that could be put in a pill -- and not a drug in its own right.

T-20, the thinking went, had too many strikes against it. It was a peptide, which can't be taken orally -- a major hurdle, given the public's aversion to alternatives such as injections. Peptides also are costly and difficult to manufacture.

There was a high probability that T-20 wouldn't work as a drug, anyway. Many peptides have a brief half-life, which means their activity is so short-lived that they aren't practical as medications. "Without a long half-life, you would need continuous IV infusion," said M. Ross Johnson, a former Trimeris CEO.

But, try as they might, Trimeris' scientists were unable to leverage the knowledge gained from T-20 into discovery of a drug that could be taken orally. That made it difficult to attract the additional financing the company needed. Another hurdle was the company's location in the Triangle, which at that time "was out of the biotech mainstream," Treu said.

But Treu and his colleagues at Domain believed strongly in Trimeris and propped up the company in its early years. Filings with the Securities and Exchange Commission show that Domain and an overseas firm that it advised provided the bulk of the \$17.6 million that Trimeris raised through March 1996.

When Johnson was hired as chief scientific officer in 1995, the company tested T-20 on rats to see just how long its half-life was.

Richard Franco, then the Trimeris CEO, remembers being awakened from a sound sleep at 3 a.m. while on a business trip in Japan. "I got a call saying, 'It has a half-life!' " Franco said. "It was like saying Frankenstein is alive."

The half-life was measured in hours, not minutes, long enough that the scientists at Trimeris could envision a drug that could be administered twice daily.

That encouraged the company to test T-20 on 16 volunteers -- four different dosages for groups of four AIDS patients each. The results were astonishing: For the group of four that took the optimum dosage, the level of HIV in the blood of all four patients

fell below detectable levels.

An expensive process

Thanks to those results in just four patients, Trimeris was able to sell stock to the public in October 1997. Its initial public offering raised \$33 million, more than doubling the \$30.5 million the company had raised privately up to that point.

Those initial tests, known as Phase I trials, marked the beginning of the time-consuming clinical trials required by federal regulators to prove a drug's safety and effectiveness. The Phase II results showed enough promise that, in 1999, Roche signed on as Trimeris' marketing partner. The deal called for Roche to split the expenses of developing Fuzeon and a second AIDS drug, T-1249, and to pay Trimeris as much as \$88 million.

Phase III trials involving about 1,000 patients, reported last year, turned out so much better than expected that Roche and Trimeris concluded the initial demand for Fuzeon would exceed the supply.

All along, producing Fuzeon on a commercial scale had been a concern. The cost of producing the drug for Phase I clinical trials was thousands of dollars per gram, said Michael Recny, Trimeris vice president of corporate development.

With a prescribed dosage of roughly 80 grams a year, that translated into hundreds of thousands of dollars per patient. To streamline the process, the company recruited three manufacturing experts from what today is GlaxoSmithKline, a giant London-based pharmaceutical company with a U.S. headquarters in Research Triangle Park. Those experts came up with a shortcut.

T-20 is a chain of 36 amino acids, and the company had been constructing it by adding a single amino acid at a time. The new team found a way to produce large quantities of three shorter chains, which could then be combined to create a fully-formed T-20.

Even so, making the drug requires 106 steps, more than 10 times the norm. About 45 pounds of raw material are needed to produce 1 pound of Fuzeon. The production cost is cited as a driving force behind Fuzeon's high price. Bolognesi, who remained at Duke in the company's early years but was recruited to be CEO four years ago, said that because the cost of making Fuzeon is at least 10 times that of existing AIDS drugs, the profit margins on Fuzeon will be "significantly less" than with other AIDS drugs.

Bolognesi also noted that, since Fuzeon must be taken by self-administered injections, its price must incorporate the cost of establishing a training network for advising patients on the proper injection technique, as well as providing essential paraphernalia such as syringes.

Another factor in the cost is the investment it took to develop the drug. Trimeris and Roche say that, combined, they've spent nearly \$600 million. Trimeris alone has racked up more than \$241 million in losses since its inception, according to securities

filings, with the bulk of that money going toward Fuzeon research and development.

Out of patients' reach?

Some AIDS activists have no patience for the companies' arguments.

"Whether [the price] is justified by the expenses of development or not is irrelevant," said Martin Delaney, founding director of Project Inform, a San Francisco AIDS advocacy group. "Paying that kind of price just isn't feasible."

Some activists cite the role that federal NIH money played in the drug's development as reason for keeping the price affordable.

"We're in favor of commercialization of NIH research," said Michael Weinstein, president of the Los Angeles-based AIDS Healthcare Foundation. "We're not in favor of gross exploitation of it."

Others are more restrained. John Paul Womble, president of the N.C. AIDS Action Network and director of development and public affairs for the Alliance of AIDS Services-Carolina, said he understands the reason for the drug's high price even though he's unhappy about it. All AIDS drugs "need to be less expensive," he said. "I wouldn't single out [Fuzeon]."

AIDS medications have been budget-busters ever since Burroughs Wellcome, now part of GlaxoSmithKline, introduced the first drug, AZT, in 1987. AZT cost patients about \$10,000 a year when it was launched. Today, GSK charges wholesalers about \$3,600 for a year's supply; the cost to patients could be a few hundred dollars more.

Seven AIDS drugs on the market today cost \$6,500 or more for a year's supply, not counting medicines that combine two or more drugs in a single pill, according to a Chicago AIDS group, Test Positive Aware Network.

Evelyn Foust, head of the HIV/STD prevention and care branch of the N.C. Division of Public Health, estimates that the state's average cost for AIDS drugs -- consisting of a regimen of several drugs -- is \$900 a month per person, or more than \$10,000 a year. The N.C. Aids Drug Assistance Program, or ADAP, hasn't yet decided whether to provide Fuzeon to low-income AIDS patients, but it faces some wrenching choices given its ongoing financial struggles.

Even without paying for Fuzeon, the program anticipates putting people on a waiting list beginning next month. In the past, it has had more than 800 patients on a waiting list.

Nonetheless, on Friday afternoon an advisory committee of health-care professionals recommended that ADAP add Fuzeon to its list of approved drugs -- but make it available only on a limited basis because of its high cost.

The woes of North Carolina's drug assistance program are echoed across the country. Nationwide, 30 programs are experiencing financial troubles, said William Arnold, co-chair of the ADAP Working Group, a Washington coalition of AIDS

organizations and drug companies. That means thousands of patients who would benefit from the drug may be unable to afford it.

Bolognesi, however, said Trimeris and Roche haven't given up hope on the ADAPs. "We want to see this drug get [to] the patients who need it," he said.

The companies are trying to make the case that Fuzeon isn't just another drug whose cost will be added to AIDS patients' existing "cocktail" of three or more drugs. Rather, they say, it can be used in place of some of those drugs, reducing the overall number of medications patients take. That would shift the focus to the overall drug bill, rather than the price of Fuzeon alone.

New level of hope

Kueny, the Durham patient, injects himself in the abdomen twice daily with the drug. He relies on the N.C. ADAP to pay for his AIDS medications.

He spent much of the winter worrying about what he would do once Fuzeon was approved and he could no longer count on getting it in the clinical trials.

"It's designed for people that have insurance, period," Kueny said in early February.

But on Feb. 27, Kueny's physician at Duke University Medical Center told him that Trimeris and Roche would continue to give him Fuzeon free of charge if that was the only way he could continue taking it.

That, Kueny said, "has offered me a level of hope that I haven't had the whole 10 years that I have been battling the disease."

Staff writer Sarah Avery contributed to this report.

TERMS

AMINO ACIDS: Principal building blocks of proteins.

HALF-LIFE: The length of time it takes for half of a substance to disintegrate.

PEPTIDE: A group of compounds formed from two or more amino acids.